Synthesis of Acyl Cyclohexenes by an Interrupted Hydrogen Borrowing Reaction



A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of

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at the

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by

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and

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source or a thesis.

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Michaelmas Term 2021

Abstract

Synthesis of Acyl Cyclohexenes by an Interrupted Hydrogen Borrowing Reaction

A thesis submitted for the degree of Doctor of Philosophy by Lewis Benjamin Smith, Lincoln College and the Chemistry Research Laboratory, Michaelmas Term 2021.

Chapter 1: Introduction

The introduction discusses the prevalence of cyclohexenes, as well as an overview of existing methods for their synthesis. This chapter also reviews the history and contemporary developments of hydrogen borrowing catalysis for carbon-carbon bond formation, with particular emphasis on the reactivity of Ph* methyl ketone.

Chapter 2: Synthesis of Acyl Cyclohexenes by an Interrupted Hydrogen Borrowing Reaction

An iridium-catalysed reaction between readily available 1,5-pentane diols and Ph* methyl ketone to prepare valuable cyclohexenes is described. An extensive optimisation found that $[Ir(COD)Cl]_2$ bearing CataCXium® A ligand was essential for the success of this transformation, which preferentially promoted an acceptorless dehydrogenation over 1,4-reduction of the acyl cyclohexene products. The substrate scope of the reaction was then explored, with a range of primary and secondary diols used to prepare multisubstituted cyclohexenes in excellent yields, and chemo- and regioselectivity. The preparation of different ring sizes and acyl groups in place of Ph* methyl ketone was also explored. Mildly acidic conditions of 2 M HCl in HFIP were developed for the retro-Friedel Crafts acylation of the acyl cyclohexene products to afford the corresponding carboxylic acid. Further derivatisation of the enone motif was also explored, such as bromination, conjugate addition and cyclopropanation, to name but a few examples.

Chapter 3: Mechanistic Investigations of the [5+1] Annulation

To shed light on the reaction mechanism for the [5+1] annulation to prepare acyl cyclohexenes, a detailed mechanistic study was undertaken, which began with performing a time course experiment and measuring the evolution of hydrogen gas. Resubjecting reaction intermediates revealed that the reaction proceeded through an unusual transition metal-free hydride shift aldol cascade. This was confirmed to be an intramolecular process by performing a double label crossover experiment. This cascade process was then confirmed to be the prevailing pathway of three related hydrogen borrowing reactions to prepare cyclohexanes, contrary to their proposed mechanisms.

Chapter 4: Cyclohexene Synthesis by Aluminium Mediated [1,5]-Hydride Shift Aldol Cascade

Based on the mechanistic insight from chapter 3, a transition metal-free methodology to prepare cyclohexenes by a tandem Horner-Wadsworth-Emmons, [1,5]-hydride shift cascade was developed. Through the screening of a range of basic and Lewis acidic conditions, the reagents alumina and aluminium *tert*-butoxide were found to uniquely promote the transformation in excellent yields. A diverse range of phosphonates were prepared, which enabled the synthesis of alkyl and aryl substituted acyl cyclohexenes. The lactol partner of the reaction was also explored, which allowed access to a diverse range of cyclohexene substitution patterns in complete regio- and stereochemical fidelity.

Chapter 5: Experimental

This chapter contains the experimental procedures and spectroscopic data for all of the compounds described within this thesis.

Chapter 6: Appendix

The HPLC calibrations, time course experiment data and hydrogen evolution data can be found in this appendix

Chapter 7: References

The references cited within the thesis can be found in this chapter.

Acknowledgements

First and foremost, I wish to thank Prof. Timothy Donohoe for being such a great supervisor over the last four years. I really appreciate all the support and guidance he provided me, and also for his excellent careers advice towards the end of my DPhil. I am especially grateful for his unending enthusiasm about Chemistry and always having an open door for discussions about good (and bad) results in the lab. My experience within his research group will stay with me for a long time. Secondly, I want to thank my industrial supervisor Dr Alex Smith. Thank you for our discussions about my research project and for hosting me at Syngenta.

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This thesis wouldn't be the same without the help of Dani, Lydia and Roly for their excellent proofreading- I really appreciate it! I've been lucky to work with several very talented post docs over the last few years; Hamish, Harry, Marvin, Nick, Roly and Simon- Thank you for advice and guidance in the lab. I would also like to particularly thank Roly for working alongside me on my research projects, helping with the syntheses of key starting materials, our stimulating chemistry discussions, and dog walks with Milo! Thank you to Hannah for being such a fantastic Part II student- It was a pleasure to work alongside you and I wish you all the success in the remainder of your MPhil.

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I've been lucky to have lived with many friends during my studies, and above all else I must thank Jack for putting up with me for the last four years. My time in Oxford wouldn't have been the same without you. Similarly, Alex, Anjali, Chris Cameron, Chris Magazzeni, Kizaki, Saik, Sofie and Tara, have all made my time in Oxford extra special.

Last but not least I want to thank my parents, Cathy and Frank for their unconditional love and never-ending support. Thank you to Sarah for your wonderful company throughout lockdown, and while I was at home writing my thesis. Also thank you to Miriam and Matt for your encouragement, and hosting excellent dinners.

Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
Ad	adamantyl
*t*Am	*tert*-amyl
Ar	aryl/aromatic
ax	axial
BEMP	2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
*n*Bu	*normal*-butyl
*t*Bu	*tert*-butyl
Cbz	carboxylbenzyl
COD	1,5-cyclooctadiene
COSY	Correlation spectroscopy
Cp*	pentamethylcyclopentadienyl
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
d	doublet
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPE	1,2-bis(diphenylphosphino)ethane

DPPF	1,1’-ferrocenediyl-bis(diphenylphosphine)
DPPP	1,3-bis(diphenylphosphino)propane
dqd	double quartet of doublets
dqt	double quartet of triplets
dr	diastereomeric ratio
e.e.	enantiomeric excess
ent	enantioenriched
eq	equatorial
eq.	equivalents
e.r.	enantiomeric ratio
e.s.	enantioselectivity; the extent of enantioretention during the reaction, calculated as (ee of product/ee of starting material)*100%
ESI	electrospray ionisation
Et	ethyl
g	gram
h	hour
hept	heptet
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
in situ	in place (latin)
in vacuo	in a vacuum (latin)
IR	infrared
J	coupling constant

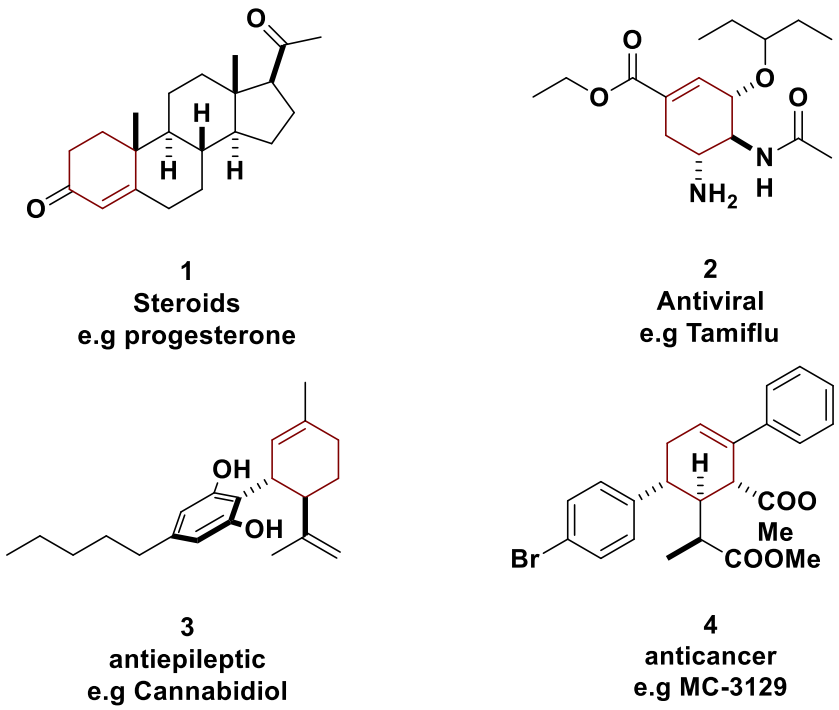
L	litre
LDA	lithium diiospropylamide
m	*meta*
m	multiplet
M	molar
Me	methyl
MeCN	acetonitrile
mg	milligrams
min	minute(s)
mL	millilitre(s)
mol%	molar percent
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
o	*ortho*
p	*para*
p	pentet
Ph	phenyl
Ph*	pentamethylphenyl
PMP	*para*-methoxyphenyl
ppm	parts per million
*i*Pr	*iso*-propyl
q	quartet
qd	quartet of doublets
rac	racemic
RP	reverse phase

r.r.	regioisomeric ratio
rt	room temperature
s	singlet
SM	starting material
t/*tert*	tertiary
Ts	tosyl
THF	tetrahydrofuran
TMS	tri-methylsilyl
t	triplet
TLC	thin layer chromatography
t_r	retention time
UV	ultraviolet
via	by way of (latin)

Chapter 1: Introduction

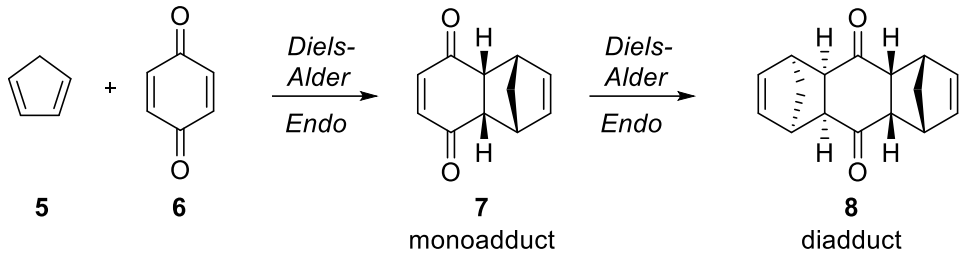
1.1 Importance and Preparation of Cyclohexenes

Cyclohexenes are of paramount importance as synthetic intermediates in organic synthesis, and also as valuable targets in their own right for the preparation of natural products and medicinally relevant compounds. Notable biologically active molecules bearing the cyclohexyl motif include steroid progesterone **1**[1], antiviral agent Tamiflu **2**[2], antiepilectic Cannabidiol **3**[3] and anticancer agent MC-3129 **4**[4], to name but a few examples (Scheme 1.1).



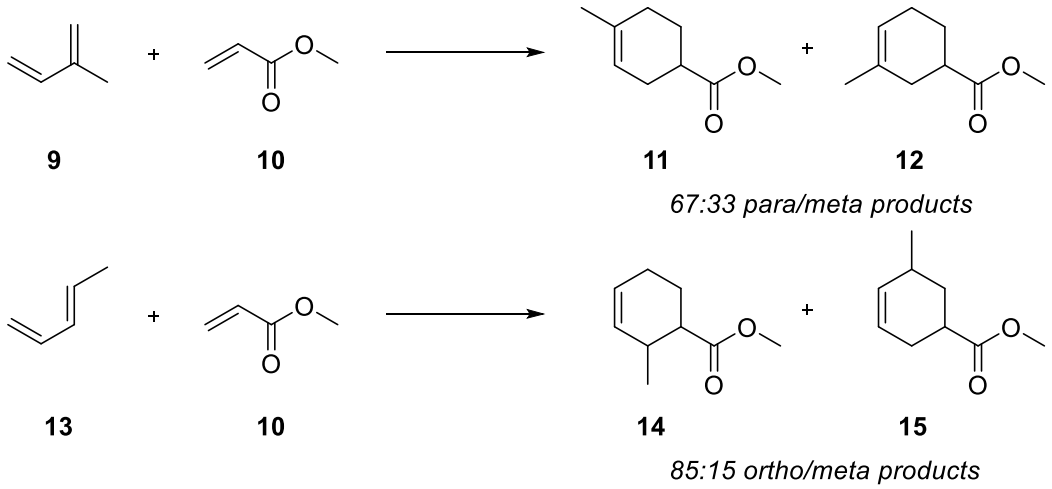
Scheme 1.1: Exemplary biologically active molecules bearing the cyclohexyl motif.

Arguably, the most powerful approach to preparing the cyclohexene core is the Diels Alder reaction. First described in 1928 by Otto Diels and Kurt Alder, this pericyclic process consists of the reaction between a conjugated diene and a dienophile, forming two new carbon-carbon bonds and a six membered ring (Scheme 1.2).[5]



Scheme 1.2: First reported Diels Alder Reaction in 1928 by Otto Diels and Kurt Alder.

However, in order to achieve high regioselectivity in the Diels Alder reaction, it is often necessary to employ sterically or electronically biased substrates. Taking the reaction between isoprene **9** and methyl acrylate **10** as the simplest example, we see that a mixture of meta and para products **11** and **12** are obtained (Scheme 1.3).[6,7,8,9] Similarly, the reaction of 1-methylbutadiene **13** with methyl acrylate **10** also affords a mixture of ortho and meta products **14** and **15**.

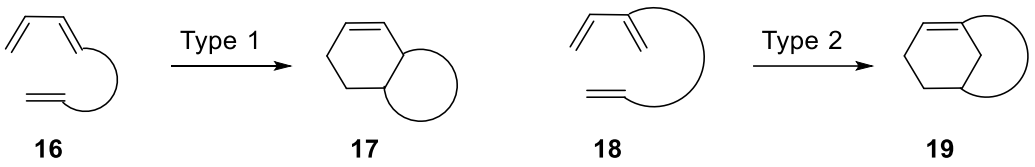


Scheme 1.3: Regioselectivity in the intermolecular Diels Alder reaction.

Because of these regioselectivity challenges, the preparation of cyclohexenes by the Diels Alder reaction is best represented when performed in an intramolecular manner. Notable approaches include tethering the diene to the dienophile, which vastly improves the regiocontrol and the overall rate of the reaction.[10] Examples of tethers employed include amide, ester and ethers, and also silicon tethered linkages.[11,12,13,14,15,16]

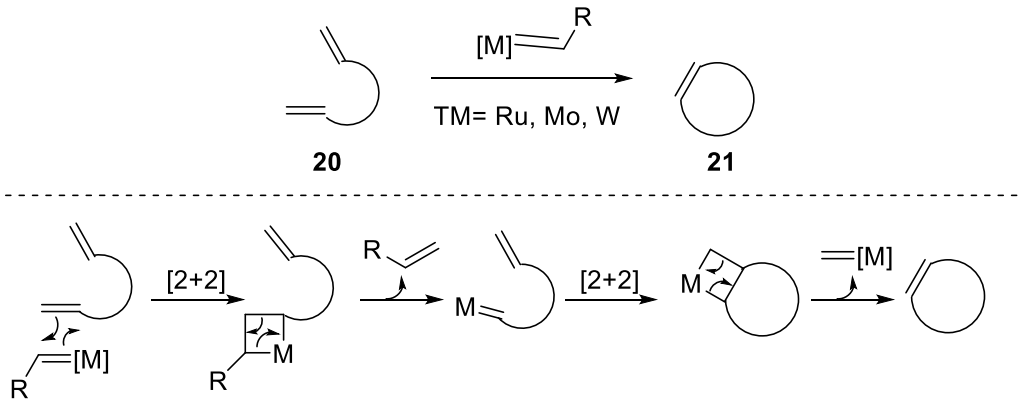
The intramolecular Diels Alder reaction has also been employed for the synthesis of bicyclic systems (Scheme 1.4).[17] The reaction is further classified as type 1, when diene **16** is substituted in the 1-position, which leads to the formation of a fused-bicyclic adduct **17**. In contrast, type 2 involves the

substitution of diene **18** at the 2-position, which results in the synthesis of bridged bicyclic system **19**. Both approaches have been applied to numerous syntheses of natural products.[10]



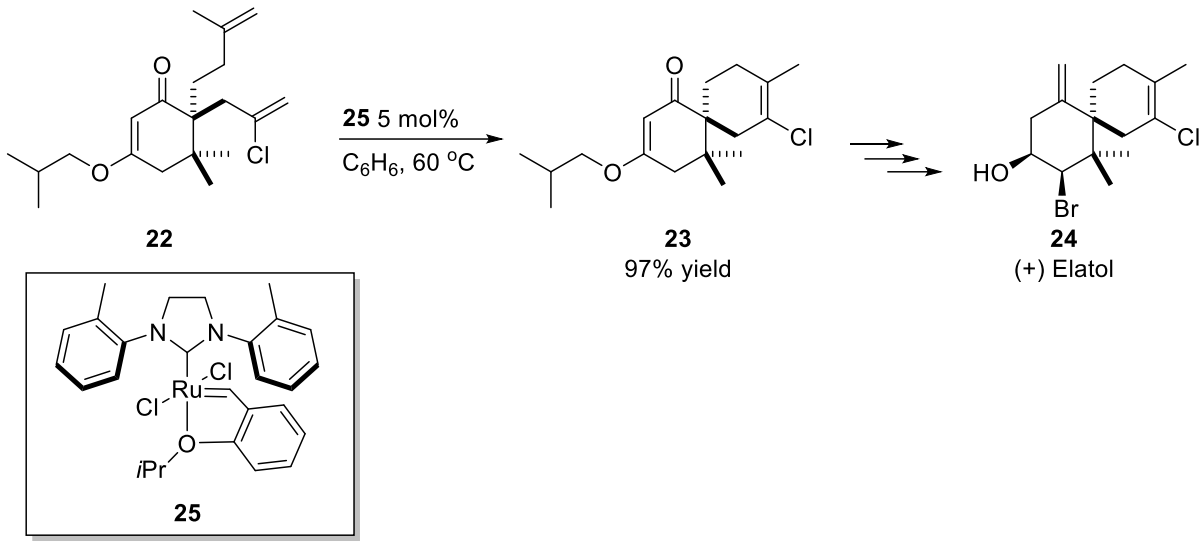
Scheme 1.4: Type 1 and type 2 intramolecular Diels Alder reaction.

The second most commonly encountered approach to the synthesis of cyclohexenes is by ring closing metathesis (RCM) (Scheme 1.5).[18] This intramolecular reaction consists of the reversible [2+2] cycloaddition between two terminal alkenes, generally catalysed by ruthenium, molybdenum or tungsten, to afford the corresponding cycloalkene **21** and ethylene gas.[19]



Scheme 1.5: generalised mechanism for ring closure metathesis

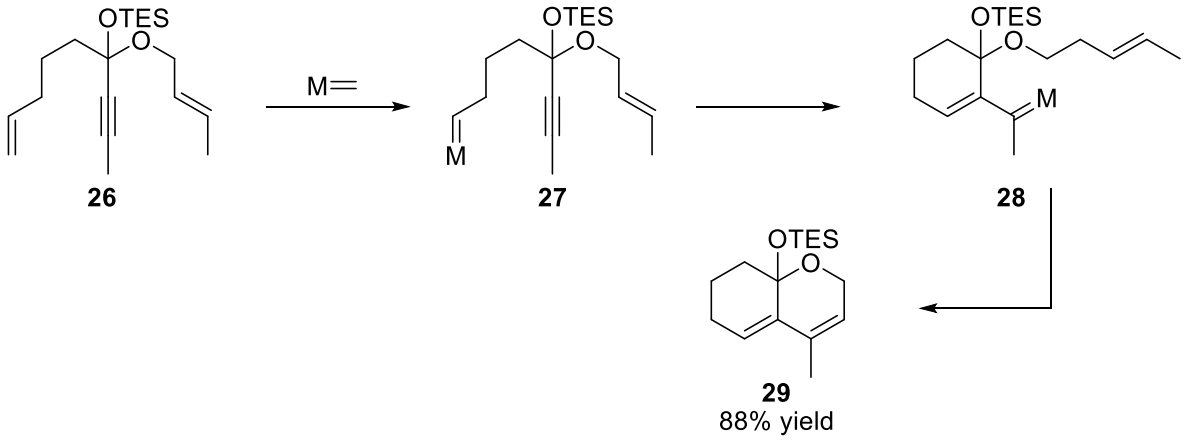
The power of this approach to synthesise cyclohexenes is best exemplified in the context of its application to synthesise natural products. For example, Stoltz and co-workers reported an efficient and general strategy for the total synthesis of (+) Elatol **24**, a member of the chamigrene family of sesquiterpenes. The key step being the RCM of **22** to prepare tetrasubstituted chlorinated olefin **23**, which formed in 97% yield.[20]



Scheme 1.6: Synthesis of (+) Elatol **24** by ring closure metathesis approach

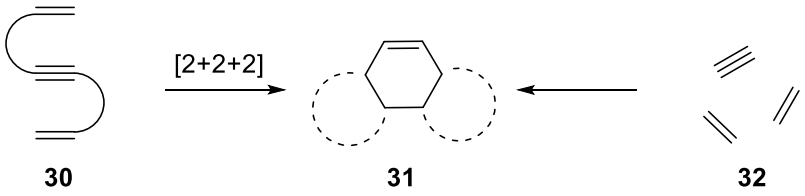
The RCM reaction also benefits from being broadly applicable to the synthesis of other ring sizes as well as heterocycles. This includes the synthesis of heterocyclic building blocks containing sulfur[21], phosphorus[21] and oxygen[22], and nitrogen[23] heteroatoms but also the preparation of medium rings[24] and macrocycles[25].

The synthesis of bicyclic ring systems has also been the subject of much attention, given the large number of natural products bearing such bicyclic structures.[26] The strategy consists of placing an alkyne in an intervening position between two olefins, such that two metatheses can occur (Scheme 1.7). This is exemplified in the synthesis of dihydropyran **29**, where the metal catalyst initiates with a [2+2] on the sterically less substituted olefin of **26**, followed by an intramolecular metathesis with the alkyne, and final metathesis with the exocyclic alkene, to afford 6,6 bicyclic structure **29** in 88% yield.



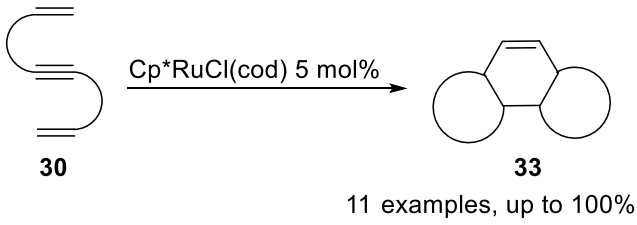
Scheme 1.7: Double metathesis strategy for the synthesis of 6,6 bicyclic structure **29**.

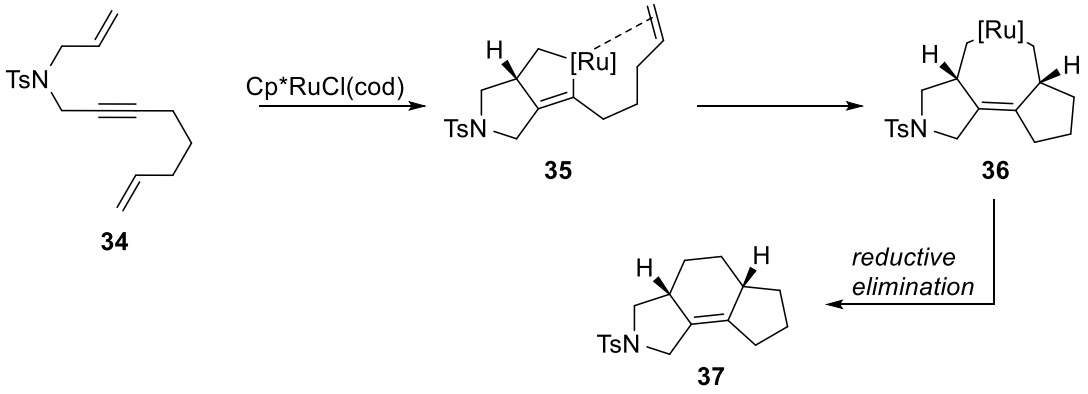
One further approach to the synthesis of cyclohexenes that has been explored extensively is cyclotrimerisation reactions.[27] This [2+2+2] approach consists of the reaction of two olefins and an alkyne promoted by a metal catalyst, to afford the corresponding cyclohexene **31**. Both intramolecular and intermolecular modes of this reaction have been reported, but the reaction is best expressed in its intramolecular form, due to control of the regiochemistry in the product.



Scheme 1.8: cyclotrimerisation approach to the synthesis of cyclohexenes

This reaction is exemplified by the work of Mori and co-workers, who reported the trimerization of tethered diene-yne compounds catalysed by Cp*Ru(COD)Cl.[28] Mechanistically, the reaction proceeds with an initial oxidative cyclisation of an alkene and alkyne to afford ruthenacyclopentene intermediate **35**. Subsequently, the ruthenium promotes a second insertion of the tethered alkene to generate ruthenacycloheptene **36**. Finally, reductive elimination gives the tricyclic compound **37**.

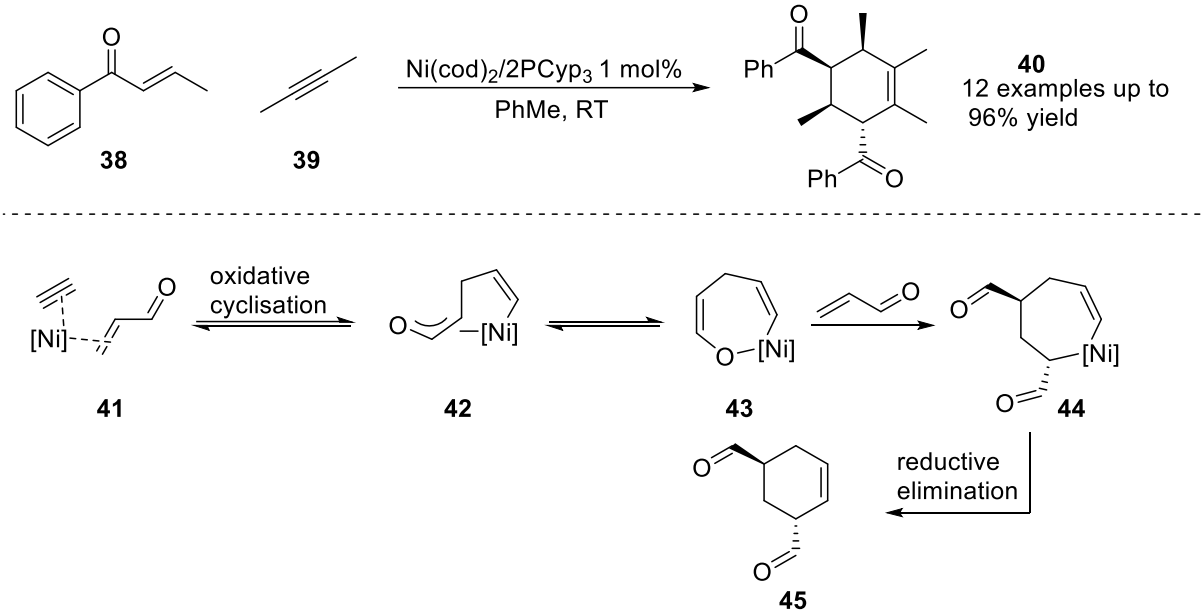




Scheme 1.9: Ruthenium-catalyzed [2 + 2 + 2] cocyclisation of diene-yne **30**.

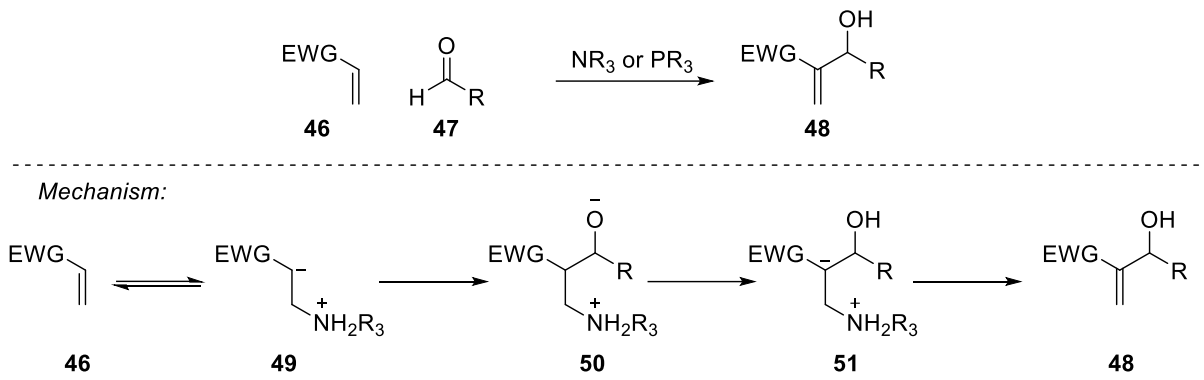
The first intermolecular example of this reaction was reported by Ohashi and co-workers in 2010, by the reaction of two enones and an alkyne in the presence of a nickel catalyst (Scheme 1.10).[29]

Mechanistically the reaction proceeds similarly to Scheme 1.9, with an initial oxidation cyclisation of the alkene and alkyne to give a η^3-oxallylnickel intermediate **42**, which is in equilibrium with seven membered η^1-*O*-nickelenolate **43**. This intermediate **43** then reacts with a second equivalent of enone to give the seven membered nickelacycle intermediate **44**. The inversion of stereochemistry of the enone motif is consistent with the reaction proceeding *via* η^1-*O*-nickelenolate.[30] Final reductive elimination of **44** affords the cycloaddition product **45**.



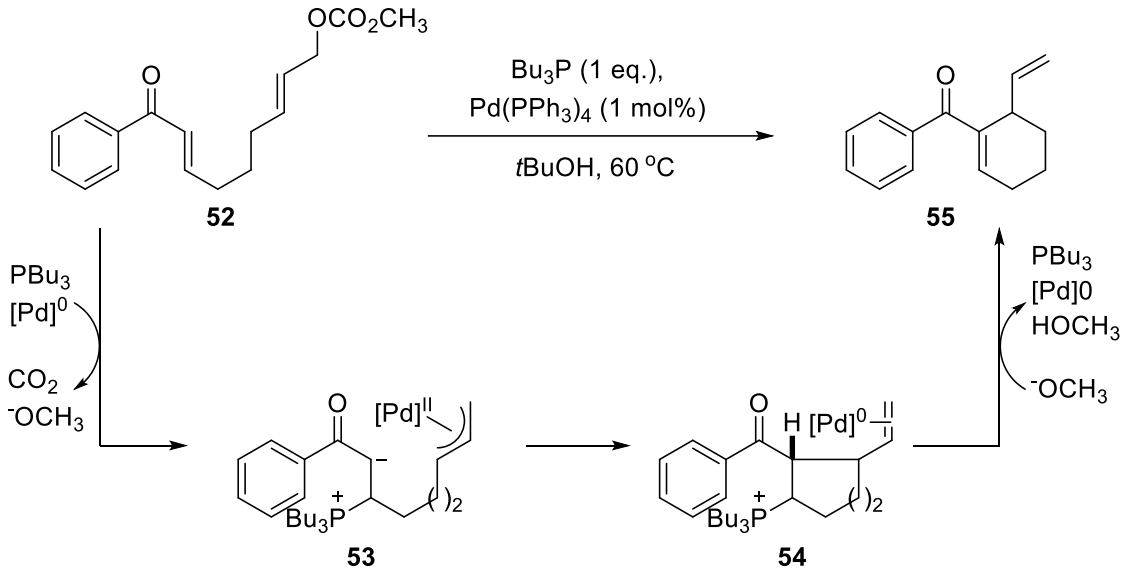
Scheme 1.10: Nickel catalysed intermolecular [2+2+2] of two enones and an alkyne.

A further approach to the cyclohexyl motif that has received much attention is the Morita-Baylis-Hillman reaction. First reported in a German patent in 1972, the process consists of the reaction between the α-position of an activated olefin and a carbon-based electrophile (Scheme 1.11).[31] Mechanistically, the reaction begins with the reversible addition of a tertiary amine or phosphine to activated alkene **46**, resulting in the formation of enolate **49**. The resulting enolate reacts with aldehyde **47** by aldol condensation, followed by proton transfer to generate alcohol **51**. Finally, **51** eliminates the tertiary amine by either E2 or E1cB to afford addition product **48**.



Scheme 1.11: Morita-Baylis-Hillman reaction and mechanism

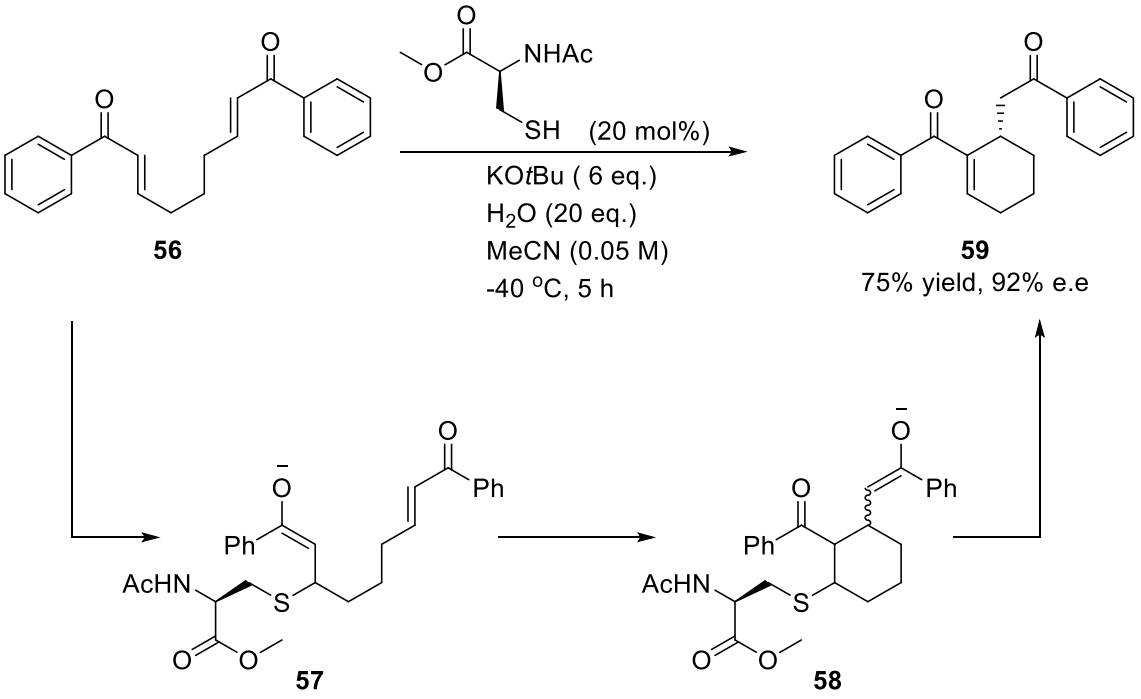
One notable report of the aforementioned reaction was by Krische and co-workers in 2003.[32] The authors demonstrated that a two-component catalyst system, combining the nucleophilic reactivity of the Morita-Baylis-Hillman reaction with the electrophilic features of the Tsuji Trost reaction, enabled the synthesis of cyclohexenes and also cyclopentenes. The use of allylic halides, and alkyl bromides as electrophiles has also been successfully implemented in this approach to access the cyclohexyl motif.[33,34]



Scheme 1.12: Synthesis of cyclohexenes by Morita-Baylis-Hillman approach.

A closely related approach to the Morita-Baylis-Hillman reaction is the Rauhut–Currier reaction, which consists of the reaction of two enones in the presence of a phosphine organocatalyst.[35] In 2007, Miller and co-workers reported an asymmetric variant of this reaction, promoted by a protected cysteine

organocatalyst (Scheme 1.13).[36] By this method, cyclohexenes bearing a range of alkyl and aryl ketones were accessible, while esters were not tolerated in the chemistry.



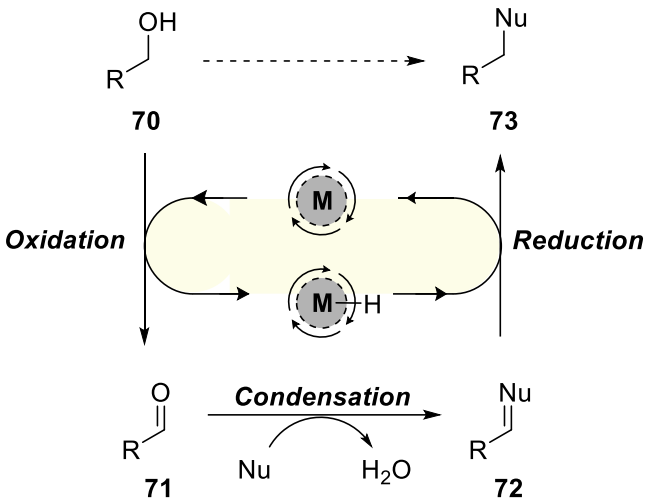
Scheme 1.13: Asymmetric synthesis of cyclohexenes by Rauhut Currier reaction.

Up to this point, a diverse range of approaches to the cyclohexyl motif have been presented. Overall, these reported reactions are best expressed as intramolecular processes, due to issues of regiocontrol, and necessitate the synthesis of the appropriately substituted precursors to access the corresponding substituted cyclohexene. Intermolecular reactions that enable the synthesis of multisubstituted cyclohexenes are much less well documented, and therefore new methods for cyclohexene synthesis that complement existing approaches (e.g Diels Alder reaction, RCM) are highly desirable. One intermolecular approach to cyclohexenes that has not been explored is by hydrogen borrowing catalysis.

1.2 Hydrogen Borrowing Catalysis for C-C and C-N Bond Formation

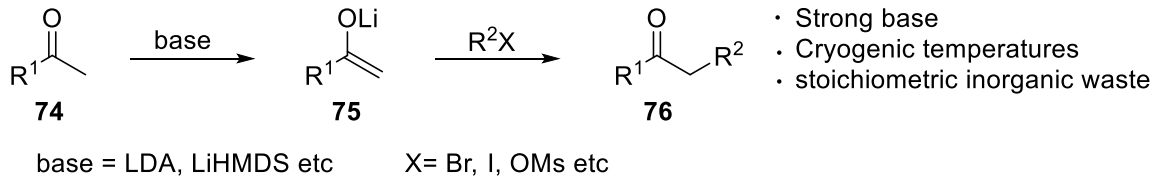
Hydrogen borrowing catalysis is a strategy for C and N alkylation that enables the indirect reaction of alcohols with carbonyls and amines. The general process consists of a combination of three key steps outlined in scheme 1.14. The first of step in this sequence is oxidation of alcohol **70** to the corresponding carbonyl **71** in the presence of a metal catalyst, generating a metal hydride. In the

second step, carbonyl **71** undergoes a condensation with a nucleophile, such as an aldol reaction with an enolate, or an imine condensation with an amine. Finally, the resulting intermediate **72** is reduced by the metal hydride, to afford alkylated product **73**.



Scheme 1.14: Generalised mechanism for hydrogen borrowing alkylation

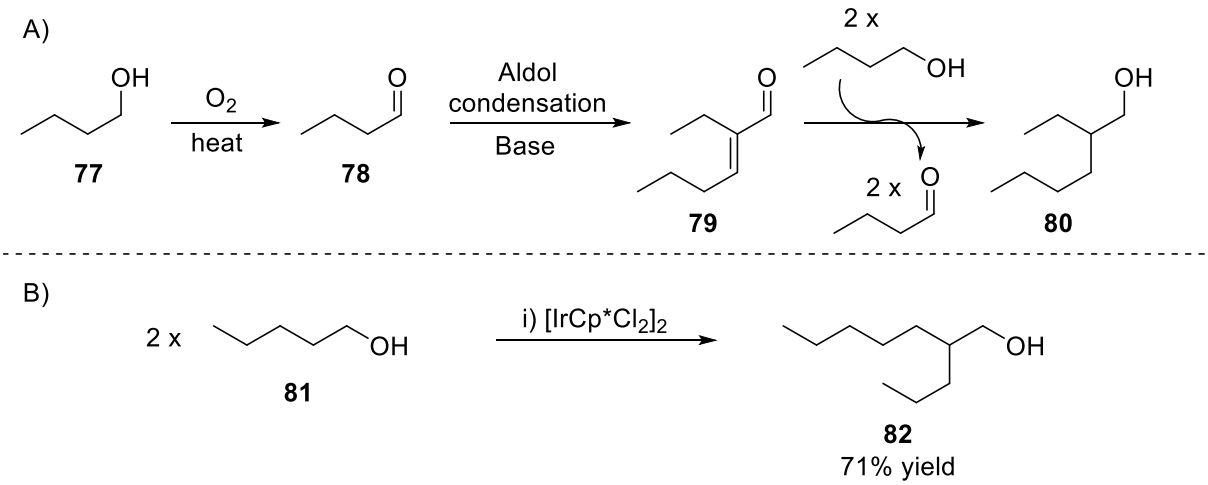
Contextually, it is important to consider the environmental impact of hydrogen borrowing when compared to the classical alkylation of carbonyl compounds (Scheme 1.15). The only by-product from a hydrogen borrowing reaction is the formation of water, which is environmentally benign. In contrast, the alkylation of carbonyl **74** with an alkyl halide or pseudohalide has several limitations. Firstly, alkylating agents have a high toxicity, and produce a stoichiometric amount of inorganic waste. Secondly, to control reactivity, these reactions necessitate the complete formation of enolate **75** using a strong high molecular weight base such as LDA, prior to the addition of the electrophile. Thirdly, the reaction conditions require the use of cryogenic temperatures. Taken together, these factors illustrate some of the limitations of a classical alkylation reaction, and highlight what the developing field of hydrogen borrowing alkylation strategies aim to address.



Scheme 1.15: Classical alkylation of carbonyl compounds.

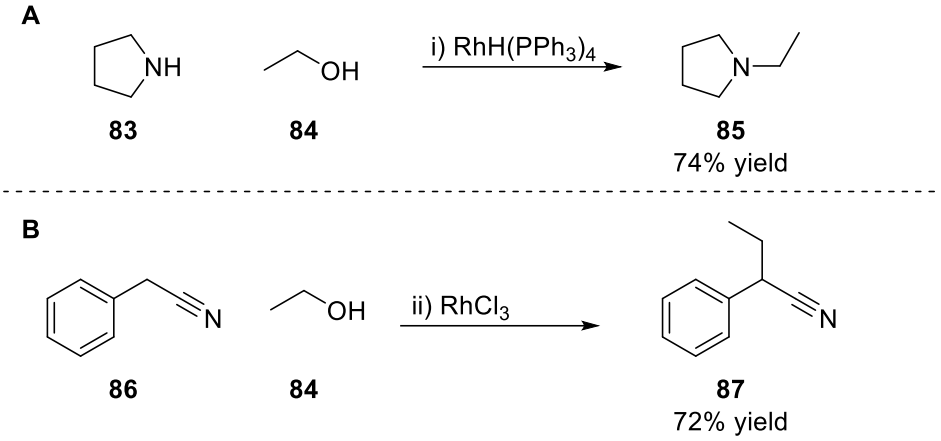
One of the earliest examples of a hydrogen borrowing-type alkylation is the Guebert reaction, first reported in 1899 (Scheme 1.16, A).[37] The reaction typically proceeds at 200 °C and higher, beginning

with the air oxidation of butanol **77** to butanal **78**. Butanal then dimerises by an aldol condensation to give enone **79**. Finally, the resulting enone is reduced with two equivalents of 1-butanol by an Meerwein-Pondorf-Verley type reaction, which generates the dimer product **80** and two further equivalents of 1-butanal, propagating the reaction. A key limitation of this reaction is the propensity for side products and oligomers to form, with competing processes including the Cannizzaro reaction and Tishchenko reaction. Much of these limitations were addressed with the implementation of transition metal catalysts, which enabled the reaction to proceed at lower temperatures.[38] For example, Ishii and co-workers reported the use of $[IrCp^*Cl_2]_2$ to catalyse the Guebert reaction of 1-pentanol, affording dimerised alcohol **82** in 71% yield (Scheme 1.16, B).[39]



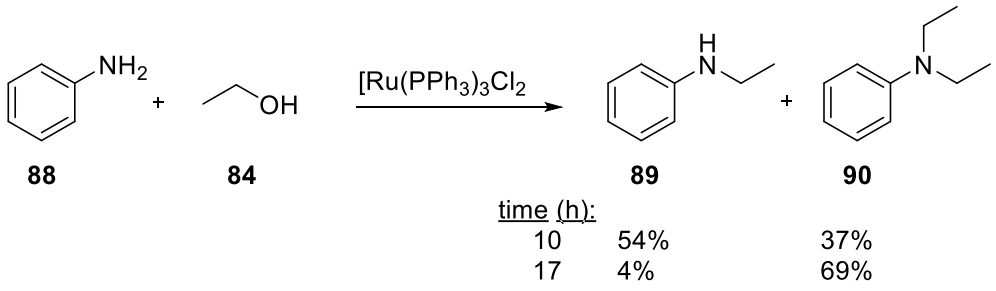
Scheme 1.16: A) Mechanism of Guebert reaction. B) Guebert reaction using an iridium catalyst. Conditions: i) $[Ir\ Cp^*Cl_2]_2$ (1 mol%), 1,7-octadiene (10 mol%), and KOtBu (40 mol%), p-xylene, 120 °C, 4 h.

One of the first homogenous transition metal catalysed hydrogen borrowing reactions that demonstrated C-N bond formation was by Grigg and co-workers in 1981, who reported the N-alkylation of primary and secondary amines with alcohols.[40] For example, pyrrolidine **83** could be alkylated with ethanol **84** using $RhH(PPh_3)_4$ to give alkylated product **85** in 74% yield. In a subsequent publication, Grigg reported the monoalkylation of arylacetonitriles with primary alcohols, which afforded nitrile **87** in 72% yield.[41]



Scheme 1.17: A) Alkylation of secondary amines with primary alcohols. B) Alkylation of arylacetonitrile with primary alcohols. Conditions: i) pyrrolidine (1 eq.), $RhH(PPh_3)_4$ (1 mol%), ethanol, reflux, 6 h. ii) $RhCl_3 \cdot 3H_2O$ (5 mol%), PPh_3 (25 mol%), Na_2CO_3 (1.1 eq.), EtOH, reflux, 48 h.

Also, in 1981, the group of Watanabe reported the N-alkylation of aniline with alcohols using a ruthenium catalyst (Scheme 1.18).[42] Generally speaking, they found that the reaction afforded dialkylated products with long reaction times. This is exemplified by the reaction in Scheme 1.18, where we see the selectivity for dialkyl amine **90** increase with changing the reaction time from 10 hours to 17 hours.

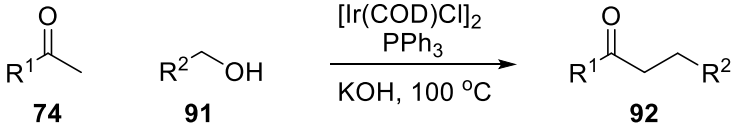


Scheme 1.18: Alkylation of aniline with primary alcohols. Conditions: $[Ru(PPh_3)_3Cl_2]$ (0.5 mol%), EtOH, 180 °C, 10-17 h.

Following these seminal publications, developments within the field of hydrogen borrowing catalysis primarily focused on new catalytic systems for the alkylation of ketones and amines with primary alcohols. This has included metals such as ruthenium[43,44,45], iridium[46,47], palladium[48,49] and iron[50], to name but a few examples.

One notable contribution was the work by Ishii and co-workers, who reported the α-alkylation of ketones with primary alcohols using $[IrCODCl_2]_2$, PPh_3 and KOH without solvent (Table 1.1).[51] The

authors obtain the alkylated product in uniformly high yields, with minimal reduction of the ketone product to the corresponding alcohol. Notably, an excess of alcohol was used, which was found to prevent the dimerisation of the ketone starting material. When the authors used ketone **100**, a lower yield of alkylated product **101** was obtained, which reflects the difficulty of alkylating non-methyl ketones, which is a recurring theme for catalytic systems in this field.



74 **91** **92**

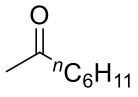
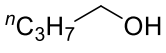
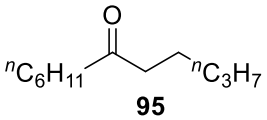
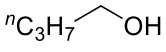
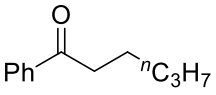
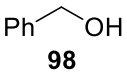
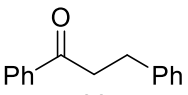
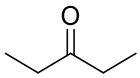
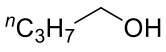
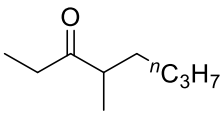
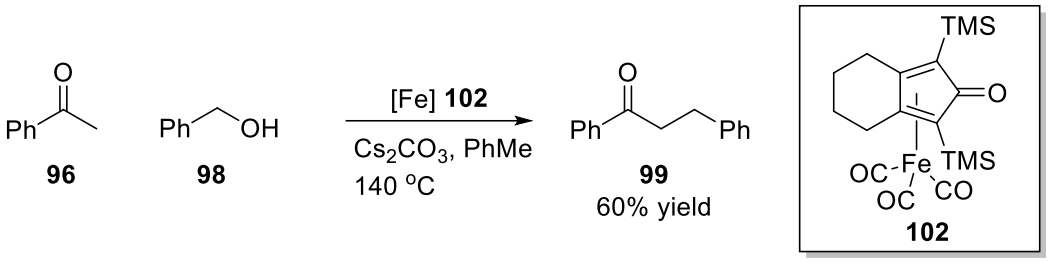
Entry	Ketone	Alcohol	Product	Yield (%)[a]
1	 **93**	 **94**	 **95**	80 (2)
2	 **96**	 **94**	 **97**	88 (4)
3	 **96**	 **98**	 **99**	81 (<3)
4[b]	 **100**	 **94**	 **101**	47 (<1)

Table 1.1: Selected susbtrate scope of Ishii's method for a-alkylation of ketones with primary alcohols. Conditions: ketone (1 eq.), alcohol (2 eq.), $[IrCODCl_2]_2$ (1 mol%), PPh_3 (4 mol%), KOH (10 mol%), 100 °C, 4h. [a] yield of corresponding alcohol in parenthesis. [b] 30 mol% of KOH used.

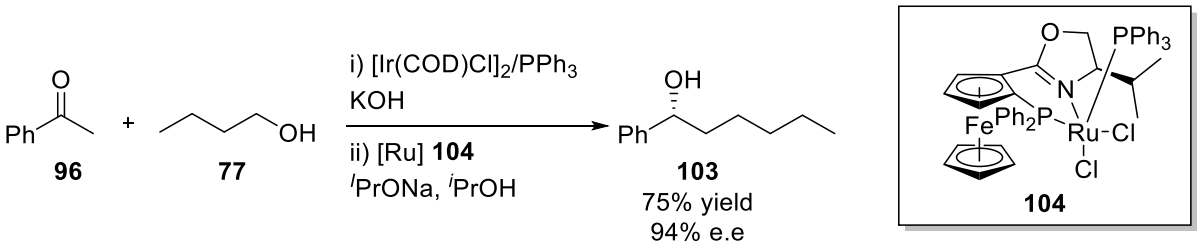
Another key contribution to the field was in 2015, when Beller and co-workers demonstrated that iron Knölker-type complex **102** was an effective catalyst for the alkylation of methyl ketones with primary alcohols.[50] Notably, this was the first example of a first-row transition metal being used in hydrogen borrowing catalysis.



Scheme 1.19: Iron catalysed α-alkylation of ketones with primary alcohols.Conditions: ketone (1 eq.), alcohol (1.5 eq.), **102** (2 mol%), PPh_3 (2 mol%), Cs_2CO_3 (10 mol%), PhMe (0.5 M), 140 °C, 24 h.

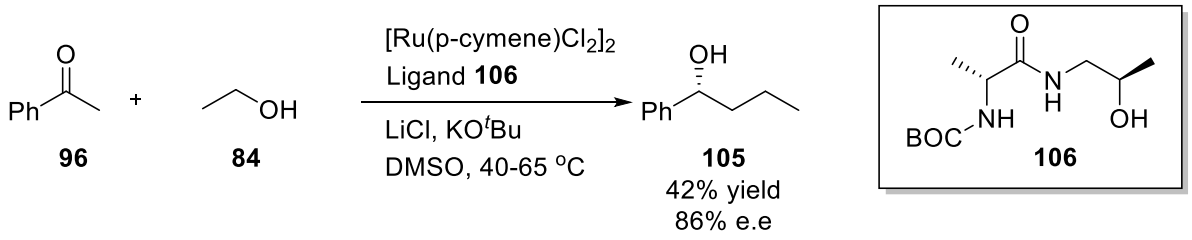
1.2.1 Asymmetric Hydrogen Borrowing Reactions

There have also been several reports of asymmetric methodologies.[52,53,54,55,56,57,58] For example, Nishibayashi and co-workers reported a dual catalyst system for the sequential α-alkylation of ketones with primary alcohols, followed by an asymmetric reduction of the ketone product to the corresponding enantioenriched alcohol (Scheme 1.20).[52] In a representative example, acetophenone **96** is alkylated with butanol **77** catalysed by $[Ir(COD)Cl_2]_2$ and PPh_3, followed by a 1,2-reduction with ruthenium catalyst **104**, giving alcohol **103** in 75% yield and 94% e.e. The reaction scope was limited to aromatic ketones, and only aliphatic alcohols were tolerated in this chemistry, with benzyl alcohol not affording any desired product.



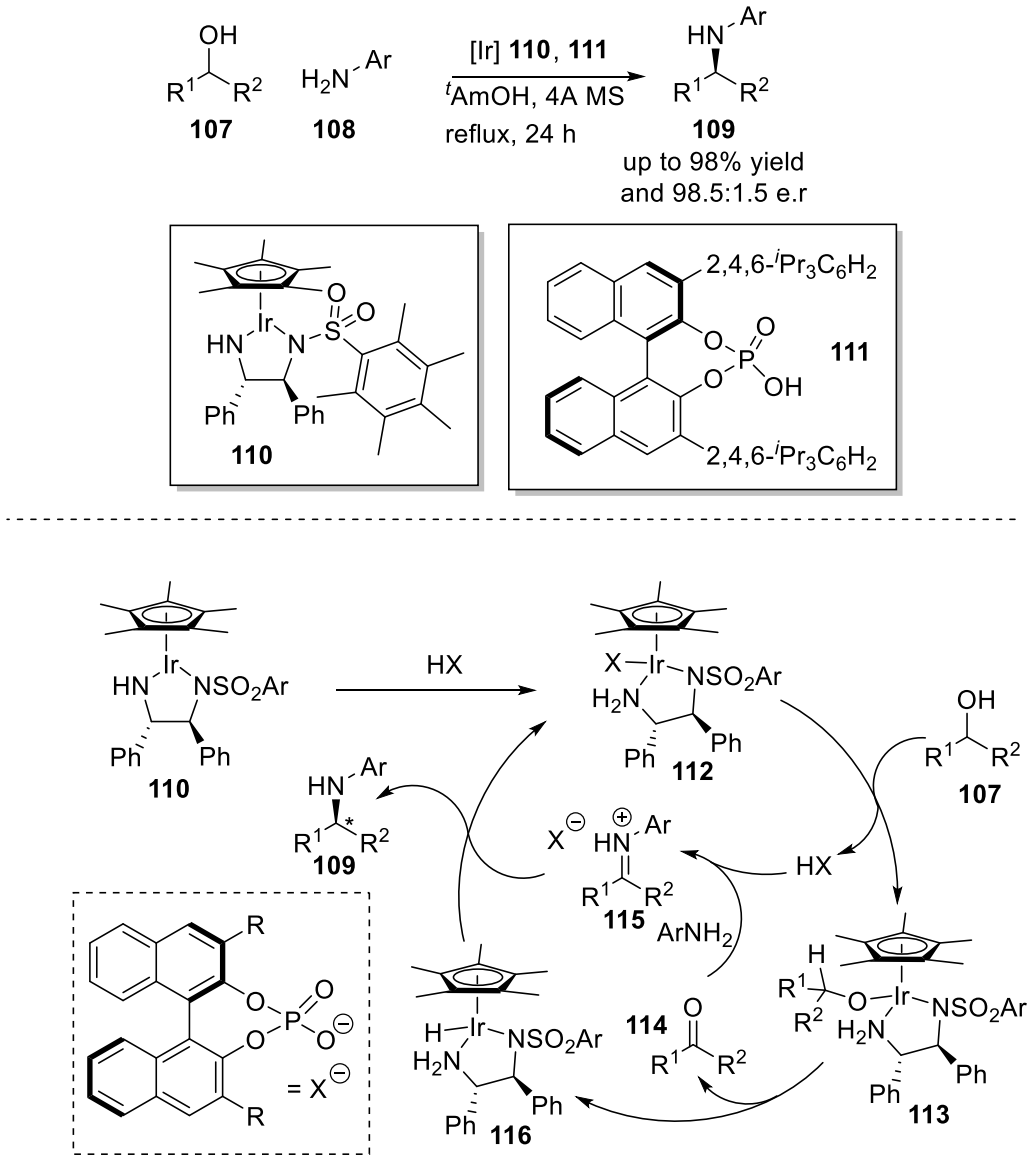
Scheme 1.20: Asymmetric α-alkylative reduction of ketones with alcohols. Conditions: $[Ir(COD)Cl]_2$ (1 mol%), PPh3 (4 mol%), KOH (5 mol%), BuOH (3 equiv), 100 °C, 4 h, (ii) [RuCl2(PPh3)(ip-foxap)] 68(1 mol%), NaO^iPr (4 mol%), ^{i}PrOH, RT, 2 h.

In a related publication, Adolfsson and co-workers reported the ruthenium catalysed tandem α–alkylation asymmetric transfer hydrogenation of acetophenone with primary alcohols (Scheme 1.21).[53] Contrary to Nishibayashi's work, which required two separate catalysts for each step, Adolfsson reported that using an amino acid derived ligand **106** with a $[Ru(p\text{-cymene})Cl_2]_2$ enabled the isolation of alkylated alcohol **105** in moderate yields and good e.e.



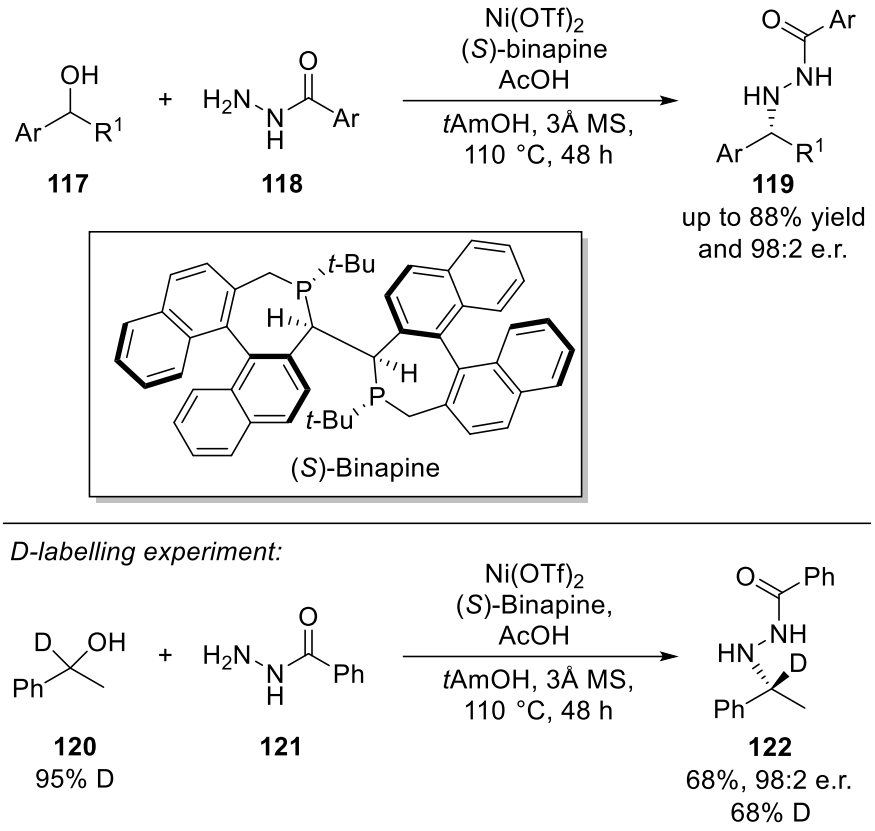
Scheme 1.21: Ruthenium catalysed tandem α–alkylation asymmetric transfer hydrogenation of acetophenone with primary alcohols. Conditions: ketone (1 eq.), alcohol (3 eq.), [Ru(*p*-cymene)Cl_2]$_2$ (0.5 mol%), ligand **106** (1 mol%), LiCl (10 mol%), KO^{t}Bu (50 mol%), DMSO, 65 °C to 40 °C, 5 h.

In 2014, Zhao and co-workers reported the first example of an asymmetric hydrogen borrowing alkylation of amines, catalysed by iridium and chiral phosphoric acid **111** (Scheme 1.22).[54] These conditions enabled the alkylation of anilines with alcohols in high yields and excellent enantiomeric excess. Mechanistically, the authors proposed that iridium catalyst **110** is protonated by phosphoric acid **111** to afford the corresponding iridium phosphate **112**, which undergoes ligand exchange with the alcohol and then oxidation to afford ketone **114**. Ketone **114** then condenses with aniline to afford imine **115**, which is protonated by the chiral phosphoric acid. The resulting iminium ion is then reduced by iridium hydride **116** to afford enantioenriched amine **109** and regenerate the catalyst. The authors later applied this approach to the asymmetric synthesis of tetrahydroquinolines.[59]



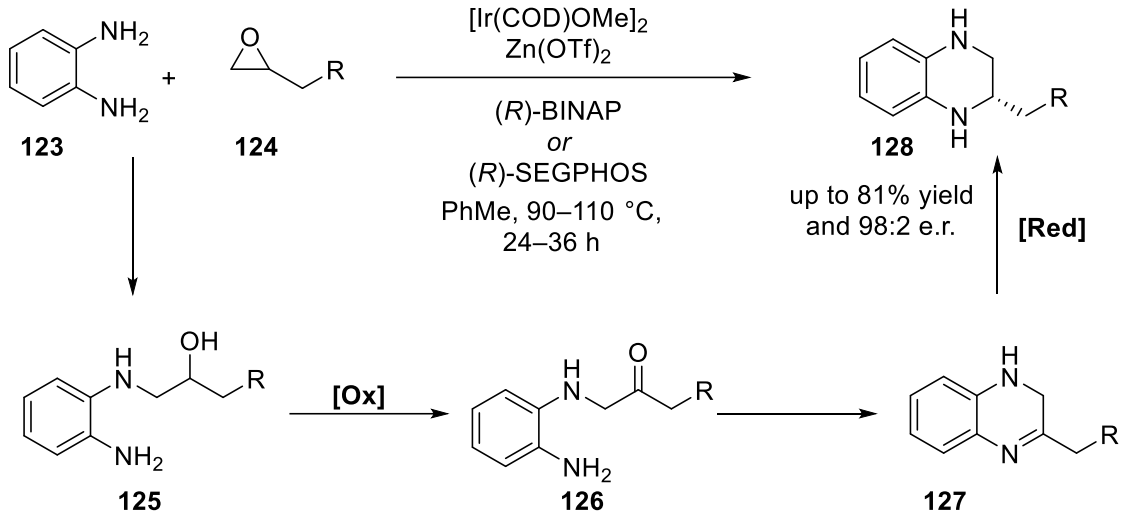
Scheme 1.22: Catalytic enantioselective amination of alcohols by hydrogen borrowing catalysis. Conditions: aniline (1 eq.), alcohol (1.5 eq.), [Ir] **110** (5 mol%), **111** (10 mol%), *t*AmOH (0.4 M), 4 Å MS, reflux, 24 h.

In 2017, Tang, Zhou and co-workers developed a highly enantioselective hydrogen borrowing reaction between benzylic alcohols and benzhydrazides using earth abundant catalyst $Ni(OTf)_2$ with *(S)*-binapine (Scheme 1.23).[60] The authors conducted deuterium labelling studies using α-deuterated benzyl alcohol **120**, which gave results that supported a hydrogen borrowing mechanism. They found that the resulting benzylamine product **122** contained 68% D, which the authors proposed was due to washout of deuterium by the reversible deprotonation/protonation of cationic Ni-D complex with protons from the alcohol solvent and acid present in the reaction mixture.



Scheme 1.23: Nickel catalysed hydrogen borrowing alkylation of benzhydrazines with racemic benzylic alcohols. Conditions: benzhydrazine (1 eq.), benzylic alcohol (3 eq.), $Ni(OTf)_2$ (5 mol%), *(S)*-binapine (6 mol%), AcOH (2 eq.), *t*AmOH (0.33 M), 3 Å MS, 110 °C, 48 h.

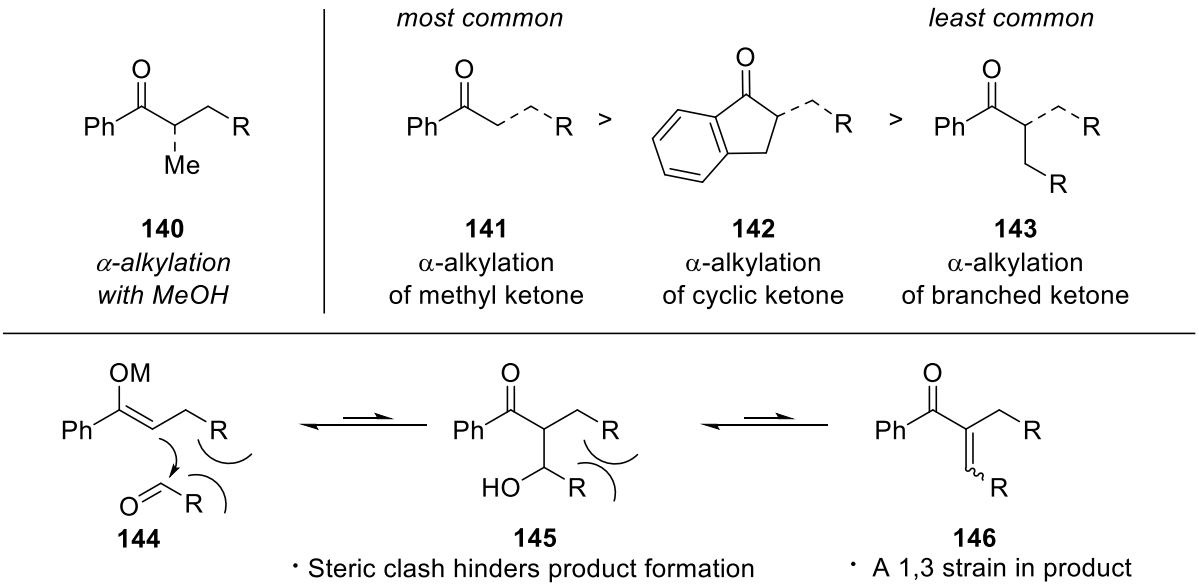
Most recently, Zhang, Xia, Zhao and co-workers reported an iridium-catalysed methodology for the asymmetric synthesis of tetrahydroquinoxalines using racemic epoxides and 1,2-diaminobenzene (Scheme 1.24).[61] Notably the authors use epoxides in place of more conventional alcohols as the non-nitrogen containing partner of the reaction. Mechanistically, the reaction begins with $Zn(OTf)_2$ catalysed epoxide opening of **124**, which occurs at the primary end of the epoxide, affording 1,5-amino alcohol **125**, which cyclises *via* an asymmetric hydrogen borrowing alkylation.



Scheme 1.24: Iridium-catalysed asymmetric synthesis of tetrahydroquinoxalines. Conditions: epoxide (1 eq.), 1,2-diaminobenzene (1.5 eq.), $Zn(OTf)_2$ (10 mol%), $[Ir(COD)OMe]_2$ (2.5 mol%), ligand (5.5 mol%), PhMe (0.4 M), 90-110 °C, 24-36 h.

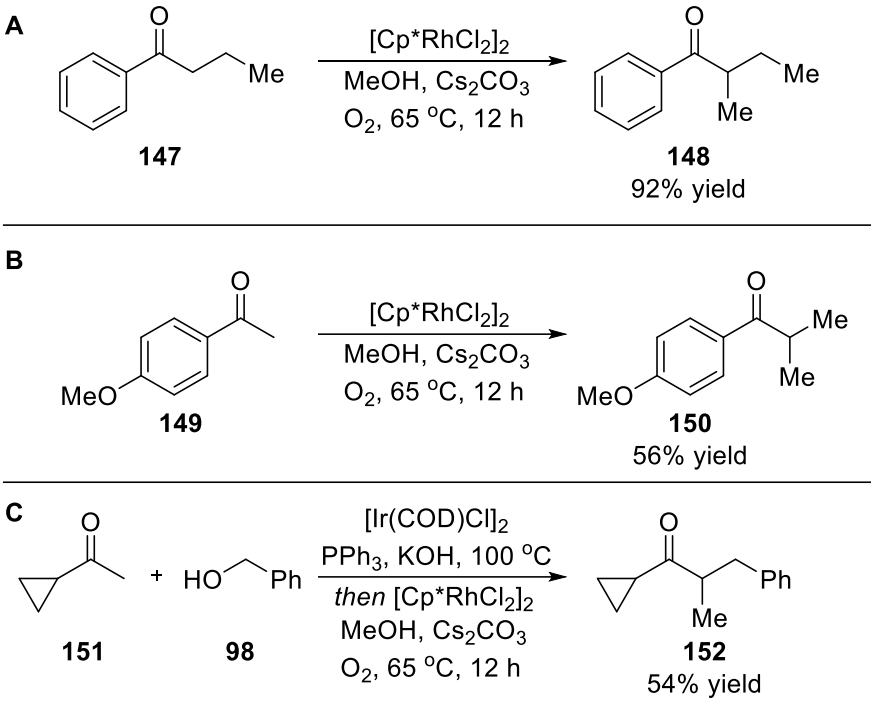
1.2.2 α-Methylation of Ketones in Hydrogen Borrowing Reactions

A significant advancement in the field for the hydrogen borrowing alkylation of carbonyls was the discovery that methanol can be used as an electrophile, which enables the formation of α-branched products (Scheme 1.25). This is notable, given up to this point, the alkylation of carbonyls has generally generated linear products, with very few examples of α-branched compounds. The likely reason for this relates to the difficulty in the aldol step of the reaction, due to steric congestion between the enolate and reacting carbonyl. In contrast, methanol, which forms formaldehyde in a hydrogen borrowing reaction, is a much smaller electrophile, thus readily forms α-branched products.



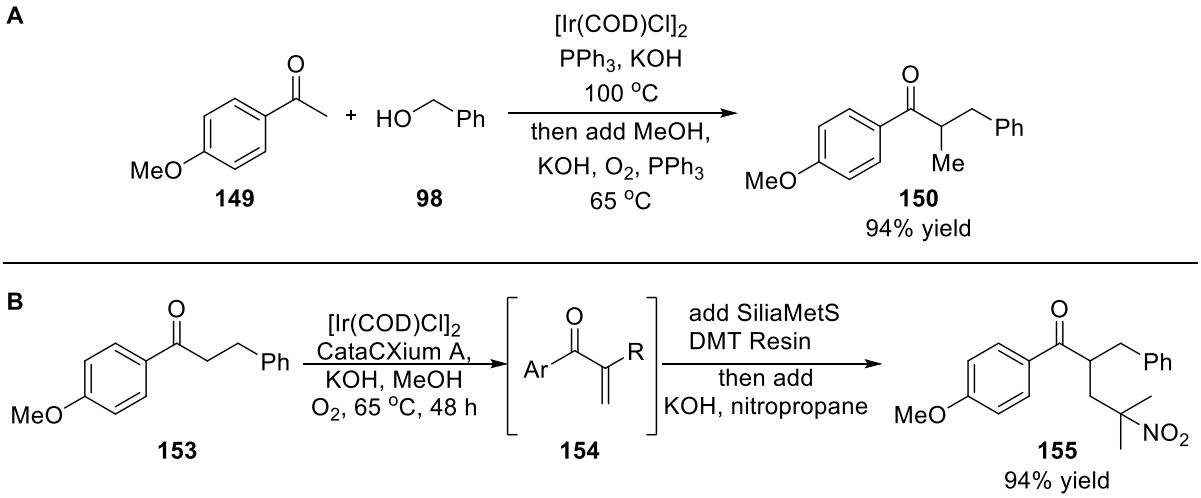
Scheme 1.25: Prevalence of α-branched products in hydrogen borrowing alkylation.

The methylation of carbonyl compounds by hydrogen borrowing catalysis was pioneered by Donohoe and co-workers in 2013.[62] For example, the authors reported that in the presence of $[Cp^*RhCl_2]_2$, oxygen, and Cs_2CO_3, ketone **147** reacts smoothly with methanol to form α-branched ketone **148** in 92% yield (A). Under the same conditions, ketone **149** reacts with two equivalents of methanol to form **150** in 56% yield (B). The authors also demonstrated that in the presence of an iridium catalyst, they can affect the sequential alkylation of cyclopropyl ketone **151** with benzyl alcohol and then methanol to afford **152** in 54% yield. Notably, the synthesis of **150** and **152** are also the first examples of double alkylation of carbonyls in hydrogen borrowing catalysis, owing to the fact the formation of α-branched compounds is feasible with methanol as an electrophile.



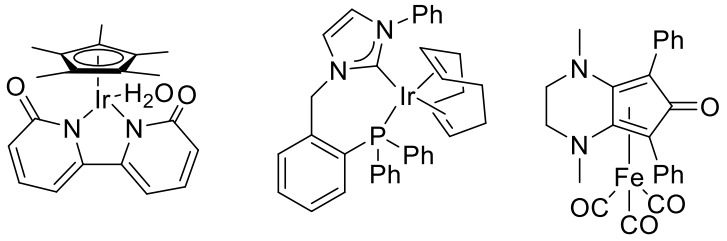
Scheme 1.26: Rhodium catalysed methylation of ketones by hydrogen borrowing catalysis

In a subsequent publication, Donohoe and co-workers found that an iridium catalyst bearing PPh_3 ligand can affect the alkylation of methyl ketones with methanol and other alcohols in the same pot, which enabled access α-branched ketone products (Scheme 1.27, A).[63] They also reported that under similar conditions with CataCXium A® ligand, they isolate the enone product, which allowed the sequential conjugate addition of a nucleophile (B).



Scheme 1.27: Hydrogen-borrowing and interrupted-hydrogen-borrowing reactions of ketones and methanol catalysed by iridium.

More recently, the research groups of Andersson,[64] Obora,[65] and Wang[66] have reported strategies for hydrogen borrowing catalysed methylation of ketones with methanol. These groups have focused on new catalyst systems, which has included $[IrCp^*Cl_2]_2$, Cp* iridium complex **156**, and N-heterocyclic carbene–phosphine iridium complex **157**. Another notable contribution to this field was by Morrill and co-workers, who reported the use of earth abundant iron Knölker-type complex **158** for the methylation of ketones.[67,68]



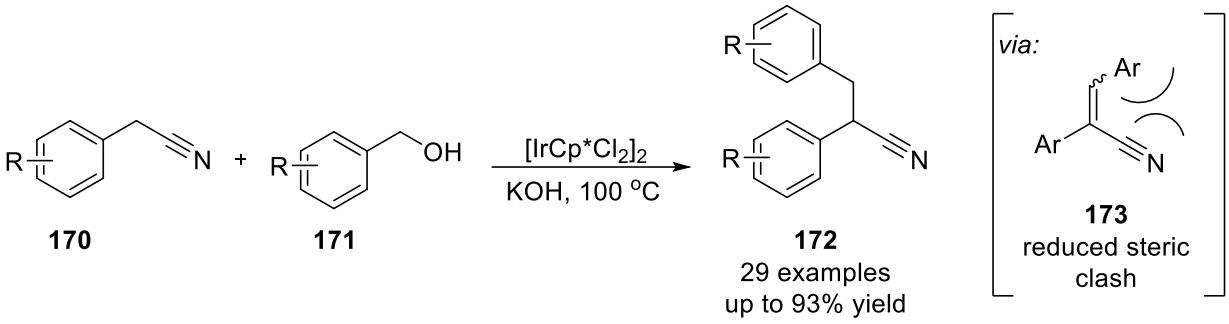
156 **157** **158**

Scheme 1.28: Catalysts reported for the α-methylation of ketones with methanol.

1.2.3 Alkylation of Methylene Centres to Form α-Branched Products

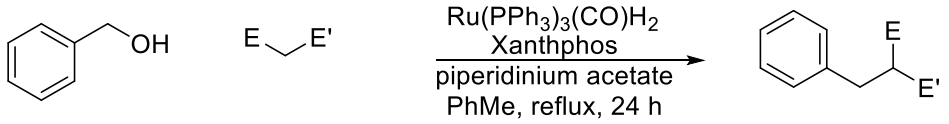
While the methylation of ketones has been reported, the alkylation of ketones with higher order alcohols to form α-branched products remained an unsolved challenge. The only cases where α-branched products formed are where the ketone starting material was cyclic in nature. Aside from ketones, there have been several noteworthy reports of hydrogen borrowing alkylations of activated methylene groups to form α-branched products.

An early example of this was reported in 2006 by Grigg and co-workers, whereby $[IrCp^*Cl_2]_2$ catalysed the alkylation of aryl acetonitriles with alcohols (Scheme 1.29).[69] Mechanistically, this proceeds analogously to the alkylation of ketones, with the deprotonated nitrile reacting with the aldehyde (formed from oxidation) by a Knoevenagel condensation, to afford acrylonitrile **173**. The resulting nitrile **173** is then reduced by the 1,4-addition of iridium hydride to afford the product. The success of this transformation stems from the linear nature of the nitrile group, which minimises steric interactions in α,β-unsaturated nitrile **173**, thus preventing the undesired retro-Aldol. Grigg and co-workers later reported that the same reaction conditions catalyse the alkylation of 1,3-dimethyl -dimethylbarbituric acid.[70] In a related study, Li and co-workers reported the α-alkylation of aryl acetonitrile using $Rh(COD)Cl]_2$ PPh_3 as a catalyst.[71]



Scheme 1.29: Alkylation of aryl acetonitriles with primary alcohols. Conditions: $[IrCp^*Cl_2]_2$ (2.5 mol%), KOH (15 mol%), nitrile (1 eq.) alcohol (3 eq.), 100 °C, 14 h.

Another notable contribution was made by Williams and co-workers, who reported the α-alkylation of activated methylene groups with a range of alcohols using $Ru(PPh_3)_3(CO)H_2$ and Xanthphos.[72] In this study, they explored the reactivity of ketonitrile **177**, which reacted with benzylic and aliphatic alcohols by a sequential oxidation, Knoevenagel condensation and reduction to afford the alkylated product. Other notable examples included the alkylation of dibenzyl malonate **174** in 78% yield, cyanoester **175** in 73% yield and sulfone **176** in 45% yield. Closely following this, Ishii and co-workers reported and iridium-catalysed system using $[Ir(COD)Cl]_2$ and PPh_3 for the same transformation.[73]



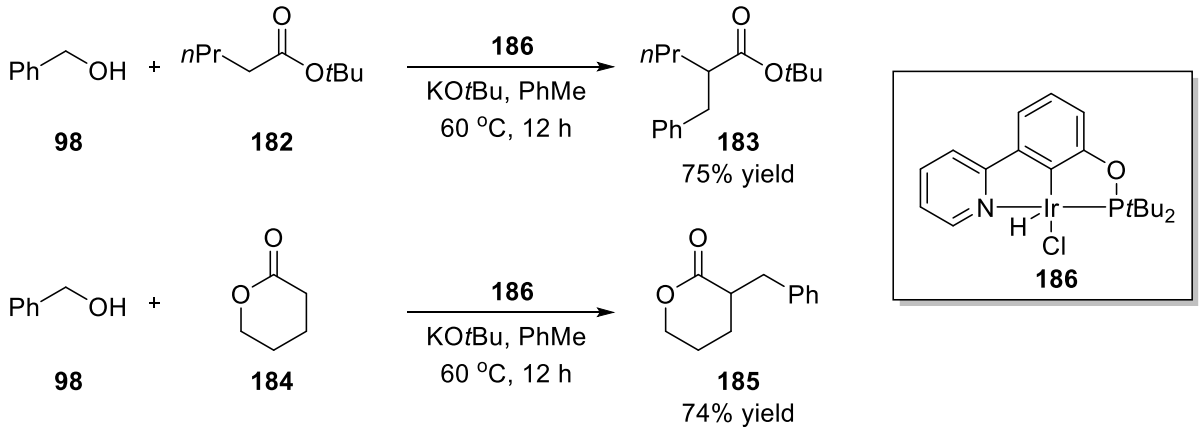
98

174 E = E' = CO_2Bn
175 E = CN, E' = CO_2Et
176 E = $PhSO_2$, E' = COPh
177 E = CN, E' = CO*t*Bu

178 E = E' = CO_2Bn, 78% yield
179 E = CN, E' = CO_2Et, 73% yield
180 E = $PhSO_2$, E' = COPh, 45% yield
181 E = CN, E' = CO*t*Bu, 78% yield

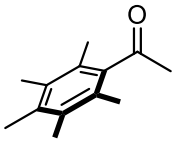
Scheme 1.30: α-Alkylation of methylene compounds using a ruthenium catalyst. Conditions: benzyl alcohol (1 eq.), methylene group (1 eq.), $Ru(PPh_3)_3(CO)H_2$ (0.5 mol%), XantPhos (0.5 mol%), piperidinium acetate (5 mol%), PhMe, 110 °C, 4 h

In a recent publication, Huang and co-workers reported the application of an iridium pincer complex **186** for the α-alkylation of esters and lactones (Scheme 1.31).[74] Notably, this is the first example of unactivated esters being used in a hydrogen borrowing reaction. However, the authors only report three examples of α-branched products with linear esters, with majority of the substrate scope utilising lactones.



Scheme 1.31: α-alkylation of unactivated esters Using alcohols catalysed by an iridium pincer complex. Conditions: ester (1.2 eq.), benzyl alcohol (1 eq.), **186** (0.5 mol%), KO*t*Bu (1.5 eq.), PhMe (1 M), 60 °C, 12 h.

The next key advancement in the field of hydrogen borrowing catalysis came from Donohoe and co-workers, with the discovery of pentamethyl acetophenone **187** (Scheme 1.32).



187

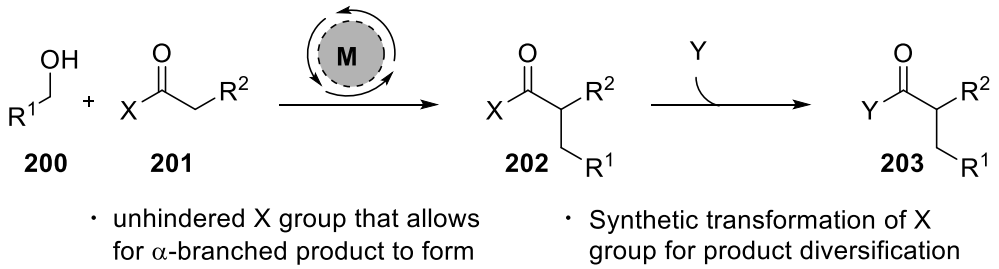
Scheme 1.32: pentamethyl acetophenone

1.3 Pentamethyl Acetophenone in Hydrogen Borrowing Alkylation

1.3.1 Discovery of the Pentamethylphenyl Group and its Use in the Alkylation of Primary and Secondary Alcohols

As discussed previously, hydrogen borrowing alkylation of ketones has been limited to the synthesis of linear products (Scheme 1.25). This is because of steric hindrance in the attack of substituted enolates with higher order aldehydes (from oxidised alcohols), and unfavourable steric interactions in the aldol product adduct, which favours retro-aldol over E1cB elimination. To solve this, Donohoe and co-workers postulated that the ketone employed must be relatively unhindered about group X to

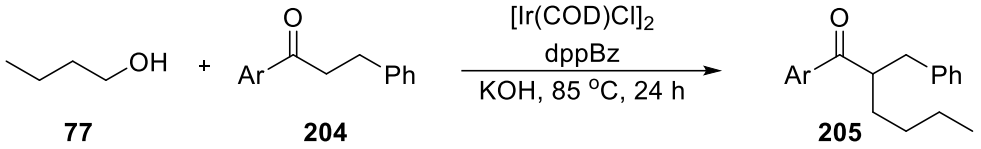
prevent retro-aldol (Scheme 1.33), and secondly, the X group introduced on the ketone must be readily transformed into other functional groups to have synthetic value.[75]



Scheme 1.33: Hypothesised design of carbonyl substrate **201** for the hydrogen borrowing alkylation to form α-branched products.

The study began with simple aryl ketones, which were successful substrates for the hydrogen borrowing methylation reaction (Scheme 1.34). While phenyl substituted ketone **99** was a poor substrate for this reaction, the addition of an *ortho* methyl group on the aromatic ring lead to a drastic improvement in product formation, with **208** obtained in 69% yield. *Ortho*-disubstituted aryl groups **209** and **211** were even more effective, with α-branched products **210** and **212** obtained in 89% and 98% yield, respectively.

A crystal structure of penthamethyl phenyl ketone **212** was obtained by single crystal X-ray diffraction, which showed that the aryl ring was twisted out of conjugation with the carbonyl. They hypothesised this was beneficial for two reasons. Firstly, by the ring being twisted out of conjugation, there is reduced steric hinderance about the α-carbon, which attenuates the rate of retro-aldol, enabling E1cB to occur. Secondly, the *ortho*-disubstitution shields the carbonyl group from 1,2 reduction and homo-aldol condensation.



77 204 205

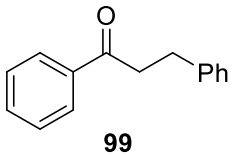
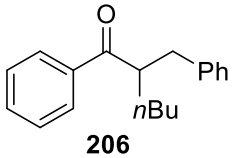
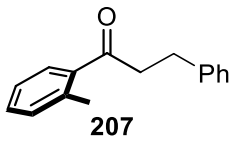
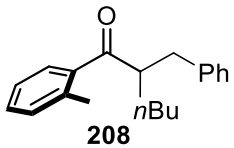
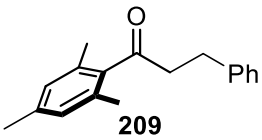
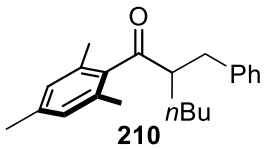
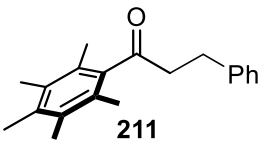
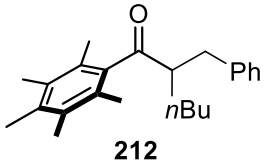
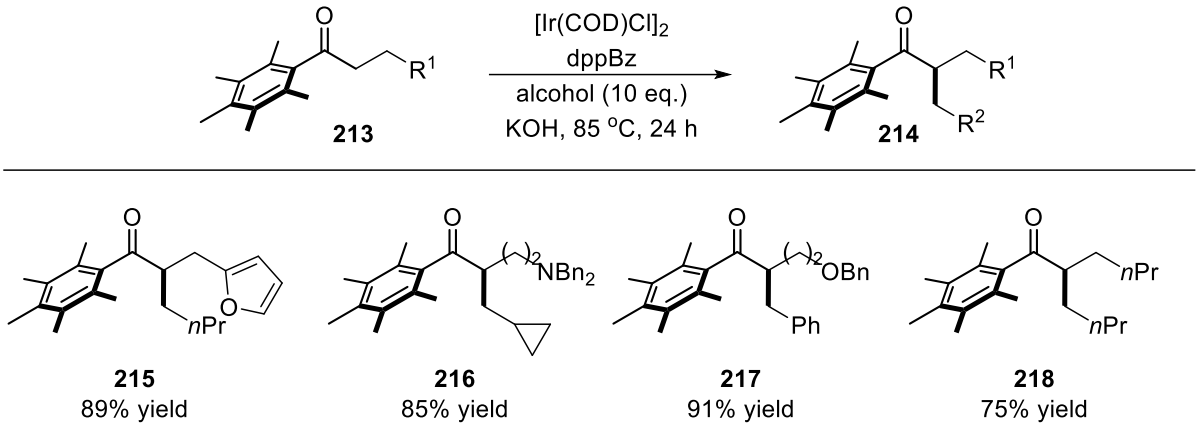
Entry	Starting material	Product	Yield (%)
1	 99	 206	<5
2	 207	 208	69
3	 209	 210	89
4	 211	 212	98

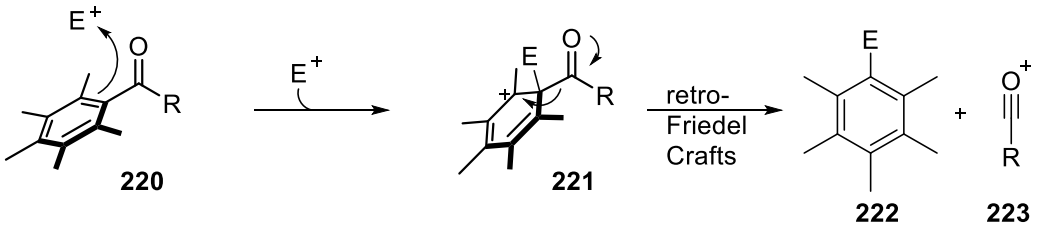
Table 1.2: Hydrogen borrowing alkylation to form α-branched products. Conditions: ketone (1 eq.), alcohol (10 eq.), $[Ir(COD)Cl]_2$ (1 mol%), dppBz (2 mol%), KOH (2 eq.), 85 °C, 24 h.

Following this, the authors surveyed the scope of the reaction for the formation of α-branched products (Scheme 1.34). Pleasingly, they found that a range of groups were tolerated, with products bearing heteroatoms and heterocycles afforded in uniformly high yields.



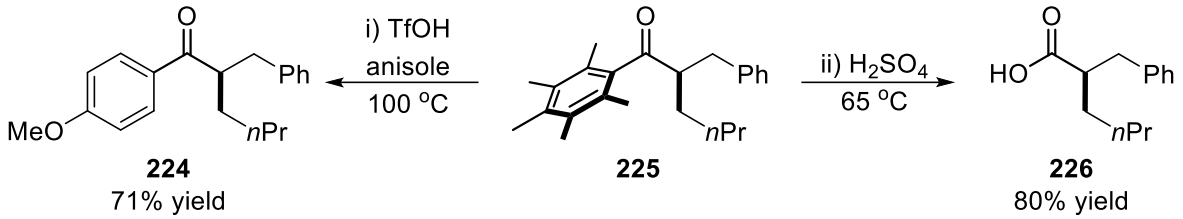
Scheme 1.34: Select substrate scope for hydrogen borrowing alkylation to form α-branched products. Conditions: ketone (1 eq.), alcohol (10 eq.), $[Ir(COD)Cl]_2$ (1 mol%), dppBz (2 mol%), KOH (2 eq.), 85 °C, 24 h.

With the pentamethylphenyl group enabling the synthesis of α-branched ketones, Donohoe and co-workers next sought a general method to functionalise the aryl-substituted products. They proposed that the aryl ring twisted out of the plane of the carbonyl would be susceptible to an *ipso* reaction with the appropriate electrophile, and then retro-Friedel Crafts acylation would afford acylium ion **223** (Scheme 1.35). This reactive carbonyl intermediate could then be reacted with nucleophiles to form a diverse range of products.



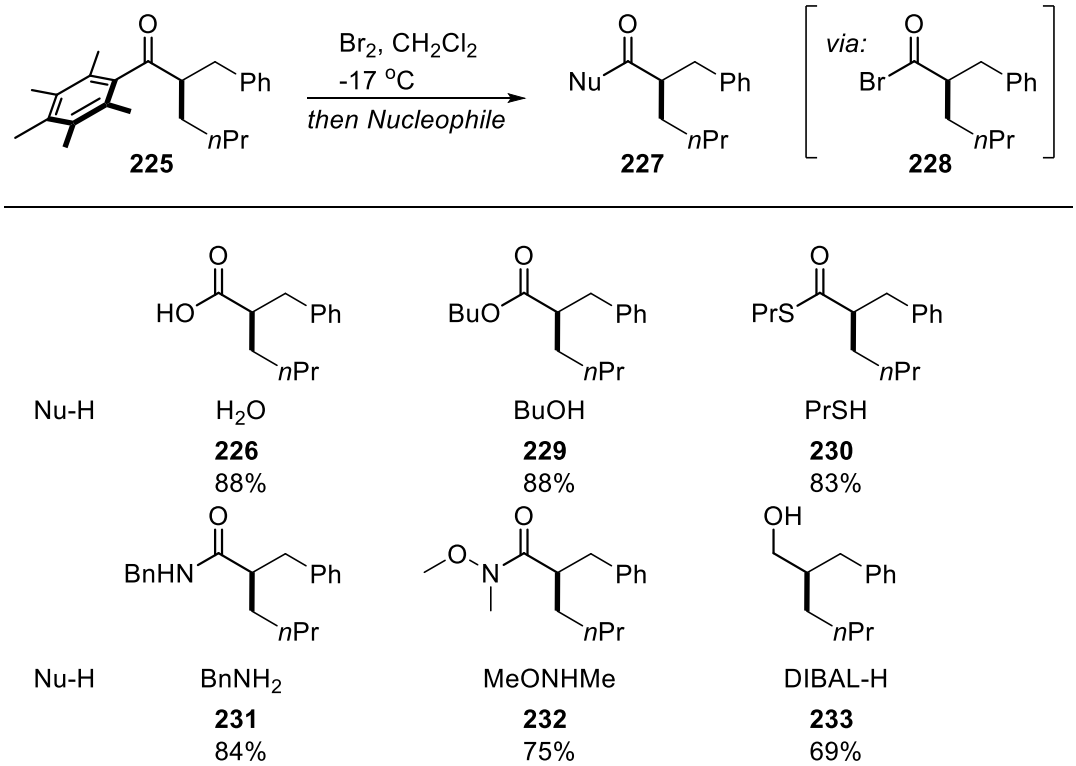
Scheme 1.35: Generalised mechanism for the *ipso* reaction of pentamethyl phenyl ketone

For example, reaction of pentamethylphenyl ketone **225** under acidic conditions lead to the isolation of carboxylic acid **226** in 80% yield, presumably with water acting as a nucleophile to trap the acylium ion (Scheme 1.36). In a related transformation, the reaction could be performed with anisole in the presence of triflic acid, which enabled the formation of trans-acylated product **224** in 71% yield.



Scheme 1.36: Ipso reaction under acidic conditions. Conditions: i) ketone (1 eq.), TfOH (1.2 eq.), anisole (3 eq.), 100 °C, 1.5 h. ii) ketone (1 eq.), H_2SO_4 (0.6 M), 65 °C, 30 min.

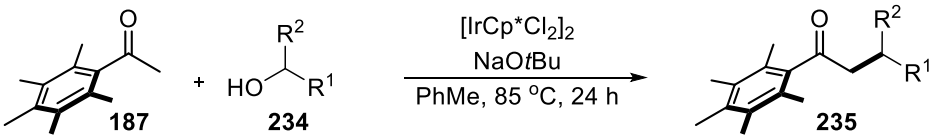
By a similar approach, the authors also found that elemental bromine promoted the ipso bromination of the pentamethylphenyl group, which enabled the formation of an acid bromide (Scheme 1.37). The resulting acid bromide could then be reacted with a range of nucleophiles *in situ*. For example, addition of three equivalents of water resulted in the formation of carboxylic acid **226** in 88% yield, whereas the addition of three equivalents of benzylamine led to the isolation of amide **231** in 84% yield.



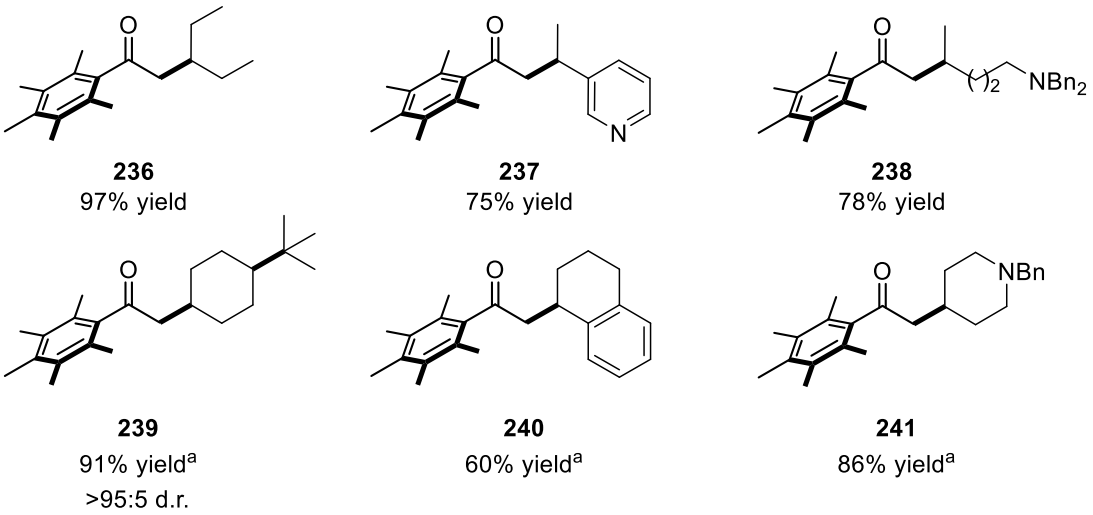
Scheme 1.37: Bromine initiated cleavage of pentamethylphenyl group. Conditions: ketone (1 eq.), bromine (1.2 eq.), CH_2Cl_2 (0.2 M), -17 °C, 15 min, *then* nucleophile (3 eq.), RT, 16 h.

In a subsequent publication, Donohoe and co-workers made another major contribution to the field of hydrogen borrowing catalysis with the discovery of the reaction between pentamethylphenyl

ketones and secondary alcohols (Scheme 1.38).[76] This advancement is notable given that alkylation strategies using secondary alcohols has been limited to nitriles and amines as substrates.[47,77,78] The success of this transformation was proposed to be due to the pentamethylphenyl group preventing homo aldol condensation and favouring the cross aldol with the oxidised secondary alcohol. Following an extensive optimisation, the authors reported that $[IrCp^*Cl_2]_2$ alongside KO*t*Bu or NaO*t*Bu smoothly afforded the alkylated product. Example products included ketones bearing heterocyclic groups, heteroatoms, and cyclic groups, which were obtained with high diastereoselectivity.



187 + **234** → **235**



236
97% yield

237
75% yield

238
78% yield

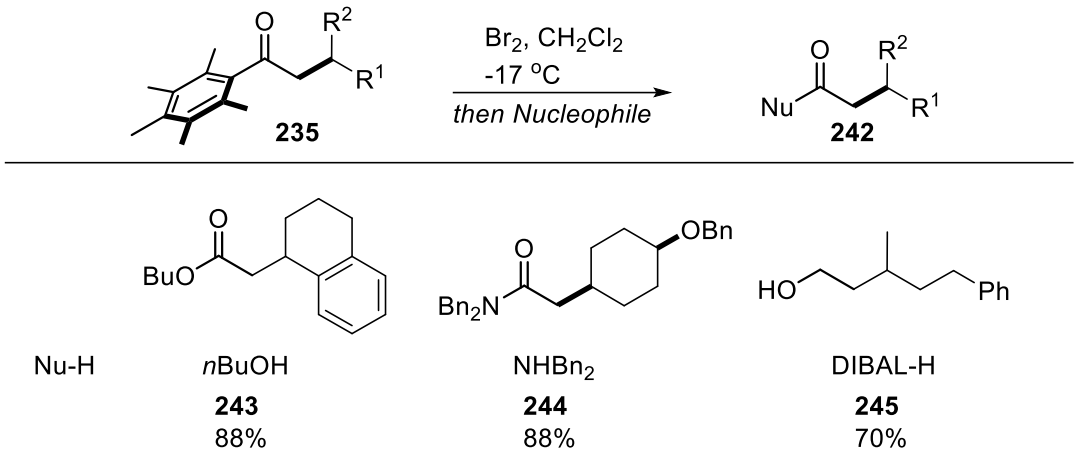
239
91% yield[a]
>95:5 d.r.

240
60% yield[a]

241
86% yield[a]

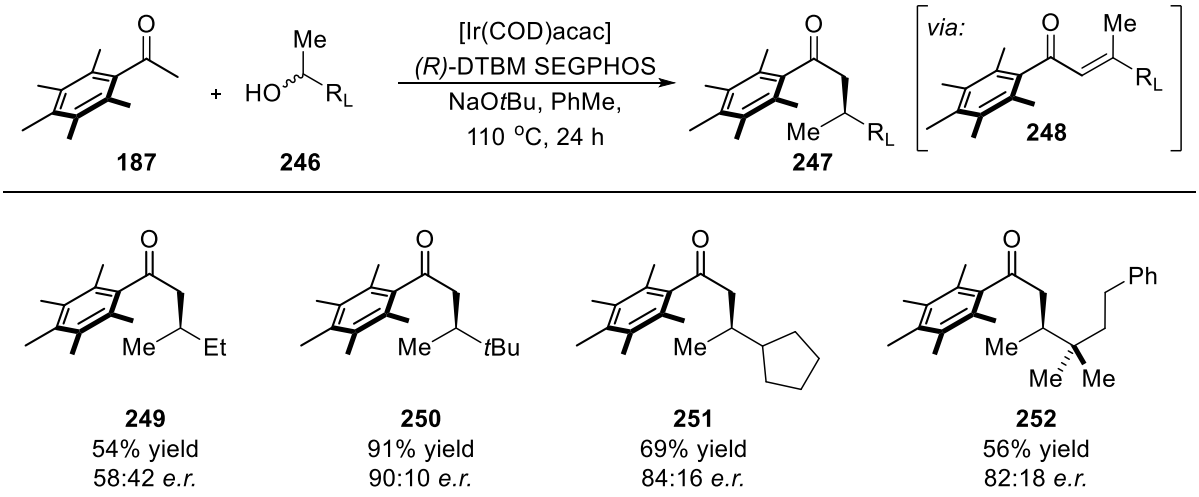
Scheme 1.38: Select substrate scope for the alkylation of pentamethylphenyl ketone with secondary alcohols. Conditions: Ph*COMe (1 eq.), secondary alcohol (1.5-2 eq.), $[IrCp^*Cl_2]_2$ (0.5-2 mol%), NaO*t*Bu (2 eq.), PhMe (4 M). [a]KO*t*Bu (3 eq.) used instead of NaO*t*Bu.

To demonstrate the synthetic utility of this methodology, the authors explored the functionalisation of the pentamethylphenyl group (Scheme 1.39). This was achieved by using the previously reported conditions for bromine mediated *retro*-Friedel-Crafts acylation. By this method, a range of alcohols, esters and amides were accessible, including industrial fragrance compound 3-methyl-5-phenylpentanol **245**, which was prepared 70% yield.



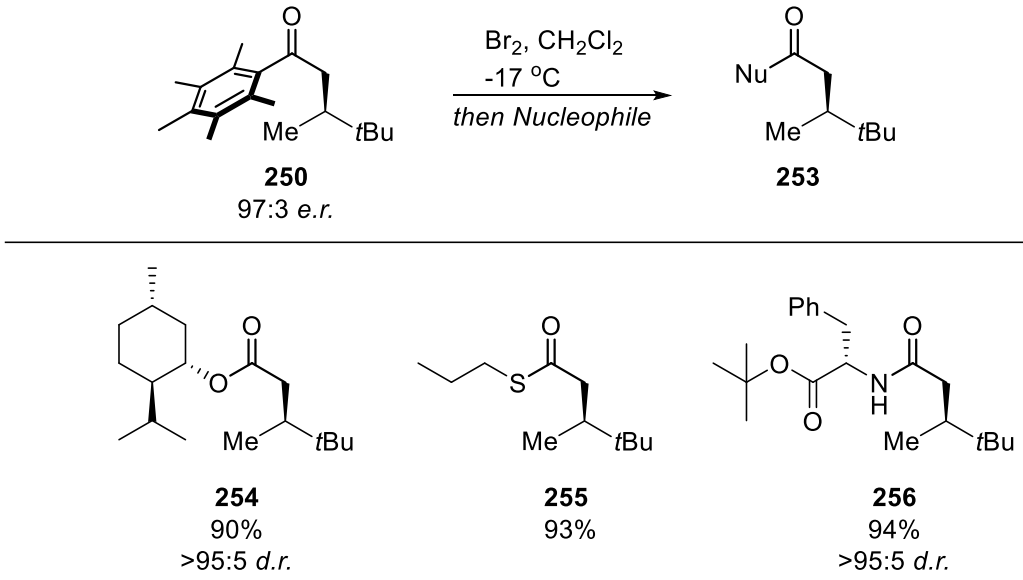
Scheme 1.39: Select substrate scope for the *retro*-Friedel-Craft acylation of pentamethylphenyl group. Conditions: ketone (1 eq.), bromine (2 eq.), CH_2Cl_2 (0.2 M), -17 °C, *then* nucleophile (3 eq.), RT.

Following this, Donohoe and co-workers developed reaction conditions for the asymmetric hydrogen borrowing alkylation with methyl-substituted secondary alcohols. The mechanism for this transformation follows a typical hydrogen borrowing cycle, with the key step involving an asymmetric 1,4-reduction of enone intermediate **248**. To obtain high enantioselectivity, it was essential for the second substituent on the secondary alcohol to be significantly larger than the methyl group. For example, when an alcohol with an ethyl group was used, the authors saw 58:42 e.r for ketone **249**, and with *tert*-butyl group the product **250** was obtained in 90:10 e.r. The authors rationalised this observation as a consequence of the sterically differentiated substituents on the alcohol leading to complete control of the enone geometric isomer, which was essential to achieve asymmetric induction.



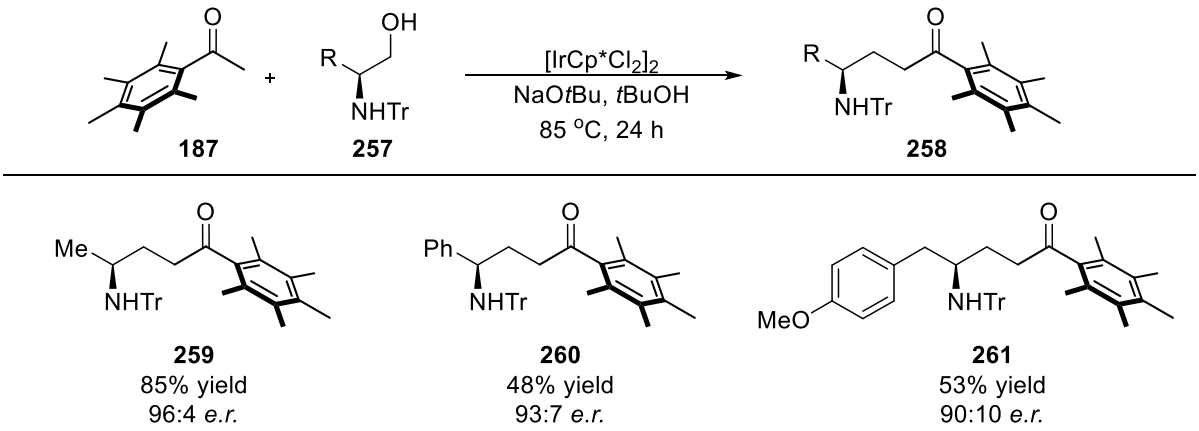
Scheme 1.40: Asymmetric synthesis of β-branched ketones by the hydrogen borrowing alkylation of secondary alcohols. Conditions: Ph*COMe (1 eq.), secondary alcohol (2 eq.), NaO*t*Bu (4 eq.), [Ir(COD)acac] (4 mol%), *(R)*-DTBM SEGPHOS (5 mol%), PhMe (3 M), 110 °C, 24 h.

The authors subsequently investigated functionalisation of the pentamethylphenyl group by retro-Friedel Craft acylation (Scheme 1.41). This was achieved using the previously reported reaction conditions, which consisted of treating the Ph* ketone with two equivalents of bromine at -17 °C, followed by the addition of a nucleophile. By this approach, ester **254** was prepared in 90% yield, thio ester **255** was synthesised in 93% yield, and amide **256** in 94% yield.



Scheme 1.41: Select substrate scope for the retro-Friedel Crafts acylation of the pentamethylphenyl group. Conditions: ketone (1 eq.), bromine (2 eq.), CH_2Cl_2 (0.2 M), -17 °C, *then* nucleophile (3 eq.), RT.

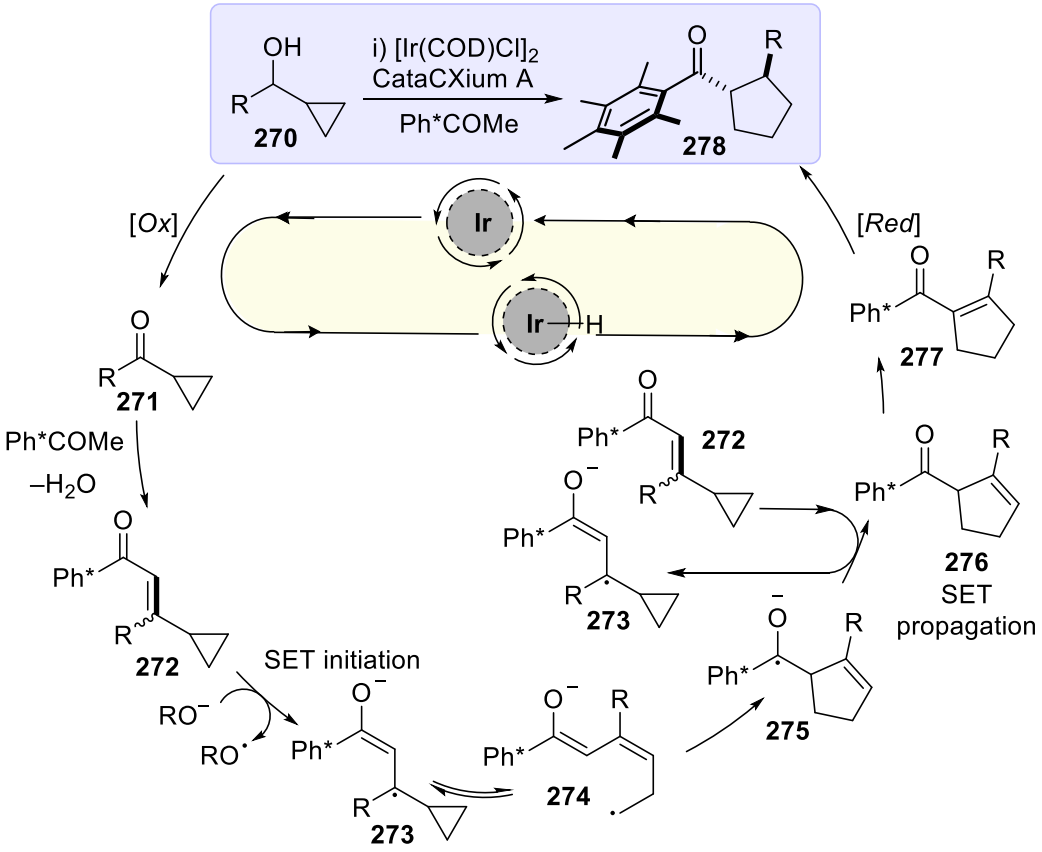
Another key advancement in the field of hydrogen borrowing catalysis was the discovery that enantioenriched 1,2-amino alcohols can be employed in the α-alkylation of Ph* ketone. This was notable given there have not been any examples of amino alcohols employed in hydrogen borrowing alkylation strategies. To prevent racemisation, the authors employed the bulky trityl protecting group on nitrogen, which shielded the α-protons of the amino aldehyde intermediate (from oxidation of the amino alcohol) from epimerization. Pleasingly, the authors found this approach to be applicable to majority of amino acid derivatives, with examples including alcohols derived from alanine, phenyl glycine and tyrosine, which were all obtained in good yield and high stereochemical fidelity. Notably, cleavage of the Ph* group under acidic conditions gave access to highly important γ-aminobutyric acid (GABA) products.



Scheme 1.42: Hydrogen borrowing alkylation of Ph* ketone with enantioenriched amino alcohols. Conditions: Ph*COMe (1.5 eq.), alcohol (1 eq.), NaO*t*Bu (0.5 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), *t*BuOH (2.5 M), 85 °C, 16 h.

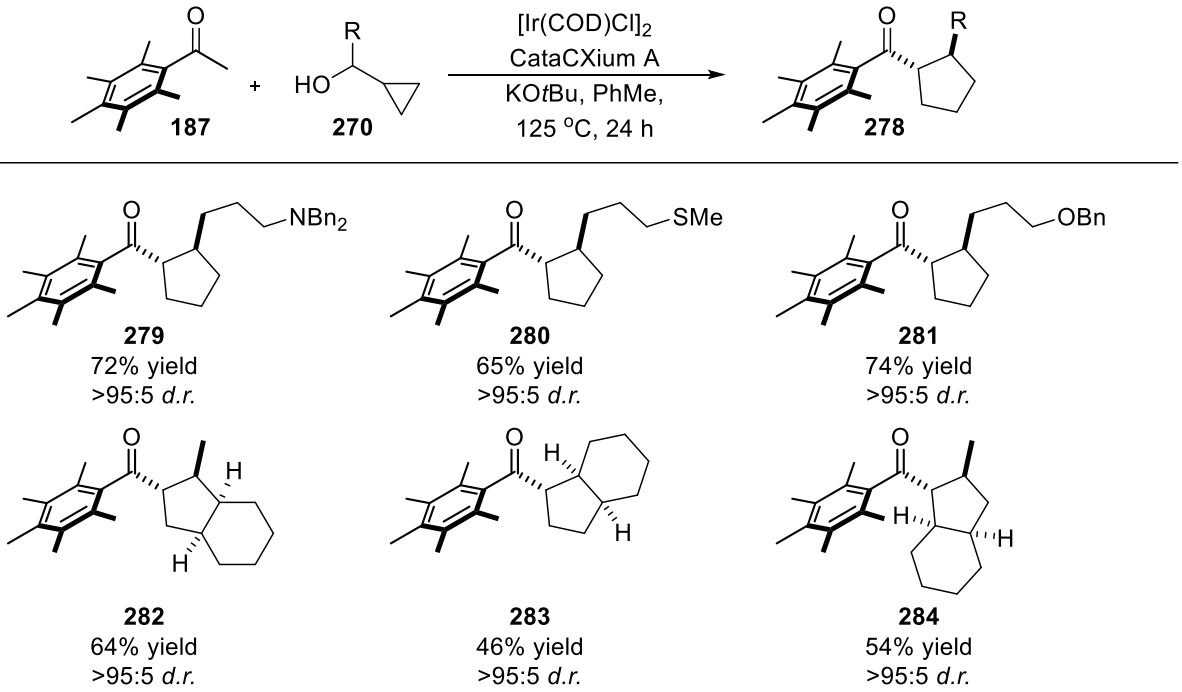
1.3.2 Synthesis of Cyclopentanes and Cyclohexanes

In a subsequent publication, Donohoe and co-workers demonstrated that stereodefined cyclopentanes can be prepared by a vinyl cyclopropane rearrangement embedded in a hydrogen borrowing alkylation with cyclopropyl alcohols and Ph* ketone.[79] Through a series of control experiments, the authors proposed the reaction mechanism outlined in Scheme 1.43. The mechanism begins with oxidation of the cyclopropyl alcohol to ketone **271**, with concomitant formation of iridium hydride. Ketone **271** subsequently undergoes aldol condensation with Ph* ketone **187**, to give enone **272**. Then, a single electron transfer (SET) can occur, possibly initiated by alkoxide or enolate, to afford radical anion **273**. The radical anion can then undergo a ring opening/ring closure rearrangement, to afford 5-membered radical anion **275**. **275** can conceivably propagate the SET chain reaction by donating an electron to enone **272**. The resulting alkene **276** can then isomerise into conjugation under the basic reaction conditions to give enone **277**, which can be reduced by iridium hydride to regenerate the catalyst and afford the cyclopentane product **278**.



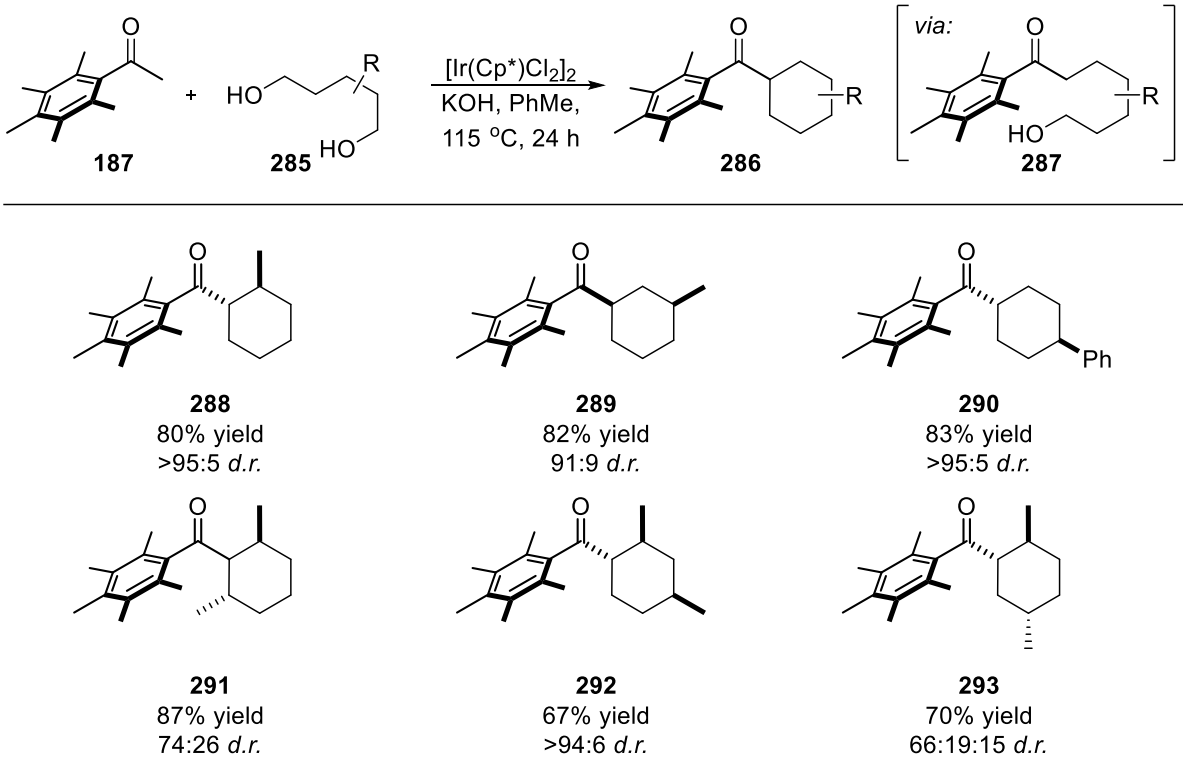
Scheme 1.43: Reaction mechanism for the hydrogen borrowing alkylation of Ph* ketone with cyclopropyl alcohols. Conditions: Ph*COMe (1 eq.), alcohol (2 eq.), $[Ir(COD)Cl]_2$ (1 mol%), CataCXium A® (8 mol%), KO*t*Bu (1 eq.), PhMe (4 M), 125 °C, 24 h.

The authors demonstrated a broad substrate scope, with the reaction tolerating sidechains bearing oxygen, nitrogen and sulfur heteroatoms (Scheme 1.44). In addition, they also found that bicyclic cyclopropyl alcohols led to the formation of *cis*-fused cyclopentane products in greater than 95:5 *d.r*. As with the previous work, the authors showed that the products bearing the pentamethylphenyl group were readily functionalised by retro-Friedel Crafts acylation, giving access to derivatised carbonyl products.

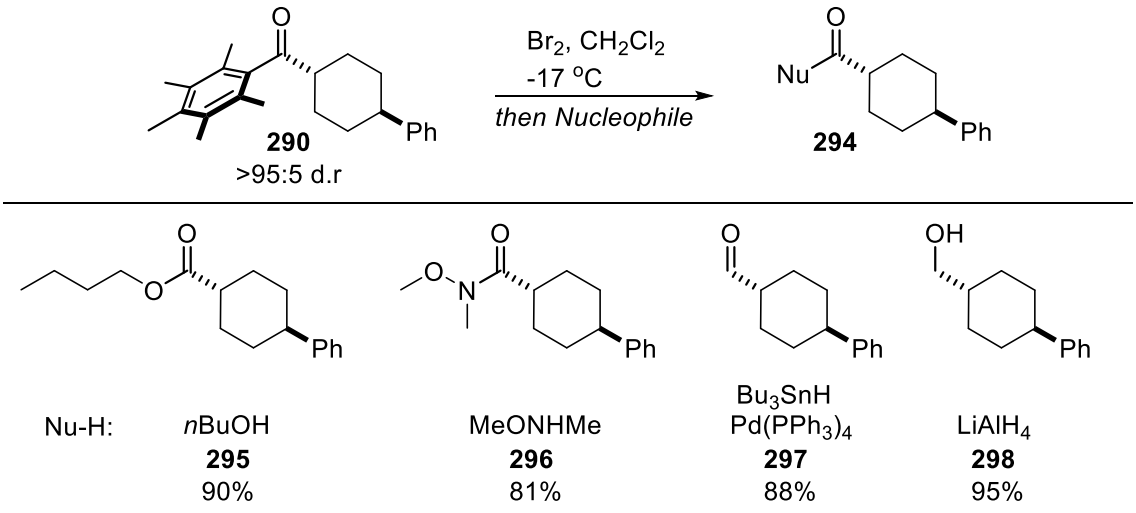


Scheme 1.44: Synthesis of cyclopentanes by the hydrogen borrowing alkylation of Ph* ketone with cyclopropyl alcohols. Conditions: Ph*COMe (1 eq.), alcohol (2 eq.), $[Ir(COD)Cl]_2$ (1 mol%), CataCXium A® (8 mol%), KO*t*Bu (1 eq.), PhMe (4 M), 125 °C, 24 h.

The next key advancement by Donohoe and co-workers was the development of an unprecedented [5+1] annulation strategy to prepare cyclohexanes from 1,5-pentane diols and Ph*COMe (Scheme 1.45).[84] Mechanistically, the authors proposed the reaction to proceed through two sequential hydrogen borrowing alkylations, *via* an intermediate hydroxyketone **287**. Using $[IrCp^*Cl_2]_2$ as a catalyst alongside KOH, the authors were able to isolate a range of cyclohexanes in excellent yield and diastereoselectivity. Furthermore, the use of bromine proved to be effective at removing the Ph* group from the products, which enabled the synthesis of esters, amides, aldehydes, and alcohols, to name but a few examples (Scheme 1.46).



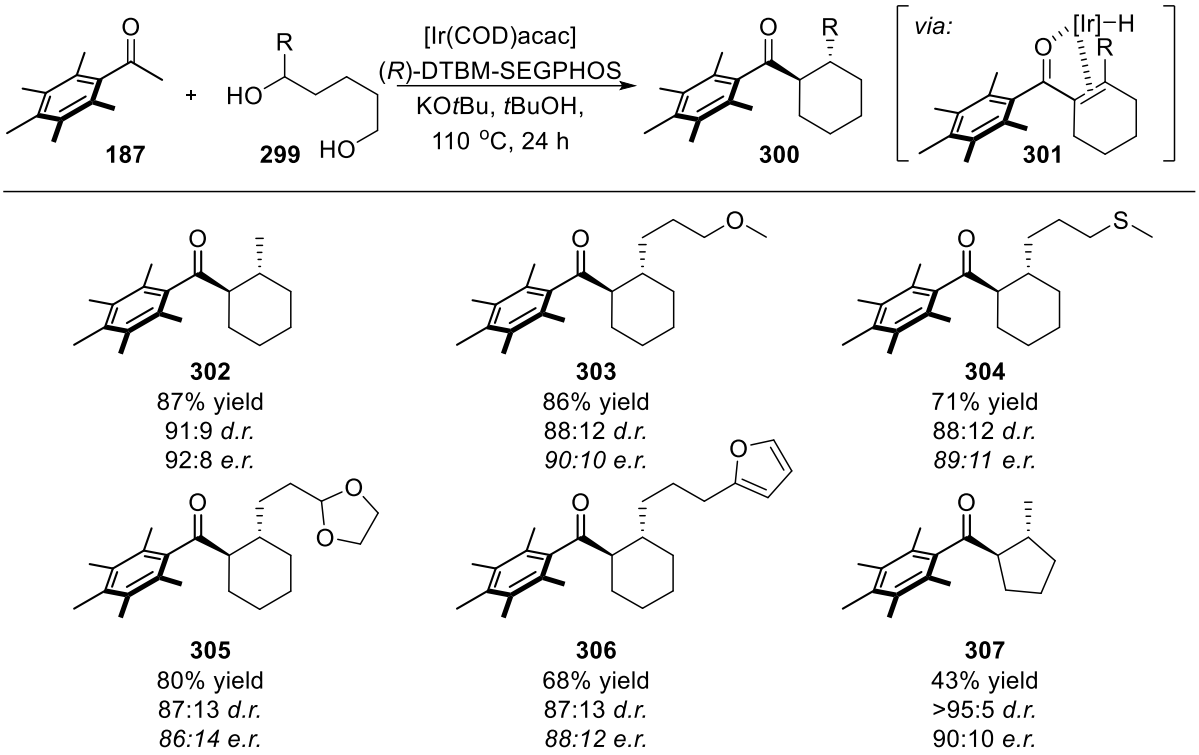
Scheme 1.45: Synthesis of cyclohexanes by the hydrogen borrowing annulation of Ph* ketone with 1,5-pentane diols. Conditions: Ph*COMe (1 eq.), alcohol (2 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 115 °C, 24 h.



Scheme 1.46: Derivatisation of cyclohexane products. Conditions: ketone (1 eq.), bromine (2 eq.), CH_2Cl_2 (0.2 M), -17 °C, *then* nucleophile (3 eq.), RT.

The most recent advancement came with the development of an enantioselective synthesis of cyclohexanes by the hydrogen borrowing alkylation of Ph*COMe with 1,5-pentane diols

(Scheme 1.47).[109] It was found that a chiral iridium complex derived from [Ir(COD)acac] and (*R*)-DTBM-SEGPHOS was the most effective catalyst for the transformation, with the stereodefining step being the 1,4-reduction of cyclohexene **301** to give enantioenriched cyclohexane **300**. By this approach, cyclohexanes bearing alkyl and aryl substituents were prepared in high yields and up to 94:6 *e.r*. This approach was also applicable to the synthesis of cyclopentanes, which were prepared from the corresponding 1,4-butane diol. In every case, the thermodynamic trans stereoisomer formed *via* epimerization of the carbonyl.



Scheme 1.47: Asymmetric synthesis of cyclohexanes by the iridium-catalysed hydrogen borrowing alkylation of Ph*COMe with 1,5-pentane diols. Conditions: Ph*COMe (1 eq.), diol (2 eq.), [Ir(COD)acac] (4 mol%), *(R)*-DTBM-SEGPHOS (5 mol%), KO*t*Bu (4 eq.), *t*BuOH (3 M), 110 °C, 24 h.

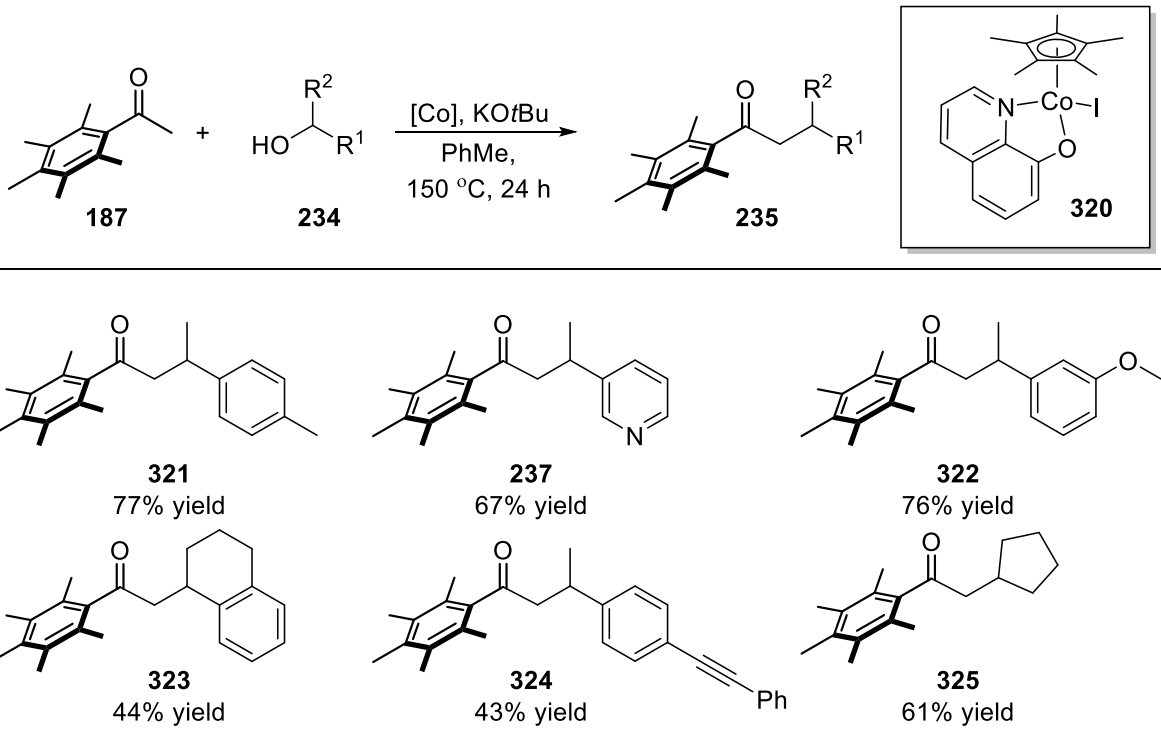
Taking these discussed publications together, the results highlight that pentamethylphenyl ketone **187** uniquely promotes the hydrogen borrowing alkylation with primary and secondary alcohols to form branched products, and diols to form carbocycles. This distinctive reactivity is a result of the pentamethylphenyl ring being twisted out of the conjugation with the adjacent carbonyl, which results in reduced steric hinderance about the α-carbon, thus allowing more sterically congested products to form. Another notable feature of the pentamethylphenyl group is that the *ortho* methyl substituents shield the carbonyl from 1,2-reduction by iridium hydride, and prevent homo aldol condensations

from occurring. Finally, the pentamethylphenyl group is readily cleaved by retro-Friedel Crafts acylation using acid or bromine, which enables access to a diverse range of derivatised products.

1.3.3 Reactions of Pentamethylphenyl ketone with Earth Abundant Metal Catalysts

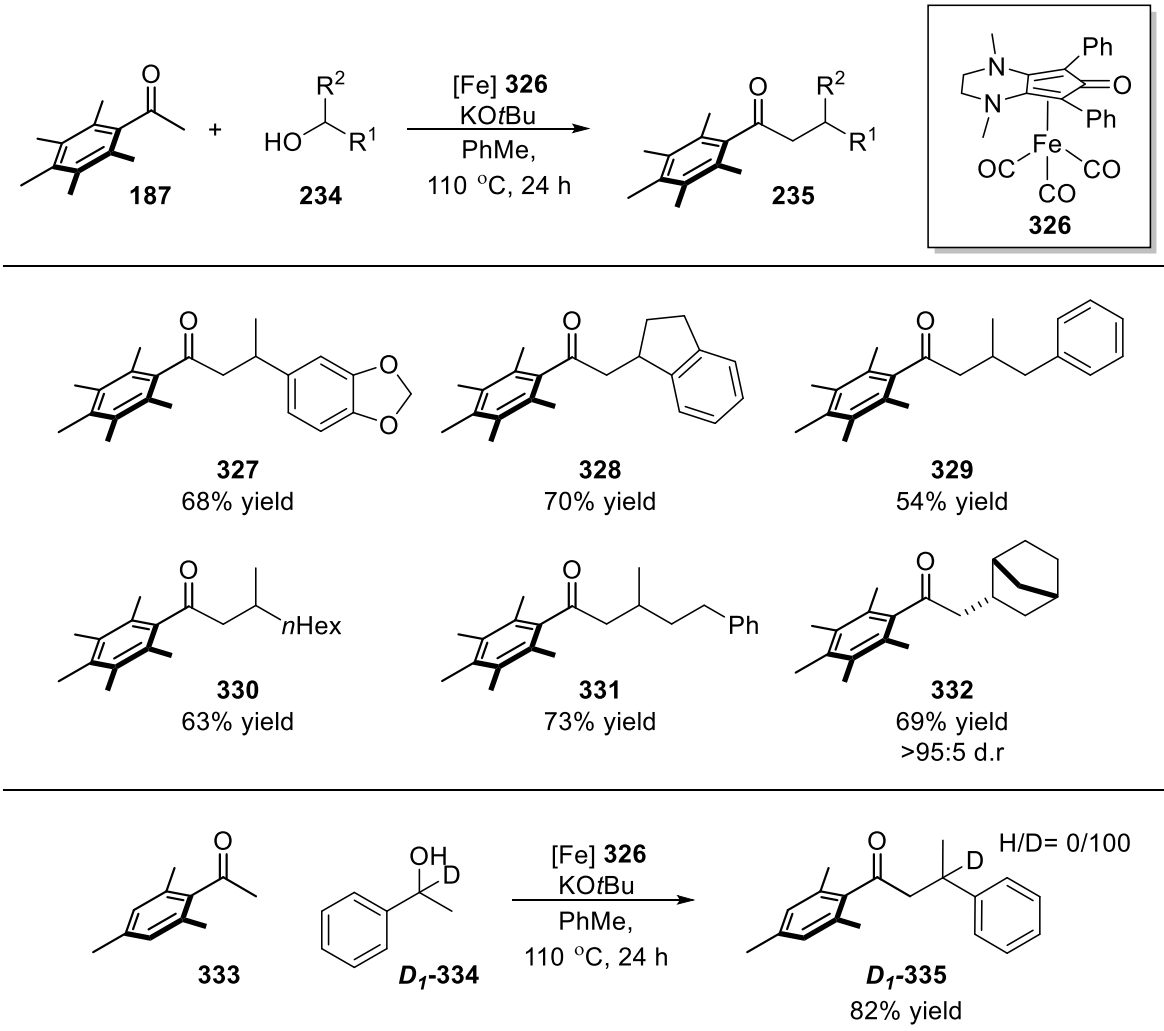
One drawback, however of the previously discussed methodologies is the use of an expensive iridium catalyst. Iridium is one of the least abundant metals in the Earth's crust,[80] thus many other research groups have focused on developing reactions that utilise earth abundant metal catalysts in place of rare-earth metals.

One notable contribution to this field was the work by Sundararaju and co-workers, who reported in 2019 the use of a high valence cobalt catalyst for the hydrogen borrowing alkylation of Ph*COMe with secondary alcohols (Scheme 1.48).[81] Inspired by the previous work by Donohoe and co-workers, the authors explored a range of secondary alcohols to form β-branched products in good yields. This included aliphatic and benzylic alcohols, bearing a range of functional groups such as pyridines, *meta*-methoxy phenyl, and alkynes. The authors also explored functionalisations of the products using the bromine mediated retro-Friedel craft acylation conditions.



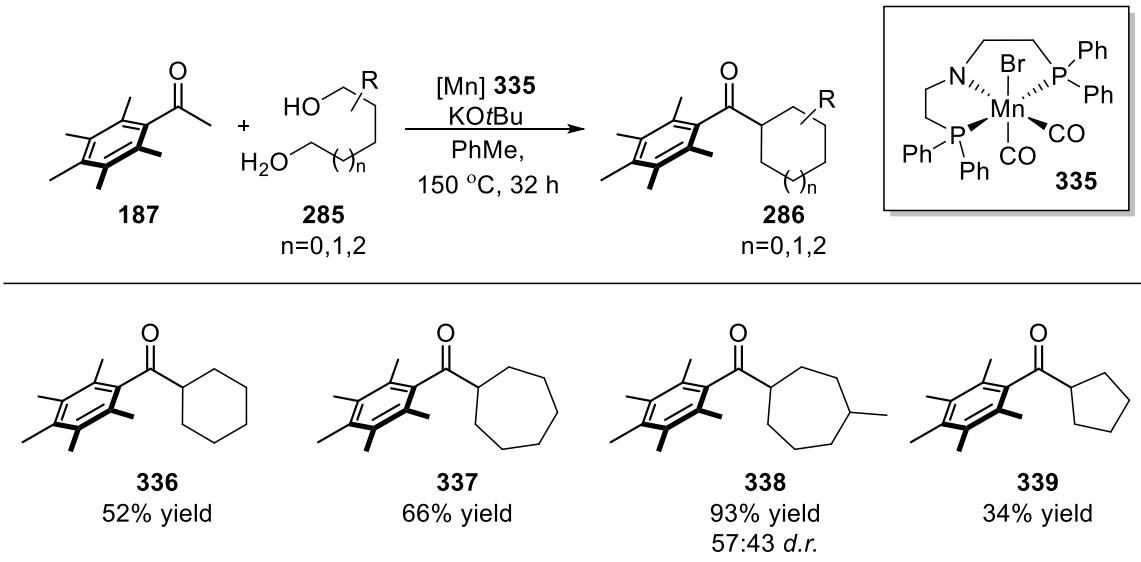
Scheme 1.48: Cobalt catalysed hydrogen borrowing alkylation of Ph*COMe with secondary alcohols. Conditions: Ph*COMe (1 eq.), alcohol (2 eq.), [Co] (2 mol%), KO*t*Bu (2 eq.), PhMe (4 M), 150 °C, 24 h.

In a related publication, Renaud and co-workers reported in 2020 the Iron catalysed hydrogen borrowing alkylation of Ph*COMe with secondary alcohols (Scheme 1.49).[82] The authors reported a very similar substrate scope to the work of Sundararaju and co-workers, with the reaction tolerating both aliphatic and benzylic alcohols to form β-branched ketones in good yields. Interestingly, the authors conducted a deuterium labelling experiment using deuterated alcohol **334** along with mesityl ketone **333**, to gain insight into the reaction mechanism. From this experiment, ketone **335** was obtained with 100% deuterium incorporation, which suggested there was no H/D crossover from any step in the reaction. This is in sharp contrast to reported deuterium incorporations from other metal complexes, and the results in this thesis, where acidic metal hydride complexes are susceptible to H/D exchange and washout of deuterium incorporation (*vide infra*).



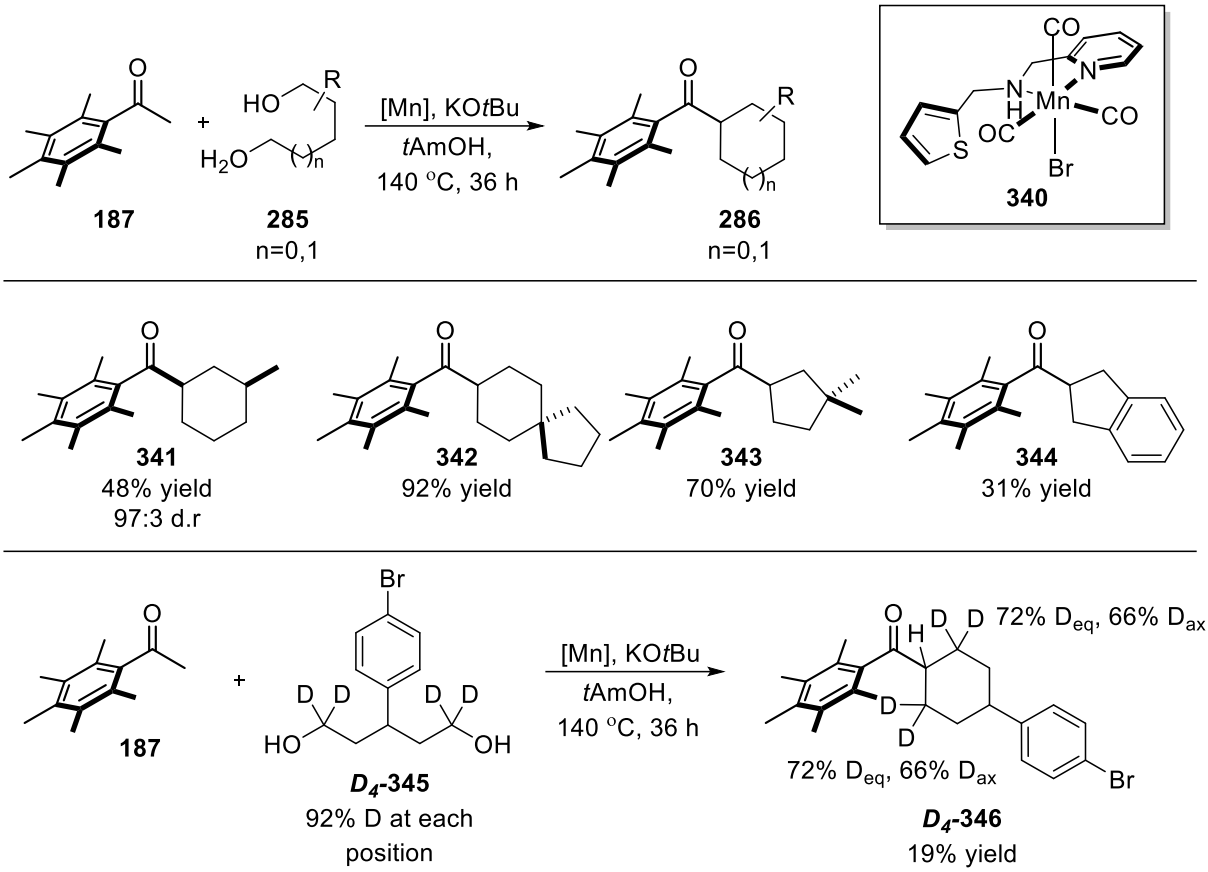
Scheme 1.49: Iron catalysed hydrogen borrowing alkylation of Ph*COMe with secondary alcohols. Conditions: Ph*COMe (1 eq.), alcohol (1.5 eq.), [Fe] (2 mol%), Me_3NO (4 mol%), NaO*t*Bu (1 eq.), PhMe (0.5 M), 110 °C, 24 h.

Another notable contribution to this field was made by Leitner and co-workers, who reported a manganese catalysed annulation strategy to prepare cycloalkanes from diols (Scheme 1.50).[110] Using manganese pincer complex **335**, cyclopentanes, cyclohexanes and cycloheptanes were all accessible in moderate yields. Analogous to Donohoe and co-workers, the authors proposed a reaction mechanism consisting of two successive hydrogen borrowing alkylations with the diol starting material.



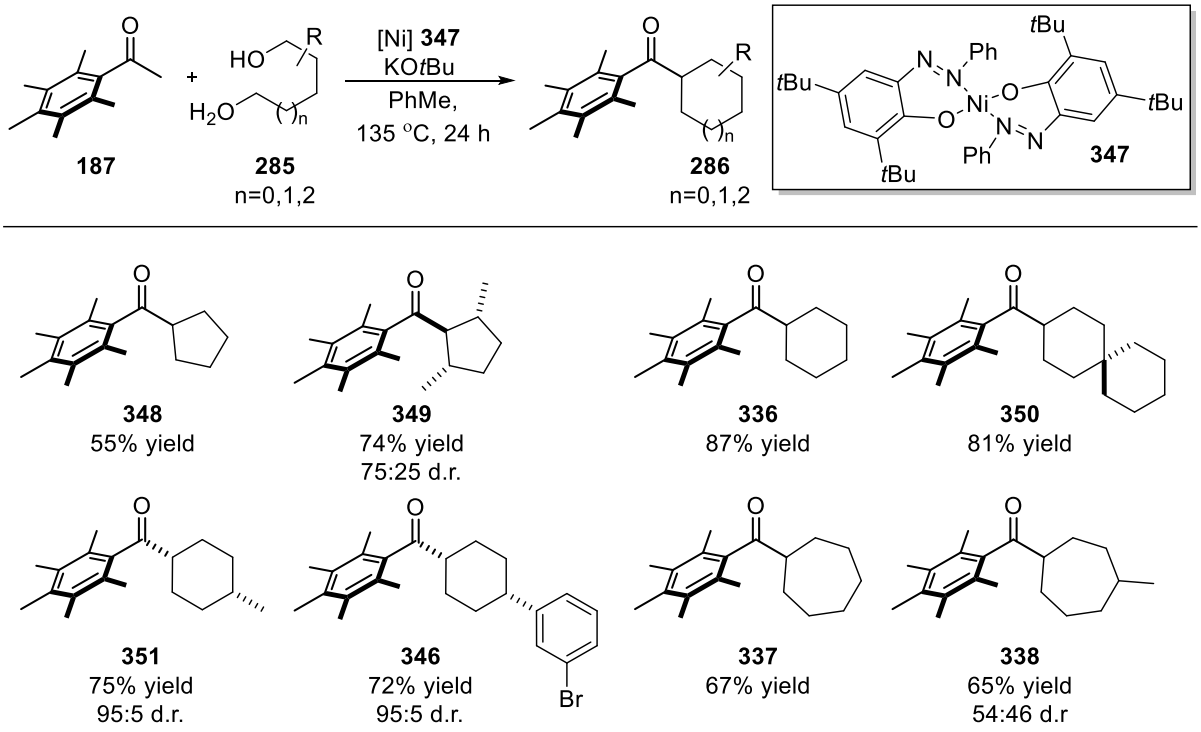
Scheme 1.50: Synthesis of cycloalkanes by manganese catalysed hydrogen borrowing alkylation with diols. Conditions: Ph*COMe (1 eq.), diol (4 eq.), [Mn] **335** (2 mol%), KO*t*Bu (4 eq.), PhMe (0.25 M), 150 °C, 32 h.

Closely relating to this, Maji and co-workers reported in 2020 a manganese complex bearing an amino pyridyl ligand **340** that catalyses the annulation of diols and Ph*COMe to prepare cyclopentanes and cyclohexanes (Scheme 1.51).[111] Mechanistically, the authors proposed the reaction to proceed through two cycles of oxidation, aldol condensation and reduction with manganese hydride. To corroborate this, they performed a deuterium labelling experiment using D_4-diol **345** and Ph*COMe **187** under their optimised conditions. The authors isolated **346** in 19% yield and found it to contain approximately 75% deuterium across the C_2 position, which was consistent with α-alkylation of the ketone starting material. The authors proposed the 25% lower incorporation was due to the H/D exchange of manganese deuteride with protons in the alcoholic solvent.



Scheme 1.51: Manganese catalysed synthesis of cyclohexanes and cyclopentanes. Conditions: Ph*COMe (1 eq.), diol (3 eq.), [Mn] **340** (4 mol%), KO*t*Bu (2 eq.), *t*AmOH (1 M), 140 °C, 36 h.

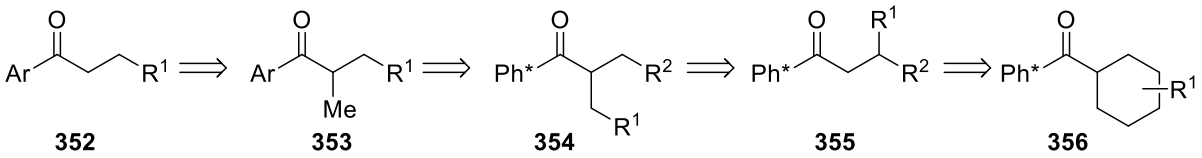
Most recently, Adhikari and co-workers reported a nickel catalyst annulation strategy to prepare cycloalkanes from diols and Ph*COMe (Scheme 1.52).[83] The authors proposed the reaction to proceed through a typical hydrogen borrowing cycle, by two sequential oxidation steps, aldol condensation and reduction steps with nickel complex **347**. By this approach, the authors prepared a range of cyclopentanes, cyclohexanes, and cycloheptane in uniformly good yields and diastereoselectivities.



Scheme 1.52: Synthesis of cycloalkanes by the Nickel catalysed hydrogen borrowing reaction of diols with Ph* ketone. Conditions: Ph*COMe (1 eq.), diol (3 eq.), KO*t*Bu (2 eq.), [Ni] **347** (7 mol%), PhMe (0.1 M), 135 °C, 24 h.

1.4 Summary

As discussed with the above examples, the field of hydrogen borrowing catalysis for the formation of carbon-carbon bonds has seen significant advancements in recent years (Scheme 1.53). This started with the α-alkylation of methylene ketones with primary alcohols to form linear ketone **352**, followed by the discovery that α-branched product **353** can be prepared using methanol as an electrophile. The next key advancement was the discovery of Ph* ketone, which enabled the formation of α-branched product **354** using higher order alcohols.

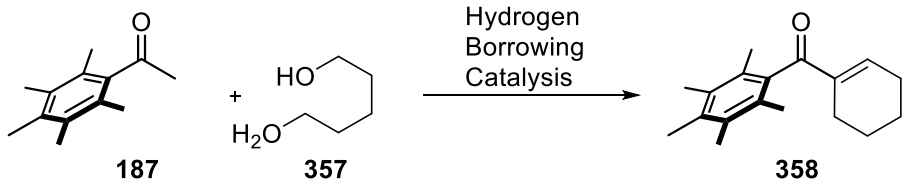


Scheme 1.53: Key advancements in the field of hydrogen borrowing catalysis to form carbon-carbon bonds.

Subsequent developments included the alkylation of Ph* ketone with secondary alcohols to form β-branched product **355**, and the reaction of diols to form cycloalkane **356**. Enantioselective variants of the hydrogen borrowing reaction using secondary alcohols and diols have been developed, as well as catalytic systems using earth abundant metal complexes.

1.5 Project Aims

In light of the previous discussion regarding the synthesis of cyclohexanes, the aim of this project at outset was to develop a new intermolecular approach to the synthesis of cyclohexenes by the hydrogen borrowing reaction of diols with Ph* ketone (Scheme 1.54). This would complement existing approaches to cyclohexene synthesis, such as Diels Alder reaction and ring closing metathesis, with a focus on the preparation of cyclohexenes with high regio- and stereocontrol. This would utilise commercial or readily accessible 1,5-pentane diols, which can be prepared by reduction of the corresponding δ–valerolactone or glutamic acid derivative. In addition to this, functionalisation of the cyclohexene products would be explored, to demonstrate the synthetic utility of this methodology.

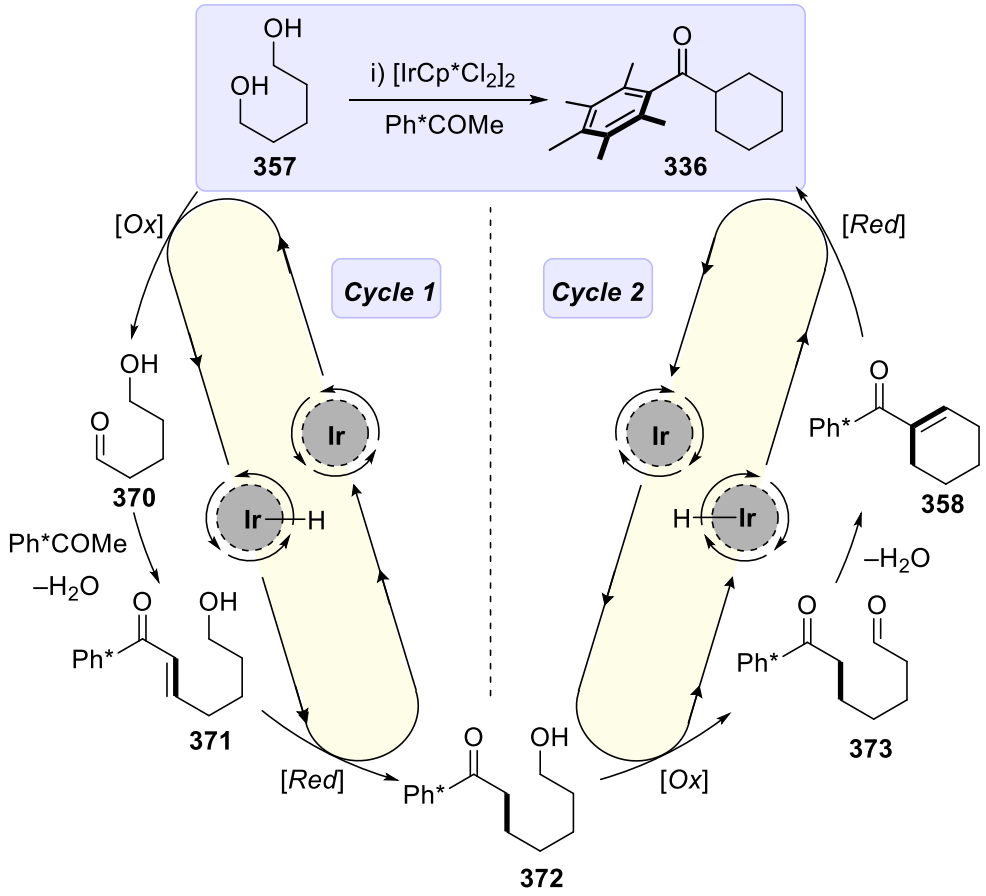


Scheme 1.54: Proposed synthesis of cyclohexenes by hydrogen borrowing catalysis.

Chapter 2: Synthesis of Acyl Cyclohexenes by an Interrupted Hydrogen Borrowing Reaction

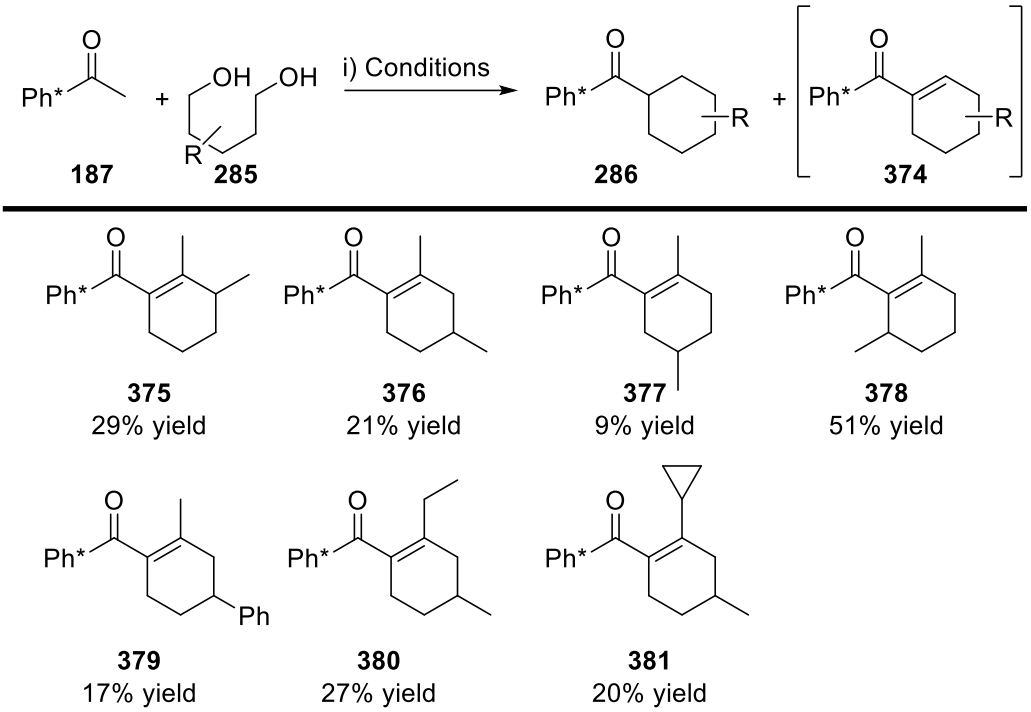
2.1 Introduction and Preliminary Results

Intermolecular methods to prepare multisubstituted carbocyles are quite rare, and new reactions that complement existing approaches (e.g Diels Alder, RCM) are highly desirable. In 2019, Donohoe and co-workers reported an unprecedented [5+1] approach to stereodefined cyclohexanes by the iridium-catalysed double alkylation of Ph*COMe with 1,5-pentane diols (Scheme 2.1).[84] This annulation reaction was proposed to consist of two successive hydrogen borrowing catalytic cycles (Cycles 1 and 2). The first cycle was initiated by oxidation of diol **357** by iridium to give hydroxyaldehyde intermediate **370** and iridium hydride. **370** undergoes aldol condensation with Ph*COMe to give acyclic enone **371**, which can undergo 1,4-reduction with iridium hydride to afford hydroxyketone **372** and complete the cycle. **372** then initiates the second catalytic cycle, which begins with oxidation of the pendant alcohol by iridium to give dicarbonyl **373** and iridium hydride. Subsequent intramolecular aldol condensation generates cyclohexene **358**, which is then reduced by iridium hydride to afford cyclohexane **336**.



Scheme 2.1: Formation of a cyclohexanes by the (5+1) annulation of Ph*COMe. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol% dimer), KOH (4 eq.), Ph*COMe (1 eq.), 1,5-hexanediol (1.1 eq.), PhMe (4 M), 115 °C, Ar, 24 h.

During the investigation of this methodology, Dr W. A. Atkhar noted that several α-substituted diols resulted in isolation of a mixture of the corresponding cyclohexane and cyclohexene. This was presumably due to a sterically hindered tetrasubstituted enone, which slowed the final reduction step by iridium hydride in cycle 2.

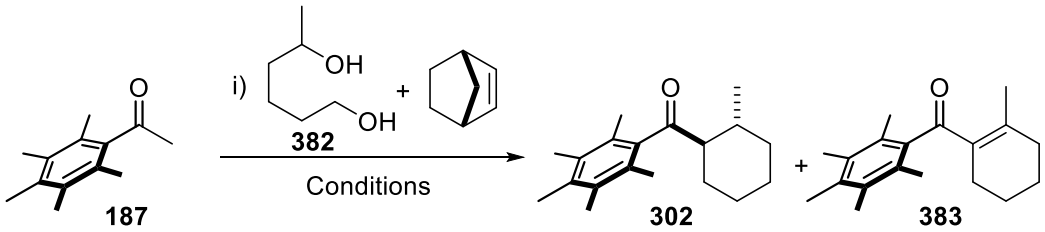


Scheme 2.2: Observed side-product formation of cyclohexenes in the synthesis of cyclohexanes. Conditions: i) $[Ir(Cp^*)Cl_2]_2$ (2 mol% dimer), KOH (4 eq.), Ph*COMe (1 eq.), diol (2 eq.), PhMe (4 M), 115 ^oC, Ar, 24 h.

Intrigued by this intermediate tetrasubstituted enone, we wondered whether the final reduction step could be prevented entirely, which would enable the selective synthesis of multisubstituted cyclohexenes. To develop such a reaction, there would be several challenges to overcome: firstly, addressing the chemoselectivity issue of reducing acylic enone **371** in cycle 1 while preventing the reduction of a cyclic enone **358** in cycle 2. Secondly, controlling the regioselectivity of C-C bond formation from diols without C2 symmetry. Thirdly, demonstrating the synthetic utility of cyclohexenes bearing a pentamethylphenyl ketone.

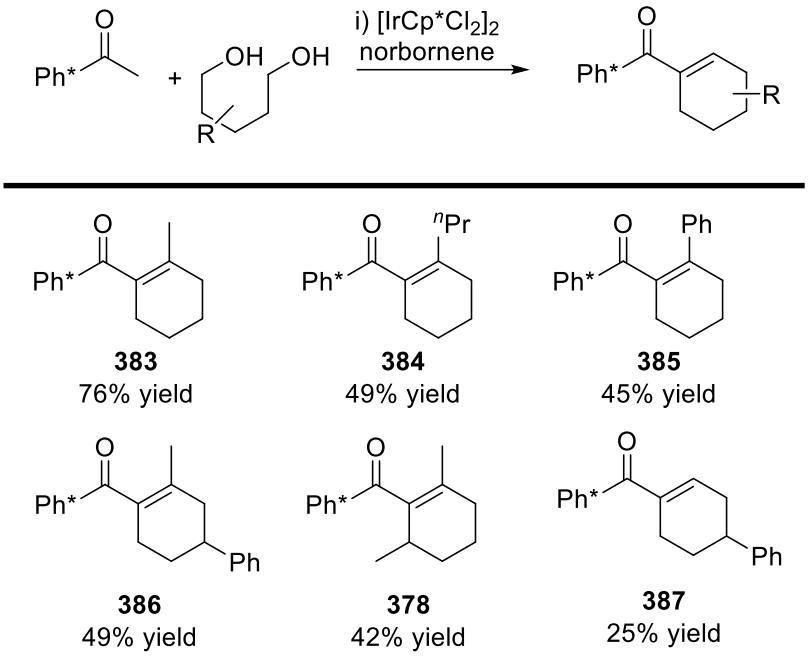
To address these challenges, we proposed to use a combination of approaches: (i) Use of a hydrogen acceptor, which could competitively intercept iridium-hydride and prevent reduction of cyclic enone **358**. (ii) Use α-substituted diols to target sterically hindered tetrasubstituted enones that are harder to reduce. (iii) Reduce the reactivity of iridium–hydride towards the tetrasubstituted enone through varying the metal centre and the ligand.

Towards this goal, D. M. Raven initially investigated this reaction and undertook an optimisation utilising norbornene as a hydrogen acceptor. He found that increasing the equivalents of norbornene had a dramatic effect on the selectivity towards cyclohexene **383** (Table 2.2). He conducted a preliminary substrate scope, which gave good yields for cyclohexene **383**, but lower yields for different α-substituted diols **384**-**387** (Scheme 2.3). Furthermore, the conditions gave a lower yield for 4-phenyl substituted cyclohexene **387**, with the corresponding cyclohexane isolated in 50% yield. This result was presumably due to poor chemoselectivity between acyclic enone **371** and cyclic enone **387**.



Entry	Norbornene (eq.)	Cyclohexane **302** (%)	Cyclohexene **383** (%)
1	0.0	(63)	(22)
2	0.5	(53)	(29)
3	1.0	(39)	(33)
4	2.0	(20)	(62)56
5	2.5	(17)	(70)
6	3.0	(18)	(65)

Table 2.2: Increasing the equivalents of hydrogen acceptor norbornene, conducted by D. M. Raven. Yields refer to isolated material after column chromatography. HPLC yield reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as a calibrated internal standard. Reagents and Conditions: (i) $[IrCp^*Cl_2]_2$ (0.5 mol% dimer), KOH (4 eq.), Ph*COMe (1 eq.), 1,5-hexanediol (1.5 eq.), norbornene (x eq.), PhMe (4 M), 115 °C, Ar, 24 h.

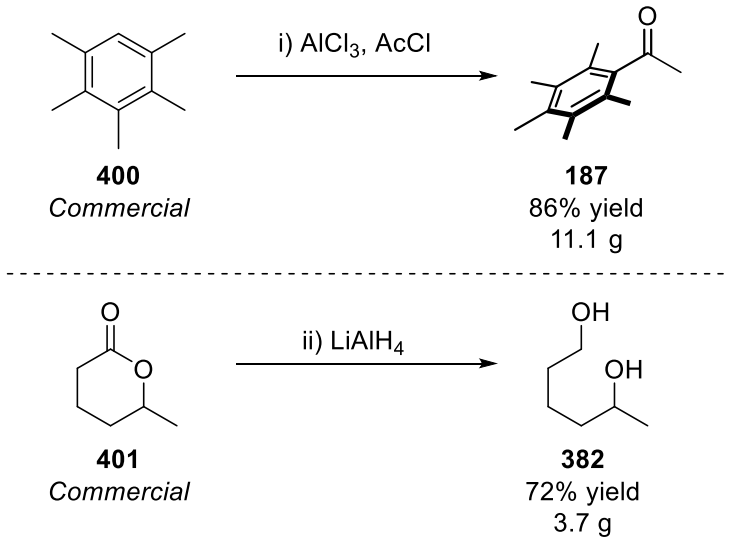


Scheme 2.3: Preliminary scope of cyclohexenes using norbornene as a hydrogen acceptor, conducted by D. M. Raven. Conditions (i) $[Cp^*IrCl_2]_2$ (0.5 mol% dimer), KOH (4 eq.), Ph*COMe (1 eq.), diol (1.5 eq.), norbornene (1.25 eq.), PhMe (0.5 M), 115 °C, 24 h.

At this point D. M. Raven left the project and I became involved, and using these results as our benchmark, this thesis describe how we addressed the outlined challenges and ultimately developed a general set of reaction conditions for the synthesis of acyl-cyclohexenes.

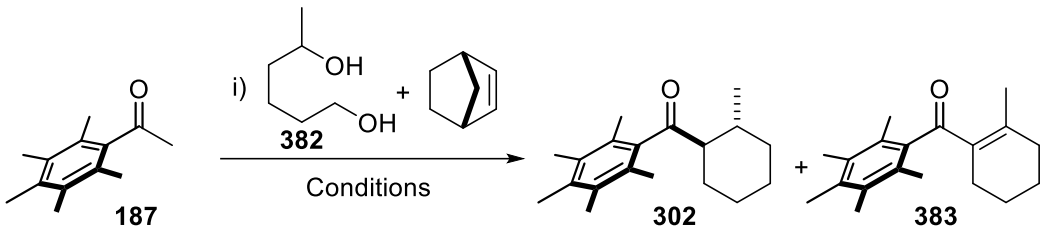
2.2 Reaction Optimisation

Based on the previous work, we chose to continue the optimisation with Ph* methyl ketone **187** and 1,5-hexane diol **382** as our model substrates. Ketone **187** was conveniently prepared on multigram scale by Friedel-Crafts acylation of acetyl chloride, while diol **382** was synthesised by $LiALH_4$ reduction of the corresponding lactone **401** (Scheme 2.4).



Scheme 2.4: Synthesis of model substrates. Conditions: (i) pentamethylbenzene (1 eq.), acetyl chloride (1.1 eq.), $AlCl_3$ (1.3 eq.), CH_2Cl_2 (0.2 M), 0 °C RT, 2 h. (ii) δ-hexalactone (1 eq.), $LiAlH_4$ (1.1 eq.), THF (0.2 M), reflux, 19 h.

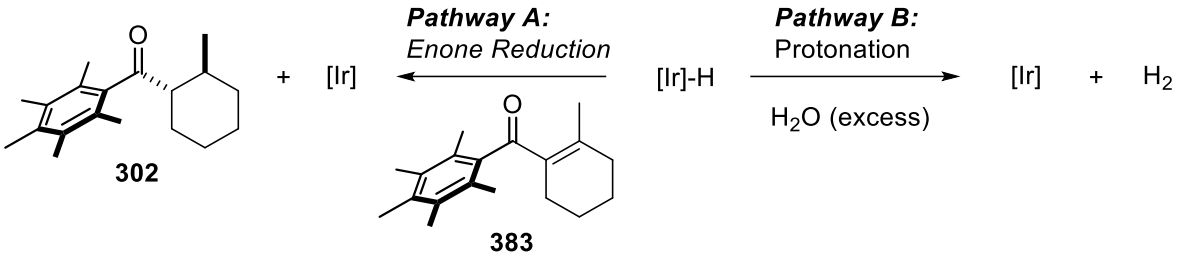
With the model substrates in-hand, we began by conducting several experiments based on the previous optimisation (Table 2.3). Firstly, we subjected the model substrates to the previously reported conditions for the synthesis of cyclohexanes (Entry 1). In line with this study, we found that the major product was cyclohexane **302**, which formed in 71% yield along with a small quantity of the desired cyclohexene **383** in 7% yield. With this result as our benchmark, we added two equivalents of norbornene, based on the previous work by D. M. Raven (Entry 2). We were pleased to find a dramatic improvement in selectivity, with cyclohexene **383** formed in 51% yield and the undesired cyclohexane **302** in 25% yield. Furthermore, lowering the catalyst loading and increasing dilution resulted in a 76% yield of cyclohexene **383** (Entry 3).



Entry	Norbornene (eq.)	$[IrCp^*Cl_2]_2$ (mol% dimer)	PhMe (M)	SM **187** (%)	Cyclohexane **302** (%)	Cyclohexene **383** (%)
1	0.00	2.0	4.0	(6)	(71)	(7)
2	2.00	2.0	4.0	(5)	(25)	(51)
3	1.25	0.5	0.4	(6)	(3)	76
4	0.00	0.5	0.4	(12)	(2)	74
5[†]	0.00	0.5	0.4	-	10	50

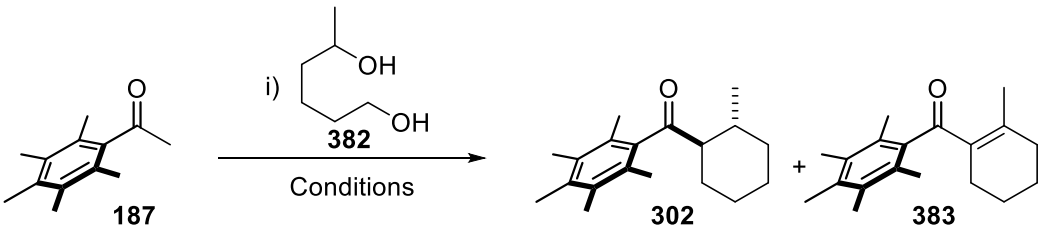
Table 2.3: Preliminary reaction optimisation with norbornene. Yields refer to isolated material after column chromatography. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (x mol% dimer), KOH (4 eq.), Ph*COMe (1 eq.), 1,5-hexanediol (2 eq.), norbornene (x eq.), PhMe (0.4-4.0 M), 115 °C, 24 h. † 1.25 equivalents of norbornane.

We then conducted a series of control experiments to confirm the origin of the reaction selectivity. Firstly, Entry 3 was repeated in deuterated toluene and the crude reaction mixture was analysed by ^{1}H and ^{13}C NMR. Complete reduction of norbornene to norbornane was observed by these methods, which supported the hypothesis of norbornene functioning as a hydrogen acceptor to perturb reduction. To show that the hydrogen acceptor was responsible for product selectivity, we conducted the reaction in the absence of norbornene (Entry 4). Contrary to our previous experiments, we still observed high selectivity for cyclohexene **383** over cyclohexane **302**. Similarly, when norbornane was used in place of norbornene (Entry 5), we still observed high selectivity of cyclohexene product **383**. We concluded from these experiments that norbornene was not responsible for product selectivity. Analysis of the reaction headspace of Entry 4 using gas chromatography with a thermal conductivity detector (GC-TCD) qualitatively detected the formation of hydrogen gas. This suggested that the process proceeded through an acceptorless dehydrogenation (pathway B) and also explained why the reaction was selective in the absence of a hydrogen acceptor (Scheme 2.5).[85]



Scheme 2.5: Explanation for the reaction chemoselectivity.

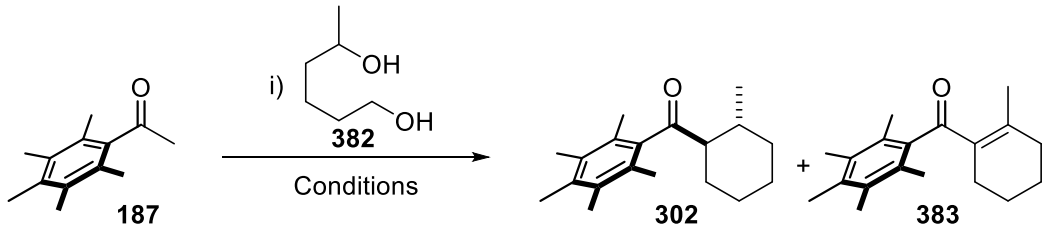
Given that norbornene was not responsible for selectivity as a hydrogen acceptor, we removed it entirely and increased the dilution of the reaction (Table 2.4). A clear trend emerged that by decreasing the concentration from 4 M to 0.25 M (Entries 1-4), the selectivity increased, and cyclohexene **383** could be obtained in 54% yield. Further dilution to 0.1 M (Entry 5) resulted in lower conversion. The benefit from increased dilution could be due to retarding the bimolecular reduction of cyclohexene **383** by iridium hydride. In contrast, the competing protonation of iridium hydride with the excess water in the reaction mixture would proceed unperturbed at higher dilution, thus would result in the evolution of hydrogen gas over 1,4-reduction of cyclohexene **383**. Taken together, these two competing reactions of iridium hydride would overall favour the formation of cyclohexene **383**.



Entry	PhMe (M)	SM **187** (%)	Cyclohexane **302** (%)	Cyclohexene **383** (%)
1	4.00	(6)	(71)	(7)
2	2.00	(7)	(61)	(16)
3	1.00	(9)	(36)	(40)
4	0.25	(20)	(7)	(54)
5	0.10	(46)	(2)	(35)

Table 2.4: Varying the reaction concentration. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol% dimer), KOH (4 eq.), Ph*COMe (1 eq.), 1,5-hexanediol (2 eq.), PhMe (0.1-4.0 M), 115 °C, 24 h.

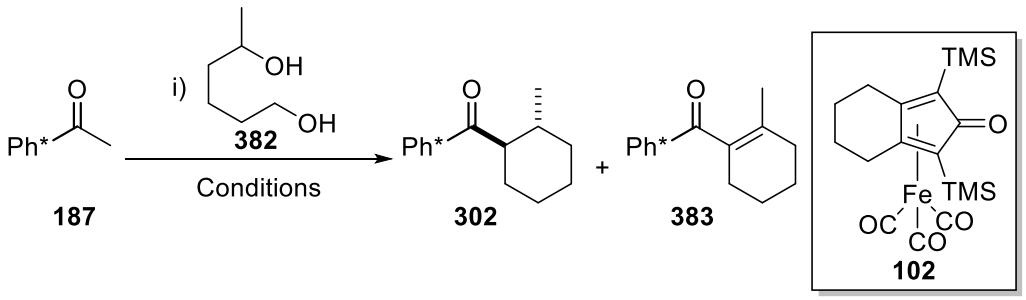
With the clear benefit of high dilution for product selectivity established, we wondered how the relative concentration of catalyst to substrate might similarly impact the rate of reduction at 0.25 M (Table 2.5). The loading of $[IrCp^*Cl_2]_2$ was lowered from 4 mol% to 1 mol% monomer, but this did not have a significant effect on the selectivity of cyclohexane **302** to cyclohexene **383**. Remarkably, the yields with low loadings were greater than those with higher loadings.



Entry	$[IrCp^*Cl_2]_2$ (mol% monomer)	SM **187** (%)	Cyclohexane **302** (%)	Cyclohexene **383** (%)
1	4.0	(20)	(7)	(54)
2	3.0	(37)	(4)	(49)
3	2.0	(26)	(3)	(62)
4	1.5	(27)	(2)	(70)
5	1.0	(21)	(4)	(60)

Table 2.5: Varying the catalyst concentration. Reagents and conditions: HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. (i) $[Cp^*IrCl_2]_2$, KOH (4 eq.), Ph*COMe (1 eq.), 1,5-hexanediol (2 eq.), PhMe (0.25 M), 115 °C, 24 h.

In parallel to varying the catalyst loading, we investigated the effectiveness of other catalysts that had previously been used for hydrogen borrowing reactions (Table 2.6).[86,87,88] Compared to $[IrCp^*Cl_2]_2$ (Entry 1), ruthenium (Entries 2 and 3), rhodium (Entries 4 and 5) and iron (Entries 6 and 7) were found to be less effective at 1.5 mol% and 4 mol% loadings. Interestingly, Ir(I) modified with PPh_3 (Entries 8 and 9) gave a comparable yield to $[IrCp^*Cl_2]$, with 1.5 mol% affording cyclohexene **383** in 71% yield and only trace of cyclohexane **302**.

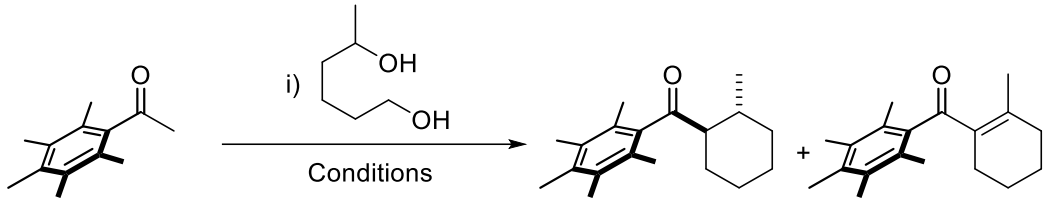


Entry	Catalyst (mol% monomer)	SM **187** (%)	Cyclohexane **302** (%)	Cyclohexene **383** (%)
1	$[IrCp^*Cl_2]_2$ (1.5)	(27)	(2)	(70)
2	$[Ru(p\text{-cymene})Cl_2]_2$ (1.5)	(42)	(1)	53
3	$[Ru(Cp^*)Cl_2]_n$ (4.0)	(75)	(1)	(18)
4	$[Rh(Cp^*)Cl_2]_2$ (1.5)	(40)	(2)	52
5	$[RhCp^*Cl_2]_2$ (4.0)	(22)	(2)	52
6	Knölker Complex **102** (1.5)	(90)	(0)	(9)
7	Knölker Complex **102** (4.0)	(72)	(0)	(14)
8	$[Ir(COD)Cl)]_2$ (4.0) PPh_3 (8.0)	(16)	(2)	(65)
9	$[Ir(COD)Cl)]_2$ (1.5) PPh_3 (3.0)	(24)	(2)	71

Table 2.6: Varying the catalyst complex. Reagents and conditions: Yields refer to isolated material after column chromatography. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. (i) KOH (4 eq.), Ph*COMe (1 eq.), 1,5-hexanediol (2 eq.), PhMe (0.25 M), 115 °C, 24 h.

In addition to considering the catalyst complex, we looked at how the nature of the base would influence the yield and selectivity for cyclohexene **383** (Table 2.7). Organic amine bases and carbonates, such as BEMP (Entry 1) and Cs_2CO_3 (Entry 2) gave no product, presumably because they were too weak to deprotonate Ph*C(O)Me to enable the annulation. Stronger alkoxide bases (Entry 4-5) promoted the annulation, however KO*t*Bu enabled reduction and gave high selectivity for the undesired cyclohexane **302**. Inorganic hydroxide bases (Entries 6-8) were also evaluated, with potassium proving the best counter-ion for the reaction. Lower equivalents of KOH were tried (Entry 9), but had a detrimental effect on conversion, possibly due to its low solubility in toluene. When higher equivalents of KOH were tried (Entries 10-12), we observed the selectivity decrease and the reaction favour reduction to cyclohexane **302**. This led us to an optimised set of conditions for the

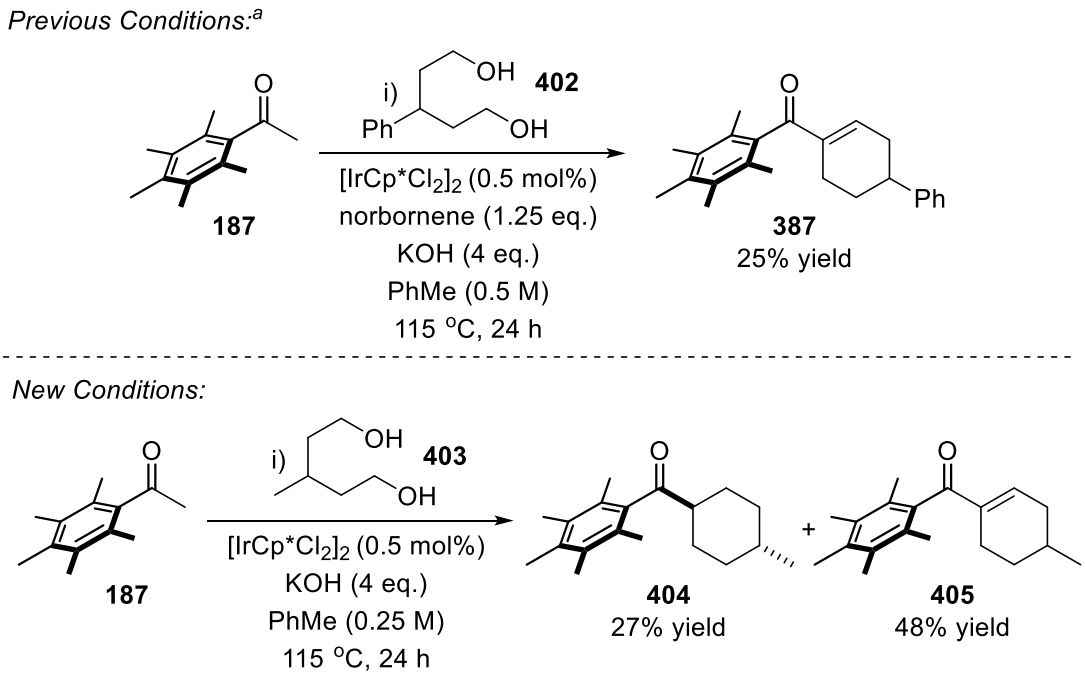
synthesis of tetrasubstituted cyclohexene **383** (Entry 1), consisting of 0.75 mol% $[IrCp^*Cl_2]_2$, four equivalents of KOH in toluene at 0.25 M.



Entry	Base (eq.)	SM **187** (%)	Cyclohexane **302** (%)	Cyclohexene **383** (%)
1	BEMP (4)	(98)	(<1)	(<1)
2	Cs_2CO_3 (4)	(88)	(<1)	(2)
3	K_2CO_3 (4)	(98)	(<1)	(<1)
4	KO^tBu (4)	(12)	(79)	(5)
5	NaO^tBu (4)	(69)	(<1)	(19)
6	NaOH (4)	(42)	(<1)	(46)
7	$CsOH.H_2O$ (4)	(19)	(8)	(59)
8	KOH (4)	(26)	(3)	(71)
9	KOH (2)	(37)	(3)	(51)
10	KOH (6)	(19)	(9)	(62)
11	KOH (8)	(22)	(32)	(37)
12	KOH (10)	(13)	(62)	(17)

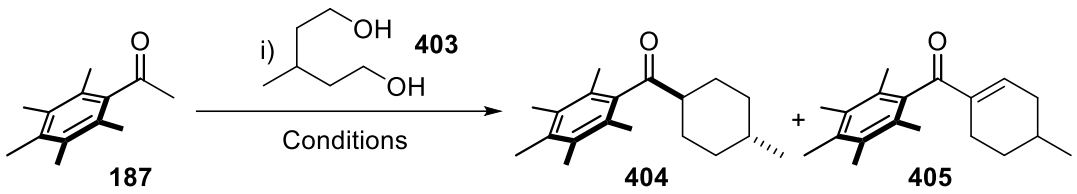
Table 2.7: Varying the base. Reagents and conditions: Yields refer to isolated material after column chromatography. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. (i) $[Cp^*IrCl_2]_2$ (0.75 mol% dimer), Ph*COMe (1 eq.), 1,5-hexanediol (1.5 eq.), PhMe (0.25 M), 115 °C, 24 h.

Using the optimisation for the synthesis of tetrasubstituted cyclohexene **383**, we next considered its applicability towards trisubstituted cyclohexenes (Scheme 2.6). Our expectation was that we would observe a significant amount of over-reduction as the trisubstituted enone products would be considerably easier to reduce than tetrasubstituted enones. We were delighted to find the conditions from Entry 1, Table 2.5 gave a 48% yield of desired cyclohexene **405**, and 27% cyclohexane **404**, which was far more selective than the conditions that used norbornene.



Scheme 2.6: Synthesis of trisubstituted cyclohexenes. (a) Experiment conducted by D. M. Raven. Conditions: $[Cp^*IrCl_2]_2$ (0.5 mol% dimer), Ph*COMe (1 eq.), 1,5-hexanediol (1.5 eq.), KOH (4 eq.), PhMe (0.25 M), 115 °C, 24 h.

Based on this promising result, we undertook a second optimisation with commercially available 3-methyl pentane-1,5-diol **403** as a model substrate (Table 2.10). Through a screen of the catalysts from Table 2.6, we found that $[Ir(COD)Cl]_2$ bearing PPh_3 (Entry 4) provided a greatly improved yield and selectivity compared to $[IrCp^*Cl_2]_2$ (Entry 1), and other hydrogen borrowing catalysts (Entries 2-3). Furthermore, the yield of 70% from Entry 4 could be further improved to 78% yield by increasing the excess of diol **403** to two equivalents. Notably, in the absence of PPh_3, Ir(I) was a poor catalyst for the reaction (Entry 6), which suggested the ligand was detrimental to its reactivity as an oxidant and a chemoselective reductant.

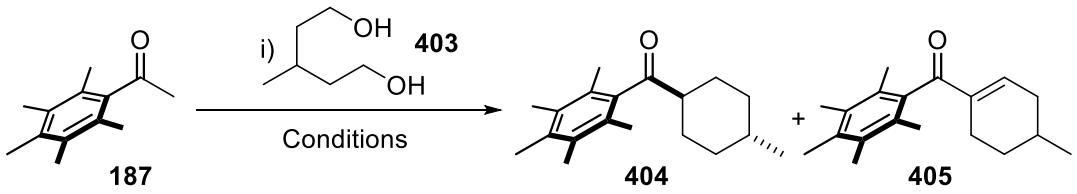


Entry	Catalyst (mol% monomer)	SM **187** (%)	Cyclohexane **404** (%)	Cyclohexene **405** (%)
1	$[IrCp^*Cl_2]_2$ (1)	(14)	(27)	(48)
2	$[Ru(p\text{-cymene})Cl_2]$ (1)	(54)	(4)	(34)
3	$[Rh(Cp^*)Cl_2]_2$ (1)	(59)	(3)	(30)
4	$[Ir(COD)Cl)]_2$ (1) PPh_3 (2)	25	5	70
5†	$[Ir(COD)Cl)]_2$ (1) PPh_3 (2)	10	6	78
6	$[Ir(COD)Cl]_2$ (1)	(82)	(2)	(8)

Table 2.10: Varying the catalyst complex with 3-methyl pentane-1,5-diol. Yields refer to isolated material after column chromatography. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. Reagents and conditions: (i) KOH (4 eq.), Ph*COMe (1 eq.), 3-methyl pentane-1,5-diol (1.5 eq.), PhMe (0.25 M), 115 °C, 24 h. † 2 eq. of 3-methyl pentane-1,5-diol instead.

Using PPh_3 as our benchmark, we undertook an extensive ligand screen with $[Ir(COD)Cl]_2$ to further improve the yield and selectivity (Table 2.11). Firstly, electron poor phosphorus ligands were evaluated under the reaction conditions, such as triphenylphosphite (Entry 1), $P(C_6F_5)_3$ (Entry 2) and MONOPHOS (Entry 3), and were found to promote the reduction of cyclohexene **405** to cyclohexane **404**. This was particularly pronounced with triphenylphosphite (Entry 1), which completely reversed the previously optimised selectivity to give cyclohexane **404** in 73% yield and trace cyclohexene **405**. A plausible explanation for this is a more electron deficient iridium is a better Lewis-acid and can better coordinate to our enone for reduction. Conversely, more electron rich aryl phosphorus ligands (Entries 5-10) were found to be highly selective for formation of cyclohexene **405**. This included bisphosphine ligands with varying bite angles (Entries 5-8), such as DPPE (Entry 5) and BINAP (Entry 7), but were generally less selective than PPh_3 (Entry 9). Dialkylmonophosphines, such as JohnPhos (Entry 4) were also tried, but gave low conversion. Increasing the σ-donor strength of PPh_3, through a *p*-methoxy group (Entry 10), did not offer any significant change. Electron rich alkyl phosphines offered excellent selectivity for cyclohexene formation (Entry 11-17). Among these ligands, the bulky ligand CataCXium® A, bearing two adamantyl groups and an *n*-butyl chain (Entry 17), gave the highest observed yield and selectivity, with an 84% yield of cyclohexene **405**, and 5% of cyclohexane **404**. Notably, alkyl

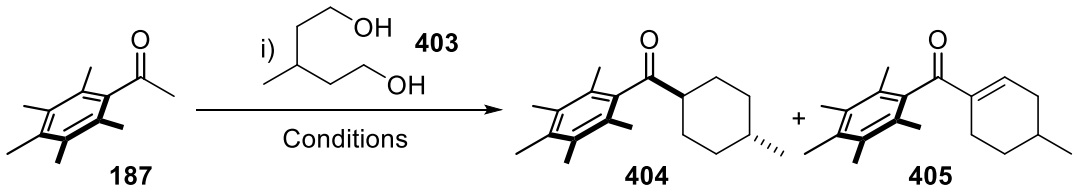
phosphines offer increased steric bulk compared to PPh_3, which would be expected to hinder conjugate reduction and therefore favour protonation of iridium to generate H_2 gas. This is in good agreement with work by Beller and co-workers, who reported CataCXium® A to be a particularly effective ligand for acceptorless dehydrogenation.[89]



Entry	Ligand (mol%)	SM **187** (%)	Cyclohexane **404** (%)	Cyclohexene **405** (%)
1	$P(OPh)_3$ (2)	(11)	(73)	(2)
2	$P(C_6F_5)_3$ (2)	(12)	(63)	(17)
3†	(*R*)-MONOPHOS (2)	(8)	(62)	(19)
4	JohnPhos (2)	(64)	(4)	(26)
5	DPPE (1)	(9)	(19)	(62)
6	DPPP (1)	(6)	(10)	(76)
7†	(*R*)-BINAP (1)	(15)	(24)	(53)
8	DPPF (1)	(8)	(7)	(73)
9	PPh_3 (2)	10	6	78
10	P(*p*-$MeOC_6H_4)_3$(2)	(13)	(10)	(78)
11	P(^{n}Bu)$_3$ (2)	(14)	(12)	(63)
12	$P(Cy)_3$ (2)	(4)	(9)	(79)
13	$P(Cy)_3.HBF_4$(2)	(9)	(15)	(68)
14	P(^{t}Bu)$_3$.HBF_4(2)	(9)	(12)	(71)
15	$P(Ad)_3$ (2)	(9)	(11)	(73)
16	CataCXium® A Bn (2)	(4)	(10)	(79)
17	CataCXium® A (2)	2	5	84

Table 2.11: Varying the ligand with 3-methyl pentane-1,5-diol. Yields refer to isolated material after column chromatography. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. Reagents and conditions: (i) $[Ir(COD)Cl)]_2$ (0.5 mol% dimer) KOH (4 eq.), Ph*COMe (1 eq.), 3-methyl pentane-1,5-diol (2 eq.), PhMe (0.25 M), 115 °C, 24 h. † racemic product by chiral HPLC.

To finish our reaction optimisation, we screened a representative range of high-boiling aprotic solvents with the conditions from Entry 17, Table 2.11 (Table 2.12). Polar solvents, such as 1,4-dioxane (Entry 4), were detrimental to the yield. Similarly, benzene (Entry 2), with the lower boiling point than toluene (Entry 1), gave a lower yield of cyclohexene **405**. Likewise, raising the boiling point to *m*-xylene (Entry 3) was not beneficial.



Entry	Solvent	SM (%)	Cyclohexane (%)	Cyclohexene (%)
1	PhMe	(2)	84	5
2	Benzene	(7)	(73)	(13)
3	*m*-Xylene	(15)	(72)	(10)
4	1,4-Dioxane	(72)	(11)	(3)

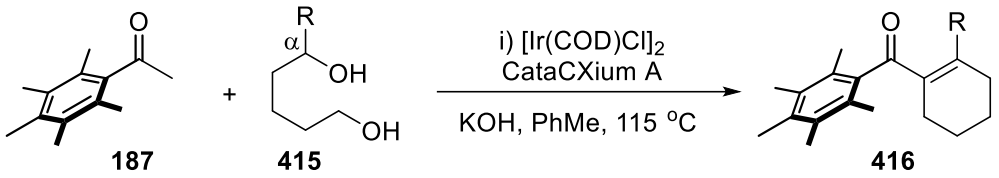
Table 2.12: Varying high boiling aprotic solvent with 3-methyl pentane-1,5-diol. Yields refer to isolated material after column chromatography. HPLC yields reported in parenthesis, determined by reverse phase HPLC against 2,3,5,6-tetramethylbenzene as an internal standard. Reagents and conditions: (i) $[Ir(COD)Cl)]_2$ (0.5 mol% dimer), CataCXium® A (2 mol%), KOH (4 eq.), Ph*COMe (1 eq.), 3-methyl pentane-1,5-diol (2 eq.), Solvent (0.25 M), 115 °C, 24 h.

2.3 Substrate Scope

2.3.1 Scope of α-substituted Diols

Having conducted a thorough optimisation for the synthesis of acyl-cyclohexenes, we looked to investigate the scope of diols bearing an α-substituent, which would produce tetrasubstituted enones. All diols used were either commercially available or synthetically accessible in a short sequence of steps (*vide infra*). Firstly, we investigated the steric effect of the α-substituent on the reaction (Table 2.13). To explore this, Diols **417**-**420** were prepared by Dr R. J. Armstrong by the addition of an appropriate Grignard reagent to tetrahydro-2H-pyran-2-ol. When we subjected diols **382**-**420** to the optimised conditions, we found that increasing the size of the substituent from methyl to *n*-propyl and *n*-butyl was beneficial to reactivity; possibly due to a beneficial Thorpe-Ingold effect, and afforded

the corresponding cyclohexenes **421** in 95% yield and **423** in 99% yield. The reaction was also efficient with branched α-substituents, with isopropyl and isobutyl cyclohexenes **422** and **424** isolated in 64% and 99% yield, respectively.



187 + **415** → **416**

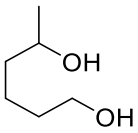
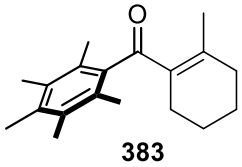
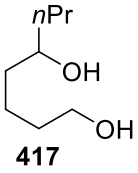
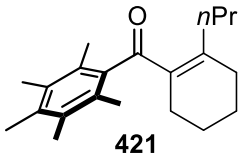
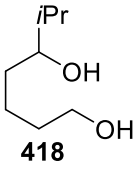
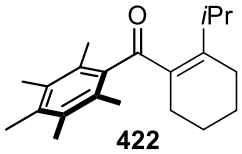
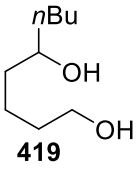
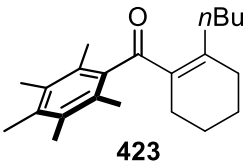
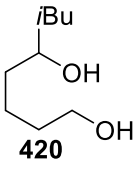
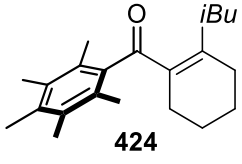
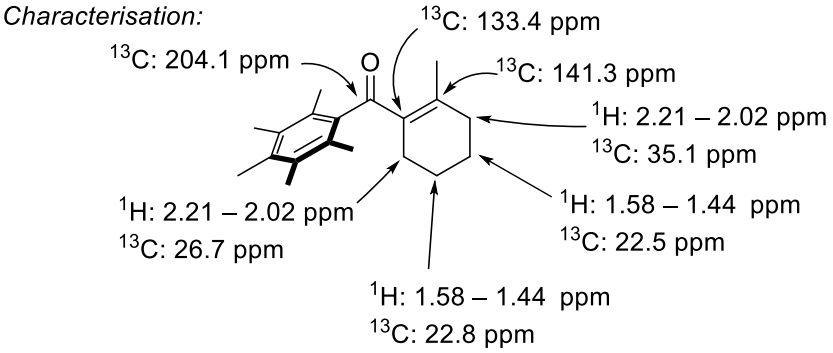
Entry	Diol[a]	Product	Yield (%)[b]
1	 **382**	 **383**	79
2	 **417**	 **421**	95
3	 **418**	 **422**	64
4	 **419**	 **423**	99
5	 **420**	 **424**	99

Table 2.13: Substrate scope of α-alkyl substituents. Conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (a) Diols were prepared previously by Dr R. J. Armstrong. (b) Yield refers to isolated material after column chromatography.

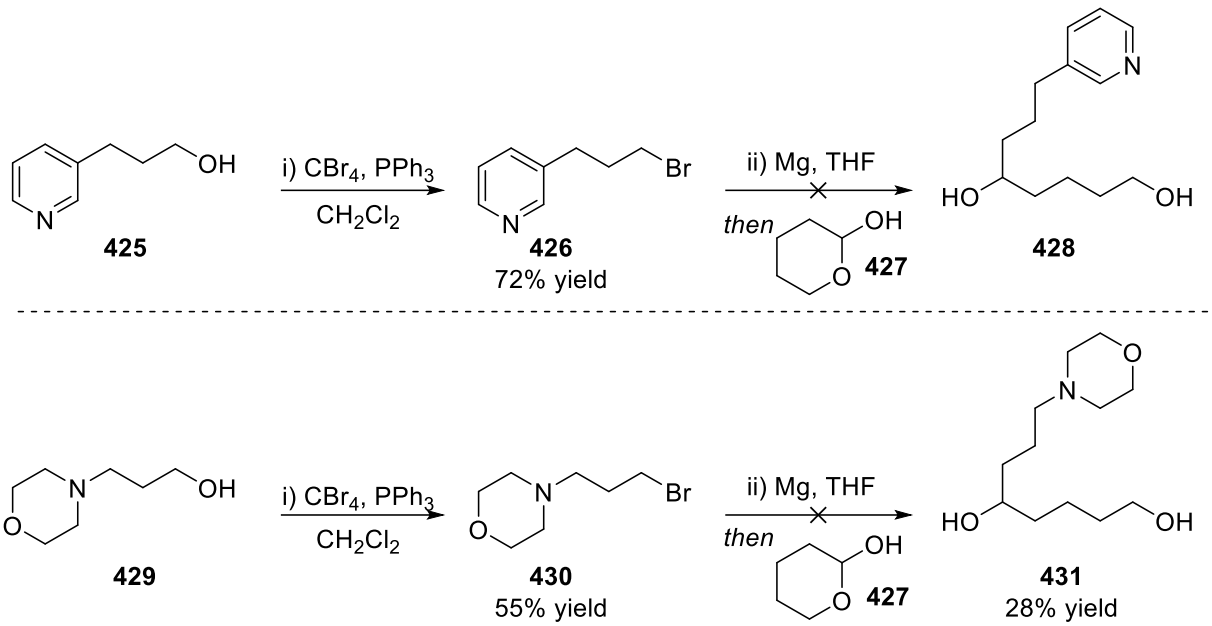
In each case, the cyclohexene products were identified by several diagnostic signals by ^{1}H and ^{13}C NMR (Scheme 2.7). In the ^{1}H NMR spectrum, we observed four CH_2 signals for the protons on the

cyclohexene ring, and three CH_3 signals for the pentamethylphenyl motif. Notably no alkene CH signals were observed by ^1H NMR, which was suggestive that the product was a tetrasubstituted alkene. By ^{13}C NMR, we observed a carbonyl peak at 204 ppm, two alkene carbon signals at approximately 140 ppm and 130 ppm, which corresponded to the tetrasubstituted enone, four aromatic carbon signals from Ph*, and four CH_2 signals for the aliphatic carbons on the cyclohexene core.



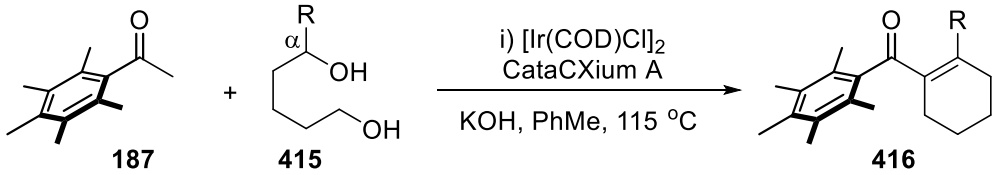
Scheme 2.7: Characterisation of tetrasubstituted enone products by ^1H and ^{13}C NMR.

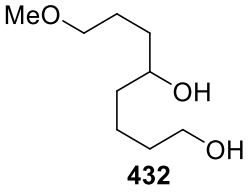
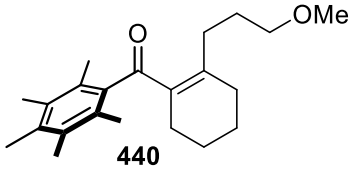
We then investigated the functional group tolerance of the reaction. Diols **432**-**439** bearing a functional group in the α-position were prepared previously by Dr R. J. Armstrong by the addition of the appropriate Grignard reagent to tetrahydro-2H-pyran-2-ol. By a similar route, the synthesis of diols bearing a nitrogen in the sidechain was also investigated (Scheme 2.8). To this end, 3-(3-bromopropyl)pyridine **426** was prepared by an Appel reaction and isolated in 72% yield. However, polymerisation was observed when we attempted to form the Grignard reagent to make diol **428**. This approach was also investigated with 4-(3-hydroxypropyl)morpholine **429**, which was brominated in 55% yield. **430** afforded diol **431** in 28% yield, but could not be isolated in sufficient purity to use in the annulation reaction.



Scheme 2.8: Attempted synthesis of diols bearing a nitrogen heteroatom in the side chain. Conditions: i) CBr4 (1.1 eq.), PPh_3 (1.1 eq.), alcohol (1 eq.), CH_2Cl_2 (0.5 M), 0 °C to RT, 24 h. ii) Mg turnings (5 eq.), bromide (3 eq.), THF (0.1 M), reflux, *then* lactol (1 eq.), 0 °C to RT, 2 h.

Upon subjecting diols **432**-**439** to our optimised conditions, we were delighted to find that cyclohexenes bearing ether **440**, thioether **441**, acetal **442**, furan **443**, trifluoromethyl **444** and benzyl **445** functional groups were all isolated in high yields without any side-products (Table 2.14). We were also pleased to find that α–phenyl diol **438** afforded cyclic chalcone **446** in 60% yield. With alkyne-bearing diol **439**, we observed complete decomposition of the starting material, suggesting that triple bonds were not tolerated in the reaction.



Entry	Diol[a]	Product	Yield (%)[b]
1	 432	 440	78

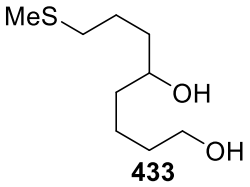
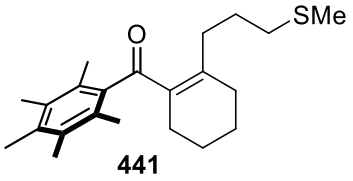
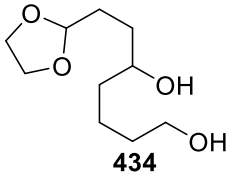
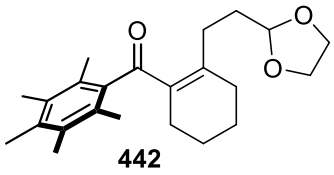
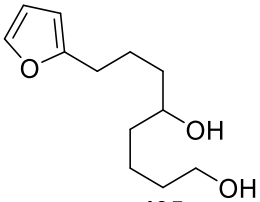
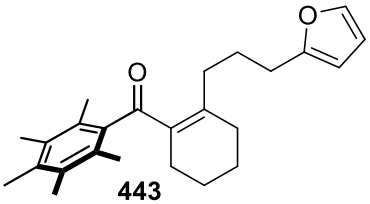
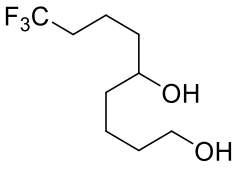
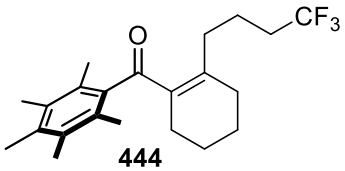
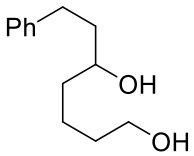
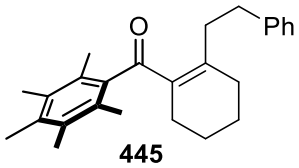
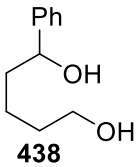
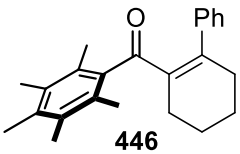
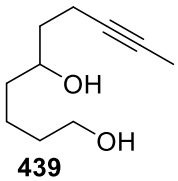
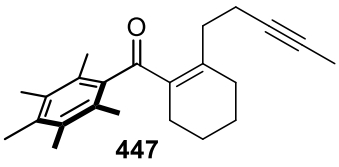
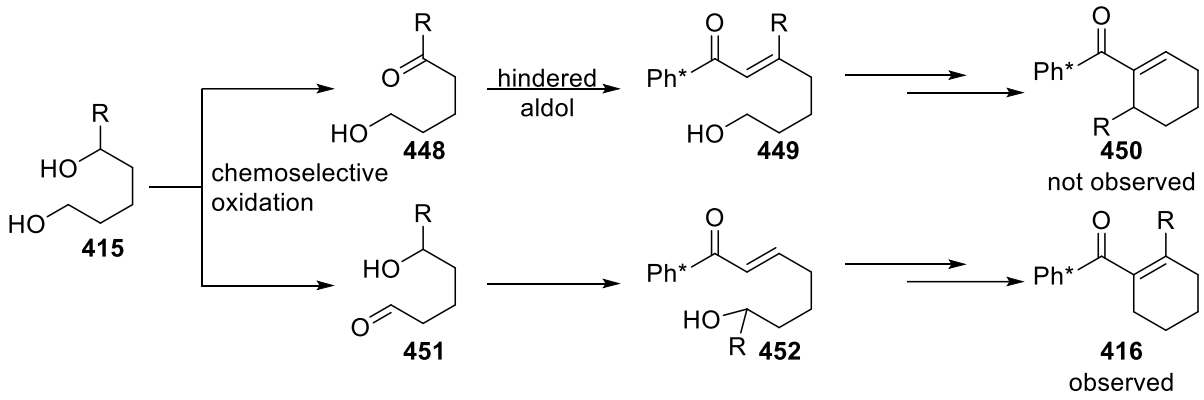
2	 **433**	 **441**	99
3	 **434**	 **442**	85
4	 **435**	 **443**	87
5	 **436**	 **444**	88
6	 **437**	 **445**	86
7	 **438**	 **446**	60
8	 **439**	 **447**	0

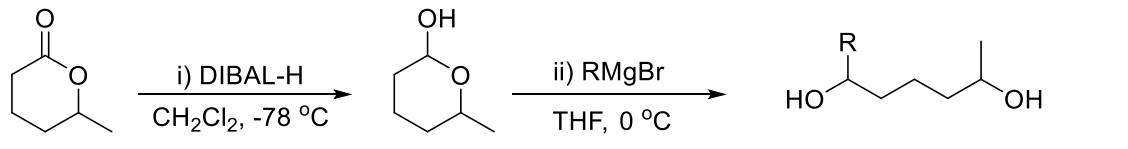
Table 2.14: Functional group tolerance of α-substituent. Conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (a) Diols were prepared previously by Dr R. J. Armstrong. (b) Yield refers to isolated material after column chromatography.

Notably, 1,2-disubstituted cyclohexene product **416** was formed as a single regioisomer in every case, and no 1,6-disubstituted cyclohexene **450** was observed (Scheme 2.9). This implied that the first C-C bond formed in the annulation occurred exclusively with the primary alcohol and not the secondary alcohol. We speculated this exquisite chemoselectivity could arise from selective oxidation by iridium to give aldehyde **451**, which may be sensitive to the steric environment of the alcohol. Alternatively, if the oxidation was partially selective or reversible, the initial aldol reaction could also dictate the regioselectivity, as one would expect an aldehyde to react significantly faster than a ketone with the hindered Ph* ketone enolate. In fact, our later results strongly supported the latter explanation (see Chapter 4).



Scheme 2.9: Rationalisation of the chemoselectivity observed with α-substituted diols.

Given that the reaction was chemoselective for primary alcohols versus secondary alcohols, we wanted to investigate the regioselectivity for a diol with two α-substituents, which would give a 1,2,6-trisubstituted cyclohexene. To accomplish this, diols **455**-**457** were prepared in a two-step sequence, by DIBAL-H reduction of commercial lactone **453** to lactol **454** in 86% yield, followed by the addition of a commercial Grignard reagent (Scheme 2.10). By this method, methyl, isopropyl and phenyl substituents were introduced to give diols **455**, **456** and **457** in 98%, 72% and 97% yield, respectively.

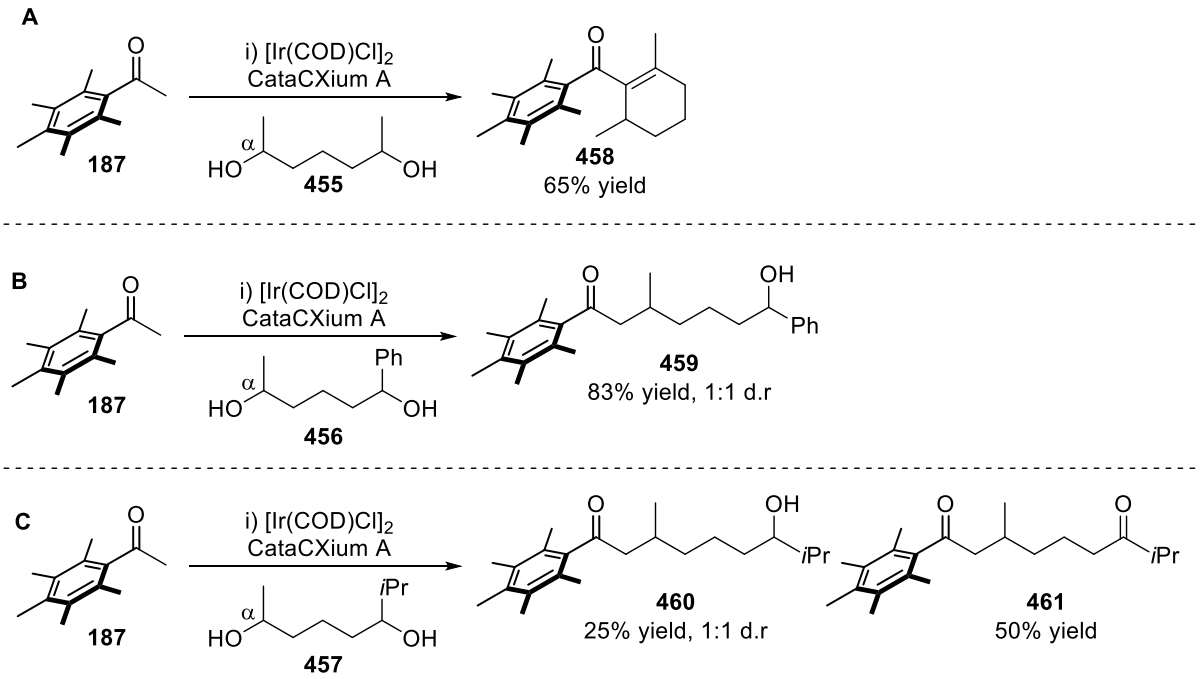


454 86% yield
3:2 anomeric mixture

455 R=Me, 98% yield*
456 R=Ph, 72% yield, 2:1 d.r
457 R=*i*Pr, 97% yield, 1:1 dr

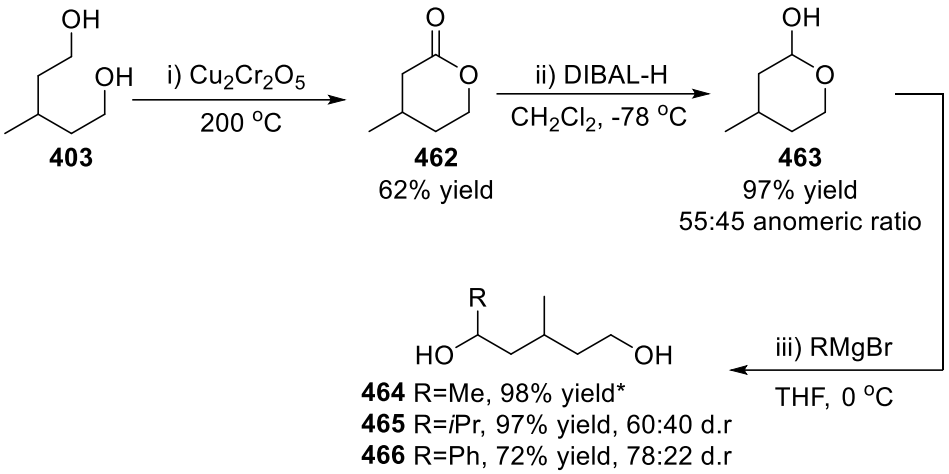
Scheme 2.10: Synthesis of 1,5-disubstituted pentane-1,5-diol. Reagents and Conditions: (i) DIBAL-H in hexanes (1.4 eq.), 5-hexanolide (1 eq.), CH_2Cl_2 (0.5 M), -78 °C, 2 h. (ii) RMgBr (3 eq.), 4-methyltetrahydro-*2H*-pyran-2-ol (1 eq.), THF (0.5 M), 0 °C to RT, 15 h. Diols formed as an inconsequential mixture of diastereomers, with the ratio determined by ^{1}H NMR. *The d.r for diol **455** could not be accurately determined by ^{1}H NMR.

With diols **455**-**457** in hand, we subjected them to the optimised reaction conditions. We were pleased to find that dimethyl diol **455** was well tolerated, giving 1,2,6-trisubstituted cyclohexene **458** in 65% yield (A, Scheme 2.11). We then subjected 1,5-phenyl,methyl diol **456** to the reaction conditions, but instead of forming a 1,2,6-trisubstituted cyclohexene, a single regioisomer of 1,7-hydroxy ketone **459** was isolated in 83% yield (B, Scheme 2.7). Similarly, 1,5-isopropyl methyl diol **457** afforded 1,7-hydroxy ketone **460** in 25% yield, and 1,7-dicarbonyl **461** in 50% yield (C). Given that diols **456** and **457** underwent the first C-C bond formation with the methyl-substituted alcohol, we inferred that the observed regioselectivity was dictated by the steric environment of the alcohol. Presumably for **459** and **460**, the bulky ketone renders the final ring closure unfavourable.



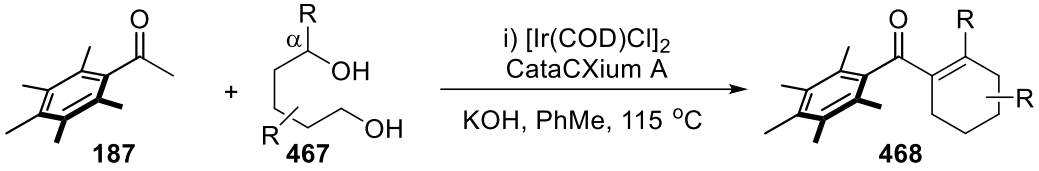
Scheme 2.11: Scope of α-disubstituted diol. Reagents and conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Yield refers to isolated material after column chromatography.

Having successfully prepared 1,2-disubstituted and 1,2,6-trisubstituted cyclohexenes, we were interested in synthesising further cyclohexene regioisomers bearing substituents in each position around the ring. To this end, commercial 3-methylpentane,1-5-diol **403** was oxidised with catalytic copper chromite to give lactone **462** in 62% yield (Scheme 2.12). Lactone **462** was then reduced with DIBAL-H to give the corresponding lactol **463** in 97% yield, to which the appropriate Grignard reagent was added. Using methyl, isopropyl and phenyl Grignard reagents, diols, **464**, **465** and **466** were prepared in 53% yield, 99% yield and 98% yield, respectively.



Scheme 2.12: Synthesis of 1,3-disubstituted pentane-1,5-diol. Reagents and Conditions: (i) diol (1 eq.), $Cu_2Cr_2O_5$ (2 mol%), 200 °C, 15 h. (ii) DIBAL-H in hexanes (1.4 eq.), 5-hexanolide (1 eq.), CH_2Cl_2 (0.5 M), -78 °C, 2 h. (iii) RMgBr (3 eq.), 4-methyltetrahydro-*2H*-pyran-2-ol (1 eq,), THF (0.5M), 0 °C to RT, 15 h. Diols formed as an inconsequential mixture of diastereomers, with the ratio determined by ^{1}H NMR. *The d.r for diol **464** could not be accurately determined by ^{1}H NMR.

With diols **464**-**466** in hand, as well as diols **469**-**472** prepared by Dr R. J. Armstrong in a similar manner, we evaluated these substrates using our optimised protocol (Table 2.15). We were delighted to find that α,γ-disubstituted diols **464**-**466** underwent the reaction to access the 1,2,4-trisubstituted cyclohexene in high yields. Additionally, 1,2,3-trisubstituted cyclohexene **476** was accessible in 87% yield, and also 1,2,5-trisubstituted cyclohexene **477** in 80% yield. We were also pleased find that using diol **471** bearing geminally disubstituted substituents enabled the synthesis of spirocyclic cyclohexene **478** in 70% yield. 1,2,4 trisubstituted cyclohexene **479** bearing a phenyl group was also accessible in 70% yield. These cyclohexenes were characterised and their structures confirmed in an analogous way to Scheme 2.7.



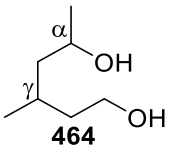
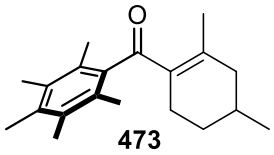
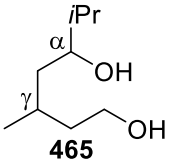
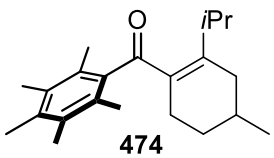
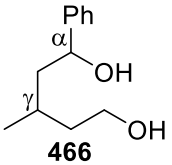
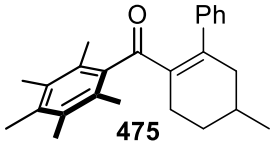
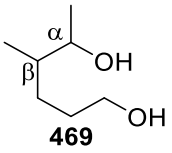
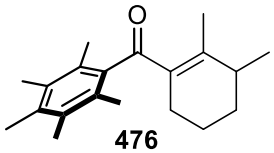
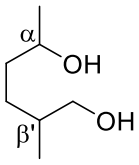
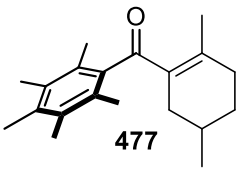
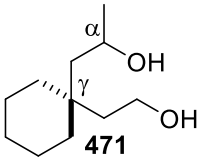
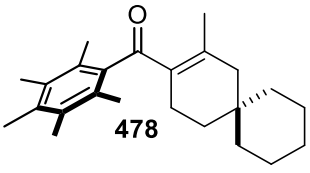
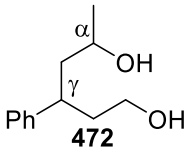
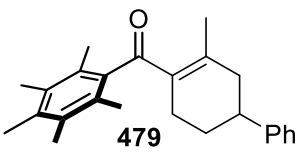
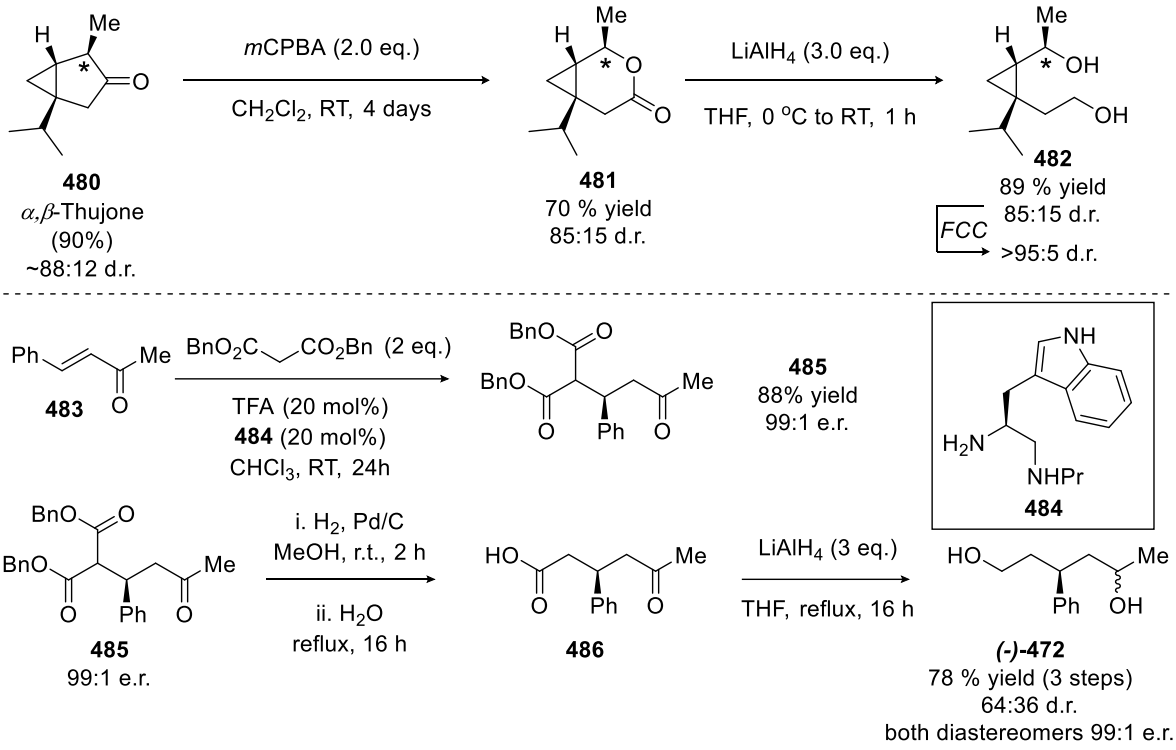
Entry	Diol	Product	Yield (%)[b]
1	 **464**	 **473**	94
2	 **465**	 **474**	70
3	 **466**	 **475**	70
4[a]	 **469**	 **476**	87
5[a]	 **470**	 **477**	80
6[a]	 **471**	 **478**	70
7[a]	 **472**	 **479**	70

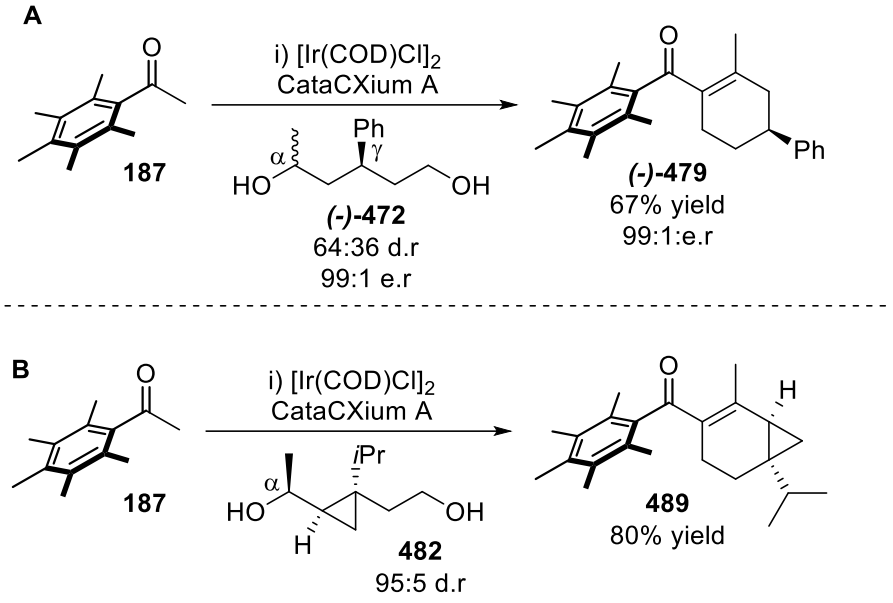
Table 2.15: Synthesis of multisubstituted cyclohexenes. Reagents and conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (a) Diols were prepared by Dr R. J. Armstrong. (b) Yield refers to isolated material after column chromatography.

Finally, we wished to demonstrate the utility of the protocol for the preparation of enantioenriched cyclohexenes. To investigate this, Dr R. J. Armstrong prepared enantioenriched diols **482** and ***(-)*-487** in a short sequence of steps (Scheme 2.13). First, α,β-thujone **480** was treated with mCPBA to afford the corresponding lactone **481** in 70% yield.[90] Lactone **481** was then reduced with $LiAlH_4$ in 89% yield and 85:15 d.r, which was improved to >95:5 d.r by flash column chromatography.[84] Similarly, enantioenriched diol ***(-)*-472** was prepared in three steps, starting with the asymmetric conjugate addition of dibenzyl malonate to benzalacetone **483**, which proceeded in 88% yield and 99:1 e.r.[91] Subsequently, tricarbonyl **485** was hydrolysed to diacid **486** on treatment with palladium on carbon and refluxing with water. The final step was reduction of diacid **486** to diol ***(-)*-472** in 78% yield, with the product obtained as an inconsequential mixture of diastereomers and greater than 99:1 e.r.[84]



Scheme 2.13: Preparation of enantioenriched diols **482** and ***(-)*-472**. Experiments performed by Dr. R. J. Armstrong.

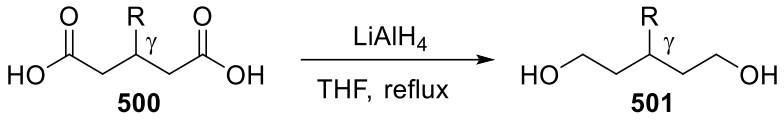
With enantioenriched diol (-)-**472** in hand, we subjected it to the optimised reaction conditions and pleasingly isolated *(-)*-cyclohexane **479** in 67% yield and 99:1 e.r, without stereochemical erosion. Similarly, when diol **482** derived from Thujone was subjected to the reaction conditions, we obtained the desired 1,2,3,4-tetrasusbsituted cyclohexene **489** in 80% yield, as a single diastereomer.



Scheme 2.14: Preparation of enantioenriched cyclohexenes. Conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Yield refers to isolated material after column chromatography.

2.3.2 Scope of Primary Diols

Having explored the scope of the reaction with α-substituted diols, we turned our attention to diols without α-substituents. As discussed previously, the trisubstituted cyclohexene products are much less hindered than the tetrasusbtituted enones products so far, and thus might be expected to reduce more easily. For this reason, we initially looked at diols with substituents in the γ-position, which most closely resemble the model substrate **403**. For example, diols **402**-**511** were conveniently prepared in one step by reduction of the corresponding commercial glutamic acid derivative. β-substituted diols **512**-**514** were also prepared by this method in good yields (Table 2.16).



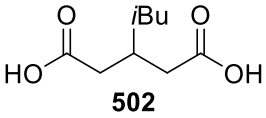
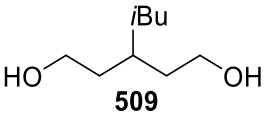
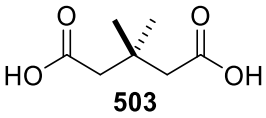
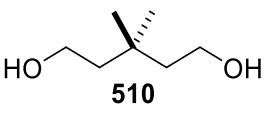
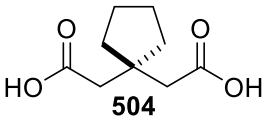
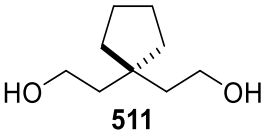
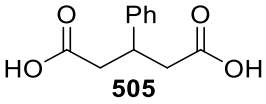
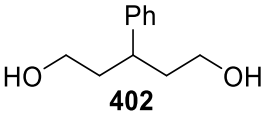
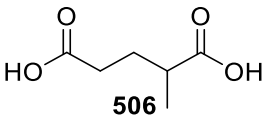
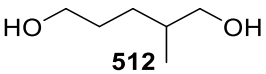
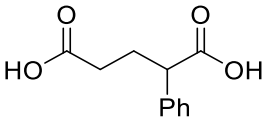
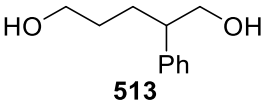
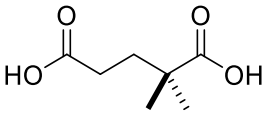
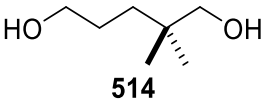
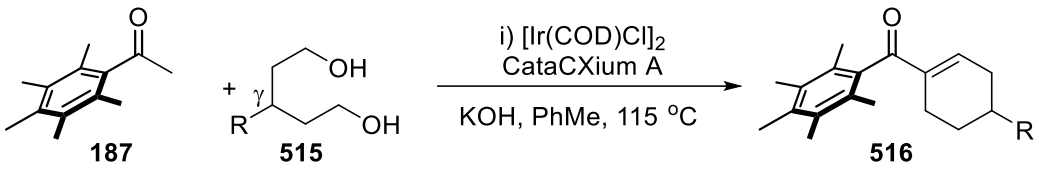
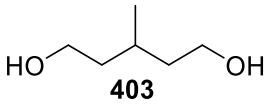
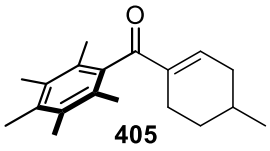
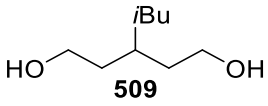
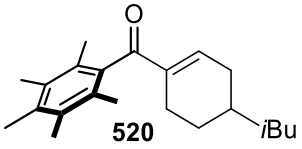
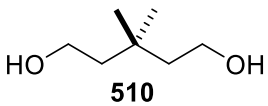
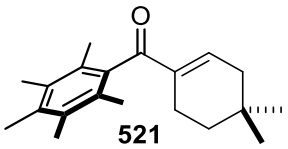
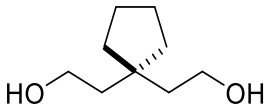
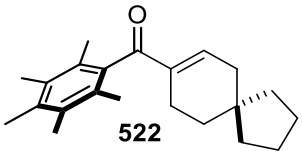
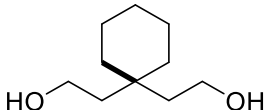
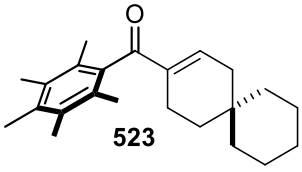
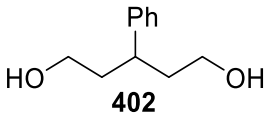
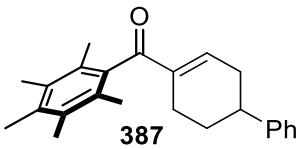
Entry	Di-acid	Diol	Yield (%)[a]
1	 **502**	 **509**	82
2	 **503**	 **510**	81
3	 **504**	 **511**	90
4	 **505**	 **402**	98
5	 **506**	 **512**	66
6	 **507**	 **513**	81
7	 **508**	 **514**	74

Table 2.16: Synthesis of γ- and β-substituted diols by reduction. Reagents and conditions: Diol (1 eq.), $LiAlH_4$ (3 eq.), THF (0.2 M), reflux, 15 h. (a) Yield refers to isolated material after column chromatography.

When the γ-substituted diols were subjected to the optimised conditions, we were delighted to find that they were also highly selective for cyclohexenes over cyclohexanes (Table 2.17). Alkyl substitution was well tolerated, giving methyl-, and isobutyl-substituted cyclohexenes **405** and **520** in 84% and 70% yield, respectively. Disubstituted and spirocyclic cylohexenes **521**-**523** could be accessed in excellent yields. In addition, arylated cyclohexenes **387** and **524**-**526**, bearing C-F and C-Cl bonds were well

tolerated. When CF_3-bearing diol **519** was evaluated, we found the desired cyclohexene formed in 42% yield. Interestingly, compounds **524**, **525** and **526** existed as rotameric mixtures, presumably due to restricted rotation about the Ar-C(O) axis. This was confirmed by variable temperature NMR spectroscopy of **524**, where we observed coalescence of the ^{1}H and ^{13}C NMR signals associated with the Ph* group above 80 ^{o}C.



Entry	Diol	Cyclohexane	Yield (%)[b]
1	 **403**	 **405**	84
2	 **509**	 **520**	70
3	 **510**	 **521**	96
4	 **511**	 **522**	94
5[a]	 **515**	 **523**	74
6	 **402**	 **387**	70

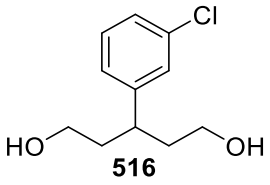
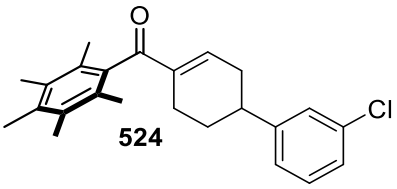
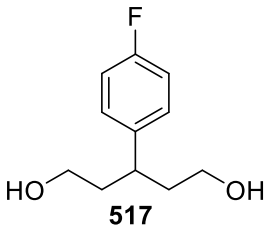
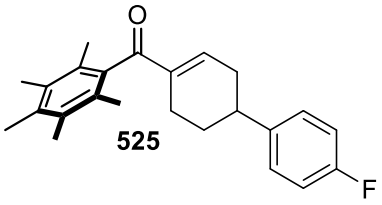
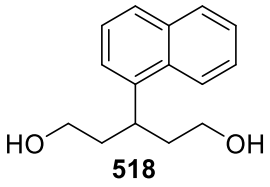
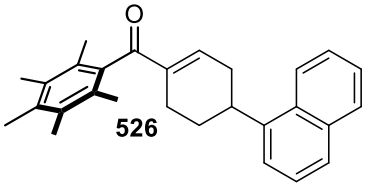
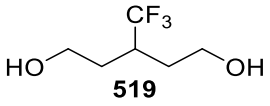
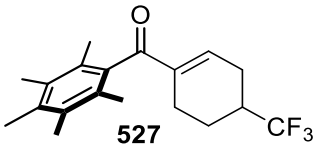
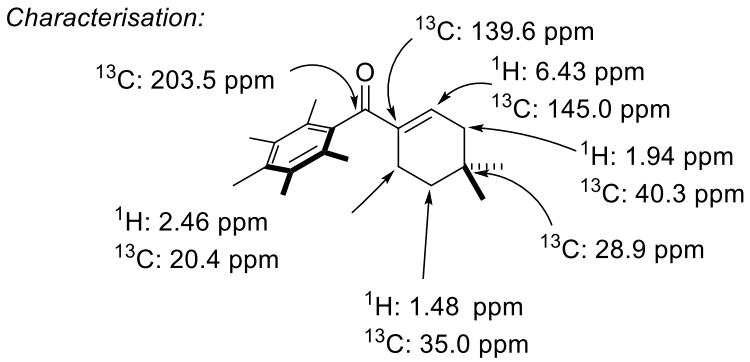
7[a]	 **516**	 **524**	87
8[a]	 **517**	 **525**	42
9[a]	 **518**	 **526**	51
10[a]	 **519**	 **527**	42

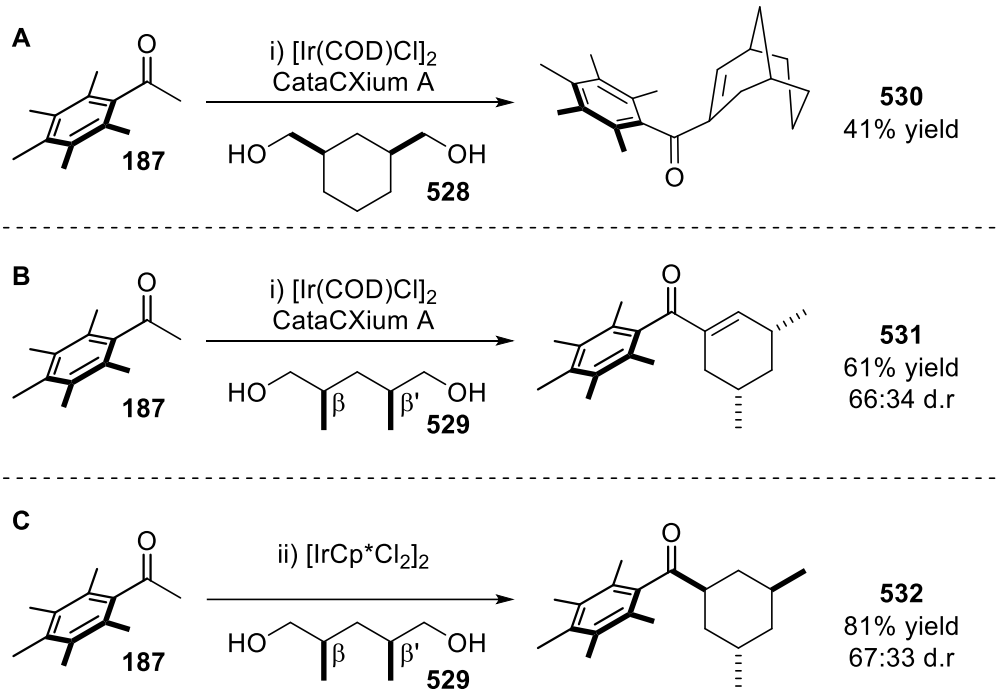
Table 2.17: Synthesis of γ-substituted cyclohexenes. Reagents and conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (a) Diols were prepared by Dr R. J. Armstrong.[84] (b) Yield refers to isolated material after column chromatography.

In each case, the structures of cyclohexenes **387**-**527** were characterised by a combination of ^{1}H and ^{13}C NMR (Scheme 2.15). Taking cyclohexene **521** as an example, we observed diagnostic signals for the characteristic enone CH at 6.43 ppm by ^{1}H NMR, alongside three CH_2 signals for the cyclohexyl ring. By ^{13}C, we observed two alkene carbons at 145.0 ppm and 139.6 ppm, alongside a carbonyl peak at 203.5, which unambiguously confirmed that we had formed a trisubstituted enone.

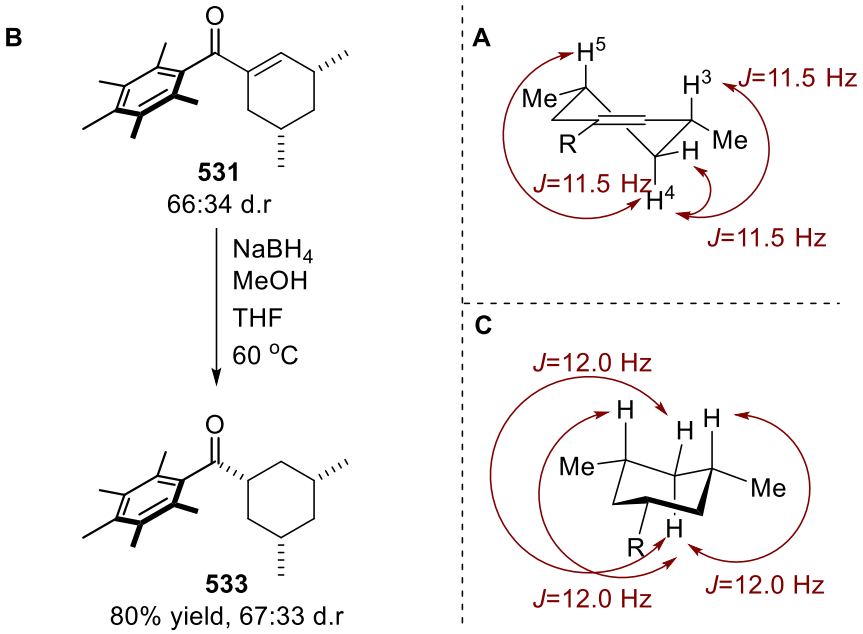


Scheme 2.15: Characterisation of trisubstituted enone product **521** by ^{1}H and ^{13}C NMR.

Having explored diols with γ-substituents, we next looked at symmetrical diols with two β-substituents. Diols **528** and **529** were prepared previously by Dr J. R. Frost and Dr W. M. Akhtar by reduction of the corresponding dicarbonyl with $LiAlH_4$.[84] We were pleased to find that *syn*-diol **528** enabled access to challenging bicyclic cyclohexene **530** in 41% yield (Scheme 2.17, A). Syn-β,β'-dimethyl diol **529** afforded the desired cyclohexene **531** in 61% yield, with moderate diastereoselectivity towards the *cis* isomer (B). Interestingly, the major diastereomer formed in this reaction possessed the opposite relative stereochemistry to C_2-symmetric cyclohexane **532**, which was formed in the previous methodology (C). In our case, diastereomer **531** would be expected to be the thermodynamic product, with both methyl groups occupying equatorial or pseudo-equatorial positions. We propose that formation of the thermodynamic product is possible *via* epimerisation through the extended enolate. The relative stereochemistry of the major cyclohexene **531** was determined by analysis of *J*-coupling constants (Scheme 2.18). The key piece of data was a large quartet for H_4, which was consistent with a large geminal coupling (J = 11.5 Hz), and two pseudo axial couplings (J = 11.5 Hz). This indicated that both methyl groups were in equatorial or pseudo-equatorial environments. This was further corroborated by reduction of cyclohexene **531** to *meso*-cyclohexane **533**, and comparing the ^{1}H and ^{13}C NMR data with that reported by our own group. Notably, the major diastereomer of **533** displays a single set of ^{1}H and ^{13}C signals for the two methyl groups, which is consistent with meso diastereomer.

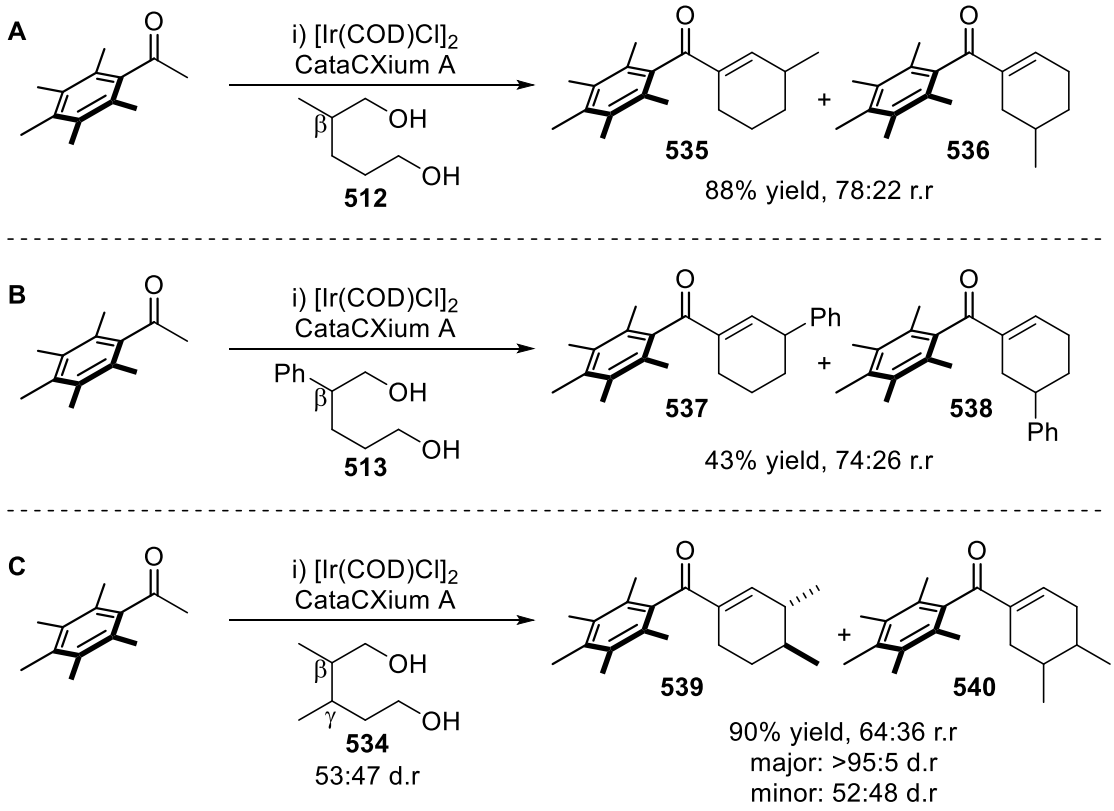


Scheme 2.17: Synthesis of cyclohexenes from β,β'-susbstituted diols: Reagents and Conditions: (i) Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (ii) Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[IrCp^*Cl_2]_2$ (2 mol%), PhMe (4 M), 115 °C, 24 h. Diol **528** and **529** were prepared previously by Dr J. R. Frost and Dr W. M. Akhtar.[84] Experiment (C) performed by Dr W. M. Akhtar. Yield refers to isolated material after column chromatography.



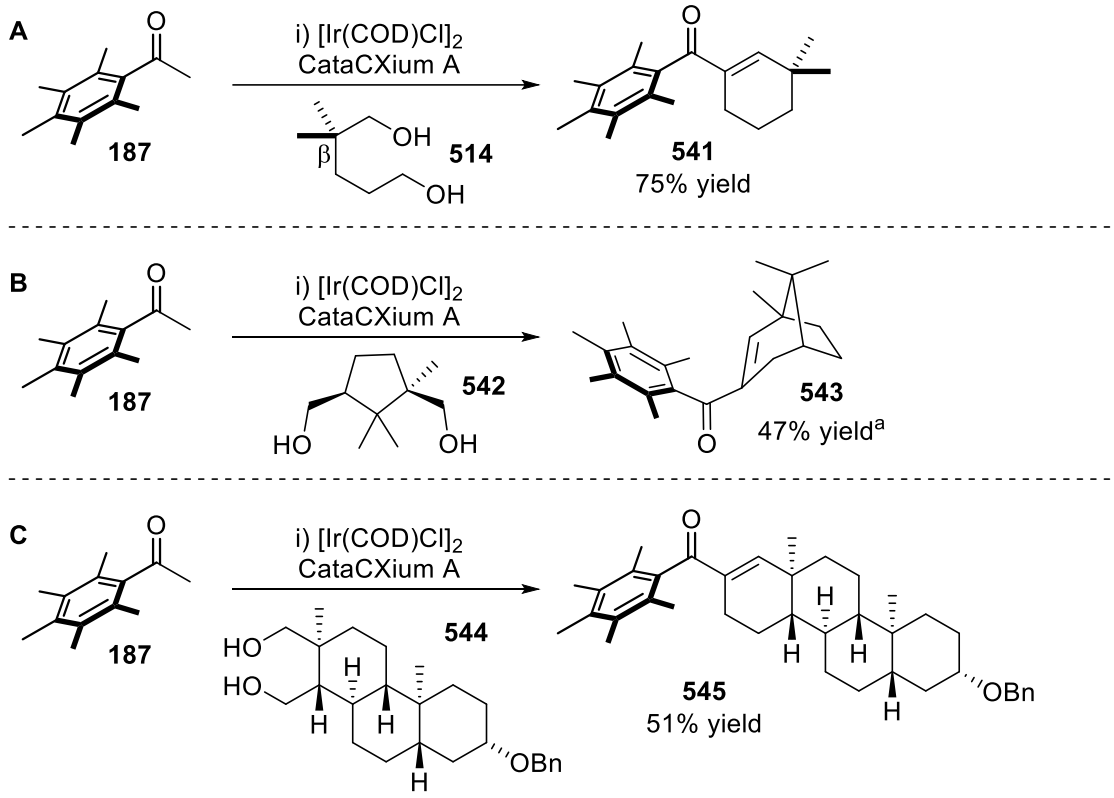
Scheme 2.18: Determination of stereochemistry of cyclohexene **531**. (A) *J*-coupling constant analysis of cyclohexene **531**. (B) By reduction of cyclohexene **531** to literature known cyclohexane **533**. (C) (A) *J*-coupling constant analysis of cyclohexane **533**. Reagents and conditions: **531** (1 eq.), $NaBH_4$ (10 eq.), 3:1 THF/MeOH (0.07 M), 60 °C, 1 h.

We then investigated non-symmetrical diols with a β-substituent (Scheme 2.19). By breaking the symmetry of the diol, we hoped these substrates might offer regioselectivity analogous to α-substituted diols, with the least hindered alcohol favoured for the initial C-C bond formation. We were pleased to find that this was the case, and diol **512** allowed access to cyclohexene **535** in 88% yield and 78:22 r.r. Similarly, phenyl-bearing diol **513** gave cyclohexene **537** in 43% yield and 74:26 r.r. When β,γ-disubstituted diol **534** prepared by Dr W. M. Akhtar was used, cyclohexene **539** was obtained in 90% yield with moderate regioselectivity.[84] The major regioisomer **539** was isolated with excellent diastereoselectivity, but the minor regioisomer **540** was isolated with 1:1 d.r. We believe this high diastereoselection was due to epimerisation *via* the extended enolate, while this epimerisation could not occur for the minor regioisomer, leading to a mixture of diastereomers.



Scheme 2.19: Synthesis of cyclohexenes from β-substituted diols: Reagents and Conditions: (i) Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Diol **534** was prepared previously by Dr W. M. Atkhar.[84]

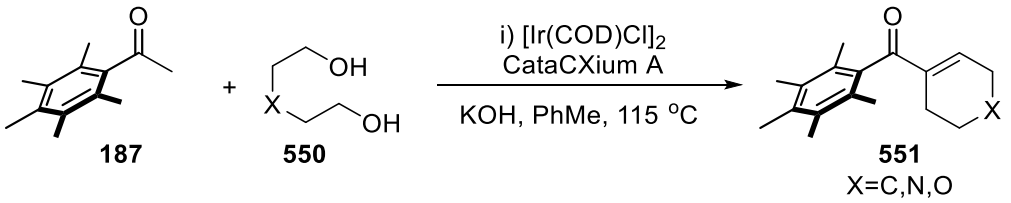
To probe this regioselectivity further, we investigated the use of diols with sterically encumbered β-substituents (Scheme 2.20). Encouragingly, dimethyl diol **514** afforded a single regioisomer of cyclohexene **541** in 75% yield. Given that dimethyl substituents offered complete regiocontrol, we evaluated diol **542** derived from Camphoric acid and steroid derivative **544**, which were both prepared previously by Dr R. J. Armstrong by $LiAlH_4$ reduction.[84,119] We were delighted to find that both of these examples gave single regioisomers in good yields.



Scheme 2.20: Synthesis of cyclohexenes from β-susbstituted diols: Reagents and Conditions: (i) Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Diols **542** and **544** were prepared by Dr R. J. Armstrong. (a) isolated as a 1:1 mixture with Ph*C(O)Me. Experiment (C) was conducted by Dr R. J. Armstrong.

2.3.3 Further Substrate Scope

Having explored a range of substituted diols, we wondered whether the reaction would tolerate unsubstituted diol **357** and diols with hetereoatoms in the backbone (Table 2.18). Subjecting 1,5-pentane diol to the reaction afforded the desired unsubstituted cyclohexane **358**, but in only 10% yield. This surprisingly poor yield could be due to the diminished Thorpe-Ingold effect driving the intramolecular aldol condensation. In addition, commercial heteroatom substituted diols **552**-**557** all returned unreacted Ph*C(O)Me, while the diol was consumed. This was presumably due to instability of the diol or corresponding hydroxy-aldehyde under the reaction conditions.



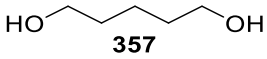
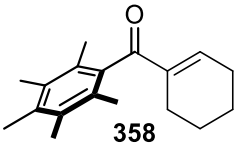
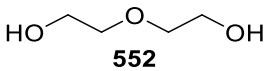
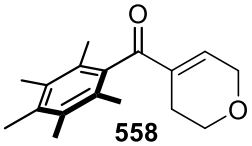
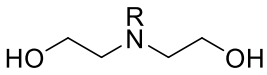
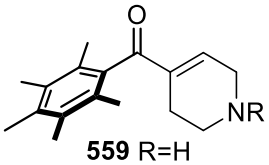
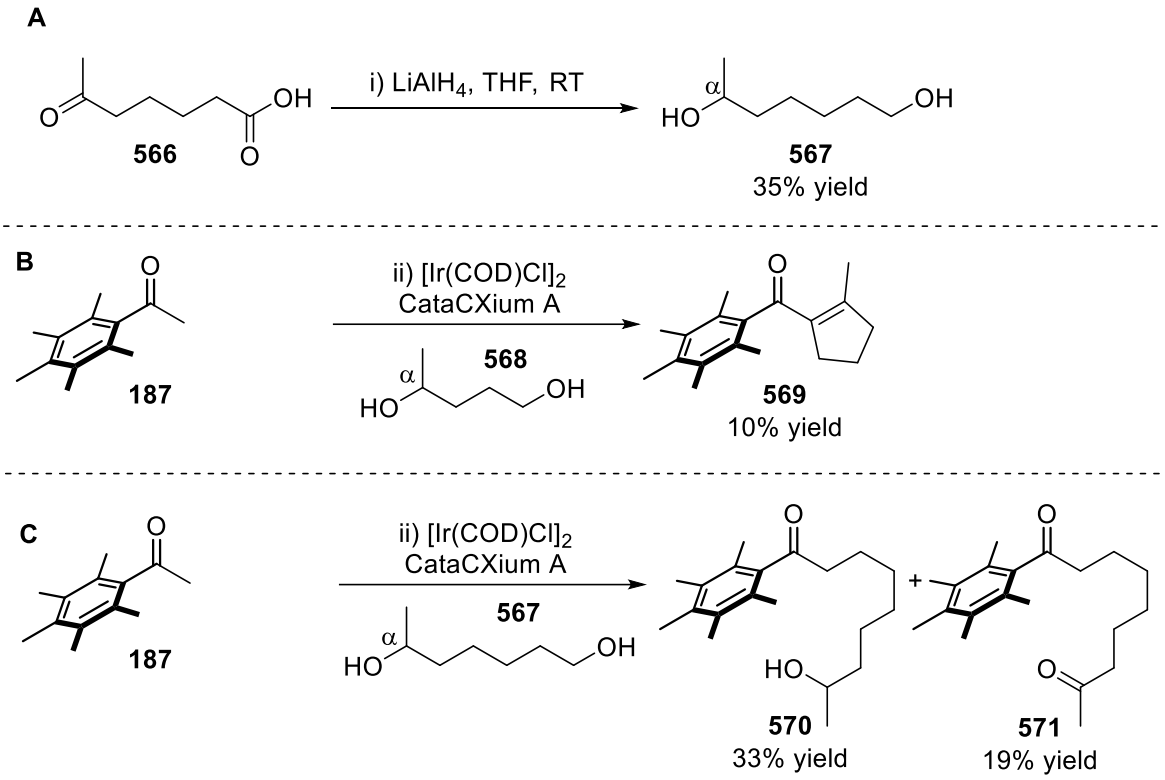
Entry	Diol	Product	Yield (%)[a]
1	 **357**	 **358**	10
2	 **552**	 **558**	0
3	 **553** R=H **554** R=Me **555** R=Bn **556** R=BOC **557** R=Ts	 **559** R=H **560** R=Me **561** R=Bn **562** R=BOC **563** R=Ts	0

Table 2.18: Synthesis of unsubstituted cyclohexenes. Reagents and conditions: Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (a) Yield refers to isolated material after column chromatography.

We also wanted to test the applicability of the reaction conditions to make other ring sizes. To explore this, 1,6-heptane diol **567** was prepared by reduction of the corresponding carboxylic acid **566**, while 1,4-pentane diol **568** was commercially available (Scheme 2.21, A). Diol **568** afforded the desired cyclopentene **569** in a significantly reduced yield, along with unreacted starting material. The

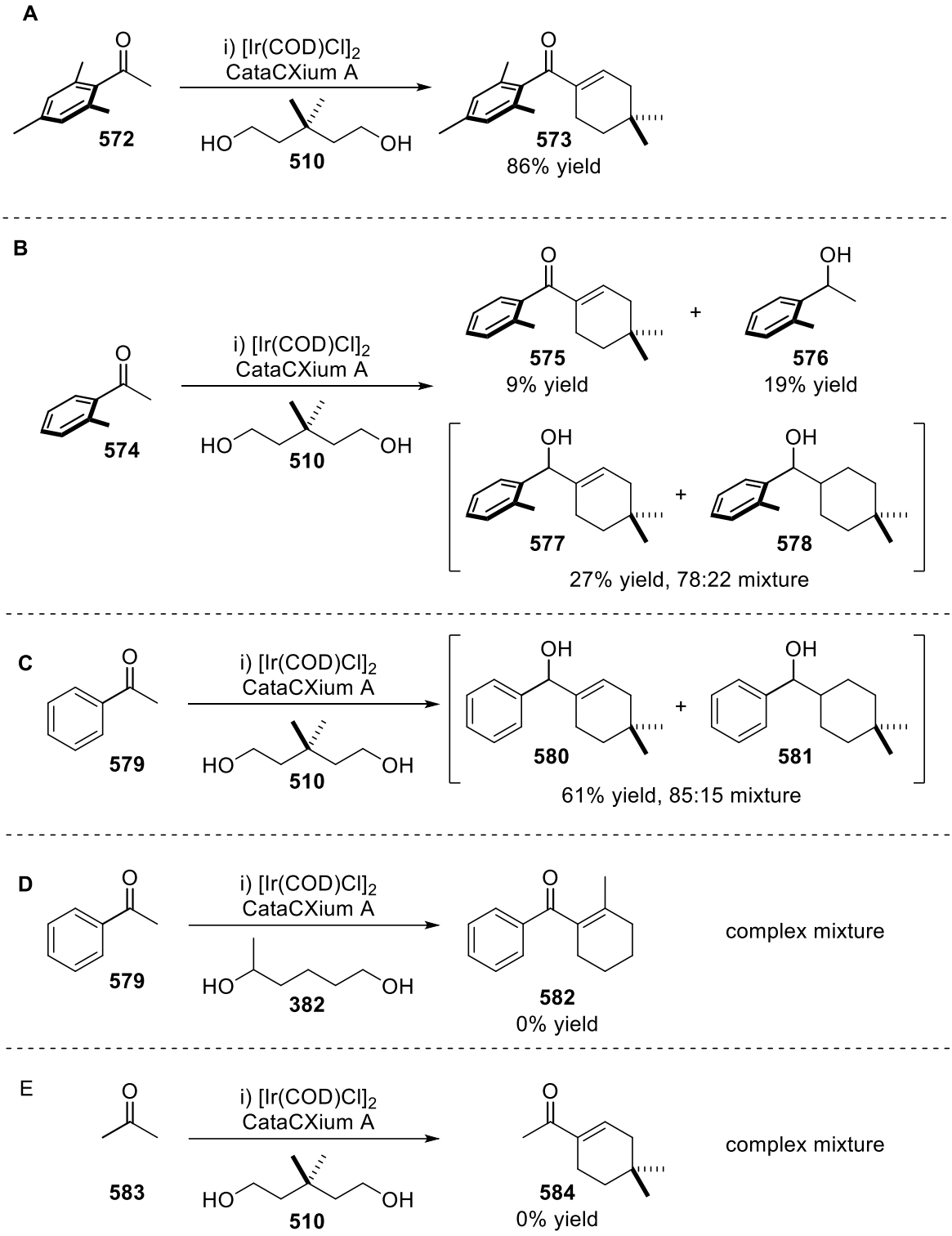
analogous reaction with 1,6-heptane diol **567** did not give any cycloheptene, but instead afforded a mixture of monoalkylated products **570** and **571**. These results suggested that the reaction was most efficient for the formation of six-membered rings, with increasing ring size making the final intramolecular aldol condensation unfavourable.



Scheme 2.21: Synthesis of cyclopentenes and cycloheptenes: Reagents and Conditions: (i) 6-Oxoheptanoic acid (1 eq.), $LiAlH_4$ (3 eq.), THF (0.2M), RT, 24h. (ii) Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h.

We also wanted to investigate the role of Ph* motif in this reaction. Firstly, we subjected mesityl ketone **572** to the optimised reaction conditions with γ-substituted diol **510**, which cleanly afforded cyclohexene **573** in 86% yield (Scheme 2.22, A). When we removed all but one methyl group with *o*-tolyl ketone **574**, the desired cyclohexene **575** was isolated in only 9% yield, along with 29% reduced starting material **576** and also a mixture of alcohol **578** and allylic alcohol **577** products in 27% yield (B). This effect was further pronounced with acetophenone **579** and diol **510**, as no cyclohexene product was observed, and only a mixture of reduced compounds **580** and **581** in 61% yield (C). Furthermore, when acetophenone **579** was used with α-substituted diol **382**, we obtained a complex mixture of cross aldol and homo aldol products (D). Removal of the aryl ring entirely, such as using

acetone **583** gave a complex mixture (E). These results suggest that the primary role of Ph* is to shield the carbonyl group from reduction, and also to promote the desired cross-aldol reaction over homo dimerisation.

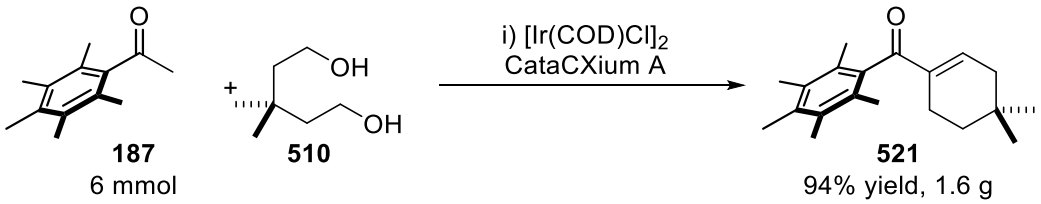


Scheme 2.22: Synthesis of cyclohexenes with other aryl groups: Reagents and Conditions: (i) ketone

(1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h.

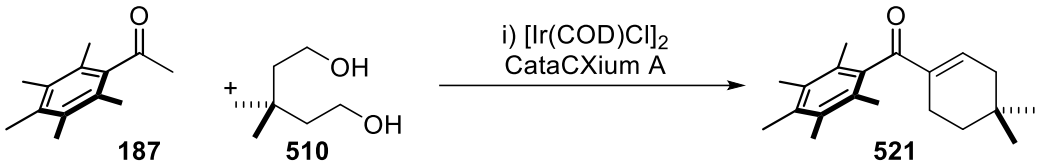
2.4 Product Derivatisation

Having developed a methodology that could produce a diverse range of acyl cyclohexenes, we wanted to explore the utility of these Ph* bearing products. To do this, we required large amounts of acyl cyclohexene products thus we investigated scaling up of the iridium-catalysed annulation (Scheme 2.23). We were delighted to find that by simply increasing the scale of the reaction 10-fold and using an ace pressure tube, we isolated 1.6 g of cyclohexene **521** in 94% yield (c.f 96% yield on 0.6 mmol scale in a microwave vial).



Scheme 2.23: Gram scale synthesis of cyclohexene **521**: Reagents and Conditions: (i) **187** (1 eq.), **510** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h.

Due to the high cost of iridium, we also wanted to investigate whether the catalyst loading could be lowered at larger scale, which would improve the overall cost and efficiency of the transformation (Table 2.19). Firstly, we tried lowering the catalyst loading at 0.6 mmol scale from 0.5 mol% dimer to 0.05 mol% for the preparation of cyclohexene **521** (Table 2.15). We found that this modification had no detrimental effect on conversion (Entries 1-2), while dropping the loading further significantly decreased the conversion (Entries 3-4). However, the drop in yield could be augmented at 0.05 mol% catalyst loading by increasing the reaction time to 48h, which enabled the isolation of cyclohexene **521** in 70% yield. Pleasingly, when we scaled up Entry 5 to 6.0 mmol scale, we isolated cyclohexene **521** in 86% yield (Entry 6).

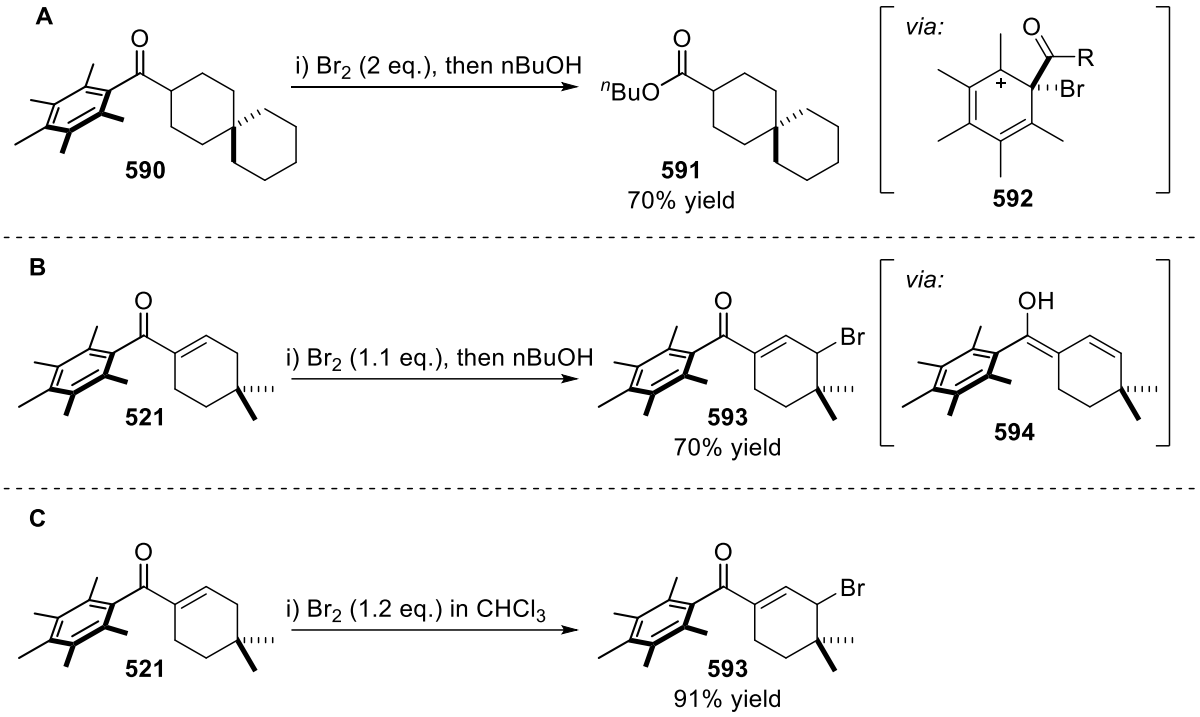


187 510 521

Entry	Catalyst loading (mol% dimer)	Reaction time (h)	Scale (mmol)	Yield **521** (%)[a]
1	0.5	24	0.6	(100) 96
2	0.25	24	0.6	(100)
3	0.1	24	0.6	(55)
4	0.05	24	0.6	(40)
5	0.1	48	0.6	(82) 70
6	0.1	48	6.0	86

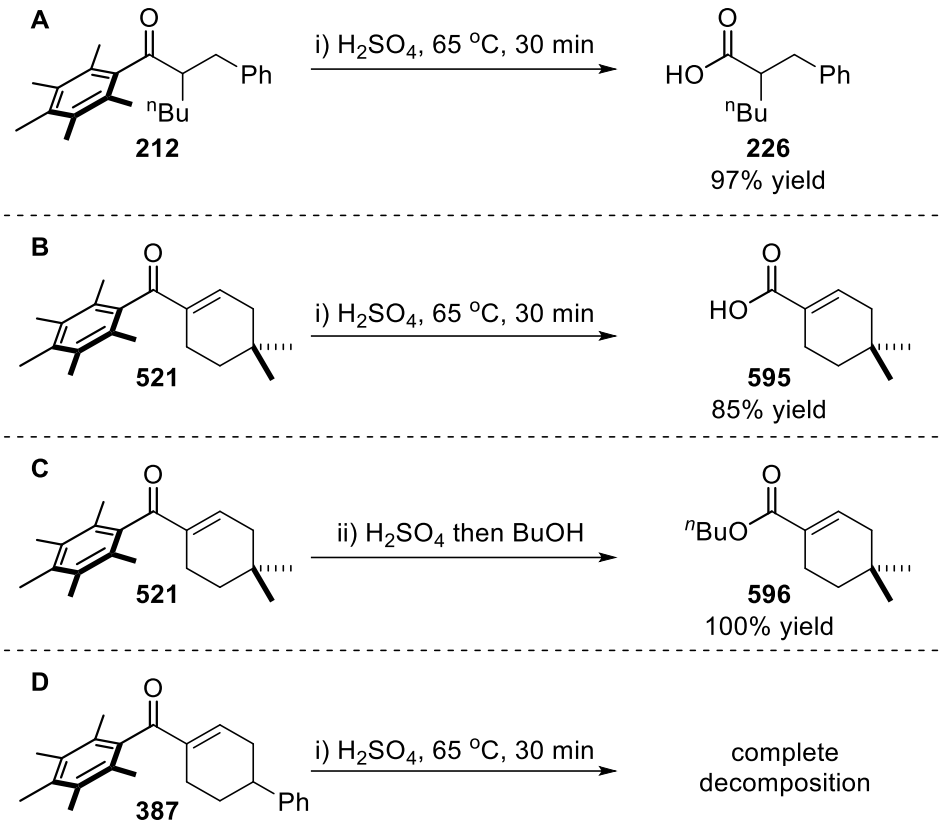
Table 2.19: Lowering the catalyst loading on gram scale synthesis of **521**. Reagents and conditions: Ph*COMe (1 eq.), **510** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.1-0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. (a) Yield refers to isolated material after column chromatography. NMR yields reported in parenthesis, determined by Q-^{1}H NMR with $CHCl_2CHCl_2$ as an internal standard.

With large quantities of **521** in hand, we wanted to demonstrate the synthetic utility of the acyl Ph* group on a cyclohexene ring. The first set of conditions we investigated utilised bromine, which had previously been used to perform an *ipso*-bromination and retro-Friedel Crafts, liberating Ph*-Br and an acylbromide (Scheme 2.24, A). While these conditions have previously been shown to be successful for a wide range of Ph* ketone substrates, in our case, the sequential addition of 1.2 equivalents of bromine and butanol to cyclohexene **521** did not result in the desired butyl ester (B). Instead, γ-brominated enone **593** was isolated in 70% yield, which could be increased to 91% yield by changing the solvent to $CHCl_3$ and removing the butanol (C). We speculate that this alternative product formed *via* electrophilic bromination of the enol tautomer **594** at the γ-position or *via* a radical pathway. For this reason, we turned our attention to Ph* cleavage conditions that did not use an electrophile that could react with the enone.



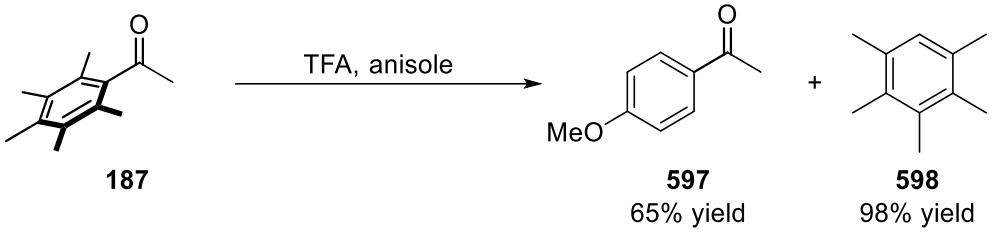
Scheme 2.24: Bromine initiated cleavage of Ph*. (A) Cleavage of cyclohexyl compound, by Dr W. M. Atkhar. (B) Attempted Ph* cleavage of cyclohexene **521**. (C) γ-bromination of cyclohexene **521**. Reagents and conditions: (i) Bromine (1.1-2 eq.), CH_2Cl_2, –17 °C, *then* BuOH (3 eq.), – 17 °C to RT. (ii) Bromine (1.2 eq.), $CHCl_3$, – 17 °C to RT.

We next investigated acid promoted cleavage of Ph* compound **521**. Analogous to bromine, we hoped that acid could carry out *ipso*-protonation of the electron rich aromatic ring, followed by subsequent collapse to afford an acylium ion, which would react with a nucleophile, such as water. Using literature conditions that utilised neat H_2SO_4 (Scheme 2.25, A), we were delighted to isolate carboxylic acid **595** in 85% yield (B). We also found that subsequent addition of butanol enabled an *in-situ* Fischer esterification to take place, affording the desired butyl ester **596** in 100% yield (C). While these conditions were excellent for cyclohexene **521**, H_2SO_4 was too harsh for aryl cyclohexene **387**, which underwent complete decomposition (D).

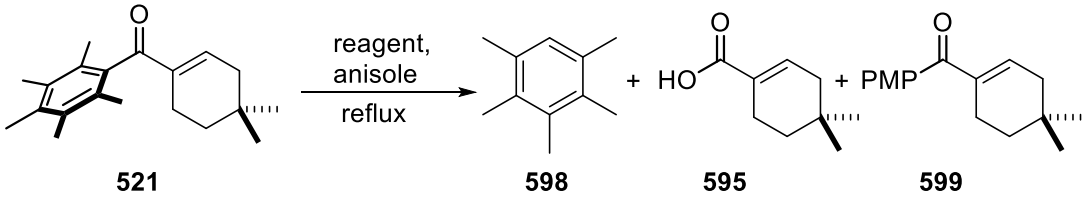


Scheme 2.25: H_2SO_4 initiated cleavage of Ph*. (A) Cleavage of branched Ph* compound **212** by Dr J. R. Frost. (B) Cleavage of **521** with HS_2O_4. (C) One-pot Ph* cleavage Fischer esterification of **521**. (D) Attempted cleavage of **387**. Reagents and conditions (i) H_2SO_4 (9.5 eq.), 65 °C, 30 min. (ii) H_2SO_4 (9.5 eq.), 65 °C, 30 min, then BuOH (0.175 M), 65 °C, 15 h.

Encouraged by these results using H_2SO_4, we looked to find alternative milder acidic conditions to cleave Ph* that would tolerate other functionality. We took inspiration from a transacylation reaction reported independently by Keumi and Olah, which used different acids and Lewis-acids to promote retro-Friedel crafts acylation of mesityl- and Ph* ketones (Scheme 2.26).[92,93] Based on this, we screened a representative range of acids and Lewis-acids in anisole (Table 2.21). While none of the reagents we tried (Entry 1-5) gave transacylated product **599**, we were pleased to find that triflic acid (Entry 1), promoted the deacylation of Ph*, forming carboxylic acid **595** along with pentamethylbenzene **598**. $ZnCl_2$ (Entry 3) and $AlCl_3$ (entry 4) caused decomposition of starting material. We were surprised to find that $Sc(OTf)_3$ and $FeCl_3$ also gave a 14% and 40% isolated yield of carboxylic acid **595**, respectively. It is likely that these results are due to the presence of adventitious water, which reacted with the Lewis-acid to generate H^+.



Scheme 2.26: Reported transacylation of Ph*COMe. Reagents and Conditions: Anisole (1 eq.), TFA (100 eq.), reflux, 20 h.

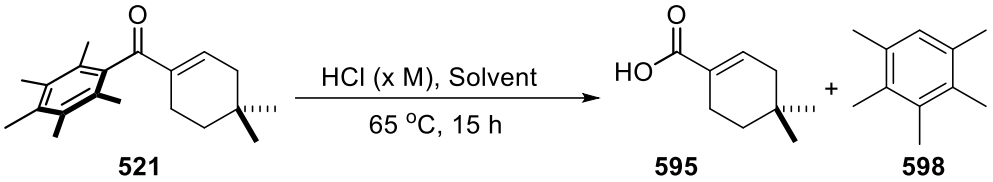


Entry	Lewis/Bronsted Acid	Yield of **598** (%)	Yield of **595** (%)	Yield of **599** (%)
1	Triflic acid	(80)	(10)	(0)
2	$Sc(OTf)_2$	(10)	(14)	(0)
3	$ZnCl_2$	(0)	(0)	(0)
4	$AlCl_3$	(0)	(0)	(0)
5	$FeCl_3$	70	40	(0)

Table 2.21: Attempted transacylation of **521** to **599**. Reagents and Conditions: **521** (1 eq., 0.1 mmol), Lewis/Bronsted Acid (1.2 eq.), anisole (3 eq.), 100 ^{o}C, 2 h. Yield refers to isolated material after column chromatography. NMR yield reported in parenthesis, determined by quantitative ^{1}H NMR with $CHCl_2CHCl_2$ as an internal standard.

Given that HCl with water could be an effective method to promote the deacylation of Ph*, we investigated the use of 37% aq. HCl diluted to 4 M solutions with a range of polar solvents (Entry 1-10, Table 2.22). We postulated that polar solvents would be beneficial for stabilising carbocation intermediate **592** upon *ipso*-protonation. Remarkably, HFIP (Entry 9) proved to be uniquely effective at promoting the reaction, giving a 99% yield of the desired carboxylic acid **595**. This unique reactivity in HFIP could be attributed to its high dielectric constant (ε = 15.7) and low nucleophilicity, which makes HFIP excellent for stabilising the acylium ion.[94] In addition to changing the solvent, the molarity of HCl in HFIP was also halved to 2 M, with no negative effective on yield (Entry 10) Notably, Ph*H **598** was also isolated in quantitative yield, which could be recycled to make more Ph*COMe. As a

testament to the importance of HFIP in the reaction, the formation of **595** was inhibited when HFIP was used with water as a co-solvent (Entry 11).

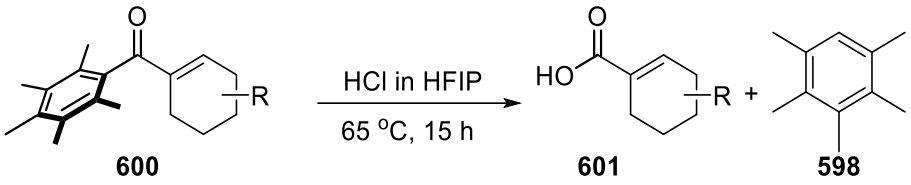


521 **595** **598**

Entry	Final [HCl]/M	Solvent (0.1 M)	Yield of **595** (%)	Yield of **598** (%)
1	4	MeCN	(0)	(0)
2	4	MeOH	(0)	(0)
3	4	DMF	(0)	(0)
4	4	DMSO	(0)	(0)
5	4	Acetone	(0)	(0)
6	4	EtOH	(0)	(0)
7	4	1,4-Dioxane	(0)	(0)
8	4	H_2O	(0)	(0)
9	4	HFIP	99	99
10	2	HFIP	100	100
11	4	80:20 HFIP/H_2O	(0)	(0)

Table 2.22: Optimisation of acid-promoted Ph* cleavage of **521**. Reagents and Conditions: **521** (1 eq., 0.1 M), solvent (0.1 M), 37% aq. HCl (2-4 M, molarity refers to final concentration after addition of stated solvent), 65 °C, 15 h. Yield refers to isolated material after column chromatography. NMR yield reported in parenthesis, determined by quantitative ^{1}H NMR with $CHCl_2CHCl_2$ as an internal standard.

With 2 M HCl in HFIP being highly efficient for the Ph* cleavage of **521**, we applied these conditions to several cyclohexenes with different substitution patterns and functional groups (Table 2.23). We were delighted to find that alkyl and aryl substituents in the 4-position were well tolerated (Entry 1, 2 and 3), contrary to using H_2SO_4. Cyclohexenes with substituents in the 2- and 3-position were also isolated in excellent yields (Entries 4, 5 and 6). We were also pleased to find that we could subject camphoric acid-derived cyclohexene **543** as an inseparable 1:1 mixture with Ph*COMe, and isolate the corresponding carboxylic acid cleanly in 98% yield (Entry 7). Presumably in this case Ph*COMe is converted into acetic acid, which is removed upon workup. In addition to carboxylic acid synthesis, Weinreb amide **608** was prepared in 75% yield by a one-pot Ph*cleavage and amide coupling using EDCI (Scheme 2.27).



600 601 598

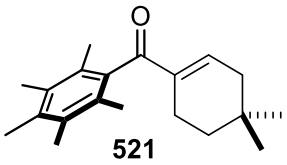
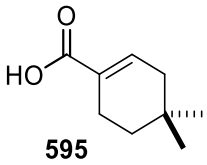
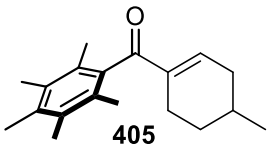
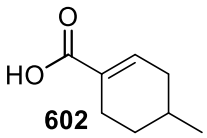
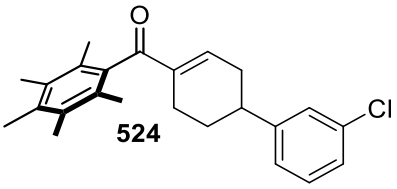
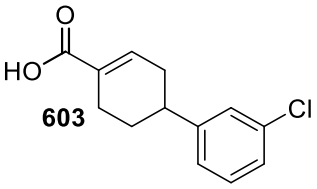
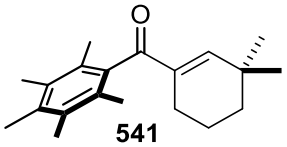
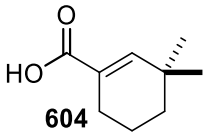
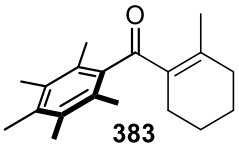
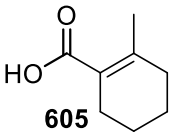
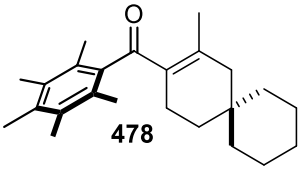
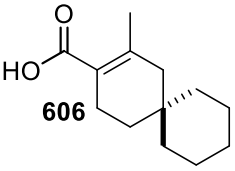
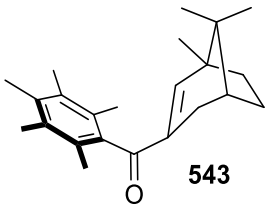
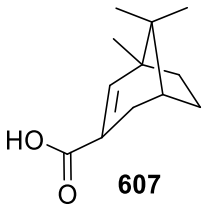
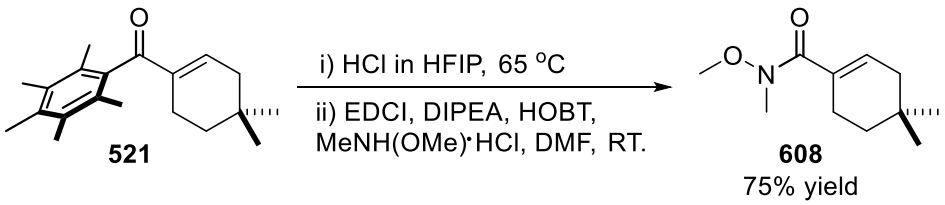
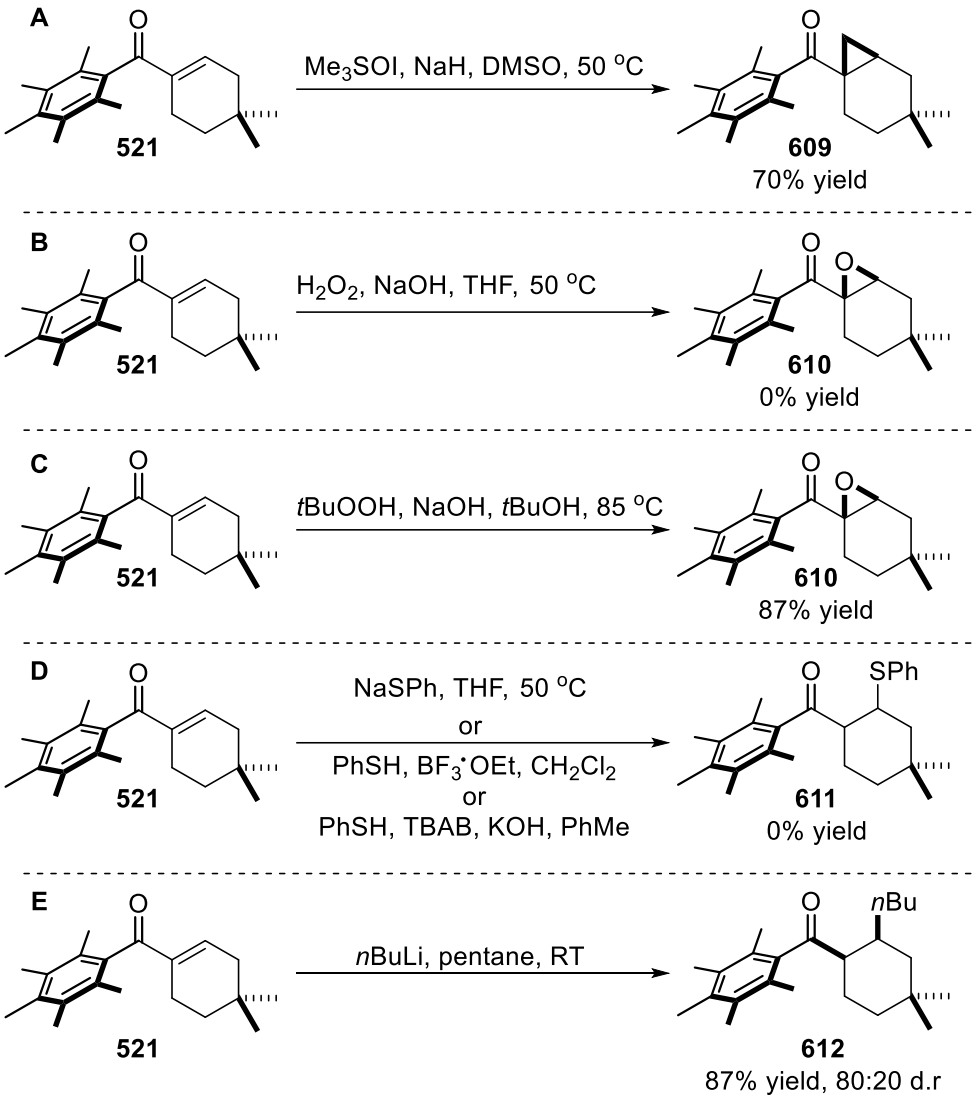
Entry	Starting Material	Product	Yield (%)
1	 521	 595	100
2	 405	 602	100
3	 524	 603	84
4	 541	 604	100
5	 383	 605	60
6	 478	 606	72
7	 543	 607	98

Table 2.23: Cleavage of Ph* ketone cyclohexenes. Reagents and Conditions: cyclohexene (1 eq., 0.1 mmol), 2 M HCl in HFIP (1 mL), 65 °C, 15 h. Yield refers to isolated material after column chromatography.



Scheme 2.27: One-pot preparation of amide **608**. Reagents and conditions: **521** (1 eq., 0.175 mmol), 2 M HCl in HFIP (1.75 mL), 65 °C, 15 h, then concentrate *in vacuo*, then EDCI (1.5 eq.), DIPEA (5 eq.), HOBT (1.5 eq.), MeNH(OMe)·HCl (1.5 eq.), DMF, RT, 15 h.

In addition to the bromination reaction described above, we also looked at 1,4-addition reactions to cyclohexene **521**. We were delighted to find that literature conditions for the Corey–Chaykovsky cyclopropanation cleanly afforded bicyclic aryl ketone **609** in 70% yield (Scheme 2.28, A). We also investigated Weitz–Scheffer epoxidation using NaOH, H_2O_2 and THF, but found no reaction occurred at room temperature, and heating above 50 °C resulted in the decomposition of hydrogen peroxide (B). Dr R. J. Armstrong found that this was remedied by switching to the more stable reagent *t*BuOOH, which enabled the isolation of epoxide **610** in 70% yield (C). Heteronucleophiles, such as thiophenol were also briefly investigated under several reaction conditions, but only starting material was recovered. Additionally, Dr R. J. Armstrong found that cyclohexene **521** underwent exclusive 1,4-addition with *n*BuLi to give **612** in 87% yield (E). 1,4-Addition reactions of organometallic reagents typically would necessitate the preparation of organocuprates to prevent 1,2-addition to the carbonyl. In our case, we attributed this unusual reactivity to the twisted nature of the Ph* group on cyclohexene **521**, which shields the carbonyl against direct 1,2-addition.



Scheme 2.28: Enone functionalisations of cyclohexene **521**. (A) Corey–Chaykovsky cyclopropanation. Reagents and Conditons: **521** (1 eq.), Me_3SOI (1.5 eq.), NaH (1.6 eq.), DMSO (0.35 M), 50 °C, 48 h. (B) Attempted Weitz–Scheffer epoxidation with H_2O_2. Reagents and Conditons: **521** (1 eq.), 30% aq. H_2O_2 (20 eq.), NaOH (6 eq.), THF (0.35 M), RT to 50 °C 2 h. (C) Weitz–Scheffer epoxidation with *t*BuOOH, performed by Dr. R. J. Armstrong. reagents and conditions: **521** (1 eq.), *t*BuOOH (5 eq.), NaOH (5 eq.), *t*BuOH (0.1 M), 85 °C, 1 h. (D) Attempted 1,4-addition of thiophenol. (E) 1,4-addition of *n*Buli, performed by Dr. R. J. Armstrong. Reagents and conditions: **521** (1 eq.), *n*BuLi (2 eq.), pentane, RT, 5 min, then 2,6-di-*tert*-butylphenol (4 eq.), RT.

2.5 Conclusion

We have developed an atom-economical methodology to prepare multisubstituted-cyclohexenes from pentamethylacetophenone and 1,5-pentane diols. This reaction was catalysed by $[Ir(COD)Cl]_2$ modified with the sterically bulky alkyl phosphine ligand CataCXium® A. This catalyst system promoted acceptorless dehydrogenation over 1,4-reduction of the desired acyl cyclohexene to the corresponding cyclohexane. The annulation was also enabled by the *ortho*-substituents of pentamethylacetophenone, which prevented self-condensation through homo-aldol reaction and undesired 1,2-reduction of the carbonyl.

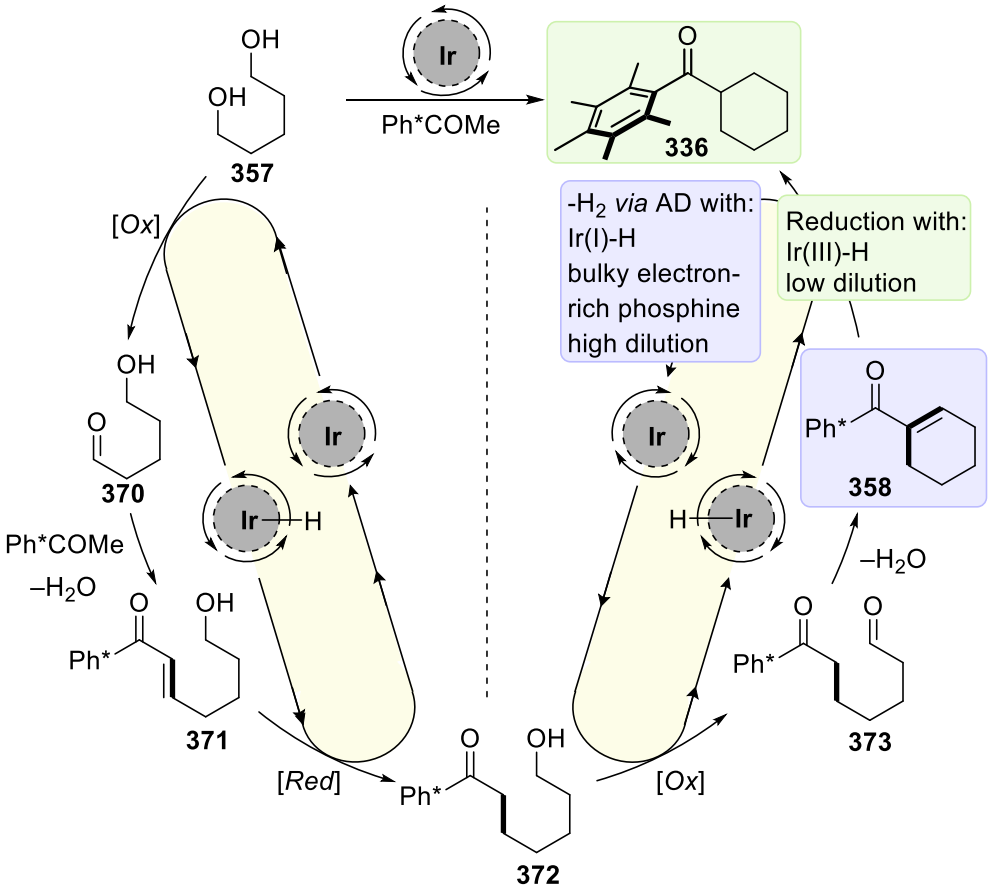
Following optimisation of the reaction, we explored the substrate scope of α- β- and γ-substituted diols, which enabled access to tetrasubstituted and trisubstituted exocyclic enones in uniformly high yields. α-Substituted diols reacted chemoselectively to afford 1,2-disusbtituted cyclohexenes over 1,6-cyclohexenes, dictated by selective initial C-C bond formation with the primary alcohol over the secondary alcohol. Regioselectivity was also seen for non-symmetrical β-substituted diols, with a preference for the least hindered alcohol in the initial C-C bond formation step. After exploring the synthesis of cyclohexenes, we looked at the preparation of other ring sizes, heterocycles, and aryl groups in place of Ph*. The reaction was also performed successfully on multigram scale.

With a general method for cyclohexene synthesis, we investigated derivatisation of the products. This was achieved by cleaving Ph* on a representative range of acyl cyclohexenes with 2M HCl in HFIP to give the corresponding carboxylic acid. To further demonstrate the versatility of Ph*, acidic cleavage conditions were also used to prepare butyl ester and Weinreb amide substituted cyclohexenes. Finally, we explored functionalisation of the Ph* enone motif, which included conjugate addition of carbon-nucleophiles, bromination, epoxidation and cyclopropanation.

Chapter 3: Mechanistic Investigations of the [5+1] Annulation.

3.1 Introduction

Having developed an efficient protocol for the synthesis of acyl-cyclohexenes, we set out to investigate the mechanism of this reaction. Our initial mechanistic proposal consisted of two catalytic cycles involving iridium: firstly, a hydrogen borrowing cycle, analogous to Scheme 2.1, which involved an initial oxidation of the diol to give hydroxyaldehyde **370** and Ir-H, subsequent aldol condensation and reduction of **371** to return the 'borrowed' hydrogen and give ketone **372**. The second cycle begins with oxidation of keto-alcohol **372** to dicarbonyl **373**, which undergoes an intramolecular aldol reaction to give cyclohexene **358**. In the presence of an Ir(III) catalyst, such as $[IrCp^*Cl_2]_2$, cyclohexene **358** is reduced by Iridium hydride to give cyclohexane **336**. In contrast, using an Ir(I) catalyst with a bulky electron rich ligand (such as cataCXium® A), the iridium hydride is protonated to recycle the catalyst and evolve hydrogen gas, which enables the isolation of cyclohexene **358**.

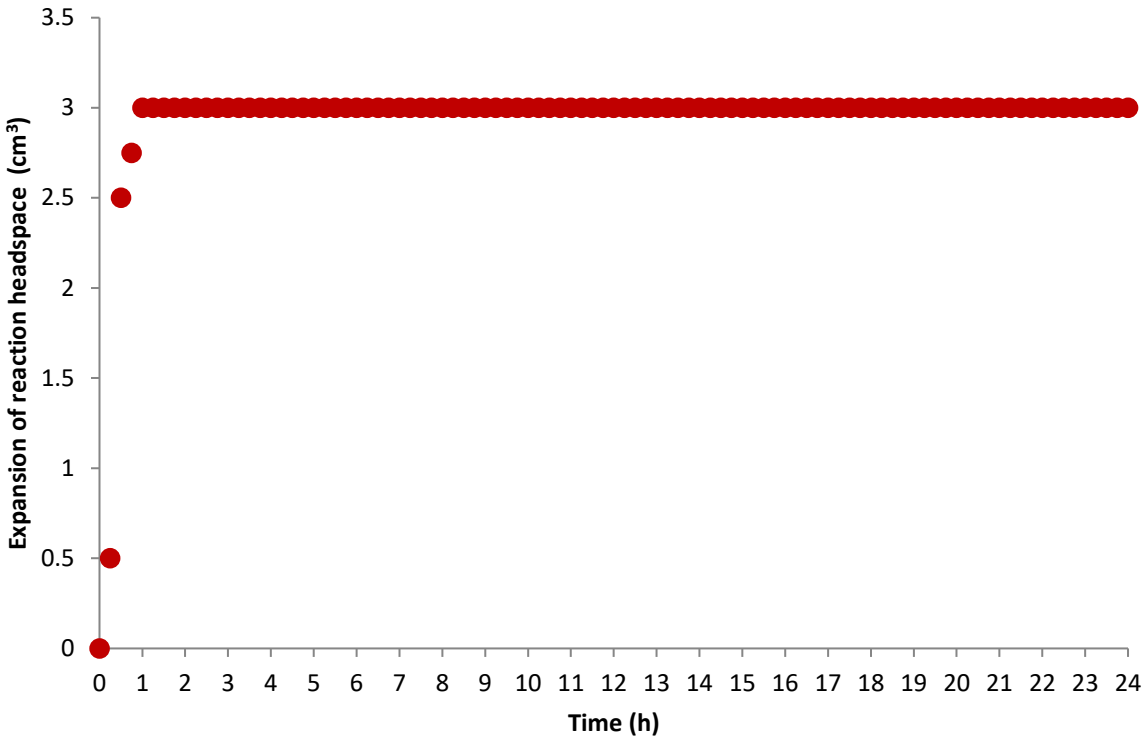


Scheme 3.1: Formation of cyclohexanes and cyclohexenes by the [5+1] annulation of Ph*COMe.

To validate our mechanistic hypothesis, we initially considered four approaches to probe the reaction mechanism. Firstly, we were interested in quantitatively measuring the evolution of hydrogen gas with time, which would be informative of whether acceptorless dehydrogenation fully accounted for the chemoselective reduction of enone **371**. Secondly, we looked to investigate the reaction profile with time, which could enable the observation of reaction intermediates, and the qualitative analysis of relative rates. Thirdly, we thought to synthesise key intermediates **370**-**373** and determine their competency under the reaction conditions. Finally, we wanted to perform the reaction with a deuterated diol and analyse the D-incorporation in the product, to confirm the oxidation of diol **357** and reduction of enone **371**.

3.2 Reaction profile for Acyl Cyclohexene Synthesis

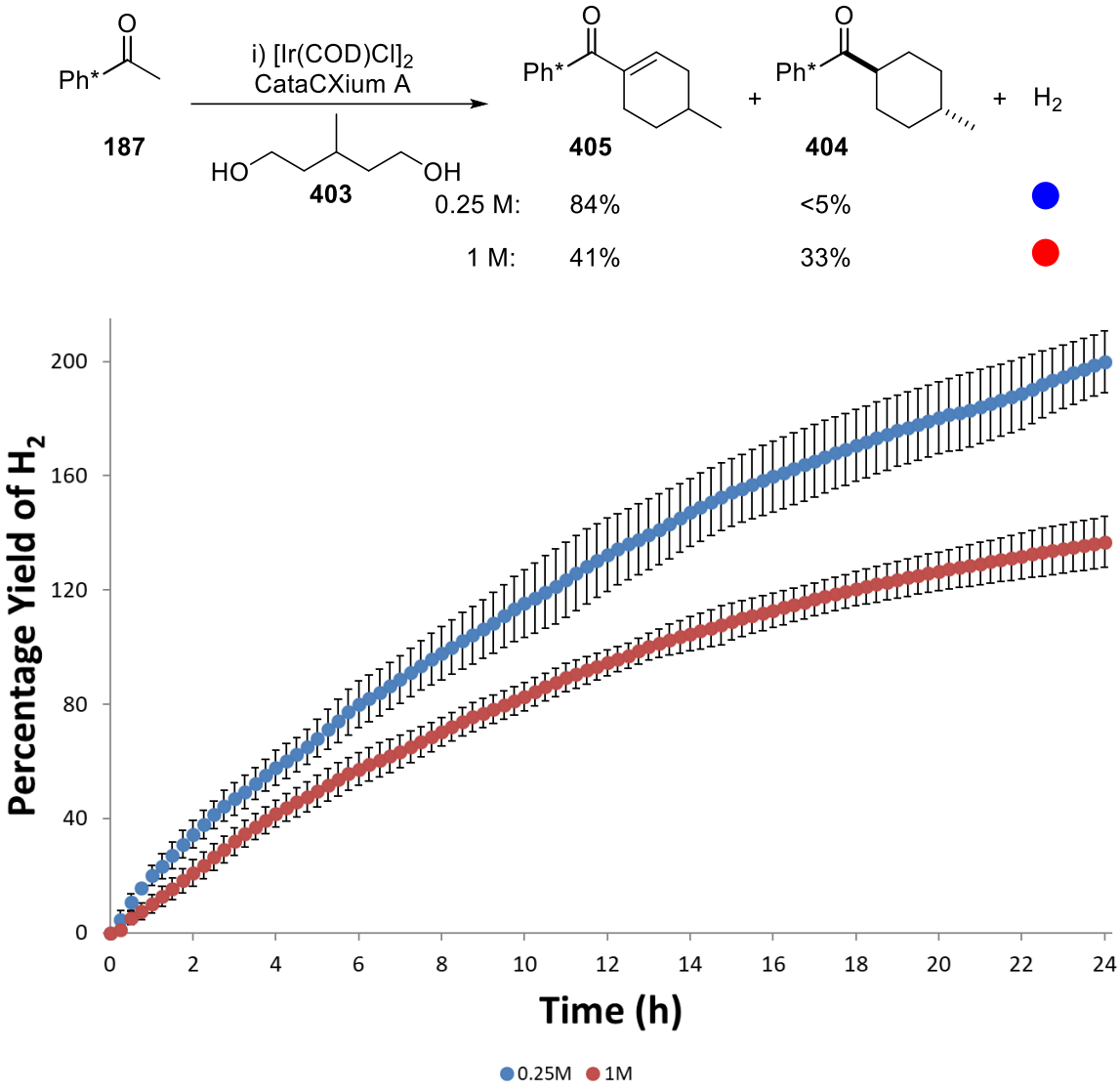
We began by looking to measure the evolution of hydrogen gas over the course of the reaction for evidence of an acceptorless dehydrogenation.[95] To accomplish this, we felt the most practical apparatus was to pierce the microwave vial septum with a narrow cannula and collect the hydrogen gas in an inverted measuring cylinder. With the help of Oxford Department of Chemistry IT, we borrowed a Canon EOS 30D camera fitted with Canon TC-80N3 Timer Remote Control, which was set to take photographs of the measuring cylinder every 15 minutes over 24 hours (for further details, see appendix). Furthermore, we recognised that heating toluene to 115 ^{o}C in a microwave vial would cause an increase in vapour pressure. To account for this, we heated toluene under the hydrogen evolution setup to measure the increase in volume. The observed expansion of the reaction headspace was complete within one hour, and amounted to approximately 3 mL of gas. This volume was deducted from all subsequent hydrogen evolution experiments (Graph 3.1).



Graph 3.1: Control experiment of heating toluene under the hydrogen evolution setup at 115 °C.

We then performed the optimised reaction using diol **403** under this setup and recorded the volume of hydrogen gas evolved. The volume was then converted to a percentage yield using the Ideal Gas Law, which assumed 1 mmol of hydrogen gas to occupy 24.2 dm^3 at 298 K.[96] This experiment was repeated three times, and plotted as an average of the three data sets with error bars representing the standard deviation (Blue, Graph 3.2). This data revealed that approximately two equivalents of hydrogen gas were steadily evolved over the course of the reaction, which afforded 84% yield of cyclohexene **405** and trace cyclohexane **404**. We believed this was consistent with a mechanism where the iridium catalyst slowly dehydrogenates diol **403** and alcohol **622**, evolving hydrogen gas, which prevents the reduction of cyclohexene **405** to cyclohexane **404** with iridium hydride.

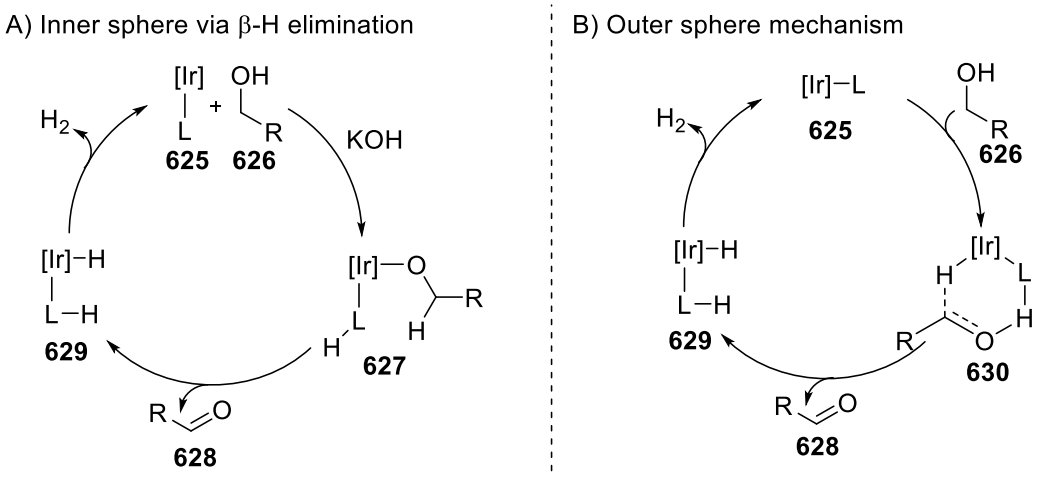
To support this hypothesis, the hydrogen evolution experiment was performed at 1 M concentration, which would be expected to favour reduction of **405** to **404** and decrease the volume of hydrogen gas evolved (Red, Graph 3.2). Pleasingly, we observed significantly less hydrogen gas evolved than at 0.25 M, and increased reduction of **405** to **404**, which was obtained in 33% yield. Overall, we felt this data supported our hypothesis that reduction of cyclohexene **405** was prevented by the catalyst evolving hydrogen gas.



Graph 3.2: Hydrogen evolution experiment at 0.25 M and 1 M concentration of toluene.

Mechanistically speaking, we believe the acceptorless dehydrogenation could plausibly occur by either of the two catalytic cycles outlined in Scheme 3.2.[97] The first proposed mechanism begins with alcohol **626** or a diol binding to metal centre **625** (Scheme 3.2, A). Following this coordination step to iridium, oxidation of the pendant alcohol occurs *via* a β-H elimination of intermediate **627**, liberating the corresponding aldehyde **628**. The resulting metal hydride **629** then can undergo protonation from the coordinated ligand, such as water present in the reaction medium, leading to the evolution of hydrogen gas.[98] An alternative mechanism, which has been proposed for iridium complexes is *via* an outer sphere mechanism where the alcohol does not bind directly to the metal centre (Scheme 3.2, B).[99] Rather, migration of proton and hydride to the ligand and the metal centre, respectively, is a

concerted process and proceeds *via* a six member transition state. Following this, the metal hydride is protonated to evolve hydrogen gas.

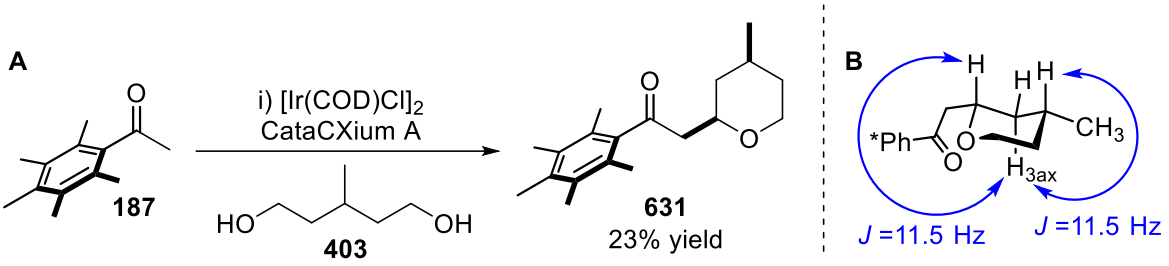


Scheme 3.2: Proposed catalytic cycles for acceptorless dehydrogenation of diol by inner sphere β-H elimination or outer sphere mechanism.

The readiness of a metal hydride to react with a proton source and release H_2 will depend on three factors: (A) the hydricity of the metal hydride, (B) the acidity of the proton source and (C) the hydricity of H_2 gas. Appel and co-workers reported values for the hydricity of iridium complexes in acetonitrile ranging between 14 and 62 kcal/mol in acetonitrile.[100] If we assume water is the proton source ($\Delta G°_{H^-}$ = 20-24 kcal/mol to release H_2 in MeCN), the Gibbs free energy to evolve hydrogen gas would need to sum to < $\Delta G°_{H^-}$ = 76 kcal/mol (hydricity of H_2 in MeCN)[101], for the evolution of hydrogen gas to be a thermodynamically feasible process. This means that iridium hydride complexes with ΔG values < 52 kcal/mol would be readily protonated by water and evolve hydrogen gas.

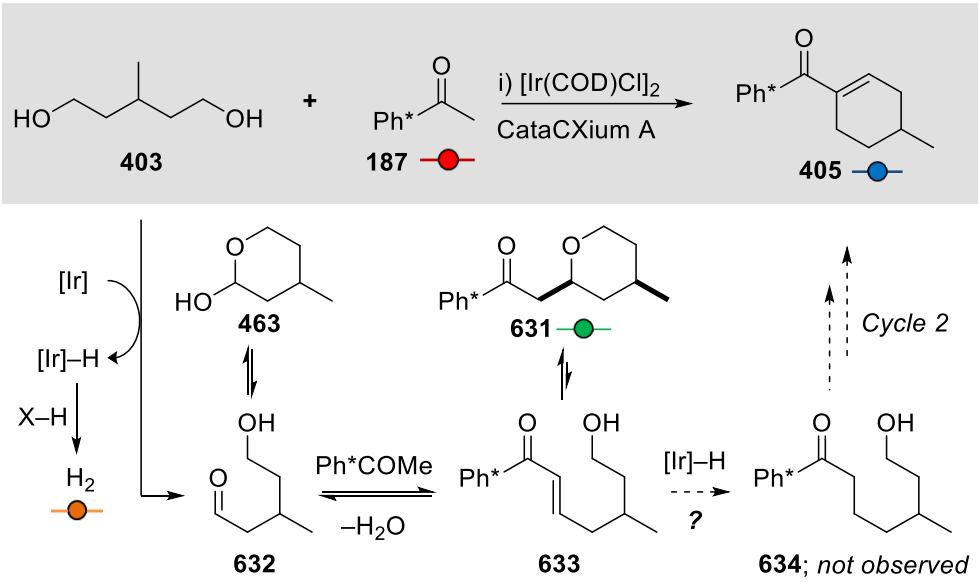
Having monitored the evolution of hydrogen gas, we looked to follow the course of the annulation over the first several hours by reverse phase HPLC (RP HPLC). To determine whether the reaction could be analysed by this method, we injected a small amount of the known starting material and products **187**, **404** and **405**. Pleasingly, the peaks for **187**, **404** and **405** could be cleanly separated using 75% acetonitrile/water as an eluent. Alongside this, we injected an aliquot of the crude reaction mixture after one hour. In addition to observing compounds **187**, **404** and **405**, we observed one unknown species in the crude RP HPLC trace. An analytical quantity of the species was isolated by preparative TLC and identified as *cis*-tetrahydropyran **631**, which was presumably an off-cycle intermediate that can equilibrate with acyclic enone **621** (Scheme 3.3). The *cis*-stereochemistry was assigned by *J*-coupling constant analysis, which showed a quartet for H_3, corresponding to a geminal coupling of

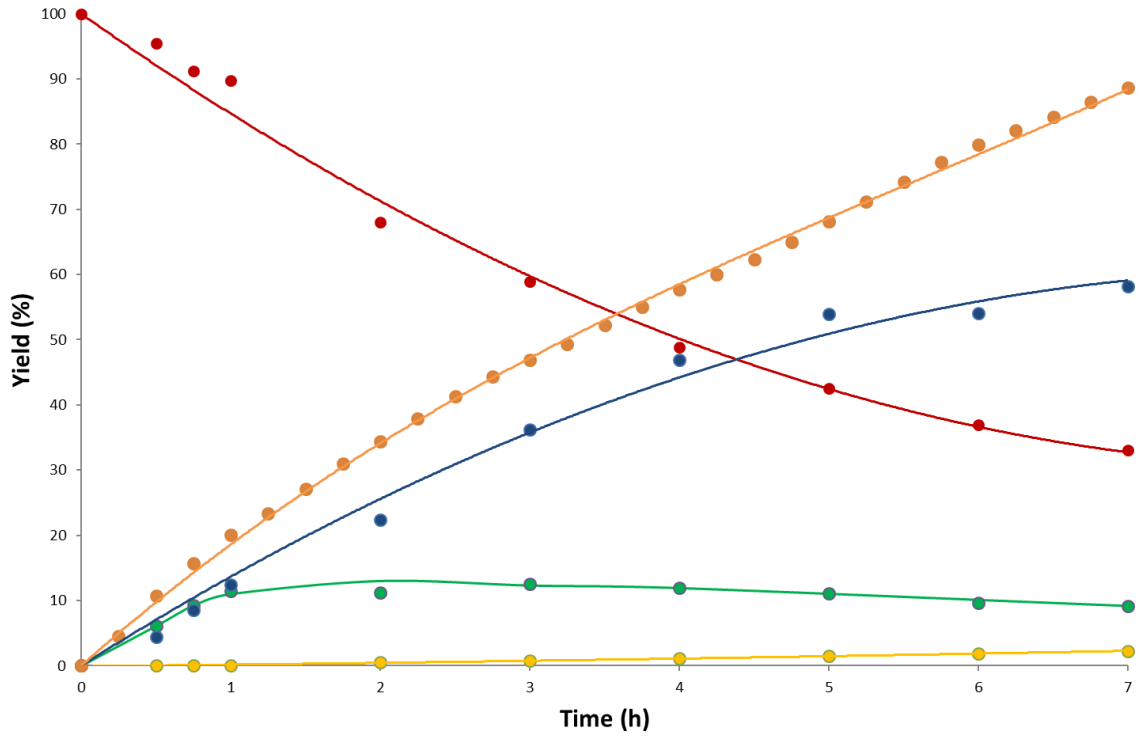
J_2=11.5 Hz and two *trans*-couplings of J_3=11.5 Hz. Subsequently, the UV absorption of **187**, **404**, **405** and **631** were calibrated against an internal standard (hexamethylbenzene) to enable accurate determination of RP HPLC yields (for details, see appendix).



Scheme 3.3: Isolation of tetrahydropyran **631** from the reaction mixture at 30 minutes conversion. Reagents and conditions: (i) Ph*COMe (1 eq.), diol (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 30 min.

Having conducted the RP HPLC calibration, the reaction was run with the addition of one equivalent of hexamethylbenzene, taking aliquots over the first seven hours (Graph 3.3). We observed that Ph*COMe (red) was slowly consumed over the course of the reaction, accompanied by the build-up of cyclohexene **405** (blue) at a comparable rate. Tetrahydropyran **631** (green) was observed to reach approximately 10% yield after one hour, and then was gradually consumed. We also observed formation of small amounts of cyclohexane **404** (yellow), which formed in less than 3% yield over seven hours. Taking this data alongside the evolution of hydrogen gas (orange), we felt this picture was consistent with a mechanism where iridium slowly dehydrogenates diol **403** to hydroxyaldehyde **632**, which likely exists in equilibrium with lactol **463**. Aldol condensation with Ph* ketone **187** would give acyclic enone **633**, which is in equilibrium with tetrahydropyran **631**. Based on our mechanistic proposal (Scheme 3.1), we would expect the next step of this sequence to be the reduction of acyclic enone **633** by iridium hydride to ketone **634**. Despite this, we were surprised that we did not observe or isolate intermediate **634** from the time course experiment. This led us to consider an alternative mechanism where acyclic enone **633** was converted directly to cyclohexene **405** independent of the iridium catalyst.

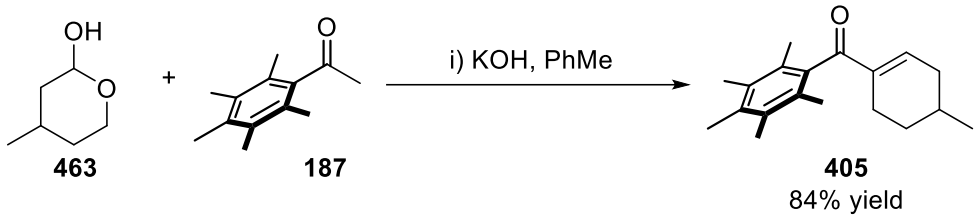




Graph 3.3: Reaction profile for iridium-catalysed annulation. Legend: Ph*COMe **187** (red), hydrogen gas (orange), tetrahydropyran **631** (green), cyclohexene **405** (blue), cyclohexane **404** (yellow). Conditions: Ph*COMe (1 eq.), diol **403** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C.

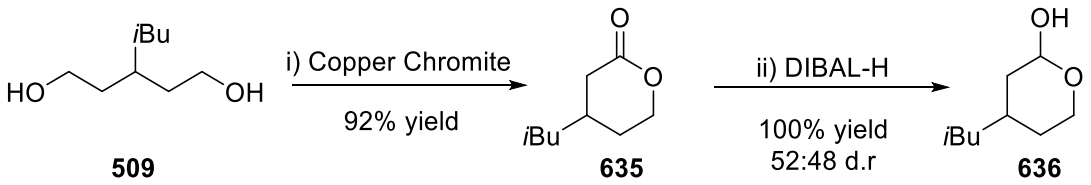
To test this hypothesis, we subjected lactol **463** to the reaction conditions in the absence of $[Ir(COD)Cl]_2$ and CataCXium® A (Scheme 3.4). We were surprised to find that under these conditions,

we isolated cyclohexene **405** in 84% yield, which confirmed that an alternative mechanism independent of iridium was operative.



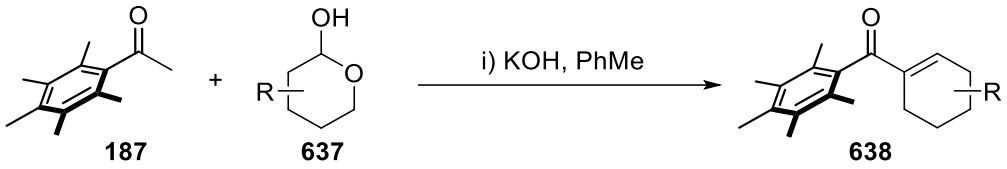
Scheme 3.4: Resubjection experiments of intermediates **463** in the absence of iridium. Conditions: Lactol **463** (2 eq.), Ph*COMe (1 eq.), KOH (4 eq.), PhMe (0.25 M), 115 °C, 24 h.

To confirm that this alternative pathway was a general process for α-,β-, and γ-substituted diols, we investigated several other lactols under the transition metal-free conditions. Lactol **636** was prepared in a two-step sequence from diol **509**, by sequential oxidation with catalytic copper chromite to lactone **635** in 92% yield, and then DIBAL-H reduction to afford lactol **636** in 100% yield as an inconsequential mixture of anomers (Scheme 3.5). Lactols **639**-**641** were prepared by the same synthetic route by Dr R. J. Armstrong.



Scheme 3.5: Preparation of Lactol **636**. Conditions: (i) Diol (1 eq.), Copper chromite (2 mol%), 200 °C, 16-41 h. (ii) lactone (1 eq.), 1M DIBAL-H in hexane (1.4 eq.), CH_2Cl_2 (0.5 M), -78 °C, 3 h.

With lactols **454**-**641** in hand, we treated them with Ph*COMe and potassium hydroxide in the absence of the iridium catalyst (Table 3.1). Pleasingly, lactol **636** afforded the corresponding cyclohexene **520** and 89% (Entries 1 and 2). Using lactols **454** and **639**, we found that 1,2-disubstituted cyclohexenes **383** and **423** could be accessed in 53% and 93% yield, respectively. Finally, with geminally substituted lactols **640** and **641**, we were able to prepare cyclohexenes **521** and **522** in 95% yield. Taken together, these transition metal-free results supported the conclusion that the optimised reaction was capable of proceeding through an iridium-free mechanism.



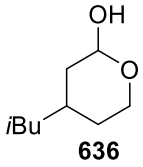
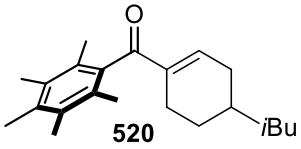
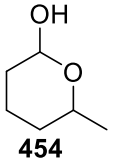
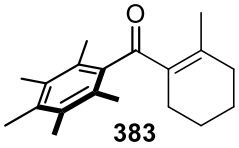
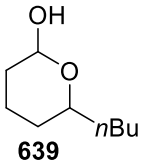
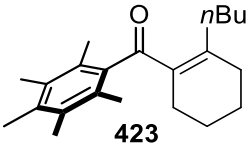
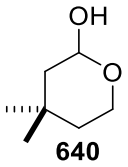
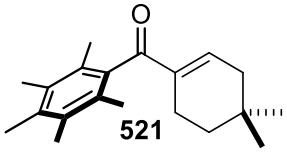
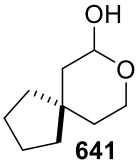
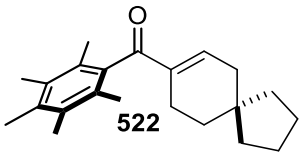
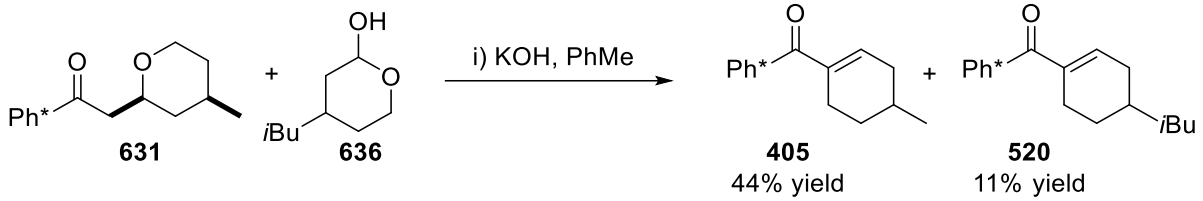
Entry	Starting material	Product	Yield (%)
1			89
2			53
3			93
4			95
5			95

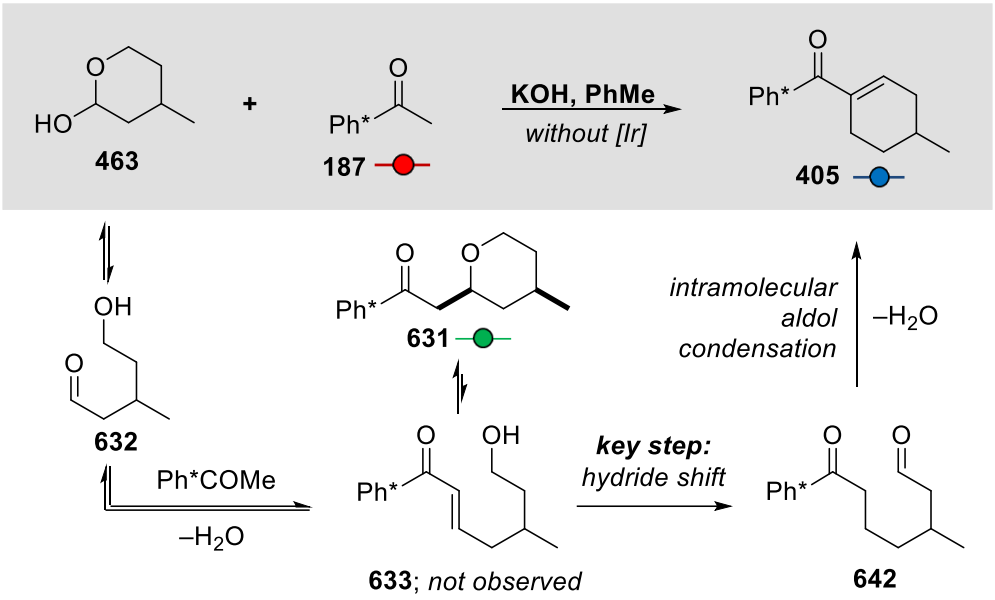
Table 3.1: Resubjection experiments of lactols **454**-**641** to the transition metal-free annulation. Conditions: lactol (2 eq.), Ph*COMe (1 eq.), KOH (4 eq.), toluene (0.2 M), 115 °C, 14 h. Yields refer to isolated material after column chromatography.

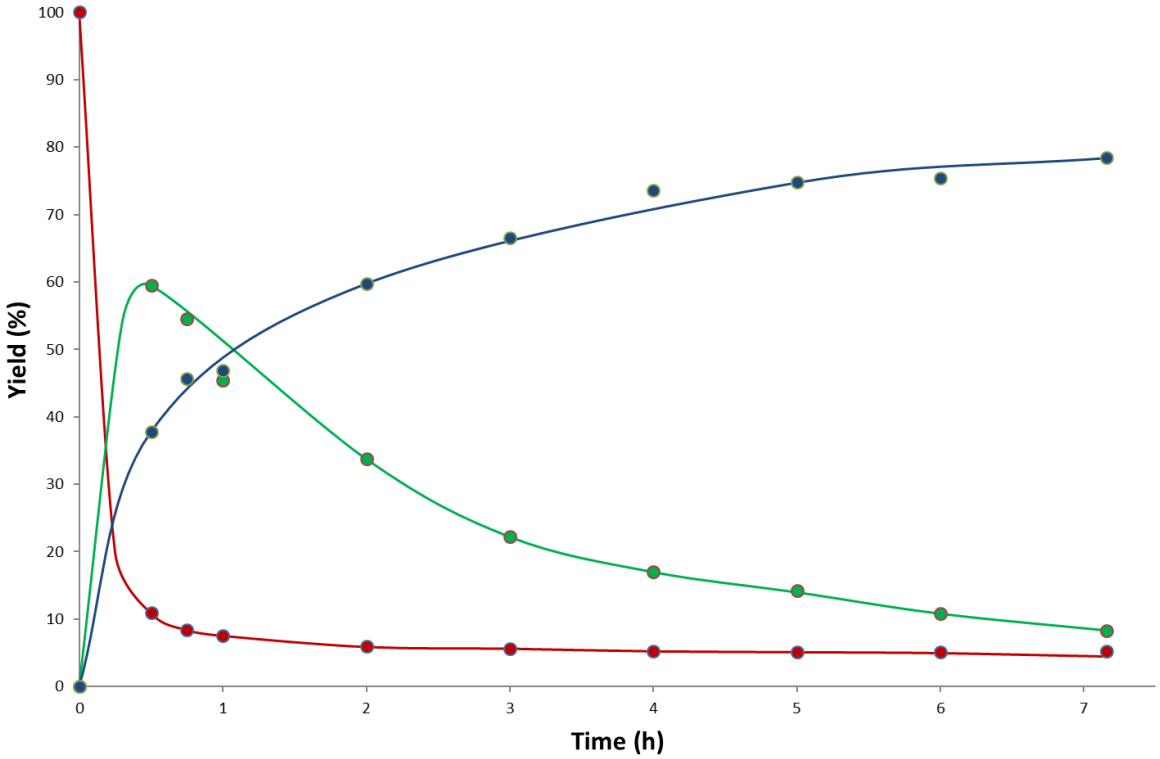
Analogously, we also investigated whether tetrahydropyran **631** was a competent precursor for the iridium-free annulation sequence. This was explored by treating tetrahydropyran **631** with *iso*butyl-lactol **636** and potassium hydroxide in toluene for 24 hours (Scheme 3.6). This resulted in the formation of a mixture of cyclohexene **405** in 44% yield and cyclohexene **520** in 11% yield. This experiment suggested that tetrahydropyran **631** was a competent precursor in the metal-free annulation. Furthermore, observation of crossover product **520** suggested that the initial C-C bond formation was partially reversible, likely *via* retro-aldol under the basic reaction conditions.



Scheme 3.6: Crossover experiment with tetrahydropyran **631**. Conditions: (i) tetrahydropyran **631** (1 eq.), lactol **636** (1 eq.), KOH (4 eq.), toluene (0.2 M), 115 ^{o}C, 24 h. Products **405** and **520** were isolated as an inseparable mixture.

To study the iridium-free annulation sequence in greater detail, we followed the reaction of lactol **463** and Ph*COMe **187** by RP HPLC (Graph 3.4). We observed that Ph*COMe (red) was rapidly consumed within the first 30 minutes of the reaction, and converted to tetrahydropyran **631** (green). This intermediate was then gradually consumed over the course the reaction, accompanied by the formation of cyclic enone **405** (blue). Compared to the reaction in Graph 3.3, we did not observe evolution of hydrogen gas or the formation of cyclohexane **404**. This suggested the iridium free-cascade was overall redox neutral, and also confirmed the role of iridium to promote acceptorless dehydrogenation over 1,4-reduction by iridium-hydride. Based on this data we proposed a mechanism whereby lactol **463** opens to hydroxyaldehyde **632** and undergoes rapid aldol condensation with Ph*COMe **187** to form enone **633**. This enone can reversibly undergo conjugate addition with the pendant alcohol to form tetrahydropyran **631**, which was isolable. We then propose that enone **633** undergoes a hydride transfer to 1,7-dicarbonyl **642**, which would cyclise to cyclohexene **405** by intramolecular aldol condensation.[102]



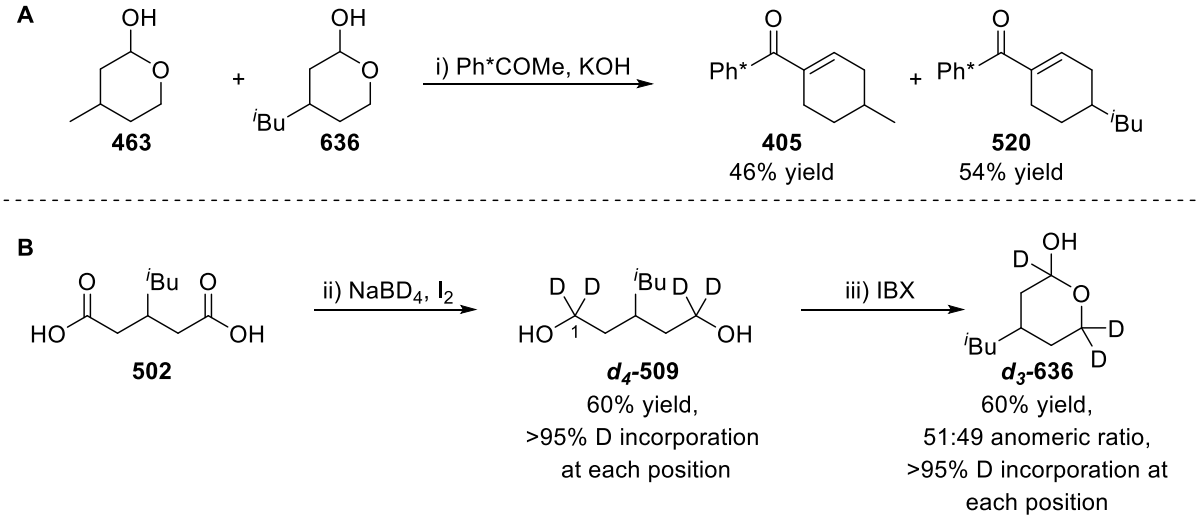


Graph 3.4: Reaction profile for iridium-free cascade Legend: Ph*COMe **187** (red), tetrahydropyran **631** (green), cyclohexene **405** (blue). Conditions: Ph*COMe (1 eq.), lactol **463** (2 eq.), KOH (4 eq.), PhMe (0.25 M), 115 °C.

3.3 Double Label Crossover Experiment for the Annulation Reaction to Synthesise Cyclohexenes

These control experiments strongly suggested a mechanism involving a transition metal-free hydride-transfer, however we cannot distinguish between an intermolecular (e.g Cannizaro disproportionation)[103] or intramolecular pathway ([1,5]-hydride shift)[120]. To probe this, we set out to perform a double-label cross over experiment with structurally similar deuterated lactol ***d*₃-636** and non-deuterated lactol **463** (Scheme 3.8). To validate the suitability of these substrates for a crossover experiment, we subjected an equimolar amount of **463** and **636** to Ph*COMe **187** and KOH in the absence of iridium. We were pleased to isolate a mixture of cyclohexenes **405** and **520** in 46% and 54% yield, respectively (Scheme 3.7, A). Additionally, we found these substrates to be separable by both RP HPLC or preparative TLC, which would enable analysis of deuterium incorporation.

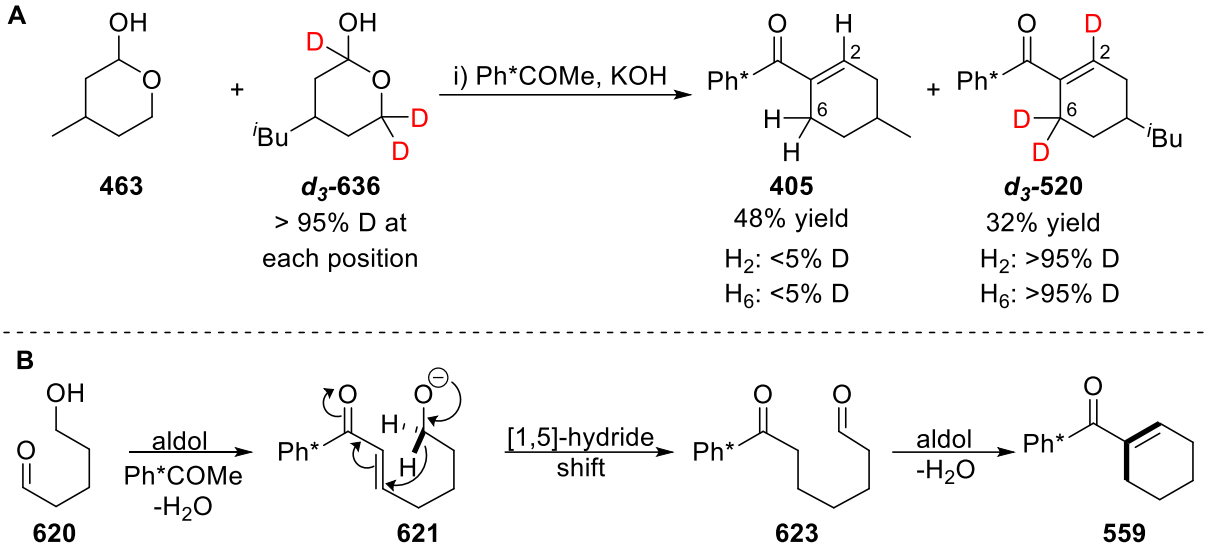
To prepare lactol ***d*₃-636**, we first reduced diacid **502** to diol ***d*₄-509** in 60% yield using deuterated borane, which was prepared *in-situ* from commercial $NaBD_4$ and iodine (Scheme 3.7, B).[104] By quantitative ^1H NMR, the measured integral for H_1 corresponded to 0.14 across the four symmetrical positions, which indicated a deuterium incorporation of greater than 95% at each site. This was further validated by ^2H NMR which showed a singlet at 3.67 ppm corresponding to deuterium at H_1. Similarly, by ^{13}C NMR we observed a 1:2:3:2:1 quintet (J=21.5 Hz) for C_1, which was consistent with two C-D couplings. Inspired by the work of Corey and co-workers in 1995[105], we were pleased to find that IBX performed a selective oxidation of ***d*₄-509** to ***d*₃-636** in 60% yield. We analysed the deuterium incorporation by quantitative ^1H, ^2H and ^{13}C NMR, which was also found to be greater than 95% at each position (For further details, see experimental).



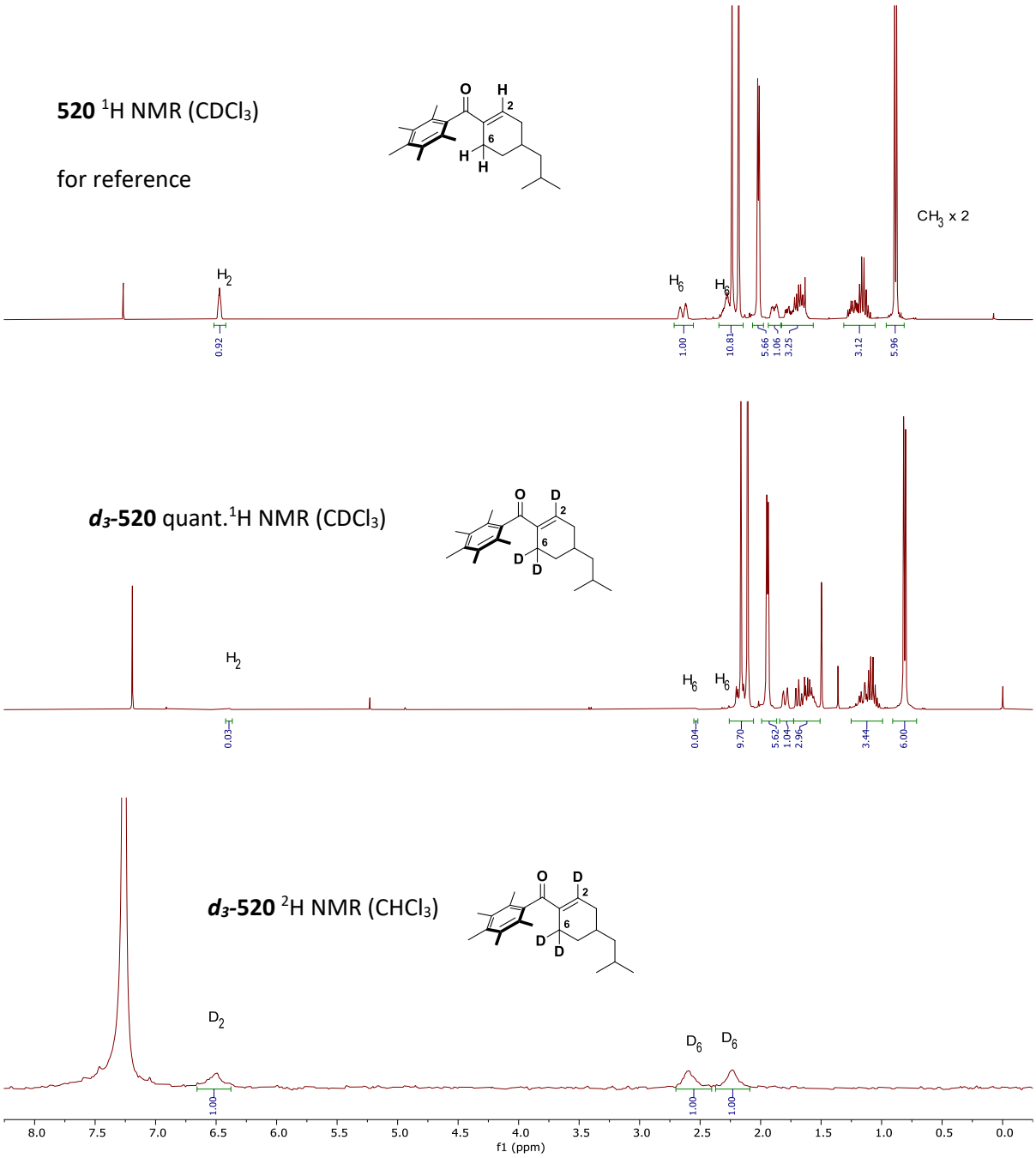
Scheme 3.7: (A) Validation of crossover experiment with substrates **463** and **636**. Conditions: lactol **463** (1 eq.), lactol **636** (1 eq.), Ph*COMe (1 eq.), KOH (4 eq.), toluene (0.2 M), 115 °C, 24 h. (B) Preparation of ***d*$_3$-636**. Conditions: (i) **502** (1 eq.), $NaBD_4$ (3 eq.), THF (0.2M), then I_2, (1.2 eq.), 0 °C to RT, 48 h. (ii) ***d*$_4$-509** (1 eq.), 30% IBX with stabiliser (1.2 eq.), 3:1 acetone/DMSO (0.1M), RT, 5 h.

With the deuterated lactol in hand, we treated a 1:1 mixture of **463** and ***d*$_3$-636** with Ph*COMe **187** and KOH in the absence of the iridium catalyst (scheme 3.8, A). This crossover experiment afforded a mixture of isobutyl-cyclohexene ***d*$_3$-520** in 32% yield and methyl-substituted cyclohexene **405** in 40% yield. These cyclohexenes were then separated by preparative TLC and the degree of deuterium incorporation was analysed by quantitative ^1H, ^2H and ^{13}C NMR (Scheme 3.9-3.11). This data revealed there was greater than 95% deuterium incorporation at C_2 and C_6 positions of labelled substrate ***d*$_3$-520**, inferred by quantitative ^1H NMR, which gave integrals of 0.03 and 0.04 respectively for these two signals, corresponding peaks in the ^2H NMR at 6.51 ppm (s, 1 x ^2H, $^2H_2$), 2.61 ppm (s, 1 x ^2H, $^2H_{6eq}$), 2.24 ppm (s, 1 x ^2H, $^2H_{6eq}$), and by ^{13}C NMR we observed a 1:1:1 triplet at C_2 from $^2J_{CD}$ coupling and 1:2:3:2:1 pentet at C_6 from $^2J_{CD}$ coupling (CD_2). Additionally, we observed no deuterium (<5%) in unlabelled substrate **405**.

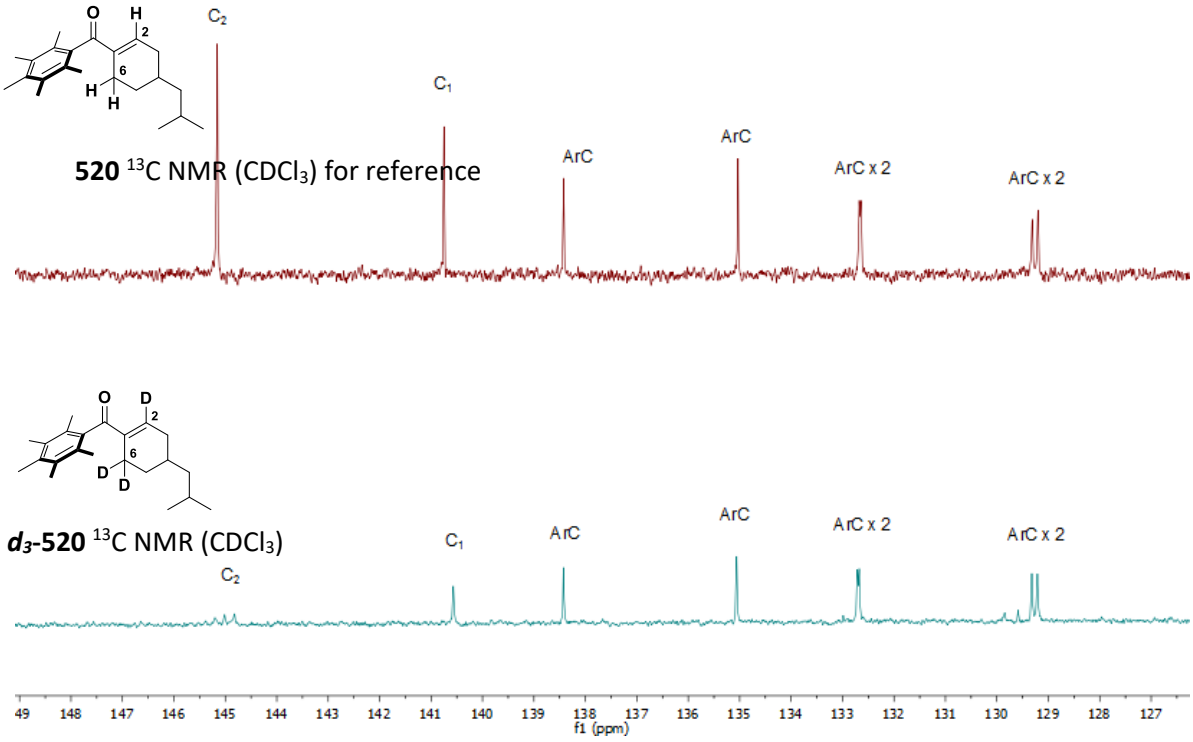
In addition to NMR, we also investigated high resolution mass spectrometry as a method to analyse the deuterium incorporation. By this approach, we were able to qualitatively confirm that the predominate species of ***d*$_3$-520** was a cyclohexene bearing three deuterium atoms, and cyclohexene **405** contained no deuterium. However, we could not use this method for quantitative analysis of the deuterium incorporation, due to overlapping ^{13}C satellite peaks affecting accurate quantification, thus we did not pursue this approach of analysis further. Due to the absence of any crossover or reduction in deuterium incorporation of ***d*$_3$-520**, we concluded that the hydride transfer step proceeded by an intramolecular mechanism (Scheme 3.7, B).



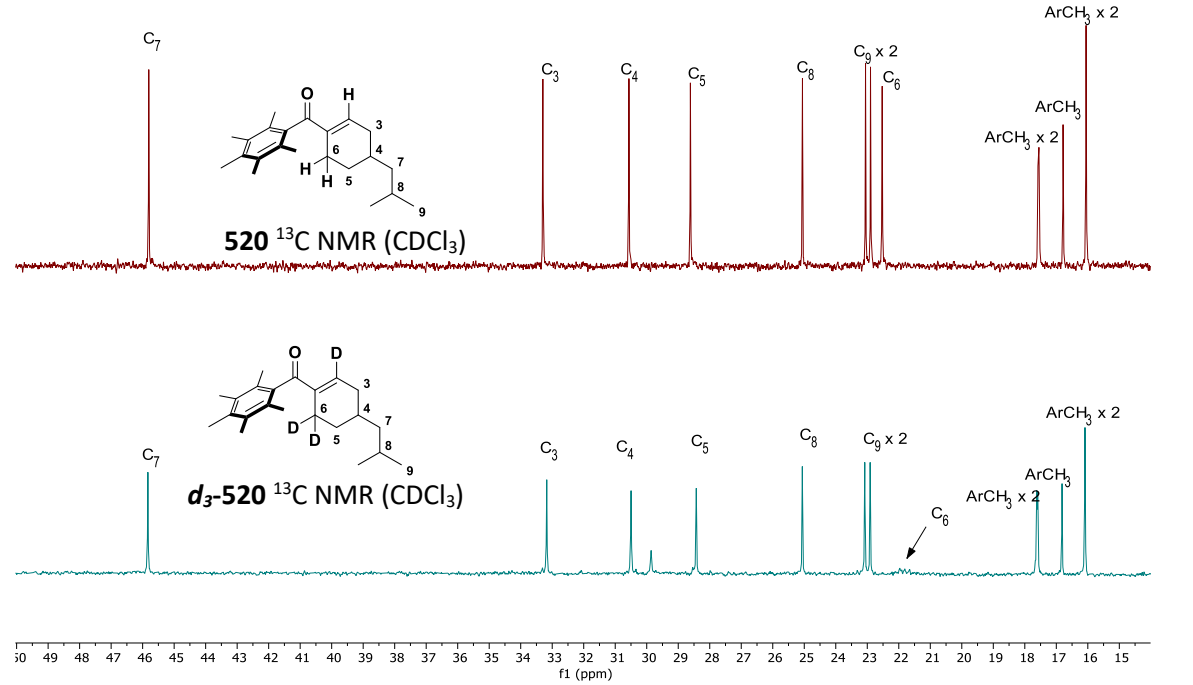
Scheme 3.8: A) Double-label crossover experiment with **463** and ***d*$_3$-636** in the absence of iridium. B) Mechanistic explanation to rationalise deuterium incorporation. Conditions: **463** (1 eq), *d*$_3$-**636** (1 eq.), Ph*COMe (1 eq.), KOH (4 eq.), PhMe (0.25 M), 115 °C, 24 h.



Scheme 3.9: Stack plot showing reference ^{1}H NMR spectrum of **520** along with quantitative ^{1}H NMR and ^{2}H NMR spectra of ***d*$_3$-520** from diol cross over experiment.



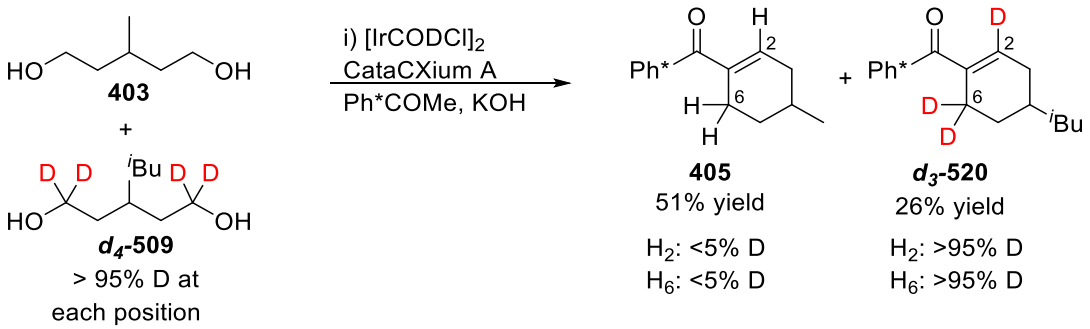
Scheme 3.10: Stack plot showing reference ^{13}C NMR spectrum of **520** (149–127 ppm) along with ^{13}C NMR spectrum of ***d₃*-520** from lactol cross over experiment. Illustrates 1:1:1 triplet at C_2 from $^{2}J_{CD}$ coupling (CD).



Scheme 3.11: Stack plot showing reference ^{13}C NMR spectrum of **520** (50–14 ppm) along with ^{13}C NMR

spectrum of ***d₃*-520** from lactol cross over experiment. Illustrates 1:2:3:2:1 pentet at C_6 from $^2J_{CD}$ coupling (CD_2).

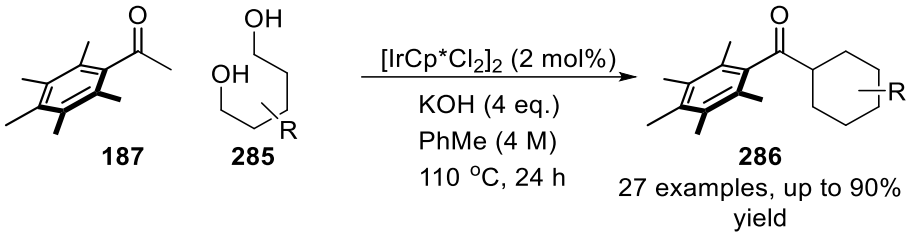
To confirm that the intramolecular hydride shift pathway was operative in the iridium-catalysed synthesis of cyclohexenes, we performed an analogous cross-over experiment using unlabelled diol **403** and deuterated diol ***d₄*-509** (Scheme 3.12). Using the optimised annulation conditions, we isolated a mixture of ***d₃*-520** and **405** in 26% yield and 51% yield, respectively. The compounds were separated by preparative TLC and analysed by quantitative ^1H, ^2H and ^{13}C spectroscopy, which revealed that ***d₃*-520** was fully deuterated (>95% D) at C_2 and C_6 positions and **405** contained no deuterium (<95% D), identical to the crossover experiment with lactol **463** and ***d₃*-636**. This pattern of deuterium incorporation strongly suggested that the transition metal-free intramolecular [1,5]-hydride shift was also involved in the iridium-catalysed annulation reaction. Furthermore, the lack of crossover or reduction in deuterium incorporation also implied that oxidation of the diol to the lactol was an irreversible process.



Scheme 3.12: Double-label crossover experiment with **403** and ***d₃*-509** under optimised conditions. Conditions: **403** (1 eq.), ***d₃*-509** (1 eq.), Ph*COMe (1 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), KOH (4 eq.), PhMe (0.25 M), 115 °C, 24 h.

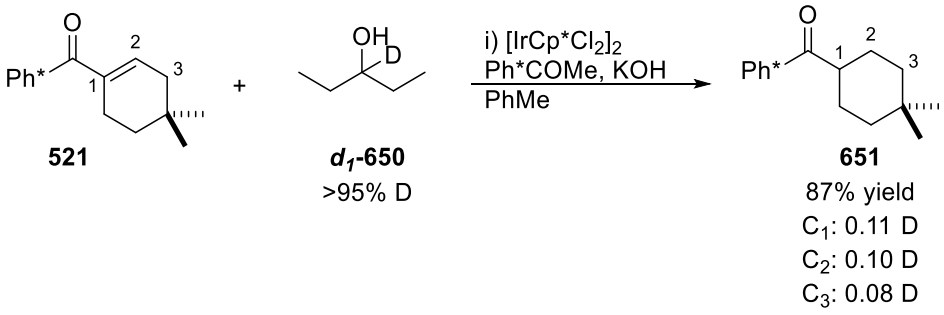
3.4 Double Label Crossover Experiments to Investigate the Annulation Reaction to Synthesise Cyclohexanes

Having shown that the iridium-catalysed annulation to synthesise cyclohexenes proceeded through an intramolecular [1,5]-hydride shift cascade, we wondered whether the previously reported method to synthesise cyclohexanes also proceeded through this mechanism, or by a hydrogen borrowing annulation (Scheme 3.13).[84]



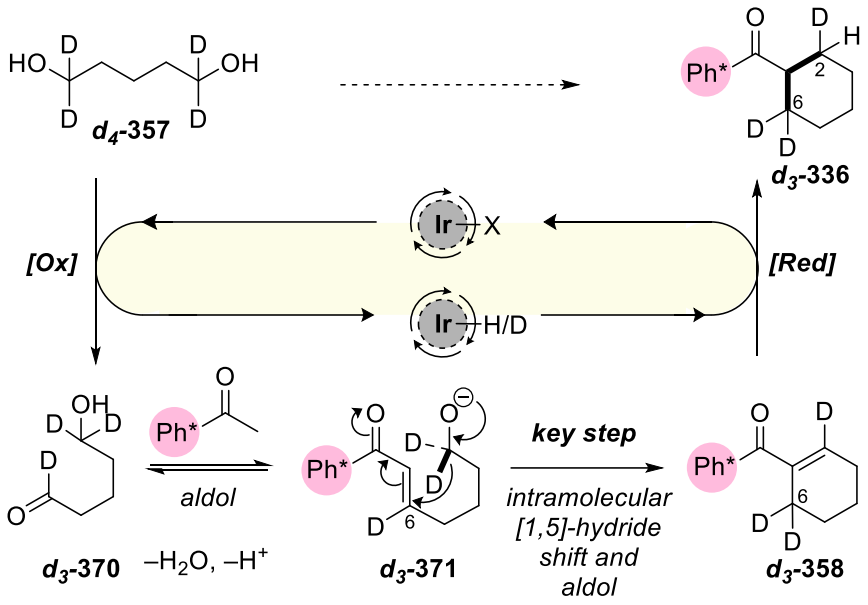
Scheme 3.13: Stereoselective Synthesis of Cyclohexanes via an Iridium Catalyzed [5 + 1] Annulation Strategy

To investigate this, we set out to perform an analogous double label crossover experiment using a deuterated diol and non-deuterated diol. One key factor to consider in this experiment is the levels of deuterium incorporation from an additional step of 1,4-reduction of cyclohexene **521** by Ir-H/D to afford the corresponding cyclohexane **651**, which we would expect to contribute a kinetic isotope effect (Scheme 3.14). When the transfer hydrogenation of **521** with ***d*$_1$-650** was performed, we expected this reaction to cleanly afford cyclohexane **651** bearing one deuterium at C_2, but this experiment instead afforded 20% D at C_2 along with similar levels of deuterium incorporation at C_1 and C_3.[106] This result implied that the iridium deuteride formed from the initial oxidation undergoes a rapid H/D exchange (wash-out) with protic species, such as water, alcohol **650** and KOH, present in the reaction mixture.[107] A plausible mechanism for this wash-out could be iridium hydride acting as an acid, undergoing deprotonation and reprotonation. In 2014, Morris calculated the pKa of 20 iridium hydride complexes to range between 43 and -3, which supports the possibility that iridium hydride could form an iridium anion under the reaction conditions.[108] Overall, the observed wash-out results in only partial deuterium incorporation at C_2, due to reduction with a mixture of Ir-H and Ir-D, and we see this effect in later experiments (*vide infra*).

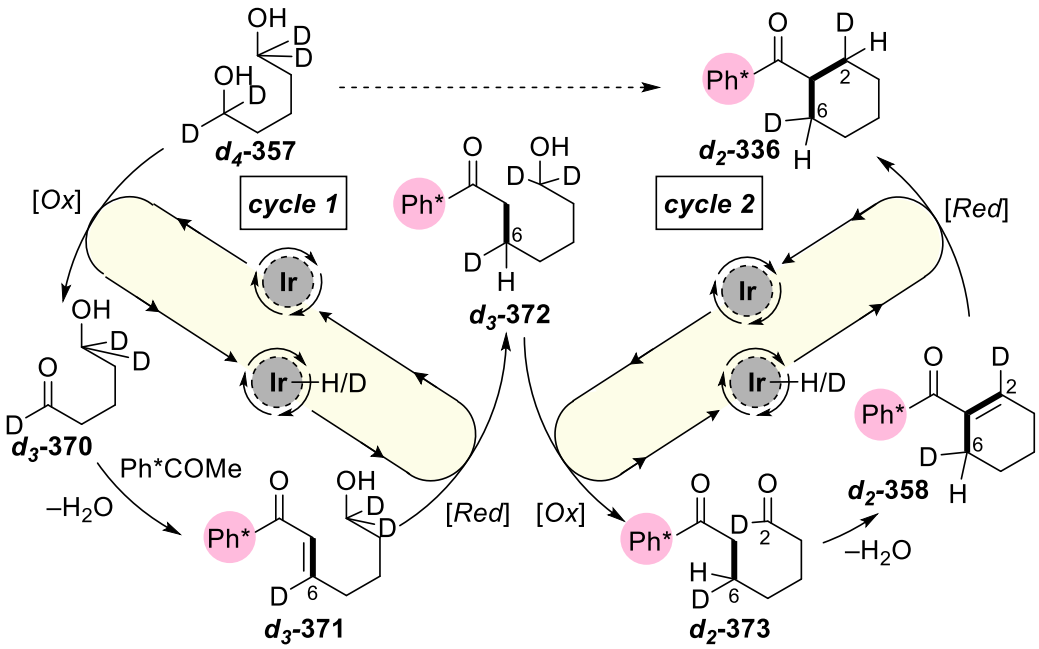


Scheme 3.14: deuterium incorporation for 1,4-reduction step by transfer hydrogenation with alcohol ***d*$_1$-650**. Conditions: **521** (1 eq), **d$_1$-650** (1 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h.

Based on this transfer hydrogenation experiment, we hypothesised that if a mechanism involving an intramolecular [1,5]-hydride shift pathway was operative (Scheme 3.15), only one reduction step with iridium hydride would occur, and we would observe incorporation of one hydrogen at C_2, and no hydrogen at C_6. Similarly, if two hydrogen borrowing cycles were to occur (Scheme 3.16), we would expect the incorporation of one hydrogen at C_2 and one hydrogen at C_6 due to two 1,4-reduction steps with iridium hydride (from washout of deuterium to hydrogen).



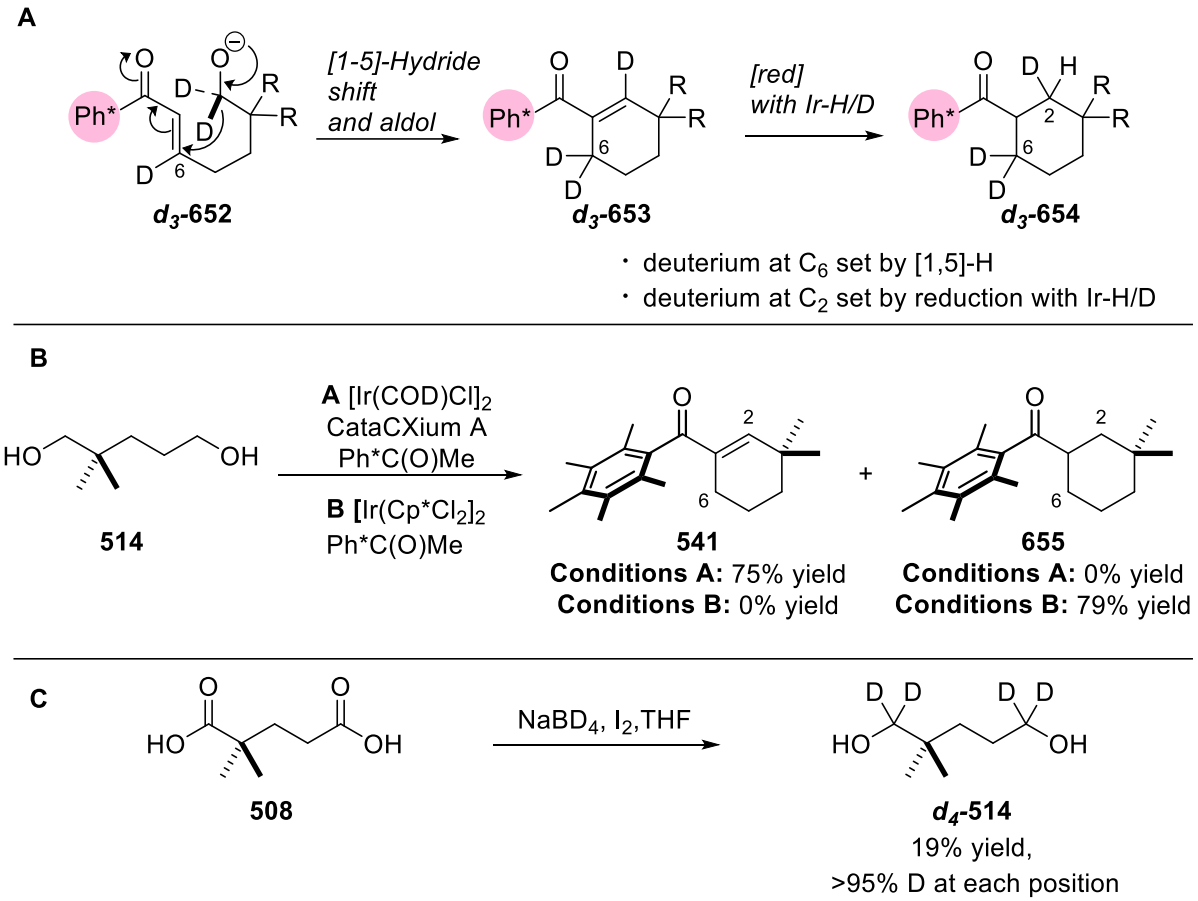
Scheme 3.15: Hypothesised deuterium incorporation for [1,5]-hydride shift mechanism.



Scheme 3.16: Hypothesised deuterium incorporation for two sequential hydrogen borrowing cycles.

To test this hypothesis, we looked to design two new unsymmetrical substrates for the double label crossover experiment (Scheme 3.17, A). To accomplish this, we proposed to prepare geminally disubstituted cyclohexane **654**. This was due to the ability to separately integrate the deuterium incorporation at C_2 and C_6 by ^{1}H NMR. Notably, if the mechanism proceeded through an intramolecular [1,5]-hydride shift step, we would expect two deuterium atoms at the C_6 position, and none in the unlabelled substrate at C_6. Similarly, the deuterium incorporation at C_2 would result from reduction of cyclohexene **653** with Ir-H and Ir-D, which we would expect to be low due to the H/D washout we observed in Scheme 3.14.

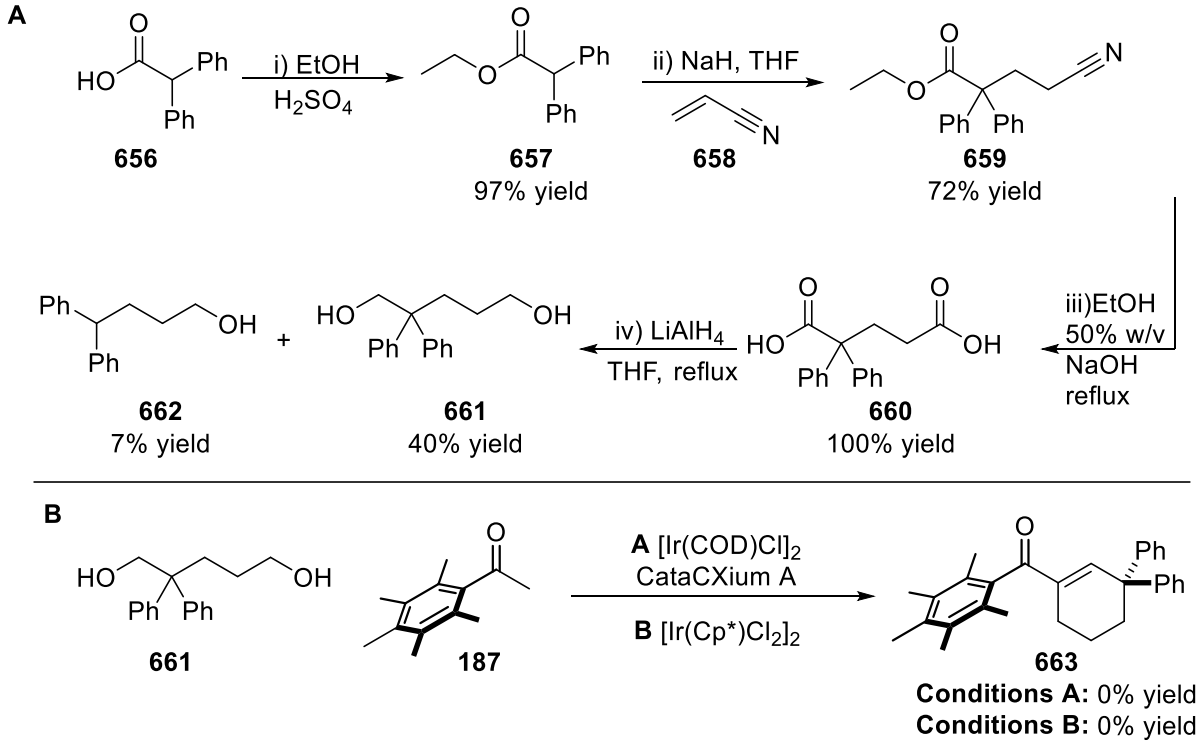
The first substrate we proposed to prepare for the double label crossover experiment was cyclohexane **655** from diol **514** (Scheme 3.17, B). Pleasingly, when diol **514** was subjected to the optimal conditions to prepare cyclohexanes, we cleanly formed **655** in 79% yield, consistent with the reported yield.[84] Furthermore, we analysed **655** by ^{1}H NMR in a range of different solvents and found that the peaks corresponding to C_2 and C_6 could be fully resolved using CD_2Cl_2. Subsequently, we prepared deuterated diol ***d*$_4$-514** in one step by reduction of diacid **508** with deuterated borane, to use as the labelled diol in the double label crossover experiment (Scheme 3.17, C).



Scheme 3.17: A) proposed class of geminally disubstituted cyclohexane **654** for the double label crossover experiment. B) competency of diol **514** under the optimal conditions to prepare cyclohexane **655** and cyclohexene **541**. Conditions A: **187** (1 eq.), **514** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Conditions B: **187** (1 eq.), **514** (2 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h. C) preparation of tetra-deuterated diol ***d*$_4$-514** for the double label crossover experiment. Conditions: (i) **508** (1 eq), $NaBD_4$ (3 eq.), THF (0.2 M), then I_2, (1.2 eq.), 0 °C to RT, 48 h.

With tetra-deuterated diol ***d*$_4$-514** in hand, we looked to prepare a second geminally disubstituted diol that could be used in the double label crossover experiment. The first substrate we proposed to prepare was a bis-phenyl diol **661**, which would hopefully generate a cyclohexane that would be separable by flash column chromatography from cyclohexane **655** (Scheme 3.18, A). This was prepared in four steps starting with carboxylic acid **656**, which was converted to ethyl ester **657** in 97% yield on multigram scale. Using NaH, the enolate of ester **657** was prepared *in-situ*, and reacted with acrylonitrile **658** in 72% yield. The resulting nitrile **659** was then saponified to liberate the 1,5-diacid **660** in quantitative yield. Finally, **660** was reduced to the desired diol **661** in 40% yield using $LiAlH_4$,

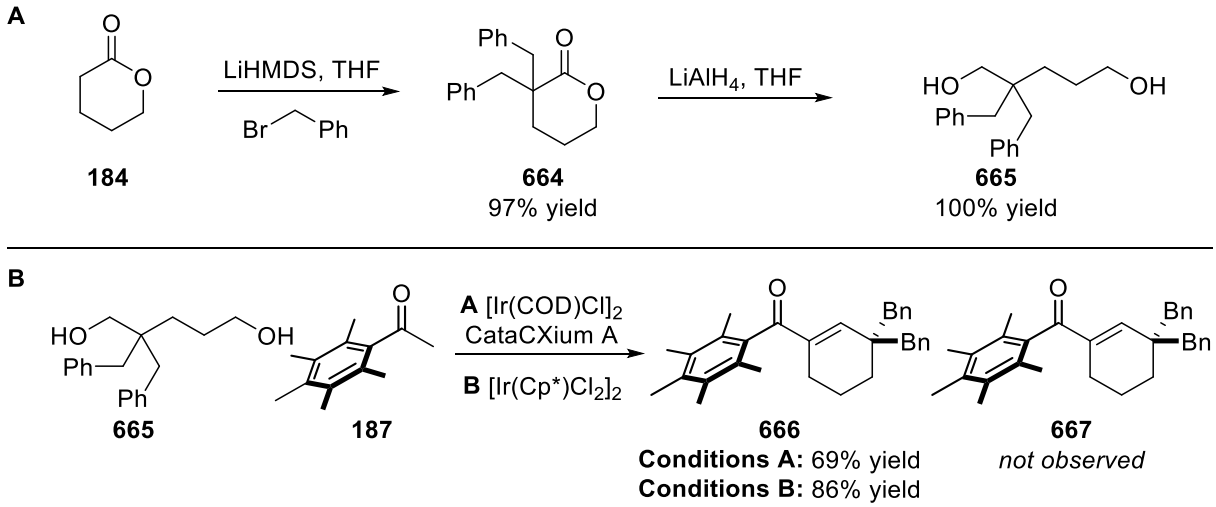
accompanied by formation of alcohol **662** in 7% yield, which likely formed through decarboxylation of **660** to form a stable benzylic anion. Diol **661** was then subjected to the reaction conditions to prepare both, cyclohexenes and cyclohexanes, but frustratingly, both reactions returned unreacted pentamethylacetophenone **187** (Scheme 3.18, B). We believed the lack of conversion to any product was due to the bulky geminal diphenyl motif, thus we looked to try smaller substituents to place in the β-position of the diol.



Scheme 3.18: A) Preparation of diol **661**. Conditions i) **656** (1 eq.), ethanol (1.6 M), conc. sulphuric acid (0.09 eq.), reflux, 15 h. ii) **657** (1 eq.), 60% wt. NaH (1.2 eq.), acrylonitrile (1.2 eq.), THF (0.08M), 0-RT, 4 h. iii) **659** (1 eq.), EtOH (0.17M), 50% Wt. NaOH in EtOH (12.5M). iv) **660** (1 eq.), $LiAlH_4$ (3 eq.), THF (0.5 M). (B) competency of diol **661** under the optimal conditions to synthesise cyclohexanes. Conditions A: **187** (1 eq.), **661** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Conditions B: **187** (1 eq.), **661** (2 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h.

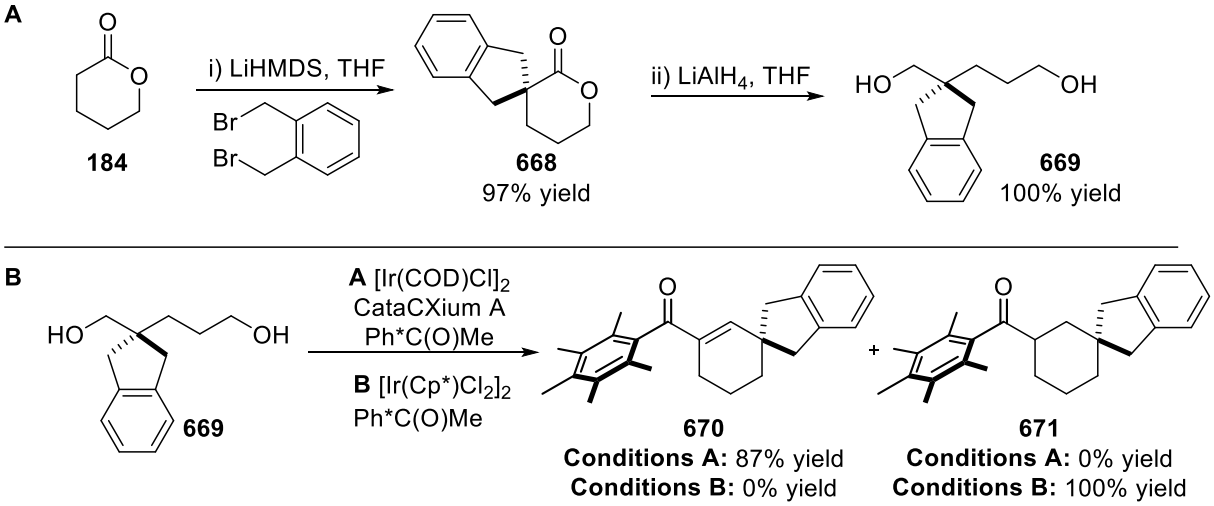
Given that biphenyl substituted diol **661** was too hindered to react, we next investigated bis-benzyl diol **665** (Scheme 3.19, A). To prepare diol **665**, we began by performing a double α-alkylation of δ-valerolactone **184** with LiHMDS and benzyl bromide in 97% yield. The resulting lactone **664** was then reduced with $LiAlH_4$ to afford **665** in quantitative yield. Diol **665** was then subjected to the optimal

conditions for the preparation of cyclohexenes and cyclohexanes (Scheme 3.19, B). To our surprise we found that both conditions gave cyclohexene **666** in good yields, with the corresponding cyclohexane **667** not observed. This implied that dibenzyl substituted cyclohexene **666** was too hindered to be reduced by 1,4-reduction by iridium hydride, thus would not be an appropriate substrate for the crossover experiment.



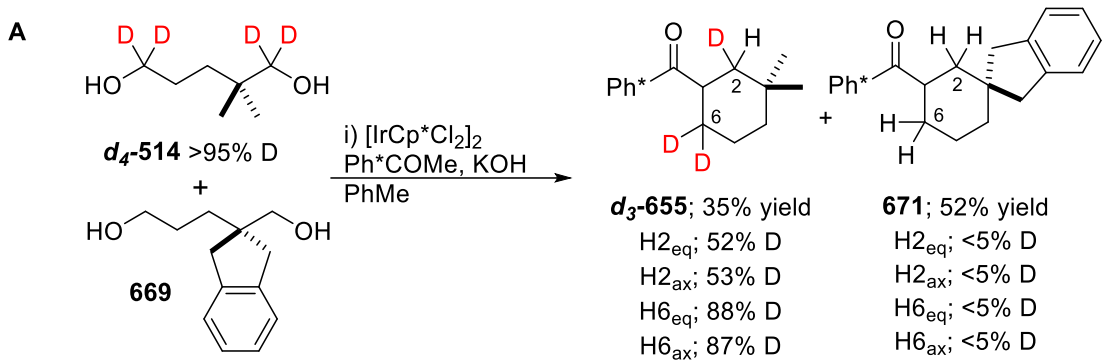
Scheme 3.19: A) Synthesis of diol **665**. B) Reaction of diol **665** under the conditions to prepare cyclohexanes and cyclohexenes. Conditions A: **187** (1 eq.), **665** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Conditions B: **187** (1 eq.), **665** (2 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h.

Due to the difficulty in the 1,4-reduction step of cyclohexene **666** to cyclohexane **667**, we decided to prepare cyclic benzyl diol **669**, which would be less hindered than the bis-benzyl diol **665** (Scheme 3.20, A). The two step sequence began with the α-alkylation of δ-valerolactone **184** using LiHMDS and α,α'-dibromo-*o*-xylene, which afforded lactone **668** in 97% yield. Lactone **668** was then reduced with $LiAlH_4$ to give the desired diol **669** in quantitative yield. Diol **669** was then subjected to the optimal conditions for the preparation of cyclohexenes and cyclohexanes (Scheme 3.20, B). We were delighted to find that using $[Ir(COD)Cl]_2$ and CataCXium® A, cyclohexene **670** was cleanly afforded in 87% yield as a single regioisomer. Conversely, when the reaction was performed at higher concentration with the more reducing catalyst $[Ir(Cp^*)Cl_2]_2$, we obtained cyclohexane **671** in 100% yield.



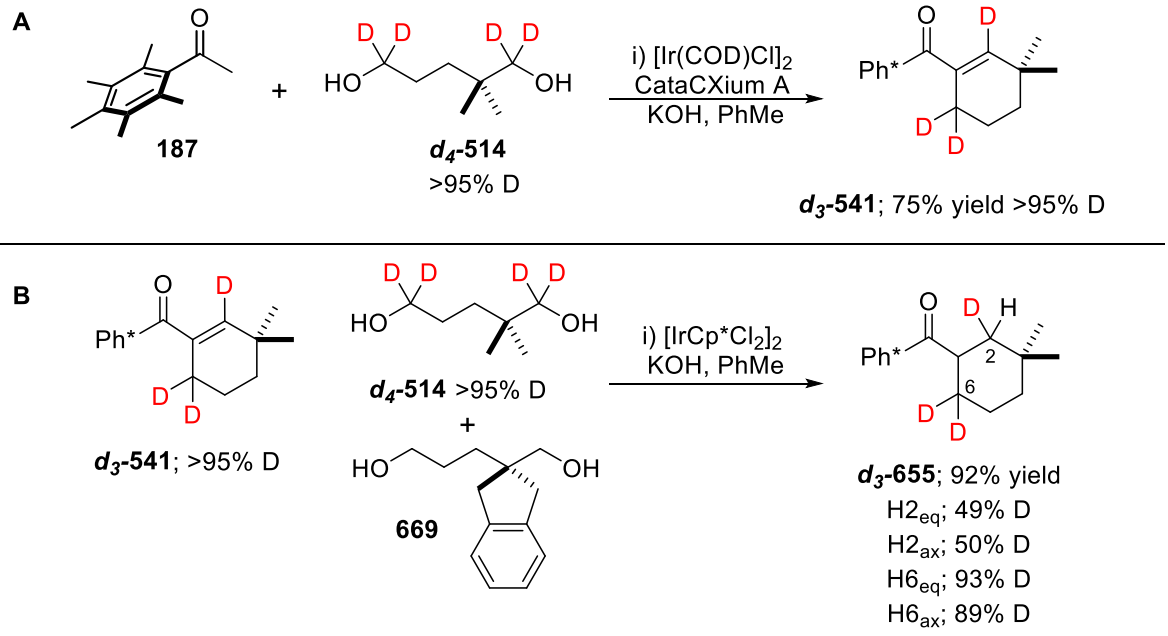
Scheme 3.20: A) Preparation of diol **669**. Conditions i) **184** (1 eq.), LiHMDS (2.2 eq.), α,α'-dibromo-*o*-xylene (1.1 eq.), THF (0.25 M). ii) **668** (1 eq.), $LiAlH_4$ (3 eq.), THF (0.2 M). B) Subjection of diol **669** to the optimal conditions to prepare cyclohexenes and cyclohexanes. Conditions A: **187** (1 eq.), **669** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. Conditions B: **187** (1 eq.), **669** (2 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h.

With tetra-deuterated diol ***d*$_4$-514** and **669** in hand, we performed a double label crossover experiment under the reported reaction conditions for the synthesis of cyclohexanes, using $[Ir(Cp^*)Cl_2]_2$ (Scheme 3.21, A). As anticipated, under these more strongly reducing conditions, we obtained exclusively cyclohexanes ***d*$_3$-655** and **671** in 35% and 52% yield, respectively. Spirocyclic benzyl cyclohexane **671** was found to contain essentially no deuterium at C_2 or C_6, with the ^1H and ^{13}C NMR data being indistinguishable from the data for **671** prepared outside of the crossover experiment. Notably, no deuterium incorporation was observed at C_2 from the 1,4-reduction step due to the wash-out effect outlined in Scheme 3.14. Dimethyl substituted cyclohexene ***d*$_3$-655** was isolated with 1.75 D at the C_6 position and 1.05 deuterium at C_2 (Scheme 3.23). This was further corroborated by ^2H NMR, where we observed the corresponding signals for the equatorial and axial deuterium atoms at C_2 and C_6. Furthermore, in the ^{13}C spectra (Scheme 3.24), we observed a 1:1:1 triplet for C_2, consistent with one deuterium at C_2, and a 1:2:3:2:1 quintet, which fitted with two deuterium atoms at C_6. Taken together, we concluded that the [1,5]-hydride shift mechanism is the predominant pathway in the reductive annulation reaction to prepare cyclohexanes.

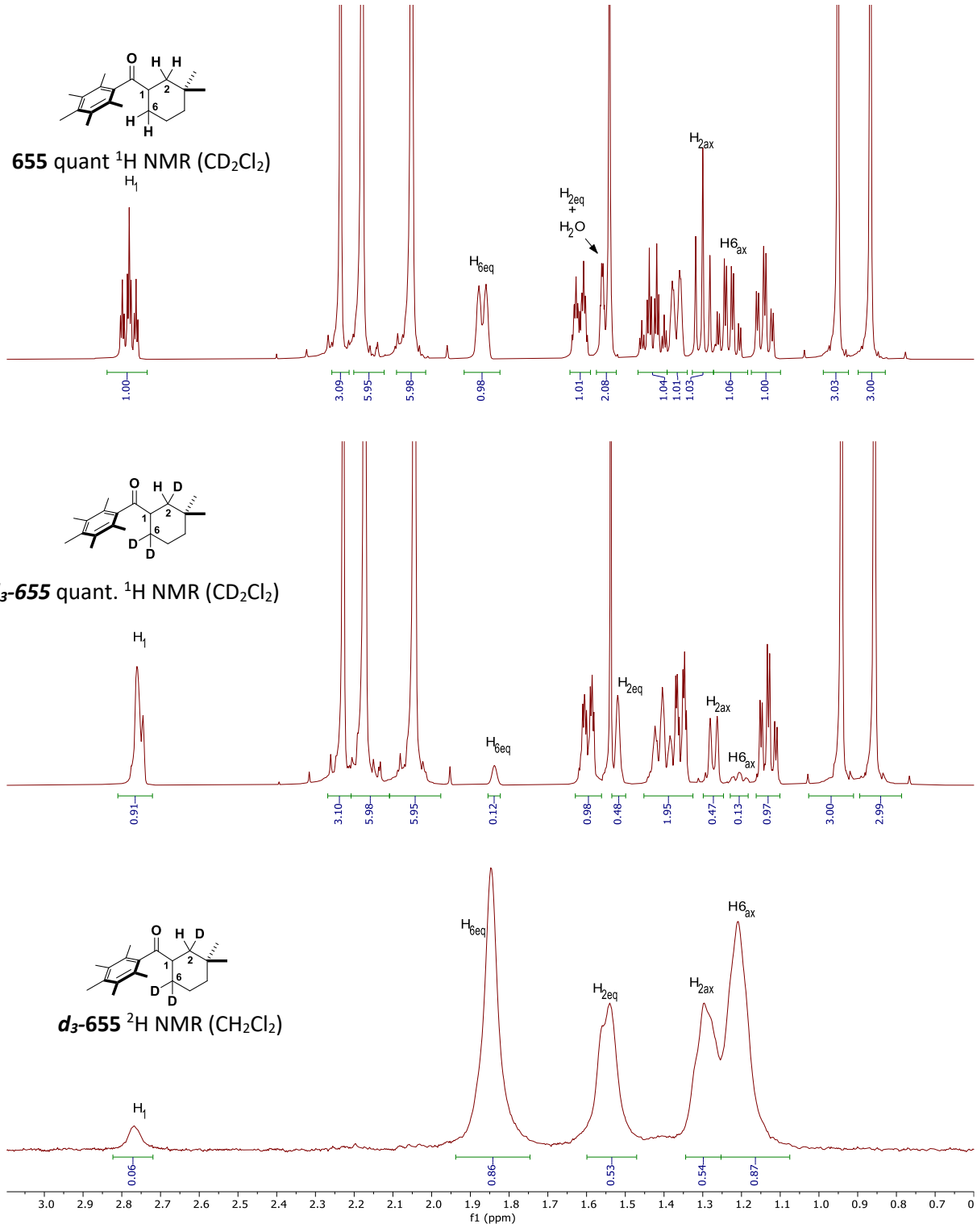


Scheme 3.21: A) Double label crossover experiment for the synthesis of cyclohexanes. Conditions: **187** (1 eq.), ***d*$_4$-514** (1 eq.), **669** (1 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h.

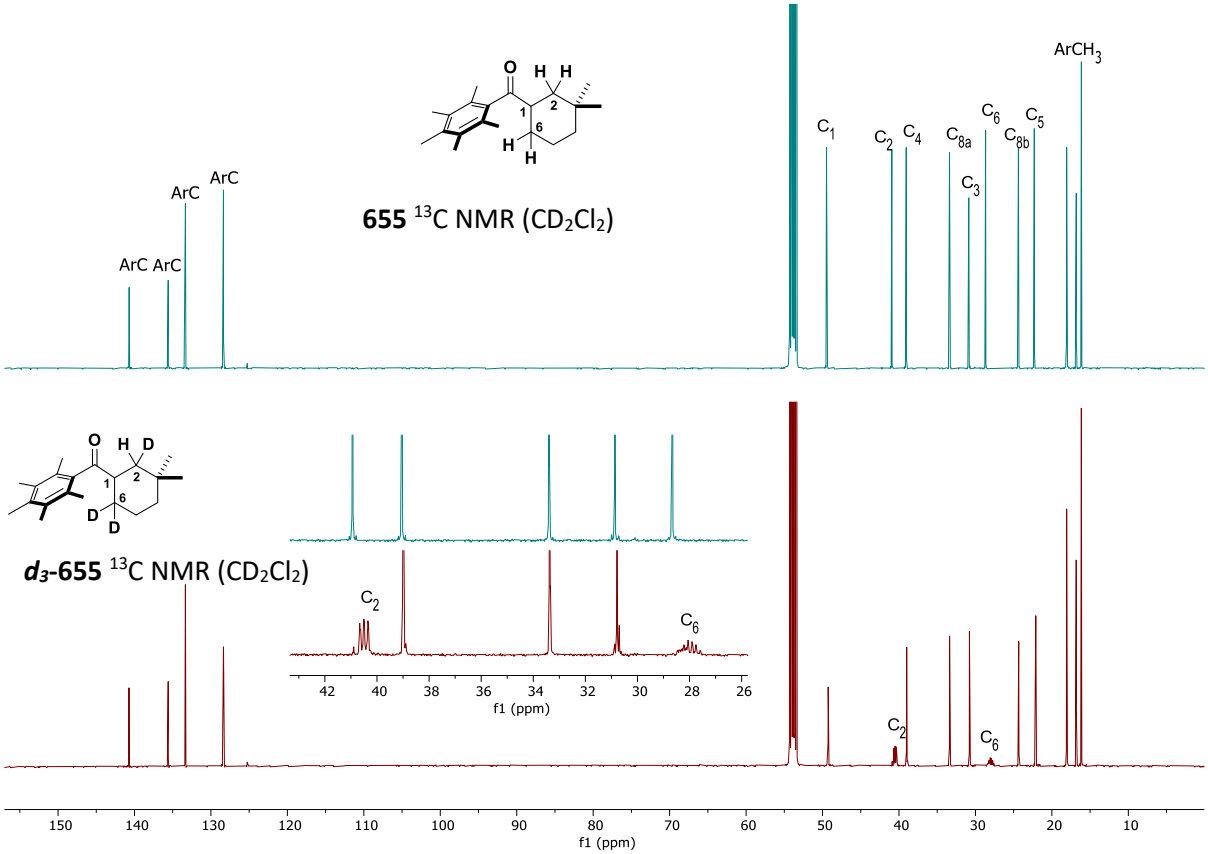
To support the conclusion that the reductive annulation reaction proceeded through the [1,5]-hydride shift cascade, we synthesised triply deuterated cyclohexene ***d*$_3$-541**, which is the proposed intermediate after the [1,5]-hydride shift, and subjected it to the same conditions for the reductive annulation in the presence of diols ***d*$_4$-514** and **669** (Scheme 3.22, A and B). From this reaction, we isolated cyclohexane ***d*$_3$-655** in 92% yield, with the deuterium incorporation being very similar to that of ***d*$_3$-655** from the crossover experiment in Scheme 3.24. Taking this data together, it seemed highly likely that the reductive annulation reaction to prepare cyclohexanes proceeded through a triply deuterated enone and therefore further supported our conclusion that the mechanism was [1,5]-hydride shift cascade.



Scheme 3.22: A) Preparation of triply deuterated cyclohexene ***d*$_3$-541**. Conditions: **187** (1 eq.), ***d*$_4$-514** (2 eq.), KOH (4 eq.), $[Ir(COD)Cl]_2$ (0.5 mol%), CataCXium® A (2 mol%), PhMe (0.25 M), 115 °C, 24 h. B) Transfer hydrogenation of ***d*$_3$-541** in the presence of diol ***d*$_4$-514** and **669**. Conditions: ***d*$_3$-541** (1 eq.), ***d*$_4$-514** (1 eq.), **669** (1 eq.), $[Ir(Cp^*)Cl_2]_2$ (2 mol%), KOH (4 eq.), PhMe (4 M), 110 °C, 24 h.



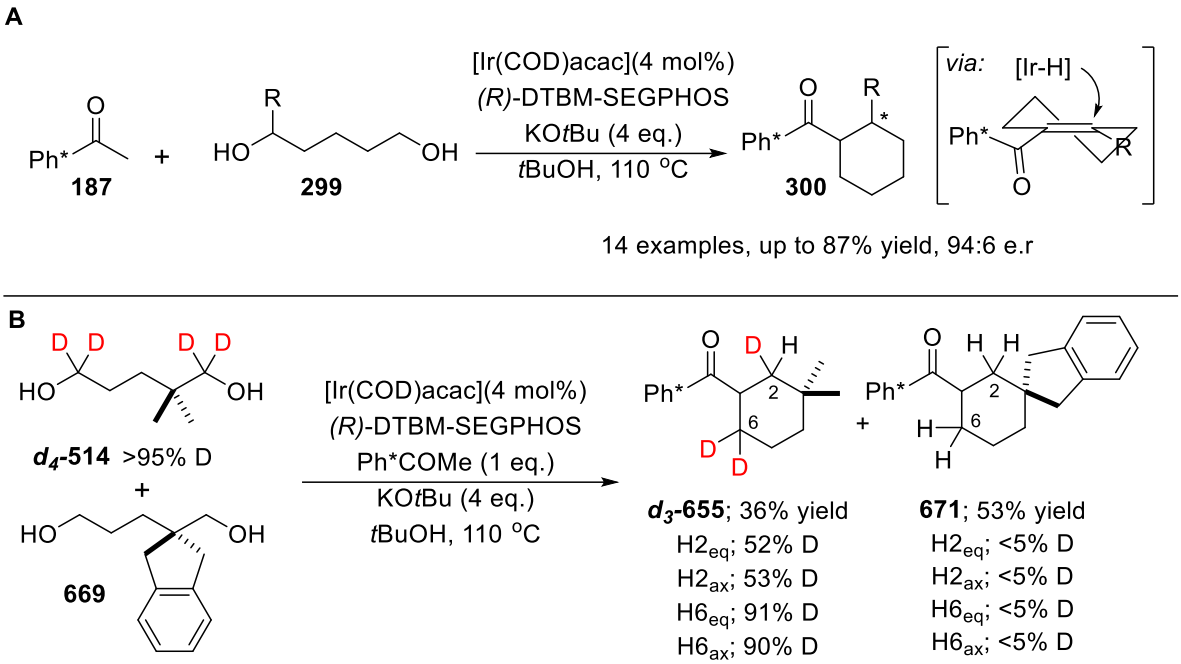
Scheme 3.23: Stack plot showing reference ^{1}H NMR spectrum of **655** along with quantitative ^{1}H NMR and ^{2}H NMR spectra of ***d*$_3$-655** from reductive cross over experiment.



Scheme 3.24: Stack plot showing reference ^{13}C NMR spectrum of **655** along with ^{13}C NMR spectra of ***d*$_3$-655** from reductive cross over experiment.

Having concluded that the reaction to prepare cyclohexenes and cyclohexanes both proceeded through a hydride shift cascade, we questioned whether several related annulation reactions reported by our group and others, also proceeded through this unusual mechanism.[109,110,111,112] The first of which that we investigated was the asymmetric synthesis of cyclohexanes using a chiral iridium complex bearing *(R)*-DTBM-SEGPHOS ligand (Scheme 3.25, A).[109] Analogous to the reductive annulation catalysed by $[Ir(Cp^*)Cl_2]_2$, this reaction was proposed to proceed through two hydrogen borrowing cycles, with the stereodetermining step being the final 1,4-reduction of the intermediate cyclohexene with Iridium hydride. To probe the mechanism of this reaction, we performed an analogous double label crossover experiment using diols ***d*$_4$-514** and **669** under the reported annulation conditions, which utilised strongly reducing conditions of [Ir(COD)acac] in conjunction with *(R)*-DTBM-SEGPHOS, potassium *tert*-butoxide in *tert*-butanol (Scheme 3.25, B). Under these conditions, no cyclohexene was observed, and we isolated 36% yield of cyclohexane ***d*$_3$-655**, and 53%

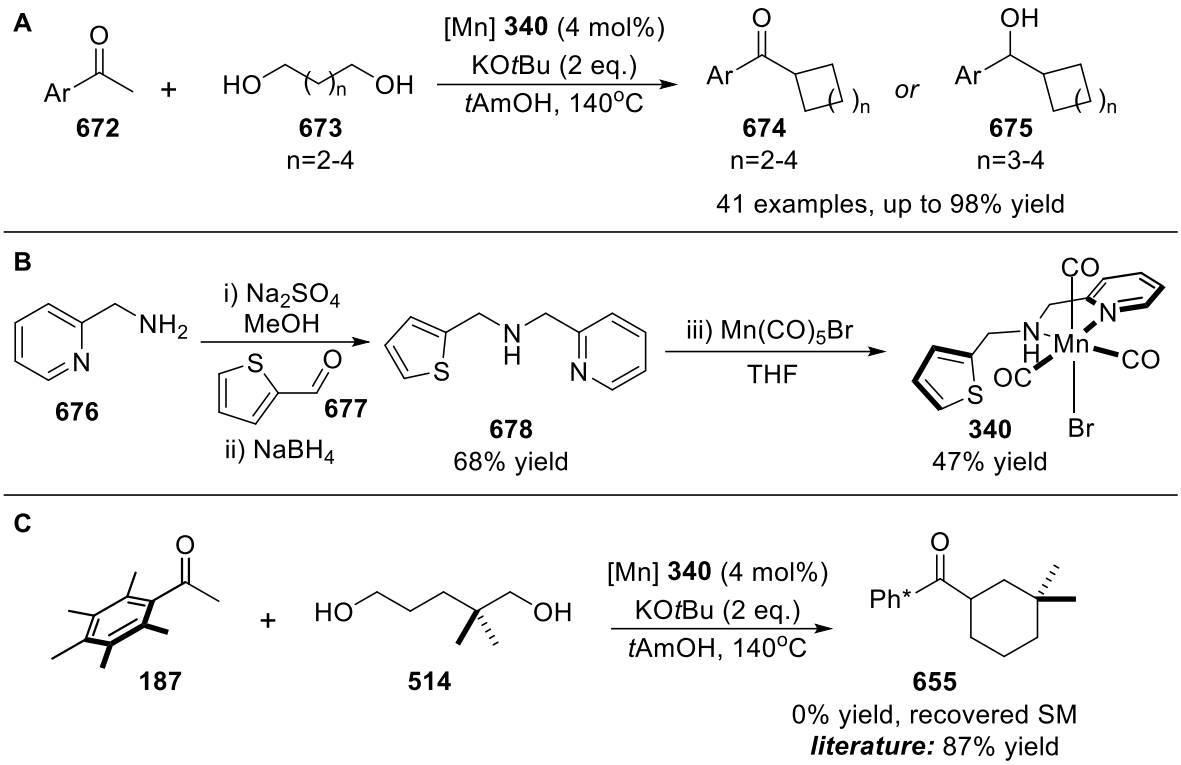
yield of cyclohexane **671**. When we analysed the deuterium incorporation of **671**, we found **671** to contain less than 5% deuterium, and notably no deuterium at C_6, which implied there was no crossover. Additionally, we observed no deuterium at C_2 from the 1,4-reduction step, consistent with [Ir(COD)acac]/*(R)*-DTBM-SEGPHOS undergoing a wash-out of deuterium as we saw in Scheme 3.14 with $[IrCp^*Cl_2]_2$. Cyclohexane ***d*$_3$-655** was found to contain 1.05 deuterium at C_2, and 1.81 deuterium at C_6. Based on this result, and the consistency between this data and the results from the crossover experiment in Scheme 3.21, we concluded that the intramolecular hydride shift mechanism was the predominant pathway for this reaction.



Scheme 3.25: A) catalytic asymmetric synthesis of cyclohexanes by hydrogen borrowing annulation. B) double label crossover experiment. Conditions: **187** (1 eq.), ***d*$_4$-514** (1 eq.), **669** (1 eq.), [Ir(COD)acac] (4 mol%), *(R)*-DTBM SEGPHOS (5 mol%), KO*t*Bu (4 eq.), ^{t}BuOH (3 M), 110 °C, 24 h.

We next wondered whether our hydride shift cascade was applicable to other transition metal-catalysed processes, such as manganese.[110,111] For example, Maji and co-workers have reported a manganese complex bearing an amino pyridyl ligand **340** that catalyses the annulation of diols and hindered ketones to prepare cyclohexanes (Scheme 3.26, A).[111] We prepared this complex by a sequential imine condensation of 2-(aminomethyl)-pyridine **676** with 2-thiophenecarboxyladehyde **677**, followed by reduction with sodium borohydride, to give ligand **678** in 68% yield (Scheme 3.26, B). Following this, **678** was reacted with manganese pentacarbonyl bromide under anhydrous conditions,

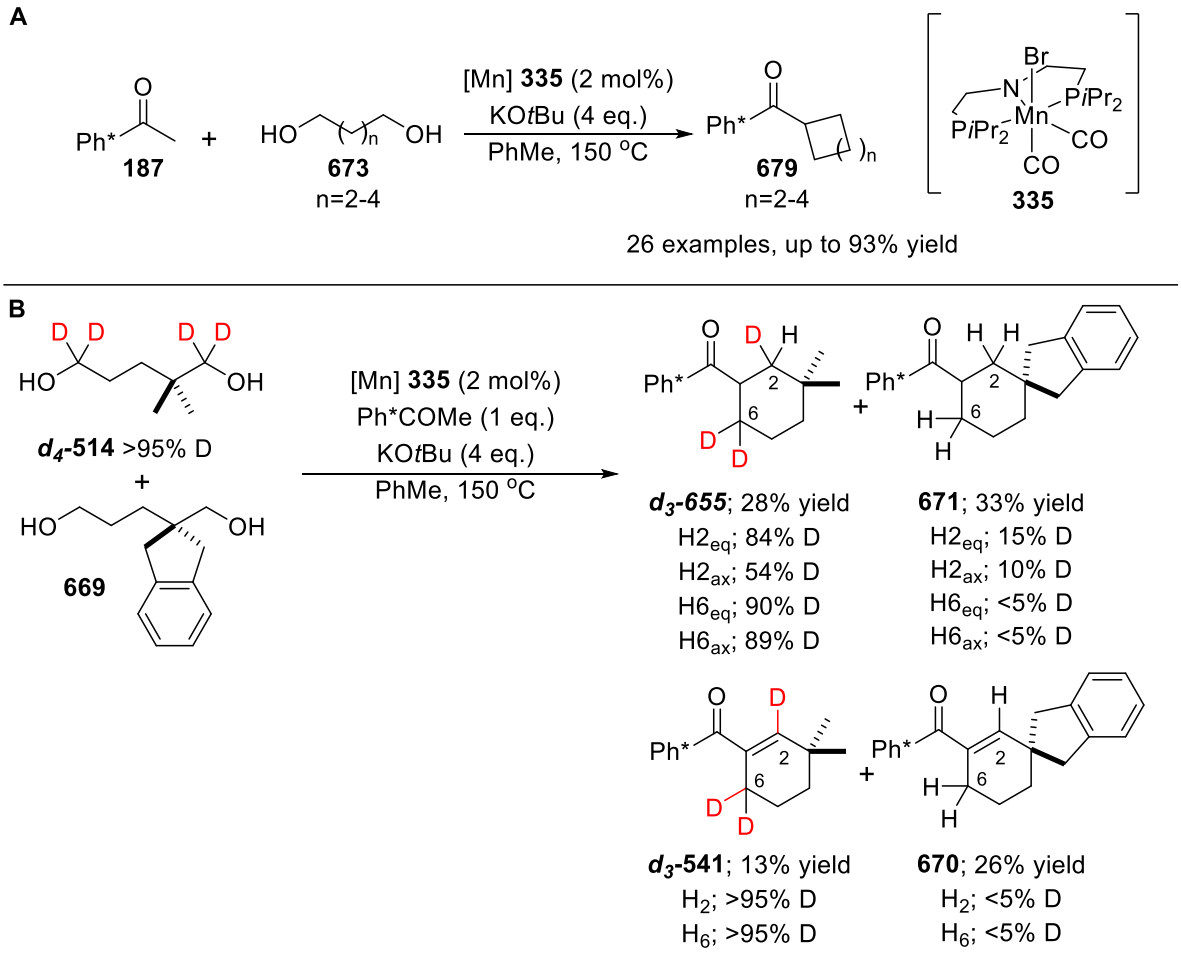
to afford manganese complex **340** in 47% yield. We then tried this catalyst **340** under the optimal conditions reported by the authors, but despite several attempts, we were unable to reproduce their results (Scheme 3.26, C).



Scheme 3.26: A) Manganese catalysed synthesis of cycloalkanes from methyl ketones and diols. B) two step synthesis of manganese complex **340**. Conditions i) 2-(aminomethyl)-pyridine (1.1 eq.) 2-thiophenecarboxyladehyde (1 eq.), Na_2SO_4 (2.5 eq.), MeOH (0.1 M), RT, 16 h. ii) $NaBH_4$, 50 °C, 1 h. C) failed repeated literature synthesis of **655**. Conditions: **187** (1 eq.), **514** (3 eq.), **340** (4 mol%), KO*t*Bu (2 eq.), *t*AmOH (1 M), 140 °C, 36 h.

Similar to the work of Maji, Leitner and co-workers reported the synthesis of cycloalkanes from diols and ketones using commercial manganese complex **335** (Scheme 3.27, A).[110] The authors proposed a mechanism consisting of two sequential hydrogen borrowing cycles, analogous to the mechanism previously proposed for the reductive annulation to prepare cyclohexanes with iridium complexes.[84] To probe this, we performed a double label crossover experiment using commercial manganese complex **335**, ketone **187**, labelled diol ***d*$_4$-514**, and diol **669** under their optimised conditions (Scheme 3.27, B). Under these reducing conditions, we obtained a mixture of cyclohexenes ***d*$_3$-541** and **670** in 13% yield and 26% yield, and cyclohexanes ***d*$_3$-655** and **671** in 28% yield and 33% yield, respectively. These were carefully separated by flash column chromatography, which enabled interrogation of the

deuterium incorporation, which revealed that cyclohexene **670** contained no deuterium at C_2 and C_6, consistent with no crossover between the labelled and unlabelled substrates. The corresponding cyclohexane **671** also contained no deuterium at C_6, and 0.25 deuterium at C_2, which was likely associated with a KIE from the 1,4-reduction of cyclohexene **670** with the manganese catalyst. Notably, we did not observe the wash-out of deuterium as we saw with iridium complexes. This could be rationalised by the reported pKa of two Manganese complexes being 14 and 20, which is several orders of magnitude less acidic than many iridium complexes reported in the literature.[108] Contrary to cyclohexene **670** and cyclohexane **671**, we found cyclohexene ***d*$_3$-541** to contain 2 deuterium atoms at C_6 and one deuterium and C_2 (>95% D at each position). The corresponding cyclohexane ***d*$_3$-655** also contained 2 deuterium atoms at C_6, and 1.38 deuterium at C_2, with the latter deuterium incorporation resulting from the KIE from the 1,4-reduction of cyclohexene ***d*$_3$-541** by the manganese catalyst. Taking the deuterium incorporation data together, it is consistent with the reaction proceeding through an intramolecular hydride shift.

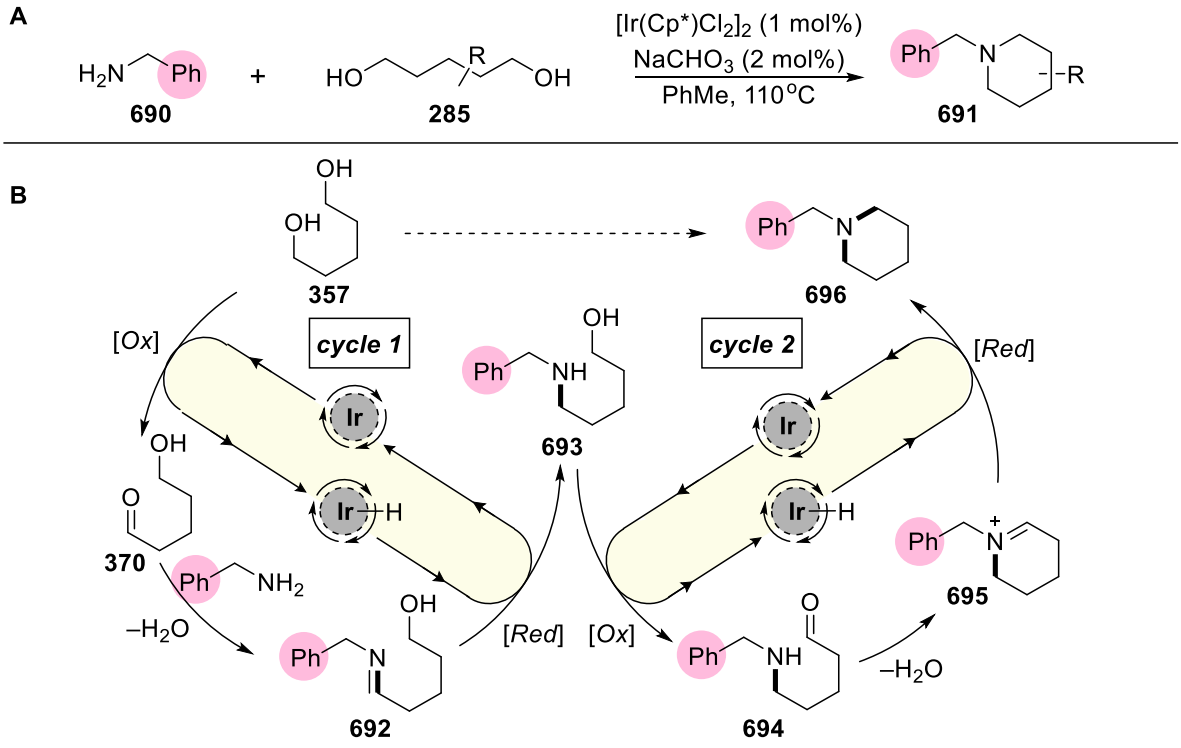


Scheme 3.27: A) Direct synthesis of cycloalkanes from diols and ketones using a homogeneous

manganese catalyst. B) Double label crossover experiment. Conditions: **187** (1 eq.), ***d*₄-514** (2 eq.), **669** (2 eq.), MnMACHO^{i}Pr complex **335** (2 mol%), KO*t*Bu (4 eq.), PhMe (0.25 M), 150 °C, 32 h.

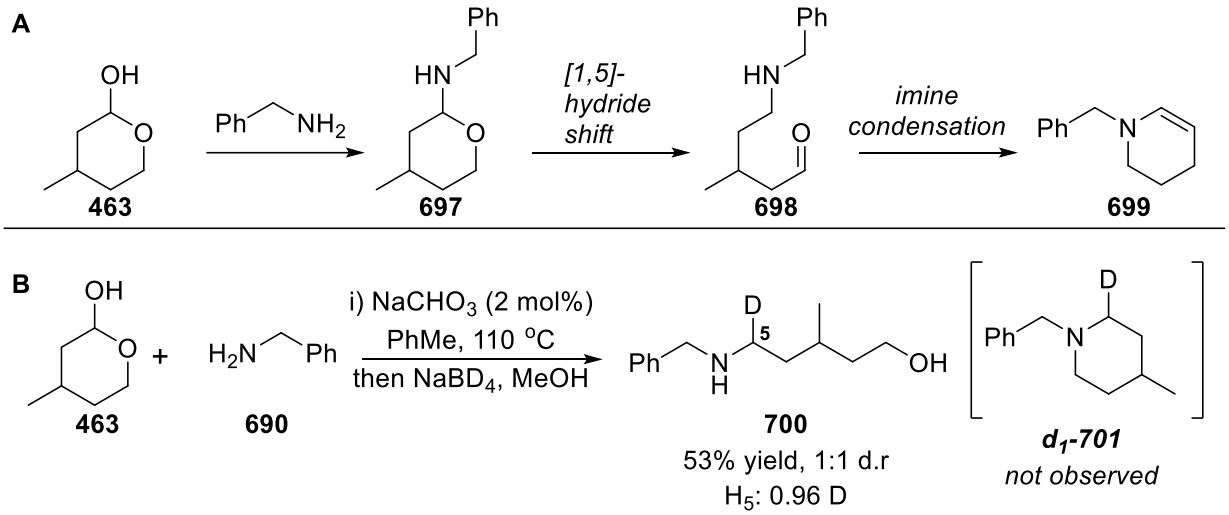
3.5 Double Label Crossover Experiment to Investigate the Annulation Reaction to Prepare Piperidines

The final reaction we investigated was the hydrogen borrowing annulation of diols and primary amines to prepare aza-heterocycles (Scheme 3.28, A).[112] This reaction has been reported by Feringa[113], Donohoe[112], Fujita[114], Williams[115] and others[116], with a range of transition metal catalysts such as iridium[112], ruthenium[117], rhodium[118] and iron[113] to name but a few. Mechanistically, the reaction is proposed to begin with oxidation of diol **357** by the transition metal catalyst such as $[Ir(Cp^*)Cl_2]_2$, to give hydroxy-aldehyde **370** (Scheme 3.28, B). Aldehyde **370** then condenses with benzylamine to give imine **692**, poised for reduction with iridium hydride to give hydroxyamine **693**. Compound **693** then enters the second hydrogen borrowing cycle, where it is oxidised to amino-aldehyde **694**. Finally, **695** self-condenses to give iminium **695**, which is reduced by iridium hydride to afford the desired piperidine.



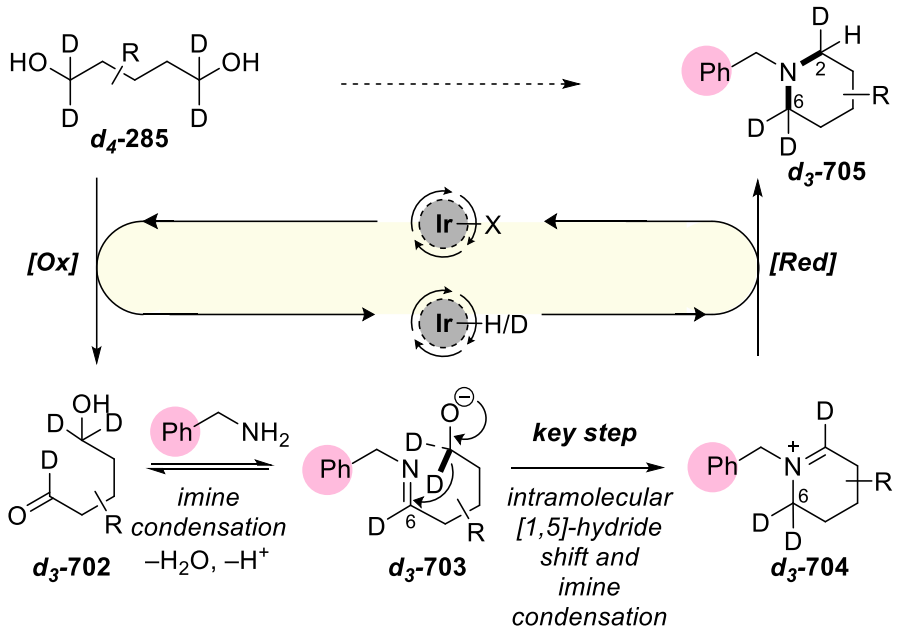
Scheme 3.28: A) Hydrogen borrowing annulation strategy for the stereocontrolled synthesis of saturated aza-heterocycles. B) Proposed reaction mechanism.

To probe this mechanism, we began by looking at whether there was a possibility of a hydride transfer step directly from imine **697** to aldehyde **698**, which would be comparable to the mechanism we uncovered for the synthesis of cyclohexanes (Scheme 3.29, A). To determine whether this was feasible, we subjected lactol **463** and benzylamine under the optimised reaction conditions in the absence of $[Ir(Cp^*)Cl_2]_2$ (Scheme 3.29, B). After heating overnight, we added $NaBD_4$, which would reduce the putative iminium **699** to give **d_1-701**. Under these conditions, the only product we isolated was amino alcohol **700**. Analysis of the deuterium incorporation revealed one deuterium at C_5, which suggested that only the condensation of benzylamine with lactol **463** occurred under these conditions, and the annulation reaction was transition metal catalysed.

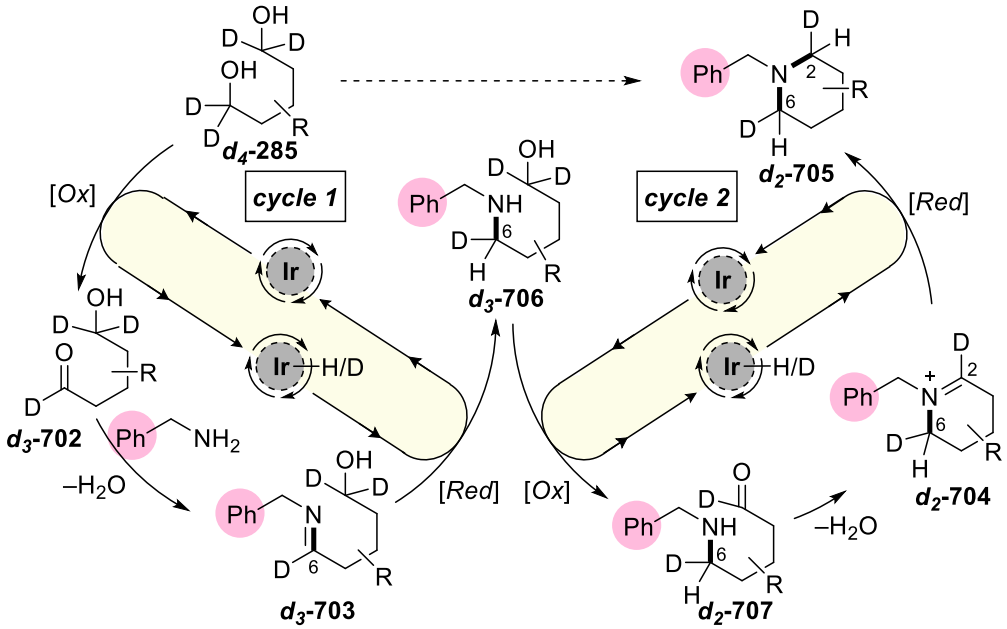


Scheme 3.29: A) Proposed hydride shift pathway for annulation reaction to prepare dihydropiperidines. B) Resubjection experiment of lactol **463** to the reaction conditions for the synthesis of aza-heterocycles. i) **463** (1 eq.), benzylamine (1.5 eq.), $NaCHO_3$ (2 mol%), PhMe (2 M), 110 °C, 16h, then MeOH (1 M), $NaBD_4$ (2 eq.), RT, 1 h.

To confirm that the reaction proceeded *via* two hydrogen borrowing cycles, catalysed by $[Ir(Cp^*)Cl_2]_2$, we set out to perform a double label crossover experiment using diols ***d_4*-514** and **669** under the optimal conditions for the synthesis of piperidines. If the reaction were to proceed through a hydride shift, we anticipate that the labelled substrate would contain two deuterium at C_6 and one deuterium at C_2, with the deuterium incorporation upon the reduction of iminium ***d_3*-704** to piperidine ***d_3*-705** being negligible due to wash-out of D/H as seen in Scheme 3.14 (Scheme 3.30). In contrast, if the reaction were to proceed through two oxidation and reduction steps, we predict the labelled piperidine ***d_2*-705** would contain only one deuterium at C_2 and one deuterium at C_6, due to 1,2-reduction of the imine with predominantly hydrogen (from wash-out of Iridium D/H) (Scheme 3.31).

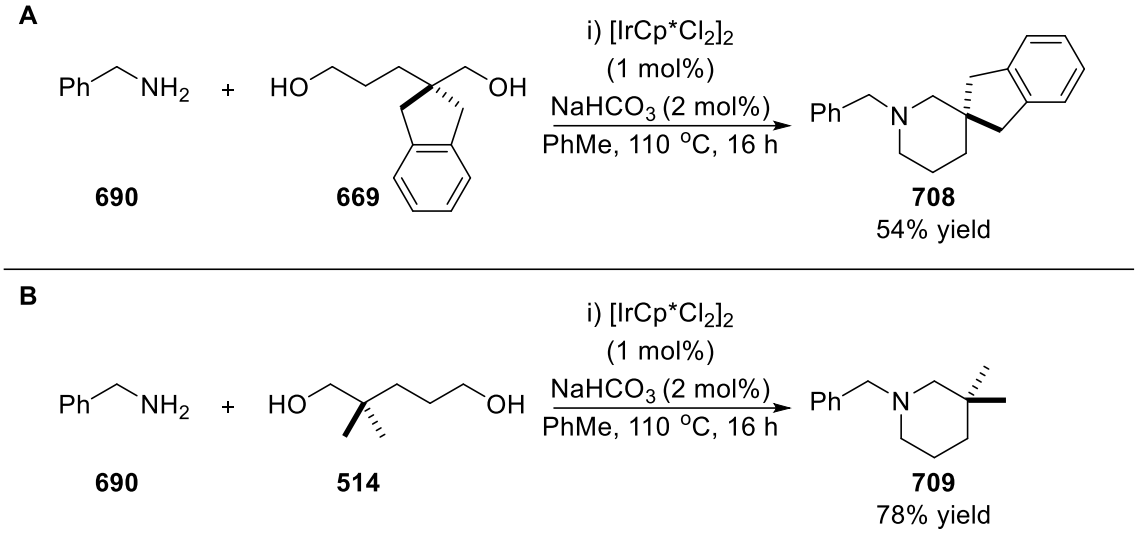


Scheme 3.30: Predicted deuterium incorporation for [1,5]-hydride shift mechanism



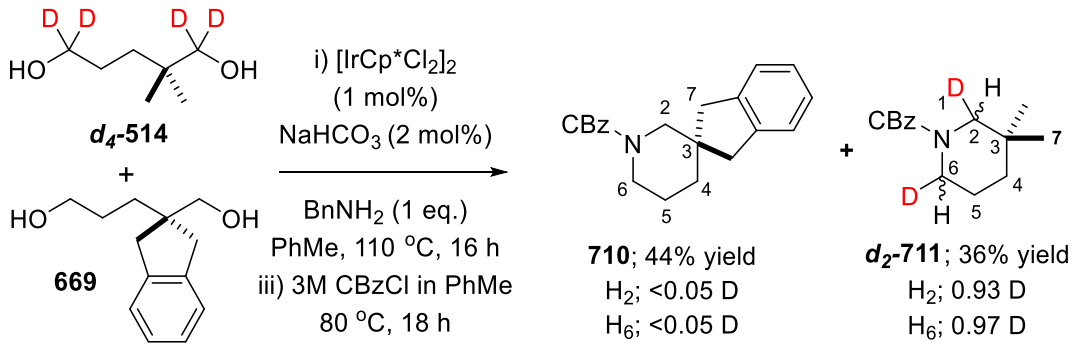
Scheme 3.31: Predicted deuterium incorporation for hydrogen borrowing mechanism

To confirm the suitability of diols **514** and **669** for a double label crossover experiment, we subjected them to the optimised reaction conditions for the annulation reaction to synthesise piperidines (Scheme 3.32). Pleasingly, we found that diol **669** afforded the corresponding piperidine **708** in a 54% yield (A). Similarly, subjecting diol **514** to the optimised reaction conditions resulted in the isolation of piperidine **709** in 78% yield.



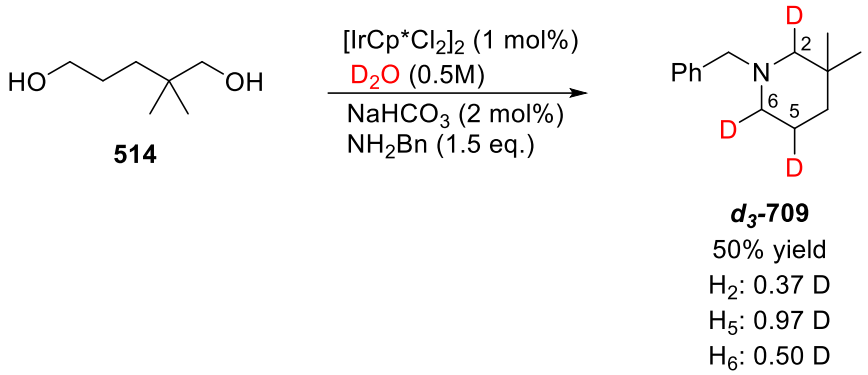
Scheme 3.32: Feasibility of diols **669** and **514** for the double label crossover experiment. Conditions: i) diol (1 eq.), benzylamine (1.5 eq.), $[IrCp^*Cl_2]_2$ (1 mol%), $NaCHO_3$ (2 mol%), PhMe (2 M), 110 °C, 16 h.

Upon performing the double label crossover experiment, we isolated an inseparable mixture of piperidines **708** and **709** in 44% yield and 36% yield, respectively (Scheme 3.33). They were then derivatised with CBzCl to cleanly separate the mixture of carbamates by flash column chromatography, which enabled analysis of the deuterium incorporation. The quantitative ^1H NMR spectrum revealed that piperidine **710** contained no detectable deuterium, consistent with a high degree of wash-out of deuterium due to iridium undergoing rapid H/D exchange as we saw in Scheme 3.14. Analysis of the deuterium incorporation of ***d*$_2$-711** showed that there was 0.93 deuterium at H_2 and 0.97 deuterium at H_6. The incorporation of one deuterium atom at each position was further corroborated by the ^2H NMR spectrum, which showed two singlets, and by ^{13}C NMR, which showed two 1:1:1: triplets. Taken together, this deuterium pattern was consistent with two sequential oxidation and reduction steps by $[Ir(Cp^*)Cl_2]_2$, and not a [1,5]-hydride shift mechanism.



Scheme 3.33: Double label crossover experiment for the synthesis of aza-heterocycles. Conditions: i) ***d*$_4$-514** (0.5 eq.), **669** (0.5 eq.), benzylamine (1.5 eq.), $[IrCp^*Cl_2]_2$ (1 mol%), $NaCHO_3$ (2 mol%), PhMe (2 M), 110 °C, 16 h. iii) 3M benzyl chloroformate in PhMe (12 eq.), 80 °C, 15 h.

As a testament to the high degree of washout of deuterium in the experiment in Scheme 3.32, we performed the hydrogen borrowing annulation reaction using diol **514** under the literature reported conditions in D_2O (Scheme 3.34).[112] From this experiment, we cleanly obtained piperidine ***d*$_3$-709** in 50% yield. Interrogation of the deuterium incorporation revealed that piperidine ***d*$_3$-709** contained 0.37 deuterium at C_2, 0.5 deuterium at C_6 and 0.97 deuterium at C_5. This remarkable result from performing the reaction in the presence of D_2O further illustrates how $[IrCp^*Cl_2]_2$ readily undergoes H/D exchange with the protic solvent, resulting in the deuteration of piperidine ***d*$_3$-709**.



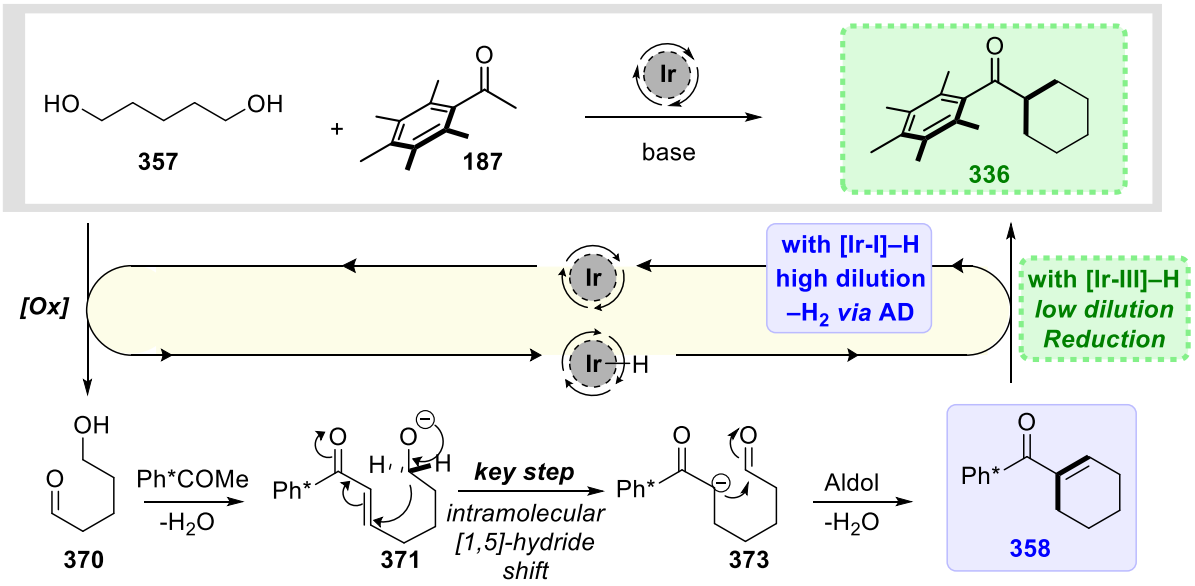
Scheme 3.34: Reaction of diol **514** in the annulation reaction to prepare piperidines in the presence of D_2O. Conditions: **514** (1.0 eq.), benzylamine (1.5 eq.), $[IrCp^*Cl_2]_2$ (1 mol%), $NaCHO_3$ (2 mol%), D_2O (0.5 M), 110 °C, 16 h.

3.6 Conclusion

In conclusion, we have undertaken a detailed mechanistic investigation of our methodology to synthesise acyl cyclohexenes from pentamethylacetophenone and 1,5-pentane diols.[119] This process was promoted by an iridium (I) catalyst bearing trialkyl phosphine ligand CataCXium® A. Through monitoring the course of the reaction, we determined that the primary role of the catalyst was to oxidise the diol to the corresponding lactol (hydroxy-aldehyde) by an acceptorless dehydrogenation, which resulted in the evolution of hydrogen gas. We subsequently found that the resulting lactol undergoes aldol condensation with pentamethylacetophenone to give tetrahydropyran **631**, which was observed in the time-course experiment and also resubjected to the reaction conditions.

We also discovered that tetrahydropyran **631** undergoes a highly unusual [1,5]-hydride shift and aldol condensation in the absence of the iridium catalyst, to furnish the desired cyclohexene product. This transition metal-free mechanistic pathway was confirmed by a double label crossover experiment under the optimised reaction conditions, which confirmed that it was indeed an intramolecular hydride shift.

Subsequently, we performed an analogous double label crossover experiment under related reaction conditions for the synthesis of cyclohexanes from diols and pentamethylacetophenone.[84] Contrary to the proposed mechanism of a 'double hydrogen borrowing' cycle, we found that this reaction also proceeded through the intramolecular [1,5]-hydride shift pathway. Consequently, this allowed us to form a unified reaction mechanism for the two reactions (Scheme 3.35), whereby the diol undergoes oxidation with the iridium catalyst to give hydroxyaldehyde **370**, which is poised for an aldol condensation with pentamethylacetophenone. The resulting enone **371** then undergoes an intramolecular [1,5]-hydride shift to afford dicarbonyl **373**, which condenses to form cyclohexene **358**. In the presence of more reducing iridium (III) hydride catalysts, such as $[IrCp^*Cl_2]_2$, cyclohexene **358** is reduced to the corresponding cyclohexane **336**, regenerating the active iridium catalyst. Alternatively, with Iridium (I) catalyst alongside bulky CataCXium® A ligand, iridium hydride is recycled by protonation, which evolves hydrogen gas, and enables isolation of the desired cyclohexene **358**.



Scheme 3.35: Unified reaction mechanism for the iridium-catalysed synthesis of cyclohexanes and cyclohexenes.

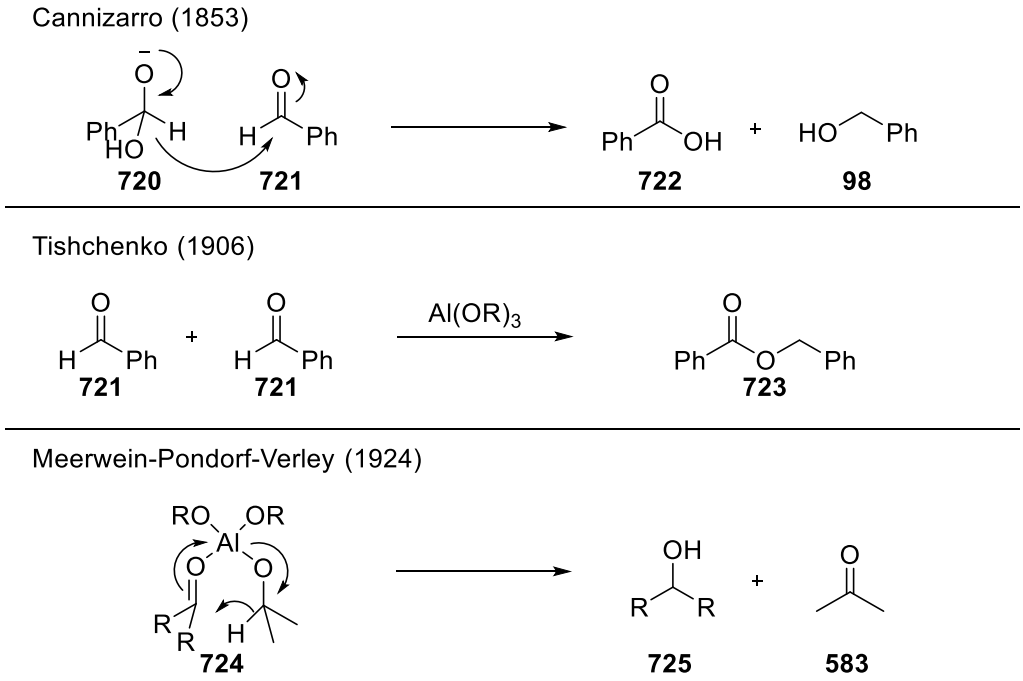
Finally, we investigated the reaction mechanism of several other related transition metal-catalysed annulation reactions that utilise diols. In this instance, we found that a manganese-catalysed annulation reaction to prepare cycloalkanes also proceeded through a [1,5]-hydride shift cascade, contrary to the author's proposed reaction mechanism.[110] Similarly, we investigated the iridium-catalysed annulation reaction to prepare aza-heterocycles from diols and found that this reaction proceeds through two hydrogen borrowing cycles and not a hydride shift cascade.[112]

Chapter 4: Cyclohexene Synthesis by Aluminium-Mediated [1,5]-Hydride Shift Aldol Cascade

4.1 Introduction

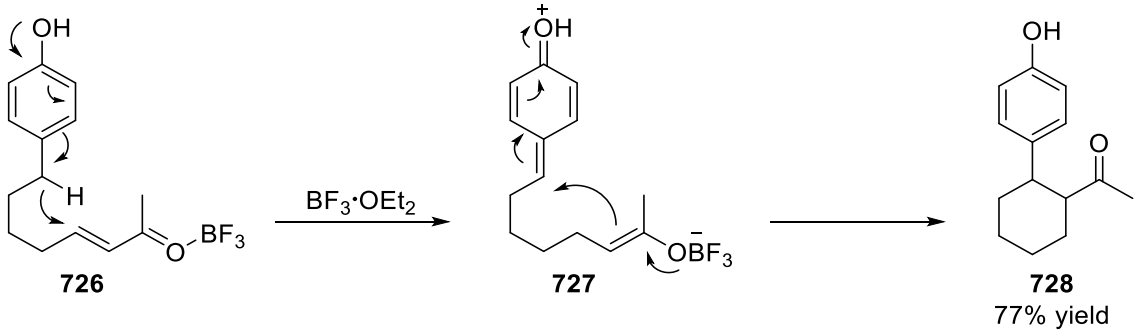
In the previous chapter, we identified through a detailed mechanistic study that our iridium-catalysed [5+1] annulation proceeded through an intramolecular [1,5]-hydride shift between an alcohol and an enone.[119]

Classically, a [1,5]-hydride shift consists of the migration of a hydrogen atom from a hydride donor to an acceptor, such as a π system.[120] The earliest reported example of this process was the Cannizzarro reaction in 1853, consisting of a base mediated disproportionation of benzaldehyde into benzoic acid **722** and benzyl alcohol **98** (Scheme 4.1).[121] Closely relating to this, the Tishchenko reaction could be considered the first example of a reaction proceeding through a hydride shift followed by a functionalisation event, which in this instance is the formation of an ester.[122] Later, in 1924, Meerwein-Pondorf-Verley reduction was reported, which mechanistically proceeds through a preorganised Al^{3+} species **724**, which coordinates the aldehyde and the alcohol for a [1,5]-hydride shift.[123,124,125]



Scheme 4.1: Illustrative [1,5]-hydride shift reactions

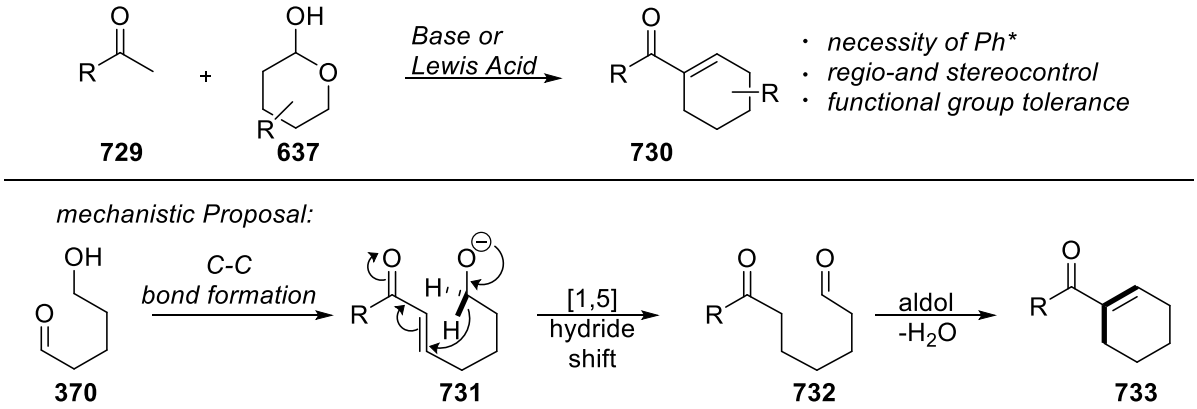
These historical reactions form the foundation for what has become a well-known C-H bond functionalisation strategy, whereby the [1,5]-hydride shift is followed by a functionalisation event. Most commonly, this consists of a ring closure step, such as the work of Atkinson, where the authors react acyclic enone **726** with boron trifluoride to form cyclohexane **728** (Scheme 4.2).[126]



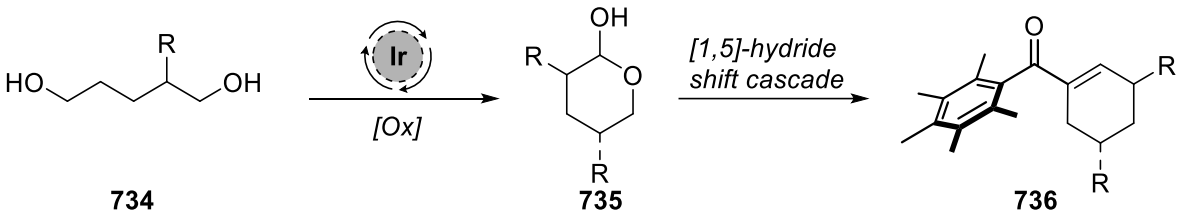
Scheme 4.2: Representative example of [1,5]-hydride shift followed by a ring closure step.

Contemporary examples of this reaction utilise a range of hydride donors, which are most commonly ethers[127], benzylic groups[128], and tertiary amines[129]. The hydride acceptor varies hugely, including ketones[130], aldehydes[131], imines[132], enones[133,134,135] and alkynes[136], to name but a few examples. The feasibility of the [1,5]-hydride shift between these donors and acceptors depends strongly on the electrophilicity of the acceptor, and the stability of the carbocation formed upon migration of the hydride. To facilitate this, Lewis acids and Bronsted acids are usually employed to increase the electrophilicity of the hydride acceptor, and more rarely bases to activate the hydride donor.[137] Examples of reagents employed to promote hydride transfer include phosphoric acid derivatives,[138] magnesium triflate,[139] gold complexes,[140,141] scandium triflate,[142,143] boron trifluoride,[144] *p*-toluene sulfonic acid[145].

Based on the wealth of literature for hydride shift reactions,[146] our aim at the outset of this project was to develop a new methodology to prepare cyclohexenes based on the intramolecular [1,5]-hydride shift cascade we uncovered in chapter three (Scheme 4.3). Notably, we wanted to address the key limitations of this previous approach. Firstly, the stringent requirement for the use of pentamethylacetophenone, and how the reaction fails when applied to other ketones. Secondly, the use of an expensive transition metal catalyst. Thirdly, the functional group tolerance of the reaction, which was limited to functionality that was compatible with iridium hydride and strongly basic conditions. Finally, when non-symmetrical pentane diols were used, a regioisomeric mixture of the corresponding hydroxy aldehyde was obtained, leading to two cyclohexene regioisomers (Scheme 4.4). This consequently limited the scope to symmetrical 1,5-diols and sterically biased diols.



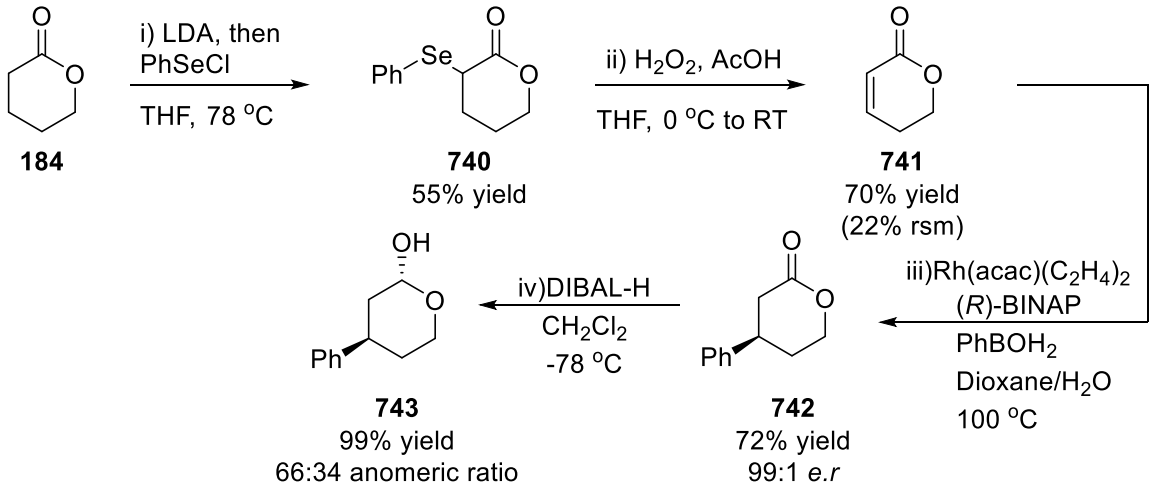
Scheme 4.3: Proposed new methodology to prepare cyclohexenes from lactols.



Scheme 4.4: Regioisomeric mixtures of acyl cyclohexenes obtained from non-symmetrical 1,5-diols.

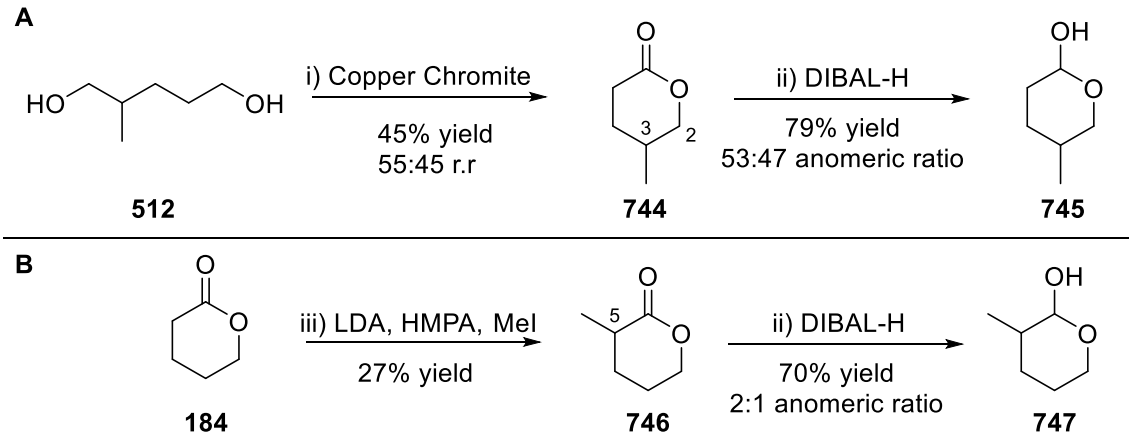
4.2 Base Promoted [1,5]-Hydride Shift Reaction

Based on our mechanistic proposal, if we were to replace our diol starting material with a preformed lactol, then we would remove the requirement for a transition metal catalyst. Additionally, if we were to prepare a non-symmetrical lactol, then we would expect to obtain a stereo- and regioisomerically pure cyclohexene, which would solve a key drawback of the previous methodology. To probe this hypothesis, we looked to prepare enantioenriched lactol **743** (Scheme 4.5). This was prepared in a four step sequence starting from δ-valerolactone **184**. The first step of the synthesis involved α-alkylation of δ-valerolactone with LDA and phenylselenyl chloride, which yielded **740** in 55% yield on multigram scale. Treatment of **740** with hydrogen peroxide triggered oxidation to the selenoxide, which underwent facile elimination in acetic acid to yield the desired enone **741** in 70% yield. Enone **741** was then subjected to literature precedented Hiyashi conjugate conditions, which enabled isolation of enantioenriched lactone **742** in 72% yield and 99:1 e.r.[147] We were pleased to find that the specific rotation of **742** matched the literature value, confirming our stereochemical assignment. Finally, lactone **742** was treated with DIBAL-H to afford the desired lactol **743** in 99% yield.



Scheme 4.5: Synthesis of enantioenriched lactol **743**. Conditions: i) LDA (1.1 eq.), δ-valerolactone (1 eq.), THF (0.4 M), -78 °C, 1 h, then PhSeCl (1.2 eq.), -78 °C, 1 h. ii) **740** (1 eq.), 30% aq. H_2O_2 (1 eq.), THF (0.4 M), 0 °C to RT, 30 min. iii) **741** (1 eq.), Rh(acac)(C_2H_4) (3 mol%), *(R)*-BINAP (4 mol%), phenyl boronic acid (5 eq), 1,4 dioxane (0.2 M), water (2 M), 100 °C, 3 h. iv) **742** (1 eq.), DIBAL-H (1.4 eq.), CH_2Cl_2 (0.5M), -78 °C, 3 h.

In addition to enantioenriched lactol **743**, regioisomerically pure lactols **745** and **747** were investigated (Scheme 4.6). Lactol **745** was prepared in two steps, starting with the oxidation of diol **512** to lactone **744**, which was performed by Dr R. J. Armstrong. This resulted in the formation of two regioisomers, which were then carefully separated by flash column chromatography. The identity of the two regioisomers were confirmed by COSY NMR, with the diagnostic signals for **744** being a correlation between the H_3 environment and H_2, which corresponded to the CH_2 adjacent to oxygen. With lactone **744** in hand, treatment with DIBAL-H gave lactol **745** in 79% yield. To prepare the corresponding lactol regioisomer **747**, δ-valerolactone **184** was treated with LDA, HMPA and MeI to α-alkylate the lactone in 27% yield. Lactone **746** was then reacted with DIBAL-H to give the desired product **747** in 70% yield.



Scheme 4.6: Preparation of lactols **745** and **747**. Conditions: i) **512** (1 eq.), Copper chromite (2 mol%), 200 °C, 16-41h. ii) **744** or **746** (1 eq.), 1M DIBAL-H in hexane (1.4 eq.), CH_2Cl_2 (0.5M), -78 °C, 3 h. iii) **184** (1 eq.), LDA (1.1 eq.), THF (0.2M), -78 °C, 1 h, then MeI (1 eq.), HMPA/THF (0.2 M), -78 °C, 3 h. **744** and **746** were prepared by Dr R. J. Armstrong.

With lactols **743**, **745** and **747** in hand, we treated them with Ph*COMe and potassium hydroxide in the absence of the iridium catalyst. Promisingly, enantiopure lactol **743** afforded a 70% yield of the desired cyclohexene, but we were disappointed to find that significant erosion of the stereochemistry had occurred, to give a near racemic mixture (58:42 *e.r*). When δ-substituted lactol **745** was investigated, we discovered that reaction delivered a 75:25 mixture of C_3 and C_5 substituted products. The erosion of regiochemistry was even more pronounced for α-substituted lactol **747**, with C_3-substituted cyclohexene observed as the major product in 74% yield (57:43 *r.r*).



187 637 374

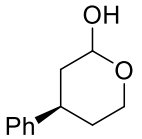
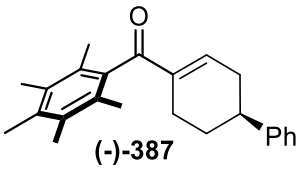
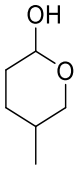
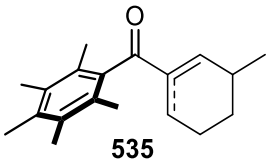
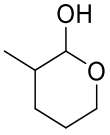
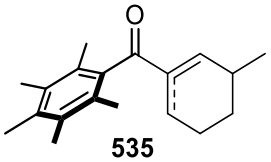
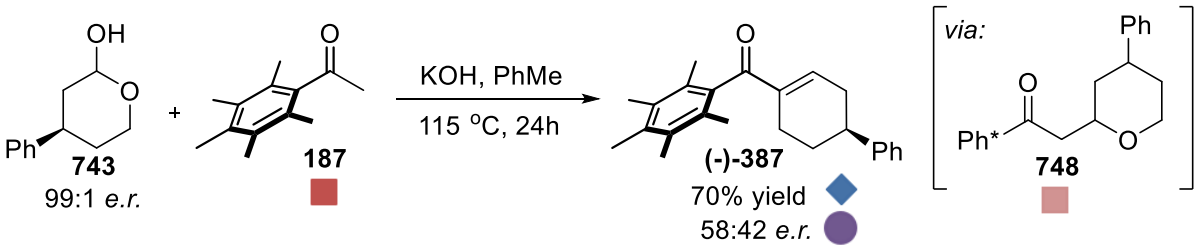
Entry	Starting material	Product	Yield (%)
1	 **743** 99:1 *e.r*	 **(-)-387**	70 58:42 *e.r*
2	 **745**	 **535**	70 75:25 *r.r*
3	 **747**	 **535**	74 57:43 *r.r*

Table 4.1: Reaction of lactols **743**, **745** and **747** under the transition metal-free annulation conditions. Conditions: lactol (2 eq.), Ph*COMe (1 eq.), KOH (4 eq.), toluene (0.2M), 115 °C, 14 h. Yields refer to

isolated material after column chromatography. Compound **535** was obtained as an inseparable mixture of regioisiomers.

To probe the observed racemisation of lactol **743**, we performed a time course experiment to monitor how the conversion and enantiomeric excess changes with time. This was performed by taking an aliquot of the reaction mixture every 30 minutes and running a quantitative ^{1}H NMR spectrum to determine the conversion, and injecting a sample into the chiral HPLC to measure the enantiomeric excess. We found that Ph*COMe **187** was steadily consumed over the first three hours, alongside concomitant formation of tetrahydropyran **748**. Cyclohexene ***(-)*-387** steadily reached full conversion within three hours. The enantiomeric excess of cyclohexene ***(-)*-387** was found to rapidly fall from 98% to approximately 30% within thirty minutes, plateauing at 16% *e.e*.



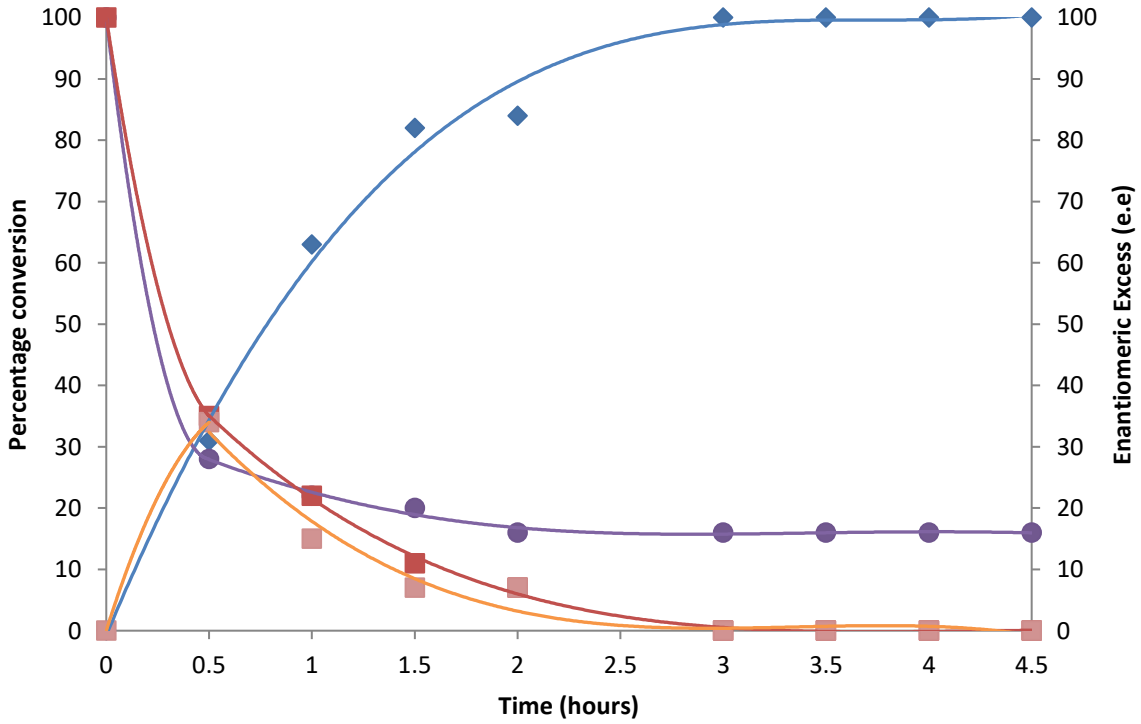
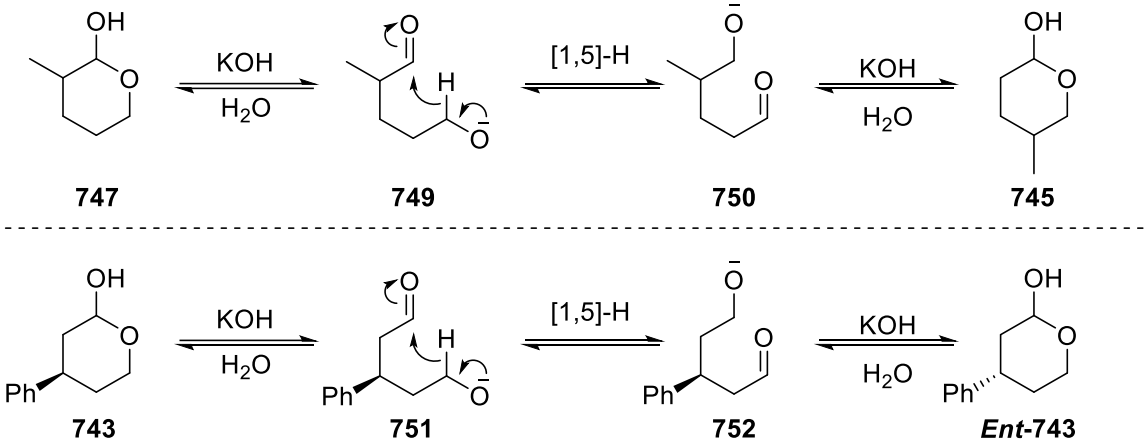


Figure 4.1: Plot of enantiomeric excess (purple line) and percentage conversion of **187** (red line), **748**

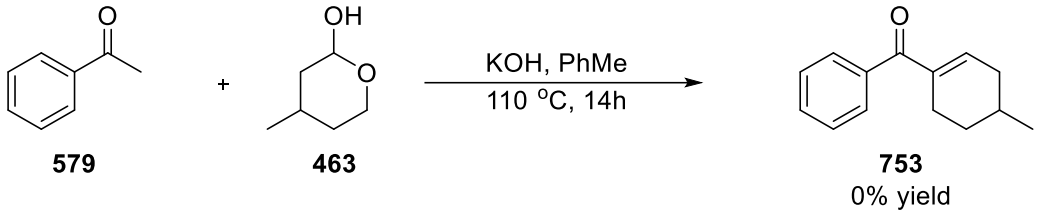
(orange line) and ***(-)*-387** (blue line) versus time (hours). Percentage conversion measured by Q ^{1}H NMR. Enantiomeric excess determined by chiral HPLC.

Based on the time course experiment and the observed yields in Table 4.1, we speculated that the stereo- and regiochemical erosion we observed was due to the lactol undergoing an unusual isomerisation pathway where the open-chain alkoxyaldehyde **749** can undergo an intramolecular [1,5]-hydride shift, affording the opposite regio- and stereoisomer (Scheme 4.6). Consequently, even if we were to subject single regio- and stereoisomers of the lactol starting material to the reaction conditions, this background isomerisation pathway completely hampers our ability to obtain cyclohexenes with high regio- and enantioselectivity.



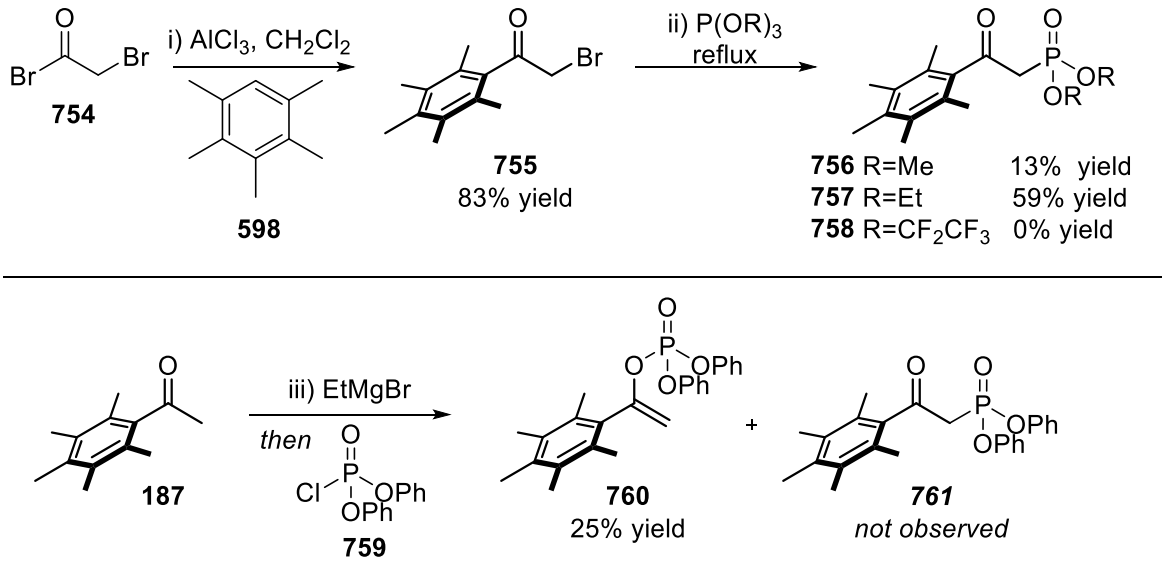
Scheme 4.6: Proposed isomerisation pathway of lactol **747** and **743** *via* an intramolecular [1,5]-hydride shift.

Further to these issues, we encountered that these basic conditions were limited to pentamethylacetophenone (Scheme 4.7). When acetophenone **579** was reacted with lactol **463**, a complex mixture of products was obtained, suggesting problems with chemoselectivity in the aldol step of the reaction. It was very clear from this result and Table 4.1 that these challenges of stereocontrol, regiocontrol and chemoselectivity needed to be addressed for us to develop a practical and general method to synthesise cyclohexenes.



Scheme 4.7: Attempted reaction of acetophenone with lactol **463**. Conditions: lactol (2 eq.), PhCOMe (1 eq.), KOH (4 eq.), toluene (0.2M), 115 °C, 14 h.

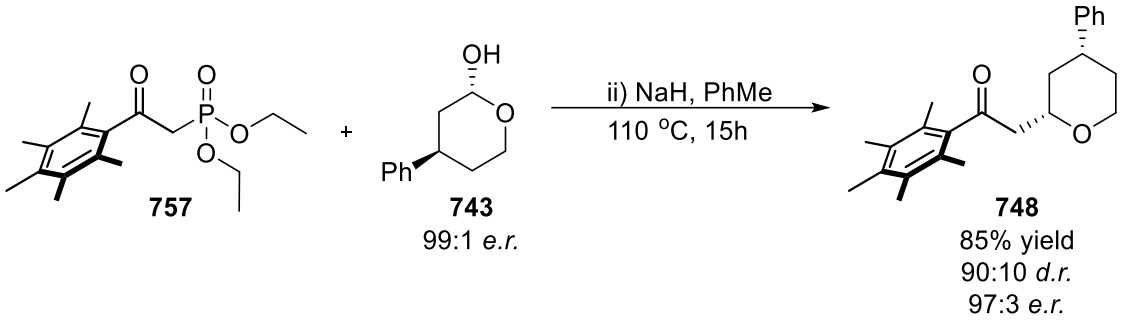
Given that the aldol step of the reaction proved challenging, we next investigated dialkyl phosphonates as nucleophiles (Scheme 4.8). To accomplish this, α-bromoacetylbromide **754** was acylated with pentamethylbenzene **598** to afford **755** in 83% yield. We then performed an Arbuzov reaction with the resulting α-bromo ketone **755**, which was refluxed with triethyl phosphite to afford the desired phosphonate **757** in 59% yield on gram scale. Trimethyl phosphite was also reacted with α-bromo ketone **755**, but only a small amount of product **756** was obtained. Similarly, perfluoroethyl phosphite afforded no product when refluxed with **755**, which was presumably due to phosphorus being too electron deficient to undergo an Arbuzov reaction with the bulky acetyl bromide.[148] We also attempted to alkylate pentamethylacetophenone **187** with chlorophosphoric acid **759**, but found that it only reacted through oxygen to give **760** in 25% yield.



Scheme 4.8: Synthesis of Horner Wadsworth Emmons reagents **756** and **757** bearing the pentamethylphenyl group. Conditions: bromoacetyl bromide (1.1 eq.), pentamethylbenzene (1 eq.), $AlCl_3$ (1.3 eq.), CH_2Cl_2 (0.2 M), 0 °C to RT, 3 h. ii) **755** (1 eq.), phosphite (1.1 eq.), reflux, 24 h. iii)

Ph*C(O)Me (1 eq.), 3M EtMgBr in diethyl ether (1.2 eq.), diethyl ether (0.3 M), 40 °C, 30 min, then diphenyl phosphoryl chloride (1 eq.), 40 °C, 3 h.

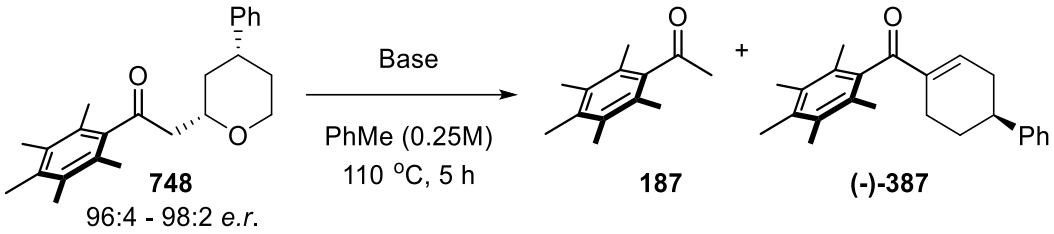
With access to multigram quantities of phosphonate **757**, we looked to perform a Horner Wadsworth Emmons reaction with lactol **743**.[149] Despite the lack of literature examples of lactols as reactive partners for this olefination reaction, we were delighted to find that lactol **743** smoothly reacted with the sodium enolate of phosphonate **757** (formed *in-situ* with sodium hydride), to afford tetrahydropyran **748** in 85% yield. Pleasingly, interrogation of the enantiomeric excess by chiral HPLC revealed that tetrahydropyran **748** had a 97:3 *e.r.*, suggesting that the HWE reaction was a superior method for preserving the stereochemistry compared to the aldol reaction in Table 4.1, which in contrast resulted in complete stereochemical erosion in cyclohexene **387**.



Scheme 4.9: Synthesis of enantioenriched tetrahydropyran **748**. Conditions: **757** (1.3 eq.), NaH (1.2 eq.), PhMe (0.5 M), RT, 15 min, then **743** (1 eq.), 110 °C, 15 h.

With enantioenriched tetrahydropyran **748** in hand, we next investigated the feasibility of the [1,5]-hydride shift cascade under basic conditions (Table 4.2). We began the optimisation using the previous conditions, consisting of four equivalents of potassium hydroxide in dry toluene, heated to 110 °C (Entry 1). Pleasingly, we obtained cyclohexene **(-)-387** in 46% yield, with 80% *e.s.*, which was significantly higher than the original result in Table 4.1. We also found that the product **(-)-387** was accompanied by the formation of Ph*COMe **187** in 50% yield, which likely formed from the retro-aldol of tetrahydropyran **748**, to afford ketone **187** and lactol **743**, which was not observed. Presumably, the formation of lactol **743** under these basic conditions resulted in racemisation of the stereocenter, causing the reduction of the *e.r.* in the product (by the mechanism outlined in Scheme 4.6). Fewer equivalents of potassium hydroxide were tried (Entries 2-3), which resulted in a reduction of the formation of Ph*COMe **187**, and an increased enantiopurity. Changing the counter ion to sodium hydroxide was also beneficial, resulting in an improved yield of 59%, and 89% *e.s.* Strong bases were also investigated, such as potassium hydride (Entry 5), potassium tert-butoxide (Entry 6), and KHMDS

(Entry 7), but were found to give comparable yield of **(-)-387** and *e.s.* to potassium hydroxide. Analogously, NaHMDS (Entry 8), sodium ethoxide (Entry 9) and sodium methoxide (Entry 10) were tried, and found to give moderate conversion to the desired cyclohexene **(-)-387**, but still underwent racemisation. Pleasingly, we found that sodium hydride (Entry 11) was most effective, with one equivalent yielding a 58% yield of cyclohexene **(-)-387** in 100% *e.s.* Increasing the stoichiometry to two equivalents of sodium hydride (Entry 12) increased the conversion to 67% yield, but saw a reduction in *e.s.* to 91%. We found that adding a sodium sulfate as a desiccant improved the reproducibility of the reaction, with cyclohexene **(-)-387** obtained in 76% yield and 100% *e.s.*



748
96:4 - 98:2 *e.r.*

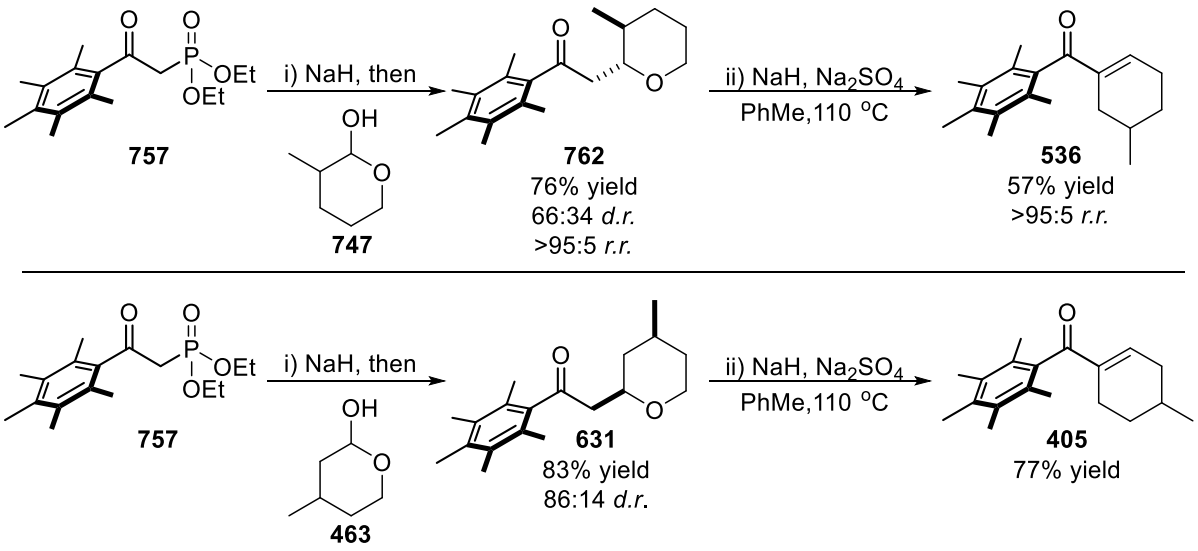
187

(-)-387

Entry	Base (eq.)	Desiccant (eq.)	Yield **748** (%)	Yield **187** (%)	Yield **(-)-387** (%)	*e.r.*[a]	*e.s.* (%)
1	KOH (4)	-	0	50	46	87:13	80
2	KOH (2)	-	0	46	46	90:10	87
3	KOH (1)	-	0	26	66	90:10	87
4	NaOH (2)	-	22	19	59	91:9	89
5	KH (1)	-	0	80	19	84:16	74
6	KO*t*Bu (2)	-	0	25	75	90:10	87
7	KHMDS (2)	-	0	10	43	86:14	78
8	NaHMDS (2)	-	0	15	56	90:10	87
9	NaOEt 21% wt in EtOH (2)	-	0	50	46	96:4	98
10	NaOMe (2)	-	0	7	56	90:10	85
11	NaH (1)	-	22	0	58	97:3	100
12	NaH (2)	-	4	5	67	92:8	91
13	NaH (3)	Na_2SO_4 (3)	0	0	(76)	97:3	100

Table 4.2: Varying the base for the [1,5] hydride Shift aldol cascade of tetrahydropyran **748**. Conditions: **748** (1 eq.), base, dry PhMe (0.2M), 110 °C, 5 h. Yield in parenthesis refers to isolated yield after column chromatography. Yield determined by Q ^{1}H NMR using $CHCl_2CHCl_2$ as an internal standard. [a] Enantiomeric ratio was determined by chiral HPLC

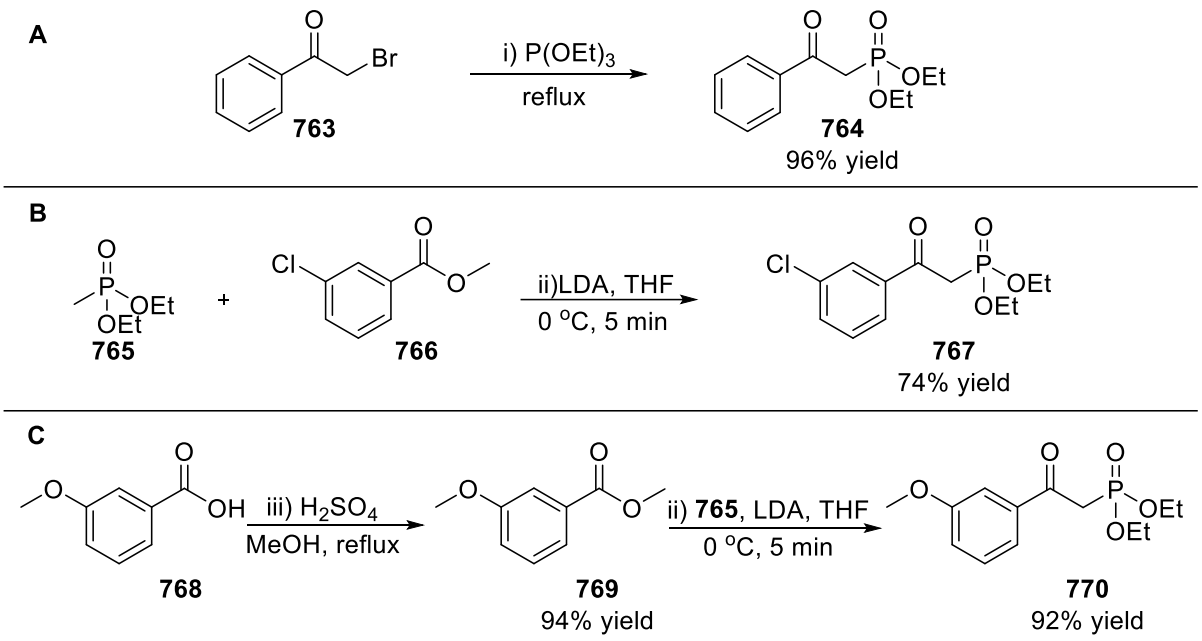
With three equivalents of sodium hydride and sodium sulfate as optimised conditions for the synthesis of enantioenriched cyclohexene **(-)-387**, we next investigated other substrates for the reaction (Scheme 4.10). Firstly, we looked at regioisomerically pure lactol **747**, which previously isomerised when reacted with Ph*COMe **187** and potassium hydroxide. We began by performing a Horner Wadsworth Emmons reaction between α-substituted lactol **747** and phosphonate **757**. Pleasingly, we found that the desired tetrahydropyran **762** was isolated in 76% yield, as a single regioisomer by quantitative ^{1}H NMR. We then subjected tetrahydropyran **762** to the optimised conditions for the [1,5]-hydride shift, treating **762** with sodium hydride and sodium sulfate. To our delight, we isolated cyclohexene **536** in 57% yield, and greater than 95:5 *r.r.* by quantitative ^{1}H NMR. Additionally, symmetrical lactol **463** was investigated under the optimised conditions. First, lactol **463** was reacted with phosphonate **757** to afford **631** in 83% yield. Subjecting the resulting tetrahydropyran **631** to sodium hydride resulted in the formation of **405** in 77% yield.



Scheme 4.10: Synthesis of regioisomerically pure cyclohexene **536** and cyclohexene **405** by base-promoted [1.5]-hydride shift cascade. Conditions: i) **757** (1.3 eq.), NaH (1.2 eq.), PhMe (0.5 M), RT, 15 min, then lactol (1 eq.), 110 °C, 15 h. ii) tetrahydropyran (1 eq.), NaH (3 eq.), Na_2SO_4 (3 eq.) dry PhMe (0.2 M), 110 °C, 5 h.

Having initially explored a representative range of lactols under the optimised basic conditions, we looked to explore the scope of the dialkyl phosphonate reagent in the reaction (Scheme 4.11). Phosphonate **764** was prepared in one step by Arbuzov reaction with **763** in 96% yield on multigram scale (A). Analogously, chlorophenyl phosphonate **767** was prepared by a Claisen reaction between methylphosphonate **765** and ester **766**. Similarly, Fischer esterification of acid **768** with methanol

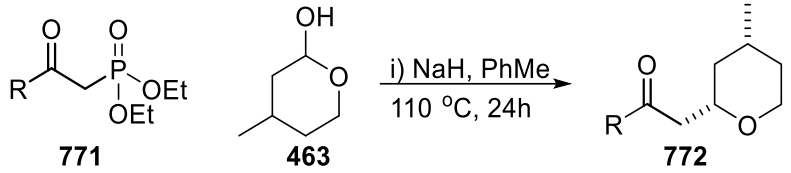
afforded ester **769** in 94% yield. Ester **769** was then reacted with methyl phosphonate **765** to give dialkyl phosphonate **770** in 92% yield.



Scheme 4.11: Synthesis of Horner Wadsworth Emmons phosphonates **764**, **767** and **770**. Conditions: i) **763** (1 eq.), triethyl phosphite (1.1 eq.), reflux, 24 h. ii) **765** (1.1 eq.), methyl ester (1 eq.), LDA (2.2 eq.), THF (0.2 M), 0 °C, 5 min. iii) **768** (1 eq.), conc. sulphuric acid (1.3 eq.), MeOH (0.5 M), reflux, 15 h.

With phosphonates **764**, **767** and **770** in hand, alongside two further phosphonates prepared by J. Hou, they were reacted with symmetrical lactol **463** by Horner Wadsworth Emmons reaction (Table 4.3). Pleasingly, the corresponding tetrahydropyrans **775**-**779** were obtained in uniformly high yields. Notably, this approach to synthesising tetrahydropyrans proved superior to the aldol approach in scheme 4.7.

In all cases, the reaction afforded the thermodynamic all-equatorial (*cis*) diastereomer, which likely formed from reversible ring-opening of the tetrahydropyran. This stereoisomer was assigned by *J*-coupling constant analysis, with the characteristic signal being a quartet for axial proton H_3, which corresponded to two large vicinal couplings and a large geminal coupling (Scheme 4.12). Diagnostic signals for the assignment of the tetrahydropyran included the presence of two proton environments adjacent to oxygen at 3.46 ppm and 4.01-3.89 ppm, which were assigned as H_6 and H_2 from the tetrahydropyran ring, and two doublet of doublets for H_8 at 3.30 ppm and 2.93 ppm. A characteristic carbonyl peak was also observed by ^{13}C at 198.5 ppm.



771 463 772

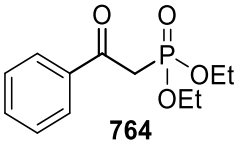
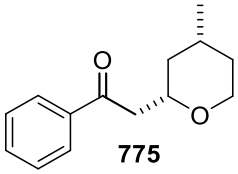
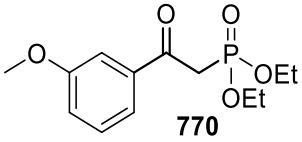
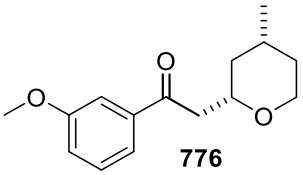
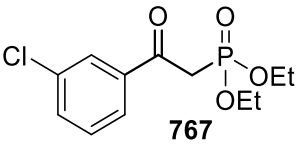
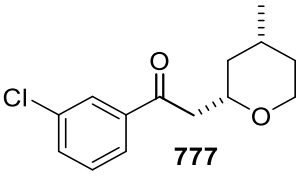
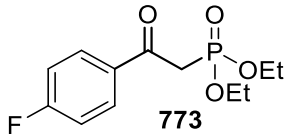
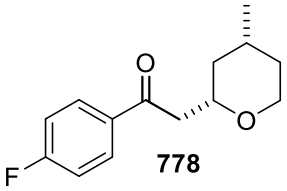
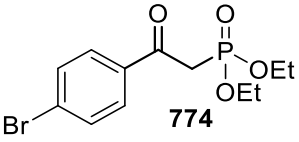
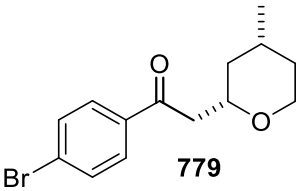
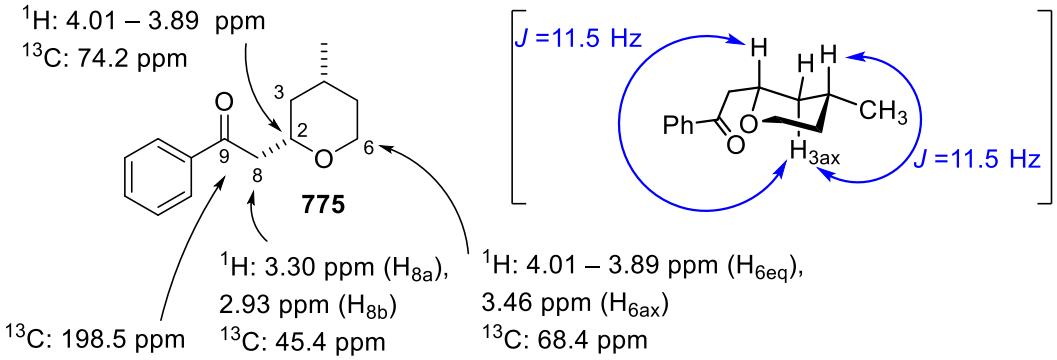
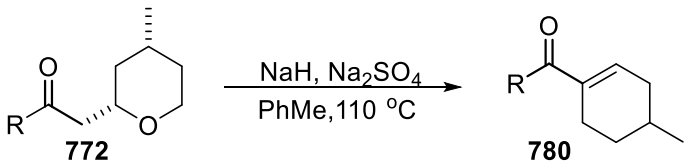
Entry	Starting material	Product	Yield (%)	d.r (*cis*:*trans*)
1	 764	 775	92	94:6
2	 770	 776	95	85:15
3	 767	 777	85	94:6
4[a]	 773	 778	71	93:7
5[a]	 774	 779	47	55:45

Table 4.3: Synthesis of tetrahydropyrans **775**-**779** by HWE reaction. Conditions: HWE reagent (1.2 eq.), 4-methyltetrahydro-*2H*-pyran-2-ol (1 eq.), NaH (1.4 eq.), PhMe (0.3 M), 110 °C, 24 h. [a] Entries 4 and 5 performed by J. Hou.



Scheme 4.12: Stereochemical assignment of tetrahydropyran **775**.

Having isolated tetrahydropyrans **775**-**779**, they were evaluated under the [1,5]-hydride shift conditions, consisting of sodium hydride and sodium sulfate (Table 4.4). These experiments were performed with J. Hou. When tetrahydropyran **775** was reacted with sodium hydride, we obtained the desired cyclohexene **753** in 70% yield (Entry 1). Methoxy substituted tetrathydropyran **776** also led to the formation of the corresponding cyclohexene **781**, but in a reduced yield of 54% (Entry 2). Tetrahydropyrans **777**, **778** and **779** bearing halogen atoms were also investigated under the optimised conditions, but were found to give low yields of the desired cyclohexene.



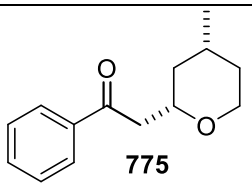
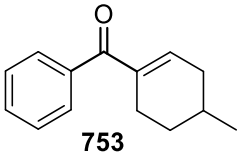
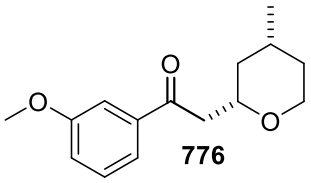
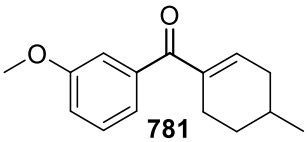
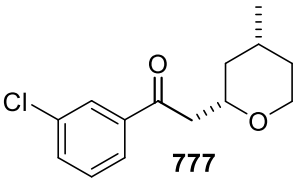
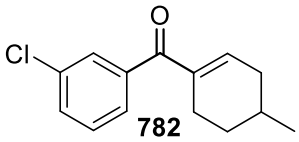
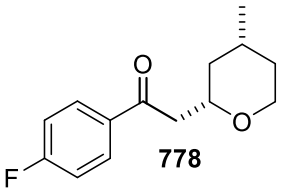
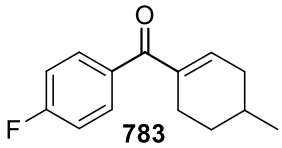
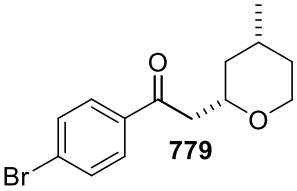
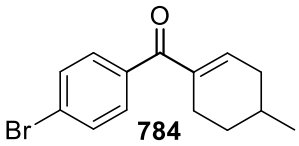
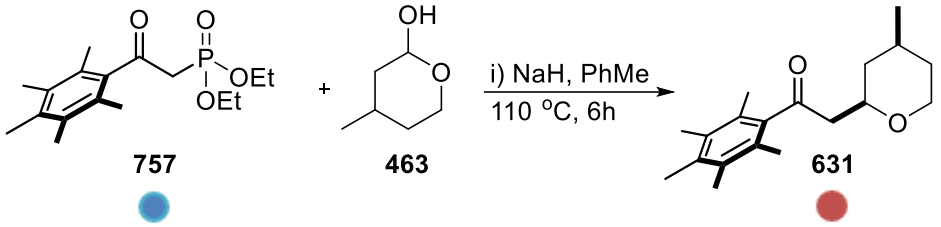
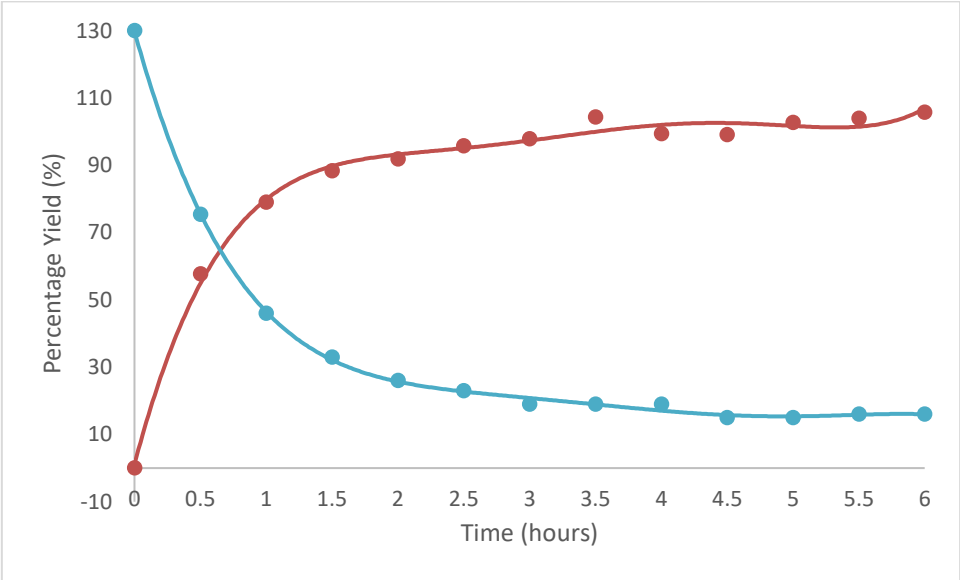
Entry	Starting material	Product	Yield (%)
1			70
2			54
3			34
4			38
5			29

Table 4.4: Synthesis of cyclohexenes by [1,5]-hydride shift aldol cascade. Conditions: tetrahydropyran (1 eq.), 60% wt. NaH (3 eq.), Na_2SO_4 (3 eq.), PhMe (0.3 M), 110 °C, 1.5 h. Entries 1-5 performed by Jingyan Hou.

To shed light on the surprisingly low yield of cyclohexenes **781**-**784**, and the reproducibility issue observed during the optimisation of the reaction, we set out to monitor the reaction profile with time. Following an HPLC calibration of internal standard hexamethylbenzene versus phosphonate **757** and tetrahydropyran **631**, we performed the Horner Wadsworth Emmons reaction, taking aliquots every thirty minutes over a six hour period (Graph 4.1). We observed the steady depletion of phosphonate **757** over a six hour period, alongside the gradual formation of tetrahydropyran **631** to a near

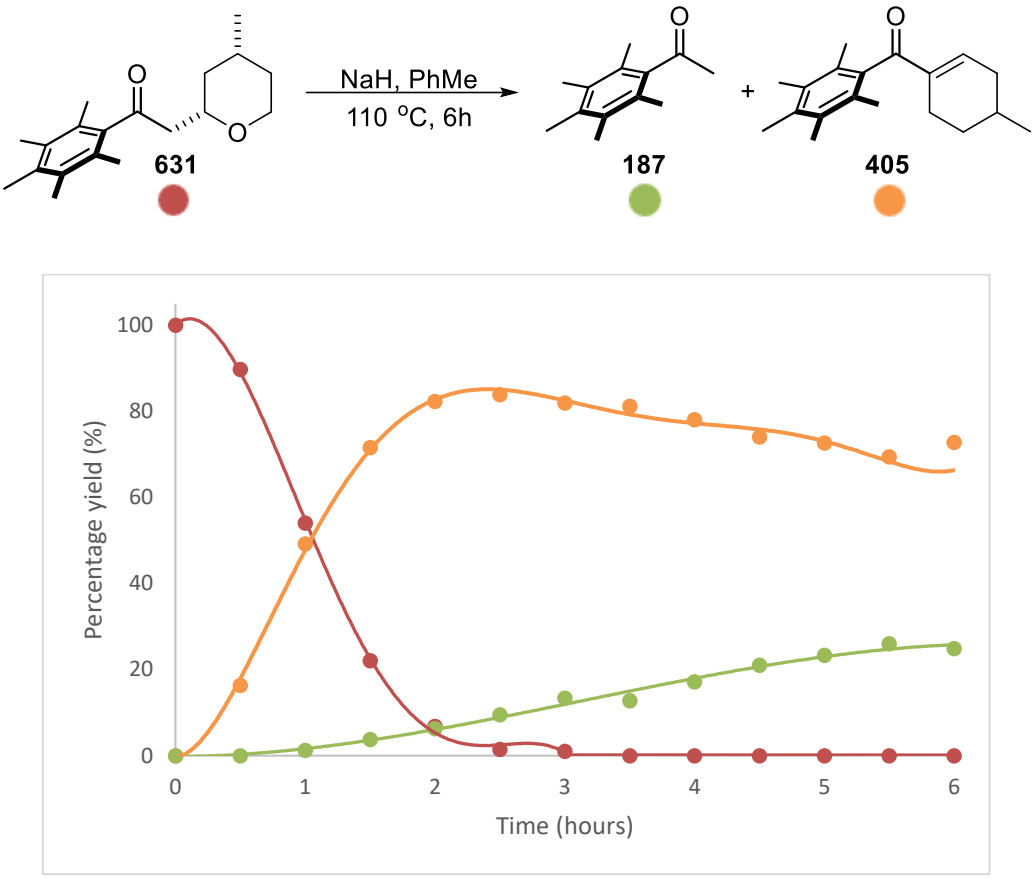
quantitative yield. By running this reaction to completion and leaving it for 24 hours, we determined that the tetrahydropyran was stable under the basic conditions, with no decomposition observed by HPLC.





Graph 4.1: reaction profile for the HWE reaction of **757** and **463** to form **631**. Conditions: **757** (1.3 eq.) NaH (1.1 eq.), **463** (1 eq.), PhMe (0.2 M), 110 °C.

Subsequently, we investigated the reaction profile of the [1,5]-hydride shift cascade from tetrahydropyran **631** to cyclohexene **405** (Graph 4.2). We observed rapid depletion of tetrahydropyran **631**, with formation of the corresponding cyclohexene **405** in approximately 80% yield within two hours. However, following the profile by HPLC for the course of the reaction, we observed decomposition of cyclohexene **405** and concomitant formation of Ph*COMe **187**. Leaving the reaction overnight led to complete decomposition of cyclohexene **405** under these basic conditions, and only Ph*COMe **187** was isolated. Taken alongside the low yields for the cyclohexenes in Table 4.4, we looked to explore alternative approaches for activation of the [1,5]-hydride shift reaction.



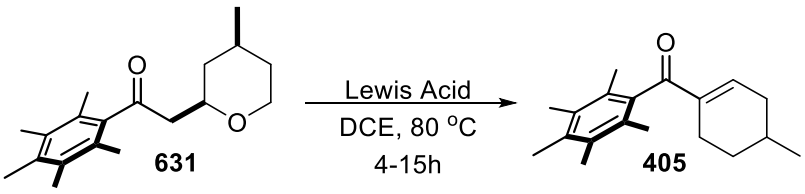
Graph 4.2: Reaction profile for the [1,5]-hydride shift aldol cascade of tetrahydropyran **631** to **405**. Conditions: **631** (1 eq.), NaH (3 eq.), Na_2SO_4 (3 eq.), PhMe (0.2M), 110 °C.

4.3 Lewis Acid Promoted [1,5]-Hydride Shift Reaction

4.3.1 Reaction Optimisation

Given that the cyclohexene product was unstable under basic conditions, we looked to investigate promoting the reaction by introducing a Lewis acid. Using tetrahydropyran **631**, we screened a representative range of Lewis acids and Bronsted acids reported for [1,5]-hydride shift processes (Table 4.5). Scandium triflate at 80 °C in dichloroethane afforded the desired cyclohexene **405** in 18% yield (Entry 1), while *p*-toluenesulfonic acid afforded no product and recovered starting material (Entry 2). In contrast, boron trifluoride resulted in the formation of 16% yield of cyclohexene **405** (Entry 3). When $AlCl_3$ was screened (Entry 4), we observed a 10% yield of **405**, alongside significant formation of

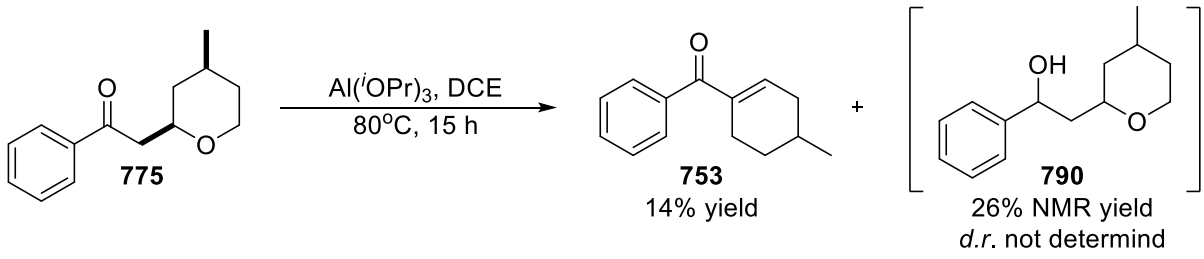
pentamethylbenzene, presumably forming from the retro-Friedel-Crafts acylation of tetrahydropyran **631**. Pleasingly, aluminium isopropoxide afforded the desired cyclohexene **405** in 73% yield (Entry 5).



Entry	Reagent (eq.)	Yield **405** (%)
1[a]	$Sc(OTf)_3$ (0.1)	18
2	TsOH (0.2)	0
3	$BF_3.OEt_2$ (1)	16
4	$AlCl_3$ (1)	10
5	$Al(OiPr)_3$ (1)	73

Table 4.5: Varying the Lewis acid for the [1,5] hydride shift reaction. Conditions: **631** (1 eq.), lewis acid (0.1-1 eq.), DCE (0.2 M), 80 °C, 15 h.[a] reaction run for 4 hours.

With the promising result from aluminium isopropoxide, we turned our attention to the reaction of phenyl substituted tetrahydropyran **775** (Scheme 4.13). Under the same conditions of one equivalent of aluminium isopropoxide and dichloroethane, we obtained a 14% yield of cyclohexene **753**. This product was accompanied by unreacted starting material, and reduction of the starting material to the corresponding benzylic alcohol **790**, presumably by a Meerwein-Pondorf-Verley reaction.



Scheme 4.13: Reaction of tetrahydropyran **775** with aluminium isopropoxide. Conditions: tetrahydropyran (1 eq.), $Al(iOPr)_3$ (1 eq.), DCE (0.2M), 80 °C, 15h.

To circumvent this, we screened a range of organic solvents with the hope that the [1,5]-hydride shift might be favoured, and at higher temperatures, conversion to cyclohexene **753** would increase (Table 4.6). Changing the solvent from DCE (Entry 1) to 1,4-dioxane (Entry 2), toluene (Entry 3), dichloromethane (Entry 4), benzene (Entry 5), anisole (Entry 6), chlorobenzene (Entry 7) or isopropyl alcohol (Entry 8) at 90 °C led to no increased yield of cyclohexene **753**. Increasing the temperature to

110 °C improved the yield to 29% (Entry 9). Consequently, anisole (Entry 10), benzene (Entry 11), DME (Entry 12) and toluene (Entry 13) were investigated at 110 °C, and all gave comparable yields, thus we continued the optimisation with toluene, which is a greener solvent than DCE.[150]

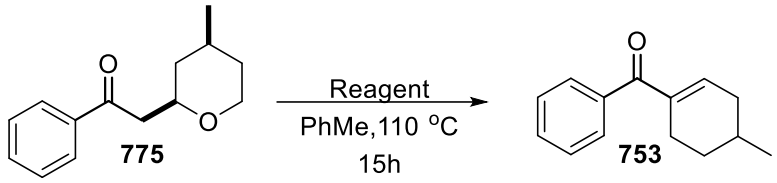


Entry	Solvent (0.2M)	Temp (°C)	Yield **753** (%)
1	DCE	80	14
2	1,4-Dioxane	90	1
3	Toluene	90	4
4	CH_2Cl_2	90	8
5	Benzene	90	10
6	Anisole	90	7
7	Chlorobenzene	90	6
8	Isopropyl alcohol	90	0
9	DCE	110	29
10	Anisole	110	16
11	Benzene	110	33
12	DME	110	26
13	Toluene	110	29

Table 4.6: Screening solvent for the Lewis acid promoted [1,5]-hydride shift reaction. Conditions: **775** (1 eq.), Al(O*i*Pr)$_3$ (1 eq.), solvent (0.2 M), 80-110 °C, 15 h.

Given that the side reaction with aluminium isopropoxide was the Meerwein-Pondorf-Verley reduction of tetrahydropyran **775**, we postulated that removing the β-hydride of aluminium isopropoxide would prevent this process (Table 4.7). First, we prepared aluminium phenoxide by the reaction of trimethyl aluminium and phenol. Pleasingly, subjecting this aluminium complex with tetrahydropyran **775** lead to the formation of cyclohexene **753** in 50% yield, alongside unreacted starting material (Entry 2). Treating tetrahydropyran **775** with one equivalent of commercial aluminium *tert*-butoxide was even more potent, with cyclohexene **753** obtained in 97% isolated yield (Entry 3). Brockmann I basic alumina proved to also be an efficient Lewis-acid for the hydride shift reaction, whereby one equivalent yielded 50% of cyclohexene **753** (Entry 4). To our delight, increasing

the excess of alumina to five equivalents resulted in a near quantitative yield of cyclohexene **753** (Entry 5).

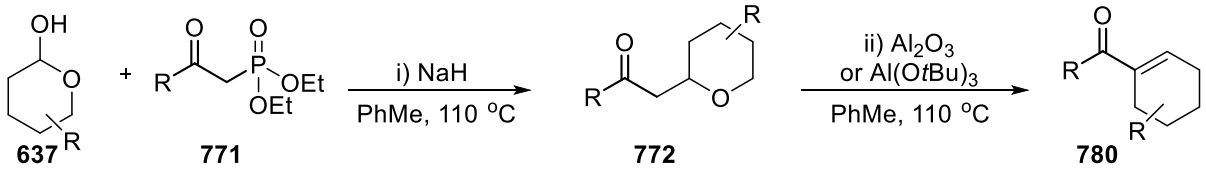


Entry	Reagent (eq.)	Yield **753** (%)
1	$Al(OiPr)_3$ (1)	29
2	$Al(OPh)_3$ (1)	50
3	$Al(OtBu)_3$ (1)	97
4	Al_2O_3 (1)	50
5	Al_2O_3 (5)	96

Table 4.7: Screening aluminium reagents for the [1,5]-hydride shift reaction. Conditions: tetrahydropyran **775**, aluminium reagent (1-5 eq.), PhMe (0.2 M), 110 °C, 15 h.

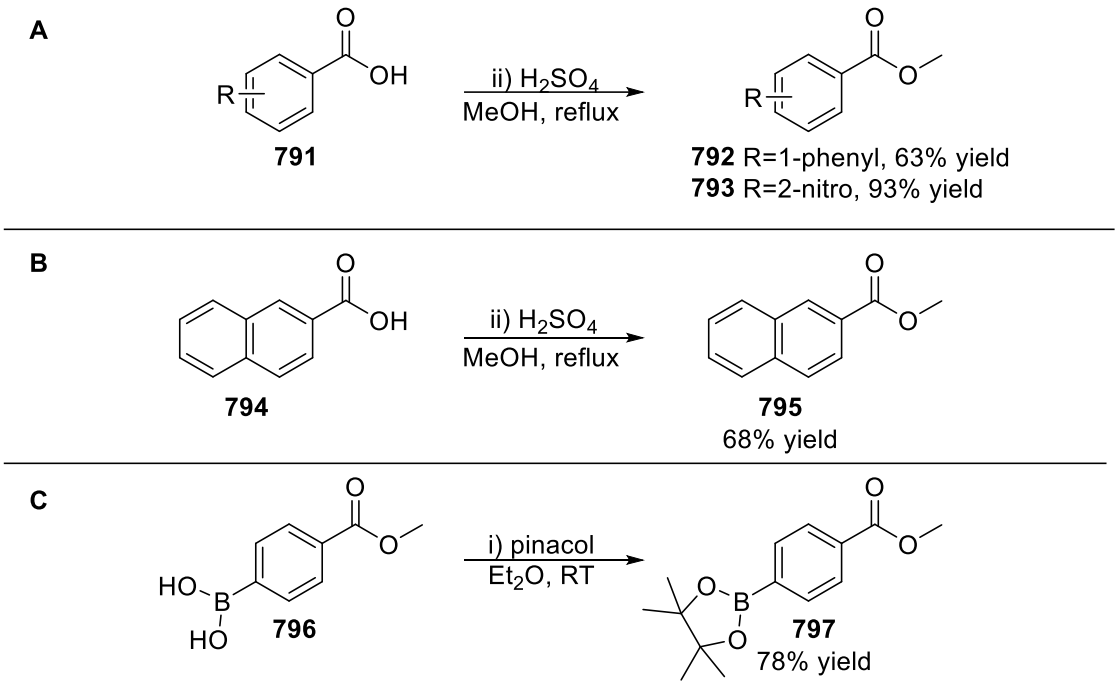
4.3.2 Substrate Scope of Electron-Withdrawing Group

Having found aluminium *tert*-butoxide and alumina to be highly efficient Lewis-Acids for the reaction, we set out to investigate the generality of the reaction, initially focusing on the electron withdrawing group. Our optimised procedure consisted of a two-step sequence, whereby a lactol would be reacted with a phosphonate by a Horner Wadsworth Emmons reaction to give an intermediate tetrahydropyran, and then treated with alumina or aluminium *tert*-butoxide to trigger the tandem [1,5]-hydride shift aldol condensation (Scheme 4.14). Generally speaking, we found alumina to be a milder Lewis acid than aluminium *tert*-butoxide, thus when we explored the substrate scope, we first reacted tetrahydropyrans with alumina and if the conversion was poor, we repeated the reaction using aluminium *tert*-butoxide (*vide infra*).



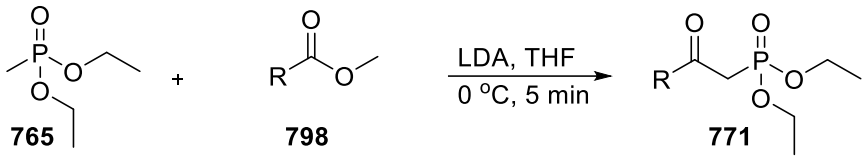
Scheme 4.14: Optimised two-step procedure for the preparation of cyclohexenes. Conditions: i) lactol (1 eq.), phosphonate (1.4 eq.), 60% wt. NaH (1.2 eq.), PhMe (0.2 M), 110 °C. ii) tetrahydropyran (1 eq.), Al_2O_3 (5 eq.) or $Al(OtBu)_3$ (1 eq.), PhMe (0.2 M), 110 °C.

To investigate the scope of the acyl group, we began by preparing a range of phosphonates for the Horner Wadsworth Emmons reaction. The synthesis began with Fischer esterification of commercial carboxylic acids (Scheme 4.15). By this method, esters bearing biphenyl, nitro arene and napthyl substituents were synthesised in uniformly high yields. Similarly, aryl boronic ester **797** was prepared in 78% yield by the reaction of boronic acid **796** with pinacol (C).



Scheme 4.15: Synthesis of esters **792**-**797**. Conditions: i) **796** (1 eq.), pinacol (1.2 eq.), 0.5M, 15 h. ii) carboxylic acid (1 eq.), H_2SO_4 (1-2 eq.), MeOH (0.3M), reflux, 15 h.

Using esters **792**, **793**, **795** and **797** and several additional commercial aryl esters, we prepared the corresponding dialkyl phosphonate (Table 4.8). This was achieved by deprotonating methyl diethyl phosphonate with LDA at 0 ^{o}C and then reacting the anion with the desired ester by a Claisen-like condensation. By this method, phosphonates bearing nitro-substituted arene **802** (Entry 1), nitrile **803** (Entry 2), and aryl ester **804** (Entry 3) were prepared in good yields. Hindered *ortho*-phenyl substituted aryl ester **792** was also well tolerated (Entry 4), and similarly, napthyl **795** (Entry 5), 3-iodo-phenyl **801** (Entry 6), and boron containing phenyl esters **797** (Entry 7) were reacted smoothly to give the corresponding phosphonates. The structure of these compounds was characterised by the presence of a diagnostic J_{HP} = 22.5 Hz vicinal coupling constant between the phosphonate group and the CH_2 group, which was also observed in ^{13}C NMR. Furthermore, all the phosphonates showed a singlet by ^{31}P NMR.



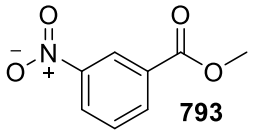
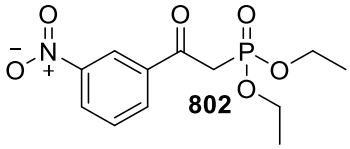
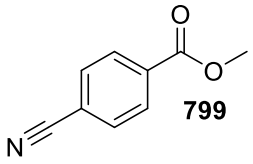
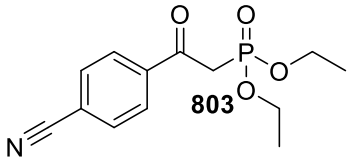
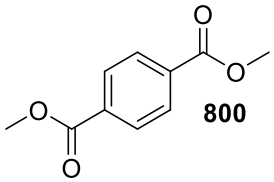
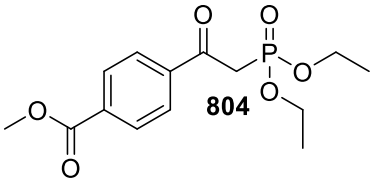
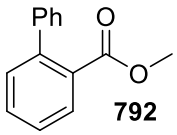
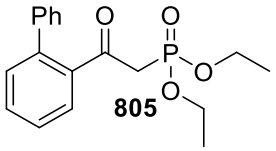
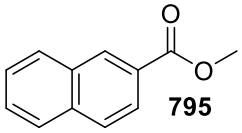
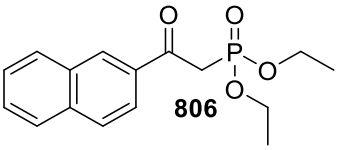
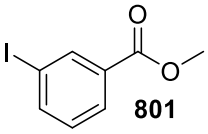
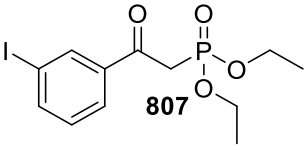
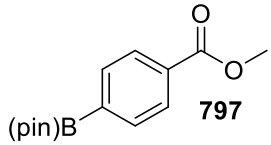
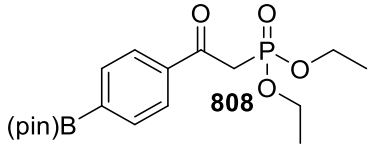
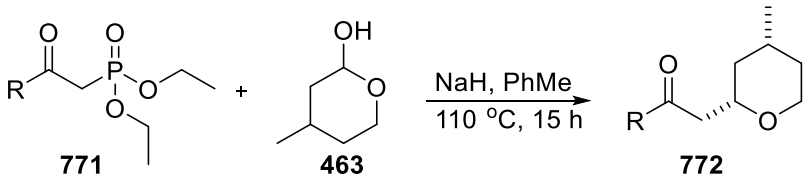
Entry	Starting Material	Product	Yield (%)
1	 793	 802	55
2	 799	 803	41
3	 800	 804	42
4	 792	 805	71
5	 795	 806	77
6	 801	 807	69
7	 797	 808	60

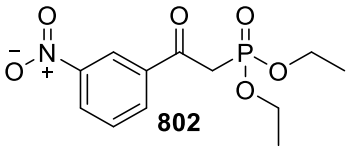
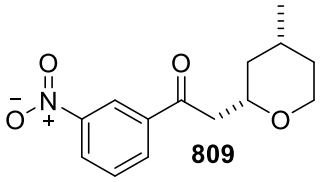
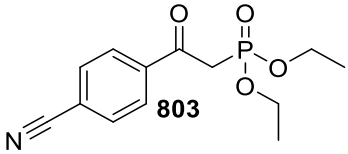
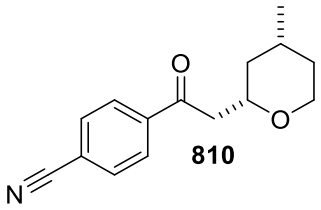
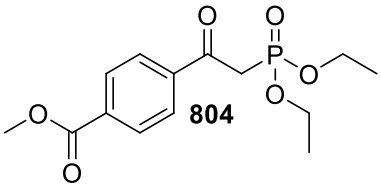
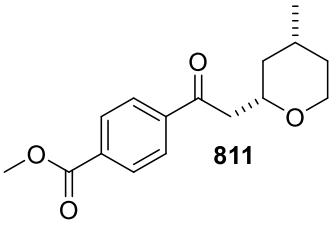
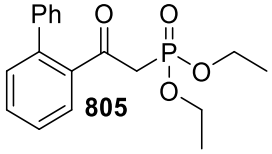
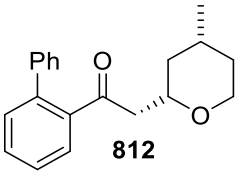
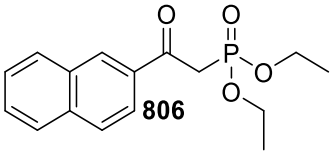
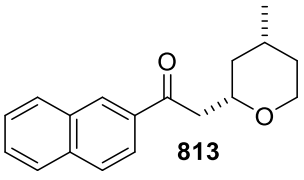
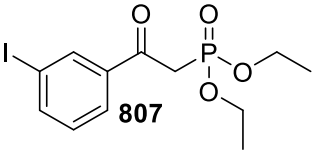
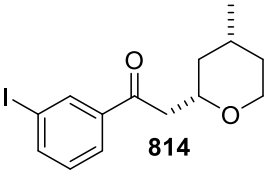
Table 4.8: Synthesis of HWE reagents **802**-**808**. Conditions: ester (1 eq.), phosphonate (1.1 eq.), diisopropylamine (2.25 eq.), *n*BuLi (2.2 eq.), dry THF (0.2 M), 5 min.

Having prepared a range of aromatic substituted phosphonates, they were deprotonated with sodium hydride and subsequently reacted with symmetrical lactol **463** to give the corresponding tetrahydropyran (Table 4.9). We were pleased to find that the reaction tolerated a range of

phosphonates substituted with aryl ketones, including electron deficient nitro arene **809** (Entry 1), 4-nitrile **810** (Entry 2), 4-methyl ester **811** (Entry 3), *ortho*-phenyl **812** (Entry 4), napthyl **813** (Entry 5), 3-iodo **814** (Entry 6), 4-BPin **815** (Entry 7), which were all obtained in good yields.



771 **463** **772**

Entry	Starting Material	Product	Yield (%)	d.r (*cis:trans*)[a]
1	 **802**	 **809**	70	92:8
2	 **803**	 **810**	100	91:9
3	 **804**	 **811**	80	92:8
4	 **805**	 **812**	100	74:26
5	 **806**	 **813**	100	83:17
6[b]	 **807**	 **814**	82	91:9

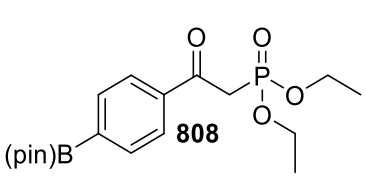
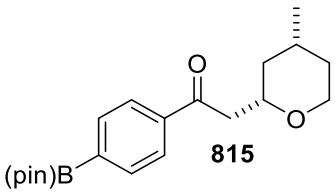
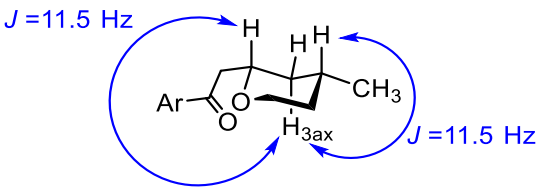
7	 **808**	 **815**	94	92:8

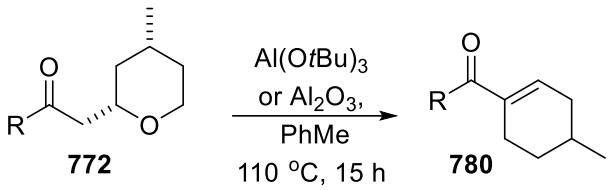
Table 4.9: Synthesis of tetrahydropyrans **809**-**815**. [a]The major diastereomer was assigned by *J*-coupling constant analysis. Conditions: HWE reagent (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, then 4-methyltetrahydro-*2H*-pyran-2-ol (1 eq.), 110 °C, 15 h. [b] 1 M LDA in THF (1.2 eq.) used instead of NaH.

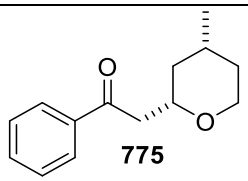
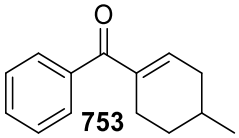
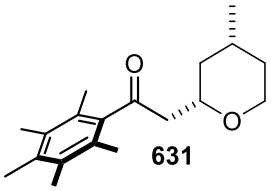
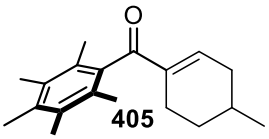
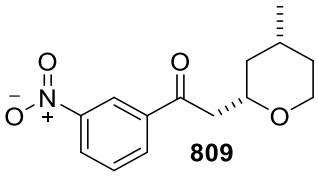
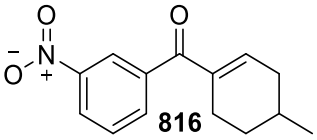
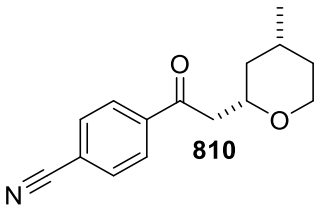
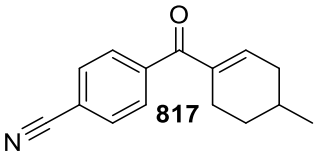
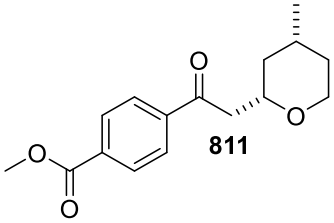
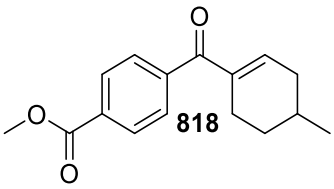
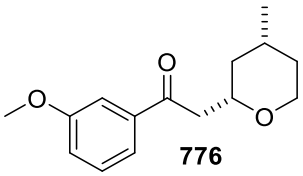
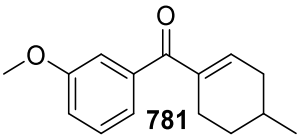
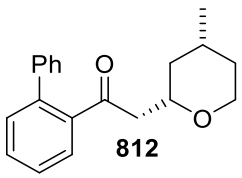
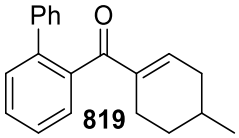
Again, we observed the thermodynamic all-equatorial (*cis*) tetrahydropyran, which most likely formed from reversible ring-opening to the corresponding enone. This stereoisomer was assigned by *J*-coupling constant analysis, with the characteristic signal being a quartet for axial proton H_3, which corresponded to two large vicinal couplings and a large geminal coupling (Scheme 4.16).



Scheme 4.16: Stereochemical assignment of the tetrahydropyran.

With a range of electron rich and deficient aryl-substituted tetrahydropyrans prepared, we set out to evaluate their reactivity under the optimised conditions for the [1,5]-hydride shift, consisting of five equivalents of alumina or one equivalent of aluminium *tert*-butoxide in toluene, heated to 110 °C (Table 4.10). We were pleased to find that Ph* ketone was still tolerated in the chemistry, affording the desired cyclohexene **405** in 96% yield (Entry 2). Electron deficient nitro arene **809** smoothly afforded cyclohexene **816** in 75% yield (Entry 3). Nitriles (Entry 4) and esters (Entry 5) were well tolerated in the reaction, giving the corresponding cyclohexene in 74% and 90% yield, respectively. Electron donating aromatics (Entry 6) also afforded the desired cyclohexene in excellent yields. Sterically hindered cyclohexenes (Entry 7-8) were also obtained in high yields. Cyclohexenes bearing aryl halides (Entry 9-10) were also excellent substrates for the reaction, with no evidence of side products. Finally, a tetrahydropyran bearing BPin group was also compatible with the reaction, affording cyclohexene **822** in 74% yield.



Entry	Starting Material	Product	Yield (%)
1	 775	 753	97
2	 631	 405	96
3[a]	 809	 816	75
4[a]	 810	 817	74
5[a]	 811	 818	90
6	 776	 781	85
7	 812	 819	88

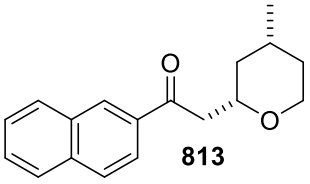
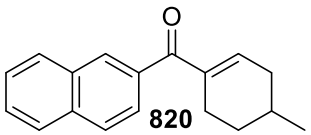
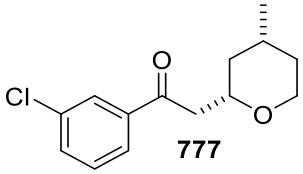
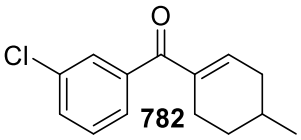
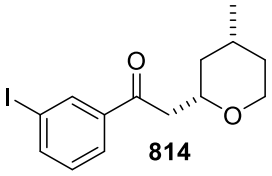
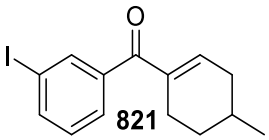
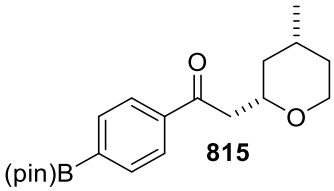
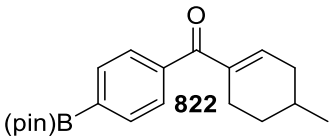
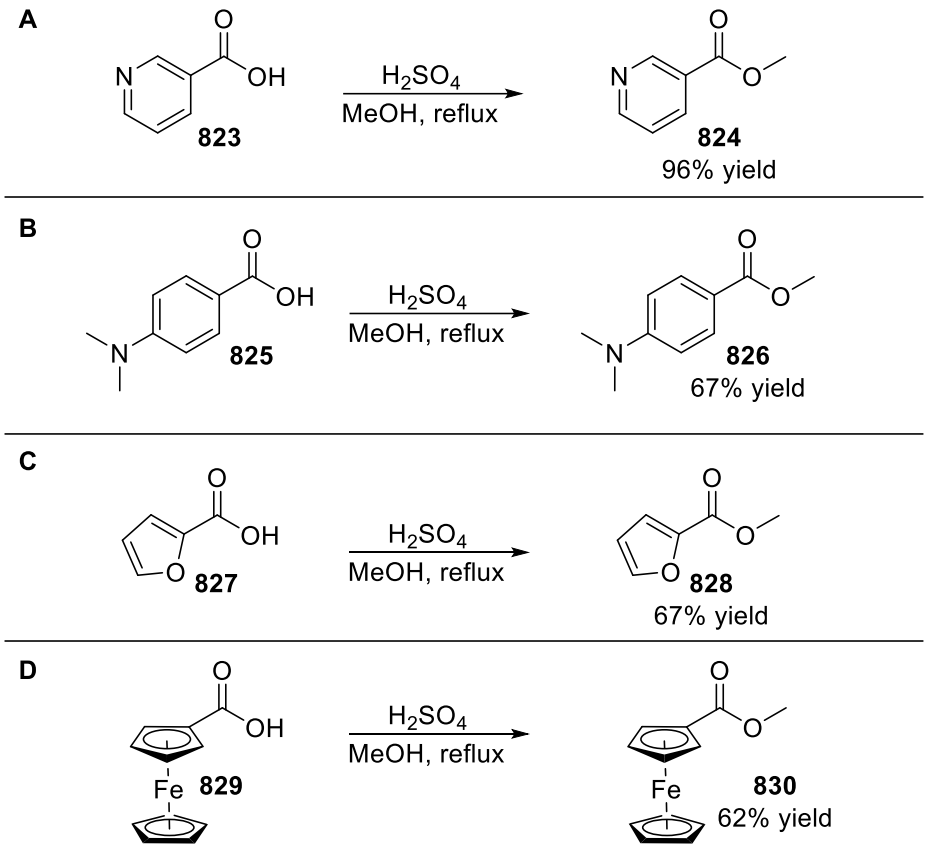
8			65
9			70
10[a]			82
11[a]			74

Table 4.10: Synthesis of cyclohexenes by [1,5]-hydride shift aldol cascade. Conditions: tetrahydropyran (1 eq.), Al_2O_3 (5 eq.), PhMe (0.2 M), 110 °C, 15 h.[a] $Al(OtBu)_3$ (1 eq.) used instead of Al_2O_3.

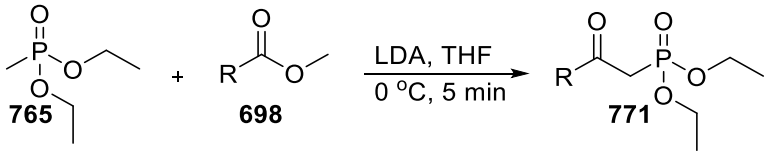
In all cases, the structure of these cyclohexene products was characterised by the presence of several diagnostic signals by ^1H and ^{13}C NMR. This included a peak for the enone C-H at approximately 6.55 ppm, and two alkene carbons at approximately 143 ppm and 139 ppm, alongside a carbonyl peak at 198 ppm. Further to this, we observed three aliphatic CH_2 groups and one CH, accounting for all six carbons about the cyclohexene ring.

We next turned our attention to preparing cyclohexenes bearing heterocycles. To explore this, we began by synthesising a range of methyl esters by Fischer esterification (Scheme 4.17). This included a derivative of nicotinic acid **824** (A), dimethylaniline **826** (B), furyl **838** (C) and metallocene **830** (D).



Scheme 4.17: Synthesis of esters by Fischer esterification. Conditions: i) carboxylic acid (1 eq.), H_2SO_4 (1-2 eq.), MeOH (0.3M), reflux, 15 h.

With these esters in hand and also commerical esters **831** and **832**, we reacted them with methyl diethyl phosphonate **765** and LDA to form the corresponding phosphonates **833**-**838** (Table 4.11). Pleasingly, when 3- and 4-pyridyl esters **824** and **831** were subjected to the reaction conditions, we obtained the desired phosphonates **833** and **834** in good yields. Similarly, quinoline **835** was prepared in 95% yield. Aniline **836** and furyl substituted phosphonate **837** were prepared in excellent yields, and ferrocene derivative **838** was prepared in quantitative yield.



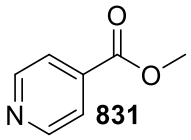
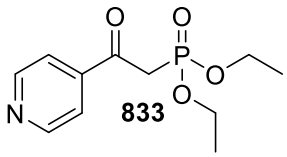
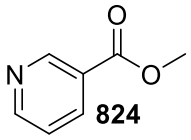
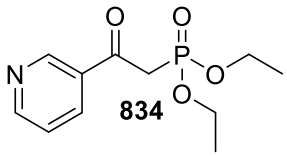
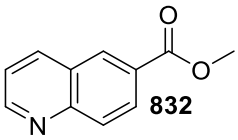
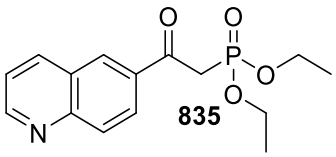
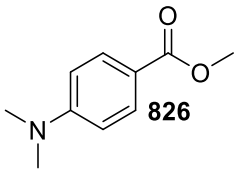
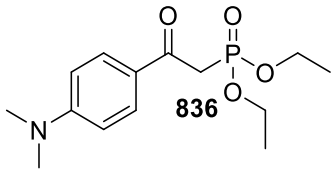
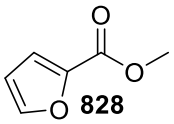
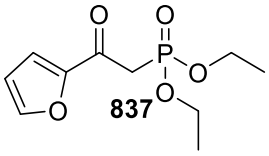
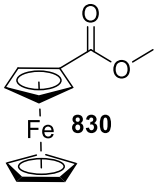
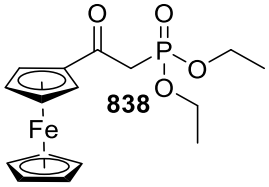
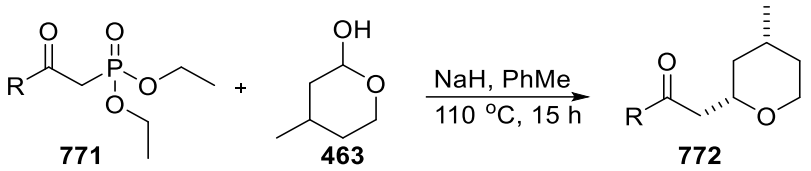
Entry	Starting Material	Product	Yield (%)
1	 831	 833	59
2	 824	 834	33
3	 832	 835	95
4	 826	 836	46
5	 828	 837	82
6	 Fe 830	 838 Fe	99

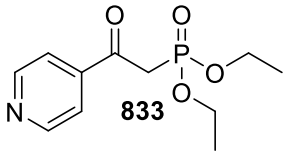
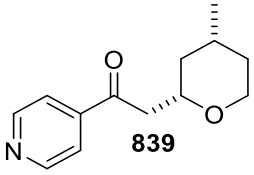
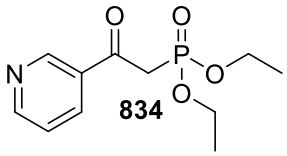
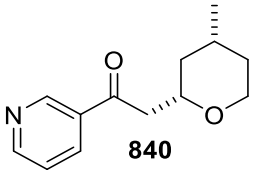
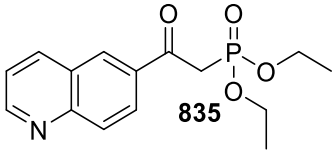
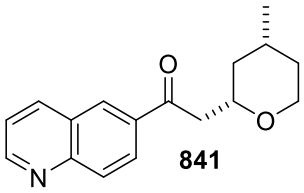
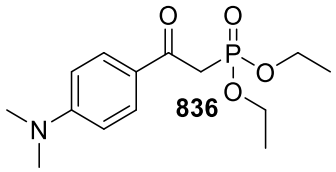
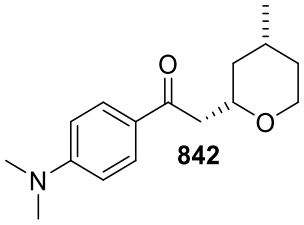
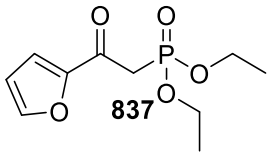
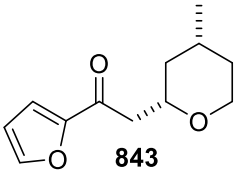
Table 4.11: Synthesis of HWE reagents **833**-**838**. Conditions: ester (1 eq.), phosphonate (1.1 eq.), diisopropylamine (2.25 eq.), nBuLi (2.2 eq.), dry THF (0.2 M), 5 min.

Having prepared a representative range of heterocyclic bearing phosphonates, we looked to apply them to the synthesis of tetrahydropyrans (Table 4.12). When 4- and 3-pyridyl phosphonates **833** and **834** were reacted with lactol **463**, we obtained tetrahydropyrans **839** and **840** in 92% and 98% yield, respectively (Entry 1 and 2). Quinoline **841** was prepared in 90% yield, and aniline **842** was prepared in quantitative yield (Entry 3 and 4). Furthemore, furyl phosphonate **837** afforded tetrahydropyran **843** in 97% yield. Finally, we were delighted to find that ferrocene substituted tetrahydropyran **844**

was accessible in quantitative yield. The relative stereochemistry of the tetrahydropyrans were assigned by *J* coupling constant analysis, analogously to the compounds in Scheme 4.16. Again, the diagnostic signal for the *cis* stereochemistry was a large quartet for H_3 axial, which corresponded to two large vicinal couplings and a large geminal coupling.



771 + **463** → **772**

Entry	Starting Material	Product	Yield (%)	d.r. (*cis:trans*)
1	 **833**	 **839**	92	94:6
2	 **834**	 **840**	98	74:26
3	 **835**	 **841**	90	64:36
4	 **836**	 **842**	100	91:9
5	 **837**	 **843**	97	72:28

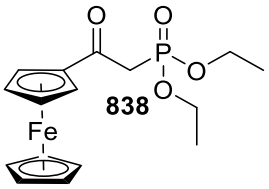
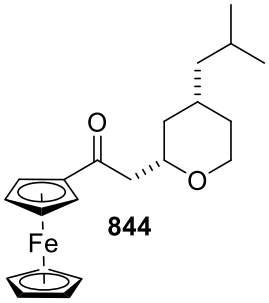
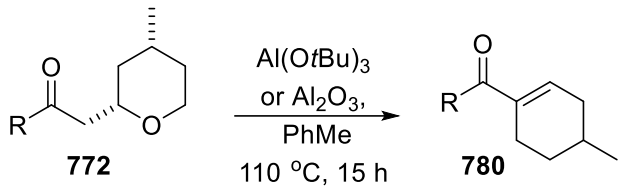
6	 **838**	 **844**	100	>95:5

Table 4.12: Synthesis of tetrahydropyrans **839**-**844**. Conditions: HWE reagent (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, then 4-methyltetrahydro-*2H*-pyran-2-ol (1 eq.), 110 °C, 15 h.

Finally, with tetrahydropyrans **839**-**844** accessed, we probed their reactivity in the [1,5]-hydride shift cascade (Table 4.13). 4-Pyridyl tetrahydropyran **839** was found to give cyclohexene **845** in 30% yield, when heated for 48 hours (Entry 1). Comparatively, 3-pyridine isomer **840** gave cyclohexene **846** in 55% yield (Entry 2). Quinoline **841** smoothly reacted to form cyclohexene **847** in 82% yield (Entry 3). Aniline derived tetrahydropyran **842** reacted in high yield to give cyclohexene **848** (Entry 4). Furyl substituted cyclohexene **849** was also accessible in excellent yield. Finally, ferrocene bearing tetrahydropyran **844** reacted cleanly to give cyclohexene **850**, with no sign of competing side reactions.



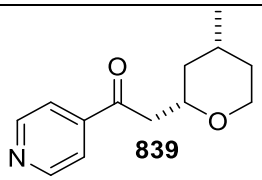
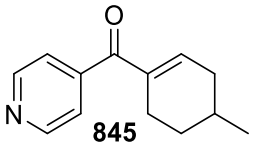
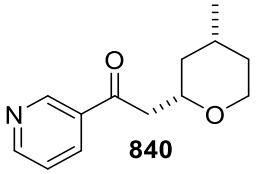
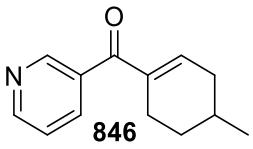
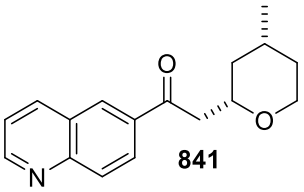
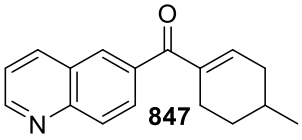
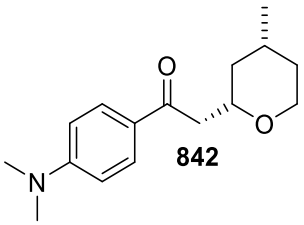
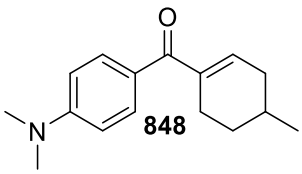
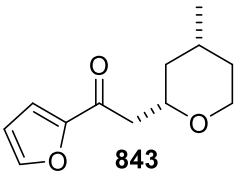
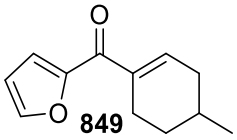
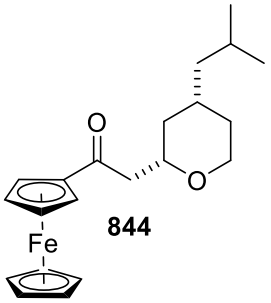
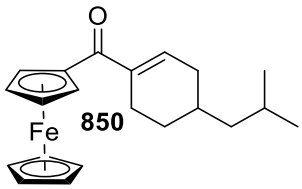
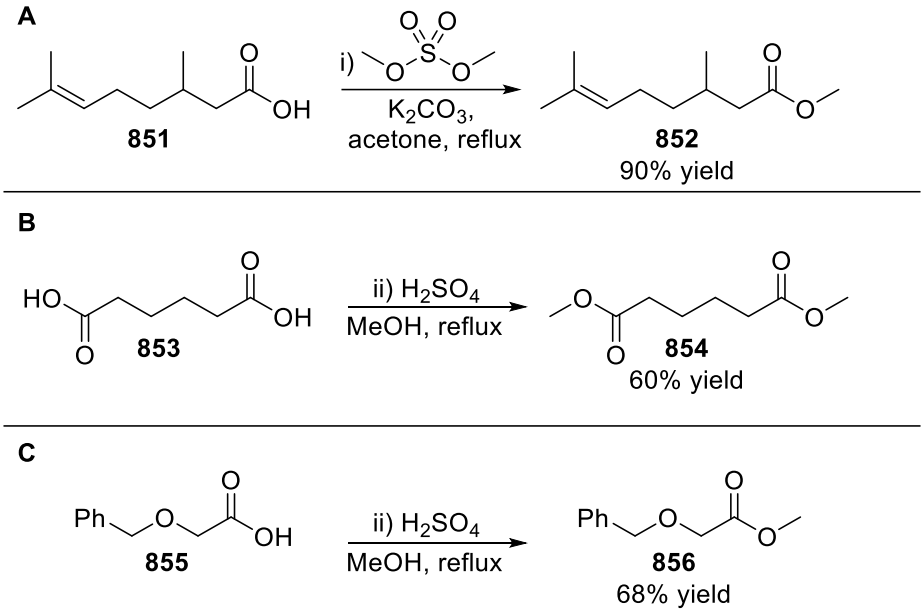
Entry	Starting Material	Product	Yield (%)
1[b]	 839	 845	30
2	 840	 846	55
3	 841	 847	82
4[a]	 842	 848	76
5	 843	 849	84
6[a]	 844	 850	59

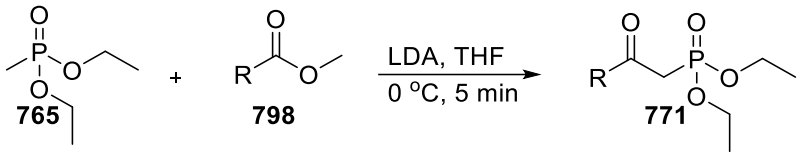
Table 4.13: Synthesis of cyclohexenes **845**-**850** by [1,5]-hydride shift aldol cascade. Conditions: tetrahydropyran (1 eq.), Al_2O_3 (5 eq.), PhMe (0.2M), 110 °C, 15 h.[a] $Al(OtBu)_3$ (1 eq.) used instead of Al_2O_3.[b] heated for 48 hours.

In addition to aryl substituted cyclohexenes, we were interested in exploring the reactivity of alkyl ketones. To investigate this, we began by synthesising a range of methyl esters, which could be converted to the corresponding phosphonate (Scheme 4.18). This included ester **852**, which was prepared by the reaction of dimethyl sulfate with citronellic acid **851** (A). Similarly, adipic acid **853** was reacted with sulphuric acid and methanol to afford diester **854** in 60% yield (B). Benzylated species **855** was also converted to methyl ester **856** in 68% yield by Fischer esterification (C).



Scheme 4.18: Synthesis of esters by esterification. i) **851** (1 eq.), dimethyl sulfate (1.2 eq.), K_2CO_3 (1.2 eq.), acetone (0.5 M), reflux, 2 h. ii) carboxylic acid (1 eq.), H_2SO_4 (1-2 eq.), MeOH (0.3M), reflux, 15 h.

Following esterification, aliphatic esters **852**, **854** and **856** and commercial esters **857** and **858** were reacted with methyl diethyl phosphonate **765** to form the corresponding alkyl Horner Wadsworth Emmons reagent (Table 4.14). Cyclohexyl ester **857** was converted to **859** in excellent yield (Entry 1). Heterocyclic phosphonate **860** was also prepared in 80% yield (Entry 2). Similarly, phosphonates bearing an alkene **861** (Entry 3), methyl ester **862** (Entry 4) and benzyl protected alcohol **863** (Entry 5) were prepared in good yield.



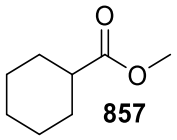
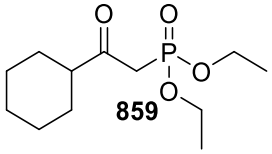
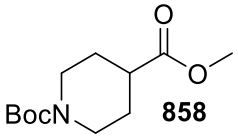
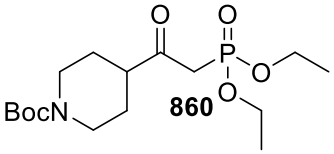
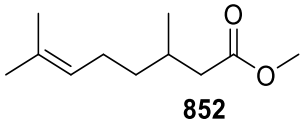
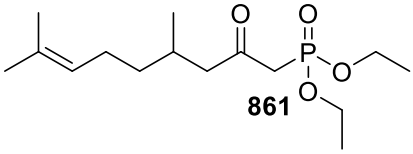
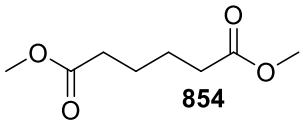
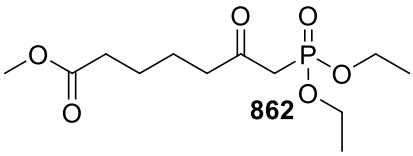
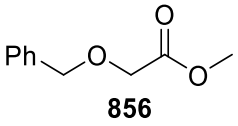
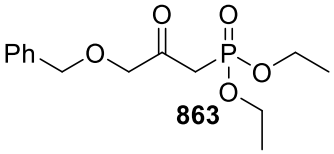
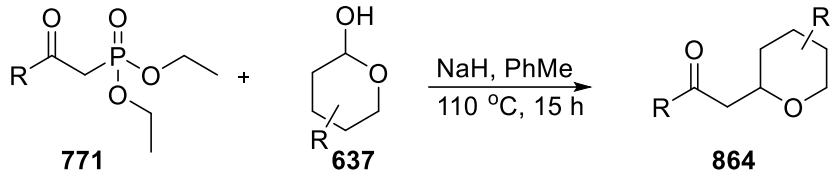
Entry	Starting Material	Product	Yield (%)
1			76
2			80
3			89
4			16
5			56

Table 4.14: Synthesis of HWE reagents **859**-**863**. Conditions: ester (1 eq.), **765** (1.1 eq.), diisopropylamine (2.25 eq.), *n*BuLi (2.2 eq.), dry THF (0.2 M), 5 min.

With aliphatic phosphonate reagents prepared, we investigated their feasibility to prepare tetrahydropyrans by Horner Wadsworth Emmons reaction (Table 4.15). Firstly, using commercial acetyl phosphonate **865**, we were delighted to find that a tetrahydropyran bearing methyl ketone substituent **866** was accessible in quantitative yield (Entry 1). Notably, the presence of a relatively unhindered ketone in the product did not result in competing side reactions. Similarly, tetrahydropyrans bearing a cyclohexyl substituent **867** (Entry 2) and BOC protected piperidine **868** (Entry 3) were both prepared in excellent yields. We were also delighted to find that the reaction tolerated substituted alkene **869** (Entry 4), methyl ester **870** (Entry 5) and benzylic alcohol **871** (Entry 6), with no evidence of side reactivity. As with the previous tetrahydropyrans, the relative stereochemistry was assigned by *J* coupling constant analysis as outlined in Scheme 4.16. Rather

unusually, tetrahydropyrans **867** and **870** were obtained as predominantly the *trans* stereoisomer. This diastereoselectivity varied between experiments due to the equilibrating reaction conditions, and presumably both **867** and **870** could be obtained as the thermodynamic *cis* stereoisomer with longer reaction times.



771 **637** **864**

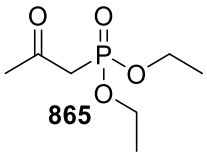
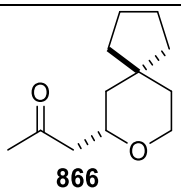
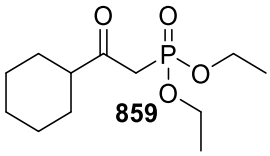
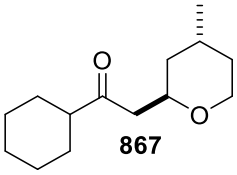
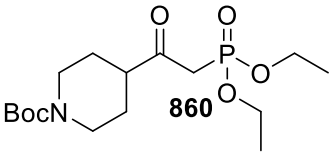
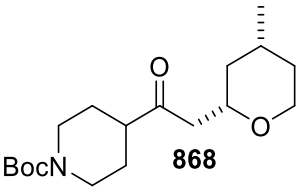
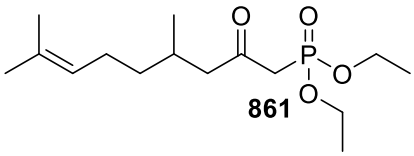
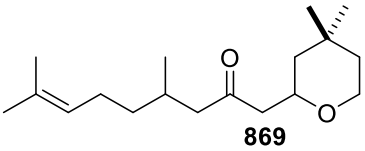
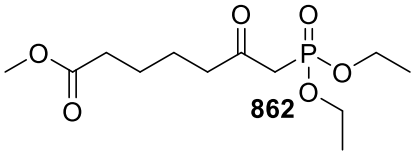
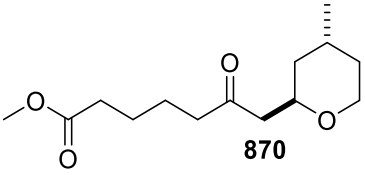
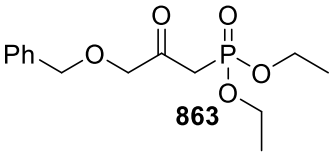
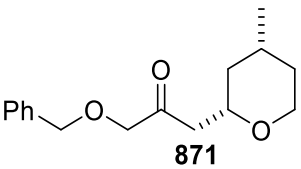
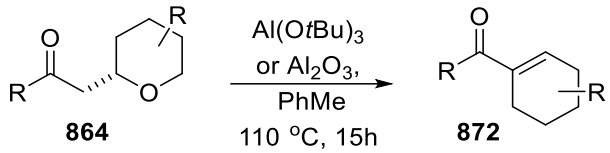
Entry	Starting Material	Product	Yield (%)	d.r. (cis:trans)
1	 **865**	 **866**	100	-
2	 **859**	 **867**	85	29:71
3	 **860**	 **868**	100	88:12
4	 **861**	 **869**	100	50:50
5	 **862**	 **870**	99	38:62
6	 **863**	 **871**	84	75:25

Table 4.15: Synthesis of tetrahydropyrans **866**-**871**. Conditions: HWE reagent (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, then 4-methyltetrahydro-*2H*-pyran-2-ol (1 eq.), 110 ^{o}C, 15 h.

With a representative range of aliphatic ketones prepared, we turned our attention to exploring their reactivity under the optimised conditions for the [1,5]-hydride shift. To our delight, we found that acetyl tetrahydropyran **866** smoothly formed cyclohexene **873** in 92% yield, despite the presence of enolizable protons in both the starting material and product (Entry 1). Secondary alkyl ketones **867** and **868** were well tolerated in the hydride shift reaction, leading to the formation of cyclohexenes **874** and **875** in 94% and 75% yield, respectively (Entry 2-3). We were also pleased to find that the reaction tolerated electron rich alkene **869**, enabling the synthesis of terpene derivative **876** in 95% yield (Entry 4). Notably, this functional group would not survive the reducing conditions of the iridium-catalysed annulation. When ester **870** was subjected to the reaction conditions, we only recovered unreacted starting material (Entry 5). Our hypothesis is that aluminium chelates to both carbonyl oxygens, preventing the hydride shift from occurring. Finally, we tried benzylic ether **871**, but found the starting material completely decomposed under the reaction conditions (Entry 6).



864 **872**

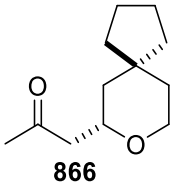
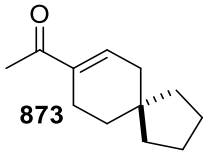
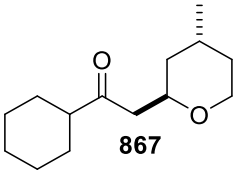
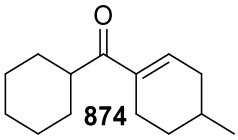
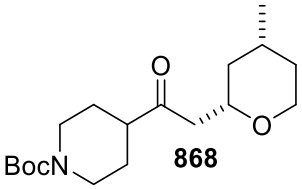
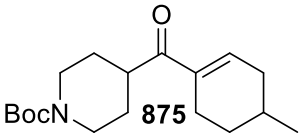
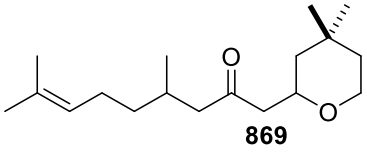
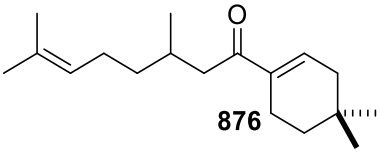
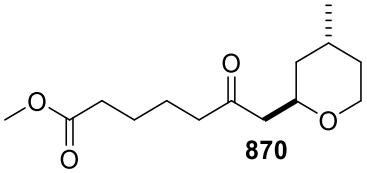
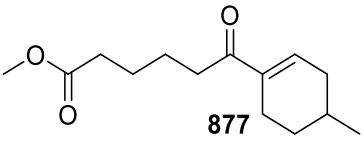
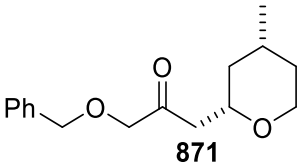
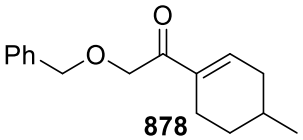
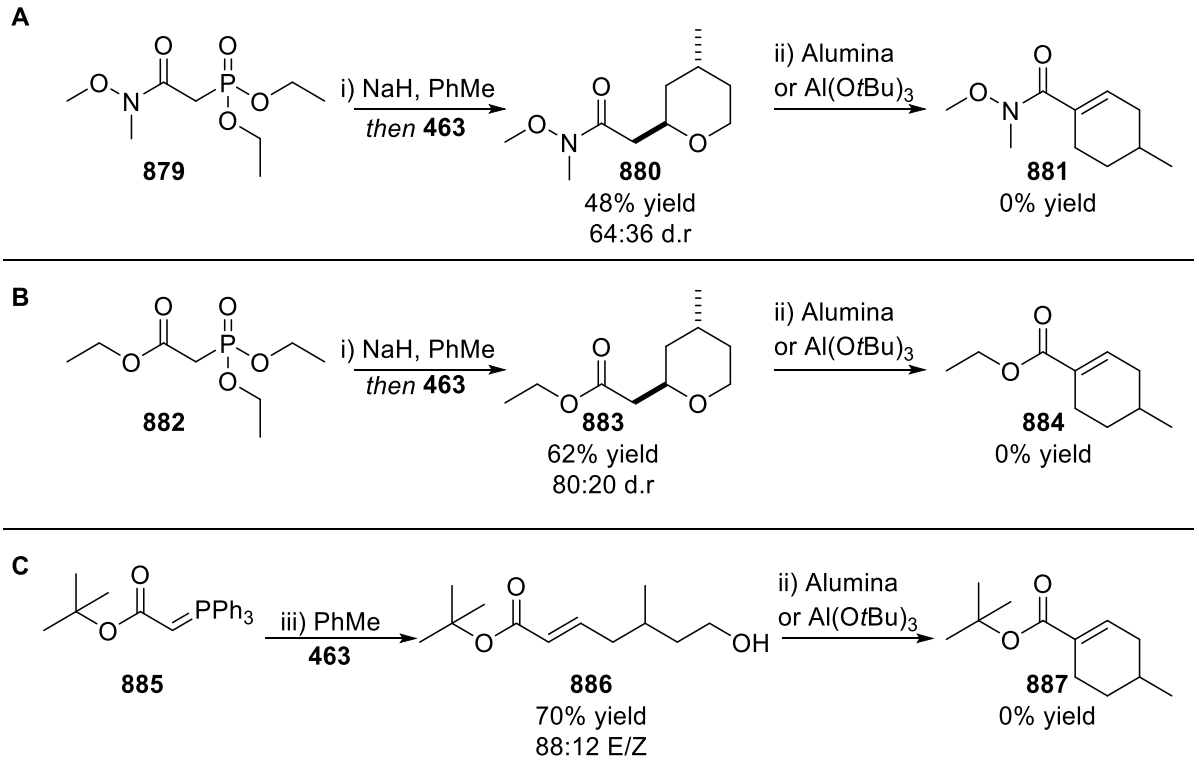
Entry	Starting Material	Product	Yield (%)
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2	 **867**	 **874**	94
3[a]	 **868**	 **875**	75
4	 **869**	 **876**	95
5	 **870**	 **877**	0
6	 **871**	 **878**	0

Table 4.16: Synthesis of cyclohexenes **873**-**878** by [1,5]-hydride shift aldol cascade. Conditions: tetrahydropyran (1 eq.), Al_2O_3 (5 eq.), PhMe (0.2M), 110 °C, 15 h.[a] $Al(OtBu)_3$ (1 eq.) used instead of Al_2O_3.

Having synthesised a range of alkyl and aryl substituted enones, we looked to explore whether other carbonyls were reactive towards a [1,5]-hydride shift (Scheme 4.19). We began by looking at whether amides were suitable substrates for the reaction (A). Using commerical Weinreb amide **879**, we

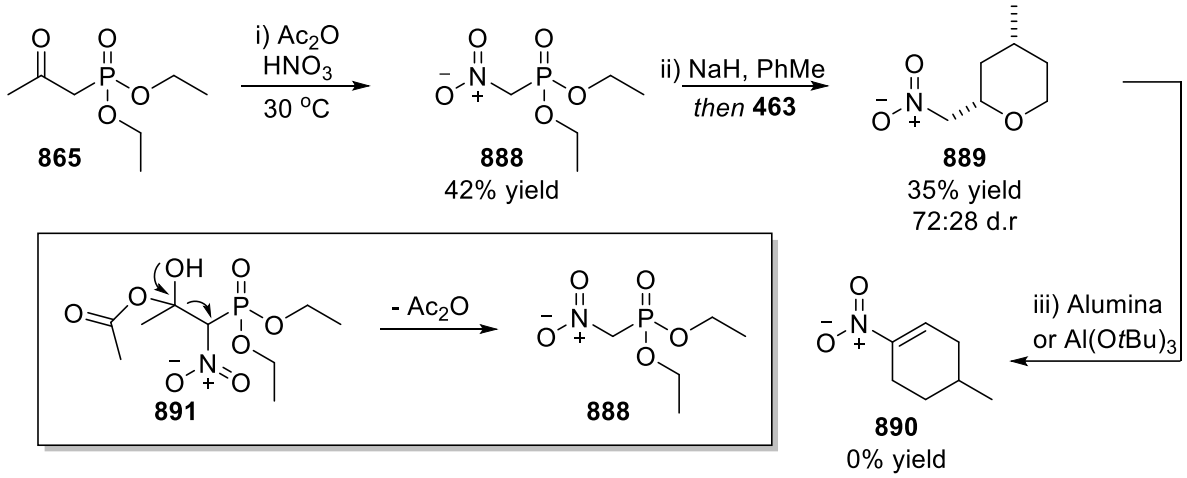
performed an HWE reaction with lactol **463**, which enabled access to *trans*-tetrahydropyran **880** in 48% yield. To rationalise the stereochemistry of **880**, it is plausible that the enone geometry from the HWE reaction could influence the stereochemical outcome, and only with longer reaction times could the thermodynamic *cis* isomer form. Disappointingly, only starting material was recovered when tetrahydropyran **880** was reacted with either alumina or aluminium *tert*-butoxide. This was presumably due to the amide not being a sufficiently electrophilic hydride acceptor.

Next, we looked at whether esters would undergo a hydride shift (B and C). To explore this, commercial ester **882** was reacted with sodium hydride and then lactol **463**, which yielded tetrahydropyran **883** in 62% yield. When **883** was subjected to the optimised conditions using alumina or aluminium *tert*-butoxide, only unreacted starting material was obtained. Similarly, *tert*-butyl ester **886** was investigated and also resulted in unreacted starting material when reacted with alumina or aluminium *tert*-butoxide (C). These results taken together suggested that esters are not sufficiently electrophilic acceptors for the [1,5]-hydride shift reaction.



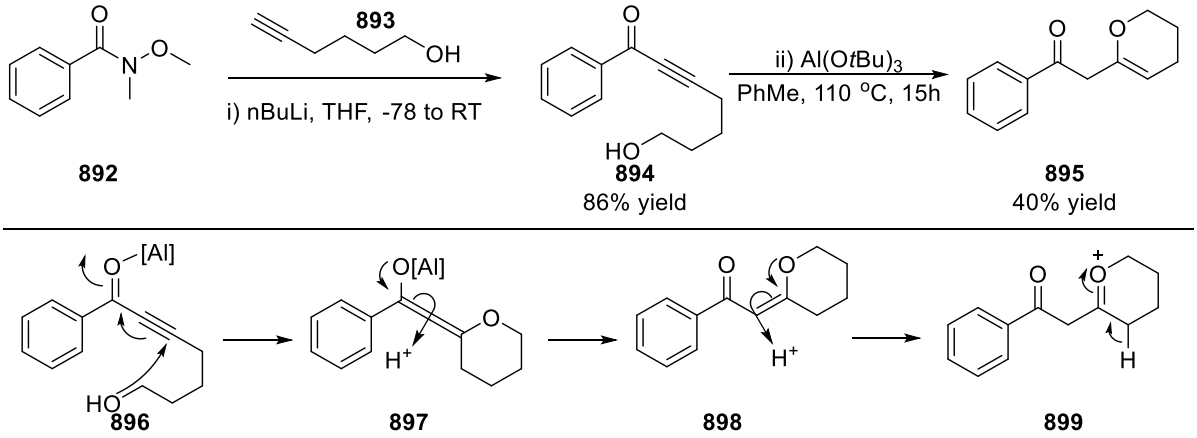
Scheme 4.19: subjection of amide **880** and esters **884** and **887** to the optimised conditions for [1,5]-hydride shift. Conditions: i) HWE reagent (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, then **463** (1 eq.), 110 ^{o}C, 15 h. ii) tetrahydropyran (1 eq.), Al_2O_3 (5 eq.) or Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2M), 110 ^{o}C, 15 h. iii) **463** (1 eq.), **885** (3 eq.), PhMe (0.2 M), RT, 48 h.

Having investigated amides, esters and ketones, we next looked to explore the reactivity of nitro olefins as hydride acceptors (Scheme 4.20). Nitro-phosphonate **888** was prepared by a literature known reaction of keto phosphonate **865** with nitric acid and acetic anhydride.[151] Following this, phosphonate **888** was reacted with sodium hydride and then lactol **463** to afford the desired tetrahydropyran **889** in 35% yield. When we subjected **889** to the optimised conditions, we were disappointed to find that no product formed, and the starting material had decomposed.



Scheme 4.20: Attempted synthesis of cyclohexene **890**. Conditions: i) **865** (1 eq.), 90% HNO_3 (1.1 eq.), Ac_2O (1.7 eq.), 30 °C, 1 h. ii) **888** (1.3 eq.), NaH (1.2 eq.), PhMe (0.3 M), RT, 15 min, *then* **463** (1 eq.), 110 °C, 15 h. iii) **889** (1 eq.), Al_2O_3 (5 eq.) or Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2M), 110 °C, 15 h.

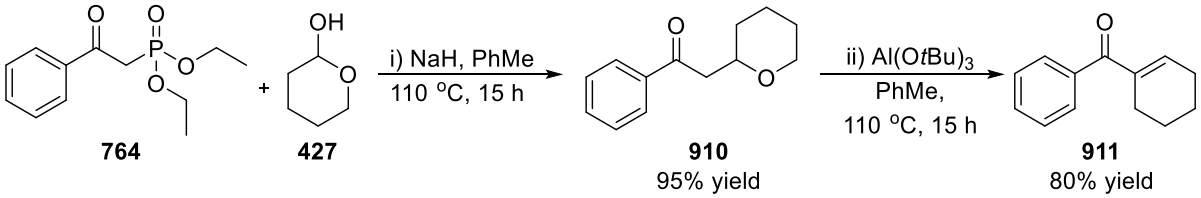
The final electron withdrawing group we investigated were ynones (Scheme 4.21). To prepare the substrate, hexyn-1-ol **893** was lithiated with *n*BuLi, and then subsequently reacted with Weinreb amide **892**, which furnished ynone **894** in 86% yield. With ynone **894** in hand, we subjected it to the optimised conditions for the [1,5]-hydride shift, and found that dihydropyran **895** formed in 40% yield. It is plausible that this formed from the conjugate addition of the alcohol to the ynone to give allenoate **897**, which could then pick up a proton, followed by tautomerization of **898** to the more stable cyclic alkene **895**. Overall, these results suggested that the [1,5]-hydride shift reaction was limited in scope to aryl and alkyl ketones as electron withdrawing groups.



Scheme 4.21: Subjection of ynone substrate **894** to the [1,5]-hydride shift cascade reaction. Conditions: i) **893** (1.2 eq.), 2.5M *n*BuLi in hexanes (2.4 eq.), dry THF (0.25 M), -78 °C, 1 h, then **892** (1 eq.), -78 °C to RT, 1 h. ii) **894** (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2M), 110 °C, 15 h.

4.3.3 Substrate Scope of Lactol Partner

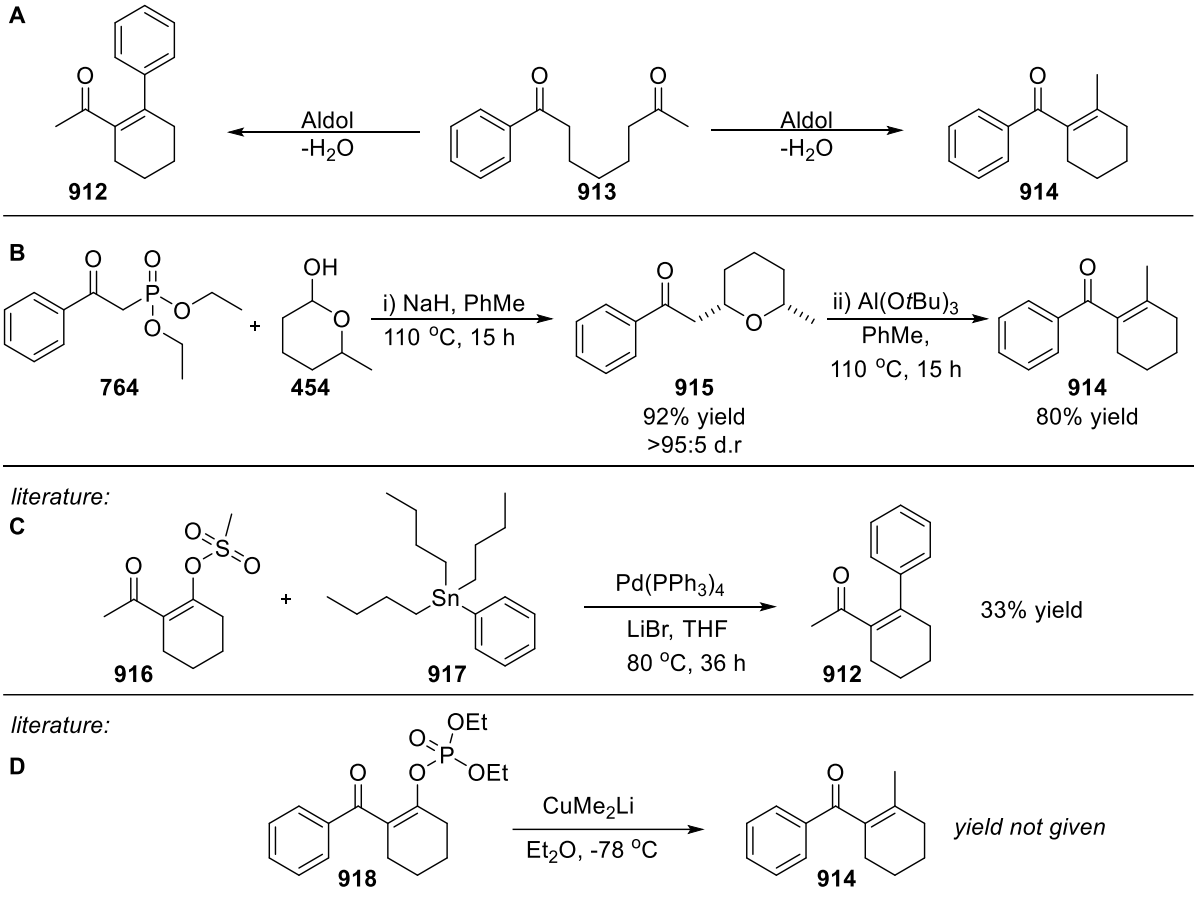
Having explored a range of electron withdrawing groups in the hydride shift reaction, we next investigated the scope of the lactol partner. We first looked at the synthesis of an unsubstituted cyclohexene (Scheme 4.22). Using lactol **427**, which was prepared by Dr R. J. Armstrong, we reacted **427** with phosphonate **764**, affording tetrahydropyran **910** in 95% yield. Subsequently, tetrahydropyran **910** was reacted with aluminium *tert*-butoxide under our optimised reaction conditions. We were delighted to find that this reaction afforded **911** in 80% yield. Notably the equivalent reaction from 1,5-pentane diol that we performed in Chapter 2 was unsuccessful, thus we had overcome one of the limitations of our previous approach to cyclohexene synthesis (Table 2.18).



Scheme 4.22: Synthesis of unsubstituted cyclohexene **911**. Conditions: i) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **427** (1 eq.), 110 °C, 15 h. ii) **910** (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 °C, 15 h. Lactol **427** was prepared by Dr R. J. Armstrong.

We next investigated 6-substituted pyran **915**, as a route to access 1,2-disubstituted cyclohexenes (Scheme 4.23). As the carbonyl does not bear pentamethylbenzene, there is a possibility that both

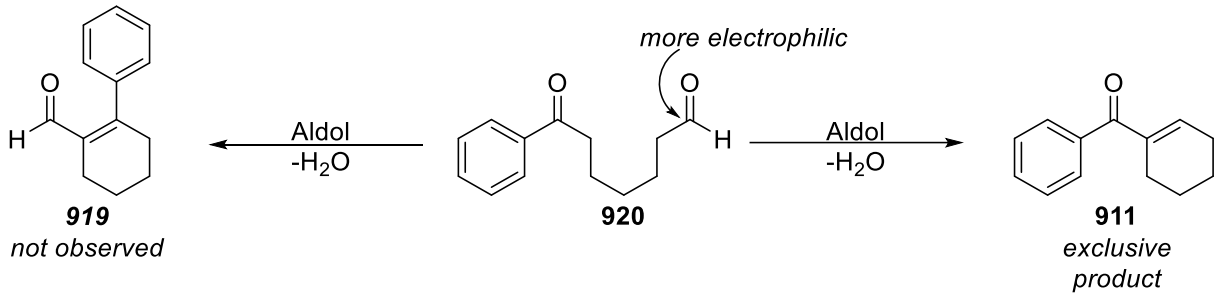
cyclohexenes **912** and **914** could form in the reaction (A). To explore this, we performed an HWE reaction with phosphonate **764** and lactol **454**, which furnished tetrahydropyran **915** in 92% yield and greater than 95:5 d.r. Subsequently, tetrahydropyran **915** was treated with aluminium *tert*-butoxide, and pleasingly was found to give 1,2-disubstituted cyclohexene **914** in 80% yield as the exclusive product (B). To confirm our assignment, we compared the NMR data to two orthogonal methods for the preparation of cyclohexenes **912** and **914**, with our data closely matching that of **914** and not **912** (C and D).[152,153] Furthermore, we observed by HMBC a three-bond correlation between the *ortho* phenyl ring C-H and the carbonyl carbon, which was consistent with regioisomer **914**. Formation of cyclohexene **914** was consistent with the methyl ketone of **913** being the more electrophilic carbonyl, thus under kinetic control, it reacted exclusively with the enolate of the phenyl ketone to give regioisomer **914**.



Scheme 4.23: A) Potential regioselectivity issue for aldol condensation. B) Synthesis of 1,2-disubstituted cyclohexene **914**. C) literature precedented palladium catalysed cross coupling of organostannanes D) Literature precedented conjugate addition of organocuprate to **914**. Conditions:

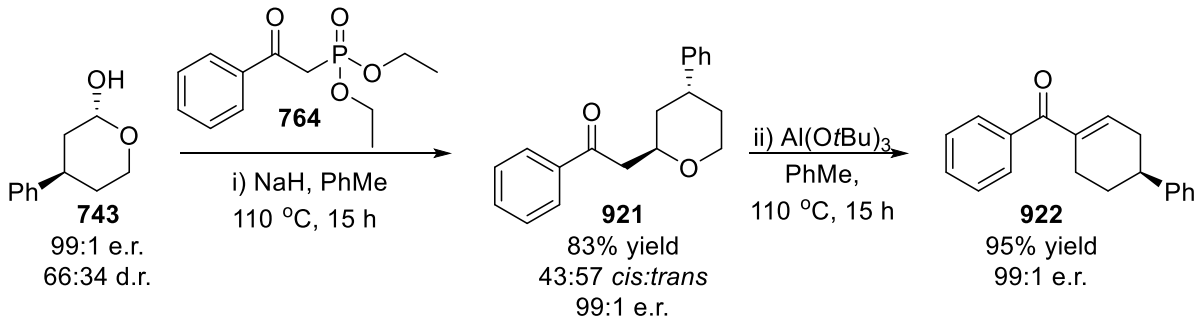
i) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **454** (1 eq.), 110 °C, 15 h. ii) **915** (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 °C, 15 h.

The result in Scheme 4.23 also led us to question the regioselectivity of the aldol condensation to form cyclohexenes from phenyl ketones and aldehydes (Scheme 4.24). Formation of cyclohexene **919** could immediately be discounted due to the absence of an aldehyde peak in any NMR spectra of cyclohexenes formed from the aluminium promoted reaction. Furthermore, in every case we observed an enone C-H peak confirming the assignment as regioisomer **911**. We rationalised the observed regiochemical outcome as a result of the aldehyde of **920** being more electrophilic than the phenyl ketone, thus the aldehyde reacted preferentially with the enolate of the phenyl ketone to afford cyclohexene **911**.



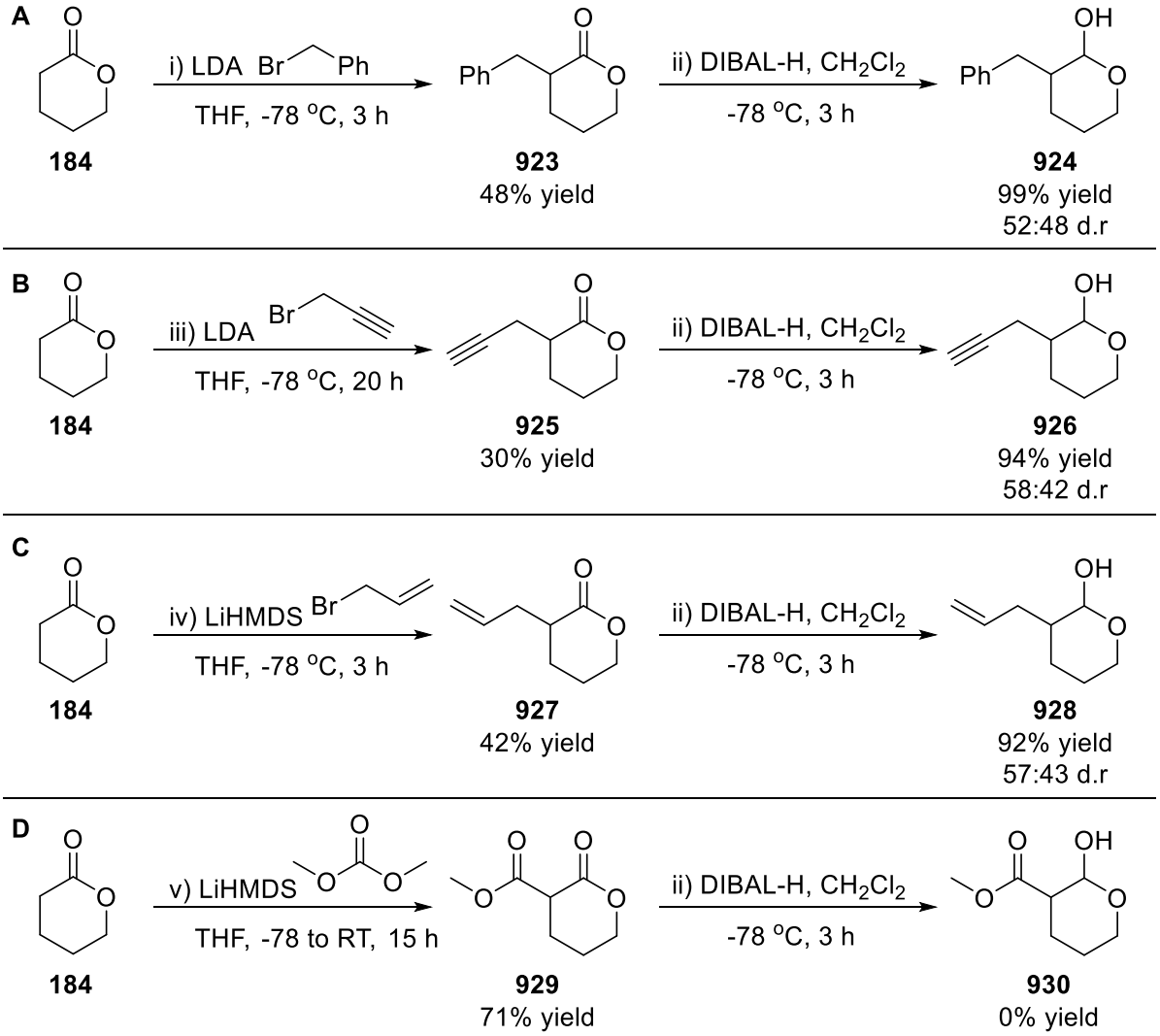
Scheme 4.24: Regioselectivity for the aldol condensation between phenyl ketones and aldehydes.

We next returned our attention to enantioenriched lactols, that previously had racemised under base-promoted [1,5]-hydride shift conditions (Table 4.1). To explore this, tetrahydropyran **921** was prepared from enantioenriched lactol **743** and phosphonate **764** in 83% yield, and 99:1 e.r. To our delight, under the new conditions using aluminium *tert*-butoxide, cyclohexene **922** was afforded in excellent yield and complete stereochemical fidelity (Scheme 4.25).



Scheme 4.25: Synthesis of enantioenriched cyclohexene **922**. Conditions: **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **743** (1 eq.), 110 ^{o}C, 15 h. ii) **921** (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 ^{o}C, 15 h.

In a similar manner to enantioenriched cyclohexenes, regioisomerically pure α-substituted lactols were previously found to yield a mixture of 1,3- and 1,5-disubstituted cyclohexenes under basic conditions (Table 4.1), thus we set out to explore how α-substituted lactols would fair with aluminium. To investigate this, we began by preparing a range of α-substituted lactols (Scheme 4.26). α-Benzyl lactol **924** was prepared in two step sequence, which commenced with an α-alkylation of δ-valerolactone **184** with benzyl bromide in 48% yield. Subsequent reduction of lactone **923** with DIBAL-H smoothly afforded lactol **924** in 99% yield. By analogy, alkynyl lactol **926** was prepared by the α-alkylation of δ-valerolactone **184** with propargyl bromide, to give lactone **925** in 30% yield. Lactone **925** was then cleanly reduced to lactol **926** in 94% yield. In addition to the above substrates, we α-alkylated lactone **184** with allyl bromide to afford **927** in 42% yield, and then reduced the product with DIBAL-H to give lactol **928** in 92% yield. Finally, we performed the α-alkylation of δ-valerolactone **184** with diethyl carbonate, which proceeded in 71% yield. The reduction of lactone **929** with DIBAL-H did not yield any product, and the starting material decomposed.

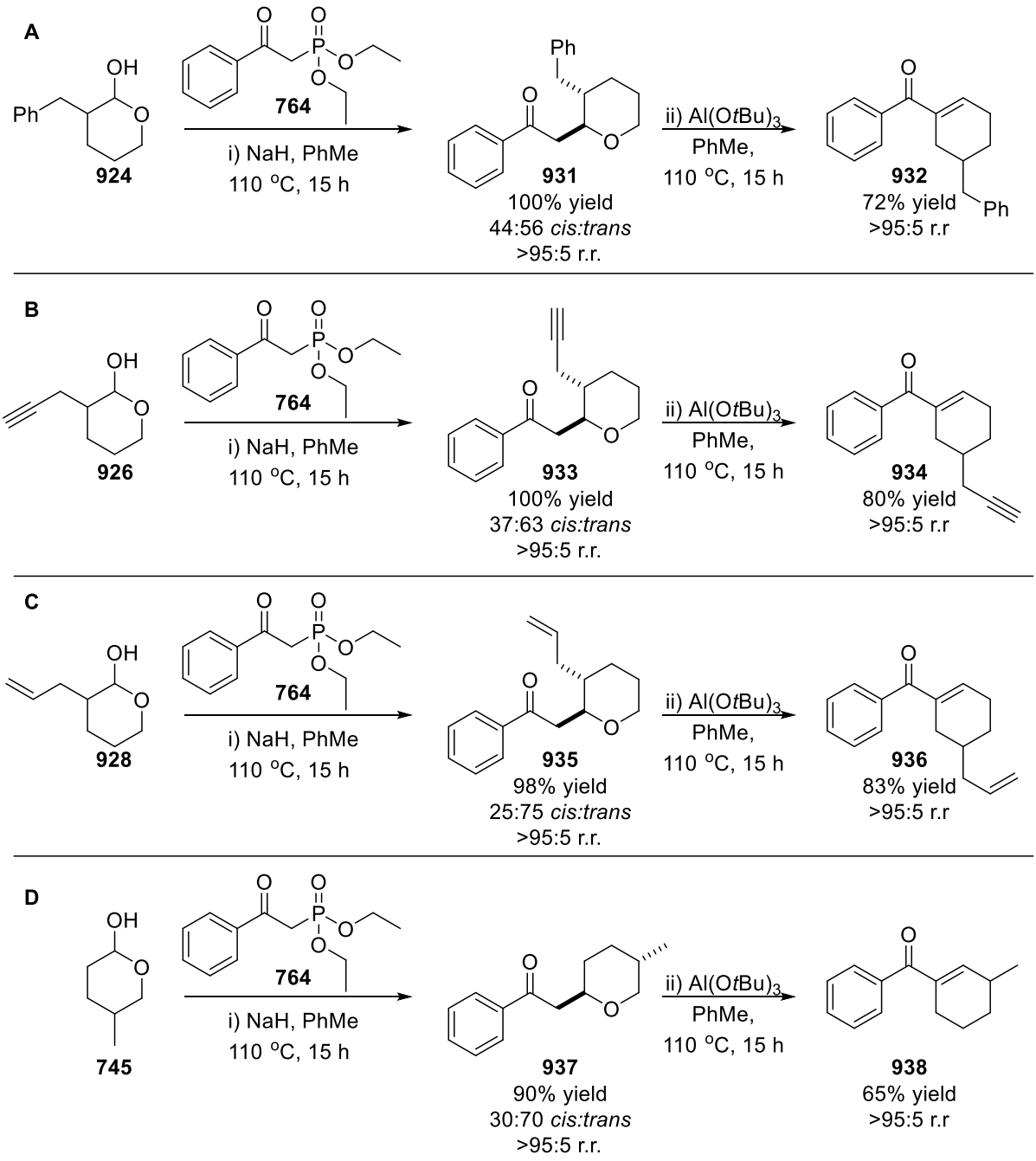


Scheme 4.26: Synthesis of α-substituted lactols. Conditions: i) **184** (1 eq.), LDA (1.1 eq.), dry THF (0.5 M), -78 °C, 30 min, then benzyl bromide (2 eq.), 3 h. ii) lactone (1 eq.), DIBAL-H (1.4 eq.), CH_2Cl_2 (0.5 M), -78 °C, 3 h. iii) **184** (2 eq.), LDA (2 eq.), dry THF (0.2 M), -78 °C, 1 h, then propargyl bromide (1 eq.), 20 h. iv) **184** (1 eq.), LiHMDS (1.1 eq.), dry THF (0.3 M), -78 °C, 30 min, then allyl bromide (1.1 eq.), 3 h. v) **184** (1 eq.) , diethyl carbonate (1.1 eq.), LiHMDS (2 eq.), dry THF (0.5 M), -78 to RT, 15 h.

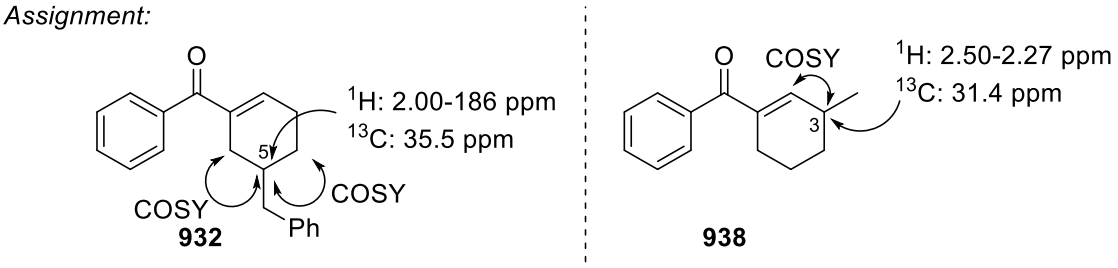
With lactols **924**, **926** and **928** prepared, we next investigated their reactivity under our newly developed conditions for the [1,5]-hydride shift (Scheme 4.27). First, lactol **924** was reacted with phosphonate **764** to give tetrahydropyran **931** in quantitative yield, and as a single regioisomer. When we subjected tetrahydropyran **931** to the optimised conditions, we obtained cyclohexene **932** in 72% yield (A). Close interrogation of the ^{1}H NMR revealed that the product obtained was greater than 95:5 *r.r.*, with the major cyclohexene being the 1,5-disubstituted regioisomer. We were also pleased to find that when alkynyl lactol **926** was subjected to the Horner Wadsworth Emmons reaction, we obtained

tetrahydropyran **933** in quantitative yield. **933** was then reacted under the optimised conditions, and we obtained 1,5-disubstituted cyclohexene **934** in 80% yield and greater than 95:5 *r.r.*, with no sign of side reactions (B). Finally, allyl lactone **928** was reacted with **764** and sodium hydride, which led to the isolation of **935** in 98% yield. We then subjected tetrahydropyran **935** to the aluminium promoted hydride shift, and pleasingly obtained cyclohexene **936** in 83% yield and greater than 95:5 *r.r.* (C). The functional group compatibility here is also notable, with alkene and alkynes well tolerated in the process. By analogy to the above reactions, Dr R. J. Armstrong subjected lactol **745** to the HWE reaction, affording tetrahydropyran **937** in 90% yield. Tetrahydropyran **937** was then treated with aluminium *tert*-butoxide, leading to the formation of 1,3-disubstituted cyclohexene **938** in 65% yield as a single regioisomer. Taken together, these results indicated our method was a very robust approach to the regiocontrolled synthesis of 1,3 and 1,5-disubstituted cyclohexenes.

In each case, the regioselectivity was determined by integration of the enone peaks by quantitative ^{1}H NMR. The major regioisomer was assigned as outlined in Scheme 4.28. The C_5 regioisomer was assigned based upon H_5 showing a diagnostic COSY correlation to two CH_2 groups (H_4 and H_6) and notably did not show a correlation to an alkene proton environment. In contrast, the C_3 regioisomer showed a diagnostic COSY correlation from H_3 to alkene proton H_2.

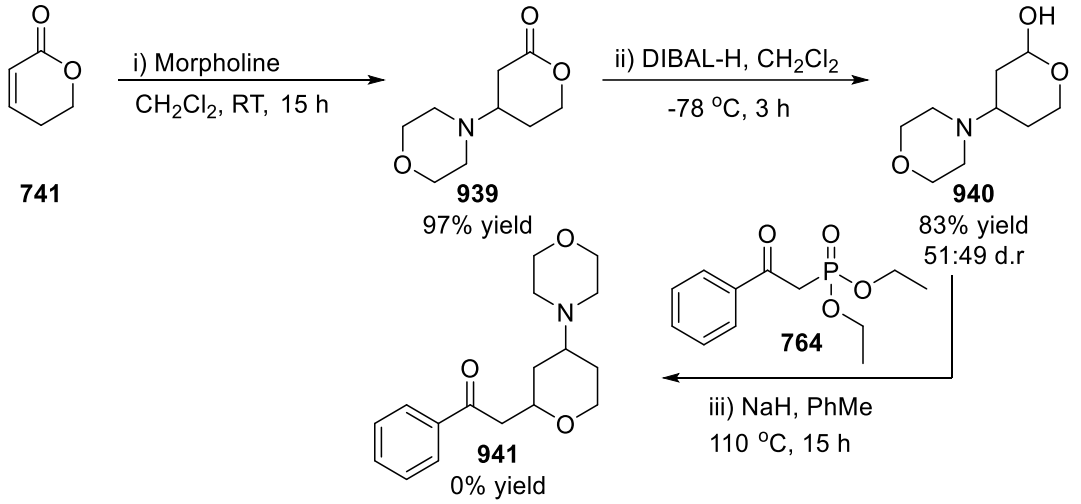


Scheme 4.27: Regiocontrolled synthesis of 1,3- and 1,5-disubstituted cyclohexenes. Conditions: i) HWE reagent (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, then lactol (1 eq.), 110 °C, 15 h. ii) tetrahydropyran (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2M), 110 °C, 15 h. Experiments in Entry D performed by Dr R. J. Armstrong.



Scheme 4.28: Assignment of C_3 and C_5 cyclohexene regioisomers

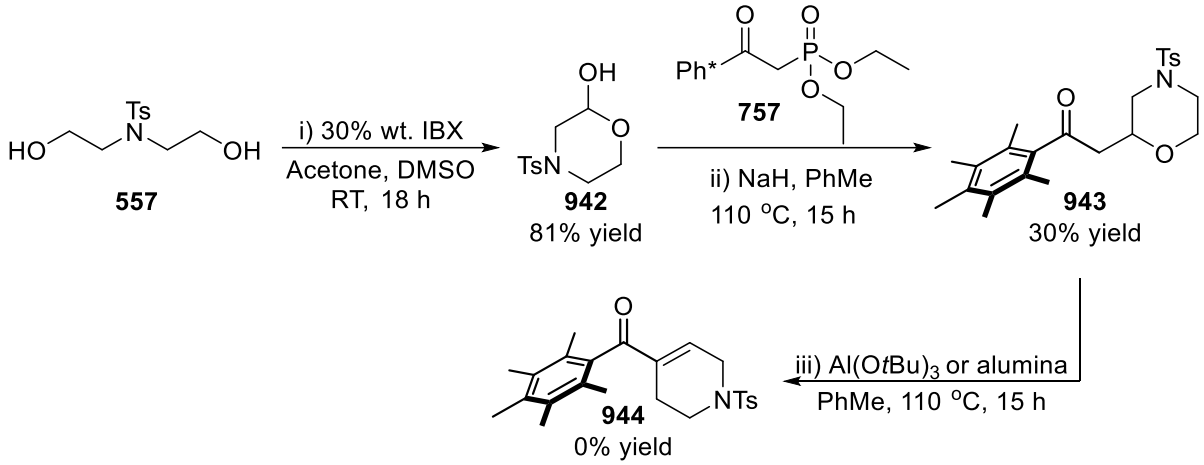
Having investigated a range of lactols bearing alkyl and aryl substituents, we were also interested in lactols bearing heteroatoms (Scheme 4.29). To explore this, morpholine was reacted with α,β-unsaturated lactone **741** to afford substituted lactone **939** in 97% yield. Lactone **939** was then reduced with DIBAL-H to afford the corresponding lactol **940** in 83% yield. With lactol **940** in hand, we performed a Horner Wadsworth Emmons reaction using phosphonate **764**. Disappointingly, the reaction did not afford any product, and lactol **940** had decomposed. We hypothesised this was due to lactol **940** undergoing E1cB elimination under the basic reaction conditions.



Scheme 4.29: Attempted synthesis of tetrahydropyran **941**. Conditions: i) **741** (1 eq.), morpholine (1 eq.), CH_2Cl_2 (0.5 M), RT, 15 h. ii) **939** (1 eq.), DIBAL-H (1.4 eq.), CH_2Cl_2 (0.5 M), -78 °C, 3 h. iii) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **940** (1 eq.), 110 °C, 15 h.

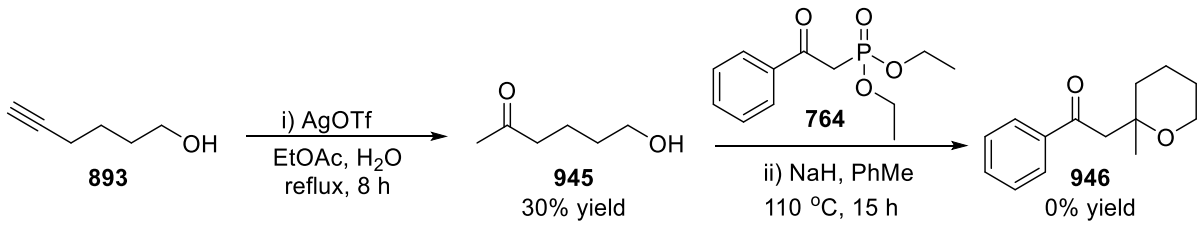
We next looked at the application of our method to the synthesis of heterocycles (Scheme 4.30). Using diethanolamine derivative **557**, we performed an IBX oxidation, which afforded lactol **942** in 81% yield. We subsequently reacted **942** with phosphonate **757**, which enabled access to morpholine **943** in 30% yield. With morpholine **943** in hand, we attempted the [1,5]-hydride shift reaction using both alumina and aluminium *tert*-butoxide, but found both conditions to only yield unreacted starting material. A

plausible explanation for the lack of reactivity is that the electronegative heteroatom in the backbone reduced the hydricity of the hydride donor.



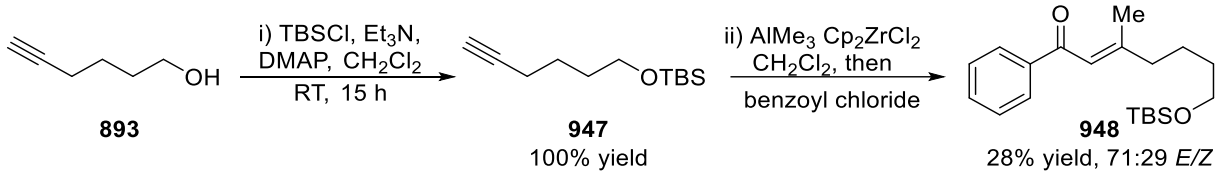
Scheme 4.30: Attempted synthesis of tetrahydropyridine **944**. Conditions: **557** (1 eq.), 30% wt. IBX with stabiliser (1.2 eq.), 4:1 acetone/DMSO (0.2 M), RT, 18 h. ii) **757** (1.2 eq.), NaH (1.2 eq.), PhMe (0.5 M), RT, 15 min, *then* **942** (1 eq.), 110 °C, 15 h. iii) **943** (1 eq.), alumina (5 eq.) or Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 °C, 15 h.

The final aspect of the substrate scope we set out to examine was the synthesis of 1,6-disubstituted cyclohexenes. Notably, this substitution pattern was completely inaccessible with the iridium-catalysed methodology, as an α-substituted diol formed a 1,2-disubstituted cyclohexene as the exclusive product due to the chemoselectivity of the initial aldol reaction (see Scheme 2.8). To explore the synthesis of 1,6-disubstituted cyclohexenes, we prepared hydroxy-ketone **954** by the silver catalysed hydration of alkyne **893** (Scheme 4.31). Subsequently, hydroxy-ketone **945** was reacted with phosphonate **764** under our optimised Horner Wadsworth Emmons conditions, but sadly did not yield any product, which was likely due to the ketone motif being too hindered for the HWE reaction. Consequently, we looked at alternative routes to access pyran **946**.



Scheme 4.31: Attempted synthesis of tetrahydropyran **946**. Conditions: i) **893** (1 eq.), AgOTf (0.1 eq.), water (3 eq.), ethyl acetate (0.3 M), reflux, 8 h. ii) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **945** (1 eq.), 110 °C, 15 h.

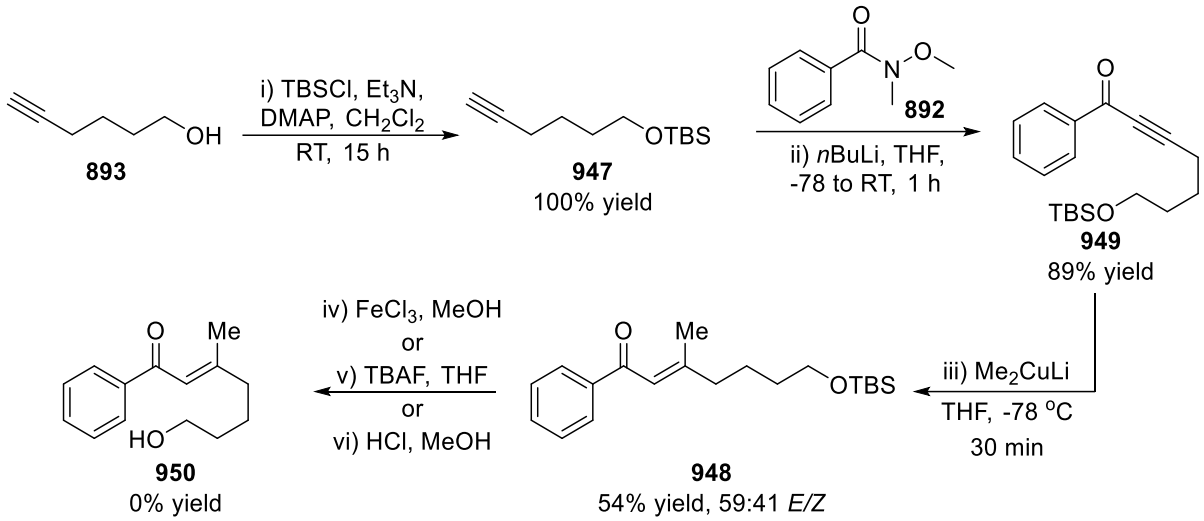
The second route to tetrahydropyran **946** we investigated was by carbometallation of TBS-protected alkyne **947**, which would enable direct access to the trisubstituted alkene needed for the [1,5]-hydride shift reaction (Scheme 4.32). Mechanistically, this approach proceeded by an initial *cis* carbometallation of alkyne **947** with zirconium, with the resulting organometallic species reacting with benzoyl chloride, to give the desired enone **948**. Pleasingly, this reaction afforded the desired TBS-protected enone **948** in 28% yield.



893 | **947** 100% yield | **948** 28% yield, 71:29 *E/Z*

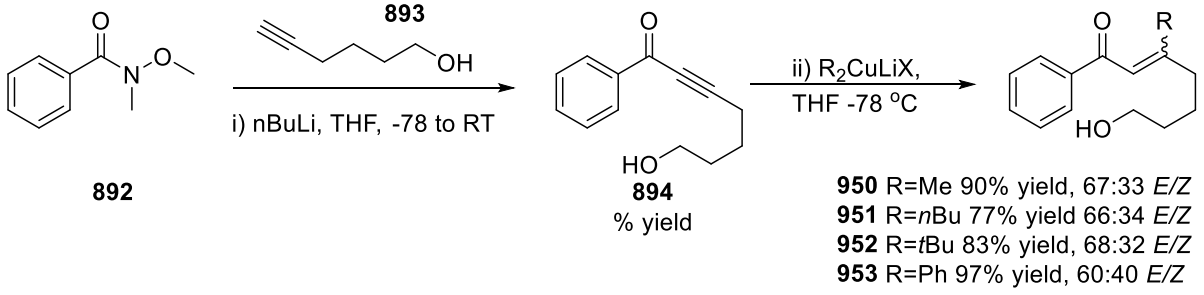
Scheme 4.32: Synthesis of trisubstituted enone **948** by carbometallation. Conditions: i) **893** (1 eq.), TBSCl (1.1 eq.), trimethylamine (1.2 eq.), DMAP (0.1 eq.), CH_2Cl_2 (0.3 M), RT, 15 h. ii) Cp_2ZrCl_2 (1eq.), 2 M $AlMe_3$ in PhMe (3 eq.), CH_2Cl_2 (0.2 M), -23 °C to RT, 2 h, *then* **947** (1 eq.), -23 °C to RT, 2 h, *then* benzoyl chloride (1.2 eq.), -23 °C to RT, 30 min.

In parallel to this, we also investigated an alternative synthetic route to trisubstituted enone **950** (Scheme 4.33). The sequence began with the TBS protection of hexyn-1-ol, which proceeded in quantitative yield. The resulting alkyne **947** was then lithiated with *n*BuLi, and added to weinreb amide **892**, to give ynone **949** in 89% yield. Ynone **949** was treated with the Gilman cuprate derived from methyl lithium to afford TBS-protected enone **948** in 54% yield. Despite several attempts, the deprotection of enone **948** resulted in decomposition of the starting material, thus we next investigated a protecting group-free strategy to enone **950**.



Scheme 4.33: Attempted synthesis of trisubstituted enone **950**. Conditions: i) **893** (1 eq.), TBSCl (1.1 eq.), trimethylamine (1.2 eq.), DMAP (0.1 eq.), CH_2Cl_2 (0.3 M), RT, 15 h. ii) **947** (1.2 eq.), 2.5 M *n*BuLi in hexanes (2.4 eq.), dry THF (0.2 M), -78 °C, 30 min, *then* **892** (1 eq.), -78 °C to RT, 1 h. iii) 1.6 M MeLi in diethyl ether (4 eq.), CuI (2 eq.), THF (0.2 M), -78 °C to 0 °C, 1 h, *then* **949** (1 eq.), -78 °C, 30 min. iv) **948** (1 eq.), $FeCl_3$ (0.1 eq.), MeOH (0.1 M), RT, 2 h. v) **948** (1 eq.), 1 M TBAF in THF (1 eq.), 0 °C, 2 h. vi) **948** (1 eq.), 1 M HCl in 4:1 CH_2Cl_2/MeOH (1 eq.), RT, 15 h.

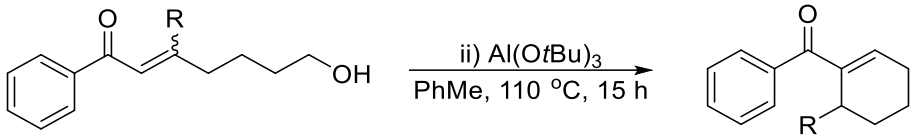
The final route we explored was a protecting group-free strategy to hydroxy-enone **950** (Scheme 4.34). The synthetic route began with the addition of lithiated hexyn-1-ol **893** to Weinreb amide **892**, which afforded ynone **894** in 86% yield. Unprotected ynone **894** was then treated with a two-fold excess of Gilman cuprate derived from methyl lithium, which to our delight afforded unprotected enone **950** in 90% yield. By this same approach, organocuprates prepared from *n*BuLi, *t*BuLi and PhLi were reacted with ynone **894**, to give the corresponding enones **951**, **952** and **953** in uniformly high yields.



Scheme 4.34: Synthesis of trisubstituted enones by cuprate addition. Conditions: i) **893** (1.2 eq.), 2.5M *n*BuLi in hexanes (2.4 eq.), dry THF (0.25 M), -78 °C, 1 h, *then* **892** (1 eq.), -78 °C to RT, 1 h. ii)

organolithium (4 eq.), CuI or CuCN (2eq.), THF (0.2 M), -78 °C to 0 °C, 1h, *then* **894** (1 eq.), -78 °C, 30 min.

With hydroxy-enones **950**-**953** in hand, we evaluated their reactivity under our optimised conditions for the [1,5]-hydride shift reaction (Table 4.17). We were delighted to find that using aluminium *tert*-butoxide, methyl substituted enone **950** smoothly afforded 1,6-disubstituted cyclohexene **956** in 83% yield (Entry 1). Similarly, larger alkyl groups were tolerated, such as *n*-butyl-substituted enone **951**, which afforded cyclohexene **957** in 67% yield (Entry 2). Sterically encumbered *t*-butyl enone **952** proved to be a more challenging substrate, with the desired cyclohexene **958** isolated in 21% yield (Entry 3). An enone bearing a phenyl substituent was also reacted under these conditions, but only the corresponding tetrahydropyran **960** was recovered in 36% yield (Entry 4).



954 **955**

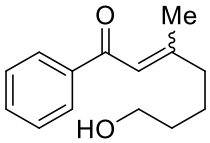
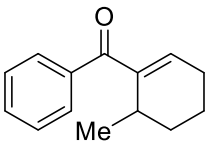
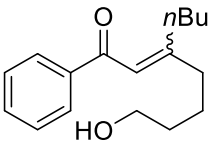
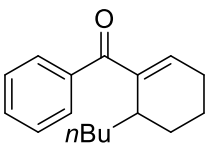
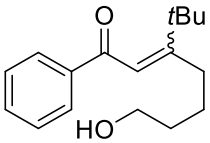
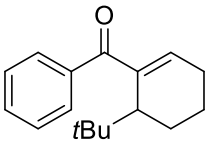
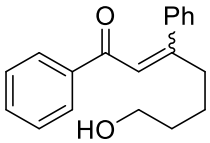
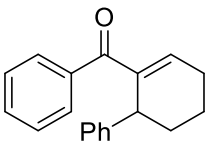
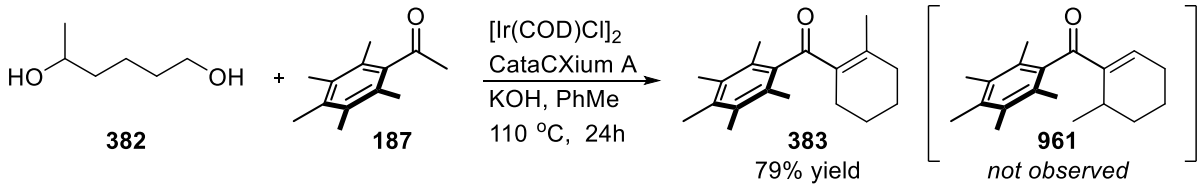
Entry	Starting Material	Product	Yield (%)	Regioselectivity (r.r.)
1	 **950**	 **956**	83	>95:5
2	 **951**	 **957**	67	>95:5
3	 **952**	 **958**	21	>95:5
4[a]	 **953**	 **959**	0	-

Table 4.17: Synthesis of 1,6 disubstituted cyclohexenes by [1,5]-hydride shift cascade. Conditions: i) hydroxy-enone **950**-**953** (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 ^{o}C, 15 h. [a] Reaction afforded tetrahydropyran **960** in 36% yield.

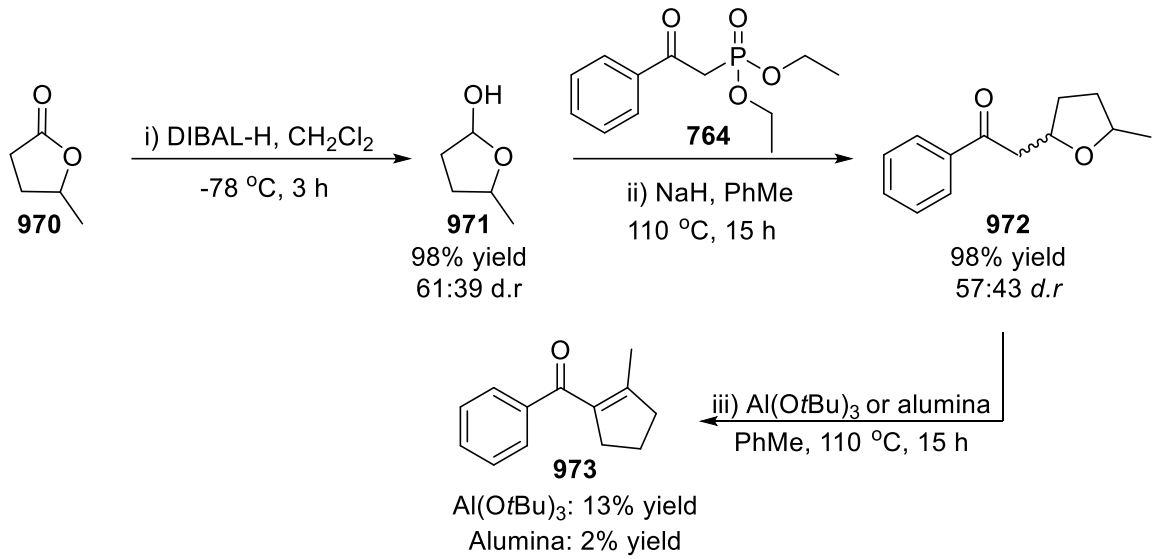
Notably, this was the first time we were able to make 1,6-disubstituted cyclohexenes. As a comparison, the reaction of 1,5-hexane diol **382** under our iridium-catalysed annulation conditions afforded 1,2-disubstituted cyclohexene **383** in 79% yield as the only product (Scheme 4.35). This was because the first C-C bond formation step occurs exclusively with the aldehyde (from oxidation of the diol) over the ketone.



Scheme 4.35: Synthesis of 1,2-disubstituted cyclohexene **383** under iridium-catalysed annulation conditions.

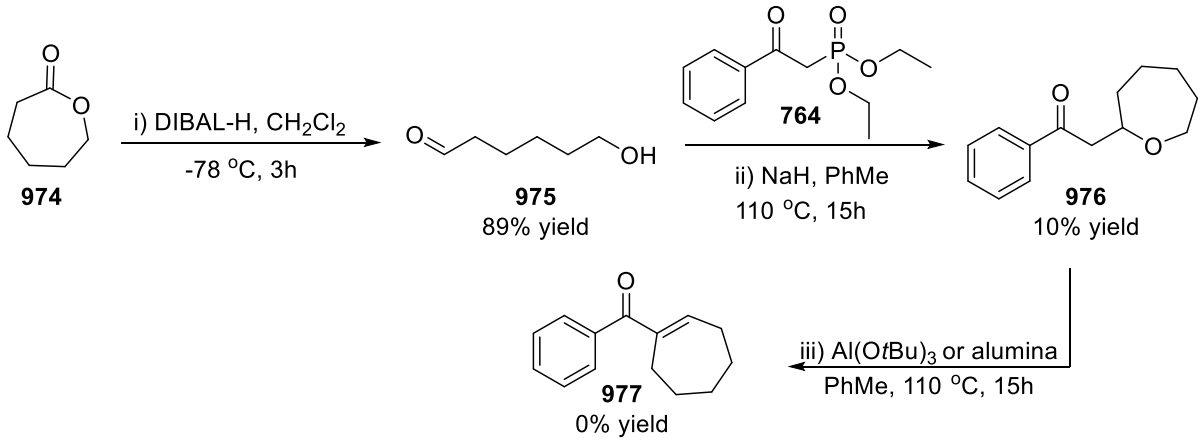
4.3.4 Synthesis of Five and Seven Membered Rings

Having demonstrated that all substitution patterns of cyclohexenes are accessible by this approach, we next wanted to investigate the feasibility of this method to prepare other ring sizes (Scheme 4.36). To explore this idea, lactone **970** was reduced with DIBAL-H to afford the corresponding lactol **971** in 98% yield as an inconsequential mixture of anomers. Lactol **971** was then reacted with phosphonate **764** by an HWE reaction, affording tetrahydrofuran **972** in 98% yield and close to 1:1 d.r. With tetrahydrofuran **972** in hand, we treated it with both alumina and aluminium *tert*-butoxide. Somewhat unsurprisingly, we obtained a low yield of cyclopentene **973**, likely due to the corresponding [1,4]-hydride shift being less favourable.



Scheme 4.36: Synthesis of cyclopentene **973** by [1,5]-hydride shift cascade. Conditions: i) **970** (1 eq.), DIBAL-H (1.4 eq.), CH_2Cl_2 (0.5 M), -78 °C, 3 h. ii) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **971** (1 eq.), 110 °C, 15 h. iii) **972** (1 eq.), alumina (5 eq.) or Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 °C, 15 h.

In addition to five-membered rings, we also investigated the synthesis of seven membered rings (Scheme 4.37). To accomplish this, ε-caprolactone **974** was partially reduced using DIBAL-H to afford hydroxyaldehyde **975** in 89% yield. Following this, aldehyde **975** was reacted with phosphonate **764** by HWE reaction to give oxepane **976** in 10% yield. With oxepane **976** in hand, we treated it with both alumina and aluminium tert-butoxide, but found neither reaction conditions to afford the desired cycloheptene **977**. Again, this result reflects the challenging nature of the [1,6]-hydride shift that would be required.

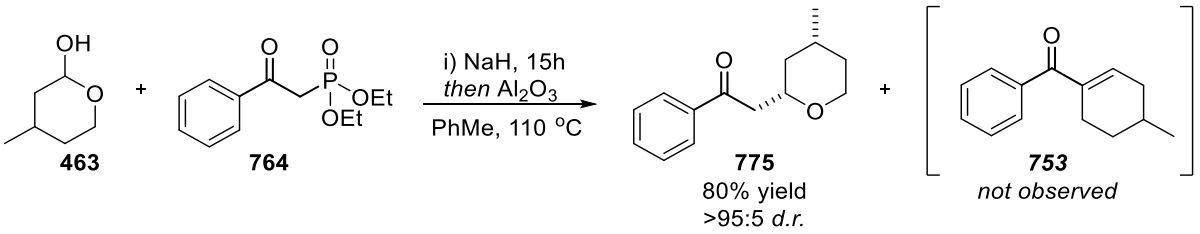


Scheme 4.37: Attempted synthesis of cycloheptene **977** by [1,5]-hydride shift cascade. Conditions: **974** (1 eq.), DIBAL-H (1.4 eq.), CH_2Cl_2 (0.5 M), -78 °C, 3h. ii) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, 15 min, *then* **975** (1 eq.), 110 °C, 15 h. iii) **976** (1 eq.), Alumina (5 eq.) or Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2M), 110 °C, 15 h.

4.3.5 One-Pot Protocol

Thus far, we have prepared a wide range of cyclohexenes in a two-step sequence consisting of a sequential Horner Wadsworth- Emmons reaction followed by a [1,5]-hydride shift-aldol condensation. Consequently, we were interested in whether the reaction could be adapted to a one-pot protocol, which would enable the synthesis of cyclohexenes in a more efficient manner.

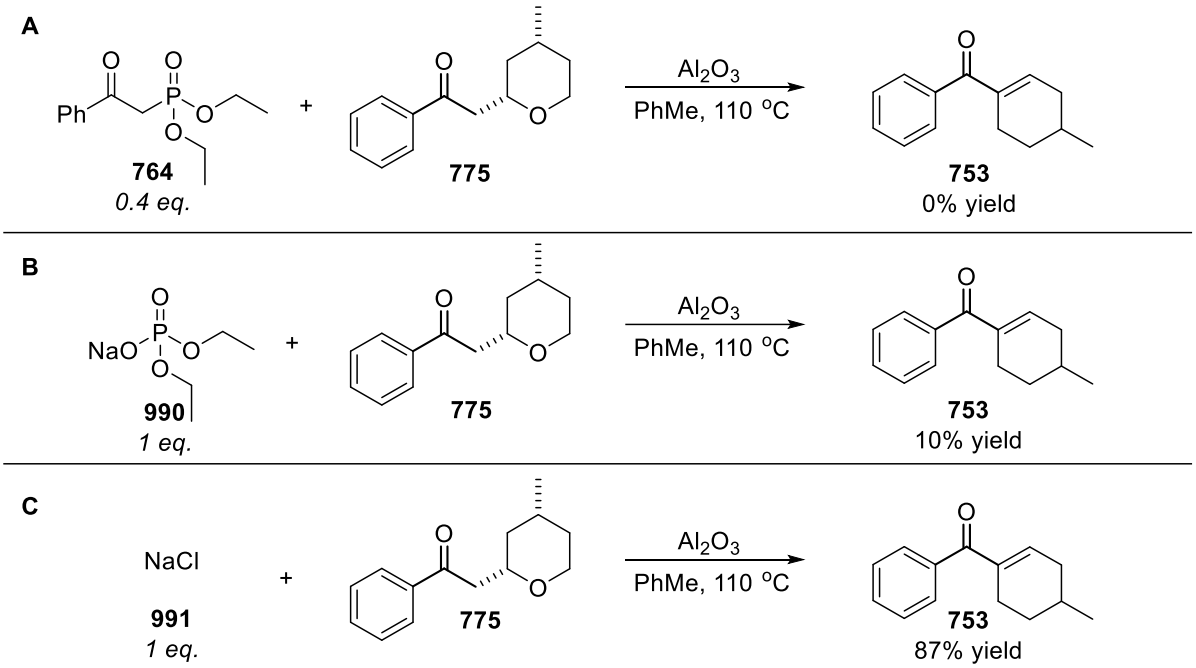
To test this hypothesis, we began by performing the Horner Wadsworth Emmons reaction using lactol **463** and phosphonate **764**, and adding the alumina in the same pot (Scheme 4.38). Disappointingly, we isolated the intermediate tetrahydropyran **775** in 80% yield, with no sign of the formation of cyclohexene **753**.



Scheme 4.38: Attempted one-pot synthesis of cyclohexene **753**. Conditions: **463** (1 eq.), **764** (1.4 eq.), 60% wt. NaH (1.2 eq.), PhMe (0.2 M), 110 °C, 15 h, *then* Al_2O_3 (5 eq.), 15 h.

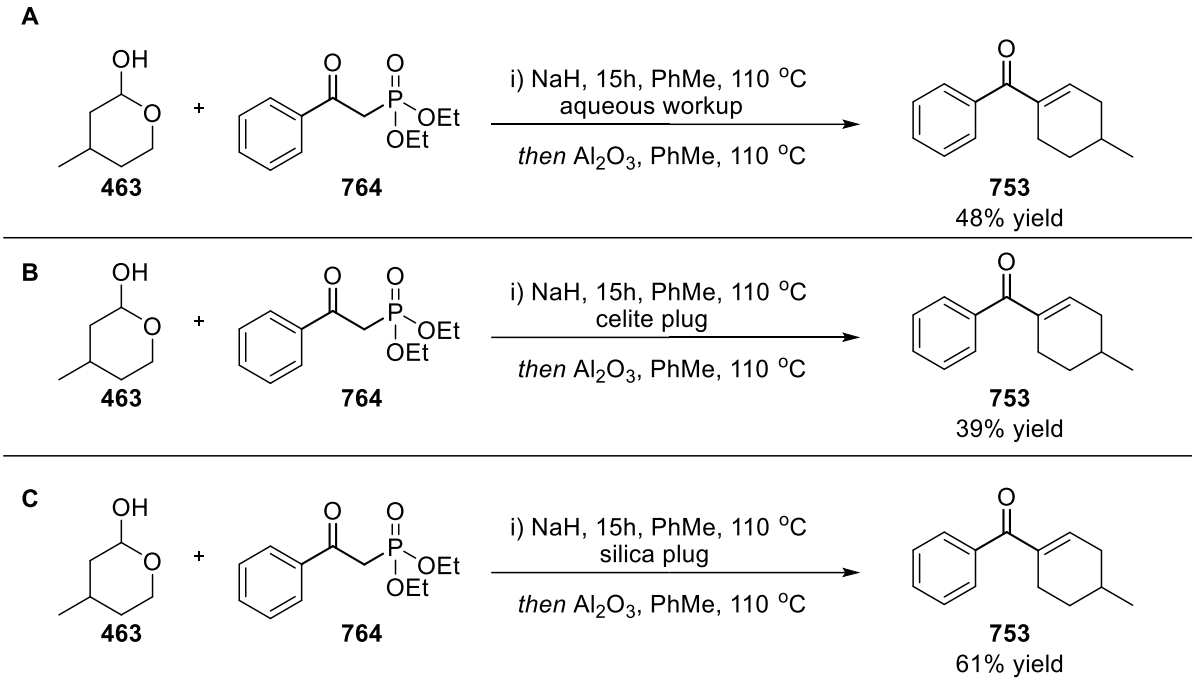
To determine the cause of the failed one-pot procedure, we conducted a series of control experiments under the reaction conditions for the [1,5]-hydride shift-aldol condensation (Scheme 4.39). Firstly, when we added 0.4 equivalents of phosphonate **764** to the reaction conditions (which is the excess phosphonate reagent from the HWE reaction), we found the hydride shift reaction to be completely supressed, with zero product **753** formed (A). Analogously, we added one equivalent of sodium phosphate **990** (the by-product from the HWE reaction) to the hydride shift reaction, which revealed that it also inhibited the formation of cyclohexene **753**, with **753** obtained in a reduced 10% yield (B). Finally, when we added one equivalent of sodium chloride to the reaction to determine whether the presence of the sodium counterion effected the reaction, we obtained cyclohexene **753** in 87% yield (C). We concluded from these experiments that the presence of phosphonate **764** and sodium

phosphate **990** had a detrimental effect on the hydride shift reaction, likely by sequestering aluminium, thus these components had to be removed from the reaction for our one-pot procedure to work.



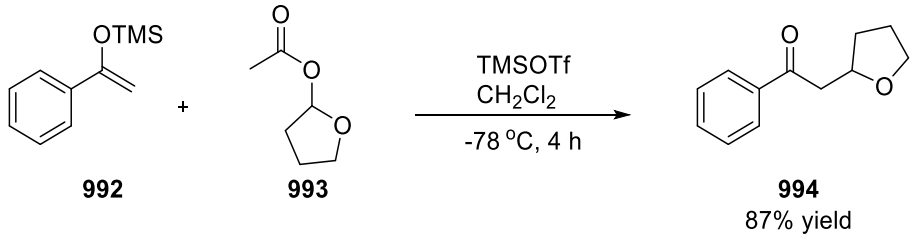
Scheme 4.39: Competition experiments with phosphonate **764** (A), sodium phosphate **990** (B) and sodium chloride **991** (C). Conditions: **775** (1 eq.), Al_2O_3 (5 eq.), PhMe (0.2 M), 110 °C, 15 h.

To overcome the inhibitory effect of phosphonate **764** and sodium phosphate **990** on the hydride shift reaction, we envisioned that performing a simple work-up between the first and second step of the reaction sequence would enable isolation of the cyclohexene (Scheme 4.40). The first approach we tried was performing an aqueous workup between the two steps, which pleasingly resulted in the isolation of cyclohexene **753** in 48% yield (A). The second approach we investigated was filtering the crude reaction mixture through a plug of celite®, from which we obtained **753** in 39% yield. The final approach we tried was filtering the crude reaction mixture through a plug of silica, washing with diethyl ether. This final approach was the highest yielding, affording cyclohexene **753** in 61% yield.



Scheme 4.40: Two step procedures for the synthesis of cyclohexene **753**. Conditions: **463** (1 eq.), **764** (1.4 eq.), 60% wt. NaH (1.2 eq.), PhMe (0.2 M), 110 °C, 15 h, *then* workup, *then* Al_2O_3 (20 eq.), PhMe (0.2 M), 110 °C.

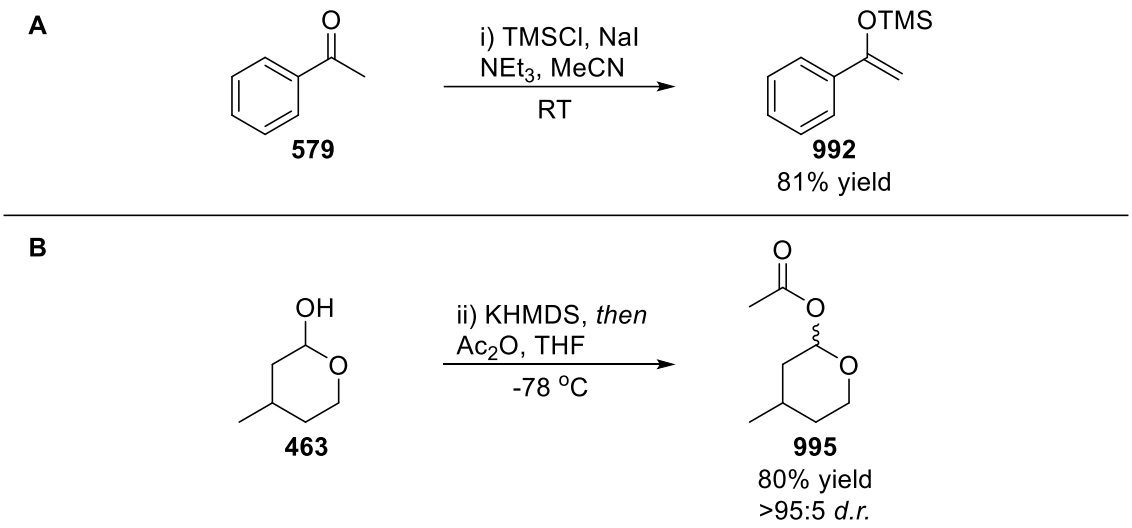
In addition to exploring procedures utilising the Horner Wadsworth Emmons reaction, we also looked at alternative disconnections to the intermediate tetrahydropyran, namely the Mukayama aldol reaction. Noyori reported in 1988 that trimethylsilyl triflate catalyses the reaction of enol trimethylsilyl ether **992** with 2-acetoxytetrahydrofuran **993** to give the corresponding β-alkoxycarbonyl **994** (Scheme 4.41).[154]



Scheme 4.41: literature precedented Mukayama Aldol reaction to prepare tetrahydrofuran **994**. Conditions: silyl enol ether (1 eq.), acetal (1.1 eq.), TMSOTf (0.05 eq.), CH_2Cl_2 (0.5 M), -78 °C, 4 h.

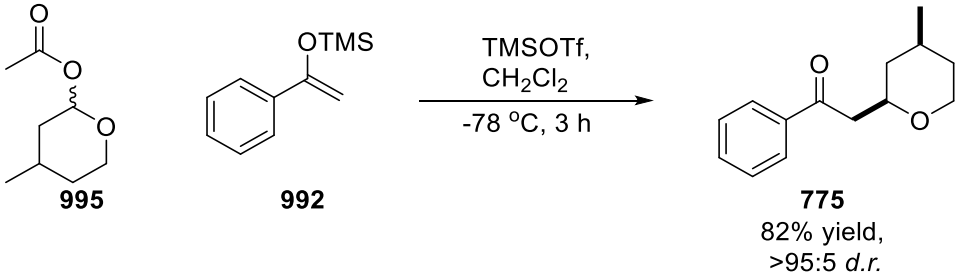
Based on this literature precedence, silyl enol ether **992** was prepared in 81% yield by the reaction of acetophenone **579** with trimethylsilyl chloride, triethylamine and sodium iodide (Scheme 4.42, A).

Additionally, lactol **463** was acylated by deprotonation with KHMDS followed by the addition of acetic anhydride, which cleanly afforded **995** in 80% yield (B).



Scheme 4.42: Synthesis of silyl enol ether **992** and acylated lactol **995**. Conditions: i) **579** (1 eq.), TMSCl (1.24 eq.), NaI (1.24 eq.), NEt_3 (1.24 eq.), MeCN (0.8 M), RT, 3 h. ii) **463** (1 eq.), 0.5 M KHMDS in PhMe (1.05 eq.), Ac_2O (3 eq.), -78 °C, 2 h.

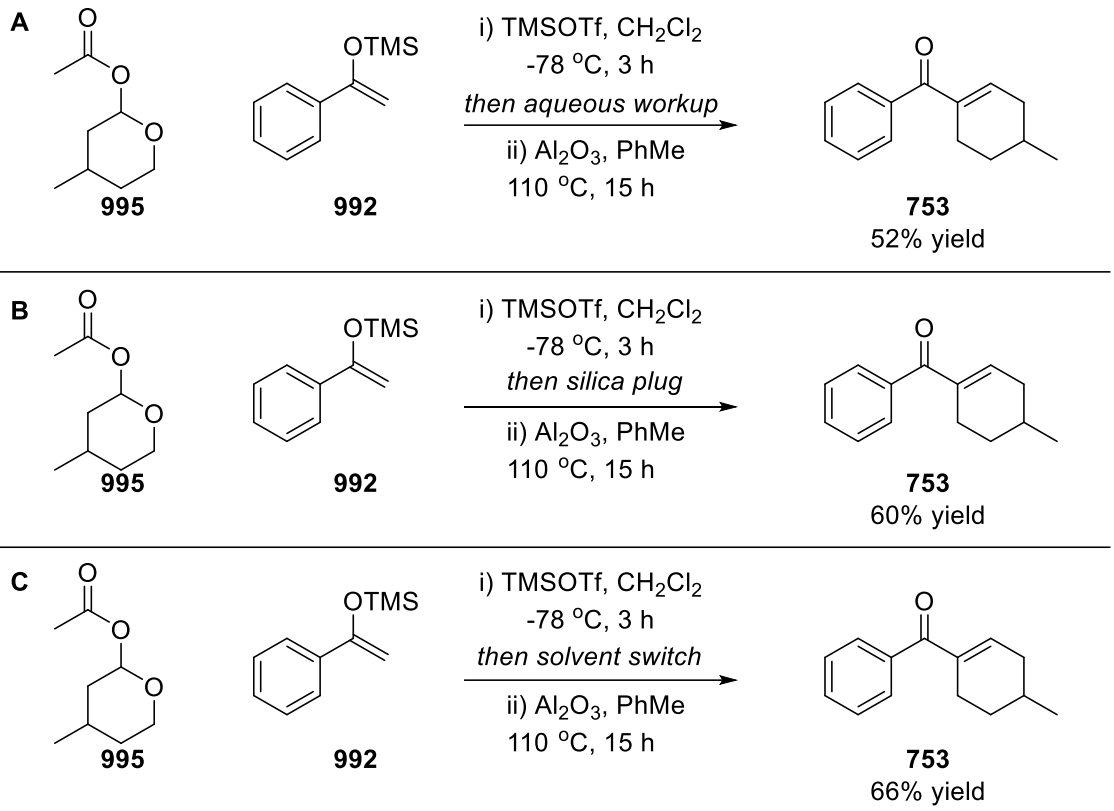
With **992** and **995** in hand, we performed the Mukayama aldol using trimethylsilyl triflate as the catalyst, in accord with the reported conditions by Noyori (Scheme 4.43). Pleasingly, tetrahydropyran **775** was afforded cleanly in 82% yield, and greater than 95:5 *d.r.*



Scheme 4.43: Synthesis of tetrahydropyran **775** by Mukayama Aldol reaction. Conditions: **992** (1 eq.), **995** (1.1 eq.), TMSOTf (0.1 eq.), CH_2Cl_2 (0.2 M), -78 °C, 3 h.

Given the success of the Mukayama aldol reaction to prepare tetrahydropyran **775**, we next investigated one-pot procedures to directly form cyclohexene **753** (Scheme 4.44). The first approach we tried was by performing an aqueous workup between the Mukayama Aldol step and the [1,5]-hydride shift reaction (A). Pleasingly, this resulted in a 52% yield of the desired cyclohexene **753**.

The next approach we investigated was filtering the reaction mixture through a plug of silica, between the first and second step of the sequence (B). This approach was also effective, leading to a 60% yield of cyclohexene **753** over the two steps. The final approach we tried was simply performing a solvent switch from dichloromethane to toluene, by removing the solvent *in vacuo* (C). This was arguably the simplest procedure, and to our delight, led to a higher yield of 66%.



Scheme 4.44: Mukayama aldol approach to the one pot synthesis of cyclohexene **753**. Conditions: **992** (1 eq.), **995** (1.1 eq.), TMSOTf (0.1 eq.), CH_2Cl_2 (0.2 M), -78 °C, 3 h, *then workup, then* Al_2O_3 (20 eq.), PhMe (0.2 M), 110 °C, 15 h.

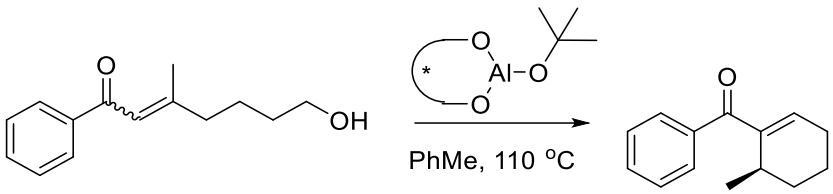
4.4 Conclusions and Future Work

In summary, we have developed a new approach to cyclohexenes *via* a tandem [1,5]-hydride shift-aldol condensation. We discovered that simple aluminium complexes, such as alumina and aluminium *tert*-butoxide are essential for this reaction, promoting the hydride shift with complete regio- and enantiocontrol. A wide range of cyclohexenes were prepared, demonstrating our ability to selectively

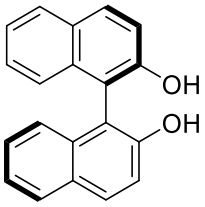
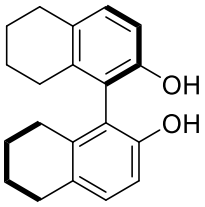
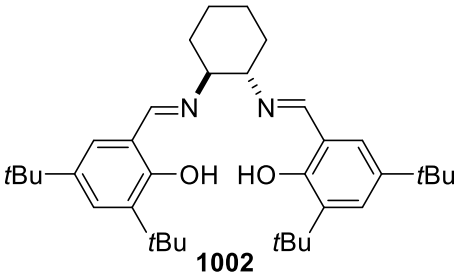
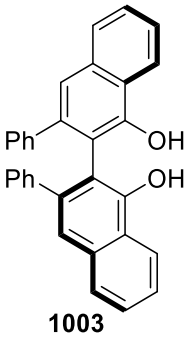
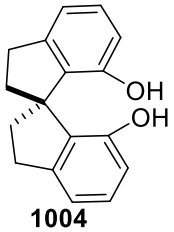
prepare the cyclohexene with a substituent at each position around the ring. Owing to the mild nature of the reaction conditions, a broad range of functional groups were tolerated, including aliphatic and aromatic products substituted with esters, nitriles, nitro group, amines and pyridines, to name but a few examples.

We have shown that the tetrahydropyran intermediate can be prepared straightforwardly by a range of reactions, including Horner Wadsworth Emmons, cuprate addition to ynones and Mukayama Aldol. While only a few routes to these compounds were explored, many more disconnections are possible, which further supports the generality of our approach to the cyclohexene motif. We also investigated one-pot procedures, which enabled direct access to cyclohexenes from readily accessible lactols and phosphonates.

A key avenue of future work is the possibility of developing an asymmetric variant of the aforementioned [1,5]-hydride shift aldol condensation. We hypothesised that by using a chiral diol in place of tert-butanol on aluminium tert-butoxide, we can affect an enantiodetermining hydride shift for enone **950**, which would allow access to enantioenriched 1,6-disubstituted cyclohexene **956**. As a preliminary study, we screened a small selection of diol ligands, which were reacted with trimethyl aluminium and *tert*-butanol, and then subjected to the hydride shift conditions with enone **950** (Table 4.18). Promisingly, when we used *(R)*-BINOL **1000**, we obtained a 12% yield of cyclohexene **956**, with an enantiomeric ratio of 57:43. Changing the ligand for *(R)*-H_8-BINOL **1001** led to an improved yield of 15% but a reduced e.r of 52:48. Jacobsen's ligand **1002** and Vanol ligand **1003** were ineffective for the chemistry, with no product being obtained. Spiro-indane ligand **1004** gave an improved yield of 20% but almost racemic product, whereas *(R)*-TADDOL **1005** afforded cyclohexene **956** in 26% yield 55.5:44.5 e.r. Changing the phenyl ring on TADDOL to a napthyl substituent **1006** had a dramatic effect on both the yield and e.e, with cyclohexene **956** obtained in a 32% yield and 30% e.e. These highly promising early results indicate the potential for a new asymmetric methodology based on the hydride shift-aldol cascade.



950 **956**

Entry	Diol Ligand	Yield of **955**[a]	e.r[b,c]
1	 **1000**	12	57:43
2	 **1001**	15	52:48
3	 **1002**	0	n/a
4	 **1003**	0	n/a
5	 **1004**	20	51:49

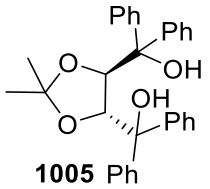
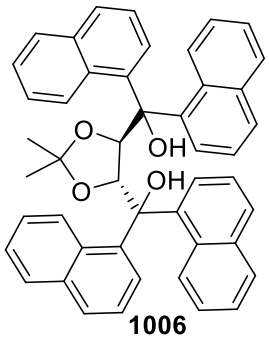
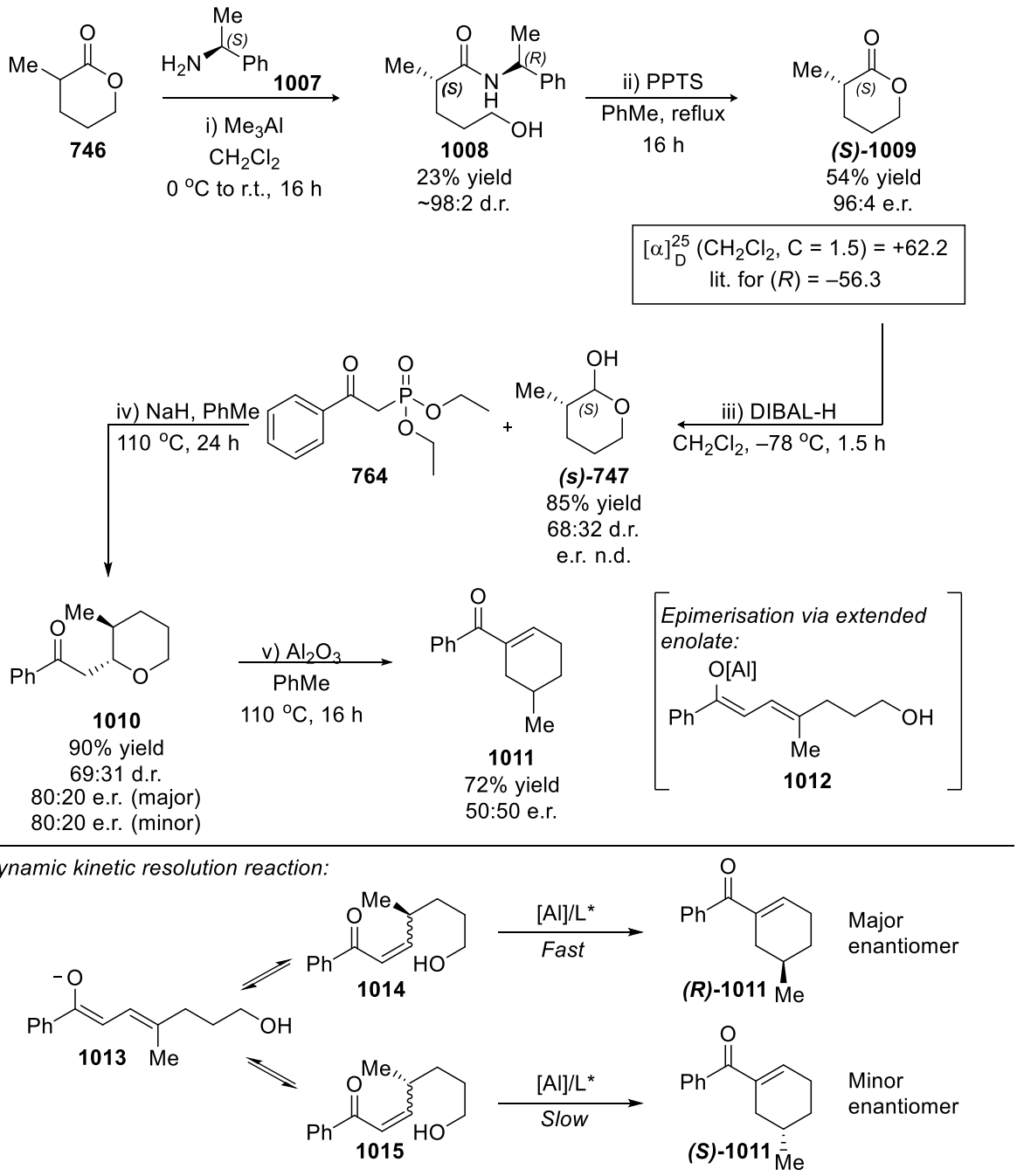
6	 **1005**	26	55.5:44.5
7	 **1006**	32	65:35

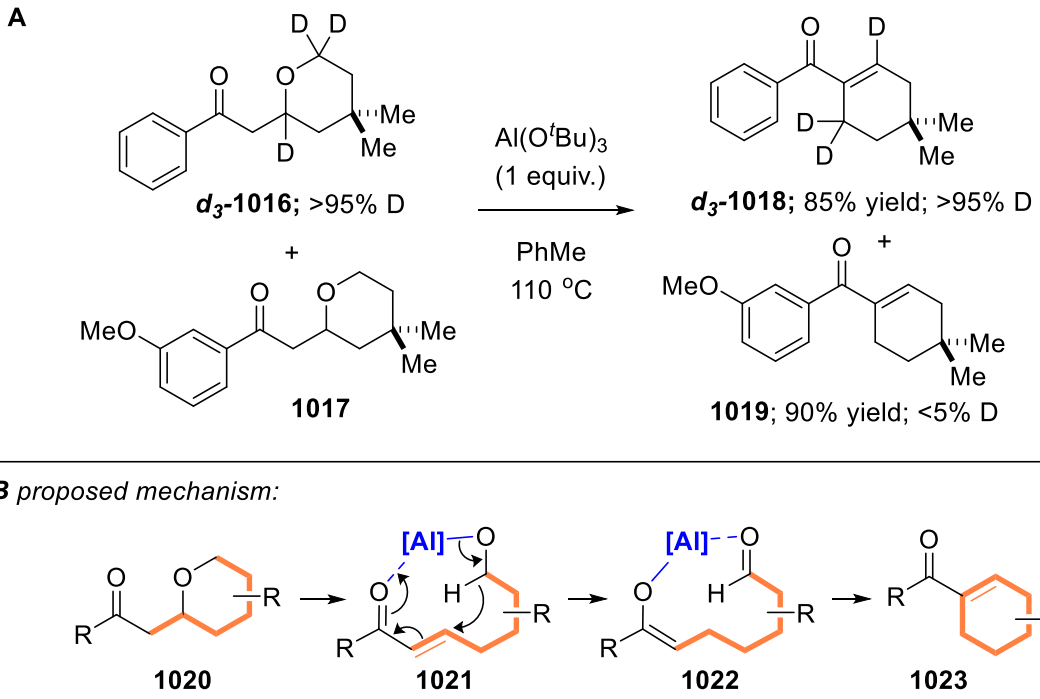
Table 4.18: Screening of chiral diols for the asymmetric synthesis of cyclohexene **956**. Conditions: diol (1 eq.), *t*BuOH (1 eq.), $AlMe_3$ (0.33 eq.), PhMe (0.2 M) *then* **950** (1 eq.), 110 °C, 15 h. [a]Yield determined by Q ^{1}H NMR with internal standard $CHCl_2CHCl_2$. [b]enantiomeric ratio determined by chiral HPLC against a racemic standard.[c] Absolute stereochemistry of the major enantiomer was unassigned.

In collaboration with Dr. R. J. Armstrong, we also investigated the reaction of enantioenriched tetrahydropyran **1010** (Scheme 4.45). **1010** was prepared in a four step sequence, starting with the reaction of chiral amine **1007** with lactone **746**. This afforded two diastereomers, which were separated by column chromatography, to give amide **1008** in 23% yield. Amide **1008** was then lactonised to give enantioenriched lactone ***(S)*-1009** in 54% yield and 96:4 *e.r*. Comparison of the specific rotation with the reported literature value confirmed we had isolated the *(S)*-stereoisomer. With lactone **1009** in hand, we performed a partial reduction with DIBAL-H, which afforded lactol ***(S)*-747** in 85% yield. Finally, lactol ***(S)*-747** was reacted with phosphonate **764** by HWE reaction to give tetrahydropyran **1010** in 90% yield. When we subjected enantioenriched tetrahydropyran **1010** to the [1,5]-hydride shift aldol conditions, **1010** underwent racemisation to afford racemic 1,5-disubstituted cyclohexene **1011**. This rapid racemisation likely occurred through the extended enolate of open chain hydroxy-enone **1012**. Based on this, we envisage that the reaction of racemic tetrahydropyrans in the presence of a chiral aluminium reagent could undergo a dynamic kinetic resolution to afford enantioenriched cyclohexenes.



Scheme 4.45: Racemisation of enantioenriched tetrahydropyran **1010** by Dr. R. J. Armstrong. Proposed use of racemic tetrahydropyran **1013** in a dynamic kinetic resolution to prepare enantioenriched cyclohexenes. Conditions: i) **746** (1 eq), amine (1.8 eq.), $AlMe_3$ (2 eq.), CH_2Cl_2 (0.2 M), 0 °C to RT, 16 h. ii) **1008** (1 eq.), PPTS (0.8 eq.), PhMe (0.2 M), reflux, 16 h. iii) **1009** (1 eq.), DIBAL-H (1.3 eq.), CH_2Cl_2 (0.2 M), -78 °C, 1.5 h. iv) **764** (1.4 eq.), NaH (1.2 eq.), PhMe (0.2 M), RT, *then* ***(S)*-747** (1 eq.), 110 °C, 24 h. iv) **1010** (1 eq.), Al_2O_3 (5 eq.), PhMe (0.2 M), 110 °C, 16 h. Enantiomeric ratio determined by chiral HPLC against a racemic standard. Experiments i) through v) performed by Dr. R. J. Armstrong.

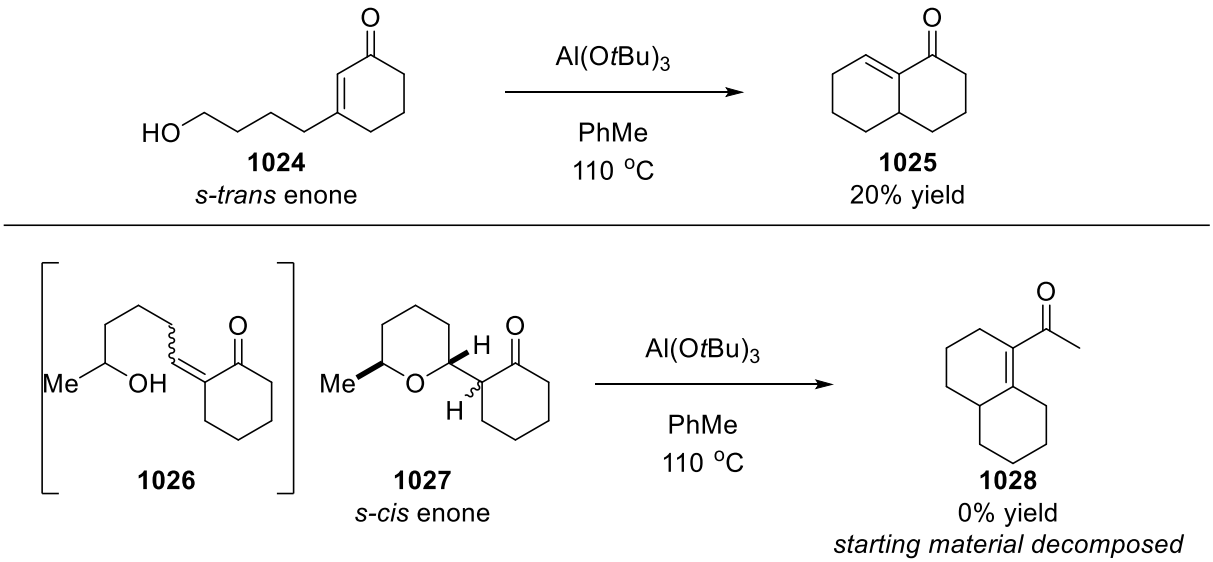
Another aspect of further work would be to investigate the mechanism of the aluminium promoted hydride shift reaction. Progress towards this includes the double label crossover experiment outlined in Scheme 4.46, A. When we subjected a mixture of fully deuterated tetrahydropyran **d_3-1016** and non-deuterated tetrahydropyran **1017**, we obtained cyclohexene **d_3-1018** with >95% D, and cyclohexene **1019** with virtually no deuterium detected. This experiment provides strong support for the proposal that aluminium is indeed promoting an intramolecular hydride shift, but it leaves room for understanding what the exact role of aluminium is in the reaction. We are particularly interested in answering the question of whether aluminium is acting as a Lewis acid and also a base, as aluminium could conceivably chelate to both the carbonyl and the alkoxide in **1021** to promote the hydride shift (Scheme 4.46, B).



Scheme 4.46: Double label crossover experiment under the aluminium promoted [1,5]-hydride shift-aldol condensation reaction. Conditions: **d_3-1016** (1 eq.), **1017** (1 eq.), Al(O*t*Bu)$_3$ (1 eq.), PhMe (0.2 M), 110 °C, 15 h. Crossover experiment performed by Dr. R. J. Armstrong.

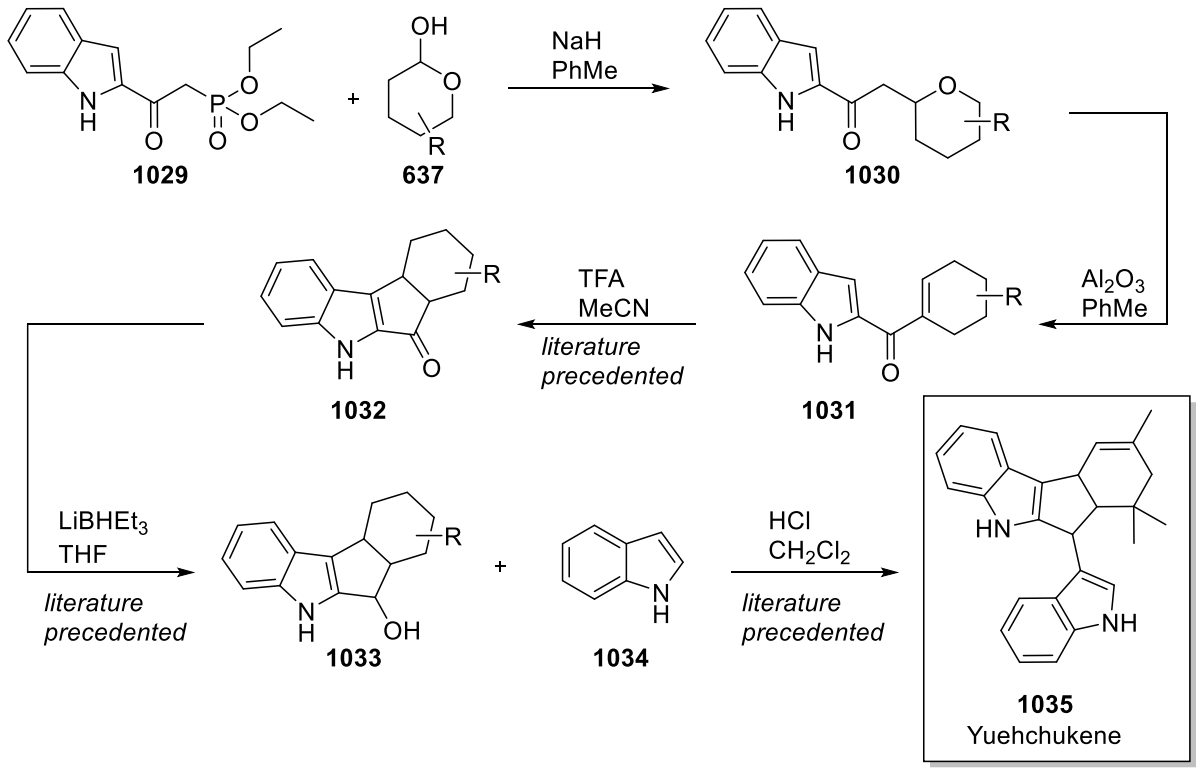
Further to investigating the reaction mechanism, it would be interesting to determine whether the geometry of the enone in the tetrahydropyran starting material affects reactivity. It is entirely plausible that both *E*- and *Z*-stereoisomers and *S-cis* and *S-trans* conformers of the enone are reactive intermediates. To probe this, we prepared enone **1024**, which exists exclusively as the *E*-stereoisomer and *S-trans* conformer. When we subjected **1024** to the optimised reaction conditions, we obtained a

20% yield of cyclohexene **1025** (Scheme 4.47). Similarly, when *s-cis* enone **1026**, which exists as tetrahydropyran **1027** was reacted with aluminium *tert*-butoxide, no product formed. Taken together, these results indicate that the *s-trans* enone is a reactive geometry for the hydride shift to occur. It would be interesting to prepare further tetrahydropyrans that are exclusively *E* and *Z* isomers, to further elucidate the mechanism of this process.



Scheme 4.47: reaction of *s-cis* and *s-trans* enones with aluminium *tert*-butoxide. Conditions: tetrahydropyran (1 eq.), Al(O*t*Bu)$_3$, PhMe (0.2 M), 110 °C, 15 h.

Finally, given the prevalence of the cyclohexyl motif, it would be valuable to investigate the application of our optimised methodology to the total synthesis of natural products. One exemplary target is the contraceptive Yuehchukene alkaloid **1035** (Scheme 4.48).[155] We envisage that analogues of this structure could be prepared in a convenient sequence starting from a range of lactols, which could be reacted with an HWE reagent derived from indole **1029**. Subsequently, the resulting tetrahydropyran **1030** could be treated with alumina to afford cyclohexene **1031**. Following literature precedented steps, cyclohexene **1031** could be cyclised by a Nazarov cyclisation, and then the resulting carbonyl **1032** could reduced with LiBHEt$_3$. The final step to access the natural product would be the condensation of **1033** with indole to give bisindole alkaloid **1035**.



Scheme 4.48: Proposed total synthesis of Yuehchukene alkaloids.

Chapter 5: Experimental Section

5.1. General Information

Procedures using oxygen and/or moisture-sensitive materials were performed with anhydrous solvents (*vide infra*) under an atmosphere of anhydrous argon/nitrogen in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F254 0.25 mm pre-coated aluminium plates and visualised using a combination of UV light (254 nm) and aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate stains or vanillin solution. The removal of solvents *in vacuo* was achieved using a Büchi rotary evaporator with an oil pump (0.1 mmHg) or diaphragm pump (15 mmHg) at bath temperatures up to 50˚C.

Flash column chromatography (FCC) was carried out using Apollo Scientific silica gel 60 (0.040 –0.063 nm) and Merck 60 Å silica gel (0.015-0.040). Pressure was applied at the column head via a flow of nitrogen with the solvent system used in parentheses.

Reactions at 0 °C were performed using an ice-water bath, which was covered with cotton and foil if overnight stirring was required. Other temperatures were obtained using a Julabo FT902 immersion cooler or the heating plate of the stirrer with an oil bath. Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H and ^{13}C NMR experiments were carried out using Bruker NMR spectrometers (400, 500 or 700 MHz) in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted to the nearest 0.5 hertz (Hz). ^{2}H NMR experiments were carried out using Bruker AVIII HD 500 (77 or 92 MHz) in protonated solvent with a single drop of the corresponding deuterated solvent as an internal reference. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), hept (heptet) and m (multiplet). ^{1}H and ^{13}C NMR peaks for diastereomers were assigned major or minor. If major or minor diastereomers cannot be distinguished, the peaks were assigned with a ‘,’ (e.g H_1 and $H_{1'}$, C_1 and $C_{1'}$). ^{1}H and ^{13}C NMR peaks for diastereotopic environments were assigned with a subscript ‘a’ and ‘b’ (e.g H_a and H_b), or subscript ‘ax.’ (axial) and ‘eq.’ (equatorial) where applicable. Assignments were made with the assistance of gCOSY, gHSQC, gHMBC or NOESY NMR spectra.

Chiral HPLC separations were achieved using an Agilent 1260 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn); all eluent systems were isocratic.

Reverse phase HPLC separations were achieved using an Dionex Ultimate 3000 HPLC unit and Chromeleon software. Agilent Poroshell 120 EC-C18 4mm column (150 × 4.6 mm), fitted with matching Agilent Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn); all eluent systems were isocratic.

Low-resolution mass spectra were recorded using a Walters LCT premier XE. High-resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford.

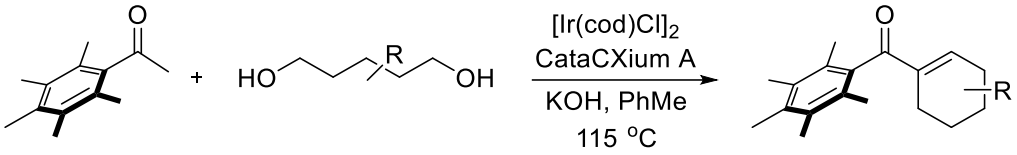
Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 600-4000 cm^{-1}.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 25°C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in $10^{-1}deg.cm^2g^{-1}$ (concentration c given as g/100mL).

Melting points were obtained using a Leica Galen III heated-stage microscope and are uncorrected.

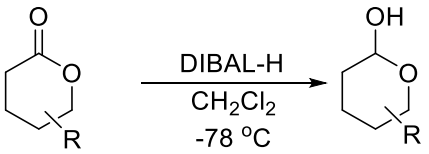
5.2 General Procedures

General Procedure 1: Synthesis of Acyl Cyclohexenes by Iridium Mediated Annulation



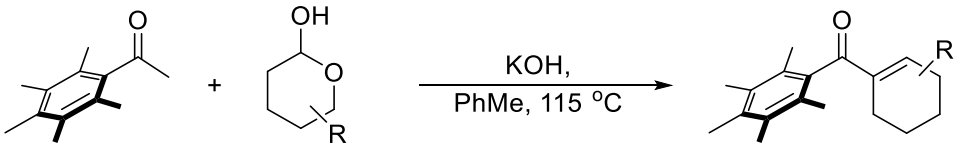
A 2–5 mL Biotage® microwave vial was charged with CataCXium® A (4.3 mg, 0.012 mmol, 2 mol%), diol (1.2 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (114 mg, 0.60 mmol, 1 eq.), $[Ir(cod)Cl]_2$ (2 mg, 0.003 mmol, 0.5 mol% dimer), KOH (134 mg, 2.40 mmol, 4 eq.) and toluene (2.4 mL, 0.25 M). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and the vial was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3M, 5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. For details of purification, see experimental procedures.

General Procedure 2: Synthesis of Lactols by Reduction



A flame dried 3-neck flask under N_2 was charged with lactone (1 eq), dry CH_2Cl_2 (0.5 M), and cooled to -78 °C. DIBAL-H in hexanes (1M, 1.4 eq.) was added dropwise and stirred at -78 °C for 2 hours. Sat. Aq. Rochelle salt (20 mL) was added, and the reaction was then warmed to RT and stirred vigorously. The layers were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

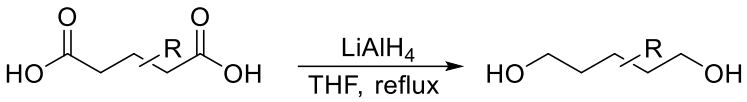
General Procedure 3: Synthesis of Enones in Absence of Iridium



A 5mL microwave vial was charged with lactol (1.2 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (114 mg, 0.600 mmol, 1 eq.), KOH (134 mg, 2.40 mmol, 4 eq.) and toluene (2.4 mL, 0.25 M). The vial was then sealed and heated at 115 °C for 24 hours. After cooling to

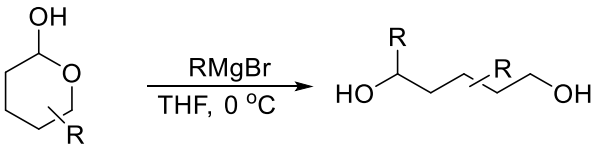
RT, the reaction mixture was diluted with 3M aq. HCl (6 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

General Procedure 4: Synthesis of Diols by Reduction



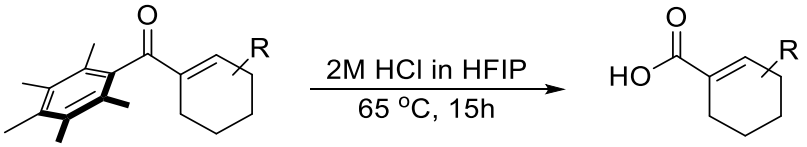
A suspension of $LiAlH_4$ (3 eq.) in dry THF (0.2M) was cooled to 0 °C, followed by the dropwise addition of the diacid (1 eq.). The reaction was then fitted with an air condenser and heated at reflux for 15 hours. The reaction was then cooled to 0 °C, diluted with Et_2O (0.2M) and quenched by sequential addition of water (1 mL/g of $LiAlH_4$), aq. NaOH (15% w/v, 1 mL/g of $LiAlH_4$), and water (3 mL/g of $LiAlH_4$), and stirred vigorously for 15 minutes. $MgSO_4$ was then added, stirred for 15 minutes, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

Procedure 5: Synthesis of Diol by Grignard Addition



A flame-dried flask under N_2 was charged with lactol (1 eq.) and dry THF (0.5 M) and cooled to 0 °C. RMgBr (3–4 eq.) was added dropwise. The flask was then warmed to RT and stirred for 15 hours. The reaction was quenched with the addition of sat. aq. NH_4Cl (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

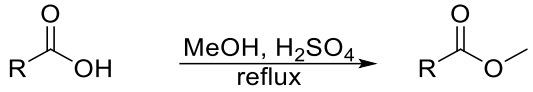
Procedure 6: Synthesis of Carboxylic Acids by Retro–Friedel–Crafts Acylation



A 2–5 mL Biotage® microwave vial was charged with enone (0.1 mmol, 1 eq.), hexafluoroisopropanol (0.88 mL) and 37% aq. HCl (12 M, 0.13 mL). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 65 °C for 15 h. The reaction was then cooled to RT,

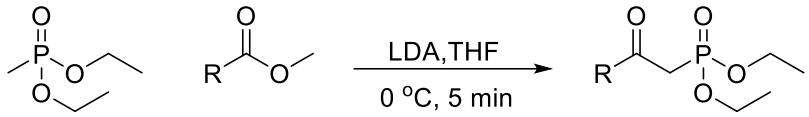
diluted with water (5 ml) and extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

Procedure 7: Synthesis of Esters by Fischer Esterification



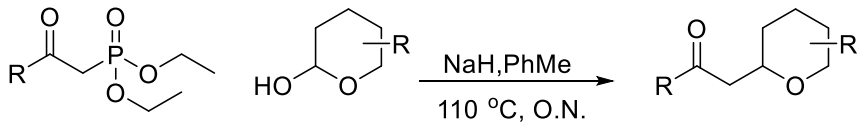
A round bottom flask fitted with a reflux condenser was charged with carboxylic acid (1 eq.), MeOH (0.3M), and cooled to 0 °C. Concentrated sulphuric acid (1.5-2 eq.) was added dropwise and then the flask was heated to relux for 15 h. The reaction was then cooled to RT, and poured onto iced water (200 mL). Solid $NaHCO_3$ was added portion wise until pH=9 was reached. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

Procedure 8: HWE Reagent Synthesis by Claisen Condensation



A flame dried RBF under an argon atmosphere was charged with diisopropylamine (2.25 eq.), dry THF (0.2M) and then cooled to 0 °C. *n*BuLi in hexanes (2.5M, 2.2 eq.) was added dropwise, and then stirred for 30 minutes at 0 °C. A separate flame dried RBF under an argon atmosphere was charged with methyl ester (1 eq.), diethyl methylphosphonate (1.1 eq.) and dry THF (0.2M) and then cooled to 0 °C. The LDA solution was then added dropwise to this flask and stirred for a further 5 minutes at 0 °C. The reaction mixture was then neutralised with 3M HCl, and then warmed to RT. The aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. For details of purification, see experimental procedures.

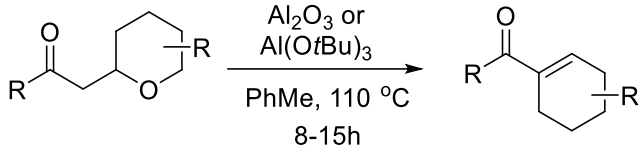
Procedure 9: Tetrahydropyran Synthesis by HWE reaction



A 10 mL flame dried RBF fitted with a reflux condenser was charged with HWE reagent (1.4 eq, 1.4 mmol) and then degassed with argon. Dry toluene (5 mL) and then 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) was added to the flask and stirred for 30 minutes at RT. The lactol (1 eq., 1 mmol) was then added to the RBF and the reaction was heated at 110 °C for 15 h. The reaction was then cooled to RT,

diluted with Et_2O (50 mL), and filtered through a plug of silica gel. For details of purification, see experimental procedures.

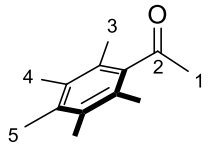
Procedure 10: Cyclohexene Synthesis by Aluminium Catalysed [1,5]-Hydride Shift



A 2–5 mL flame dried Biotage® microwave vial was charged with tetrahydropyran (0.3 mmol, 1 eq.), and Brockmann I basic alumina (5 eq. 150 mg) or aluminium tert-butoxide (74 mg, 1 eq.) and then degassed with argon. Dry toluene (1.5 mL, 0.2M) was then added and the reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 110 °C for 8-15 h. The reaction was then cooled to RT, diluted with Et_2O (50 mL), filtered through a plug of silica gel and concentrated *in vacuo*. For details of purification, see experimental procedures.

5.3 Experimental Procedures

1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one 187



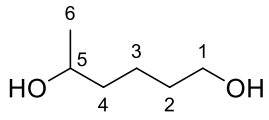
To a solution of pentamethylbenzene (10.0 g, 67.4 mmol, 1.0 eq.) and acetyl chloride (5.30 mL, 74.2 mmol, 1.1 eq) in dry CH_2Cl_2 (300 mL, 0.225 M) at 0 °C was added $AlCl_3$ (11.2 g, 84.3 mmol, 1.3 eq.) in several portions over 30 minutes. The reaction was warmed to RT and stirred for 2 h and then poured over crushed ice. Once the ice had melted, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5→10% Et_2O:pentane) followed by recrystallization (heptane) as a white solid (11.1 g, 58.2 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H, 3 x H_1), 2.24 (s, 3H, 3 x H_5), 2.19 (s, 6H, 6 x H_3), 2.14 (s, 6H, 6 x H_4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2 (C_2), 141.1 (ArC), 135.5 (ArC), 133.2 (ArC x 2), 127.1 (ArC x 2), 33.2 (C_1), 17.2 (C_4 x 2), 16.8 (C_5), 16.1 (C_3 x 2).

The spectroscopic data matched that previously reported in the literature.[84]

Hexane-1,5-diol 382



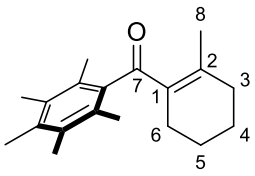
δ-Hexalactone (5.00 g, 43.8 mmol, 1 eq.), dry THF (240 mL) and $LiAlH_4$ (1.91 g, 50.4 mmol, 1.1 eq.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (9% MeOH/CH_2Cl_2) as a colourless oil (3.70 g, 31.3 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 – 3.72 (m, 1H, H_5), 3.68 – 3.55 (m, 2H, 2 x H_1), 2.82 – 2.21 (m, 2H, 2 x OH), 1.66 – 1.29 (m, 6H, 2 x H_2 , 2 x H_3 , 2 x H_4), 1.16 (d, 3H, J = 6.5 Hz, 3 x H_6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 67.9 (C_5), 62.5 (C_1), 38.9 (C_4), 32.5 (C_2), 23.6 (C_6), 22.0 (C_3).

The spectroscopic data matched that previously reported in the literature.[156]

(2-Methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 383



Method 1: Hexane-1,5-diol (142 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (128 mg, 0.473 mmol, 79% yield).

Method 2: 6-Methyltetrahydro-*2H*-pyran-2-ol (143 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (86 mg, 0.32 mmol, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 – 2.02 (m, 13H, $ArCH_3$ x 3, H_3 x 2 and H_6 x 2), 1.98 (s, 6H, $ArCH_3$ x 2), 1.79 (s, 3H, H_8 x 3), 1.58 – 1.44 (m, 4H, H_4 x 2 and H_5 x 2).

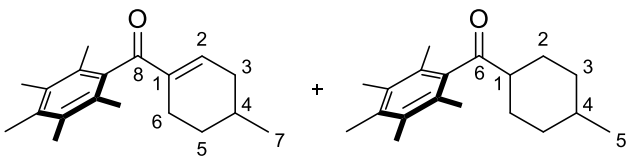
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (C_7), 148.9 (ArC), 141.3 (C_2), 135.0 (ArC), 133.4 (C_1), 133.0 (ArC x 2), 128.3 (ArC x 2), 35.1 (C_3), 26.7 (C_6), 22.8 (C_5), 22.5 (C_4), 22.2 (C_8), 17.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): $C_{19}H_{27}O$ requires 271.2056, found $[M+H]^+$=271.2056, Δ -0.17 ppm

IR (film) ν_{max}/cm^{-1} 2923, 1666, 1600, 1422, 1305, 1172, 906, 709

m.p.: 116-118 °C

(4-Methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 405



Method 1: 3-Methylpentane-1,5-diol (142 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1** The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (136

mg, 0.50 mmol, 84% yield). (4-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone was also isolated as a white solid (8 mg, 0.03 mmol, 5% yield).

Method 2: 4-Methyltetrahydro-*2H*-pyran-2-ol (143 mg, 1.2 mmol, 2 eq) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (5% pentane: Et_2O) as a white solid (136 mg, 0.5 mmol, 84% yield).

Method 3: A flame-dried 2-5 mL Biotage® microwave vial was charged with 2-(4-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (86.5 mg, 0.3 mmol, 1 eq.), oven dried Na_2SO_4 (128 mg, 0.9 mmol 3 eq.), 60% wt. NaH (36 mg, 0.9 mmol, 3 eq.), and then sealed with a microwave vial cap (containing a Reseal™ septum) and degassed, and fitted with an argon balloon. Dry toluene (1.0 mL, 0.3 M) was then added, and once the effervescence had stopped, the balloon was removed and the reaction was heated at 110 °C for 5 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (62 mg, 0.231 mmol, 77% yield).

Method 4: 2-(4-methyltetrahydro-*2H*-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (86.5 mg, 0.3 mmol, 1 eq.) was subjected to **General Procedure 10**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (78 mg, 0.288 mmol, 96% yield).

Data for (4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 405:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 – 6.43 (m, 1H, H_2), 2.70 – 2.58 (m, 1H, H_{6a}), 2.35 – 2.11 (m, 11H, H_{3a}, H_{6b} and $ArCH_3$ x 3), 2.01 (s, 6H, $ArCH_3$ x 2), 1.90 – 1.63 (m, 3H, H_{3b}, H_4 and H_{5a}), 1.27 (dtd, *J* = 13.0, 10.5, 5.5 Hz, 1H, H_{5b}), 0.99 (d, *J* = 6.5 Hz, 3H, H_7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5 (C_8), 145.2 (C_2), 140.5 (C_1), 138.4 (ArC), 135.0 (ArC), 132.7 (ArC x 2), 129.2 (ArC x 2), 34.8 (C_3), 30.4 (C_5), 28.0 (C_4), 22.5 (C_6), 21.5 (C_7), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 271.2055; $C_{19}H_{27}O$ requires 271.2056, Δ –0.39 ppm

IR (film) ν_{max}/cm^{-1} 2931, 1652, 1633, 1192, 1168, 700

m.p.: 143-144 °C

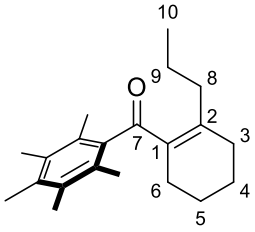
Data for (4-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone 404:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (tt, *J* = 12.0, 3.5 Hz, 1H, H_1), 2.24 (s, 3H, $ArCH_3$), 2.19 (s, 6H, $ArCH_3$ x 2), 2.09 (s, 6H $ArCH_3$ x 2), 1.99 – 1.88 (m, 2H, H_2 x 2), 1.84 – 1.71 (m, 2H, H_3 x 2), 1.55 – 1.29 (m, 3H, H_2 x 2, H_4), 1.00 – 0.84 (m, 5H, H_3 x 2, H_5 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 (C_6), 140.5 (ArC), 135.5 (ArC), 133.2 (ArC x 2), 128.3 (ArC x 2), 53.1 (C_1), 34.8 (C_3 x 2), 32.4 (C_4), 28.4 (C_2 x 2), 22.6 (C_5), 18.0 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

The spectroscopic data matched that previously reported in the literature.[84]

(2,3,4,5,6-Pentamethylphenyl)(2-propylcyclohex-1-en-1-yl)methanone 421



Octane-1,5-diol (175 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a colourless oil that solidified on standing at room temperature (170 mg, 0.570 mmol, 95% yield).

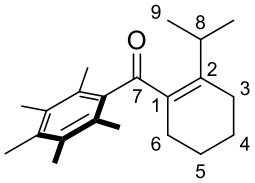
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (t, *J* = 7.5 Hz, 2H, H_8 x 2), 2.16 – 1.94 (m, 19H, $ArCH_3$ x 5, H_3 x 2 and H_6 x 2), 1.56 – 1.44 (m, 4H, H_4 x 2 and H_5 x 2), 1.35 (h, *J* = 7.5 Hz, 2H, H_9 x 2), 0.74 (t, *J* = 7.5 Hz, 3H, H_{10} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C_7), 153.0 (ArC), 141.1 (C_2), 134.7 (ArC), 132.7 (C_1), 132.7 (ArC x 2), 128.2 (ArC x 2), 37.5 (C_8), 32.4 (C_3), 27.0 (C_6), 22.8 (C_4), 22.3 (C_5), 21.9 (C_9), 17.1 ($ArCH_3$ x 2), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$ x 2), 14.4 (C_{10}).

HRMS (ESI+): Found $[M+H]^+$ = 299.2369; $C_{21}H_{31}O$ requires 299.2369, Δ –0.32 ppm

IR (film) ν_{max}/cm^{-1} 2927, 2858, 1667, 1598, 1450, 1305, 1264, 1166, 913

(2-Isopropylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 422



6-Methylheptane-1,5-diol (175 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a white solid (114 mg, 0.382 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 – 3.48 (m, 1H, H_8), 2.26 – 2.03 (m, 19H, $ArCH_3$ x 5, H_6 x 2 and H_3 x 2), 1.63 – 1.49 (m, 4H, H_4 x 2 and H_5 x 2), 0.98 (d, *J* = 6.8 Hz, 6H, H_9 x 6).

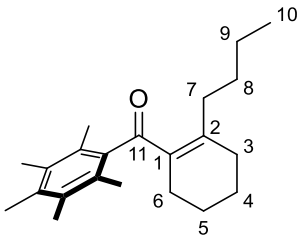
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (C_7), 156.4 (ArC), 141.2 (C_2), 134.9 (ArC), 132.9 (ArC x 2), 132.3 (C_1), 128.4 (ArC x 2), 30.3 (C_8), 27.2 (C_3), 24.7 (C_6), 22.9 (C_5), 22.3 (C_4), 20.8 (C_9 x 2), 17.2 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 299.2368; $C_{21}H_{31}O$ requires 299.2369, Δ -0.52 ppm

IR (film) ν_{max}/cm^{-1} 2930, 2870, 1664, 1604, 1450, 1303, 1262, 1165, 1010, 707

m.p.: 90-92 °C

(2-Butylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 423



Method 1: Nonane-1,5-diol (192.3 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a colourless oil that solidified on standing at room temperature (185 mg, 0.594 mmol, 99% yield).

Method 2: 6-Butyltetrahydro-2H-pyran-2-ol (189.8 mg, 1.2 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a colourless oil that solidified on standing at room temperature (174 mg, 0.558 mmol, 93% yield).

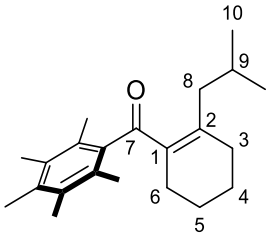
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 – 2.09 (m, 15H, $ArCH_3$ x 3, H_3 x 2, H_6 x 2, H_7 x 2), 2.06 (s, 6H, $ArCH_3$ x 2), 1.68 – 1.50 (m, 4H, H_4 x 2, H_5 x 2), 1.33 (p, *J* = 8.5 Hz, 2H, H_8 x 2), 1.25 – 1.10 (m, 2H, H_9 x 2), 0.82 (t, *J* = 7.5 Hz, 3H, H_{10} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C_{11}), 153.3 (ArC), 141.3 (C_2), 134.9 (ArC), 132.9 (ArC x 2), 132.8 (C_1), 128.4 (ArC x 2), 35.5 (C_7), 32.6 (C_3), 30.9 (C_8), 27.0 (C_6), 23.3 (C_9), 22.9 (C_5), 22.4 (C_4), 17.3 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2), 14.0 (C_{10}).

HRMS (ESI+): Found $[M+H]^+$ = 313.2521; $C_{22}H_{33}O$ requires 313.2526, Δ -1.55 ppm

IR (film) ν_{max}/cm^{-1} 2929, 2865, 1666, 1596, 1450, 1381, 1305, 1164, 904

(2-Isobutylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 424



7-Methyloctane-1,5-diol (192 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a colourless oil (186 mg, 0.594 mmol, 99% yield).

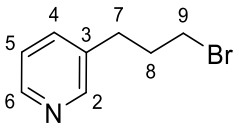
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 – 2.22 (m, 2H, H_8 x 2), 2.19 – 1.94 (m, 19H, $ArCH_3$ x 5, H_6 x 2 and H_3 x 2), 1.94 – 1.81 (m, 1H, H_9), 1.55 – 1.42 (m, 4H, H_4 x 2 and H_5 x 2), 0.79 (d, *J* = 6.5 Hz, 6H, H_{10} x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_7), 152.4 (ArC), 141.0 (C_2), 134.7 (ArC), 133.4 (C_1), 132.7 (ArC x 2), 128.2 (ArC x 2), 43.6 (C_8), 33.0 (C_3), 27.6 (C_6), 27.5 (C_9), 22.8 (C_5), 22.7 (C_{10} x 2), 22.2 (C_4), 17.1 ($ArCH_3$ x 2), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 313.2524; $C_{22}H_{33}O$ requires 313.2526, Δ -0.77 ppm

IR (film) ν_{max}/cm^{-1} 2928, 2866, 1666, 1591, 1449, 1304, 1164, 909, 711

3-(3-bromopropyl)pyridine 426



Tetrabromomethane (13.26 g, 40 mmol, 1.1 eq.) was added dropwise at 0 °C to a stirred solution of 3-pyridinepropanol (5 g, 36.4 mmol, 1 eq.) PPh_3 (10.5 g, 40 mmol, 1.1 eq.) in dry CH_2Cl_2 (72 mL, 0.5 M). The reaction was then warmed to room temperature and stirred for 24 h. Water (50 mL) was added

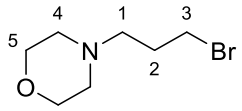
to the reaction, and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was triturated with Et_2O to remove Ph_3PO, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (60% Et_2O/pentane) as a colourless oil (5.2 g, 26.1 mmol, 72% yield).

1H NMR (400 MHz, Chloroform-d) δ 8.48 – 8.43 (m, 2H, H_2, H_6), 7.51 (ddt, J = 8.0, 2.5, 1.0 Hz, 1H, H_4), 7.21 (ddd, J = 8.0, 5.0, 1.0 Hz, 1H, H_5), 3.38 (t, J = 6.5 Hz, 2H, H_9 x 2), 2.78 (t, J = 7.0 Hz, 2H, H, H_7 x 2), 2.20 – 2.12 (m, 2H, H_8 x 2).

13C NMR (101 MHz, $CDCl_3$) δ 150.1 (C_2), 147.9 (C_6), 136.1 (C_4), 135.9 (C_3), 123.5 (C_5), 33.8 (C_8), 32.6 (C_9), 31.2 (C_7).

The spectroscopic data matched that previously reported in the literature.[157]

4-(3-bromopropyl)morpholine 430



Tetrabromomethane (12.56 g, 37.9 mmol, 1.1 eq.) was added dropwise at 0 °C to a stirred solution of 4-(3-Hydroxypropyl)morpholine (5 g, 34.4 mmol, 1 eq.) PPh_3 (9.93 g, 37.9 mmol, 1.1 eq.) in dry CH_2Cl_2 (70 mL, 0.5 M). The reaction was then warmed to room temperature and stirred for 24 h. Water (50 mL) was added to the reaction, and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was triturated with Et_2O to remove Ph_3PO, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→40% Et_2O/pentane) as a colourless oil (4 g, 19 mmol, 55% yield).

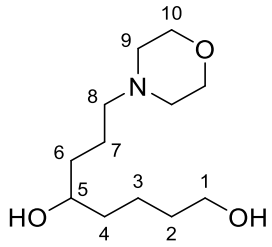
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 – 3.66 (m, 4H, H_5 x 4), 3.46 (t, *J* = 6.5 Hz, 2H, H_3 x 2), 2.51 – 2.39 (m, 6H, H_1 x 2, H_4 x 4), 2.02 (p, *J* = 6.5 Hz, 2H, H_2 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 67.1 (C_5 x 2), 57.0 (C_1), 53.9 (C_4 x 2), 31.8 (C_3), 29.8 (C_2).

HRMS (ESI+): Found $[M+H]^+$ = 208.0335 ; $C_7H_{15}ON^{79}Br$ requires 208.3315, Δ 1.49 ppm

IR (film) ν_{max}/cm^{-1} 2941, 2808, 1446, 1253, 1116, 1009, 869

8-morpholinooctane-1,5-diol 431



A suspension of magnesium turnings (369 mg, 15 mmol, 5 eq.) in THF (10 mL) was stirred at RT and a single crystal of iodine was added followed by addition of 4-(3-bromopropyl)morpholine (1.9 mL, 9.1 mmol, 3 eq.) at such a rate as to maintain gentle reflux. After the addition was complete the resulting suspension was heated to reflux for a further 10 min and then cooled to RT, diluted with THF (10 mL) and decanted away from the excess magnesium turnings by cannulation washing with THF (2 x 5 mL). The resulting Grignard solution was cooled to 0 °C and tetrahydro-*2H*-pyran-2-ol (310 mg, 3 mmol, 1eq.) was added dropwise. The reaction mixture was then warmed to RT and stirred for 2 h and then cooled to 0 °C, and quenched by dropwise addition of sat. aq. NH_4Cl (10 mL). The organic layer extracted with EtOAc (3 x 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (3→8% MeOH/CH_2Cl_2) afforded the title compound as a colourless oil (193 mg, 0.82 mmol, 28%), with an inseparable, unknown impurity (~20%).

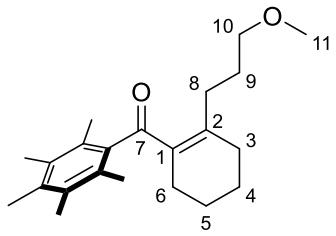
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 – 3.68 (m, 5H, H_5, H_{10} x 4), 3.63 (t, *J* = 6.5 Hz, 2H, H_1 x 2), 3.55 – 3.46 (m, 2H, OH x 2), 2.49 – 2.34 (m, 6H, H_8 x 2, H_9 x 4), 1.86 – 1.16 (m, 10H, H_2 x 2, H_3 x 2, H_4 x 2, H_6 x 2, H_7 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 71.5 (C_5), 66.7 (C_{10} x 2), 62.9 (C_1), 59.4 (C_9 x 2), 53.6 (C_8), 37.5 (C_6), 37.3 (C_4), 32.8 (C_2), 23.8 (C_7), 22.2 (C_3).

HRMS (ESI+): Found $[M+H]^+$ = 232.1908 ; $C_{12}H_{26}O_3N$ requires 232.1907, Δ 0.14 ppm

IR (film) ν_{max}/ cm^{-1} 3380, 2933, 2860, 1458, 1114, 864

(2-(3-Methoxypropyl)cyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 440



8-Methoxyoctane-1,5-diol (212 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a white solid (153 mg, 0.466 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 – 3.21 (m, 5H, H_{10} x 2 and H_{11} x 3), 2.43 – 2.30 (m, 2H, H_8 x 2), 2.28 – 1.99 (m, 19H, H_3 x 2, H_6 x 2 and $ArCH_3$ x 5), 1.76 – 1.64 (m, 2H, H_9 x 2), 1.64 – 1.51 (m, 4H, H_4 x 2 and H_5 x 2).

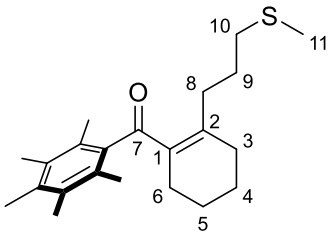
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_7), 152.6 (ArC), 141.0 (C_2), 134.9 (ArC), 133.0 (C_1), 132.9 (ArC x 2), 128.3 (ArC x 2), 73.0 (C_{10}), 58.6 (C_{11}), 32.6 (C_3), 32.3 (C_8), 28.6 (C_9), 27.2 (C_6), 22.8 (C_5), 22.4 (C_4), 17.2 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 329.2478; $C_{22}H_{33}O_2$ requires 329.2475, Δ 0.92 ppm

IR (film) ν_{max}/cm^{-1} 2926, 2860, 1666, 1597, 1449, 1305, 1174, 1117, 707

m.p.: 60-62 °C

(2-(3-(Methylthio)propyl)cyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 441



8-(Methylthio)octane-1,5-diol (231 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (2→5% Et_2O/pentane) as a colourless oil (205 mg, 0.594 mmol, 99% yield).

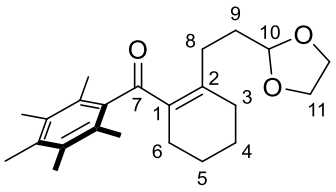
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 – 2.31 (m, 4H, H_8 x 2, H_{10} x 2), 2.25 – 2.20 (m, 5H, $ArCH_3$, H_3 x 2), 2.17 (s, 6H, $ArCH_3$ x 2), 2.15 – 2.04 (m, 11H, $ArCH_3$ x 2, H_6 x 2, H_{11} x 3), 1.70 (p, *J* = 8.0 Hz, 2H, H_9 x 2), 1.63 – 1.51 (m, 4H, H_4 x 2, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_7), 151.9 (ArC), 141.1 (C_2), 135.0 (ArC), 133.3 (C_1), 132.9 (ArC x 2), 128.3 (ArC x 2), 35.1 (C_8), 34.6 (C_{10}), 32.7 (C_3), 28.4 (C_9), 27.1 (C_6), 22.8 (C_5), 22.4 (C_4), 17.3 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2), 15.6 (C_{11}).

HRMS (ESI+): Found $[M+H]^+$ = 345.2244 ; $C_{22}H_{33}OS$ requires 345.2247, Δ -0.77 ppm

IR (film) ν_{max}/cm^{-1} 2927, 2859, 1665, 1598, 1449, 1305, 1170

(2-(2-(1,3-Dioxolan-2-yl)ethyl)cyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 442



A 5mL microwave vial was charged with CataCXium® A (2.2 mg, 0.0060 mmol, 2 mol%), 7-(1,3-dioxolan-2-yl)heptane-1,5-diol (126 mg, 0.600 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (57 mg, 0.30 mmol, 1 eq), $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol, 0.5 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) and toluene (1.2 mL, 0.25 M). The vial was then sealed and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL), extracted with CH_2Cl_2 (4 x 10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (25% Et_2O/pentane) as a white solid (91.0 mg, 0.255 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (t, *J* = 5.0 Hz, H_{10}), 3.98 – 3.77 (m, 4H, H_{11} x 4), 2.46 (t, *J* = 8.5 Hz, 2H, H_8 x 2), 2.28 – 2.18 (m, 5H, $ArCH_3$ and H_3 x 2), 2.16 (s, 6H, $ArCH_3$ x 2), 2.05 (s, 8H, $ArCH_3$ x 2, H_6 x 2), 1.78 (dt, *J* = 13.0, 5.0 Hz, 2H, H_9), 1.61 – 1.52 (m, 4H, H_4 x 2 and H_5 x 2).

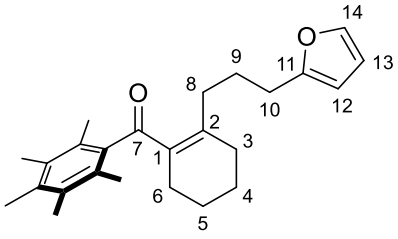
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C_7), 151.9 (ArC), 140.9 (C_2), 134.9 (ArC), 133.2 (C_1), 132.9 (ArC x 2), 128.3 (ArC x 2), 104.7 (C_{10}), 64.9 (C_{11} x 2), 32.8 (C_9), 32.6 (C_3), 30.3 (C_8), 27.2 (C_6), 22.8 (C_5), 22.4 (C_4), 17.3 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ =357.2428; $C_{23}H_{33}O_3$ requires 357.2424, Δ 1.05 ppm

IR (film) ν_{max}/cm^{-1} 2928, 1665, 1598, 1449, 1305, 1130, 1032, 878, 707

m.p.: 78-80 °C

(2-(3-(Furan-2-yl)propyl)cyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 443



8-(Furan-2-yl)octane-1,5-diol (255 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a colourless oil (190 mg, 0.521 mmol, 87% yield).

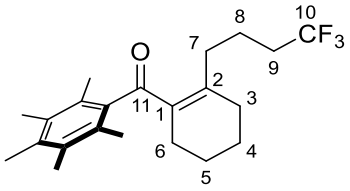
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 2.0, 1.0 Hz, 1H, H_{14}), 6.26 (dd, *J* = 3.0, 2.0 Hz, 1H, H_{13}), 5.96 (d, *J* = 3.0 Hz, 1H, H_{12}), 2.55 – 2.41 (m, 2H, H_{10} x 2), 2.40 – 2.27 (m, 2H, H_8 x 2), 2.24 – 2.19 (m, 5H, $ArCH_3$, H_3 x 2), 2.17 (s, 6H, $ArCH_3$ x 2), 2.15 – 2.09 (m, 2H, H_6 x 2), 2.06 (s, 6H, $ArCH_3$ x 2), 1.73 (q, *J* = 8.0 Hz, 2H, H_9 x 2), 1.63 – 1.46 (m, 4H, H_4 x 2, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_7), 156.3 (C_{11}), 152.3 (C_2), 141.2 (ArC), 140.8 (C_{14}), 135.0 (ArC), 133.3 (C_1), 132.9 (ArC x 2), 128.4 (ArC x 2), 110.2 (C_{13}), 104.8 (C_{12}), 35.3 (C_8), 32.5 (C_3), 28.4 (C_{10}), 27.1 (C_9), 27.1 (C_6), 22.8 (C_5), 22.4 (C_4), 17.3 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 365.2467 ; $C_{25}H_{33}O_2$ requires 365.2475, Δ -2.11 ppm

IR (film) ν_{max}/cm^{-1} 2929, 2860, 1665, 1597, 1449, 1171, 726

(2,3,4,5,6-Pentamethylphenyl)(2-(4,4,4-trifluorobutyl)cyclohex-1-en-1-yl)methanone 444



9,9,9-Trifluorononane-1,5-diol (257 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a white solid (193 mg, 0.527 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 – 2.21 (m, 2H, H_7 x 2), 2.19 – 2.08 (m, 11H, H_3 x 2, $ArCH_3$ x 3), 2.07 – 2.02 (m, 2H, H_6 x 2), 1.98 (s, 6H, $ArCH_3$ x 2), 1.93 – 1.74 (m, 2H, H_9 x 2), 1.66 – 1.44 (m, 6H, H_4 x 2, H_5 x 2, H_8 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C_{11}), 150.5 (ArC), 140.8 (C_2), 135.1 (ArC), 133.9 (C_1), 132.9 (ArC x 2), 128.2 (ArC x 2), 127.1 (q, *J* = 276.5 Hz, C_{10}), 34.3 (C_7), 33.7 (q, *J* = 28.5 Hz, C_9), 32.2 (C_3), 26.9 (C_6), 22.6 (C_5), 22.2 (C_4), 20.9 (q, *J* = 3.0 Hz, C_8), 17.1 ($ArCH_3$ x 2), 16.7 ($ArCH_3$), 15.9 ($ArCH_3$ x 2).

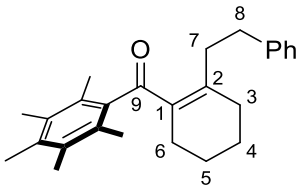
^{19}F NMR (376 MHz, $CDCl_3$) δ -66.4.

HRMS (ESI+): Found $[M+H]^+$ = 367.2242 ; $C_{22}H_{30}OF_3$ requires 367.2443, Δ -0.39 ppm

IR (film) ν_{max}/cm^{-1} 2931, 1666, 1599, 1461, 1384, 1250, 1195, 1128, 1011

m.p.: 60-62 °C

(2,3,4,5,6-Pentamethylphenyl)(2-phenethylcyclohex-1-en-1-yl)methanone 445



7-Phenylheptane-1,5-diol (250 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a white solid (187mg, 0.519 mmol, 86% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.06 (m, 5H, ArCH x 5), 2.78 – 2.50 (m, 4H, H_7 x 2, H_8 x 2), 2.29 – 2.21 (m, 5H, $ArCH_3$, H_3 x 2), 2.17 (s, 8H, $ArCH_3$ x 2, H_6 x 2), 2.08 (s, 6H, $ArCH_3$ x 2), 1.65 – 1.55 (m, 4H, H_4 x 2, H_5 x 2).

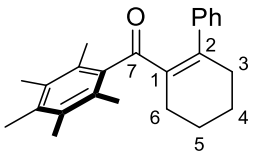
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C_9), 152.1 (ArC), 142.3 (C_2), 141.1 (ArC), 135.0 (ArC), 133.3 (C_1), 132.9 (ArC x 2), 128.4 (ArC x 2), 128.3 (ArC x 2), 128.2 (ArC x 2), 125.7 (ArC), 38.4 (C_8), 34.8 (C_7), 32.8 (C_3), 27.0 (C_6), 22.7 (C_5), 22.3 (C_4), 17.2 ($ArCH_3$ x 2), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 361.2523; $C_{26}H_{33}O$ requires 361.2526, Δ -0.76 ppm

IR (film) ν_{max}/cm^{-1} 2927, 2859, 1665, 1602, 1452, 1306, 1173, 1068, 903, 700

m.p.: 100-102 °C

(2,3,4,5,6-Pentamethylphenyl)(3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone 446



1-Phenylpentane-1-5-diol (216 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a white solid (119 mg, 0.36 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.77 (m, 3H, ArCH x 3), 6.76 – 6.59 (m, 2H, ArCH x 2), 2.64 – 2.51 (m, 2H, H_6 x 2), 2.35 – 2.23 (m, 2H, H_3 x 2), 2.00 (s, 3H, $ArCH_3$), 1.92 (s, 6H, $ArCH_3$ x 2), 1.91 (s, 6H, $ArCH_3$ x 2), 1.81 – 1.68 (m, 4H, H_4 x 2, H_5 x 2).

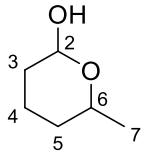
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C_7), 151.7 (C_2), 143.0 (C_1), 140.9 (ArC), 136.5 (ArC), 134.7 (ArC), 132.2 (ArC x 2), 128.6 (ArC x 2), 126.6 (ArC x 2), 126.1 (ArC x 2), 125.7 (ArC), 36.5 (C_3), 25.9 (C_6), 22.9 (C_5), 22.5 (C_4), 18.2 ($ArCH_3$ x 2), 16.5 ($ArCH_3$), 15.7 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 333.2213; $C_{24}H_{29}O$ requires 333.2213, Δ 0.05 ppm.

IR (film) ν_{max}/cm^{-1} 2922, 2859, 1636, 1618, 1443, 1304, 1194, 757, 700

m.p.: 78-80 °C

6-Methyltetrahydro-*2H*-pyran-2-ol 454



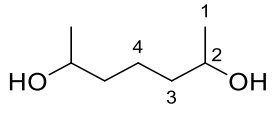
DIBAL-H in hexanes (1 M, 61 mL, 61 mmol, 1.4 eq.), 5-hexanolide (5.0 g, 43 mmol, 1 eq.) and CH_2Cl_2 (100 mL) were subjected to **General Procedure 2.** The title compound was afforded after purification by FCC (20→40% Et_2O/pentane) as a colourless oil (4.3 g, 37 mmol, 86% yield, 3:2 mixture of anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 – 5.16 (m, 1H minor, H_2), 4.78 – 4.57 (m, 1H major H_2), 4.19 – 3.96 (m, 1H, minor H_6), 3.86 – 3.62 (m, 1H, major OH), 3.59 – 3.47 (m, 1H major H_6), 3.24 – 3.00 (m, 1H, minor OH), 1.91 – 1.09 (m, 15H, minor H_3 x 2, minor H_4 x 2 and minor H_5 x 2, major H_7 x 3, major H_3 x 2, major H_4 x 2 and major H_5 x 2), 1.09 – 1.04 (m, 3H minor H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 96.5 (minor C_2), 91.7 (major C_2), 72.6 (major C_6), 65.0 (minor C_6), 33.1 (major C_5), 32.4 (major C_4), 32.3 (minor C_5), 29.7 (minor C_4), 22.2 (major C_3), 21.7 (minor C_7), 21.6 (major C_7), 17.5 (minor C_3).

The spectroscopic data matched that previously reported in the literature.[158]

Heptane-2,6-diol 455



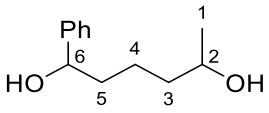
6-Methyltetrahydro-*2H*-pyran-2-ol (1 g, 8.6 mmol, 1 eq.), dry THF (30 mL) and MeMgBr in Et_2O (3 M, 8.60 mL, 25.8 mmol, 3 eq.) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5→10% MeOH/CH_2Cl_2) as a colourless oil (1.12 g, 8.47 mmol, 98% yield, inseparable mixture of diastereomers, d.r. could not be accurately determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (h, *J* = 6.0 Hz, 4H, major H_2 x 2, minor H_2 x 2), 2.10 – 1.82 (m, 4H, major OH x 2, minor OH x 2), 1.60 – 1.29 (m, 12H, major H_3 x 4, major H_4 x 2, minor H_3 x 4, minor H_4 x 2), 1.17 (d, *J* = 6.5 Hz, 12H, major H_1 x 6, minor H_1 x 6). No separate signals were observed by ^{1}H NMR so a d.r. could not be accurately determined.

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.1 (major C_2 x 2), 67.9 (minor C_2 x 2), 39.2 (major C_3 x 2), 39.1 (minor C_3 x 2), 23.7 (minor C_1 x 2), 23.6 (major C_1 x 2), 22.0 (minor C_4), 21.9 (major C_4).

The spectroscopic data matched that previously reported in the literature.[4]

1-Phenylhexane-1,5-diol 456



6-Methyltetrahydro-*2H*-pyran-2-ol (1.0 g, 8.6 mmol, 1 eq.), dry THF (30 mL) and PhMgBr in THF (1M, 25.8 mL, 25.8 mmol, 3 eq.) were subjected to **General Procedure 5**. The title compound was afforded after purification by two FCC (4% MeOH/CH_2Cl_2, then 50% EtOAc/pentane) as a colourless oil (1.2 g, 6.2 mmol, 72% yield, inseparable mixture of diastereomers, 2:1 d.r.).

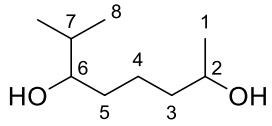
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.14 (m, 10H, major ArCH x 5, minor ArCH x 5), 4.68 – 4.52 (m, 2H, major H_6, minor H_6), 3.80 – 3.60 (m, 2H, major H_2, minor H_2), 2.32 (s, 2H, OH x 2), 2.23 (s, 2H, OH x 2), 1.83 – 1.54 (m, 6H, major H_{3a}, major H_5 x 2, minor H_{3a}, minor H_5 x 2), 1.54 – 1.14 (m, 6H, major H_{3b}, major H_4 x 2, minor H_{3b}, minor H_4 x 2), 1.09 (d, *J* = 6.5 Hz, 6H, major H_1 x 3, minor H_1 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (ArC minor), 144.9 (ArC major), 128.6 (ArC minor x 2, ArC major x 2), 127.6 (ArC minor, ArC major), 126.0 (ArC major x 2), 126.0 (ArC minor x 2), 74.6 (C_6 major), 74.5 (C_6 minor), 68.1 (C_2 major), 67.9 (C_2 minor), 39.1 (C_3 major), 39.1 (C_5 major), 39.0 (C_3 minor), 39.0 (C_5 minor), 23.6 (C_1 minor), 23.6 (C_1 major), 22.2 (C_4 minor), 22.0 (C_4 major).

HRMS (ESI+): Found $[M+Na]^+$ = 217.1202 ; $C_{12}H_{18}O_2Na$ requires 217.1199, Δ 3.50 ppm

IR (film) ν_{max}/cm^{-1} 3342, 2971, 2933, 1453, 1376, 1131, 1069, 943, 761, 700

7-Methyloctane-2,6-diol 457



6-Methyltetrahydro-*2H*-pyran-2-ol (1.0 g, 8.6 mmol, 1 eq.), dry THF (30 mL) and *i*PrMgCl in THF (2M, 13.0 mL, 25.8 mmol, 3 eq.) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (5→10% MeOH/CH_2Cl_2) as a colourless oil (1.34 g, 8.36 mmol, 97% yield, inseparable mixture of diastereomers, 1:1 d.r.).

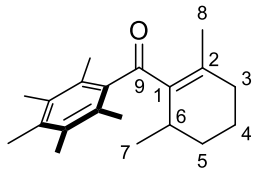
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (h, *J* = 6.5 Hz, 2H, H_2 major and H_2 minor), 3.41 – 3.24 (m, 2H, H_6 major and H_6 minor), 2.24 (d, *J* = 11.5 Hz, 1H, OH minor), 2.07 (d, *J* = 17.0 Hz, 2H, OH major and OH minor), 1.89 (s, 1H, OH major), 1.68 – 1.27 (m, 14H, H_3 x 2 major, H_4 x 2 major , H_5 x 2 major, H_7 x 1 major, H_3 x 2 minor, H_4 x 2 minor, H_5 x 2 minor and H_7 x 1 minor), 1.17 (d, *J* = 6.0 Hz, 6H, H_1 x 3 major and H_1 x 3 minor), 0.89 (dd, *J* = 7.0, 1.0 Hz, 12H, H_8 x 6 major, and H_8 x 6 minor).

^{13}C NMR (101 MHz, $CDCl_3$) δ 76.7 (C_2 major), 76.6 (C_2 minor), 68.1 (C_6 major), 67.8 (C_6 minor), 39.3 (C_3 major), 39.1 (C_3 minor), 34.1 (C_4 major) , 33.8 (C_4 minor), 33.8 (C_7 minor), 33.7 (C_7 major), 23.7 (C_1 minor), 23.6 (C_1 major), 22.3 (C_5 minor), 22.2 (C_5 major), 18.9 (C_{8a} major), 18.9 (C_{8a} minor), 17.4 (C_{8b} minor), 17.4 (C_{8b} major).

HRMS (ESI+): Found $[M+Na]^+$ = 183.1358 ; $C_9H_{20}O_2Na$ requires 183.1356, Δ -0.50 ppm

IR (film) ν_{max}/cm^{-1} 3340, 2960, 2933, 1462, 1330, 1127, 958

(2,6-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 458



Heptane-2,5-diol (159 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a white solid (111 mg, 0.39 mmol, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 – 2.77 (m, 1H, H_6), 2.23 (s, 3H, $ArCH_3$), 2.21 – 2.13 (m, 8H, $ArCH_3$ x 2, H_3 x 2), 1.78 – 1.63 (m, 6H, $ArCH_3$ x 2), 1.63 – 1.52 (m, 7H, H_4 x 2, H_5 x 2, H_8 x 3), 1.01 (d, *J* = 7.0 Hz, 3H, H_7 x 3).

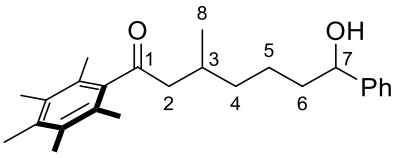
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1 (C_9), 149.2 (C_2), 141.5 (C_1), 139.4 (ArC), 135.1 (ArC), 133.1 (ArC x 2), 128.8 (ArC x 2), 35.4 (C_3), 30.2 (C_5), 29.0 (C_6), 22.2 (C_8), 20.8 (C_7), 17.7 (C_4), 17.3 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.2 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 285.2213; $C_{24}H_{29}O$ requires 285.2213, Δ -0.03 ppm.

IR (film) ν_{max}/cm^{-1} 2912, 2866, 1630, 1610, 1448, 1271, 1219, 1152, 893, 704

m.p.: 100-102 °C

7-Hydroxy-3-methyl-1-(2,3,4,5,6-pentamethylphenyl)-7-phenylheptan-1-one 459



1-Phenylhexane-1,5-diol (233 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (2→10% Et_2O/pentane) as a white solid (182 mg, 0.498 mmol, 83% yield, inseparable mixture of diastereomers, 1:1 d.r. by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.09 (m, 10H, ArCH x 5 and ArCH' x 5), 4.60 (ddt, *J* = 8.5, 6.0, 3.0 Hz, 2H, H_7 and $H_{7'}$), 2.56 (ddd, *J* = 19.0, 5.0, 1.5 Hz, 2H, H_{2a} and $H_{2a'}$), 2.42 (ddd, *J* = 19.0, 7.5, 2.5 Hz, 2H, H_{2b} and $H_{2b'}$), 2.15 (s, 6H, $ArCH_3$ and $ArCH_{3'}$), 2.10 (s, 14H, $ArCH_3$ x 2 and $ArCH_{3'}$ x 2, H_3 and $H_{3'}$), 2.00 (s, 12H, $ArCH_3$ x 2 and $ArCH_{3'}$ x 2), 1.78 – 1.56 (m, 4H, H_6 x 2 and $H_{6'}$ x 2), 1.51 – 1.10 (m, 8H, H_4 x 2 and $H_{4'}$ x 2, H_5 x 2 and $H_{5'}$ x 2), 0.93 (d, *J* = 6.5 Hz, 6H, H_8 x 3 and $H_{8'}$x 3). n.b OH peak not observed

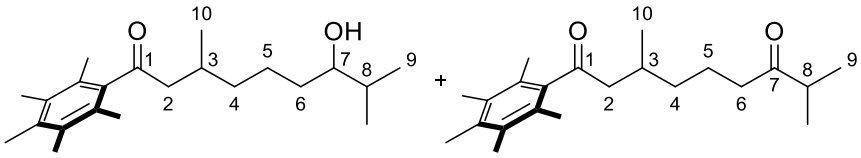
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2 (C_1), 211.2 ($C_{1'}$), 144.9 (ArC and ArC'), 135.3 (ArC and ArC'), 133.0 (ArC and ArC'), 128.5 (ArC x 2 and ArC' x 2), 127.5 (ArC x 2 and ArC' x 2), 127.3 (ArC x 2 and ArC' x 2), 126.8 (ArC and ArC'), 125.9 (ArC x 2 and ArC' x 2), 74.6 (C_7), 74.5 ($C_{7'}$), 52.9 (C_2), 52.8 ($C_{2'}$), 39.2 (C_6), 39.1 ($C_{6'}$), 36.6 (C_4), 36.5 ($C_{4'}$), 27.8 (C_3), 27.7 ($C_{3'}$), 23.3 (C_5), 23.0 ($C_{5'}$), 20.0 (C_8), 20.0 ($C_{8'}$), 17.0 ($ArCH_3$ x 2 and $ArCH_3$' x 2), 16.7 ($ArCH_3$ and $ArCH_3$'), 15.9 ($ArCH_3$ x 2 and $ArCH_3$' x 2).

HRMS (ESI+): Found $[M+Na]^+$ = 389.2450 ; $C_{25}H_{34}O_2Na$ requires 389.2451, Δ -0.26 ppm

IR (film) ν_{max}/cm^{-1} 3400, 3981, 2930, 1697, 1493, 1452, 758, 700

m.p.: 122-124 °C

7-Hydroxy-3,8-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one 460 and 3,8-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)nonane-1,7-dione 461



7-Methyloctane-2,6-diol (192 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (2→10% Et_2O/pentane) as a colourless oil than solidified on standing at room temperature (50 mg, 0.15 mmol, 25% yield, inseparable mixture of diastereomers, 1:1 d.r. by ^1H NMR). 3,8-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)nonane-1,7-dione was also isolated as a white solid (99 mg, 0.30 mmol, 50% yield)

Data for 7-hydroxy-3,8-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one 460:

^1H NMR (400 MHz, $CHCl_3$) δ 3.34 – 3.21 (m, 2H, H_7 and $H_{7'}$), 2.60 (dd, *J* = 19.0, 5.0 Hz, 2H, H_{2a} and $H_{2a'}$), 2.45 (dd, *J* = 19.0, 8.0 Hz, 2H, H_{2b} and $H_{2b'}$), 2.15 (s, 6H, $ArCH_3$ and $ArCH_{3'}$), 2.12 – 2.07 (m, 14H, $ArCH_3$ x 2 and $ArCH_{3'}$ x 2, H_3 and $H_{3'}$), 2.03 (s, 12H, $ArCH_3$ x 2 and $ArCH_{3'}$ x 2), 1.67 – 1.50 (m, 2H, H_8 and $H_{8'}$), 1.51 – 1.07 (m, 12H, H_4 x 2 and $H_{4'}$ x 2, H_5 x 2 and $H_{5'}$ x 2, H_6 x 2 and $H_{6'}$ x 2), 0.96 (d, *J* = 6.5 Hz, 6H, H_{10} x 3 and $H_{10'}$ x 3), 0.84 (d, *J* = 7.0 Hz, 6H, H_{9a} x 3 and $H_{9a'}$ x 3), 0.83 (d, *J* = 7.0 Hz, 6H, H_{9b} x 3 and $H_{9b'}$ x 3). n.b OH peak not observed

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C_1), 211.4 ($C_{1'}$), 140.9 (ArC and ArC'), 135.4 (ArC and ArC'), 133.2 (ArC x 2and ArC' x 2), 127.4 (ArC x 2 and ArC' x 2), 76.8 (C_7 and $C_{7'}$), 53.0 (C_2 and $C_{2'}$), 37.0 (C_4), 37.0 ($C_{4'}$), 34.4 (C_6), 34.3 ($C_{6'}$), 33.7 (C_8), 33.7 ($C_{8'}$), 28.0 (C_3), 28.0 ($C_{3'}$), 23.6 (C_5), 23.4 ($C_{5'}$), 20.1 (C_{10}), 20.1 ($C_{10'}$), 19.0 (C_{9a} and $C_{9a'}$), 17.3 (C_{9b}), 17.2 ($C_{9b'}$), 17.2 ($ArCH_3$ x 2 and $ArCH_3$' x 2), 16.8 ($ArCH_3$ and $ArCH_3$'), 16.1 ($ArCH_3$ x 2 and $ArCH_3$' x 2).

HRMS (ESI+): Found $[M+H]^+$ = 333.2789 ; $C_{22}H_{37}O_2$ requires 333.2788, Δ 0.19 ppm

IR (film) ν_{max}/cm^{-1} 3446, 2930, 1698, 1461, 1381, 999

Data for 3,8-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)nonane-1,7-dione 461:

^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 19.0, 5.0 Hz, 1H, H_{2a}), 2.60 (hept, *J* = 7.0 Hz, 1H, H_8), 2.53 (dd, *J* = 19.0, 7.5 Hz, 1H, H_{2b}), 2.46 (ddd, *J* = 8.0, 6.5, 3.0 Hz, 2H, H_6 x 2), 2.25 – 2.13 (m, 10H, $ArCH_3$ x 3, H_3),

2.10 (s, 6H, $ArCH_3$ x 3), 1.74 – 1.49 (m, 2H, H_5 x 2), 1.45 – 1.34 (m, 1H, H_{4a}), 1.27 – 1.14 (m, 1H, H_{4b}), 1.09 (d, *J* = 7.0 Hz, 6H, H_9 x 6), 1.04 (d, *J* = 6.5 Hz, 3H, H_{10} x 3).

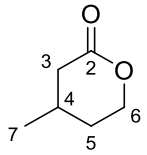
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9 (C_7), 211.3 (C_1), 140.8 (ArC), 135.4 (ArC), 133.2 (ArC x 2), 127.4 (ArC x 2), 52.9 (C_2), 41.0 (C_8), 40.4 (C_6), 36.4 (C_4), 27.8 (C_3), 21.2 (C_5), 20.0 (C_{10}), 18.4 (C_9 x 2), 17.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.0 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 331.2632 ; $C_{22}H_{35}O_2$ requires 333.2788, Δ 0.17 ppm

IR (film) ν_{max}/cm^{-1} 2969.28, 1701.52, 1463, 1382, 1403, 1382, 1094, 927

m.p.: 48-50 °C

4-Methyltetrahydro-*2H*-pyran-2-one 462



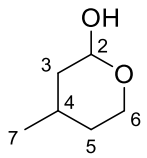
A flame dried 3-neck flask fitted with a reflux condenser was charged with commercial 3-methyl-1,5-pentane-diol (25 g, 211 mmol, 1 eq.) and copper chromite (1.25 g, 4.22 mmol, 2 mol%). The reaction was heated to 200 °C for 2 hours and then cooled to RT. The title compound was afforded after purification by FCC (30% EtOAc/pentane) as a colourless oil (15 g, 131 mmol, 62% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 4.44 – 4.35 (m, 1H, H_{6a}), 4.29 – 4.19 (m, 1H, H_{6b}), 2.72 – 2.59 (m, 1H, H_{3a}), 2.16 – 1.99 (m, 2H, H_{3b} and H_4), 1.96 – 1.84 (m, 1H, H_{5a}), 1.56 – 1.43 (m, 1H, H_{5b}), 1.04 (d, *J* = 6.0 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C_2), 68.7 (C_6), 38.4 (C_3), 30.8 (C_5), 26.7 (C_4), 21.6 (C_7).

The spectral data matched that previously reported in the literature.[159]

4-Methyltetrahydro-*2H*-pyran-2-ol 463



Method 1: DIBAL-H in hexanes (1M, 17.2 mL, 17.2 mmol, 1.37 eq.), 4-methyltetrahydro-*2H*-pyran-2-one (1.40 g, 13.1 mmol, 1 eq.) and CH_2Cl_2 (25 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (100% Et_2O) as a colourless oil (1.46 g, 12.8 mmol, 97% yield, 55:45 mixture of anomers).

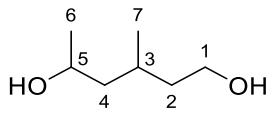
Method 2: A 25 mL RBF under argon atmosphere was charged with IBX (30% w/w with stabilizer, 1.87 g, 2.03 mmol, 1.2 eq.), dry DMSO (1.4 mL) and acetone (5 mL), and stirred for 1h at RT. 3-methylpentane-1,5-diol (200 mg, 1.69 mmol, 1 eq.) was added, stirring for 3 hours at RT. The reaction was then diluted with water (10 mL) and filtered. The resulting aqueous solution was extracted with Et_2O (4 x 20 mL). The organic phase was then washed with sat. aq. Na_2CO_3 (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→30% Et_2O/pentane) as a colourless oil (79.0 mg, 0.677 mmol, 40% yield, 55:45 mixture of anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29-5.25 (m, 1H, minor H_2), 4.65 (ddd, *J* = 9.5, 6.0, 2.0 Hz, 1H, major H_2), 4.08 – 3.91 (m, 2H, major H_{6a} and minor H_{6a}), 3.62 (ddd, *J* = 11.0, 5.0, 2.0 Hz, 1H, minor H_{6b}), 3.55 – 3.29 (m, 2H, major H_{6b} and OH), 2.96 – 2.72 (m, 1H, OH), 2.07-1.93 m (m, 1H, minor H_4), 1.89 (ddt, *J* = 13.0, 4.0, 2.0 Hz, 1H, major H_{3a}), 1.84 – 1.61 (m, 2H, major H_4 and minor H_{3a}), 1.61 – 1.53 (m, 1H, minor H_{5a}), 1.52 – 1.44 (m, 1H, major H_{5a}), 1.37 – 1.10 (m, 3H, minor H_{3b}, major H_{5b} and minor H_{5b}), 1.07 – 0.99 (m, 1H, major H_{3b}), 0.97 (d, *J* = 6.5 Hz, 3H major CH_3), 0.91 (d, *J* = 6.5 Hz, 3H, minor CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 96.3 (major C_2), 91.9 (minor C_2), 65.8 (major C_6), 59.9 (minor C_6), 41.8 (major C_3), 38.8 (minor C_3), 34.2 (minor C_5), 33.7 (major C_5), 29.5 (major C_4), 23.7 (minor C_4), 22.2 (major CH_3), 21.9 (minor CH_3).

The spectroscopic data matched that previously reported in the literature.[160]

3-Methylhexane-1,5-diol 464



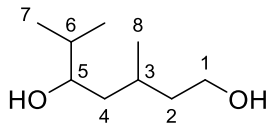
4-Methyltetrahydro-*2H*-pyran-2-ol (800 mg, 6.89 mmol, 1 eq.), dry THF (10 mL) and MeMgBr in Et_2O (3.2 M, 9.1 mL, 27 mmol, 4 eq.) were subjected to **General Procedure 5.** The title compound was afforded after purification by FCC (100% Et_2O) as an inseparable mixture of diastereomers as a yellow oil (480 mg, 3.63 mmol, 53% yield, d.r. could not be accurately determined by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 – 3.84 (m, 1H, H_5), 3.78 – 3.60 (m, 2H, 2 x H_1), 2.35 – 1.87 (m, 1H, OH) 1.86 – 1.56 (m, 2H, H_3 and OH), 1.56 – 1.46 (m, 2H, 2 x H_2), 1.46 – 1.27 (m, 2H, 2 x H_4), 1.26 – 1.11 (m, 3H, 3 x H_6), 0.99 – 0.89 (m, 3H, 3 x H_7). No separate signals were observed by ^{1}H NMR so a d.r. could not be accurately determined.

^{13}C NMR (101 MHz, $CDCl_3$) δ 66.0 (C_5), 65.8 ($C_{5'}$), 61.1 (C_1), 61.0 ($C_{1'}$), 46.9 (C_4), 40.4 (C_2), 39.1 ($C_{4'}$ or $C_{2'}$), 39.0 ($C_{4'}$ or $C_{2'}$), 26.4 (C_3), 26.3 ($C_{3'}$), 24.6 (C_6), 23.9 ($C_{6'}$), 20.8 (C_7), 20.1 ($C_{7'}$).

The spectroscopic data matched that previously reported in the literature.[84]

3,6-Dimethylheptane-1,5-diol 465



4-Methyltetrahydro-*2H*-pyran-2-ol (1.0 g, 8.6 mmol, 1 eq.), dry THF (17 mL) and isopropyl magnesium bromide in THF (2 M, 13.0 mL, 25.8 mmol, 3 eq.) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (6% MeOH/CH_2Cl_2) as an inseparable mixture of diastereomers as a colourless oil (1.36 g, 8.49 mmol, 99% yield, 60:40 d.r. by ^{1}H NMR).

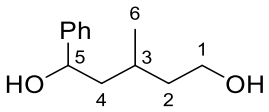
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 – 3.57 (m, 4H, major H_1 x 2 and minor H_1 x 2), 3.57 – 3.39 (m, 2H, major H_5 and minor H_5), 2.28 – 1.67 (m, 7H, major H_3 and minor H_3, minor H_{2a}, minor OH x 2 and major OH x 2), 1.68 – 1.58 (m, 2H, major H_6 and minor H_6), 1.59 – 1.25 (m, 6H, major H_{2a}, minor H_{2b}, major H_4 x 2, minor H_4 x 2), 1.25 – 1.13 (m, 1H major H_{2b}), 1.00 – 0.89 (m, 18H, major CH_3 x 3 and minor CH_3 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 74.7 (major C_5), 74.2 (minor C_5), 61.2 (major C_1), 60.7 (minor C_1), 41.7 (major C_4), 40.8 (major C_2), 40.7 (minor C_4), 38.7 (minor C_2), 34.4 (minor C_6), 33.9 (major C_6), 26.5 (major C_3), 26.3 (minor C_3), 21.2 (major C_8), 20.0 (minor C_8), 19.0 (major C_{7a}), 18.8 (minor C_{7a}), 17.5 (major C_{7b}), 17.2 (minor C_{7b}).

HRMS (ESI+): Found $[M+Na]^+$ = 183.1358; $C_9H_{20}O_2Na$ requires 183.1356, Δ 1.54 ppm

IR (film) ν_{max}/cm^{-1} 3332, 2957, 2931, 1465, 1382, 1056, 991

3-Methyl-1-phenylpentane-1,5-diol 466



4-Methyltetrahydro-*2H*-pyran-2-ol (1.0 g, 8.6 mmol, 1 eq.), dry THF (17 mL) and phenyl magnesium bromide in THF (1 M, 26.0 mL, 25.8 mmol, 3 eq.) were subjected to **General Procedure 5**. The title compound was afforded after purification by FCC (2→5% MeOH/CH_2Cl_2) as an inconsequential mixture of diastereomers as a colourless oil (1.63 g, 8.39 mmol, 98% yield, 78:22 d.r. by ^{1}H NMR).

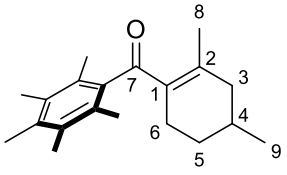
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.11 (m, 10H, major ArCH x 5, minor ArCH x 5), 4.85 – 4.52 (m, 2H, major H_1, minor H_1), 3.76 – 3.42 (m, 4H, major H_5 x 2, minor H_5 x 2), 2.77 (s, 1H major OH), 2.44 (s, 1H minor OH), 2.12 (s, 1H major OH), 1.97 (s, 1H minor OH), 1.89 – 1.71 (m, 2H, minor H_3 and minor H_{2a}), 1.71 – 1.50 (m, 4H, major H_2 x 2, major H_3, major H_{4a}), 1.45 (q, *J* = 6.5 Hz, 2H, minor H_4 x 2), 1.38 – 1.23 (m, 2H, major H_{4b} and minor H_{2b}), 0.93 (d, *J* = 6.5 Hz, 3H, minor H_6 x 3), 0.88 (d, *J* = 6.0 Hz, 3H, major H_6 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (minor ArC), 145.1 (major ArC), 128.6 (major ArC x 2, minor ArC x 2), 127.6 (major ArC), 127.5 (minor ArC), 126.0 (major ArC x 2), 125.8 (minor ArC x 2), 72.6 (minor C_1), 72.3 (major C_1), 60.9 (major C_5), 60.5 (minor C_5), 46.6 (major C_2), 46.4 (minor C_2), 40.3 (minor C_4), 39.0 (major C_4), 26.4 (major C_3), 26.4 (minor C_3), 20.7 (major C_6), 20.0 (minor C_6).

HRMS (ESI+): Found $[M+Na]^+$ = 217.1200; $C_{12}H_{18}O_2Na$ requires 217.1199, Δ 0.64 ppm

IR (film) ν_{max}/cm^{-1} 3330, 2980, 2929, 1494, 1380, 1056, 700

(2,4-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 473



3-Methylhexane-1,5-diol (159 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (2→4% Et_2O/pentane) as a white solid (160 mg, 0.564 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 – 2.24 (m, 2H, H_{3a} and H_{6a}), 2.22 (s, 3H, $ArCH_3$), 2.17 (s, 6H, $ArCH_3$ x 2), 2.15 – 2.08 (m, 1H, H_{6b}), 2.05 (s, 6H, $ArCH_3$ x 2), 1.94 – 1.78 (m, 4H, H_8 x 3 and H_{3b}), 1.76 – 1.60 (m, 2H, H_4 and H_{5a}), 1.15 (dtd, *J* = 12.5, 10.5, 5.5 Hz, 1H, H_{5b}), 0.96 (d, *J* = 6.5 Hz, 3H, H_9 x 3).

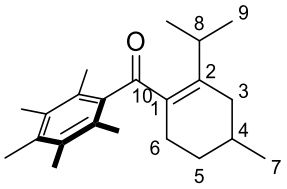
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C_7), 148.6 (ArC), 141.4 (C_2), 135.0 (ArC), 133.0 (ArC x 2), 132.9 (C_1), 128.2 (ArC x 2), 43.7 (C_3), 30.9 (C_5), 28.4 (C_4), 26.7 (C_6), 22.1 (C_8), 21.5 (C_9), 17.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 285.2209; $C_{20}H_{29}O$ requires 285.2213, Δ –1.32 ppm

IR (film) ν_{max}/cm^{-1} 2942, 1666, 1602, 1172, 715

m.p.: 126-127 °C

(2-Isopropyl-4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 474



3,6-Dimethylheptane-1,5-diol (192 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3% Et_2O/pentane) as a white solid (131 mg, 0.420 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (hept, *J* = 6.0 Hz, 1H, H_8), 2.37 – 2.25 (m, 1H, H_{3a}), 2.25 – 2.13 (m, 10H, $ArCH_3$ x 3, H_{6a}), 2.07 (s, 7H, $ArCH_3$ x 2, H_{6b}), 1.80 – 1.52 (m, 3H, H_{3a}, H_4, H_{5a}), 1.11 (dtd, *J* = 12.5, 10.5, 6.0 Hz, 1H, H_{5b}), 1.00 – 0.93 (m, 9H, H_9 x 6, H_7 x 3).

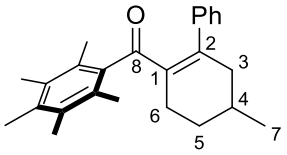
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (C_{10}), 155.8 (ArC), 141.3 (C_2), 135.0 (ArC), 132.9 (ArC x 2), 131.8 (C_1), 128.4 (ArC x 2), 33.3 (C_3), 30.9 (C_5), 30.1 (C_8), 28.1 (C_4), 27.3 (C_6), 21.7 (C_{9a}), 21.0 (C_7), 20.5 (C_{9b}), 17.3 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 313.2524; $C_{22}H_{33}O$ requires 313.2526 Δ -0.47 ppm

IR (film) ν_{max}/cm^{-1} 2953, 2925, 1663, 1604, 1456, 1381, 1166, 863, 716

m.p.: 96-98 °C

(5-Methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone 475



3-Methyl-1-phenylpentane-1,5-diol (233 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→4% Et_2O/pentane) as a white solid (146 mg, 0.420 mmol, 70% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 6.92 – 6.82 (m, 3H, ArCH x 3), 6.71 – 6.63 (m, 2H, ArCH x 2), 2.89 – 2.74 (m, 1H, H_{6a}), 2.52 – 2.28 (m, 2H, H_{6b}, H_{3a}), 2.02 – 1.85 (m, 17H, $ArCH_3$ x 5, H_{3b}, H_{5a}), 1.88 – 1.72 (m, 1H, H_4), 1.41 – 1.22 (m, 1H, H_{5b}), 1.01 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

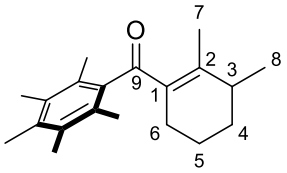
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6 (C_8), 151.4 (ArC), 142.8 (ArC), 140.8 (C_2), 136.0 (ArC), 134.7 (C_1), 132.1 (ArC x 2), 128.6 (ArC x 2), 126.6 (ArC x 2), 126.0 (ArC x 2), 125.7 (ArC), 44.9 (C_3), 30.6 (C_5), 28.8 (C_4), 25.9 (C_6), 21.4 (C_7), 18.2 ($ArCH_3$ x 2), 16.5 ($ArCH_3$), 15.7 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 347.2367; $C_{25}H_{31}O$ requires 347.2369, Δ -0.79 ppm

IR (film) ν_{max}/cm^{-1} 2922, 1642, 1595, 1418, 1314, 1268, 1195, 811, 755, 699

m.p.: 60-62 °C

(2,3-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 476



4-Methylhexane-1,5-diol (159 mg, 1.2 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a white solid (148 mg, 0.522 mmol, 87% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 4H, $ArCH_3$, H_3), 2.10 (s, 6H, $ArCH_3$ x 2), 2.09 – 1.98 (m, 2H, H_6 x 2), 1.98 (s, 6H, $ArCH_3$ x 2), 1.84 (s, 3H, H_7 x 3), 1.66 – 1.40 (m, 3H, H_5 x 2, H_{4a}), 1.38 – 1.27 (m, 1H, H_{4b}), 1.05 (d, *J* = 7.0 Hz, 3H, H_8 x 3).

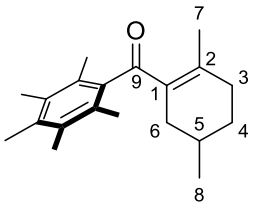
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8 (C_9), 152.2 (ArC), 141.2 (C_2), 135.0 (ArC), 133.1 (C_1), 132.9 (ArC x 2), 128.2 (ArC x 2), 37.5 (C_3), 30.4 (C_4), 27.3 (C_6), 20.9 (C_7), 19.7 (C_8), 19.3 (C_5), 17.1 ($ArCH_2$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 285.2208; $C_{20}H_{29}O$ requires 285.2213, Δ -1.85 ppm

IR (film) ν_{max}/cm^{-1} 2930, 2870, 1666, 1610, 1454, 1305, 1159, 968

m.p.: 80-82 °C

(2,5-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 477



2-Methylhexane-1,5-diol (159 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1.** The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a white solid (137 mg, 0.480 mmol, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 – 2.30 (m, 1H, H_{6a}), 2.26 – 2.19 (m, 4H, $ArCH_3$, H_{3a}) 2.19 – 2.13 (m, 7H, $ArCH_3$ x 2, H_{3b}), 2.05 (s, 6H, $ArCH_3$ x 2), 1.81 (s, 3H, H_7 x 3), 1.76 – 1.53 (m, 3H, H_{4a}, H_5, H_{6b}), 1.25 – 1.13 (m, 1H, H_{4b}), 0.94 (d, *J* = 6.5 Hz, 3H, H_8 x 3).

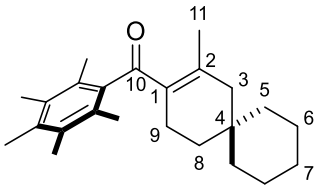
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (C_9), 148.6 (ArC), 141.4 (C_2), 135.0 (ArC), 133.0 (C_1), 133.0 (ArC x 2), 128.2 (ArC x 2), 35.2 (C_3), 34.7 (C_6), 30.6 (C_4), 28.7 (C_5), 21.8 (C_7), 21.6 (C_8), 17.1 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 285.2213; $C_{20}H_{29}O$ requires 285.2213, Δ -0.14 ppm

IR (film) ν_{max}/cm^{-1} 2921, 1667, 1621, 1454, 1306, 1266, 1176, 891, 709

m.p.: 84-86 °C

(2-Methylspiro[5.5]undec-2-en-3-yl)(2,3,4,5,6-pentamethylphenyl)methanone 478



1-(1-(2-Hydroxyethyl)cyclohexyl)propan-2-ol (224 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a white solid (142 mg, 0.420 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H, $ArCH_3$), 2.09 (s, 8H, $ArCH_3$ x 2 and H_9 x 2), 2.00 – 1.91 (m, 8H, $ArCH_3$ x 2 and H_3 x 2), 1.80 (s, 3H, H_{11} x 3), 1.42 – 1.27 (m, 8H, H_6 x 4, H_7 x 2, H_8 x 2), 1.18 (t, *J* = 5.5 Hz, 4H, H_5 x 4).

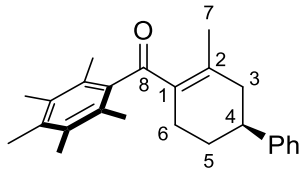
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C_{10}), 148.2 (ArC), 141.4 (C_2), 134.9 (ArC), 132.9 (ArC x 2), 132.0 (C_1), 128.2 (ArC x 2), 47.4 (C_3), 36.6 (C_5 x2), 32.4 (C_8), 31.4 (C_4), 26.7 (C_7), 23.5 (C_9), 22.5 (C_{11}), 21.9 (C_6 x 2), 17.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 339.2679; $C_{24}H_{35}O$ requires 339.2682, Δ -0.97 ppm

IR (film) ν_{max}/cm^{-1} 2921, 1667, 1620, 1445, 1305, 1266, 1159, 851

m.p.: 94-96 °C

(5-Methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone 479 and (*S*)-(5-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone *(-)*-479



(5-Methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone 479: 3-phenylhexane-1,5-diol (233 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4.5→6% Et_2O/pentane) as a white solid (146 mg, 0.420 mmol, 70% yield).

(*S*)-(5-Methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone *(-)*-479: A 5mL microwave vial was charged with CataCXium® A (2.2 mg, 0.0060 mmol, 2 mol%), (3*S*)-3 Phenylhexane-1,5-diol (117 mg, 0.600 mmol, 2 eq. >99:1 e.r., 60:40 d.r.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (57 mg, 0.30 mmol, 1 eq), $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol, 0.5 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) and toluene (1.2 mL, 0.25 M). The vial was then sealed and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The title compound was afforded after purification by FCC (4.5→6% pentane: Et_2O) as a white solid (70.0 mg, 0.201 mmol, 67% yield, >99:1 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H, ArCH x 2), 7.25 – 7.17 (m, 3H, ArCH x 3), 2.81 (ddt, *J* = 17.5, 8.5, 3.0 Hz, 1H, H_4), 2.53 – 2.32 (m, 3H, H_3 x 2, H_{6a}), 2.29 – 2.14 (m, 10H, $ArCH_3$ x 3, H_{6b}), 2.09 (s, 6H, $ArCH_3$ x 2), 2.02 – 1.86 (m, 4H, H_7 x 3, H_{5a}), 1.70 (dtd, *J* = 12.5, 11.0, 5.0 Hz, 1H, H_{5b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C_8), 148.3 (ArC), 146.1 (ArC), 141.2 (C_2), 135.1 (ArC), 133.0 (ArC x 2), 133.0 (C_1), 128.6 (ArC x 2), 128.2 (ArC x 2), 126.9 (ArC x 2), 126.4 (ArC), 43.0 (C_3), 39.9 (C_4), 29.8 (C_5), 27.2 (C_6), 22.0 (C_7), 17.2 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 347.2369 ; $C_{25}H_{31}O$ requires 347.2369, Δ -0.10 ppm

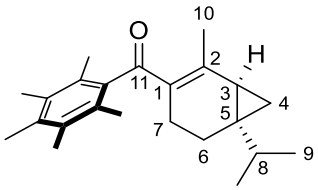
m.p.: 126-128 °C

IR (film) ν_{max}/cm^{-1} 2927, 1668, 1619, 1453, 1379, 1265, 1168, 896, 757, 700

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (98.3:1.7 hexane:IPA, 0.5 mL min^{-1}, 210 nm, room temperature),; t_r (minor)=16.1 min, tr (major)=16.8 min. >99:1 e.r.

$[\alpha]^{25}_D$= -93.2 (c=1.0, $CHCl_3$)

((1*S*,6*R*)-6-Isopropyl-2-methylbicyclo[4.1.0]hept-2-en-3-yl)(2,3,4,5,6 pentamethylphenyl)methanone 489



2-((1*S*,2*S*)-2-((*S*)-1-Hydroxyethyl)-1-isopropylcyclopropyl)ethan-1-ol (208 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4→10% Et_2O/pentane) as a white solid (157 mg, 0.480 mmol, 80% yield, 5% inseparable impurity of Ph*COMe).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 – 2.30 (m, 1H, H_{7a}), 2.22 (s, 3H, $ArCH_3$), 2.17 (s, 6H, $ArCH_3$ x 2), 2.10 – 1.97 (m, 9H, $ArCH_3$ x 2, H_{10} x 3), 1.88 – 1.71 (m, 2H, H_{7b}, H_{6a}), 1.48 – 1.34 (m, 1H, H_{6b}), 1.24 – 1.04 (m, 3H, H_3, H_{4a}, H_8), 0.98 (d, *J* = 7.0, 3H, H_{9a} x 3), 0.96 (d, *J* = 7.0, 3H, H_{9b} x 3), 0.77 (ddd, *J* = 8.5, 4.0, 1.0 Hz, 1H, H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1 (Br, C_{11}), 154.3 (ArC), 141.6 (Br, C_2), 134.8 (ArC), 133.2 (Br, C_1), 132.9 (ArC x 2), 128.2 (ArC x 2), 36.6 (C_3), 32.6 (C_5), 28.0 (C_8), 23.2 (Br, C_{10}), 22.6 (Br, C_7), 19.4 (C_{9a}), 19.3 (C_{9b}), 19.1 (C_6), 18.2 (C_4), 17.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

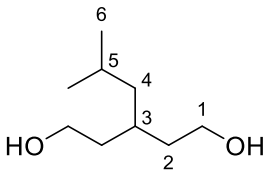
HRMS (ESI+): Found $[M+H]^+$ = 325.2524; $C_{23}H_{33}O$ requires 325.2526, Δ -0.46 ppm

IR (film) ν_{max}/cm^{-1} 2957, 2925, 1659, 1603, 1463, 1307, 1269, 1170, 884, 713

m.p.: 78-80 °C

$[\alpha]^{25}_D$= 139.1 (c=1.0, $CHCl_3$)

3-Isobutylpentane-1,5-diol 509



Method 1: $LiAlH_4$ (6.00 g, 159 mmol, 3 eq.), 3-isobutylglutaric acid (10.0, 53.1 mmol, 1 eq.) and dry THF (150 mL, 0.3 M) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (7.00 g, 43.5 mmol, 82% yield).

Method 2: Iodine (1.60 g, 6.36 mmol 1.2 eq) in dry THF (25 mL) was added dropwise *via* dropping funnel to a 250 mL three necked flask at 0 °C under argon atmosphere charged with 3-isobutylglutaric acid (1.0 g, 5.3 mmol, 1 eq.), $NaBH_4$ (600 mg, 15.9 mmol, 3 eq.) and dry THF (40 mL). The reaction mixture was then warmed to RT and stirred for 30 hours. The reaction was quenched with MeOH (4 mL) at 0 °C, and then concentrated *in vacuo*. The resulting residue was diluted with water (20 mL), extracted with EtOAc (4 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (750 mg, 4.68 mmol, 88% yield).

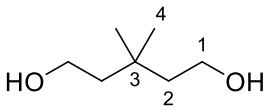
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (dt, *J* = 10.5, 6.5 Hz, 2H, H_{1a} x 2), 3.67 (dt, *J* = 10.5, 6.5 Hz, 2H, H_{1b} x 2), 2.02 (s, 2H, OH x 2), 1.74 – 1.44 (m, 6H, H_2 x 4, H_3 and H_5), 1.13 (t, *J* = 7.0 Hz, 2H, H_4 x 2), 0.87 (d, *J* = 6.5 Hz, 6H, H_6 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 61.0 (C_1 x 2), 44.8 (C_4), 37.1 (C_2 x 2), 29.2 (C_3), 25.4 (C_5), 23.0 (C_{6a} and C_{6b}).

HRMS (ESI+): Found $[M+H]^+$ = 161.1537; $C_9H_{21}O_2$ requires 161.1536, Δ 0.40 ppm

IR (film) ν_{max}/cm^{-1} 3313, 2953, 2926, 2869, 2467, 1367, 1055, 1009

3,3-Dimethylpentane-1,5-diol 510



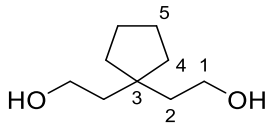
$LiAlH_4$ (3.5 g, 92 mmol, 3 eq.), dry THF (100 mL) and 3,3-dimethylglutaric acid (5.0 g, 31 mmol, 1 eq.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (3.33 g, 25.2 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.7.0 (t, J=7.0 Hz, 4H, H_1 x 4), 2.65 (s, 2H, OH x 2), 1.55 (t, *J* = 7.0 Hz, 4H, H_2 x 4), 0.93 (s, 6H, H_4 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 59.5 (C_1 x 2), 44.1 (C_2 x 2), 31.8 (C_3), 28.3 (C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[84]

2,2'-(cyclopentane-1,1-diyl)bis(ethan-1-ol) 511



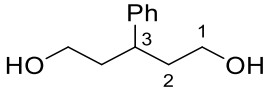
$LiAlH_4$ (6.1 g, 161 mmol, 3 eq.), dry THF (200 mL) and 3,3-tetramethylglutaric acid (10.0 g, 53.7 mmol, 1 eq.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (7.65 g, 48.3 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (t, J = 6.9 Hz, 4H, H_1 x 4), 2.75 (s, 2H, OH x 2), 1.69 – 1.51 (m, 8H, H_2 x 4, H_5 x 4), 1.48 – 1.36 (m, 4H, H_4 x 4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 60.3 (C_1 x 2), 43.5 (C_3), 41.1 (C_2 x 2), 38.5 (C_4 x 2), 24.3 (C_5 x 2).

The spectroscopic data matched that previously reported in the literature.[84]

3-Phenylpentane-1,5-diol 402



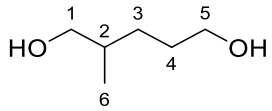
$LiAlH_4$ (1.09 g, 28.8 mmol, 3 eq.), dry THF (50 mL) and 3-phenylglutaric acid (2.00 g, 9.60 mmol, 1 eq.) were subjected to **General Procedure 4.** The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (1.68 g, 9.41 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H, 2 x ArH), 7.25 – 7.14 (m, 3H, 3 x ArH), 3.61 – 3.41 (m, 4H, 4 x H_1), 2.94 (tt, *J* = 9.5, 5.4 Hz, 1H, H_3), 2.51 – 2.18 (m, 2H, 2 x OH), 2.00 – 1.71 (m, 4H, 4 x H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (ArC), 128.7 (ArC x 2), 127.7 (ArC x 2), 126.5 (ArC), 60.7 (C_1 x 2), 39.3 (C_2 x 2), 38.6 (C_3).

The spectroscopic data matched that previously reported in the literature.[84]

2-Methylpentane-1,5-diol 512



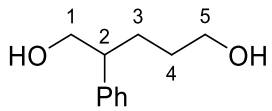
$LiAlH_4$ (1.9 g, 51 mmol, 3 eq.), dry THF (90 mL) and 2-methylglutaric acid (2.5 g, 17 mmol, 1 eq.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (5→10% MeOH/CH_2Cl_2) as a colourless oil (1.33 g, 11.3 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.0 Hz, 2H, 2 x H_5), 3.47 (d, *J* = 6.0 Hz, 2H, 2 x H_1), 2.75 – 2.22 (m, 2H, 2 x OH), 1.72 – 1.47 (m, 4H, H_2, 2 x H_3 and H_4), 1.24 – 1.13 (m, 1H, H_4), 0.92 (d, *J* = 6.5 Hz, 3H, 3 x H_6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 67.9 (C_5), 63.0 (C_1), 35.4 (C_2), 29.9 (C_3), 29.2 (C_4), 16.7 (C_6).

The spectroscopic data matched that previously reported in the literature.[84]

2-Phenylpentane-1,5-diol 513



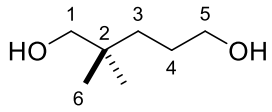
$LiAlH_4$ (597 mg, 15.8 mmol, 2.5 eq.), Dry THF (32 mL) and phenyl glutaric anhydride (1.2 g, 6.3 mmol, 1 eq.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (5→10% MeOH/CH_2Cl_2) as a colourless oil (920 mg, 5.10 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H, 2 x ArCH), 7.25 – 7.15 (m, 3H 3 x ArCH), 3.69 (d, *J* = 6.5 Hz, 2H, 2 x H_1), 3.53 (t, *J* = 7.0 Hz, 2H, 2 x H_5), 2.81 – 2.69 (m, 1H, H_2), 2.53 – 2.24 (m, 2H, 2 x OH), 1.94 – 1.75 (m, 1H, H_3), 1.70 – 1.32 (m, 3H, H_3, 2 x H_4).

13C NMR (101 MHz, $CDCl_3$) δ 142.3 (ArC), 128.7 (ArC x 2), 128.1 (ArC x 2), 126.8 (ArC), 67.5 (C_1), 62.6 (C_5), 48.3 (C_2), 30.3 (C_4), 28.2 (C_3).

The spectroscopic data matched that previously reported in the literature.[84]

2,2-dimethylpentane-1,5-diol 514



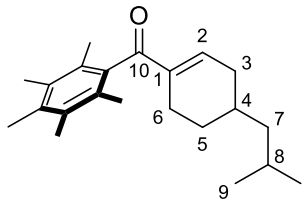
$LiAlH_4$ (2.2 g, 56 mmol, 3 eq.), dry THF (60 mL) and 3,3-dimethylglutaric acid (3.0 g, 18.8 mmol, 1 eq.) were subjected to **General Procedure 4**. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (1.85 g 14.0 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (td, *J* = 6.5, 3.0 Hz, 2H, H_5 x 2), 3.32 (d, *J* = 4.5 Hz, 2H, H_1 x 2), 2.09 (t, *J* = 4.5 Hz, 1H, OH), 2.00 (t, *J* = 3.0 Hz, 1H, OH), 1.59 – 1.47 (m, 2H, H_4 x 2), 1.35 – 1.25 (m, 2H, H_3 x 2), 0.87 (s, 6H, H_6 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 71.5 (C_1), 63.7 (C_5), 35.0 (C_2), 34.4 (C_3), 27.1 (C_4), 24.2 (C_6 x 2).

The spectroscopic data matched that previously reported in the literature.[84]

(4-Isobutylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 520



Method 1: 3-Isobutylpentane-1,5-diol (192mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a white solid (140 mg, 0.448 mmol, 75% yield).

Method 2: 4-isobutyltetrahydro-*2H*-pyran-2-ol (143 mg, 1.20 mmol, 2 eq) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (167 mg, 0.534 mmol, 89% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (ddt, *J* = 5.0, 3.0, 2.0 Hz, 1H, H_2), 2.69 – 2.59 (m, 1H, H_{6a}), 2.34 – 2.21 (m, 5H, $ArCH_3$, H_{3a} and H_{6b}), 2.18 (s, 6H, $ArCH_3$ x 2), 2.03 (s, 3H, $ArCH_3$), 2.01 (s, 3H, $ArCH_3$), 1.89 (dddd, *J* = 13.5, 6.0, 5.0, 3.0 Hz, 1H, H_{5a}), 1.82 – 1.57 (m, 3H, H_{3b}, H_4 and H_8), 1.29 – 1.19 (m, 1H, H_{5b}) 1.16 (h, 2H, *J* = 6.5 Hz, H_7 x 2), 0.89 (d, *J* = 6.5, 3H, H_{9a} x 3), 0.89 (d, *J* = 6.5, 3H, H_{9b} x 3).

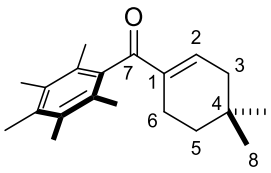
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5 (C_{10}), 145.2 (C_2), 140.8 (C_1), 138.4 (ArC), 135.0 (ArC), 132.7 (ArC), 132.6 (ArC), 129.3 (ArC), 129.2 (ArC), 45.8 (C_7), 33.3 (C_3), 30.6 (C_4), 28.6 (C_5), 25.1 (C_8), 23.1 (C_{9a}), 22.9 (C_{9b}), 22.5 (C_6), 17.6 ($ArCH_3$), 17.6 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 313.2525; $C_{22}H_{33}O$ requires 313.2527, Δ -0.29 ppm

IR (film) ν_{max}/cm^{-1} 3014, 2956, 1651, 1638, 1467, 1188, 861

m.p.: 100-102 °C

(4,4-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 521



Method 1: 3,3-Dimethylpentane-1,5-diol (158.6 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a white solid (164 mg, 0.576 mmol, 96% yield).

Method 2: A 100 mL sealed tube was charged with 3,3-dimethylpentane-1,5-diol (1.59 g, 12.0 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (1.14 g, 6.00 mmol, 1 eq), CataCXium® A (43 mg, 0.12 mmol, 2 mol%), $[Ir(COD)Cl]_2$ (20 mg, 0.030 mmol, 0.5 mol%), KOH (1.43 g, 24.0 mmol, 4 eq.) and toluene (24 mL, 0.25 M). The reaction was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with 3M aq. HCl (30 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The title

compound was afforded after purification by FCC (4% Et_2O/pentane) as a white solid (1.60 g, 5.64 mmol, 94% yield).

Method 3: 4,4-Dimethyltetrahydro-*2H*-pyran-2-ol (156.2 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a white solid (162 mg, 0.57 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (tt, *J* = 4.0, 1.5 Hz, 1H, H_2), 2.46 (tq, *J* = 6.5, 2.5 Hz, 2H, H_6 x 2), 2.23 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.01 (s, 6H, $ArCH_3$ x 2), 1.94 (dt, *J* = 4.5, 2.5 Hz, 2H, H_3 x 2), 1.48 (t, *J* = 6.5 Hz, 2H, H_5 x 2), 0.93 (s, 6H, H_8 x 6).

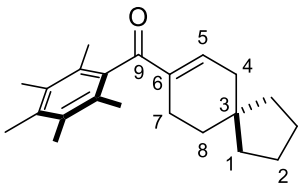
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5 (C_7), 145.0 (C_2), 139.6 (C_1), 138.4 (ArC), 135.1 (ArC), 132.7 (ArC x 2), 129.2 (ArC x 2), 40.3 (C_3), 35.0 (C_5), 28.9 (C_4), 28.2 (C_8 x 2), 20.4 (C_6), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 285.2213; $C_{20}H_{29}O$ requires 285.2213, Δ –0.24 ppm

IR (film) ν_{max}/cm^{-1} 2961, 2922, 2866, 1651, 1636, 1424, 1170, 1129, 810

m.p.: 110-112 °C

(2,3,4,5,6-Pentamethylphenyl)(spiro[4.5]dec-7-en-8-yl)methanone 522



Method 1: 2,2'-(Cyclopentane-1,1-diyl)bis(ethan-1-ol) (190 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4→5% Et_2O/pentane) as a white solid (175 mg, 0.56 mmol, 94% yield).

Method 2: 8-Oxaspiro[4.5]decan-7-ol (187 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (4→5% Et_2O/pentane) as a white solid (177 mg, 0.57 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (tt, *J* = 4.0, 1.5 Hz, 1H, H_5), 2.41 (tq, *J* = 6.5, 2.0 Hz, 2H, H_7 x 2), 2.16 (s, 3H, $ArCH_3$), 2.11 (s, 6H, $ArCH_3$ x 2), 1.97 (dt, *J* = 4.5, 2.5 Hz, 2H, H_4 x 2), 1.94 (s, 6H, $ArCH_3$ x 2), 1.61 – 1.53 (m, 4H, H_1 x 4), 1.52 (t, *J* = 6.5 Hz, 2H, H_8 x 2) 1.42 – 1.23 (m, 4H, H_2 x 4).

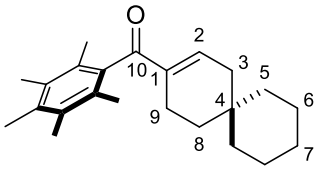
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6 (C_9), 145.4 (C_5), 140.4 (C_6), 138.4 (ArC), 135.1 (ArC), 132.7 (ArC x 2), 129.2 (ArC x 2), 40.7 (C_3), 39.1 (C_4), 38.3 (C_2 x 2), 33.4 (C_8), 24.5 (C_1 x 2), 21.1 (C_7), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 311.2366; $C_{22}H_{31}O$ requires 311.2369, Δ –1.09 ppm

IR (film) ν_{max}/cm^{-1} 2924, 2860, 1654, 1636, 1449, 138, 1268, 1192, 857

m.p.: 90-92 °C

(2,3,4,5,6-Pentamethylphenyl)(spiro[5.5]undec-2-en-3-yl)methanone 523



2,2'-(Cyclohexane-1,1-diyl)bis(ethan-1-ol) (207 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4→5% Et_2O/pentane) as a white solid (144mg, 0.444 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (tt, *J* = 4.0, 2.0 Hz, 1H, H_2), 2.35 (tq, *J* = 6.5, 2.0 Hz, 2H, H_9 x 2), 2.16 (s, 3H, $ArCH_3$), 2.11 (s, 6H $ArCH_3$ x 2), 1.96 – 1.87 (m, 8H $ArCH_3$ x 2, H_3 x 2), 1.50 (t, *J* = 6.5 Hz, 2H, H_8 x 2), 1.46 – 1.29 (m, 6H, H_6 x 4, H_7 x 2), 1.28 – 1.09 (m, 4H, H_5 x 4).

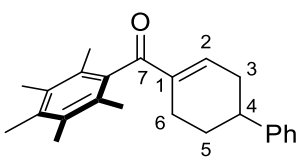
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4 (C_{10}), 144.7 (C_2), 139.9 (C_1), 138.4 (ArC), 135.1 (ArC), 132.7 (ArC x 2), 129.3 (ArC x 2), 38.4 (C_3), 36.5 (C_5 x 2), 32.0 (C_8), 31.4 (C_4), 26.7 (C_7), 21.9 (C_6 x 2), 19.5 (C_9), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 325.2533; $C_{23}H_{33}O$ requires 325.2526, Δ 2.26 ppm

IR (film) ν_{max}/cm^{-1} 2922, 2855, 1653, 1638, 1451, 1381, 1268, 1197, 858

m.p.: 100-102 °C

(2,3,4,5,6-Pentamethylphenyl)(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methanone 387



3-Phenylpentane-1,5-diol (216 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (140 mg, 0.47 mmol, 70% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H, ArCH x 2), 7.25 – 7.18 (m, 3H, ArCH x 3), 6.62 – 6.54 (m, 1H, H_2), 2.91 – 2.80 (m, 1H, H_4), 2.80 – 2.69 (m, 1H, H_{6a}), 2.54 – 2.36 (m, 2H, H_{6b}, H_{3a}), 2.37 – 2.26 (m, 1H, H_{3b}), 2.25 (s, 3H, $ArCH_3$), 2.20 (s, 6H, $ArCH_3$ x 2), 2.12 (dddt, *J* = 11.5, 5.5, 2.5, 1.5 Hz, 1H, H_{5a}), 2.08-2.03 (m, 6H, $ArCH_3$ x 2), 1.86 – 1.72 (m, 1H, H_{5b}).

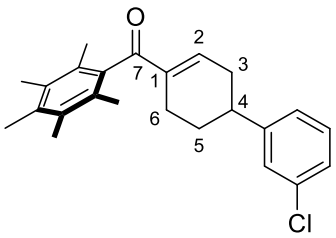
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3 (C_7), 146.1 (ArC), 144.6 (C_2), 140.6 (C_1), 138.3 (ArC), 135.2 (ArC), 132.8 (ArC x 2), 129.3 (ArC), 129.2 (ArC), 128.7 (ArC x 2), 127.0 (ArC x 2), 126.5 (ArC), 39.6 (C_4), 34.4 (C_3), 29.5 (C_5), 23.2 (C_6), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis

HRMS (ESI+): Found $[M+H]^+$ = 333.2214; $C_{24}H_{29}O$ requires 333.2213, Δ 0.30 ppm

IR (film) ν_{max}/cm^{-1} 2931, 1650, 1635, 1451, 1428, 1379, 1311, 1265, 1181, 852, 756, 699

m.p.: 160-162 °C

(3'-Chloro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone 524



3-(3-Chlorophenyl)pentane-1,5-diol (258 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a white solid (192 mg, 0.522 mmol, 87% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.10 (m, 3H, ArCH x 3), 7.03 (dt, *J* = 7.5, 1.5 Hz, 1H, ArCH), 6.53 – 6.43 (m, 1H, H_2), 2.84 – 2.71 (m, 1H, H_4), 2.71 – 2.59 (m, 1H, H_{6a}), 2.47 – 2.29 (m, 2H, H_{3a} and H_{6b}), 2.26 – 1.93 (m, 17H, H_{3a}, H_{5a} and $ArCH_3$ x 5), 1.78 – 1.65 (m, 1H, H_{5b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2 (C_7), 148.0 (ArC), 144.1 (C_2), 140.6 (ArC), 138.1 (C_1), 135.3 (ArC), 134.4 (ArC), 132.8 (ArC x 2), 129.9 (ArC), 129.3 (ArC), 129.2 (ArC), 127.1 (ArC), 126.7 (ArC), 125.3 (ArC),

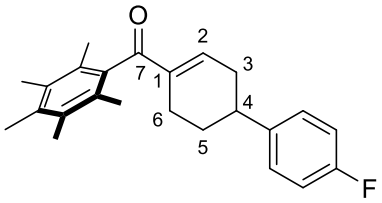
39.2 (C_4), 34.0 (C_3), 29.2 (C_5), 22.9 (C_6), 17.7 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 367.1823; $C_{24}H_{28}O^{35}Cl$ requires 367.1823, Δ -0.19 ppm

IR (film) ν_{max}/cm^{-1} 2927, 1856, 1691, 1686, 1596, 1448, 830, 656.

m.p.: 98-100 °C

(4'-Fluoro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone 525



3-(4-Fluorophenyl)pentane-1,5-diol (238 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (88 mg, 0.25 mmol, 42% yield).

1H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.01 (m, 2H, ArCH x 2), 6.97 – 6.85 (m, 2H, ArCH x 2), 6.48 (dq, *J* = 6.0, 2.0 Hz, 1H, H_2), 2.76 (ddq, *J* = 14.5, 8.0, 3.0 Hz, 1H, H_4), 2.71 – 2.61 (m, 1H, H_{6a}), 2.45 – 2.28 (m, 2H, H_{6b}, H_{3a}), 2.24 – 1.94 (m, 17H, $ArCH_3$ x 5, H_{3b}, H_{5a}), 1.69 (dtd, *J* = 13.0, 11.0, 5.5 Hz, 1H, H_{5b}).

13C NMR (101 MHz, $CDCl_3$) δ 203.1 (C_7), 161.4 (d, *J* = 244.0 Hz, ArC), 144.2 (C_2), 141.6 (d, *J* = 3.0 Hz, ArC), 140.5 (ArC), 138.0 (C_1), 135.1 (ArC), 132.7 (ArC), 132.7 (ArC), 128.2 (d, *J* = 7.7 Hz, ArC x 2), 128.1 (ArC x 2), 115.3 (d, *J* = 21.0 Hz, ArC x 2), 38.7 (C_4), 34.3 (C_3), 29.5 (C_5), 23.0 (C_6), 17.5 ($ArCH_3$ x 2), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

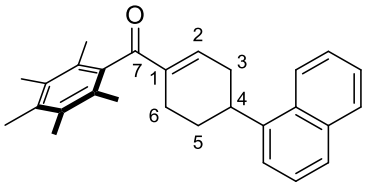
^{19}F NMR (377 MHz, $CDCl_3$) δ -116.9.

HRMS (ESI+): Found $[M+H]^+$ = 351.2119; $C_{24}H_{28}OF$ requires 351.2119, Δ 0.12 ppm

IR (film) ν_{max}/cm^{-1} 2928, 2860, 1653, 1637, 1510, 1381, 1627, 1182, 1159, 833

m.p.: 198-200 °C

(4-(Naphthalen-1-yl)cyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 526



3-(Naphthalen-1-yl)pentane-1,5-diol (276 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (50→70% CH_2Cl_2/pentane) as a white solid (117 mg, 0.306 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 1H, ArCH), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H, ArCH), 7.66 (d, *J* = 8.2 Hz, 1H, ArCH), 7.50 – 7.25 (m, 4H, ArCH x 4), 6.57 (qd, *J* = 3.0, 1.0 Hz, 1H, H_2), 3.62 (tdd, *J* = 10.5, 5.0, 2.5 Hz, 1H, H_4), 2.71 (dtdd, *J* = 18.0, 4.5, 2.5, 1.0 Hz, 1H, H_{6a}), 2.60 (dtt, *J* = 19.0, 5.5, 2.0 Hz, 1H, H_{3a}), 2.49 (ddddt, *J* = 14.5, 10.9, 5.7, 3.7, 2.1 Hz, 1H, H_{6b}), 2.39 – 2.26 (m, 1H, H_{3b}), 2.24 – 2.09 (m, 10H, $ArCH_3$ x 3, H_{5a}), 2.09 – 1.85 (m, 7H, $ArCH_3$ x 2, H_{5b}).

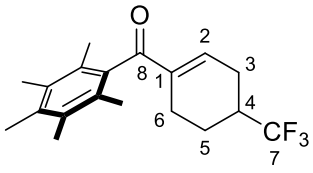
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2 (C_7), 144.7 (C_2), 141.6 (ArC), 140.6 (ArC), 138.1 (C_1), 135.1 (ArC), 134.0 (ArC), 132.7 (ArC), 132.7 (ArC), 131.4 (ArC), 129.2 (ArC), 129.1 (ArC x 2), 126.9 (ArC), 126.0 (ArC), 125.6 (ArC), 125.5 (ArC), 123.0 (ArC), 122.4 (ArC), 34.2 (C_4), 34.0 (C_3), 28.9 (C_5), 23.3 (C_6), 17.6 ($ArCH_3$), 17.6 ($ArCH_3$), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 383.2368; $C_{28}H_{31}O_2$ requires 383.2369, Δ -0.33 ppm

IR (film) ν_{max}/cm^{-1} 2927, 1652, 1636, 1379, 1267, 1183, 856, 797, 778

m.p.: 156-158 °C

(2,3,4,5,6-Pentamethylphenyl)(4-(trifluoromethyl)cyclohex-1-en-1-yl)methanone 527



3-(Trifluoromethyl)pentane-1,5-diol (206 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (5 → 8% Et_2O/pentane) as a white solid (81 mg, 0.25 mmol, 42% yield). Additionally, (2,3,4,5,6-pentamethylphenyl)(p-tolyl)methanone was

isolated as a white solid (16 mg, 0.060 mmol, 10% yield) and 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one) as a white solid (25.0 mg ,0.126, 21% yield).

^{1}H NMR (400 MHz, $CDCl_3$) 6.49 – 6.40 (m, 1H, H_2), 2.88 – 2.77 (m, 1H, H_{6a}), 2.43 – 2.26 (m, 4H, H_3 x 2, H_4, H_{6b}), 2.26 – 2.23 (m, 4H, $ArCH_3$, H_{5a}), 2.14 (s, 6H, $ArCH_3$ x 2), 2.02 (s, 6H, $ArCH_3$ x 2), 1.59 (dtd, *J* = 13.0, 11.5, 5.5 Hz, 1H, H_{5b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7 (C_8), 141.2 (C_2), 140.5 (C_1), 137.6 (ArC), 135.4 (ArC), 132.8 (ArC x 2), 127.6 (q, J= 278.0 Hz, C_7), 127.1 (ArC x 2), 37.97 (q, *J* = 27.4 Hz, C_4), 25.2 (C_3), 21.7 (C_6), 21.1 (C_5), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.0 ($ArCH_3$ x 2).

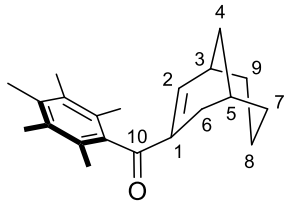
^{19}F NMR (377 MHz, $CDCl_3$) δ -73.5.

HRMS (ESI+): Found $[M+H]^+$ = 325.1773; $C_{19}H_{24}OF_3$ requires 325.1774, Δ -0.23 ppm

IR (film) ν_{max}/cm^{-1} 2935, 2875, 1701, 1658, 1436, 1331, 1273, 1191, 1116, 856

m.p.: 94-96 °C

Bicyclo[3.3.1]non-2-en-3-yl)(2,3,4,5,6-pentamethylphenyl)methanone 530



Cyclohexane-1,3-diyldimethanol (173 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a white solid (127 mg, 0.246 mmol, 41% yield, as a 47:53 inseparable mixture with 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 6.5, 2.0 Hz, 1H, H_2), 2.64 (dd, *J* = 19.0, 7.0 Hz, 1H, H_{6a}), 2.39 (d, *J* = 19.0 Hz, 1H, H_{6b}), 2.49-2.43 (m, 1H, H_3), 2.25 – 2.22 (m, 4H, $ArCH_3$, H_5), 2.19 (s, 6H, $ArCH_3$ x 2), 2.06 (s, 3H, $ArCH_3$), 2.04 (s, 3H, $ArCH_3$) 1.73 – 1.17 (m, 8H, H_4 x 2, H_7 x 2, H_8 x 2, H_9 x 2).

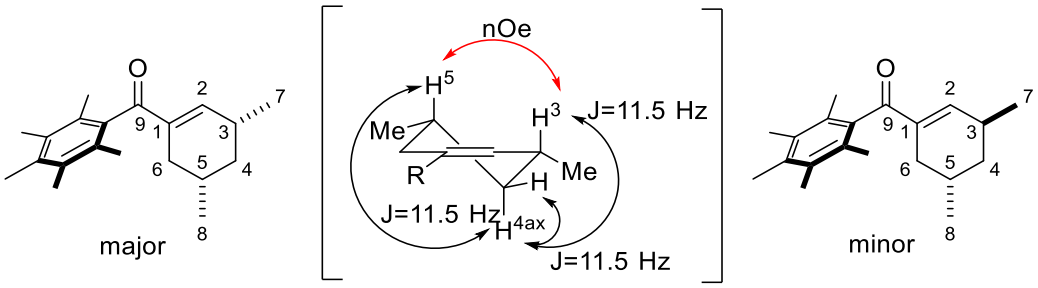
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3 (C_{10}), 149.3 (C_2), 142.5 (C_1), 138.2 (ArC), 134.9 (ArC), 132.6 (ArC), 132.5 (ArC), 129.2 (ArC), 129.1 (ArC), 33.8 (C_4), 30.9 (C_6), 30.5 (C_3), 29.4 (C_7), 28.8 (C_9), 26.4 (C_5), 18.4 (C_8), 17.6 ($ArCH_3$), 17.5 ($ArCH_3$), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 297.2213; $C_{21}H_{29}O$ requires 297.2213, Δ -0.13 ppm

IR (film) ν_{max}/cm^{-1} 2926, 2849, 1653, 1634, 1450, 1381, 1307, 1266, 1195, 1167, 1069

m.p.: 82-84 °C

(3,5-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 531



3,6-Dimethylheptane-1,5-diol (192 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a white solid (104 mg, 0.366 mmol, 61% yield, inseparable diastereomeric mixture with 66:34 d.r). The relative stereochemistry was assigned by *J*-coupling constant analysis.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (td, *J* = 2.0, 1.0 Hz, 1H, H_2), 2.72 – 2.63 (m, 1H, H_{6a}), 2.47 – 2.31 (m, 1H, H_3), 2.24 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.01 (s, 6H, $ArCH_3$ x 2), 1.80 (ddd, *J* = 11.5, 4.0, 2.5 Hz, 1H, H_{4eq}), 1.78 – 1.66 (m, 2H, H_5, H_{6b}), 1.06 (d, *J* = 6.5 Hz, 3H, H_8 x 3), 0.96 (d, *J* = 7.0 Hz, 3H, H_7 x 3), 0.85 (q, *J* = 11.5 Hz, 1H, H_{4ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C_9), 150.6 (C_2), 139.8 (C_1), 138.4 (ArC), 135.0 (ArC), 132.7 (ArC x 2), 129.3 (ArC), 129.1 (ArC), 40.1 (C_4), 32.8 (C_3), 31.2 (C_6), 29.0 (C_5), 22.2 (C_8), 20.8 (C_7), 17.7 ($ArCH_3$), 17.6 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the Ar-C(O) axis.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (td, *J* = 4.0, 2.0Hz, 1H, H_2), 2.66 – 2.55 (m, 1H, H_{6a}), 2.47 – 2.38 (m, 1H, H_3), 2.24 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.01 (s, 6H, $ArCH_3$ x 2), 1.96 – 1.83 (m, 2H, H_5, H_{6b}), 1.49 – 1.39 (m, 2H, H_4 x 2), 1.03 (d, *J* = 6.5 Hz, 3H, H_8 x 3), 0.99 (d, *J* = 7.0 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (C_9), 150.1 (C_2), 139.0 (C_1), 138.4 (ArC), 135.0 (ArC), 132.7 (ArC x 2), 129.3 (ArC), 129.2 (ArC), 37.2 (C_4), 30.6 (C_6), 29.7 (C_3), 24.4 (C_5), 21.2 (C_8), 20.4 (C_7), 17.6 ($ArCH_3$), 17.6

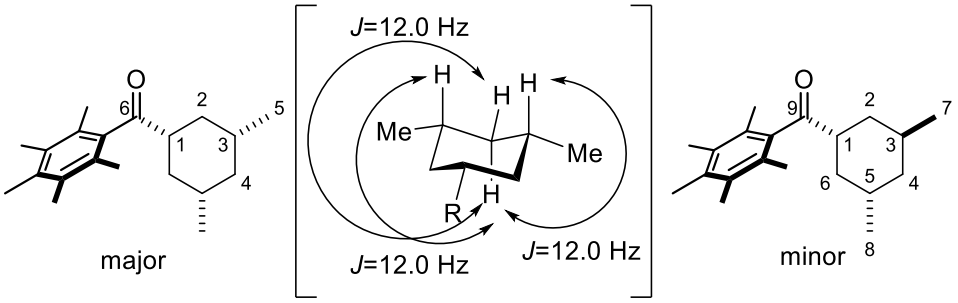
($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the Ar-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 285.2210; $C_{20}H_{29}O$ requires 285.2213, Δ –0.99 ppm

IR (film) ν_{max}/cm^{-1} 2953, 2925, 1652, 1630, 1455, 1380, 1308, 1268, 1182, 1026, 699

m.p.: 103-105 °C

3,5-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone 533



A microwave vial was charged with (3,5-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (20 mg, 0.07 mmol, 1 eq.), MeOH (0.25 mL), dry THF (0.75 mL), and $NaBH_4$ (40 mg, 0.7 mmol, 10 eq.). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum), fitted with an argon balloon and heated at 60 °C for 1h. The reaction mixture was then cooled to RT, and filtered through a silica plug, washing with Et_2O. The title compound was afforded after purification by FCC (3% Et_2O)/pentane) as a white solid, and an inseparable mixture of diastereomers (16 mg, 0.056 mmol, 80% yield, 67:33 d.r).

Data for major diastereomer:

^1H NMR ($CDCl_3$, 400 MHz) δ = 2.72 (1H, tt, *J* = 12.5, 3.5 Hz, H_1), 2.24 (3H, s, $ArCH_3$), 2.19 (6H, s, $ArCH_3$ x 2), 2.09 (6H, s, $ArCH_3$ x 2), 1.86 (2H, broad d, *J* = 12.0 Hz, H_{2eq} x 2), 1.65 (1H, broad d, *J* = 12.0 Hz, H_{4eq}), 1.47–1.35 (2H, m, H_3 x 2), 1.04 (2H, q, *J* = 12.5 Hz, 2 × H_{2ax}), 0.91 (6H, d, *J* = 6.5 Hz, H_5 x 6), 0.59 (1H, q, *J* = 12.0 Hz, H_{4ax}).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.9 (C_6), 140.4 (ArC), 135.5 (ArC), 133.2 (ArC x 2), 128.3 (ArC x 2), 53.3 (C_1), 43.7 (C_4), 36.2 (C_2 x 2), 32.3 (C_3 x 2), 22.6 (C_5 x 2), 18.1 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.2 ($ArCH_3$ x 2).

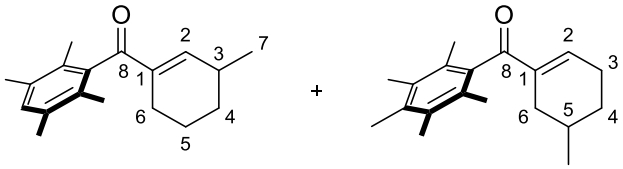
Diagnostic peaks for minor diastereomer:

^{1}H NMR (CDCl3, 400 MHz) δ = 2.92 (1H, tt, *J* = 1201, 3.5 Hz, H_1), 0.96 (3H, d, *J* = 7.0 Hz, H_8 x 3), 0.88 (3H, d, *J* = 6.5 Hz, H_7 x 3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.5 (C_9), 47.6 (C_1), 22.9 (C_7), 18.5 (C_8).

The spectroscopic data matched that previously reported in the literature.[84]

(3-Methylcyclohex-1-en-1-yl) (2,3,4,5,6-pentamethylphenyl)methanone 535 and
(5 Methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 536



535 **536**

Method 1: 2-Methylpentane-1,5-diol (142 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4% pentane: Et_2O) as a white solid (143 mg, 0.528 mmol, 88% yield, inseparable regioisomeric mixture 78:22 of **535**:**536**).

Method 2: 5-Methyltetrahydro-*2H*-pyran-2-ol (143 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (114 mg, 0.420 mmol, 70% yield, inseparable regioisomeric mixture 75:25 of **535**:**536**).

Method 3: 3-Methyltetrahydro-*2H*-pyran-2-ol (143 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (120 mg, 0.444 mmol, 74% yield, inseparable regioisomeric mixture 57:43 of **535**:**536**).

Major regioisomer 535: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 – 6.29 (m, 1H, H_2), 2.53 – 2.40 (m, 1H, H_{6a}), 2.38 – 2.15 (m, 11H, H_3, H_{6b}, $ArCH_3$ x 3), 2.01 (s, 6H, $ArCH_3$ x 2), 1.92 – 1.77 (m, 2H, H_{4a}, H_{5a}), 1.67 – 1.49 (m, 1H, H_{4b}), 1.32 – 1.15 (m, 1H, H_{5b}), 0.97 (d, *J* = 7.0 Hz, 2H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (C_8), 150.7 (C_2), 139.8 (ArC), 138.3 (C_1), 135.0 (ArC), 132.7 (ArC x 2), 129.3 (ArC), 129.2 (ArC), 31.3 (C_3), 30.5 (C_5), 22.6 (C_6), 20.9 (C_4), 20.6 (C_7), 17.6 ($ArCH_3$), 17.6 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

Diagnostic peaks for minor regioisomer 536: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 – 6.45 (m, 1H, H_2), 2.74 – 2.62 (m, 1H, H_{6a}), 1.77 – 1.66 (m, 1H, H_{5a} or H_{4a}), 1.06 (d, *J* = 6.4 Hz, 3H, H_7 x 3).

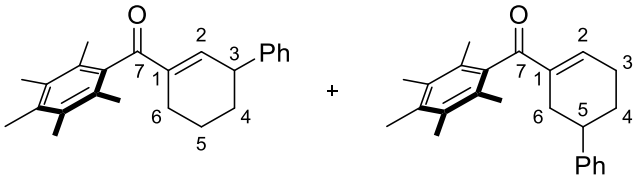
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (C_2), 140.3 (C_1), 21.6 (C_7)

HRMS (ESI+): Found $[M+H]^+$ = 271.2054; $C_{19}H_{27}O$ requires 271.2056, Δ –0.95 ppm

IR (film) ν_{max}/cm^{-1} 2926, 2856, 1654, 1634, 1455, 1308, 1268, 1192

m.p.: 96-98 °C

(2,3,4,5,6-Pentamethylphenyl)(1,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)methanone 537 and (2,3,4,5,6-pentamethylphenyl)(1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)methanone 738



537 **538**

2-Phenylpentane-1,5-diol (216 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a colourless oil that solidified on standing (86.0 mg, 0.258 mmol, 43% yield, inseparable regioisomeric mixture 74:26 of **537**:**538**)

Major regioisomer 537: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 3H, ArCH x 3), 7.10 – 7.02 (m, 2H ArCH x 2), 6.51 (dt, *J* = 3.5, 1.5 Hz, 1H, H_2), 3.53 (ddq, *J* = 8.5, 6.0, 3.0 Hz, 1H, H_3), 2.69 – 2.54 (m, 1H, H_{6a}), 2.52 – 2.38 (m, 1H, H_{6b}), 2.19 (s, 3H, $ArCH_3$), 2.14 (s, 6H, $ArCH_3$ x 2), 2.11 (s, 3H $ArCH_3$), 2.06 (s, 1H, H_{4a}), 2.04 (s, 3H $ArCH_3$), 1.93 (ddq, *J* = 14.5, 7.5, 2.5 Hz, 1H, H_{5a}), 1.83 – 1.63 (m, 1H, H_{5b}), 1.62 – 1.50 (m, 1H, H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C_7), 147.1 (C_2), 144.8 (ArC), 141.5 (C_1), 138.0 (ArC), 135.2 (ArC), 132.8 (ArC x 2), 128.7 (ArC x 2), 128.6 (ArC x 2), 127.9(ArC x 2), 126.6 (ArC), 43.2 (C_3), 32.3 (C_5), 22.6 (C_6), 21.0 (C_4), 17.7 ($ArCH_3$ x 2), 17.6 ($ArCH_3$), 16.7 ($ArCH_3$), 16.0 ($ArCH_3$).

Diagnostic peaks for minor regioisomer 538: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 – 6.53 (m, 1H, H_2), 3.00 – 2.89 (m, 1H, H_{3a}), 2.90 – 2.77 (m, 1H, H_5), 2.60 – 2.48 (m, 1H, H_{3b}), 2.38 – 2.31 (m, 2H, H_6 x 2).

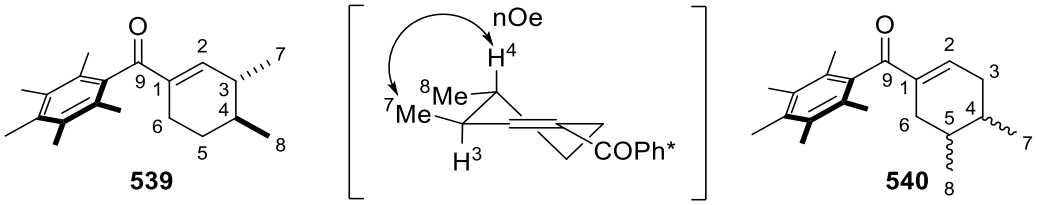
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3 (C_7), 145.0 (C_2), 39.6 (C_5), 30.3 (C_3), 27.0 (C_6).

HRMS (ESI+): Found $[M+H]^+$ = 333.2212; $C_{24}H_{29}O$ requires 333.2219, Δ –0.3 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2931, 1654, 1635, 1380, 1313, 1271, 1181, 756, 700

((3,4-*trans*)-3,4-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 539

(4,5-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 540



2,3-Dimethylpentane-1,5-diol (159 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (3→4% Et_2O/pentane) as a white solid (154 mg, 0.540 mmol, 90% yield, 2:1 inseparable mixture of regioisomers **539**:**540**; major regioisomer **539** >20:1 d.r., minor regioisomer **540** 1:1 d.r.).

Major regioisomer 539: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (dt, *J* = 3.0, 1.0 Hz, 1H, H_2), 2.63 – 2.52 (m, 1H, H_{6a}), 2.38 – 2.26 (m, 1H, H_{6b}), 2.24 (s, 3H, $ArCH_3$), 2.19 (s, 6H, $ArCH_3$ x 2), 2.02 (s, 6H, $ArCH_3$ x 2), 1.95 – 1.77 (m, 2H, H_3, H_{5a}), 1.37 – 1.22 (m, 2H, H_4, H_{5b}), 1.01 (d, *J* = 6.0 Hz, 3H, H_8 x 3), 0.99 (d, *J* = 7.0 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_9), 150.6 (C_2), 139.5 (ArC), 138.4 (C_1), 135.0 (ArC), 132.6 (ArC x 2), 129.2 (ArC), 129.1 (ArC), 38.7 (C_3), 35.3 (C_4), 30.0 (C_5), 22.4 (C_6), 20.1 (C_8), 19.0 (C_7), 17.6 ($ArCH_3$), 17.5 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

diagnostic peaks for minor regioisomer 540 (1:1 mixture of diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 – 6.41 (m, 1H, H_2) , 6.39 – 6.36 (m, 1H, $H_{2'}$), 2.74 – 2.65 (m, 1H, H_6 or $H_{6'}$), 1.04 (d, *J* = 6.0 Hz, 3H, CH_3 or $CH_{3'}$), 0.92 – 0.84 (m, 6H, CH_3x 2 or $CH_{3'}$ x 2).

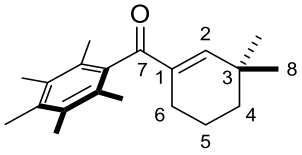
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C_9 or $C_{9'}$), 203.6(C_9 or $C_{9'}$), 150.7 (C_2), 145.0($C_{2'}$), 35.1 (C_3 or $C_{3'}$), 31.0 (C_6 or $C_{6'}$), 19.5 (CH_3 or $CH_{3'}$), 19.3 (CH_3 or $CH_{3'}$), 16.5 (CH_3 or $CH_{3'}$), 14.7 (CH_3 or $CH_{3b'}$).

IR (film) ν_{max}/cm^{-1} 2954, 2925, 2872, 1653, 1636, 1455, 1383, 1306, 1266, 1192, 854

HRMS (ESI+): Found $[M+H]^+$ = 285.2209; $C_{20}H_{29}O$ requires 285.2213, Δ -1.32 ppm

m.p.: 98-100 °C

(3,3-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 541



2,2-Dimethylpentane-1,5-diol (158 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1.** The title compound was afforded after purification by FCC (2→3% Et_2O/pentane) as a white solid (128 mg, 0.450 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (t, *J* = 2.0 Hz, 1H, H_2), 2.36 (td, *J* = 6.5, 2.0 Hz, 2H, H_6 x 2), 2.25 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.00 (s, 6H, $ArCH_3$ x 2), 1.76 – 1.66 (m, 2H, H_5 x 2), 1.52 – 1.44 (m, 2H, H_4 x 2), 0.97 (s, 6H, H_8 x 6).

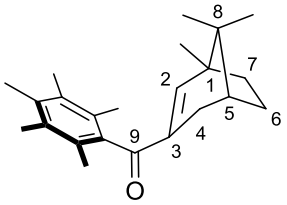
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2 (C_7), 154.2 (C_2), 138.4 (ArC), 138.2 (C_1), 135.0 (ArC), 132.7 (ArC x 2), 129.3 (ArC x 2), 36.8 (C_4), 33.0 (C_3), 28.9 (2x C_8), 22.8 (C_6), 19.3 (C_5), 17.5 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x2).

HRMS (ESI+): Found [M+H]+ = 285.2211; $C_{20}H_{29}O$ requires 285.2213, Δ –0.61 ppm

IR (film) ν_{max}/cm^{-1} 2954, 1651, 1631, 1456, 699

m.p.: 129-130 °C

(2,3,4,5,6-Pentamethylphenyl)((1S,5S)-1,8,8-trimethylbicyclo[3.2.1]oct-2-en-3-yl)methanone 543



((1*R*,3*S*)-1,2,2-Trimethylcyclopentane-1,3-diyl)dimethanol (207 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**, heating for 48 h instead of 24 h. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a white solid (145 mg, 0.282 mmol, 47% yield, 1:1 inseparable mixture with 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.28 (1H, s, H_2), 2.67-258 (1H, m, H_{4a}), 2.38-2.30 (1H, m, H_{4b}), 2.24 (3H, s, $ArCH_3$), 2.20 (3H, s, $ArCH_3$), 2.18 (3H, s, $ArCH_3$), 2.06–1.92 (8H, m, $ArCH_3$ x 2, H_{6a} and H_5), 1.82 – 1.67

(2H, m, H_7 x 2), 1.34 (1H, ddd, *J* = 13.0, 9.0, 6.0 Hz, H_{6b}), 0.94 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.90 (3H, s, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 203.9 (C_9), 156.9 (C_2), 138.2 (ArC), 137.4 (C_3), 135.0 (ArC), 132.7 (ArC), 132.6 (ArC), 129.2 (ArC), 129.0 (ArC), 46.0 (C_1), 43.7 (C_5), 42.5 (C_8), 40.8 (C_7), 32.3 (C_4), 29.0 (C_6), 23.4 (CH_3), 19.3 (CH_3), 17.9 (CH_3), 17.5 ($ArCH_3$), 17.5 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the C_1-C(O) axis.

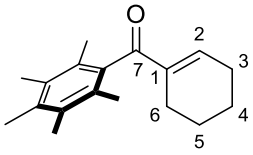
HRMS (ESI+): Found $[M+H]^+$ = 325.2522; $C_{23}H_{33}O$ requires 325.2526, Δ -1.31 ppm

IR (film) ν_{max}/cm^{-1} 2947, 1865, 1650, 1628, 1445, 1389, 1307, 1272, 1166, 865

m.p.: 58-60 °C

$[\alpha]^{25}_{589}$= −45.6 (c=1.0, $CHCl_3$)

Cyclohex-1-en-1-yl(2,3,4,5,6-pentamethylphenyl)methanone 358



Commercial pentane-1,5-diol (125mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4% pentane/Et_2O) as a white solid (75 mg, 0.060 mmol, 10% yield, inseparable mixture from 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one) in 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (tt, *J* = 4.0, 1.5 Hz, 1H, H_2), 2.43 (ddt, *J* = 6.0, 4.0, 2.0 Hz, 2H, H_6 x 2), 2.28 – 2.11 (m, 11H, $ArCH_3$ x 3, H_3 x 2), 2.03 (s, 6H, $ArCH_3$ x 2), 1.76 – 1.68 (m, 2H, H_4 x 2), 1.65 (tdd, *J* = 8.0, 5.0, 2.0 Hz, 2H, H_5 x 2).

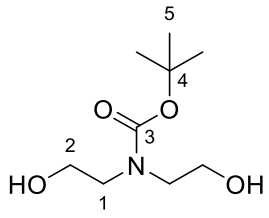
^{13}C NMR (101 MHz, CDCl3) δ 203.7 (C_7), 145.7 (C_2), 140.7 (ArC), 138.3 (C_1), 135.0 (ArC), 132.6 (ArC x 2), 129.2 (ArC x 2), 26.4 (C_3), 22.5 (C_6), 22.1 (C_4), 21.8 (C_5), 17.6 ($ArCH_3$ x 2), 17.2 ($ArCH_3$), 16.8 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 257.1899; $C_{18}H_{25}O$ requires 257.1900, Δ -0.2 ppm

IR (film) ν_{max}/cm^{-1} 2981, 1696, 1652, 1384, 1350, 1268, 1167, 935

m.p.: 70-72 °C

Tert-butyl bis(2-hydroxyethyl)carbamate 556



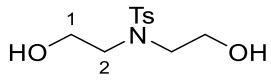
Diethanolamine (4.21 g, 40 mmol, 1 eq.) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (9.6 g, 44 mmol, 1.1 eq.) in dry THF (100 mL, 0.4 M) at 0 °C. The reaction was then warmed to RT and stirred for 15 h. The solvent was then removed under reduced pressure. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a colourless oil (5.8 g, 28.3 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 6H, H_2 x 4, OH x 2), 3.41 (s, 4H, H_1 x 4), 1.45 (s, 9H, H_5 x 9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C_3), 80.5 (C_4), 62.1 (C_2 x 2), 52.4 (C1 x 2), 28.6 (C_5 x 3).

The spectroscopic data matched that previously reported in the literature.[161]

***N,N*-Bis(2-hydroxyethyl)-4-methylbenzenesulfonamide 557**



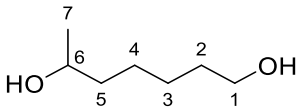
To a 100mL RBF charged with diethanolamine (2.50 g, 23.8 mmol, 1.2 eq.), trimethylamine (6.0 g, 60 mmol, 3 eq.) and CH_2Cl_2 (15 mL), was added tosyl chloride (3.8 g, 20 mmol, 1 eq.) in CH_2Cl_2 (15 mL) and then stirred at RT for 4h. The reaction mixture was then diluted with water (10 mL), extracted with CH_2Cl_2 (15 mL x 3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a white solid (4.72 g, 18.2 mmol, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 7.31 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 3.96 (t, *J* = 5.0 Hz, 2H, OH x 2), 3.84 (q, *J* = 5.0 Hz, 4H, H_1 x 4), 3.25 (t, *J* = 5.0 Hz, 4H, H_2 x 4), 2.42 (s, 3H, $ArCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (ArC), 135.4 (ArC), 130.0 (ArC x 2), 127.4 (ArC x 2), 62.3 (C_1 x 2), 53.1 (C_2 x 2), 21.6 ($ArCH_3$).

The spectroscopic data matched that previously reported in the literature.[162]

Heptane-1,6-diol 567



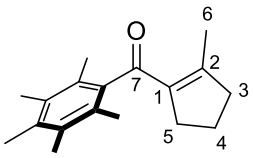
6-Oxoheptanoic acid (5.0 g, 35 mmol, 1 eq.), dry THF (115 mL) and $LiAlH_4$ (3.90 g, 105 mmol, 3 eq.) were subjected to **General Procedure 4.** The reaction was stirred at RT for 24 h. The title compound was afforded after purification by FCC (4% MeOH/CH_2Cl_2) as a colourless oil (1.60 g, 12.1 mmol, 35% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 – 3.73 (m, 1H, H_6), 3.64 (t, *J* = 6.5 Hz, 2H, H_1 x 2), 3.47 (s, 1H, OH), 1.73 (s, 1H, OH), 1.64 – 1.27 (m, 8H, H_2 x 2, H_3 x 2, H_4 x 2, H_5 x 2), 1.18 (d, *J* = 6.0 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.2 (C_6), 63.0 (C_1), 39.4 (C_5), 32.8 (C_2), 25.9 (C_3 or C_4), 25.6 (C_3 or C_4), 23.7 (C_7).

The spectroscopic data identical to previously reported in the literature.[163]

(2-Methylcyclopent-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 569



Pentane-1,4-diol (125mg, 1.2 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as an inseparable mixture of Ph*C(O)Me (0.23 mmol, 39% yield) and **569** as a white solid (58 mg, 0.090 mmol, 15% yield). The yield and mmol of each component was determined by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (ddq, *J* = 9.5, 6.0, 2.0 Hz, 2H, H_5 x 2), 2.52 – 2.43 (m, 2H, H_3 x 2), 2.17 – 1.99 (m, 9H, $ArCH_3$ x 3), 1.97 (s, 6H $ArCH_3$ x 2), 1.74 (p, *J* = 8.0 Hz, 2H, H_4 x 2), 1.53 – 1.42 (m, 3H, H_6 x 3).

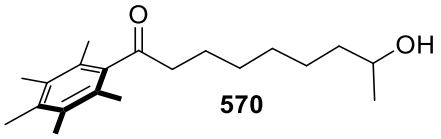
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6 (C_7), 156.9 (C_2), 140.8 (ArC), 137.6 (C_1), 135.0 (ArC), 133.0 (ArC x 2), 128.0 (ArC x 2), 42.3 (C_3), 33.5 (C_5), 21.1 (C_4), 17.1 (ArC x 2), 16.8 (ArC), 16.1 (ArC x 2), 16.0 (C_6).

HRMS (ESI+): Found $[M+H]^+$ = 257.1900; $C_{18}H_{25}O$ requires 257.1900, Δ -0.15 ppm

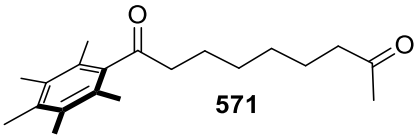
IR (film) ν_{max}/cm^{-1} 2982, 2860, 1696, 1614, 1416, 1350, 1167, 949

m.p.: 72-74 °C

8-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one 570 and (2,3,4,6-tetramethyl-5-(10-oxoundecanoyl)phenyl)methylium 571



570



571

Heptane-1,6-diol (79 mg, 0.6 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was not observed. Purification by FCC (5 → 40% Et_2O/pentane) afforded 8-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one **570** as a colourless oil (32mg, 0.10 mmol, 33% yield), (2,3,4,6-tetramethyl-5-(10-oxoundecanoyl)phenyl)methylium **571** as a colourless oil (17 mg, 0.056 mmol, 19%), and 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **187** as a white solid (18 mg, 0.094 mmol, 32% yield).

8-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one 570

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 – 3.69 (m, 1H, H_8), 2.67 (t, *J* = 7.5 Hz, 2H, H_2 x 2), 2.23 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.09 (s, 6H, $ArCH_3$ x 2), 1.78 – 1.65 (m, 2H, H_3 x 2), 1.65 – 1.23 (m, 7H, OH, H_4 x 2, H_5 x 2, H_7 x 2), 1.19 (d, *J* = 6.0 Hz, 3H, H_9 x 3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.3 (C_1), 141.0 (ArC), 135.4 (ArC), 133.2 (ArC x 2), 127.4 (ArC x 2), 67.6 (C_8), 45.7 (C_2), 39.4 (C_5), 29.3 (C_7), 25.8 (C_4), 23.6 (C_9), 23.3 (C_5), 17.3 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 305.2475 ; $C_{20}H_{33}O_2$ requires 305.2475, Δ 4.50 ppm

IR (film) ν_{max}/cm^{-1} 3425, 2941, 2860, 1693, 1456, 1377, 1303, 1127, 939

(2,3,4,6-tetramethyl-5-(10-oxoundecanoyl)phenyl)methylium 571

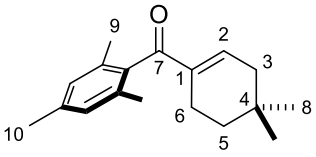
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (t, J = 7.5 Hz, 2H, H_2 x 2), 2.43 (t, J = 7.5 Hz, 2H, H_2 x 2), 2.23 (s, 3H, H_9 x 3), 2.18 (s, 6H $ArCH_3$ x 2), 2.13 (s, 3H $ArCH_3$), 2.09 (s, 6H $ArCH_3$ x 2), 1.71 (p, J = 7.5 Hz, 2H, H_3 x 2), 1.59 (p, J = 7.5 Hz, 2H, H_6 x 2), 1.42 – 1.26 (m, 4H, H_4 x 2, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6 (C_1), 209.3 (C_8), 140.9 (ArC), 135.5 (ArC), 133.2 (ArC x 2), 127.4 (ArC x 2), 45.7 (C_2), 43.8 (C_7), 29.8 (C_9), 29.2 (C_5), 29.1 (C_4), 23.8 (C_6), 23.2 (C_3), 17.3 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+Na]^+$ = 325.21381; $C_{20}H_{30}O_2Na$ requires 325.21380, Δ 0.01 ppm

IR (film) ν_{max}/cm^{-1} 2923, 2851, 1701, 1463, 1407, 1260, 1166, 1120

(4,4-dimethylcyclohex-1-en-1-yl)(mesityl)methanone 573



A 2–5 mL Biotage® microwave vial was charged with CataCXium® A (2.2 mg, 0.006 mmol, 2 mol%), 3,3-dimethylpentane-1,5-diol (79 mg, 0.6 mmol, 2 eq.), 2-Acetylmesitylene (49 mg, 0.3 mmol, 1 eq.), $[Ir(cod)Cl]_2$ (1 mg, 0.0015 mmol, 0.5 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) toluene (1.2 mL, 0.25 M). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and the vial was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was filtered through a silica plug, eluting with diethyl ether, and concentrated in vacuo. Purification by FCC (3% Et_2O/pentane) afforded the title compound as a colourless oil (66 mg, 0.257 mmol, 86% yield).

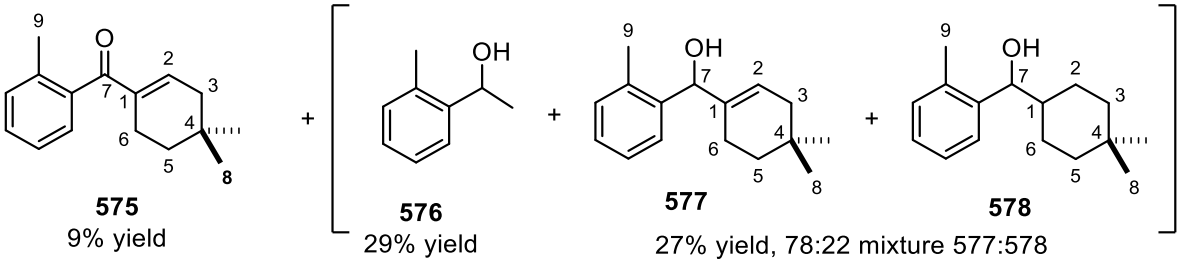
^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H, ArCH x 2), 6.43 (tt, J = 4.0, 1.5 Hz, 1H, H_2), 2.44 (tq, J = 6.0, 2.0 Hz, 2H, H_6 x 2), 2.28 (s, 3H, H_{10} x 3), 2.10 (s, 6H, H_9 x 6), 1.95 (dt, J = 4.5, 2.5 Hz, 2H, H_3 x 2), 1.48 (t, J = 6.5 Hz, 2H, H_5 x 2), 0.93 (s, 6H, H_8 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1 (C_7), 144.6 (C_2), 139.3 (ArC), 137.9 (ArC), 137.7 (C_1), 134.2 (ArC x 2), 128.1 (ArC x 2), 40.3 (C_3), 34.9 (C_5), 28.8 (C_4), 28.2 (C_8 x 2), 21.2 (C_{10}), 20.4 (C_6), 19.3 (C_9 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 257.19006; $C_{18}H_{25}O$ requires 257.18999, Δ 0.28 ppm

IR (film) ν_{max}/cm^{-1} 2950, 2921, 2864, 1651, 1635, 1611, 1433, 1259, 1165, 1101, 848

(4,4-dimethylcyclohex-1-en-1-yl)(*o*-tolyl)methanone 575



A 2–5 mL Biotage® microwave vial was charged with CataCXium® A (2.2 mg, 0.006 mmol, 2 mol%), 3,3-dimethylpentane-1,5-diol (79 mg, 0.6 mmol, 2 eq.), *o*-Methylacetophenone (40 mg, 0.3 mmol, 1 eq.), $[Ir(cod)Cl]_2$ (1 mg, 0.0015 mmol, 0.5 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) toluene (1.2 mL, 0.25 M).

The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and the vial was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was filtered through a silica plug, eluting with diethyl ether, and concentrated in vacuo. Purification by FCC (3→15% Et_2O/pentane) afforded (4,4-dimethylcyclohex-1-en-1-yl)(o-tolyl)methanone **575** as a colourless oil (6 mg, 0.026 mmol, 9% yield), 1-(o-tolyl)ethan-1-ol[164] **576**, as a colourless oil (12 mg, 0.088 mmol, 29% yield), and an inseparable mixture of (4,4-dimethylcyclohex-1-en-1-yl)(o-tolyl)methanol **577** and (4,4-dimethylcyclohexyl)(o-tolyl)methanol as a colourless oil **578** (19 mg, 0.081 mmol, 27% yield)

(4,4-dimethylcyclohex-1-en-1-yl)(*o*-tolyl)methanone 575

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 1H, ArCH), 7.22 – 7.13 (m, 3H, ArCH x 3), 6.41 (tt, J = 4.0, 1.5 Hz, 1H, H_2), 2.45 (ttd, J = 6.5, 2.5, 1.5 Hz, 2H, H_6 x 2), 2.26 (s, 3H, H_9 x 3), 1.99 (dt, J = 5.0, 2.5 Hz, 2H, H_3 x 2), 1.48 (t, J = 6.5 Hz, 2H, H_5 x 2), 0.95 (s, 6H, H_8 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3 (C_7), 145.7 (C_2), 140.0 (ArC), 139.0 (C_1), 135.7 (ArC), 130.6 (ArC), 129.3 (ArC), 127.6 (ArC), 125.1 (ArC), 40.4 (C_3), 35.0 (C_5), 28.8 (C_4), 28.3 (C_8 x 2), 20.9 (C_6), 19.7 (C_9).

HRMS (ESI+): Found $[M+H]^+$ = 229.15886; $C_{16}H_{21}O$ requires 229.15869, Δ 0.73 ppm

IR (film) ν_{max}/cm^{-1} 2952, 2924, 1651, 1634, 1455, 1380, 1260, 1098, 759, 732

(4,4-dimethylcyclohex-1-en-1-yl)(*o*-tolyl)methanol 577

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.5, 1.5 Hz, 1H, ArCH), 7.25 – 7.10 (m, 3H, ArCH x 3), 5.75 – 5.66 (m, 1H, H_2), 5.28 (s, 1H, H_7), 2.30 (s, 3H, H_9 x 3), 2.01 – 1.71 (m, 4H, H_3 x 2, H_6 x 3), 1.35 (t, J = 6.5 Hz, 2H, H_5 x 2), 0.90 (s, 3H, H_8 x 3), 0.85 (s, 3H, H_8 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (ArC), 137.3 (ArC), 135.6 (C_1), 130.4 (ArC), 127.3 (ArC), 126.0 (ArC), 126.0 (ArC), 123.4 (C_2), 74.8 (C_7), 39.2 (C_3), 35.5 (C_5), 28.9 (C_4), 28.6 (C_8), 28.1 (C_8), 22.8 (C_6), 19.3 (C_9).

HRMS (ESI+): Found $[M+H]^+$ = 231.13811; $C_{16}H_{23}O$ requires 231.17434, Δ 0.83 ppm

IR (film) ν_{max}/cm^{-1} 3346, 2948, 2908, 1459, 1383, 1054, 1008, 988, 782, 735

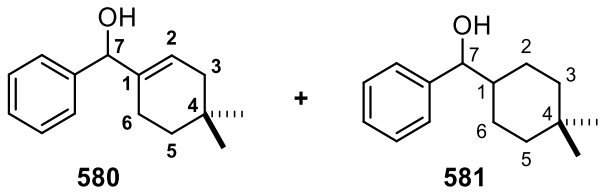
(4,4-dimethylcyclohexyl)(*o*-tolyl)methanol 578

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.5, 1.5 Hz, 1H, ArCH), 7.25 – 7.07 (m, 3H, ArCH x3), 4.69 (d, J = 7.0 Hz, 1H, H_7), 2.35 (s, 3H, H_9 x 3), 1.63 – 1.50 (m, 1H, H_1) 1.48 – 1.04 (m, 8H, H_2 x 2, H_3 x 2, H_5 x 2, H_6 x 2), 0.89 (s, 3H, H_8 x 3), 0.88 (s, 3H, H_8 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2 (ArC), 135.2 (ArC), 130.4 (ArC), 127.2 (ArC), 126.4 (ArC), 126.2 (ArC), 75.1 (C_7), 44.7 (C_1), 39.2, 39.0, 33.1 (C_8), 30.1, 25.5, 24.4, 24.4 (C_8), 19.6 (C_9).

HRMS (ESI+): Found $[M+H]^+$ = 233.15372; $C_{16}H_{25}O$ requires 233.18999, Δ 0.61 ppm

(4,4-dimethylcyclohex-1-en-1-yl)(phenyl)methanol 580 and
(4,4-dimethylcyclohexyl)(phenyl)methanol 581



580 **581**

A 2–5 mL Biotage® microwave vial was charged with CataCXium® A (2.2 mg, 0.006 mmol, 2 mol%), 3,3-dimethylpentane-1,5-diol (79 mg, 0.6 mmol, 2 eq.), acetophenone (36 mg, 0.3 mmol, 1 eq.), $[Ir(cod)Cl]_2$ (1 mg, 0.0015 mmol, 0.5 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) toluene (1.2 mL, 0.25 M). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and the vial was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was filtered through a silica plug, eluting with diethyl ether, and concentrated in vacuo. Purification by FCC (3→15% Et_2O/pentane) afforded an inseparable mixture of (4,4-dimethylcyclohex-1-en-1-yl)(phenyl)methanol **580** and (4,4-dimethylcyclohexyl)(phenyl)methanol **581** as a colourless oil (85:15 mixture, 40 mg, 0.183 mmol, 61% yield).

(4,4-dimethylcyclohex-1-en-1-yl)(phenyl)methanol 580

1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H, ArCH x 5), 5.92 – 5.75 (m, 1H, H_2), 5.16 – 5.06 (m, 1H, H_7), 1.96 – 1.69 (m, 4H, H_3 x 2, H_6 x 2), 1.32 (t, J = 6.5 Hz, 3H,H_5 x 2) 0.89 (s, 3H, CH_3), 0.85 (s, 3H, CH_3).

13C NMR (101 MHz, $CDCl_3$) δ 142.8 (ArC), 138.3 (C_1), 128.4 (ArC x 2), 127.4 (ArC), 126.4 (ArC x 2), 122.6 (C_2), 78.1 (C_7), 39.2 (C_3), 35.4 (C_5), 28.9 (C_4), 28.6 (CH_3), 28.1 (CH_3), 22.0 (C_6).

HRMS (ESI+): Found $[M+H]^+$ = 217.15873; $C_{15}H_{21}O$ requires 217.15869, Δ 0.17 ppm

IR (film) ν_{max}/cm^{-1} 3356, 2948, 2908, 1451, 1052, 1007, 760, 700

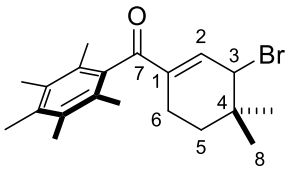
(4,4-dimethylcyclohexyl)(phenyl)methanol 581

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (dd, J = 7.5, 2.0 Hz, 1H, H_7), 1.57 – 1.47 (m, 1H, H_1), 1.46 – 1.01 (m, 8H, H_2 x 2, H_3 x 2, H_5 x 2, H_6 x 2), 0.96 (s, 3H, CH_3), 0.88 (s, 3H, CH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (ArC), 128.4 (ArC), 127.6 (ArC), 126.7 (ArC), 79.4 (C_7), 45.1, 39.0, 38.9, 33.0 (CH_3), 30.1 (C_1), 25.3, 24.7, 24.4 (CH_3).

HRMS (ESI+): Found $[M+H]^+$ = 219.17440; $C_{15}H_{23}O$ requires 217.17434, Δ 0.24 ppm

(3-Bromo-4,4-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 593



Bromine in $CHCl_3$ (1.9 mL, 0.10 M, 1.2 eq) was added dropwise at -17 °C to a 5 mL microwave vial charged with (4,4-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (50.0 mg, 0.175 mmol, 1 eq.) in $CHCl_3$ (1 mL). The reaction mixture was then warmed to room temperature, stirred for 3 hours and then concentrated *in vacuo*. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a white solid (58 mg, 0.16 mmol, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dt, *J* = 4.5, 1.8 Hz, 1H, H_2), 4.46 (dq, *J* = 4.5, 1.5 Hz, 1H, H_3), 2.67 (dddt, *J* = 19.0, 6.0, 4.5, 1.5 Hz, 1H, H_{6a}), 2.48 (dddt, *J* = 19.0, 8.5, 6.5, 2.0 Hz, 1H, H_{6b}), 2.24 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.03 (s,3H, $ArCH_3$), 1.99 (s,3H, $ArCH_3$), 1.89 (ddd, *J* = 13.5, 9.0, 6.0 Hz, 1H, H_{5a}), 1.52 (dddd, *J* = 13.5, 6.0, 4.5, 1.5 Hz, 1H, H_{5b}), 1.13 (s, 3H, H_{8a} x 3), 1.06 (s, 3H, H_{8b} x 3).

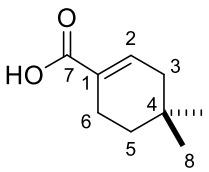
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5 (C_7), 142.6 (C_2), 139.3 (C_1), 137.4 (ArC), 135.6 (ArC), 132.9 (ArC x 2), 129.4 (ArC), 129.1 (ArC), 59.6 (C_3), 33.8 (C_4), 31.0 (C_5), (C_{8a}), 25.3 (C_{8b}), 20.3 (C_6), 17.5 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the Ar-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 363.1319; $C_{20}H_{28}O^{79}Br$ requires 363.1318, Δ 0.25 ppm

IR (film) ν_{max}/cm^{-1} 2926, 2854, 1657, 1633, 1453, 1267, 1199, 1166, 891

m.p.: 98-100 °C

4,4-Dimethylcyclohex-1-ene-1-carboxylic acid 595



(4,4-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (28.4 mg, 0.100 mmol, 1 eq.) was subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (2→4% MeOH/CH_2Cl_2) as a white solid (15.4 mg, 0.100 mmol, 100% yield). 1,2,3,4,5-Pentamethylbenzene was also isolated as a white solid (14.8 mg, 0.100 mmol, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H, OH), 7.07 (tt, *J* = 4.0, 2.0 Hz, 1H, H_2), 2.29 (tq, *J* = 6.5, 2.5 Hz, 2H, H_6 x 2), 2.00 (dt, *J* = 5.0, 2.0 Hz, 2H, H_3 x 2), 1.42 (t, *J* = 6.5 Hz, 2H, H_5), 0.92 (s, 6H, H_8 x 6).

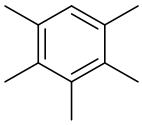
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C_7), 141.9 (C_2), 128.7 (C_1), 40.0 (C_3), 35.0 (C_5), 28.4 (C_4), 28.2 (C_8 x 2), 21.8 (C_6).

HRMS (ESI-): Found $[M+H]^-$ = 153.0922; $C_9H_{13}O_2$ requires 153.0921, Δ 0.89 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2888, 1663, 1640, 1383, 1295, 1155, 1086, 955

m.p.: 107-109 °C

1,2,3,4,5-Pentamethylbenzene 598

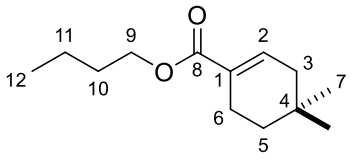


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H, ArCH), 2.41 (s, 3H, CH_3), 2.38 (s, 6H CH_3 x 2), 2.34 (s, 6H CH_3 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0 (ArC), 133.3 (ArC x 2), 132.4 (ArC x 2), 129.1 (ArCH), 20.6 (CH_3 x 2), 16.4 (CH_3), 16.0(CH_3 x 2).

The spectroscopic data matched that previously reported in the literature.[165]

Butyl 4,4-dimethylcyclohex-1-ene-1-carboxylate 596



A microwave vial was charged with (4,4-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl) methanone (50.0 mg, 0.175 mmol, 1 eq.), H_2SO_4 (98% wt., 0.3 mL), then sealed and heated at 65 °C. After 30 minutes, *n*-butanol (1 mL) was added and heated for 24 hours. The reaction mixture was then

cooled to RT, diluted with water (5 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a colourless oil (37 mg, 0.175 mmol, 100% yield).

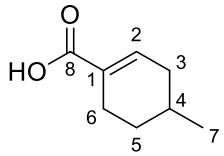
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (tt, *J* = 4.0, 2.0 Hz, 1H, H_2), 4.12 (t, *J* = 6.5 Hz, 2H, H_9 x 2), 2.28 (dddd, *J* = 9.0, 6.5, 2.5, 2.0 Hz, 2H, H_6 x 2), 1.97 (dt, *J* = 5.0, 2.5 Hz, 2H, H_3 x 2), 1.72 – 1.56 (m, 2H, H_{10} x 2), 1.49 – 1.32 (m, 4H, H_5 x 2, H_{11} x 2), 0.94 (t, *J* = 7.4 Hz, 3H, H_{12} x 3), 0.91 (s, 6H, H_7 x 6).

13C NMR (101 MHz, $CDCl_3$) δ 167.8 (C_8), 138.8 (C_2), 129.4 (C_1), 64.2 (C_9), 39.8 (C_3), 35.1 (C_5), 30.9 (C_{10}), 28.5 (C_4), 28.3 (C_7 x 2), 22.2 (C_6), 19.4 (C_{11}), 13.9 (C_{12}).

HRMS (ESI+): Found $[M+H]^+$ = 211.1695; $C_{13}H_{23}O_2$ requires 211.1693, Δ 1.20 ppm

IR (film) ν_{max}/cm^{-1} 2956, 1711, 1650, 1249, 1180, 1084, 715

4-Methylcyclohex-1-ene-1-carboxylic acid 602



(4-Methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (27.4 mg, 0.100 mmol, 1 eq.) was subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (2→5% MeOH/CH_2Cl_2) as a white solid (14.2 mg, 0.100 mmol, 100% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H, OH), 7.09 (dtd, *J* = 5.0, 2.5, 1.0 Hz, 1H, H_2), 2.47 – 2.26 (m, 2H, H_{6a}, H_{3b}), 2.26 – 2.11 (m, 1H, H_{6a}), 1.88 – 1.74 (m, 2H, H_{3b}, H_{5a}), 1.73 – 1.59 (m, 1H, H_4), 1.31 – 1.16 (m, 1H, H_{5b}), 0.98 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

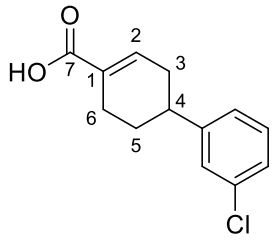
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C_8), 142.2 (C_2), 129.6 (C_1), 34.5 (C_3), 30.4 (C_5), 27.6 (C_4), 23.9 (C_6), 21.5 (C_7).

HRMS (ESI-): Found $[M-H]^-$ = 139.0764 ; $C_8H_{11}O_2$ requires 139.0765, Δ -0.72 ppm

IR (film) ν_{max}/cm^{-1} 2922, 2860, 1674, 1638, 1421, 1227, 738, 705

m.p.: 104-106 °C

3'-Chloro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-carboxylic acid 603



(3'-Chloro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone (37 mg, 0.10 mmol, 1 eq.) was subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (1% MeOH/CH_2Cl_2) as a white solid (20 mg, 0.084 mmol, 84% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ, 10.5 (s, OH), 7.21 – 7.10 (m, 4H, ArCH x 3, H_2), 7.03 (dt, *J* = 7.5, 1.5 Hz, 1H, ArCH), 2.81 – 2.63 (m, 1H, H_4), 2.56 – 2.38 (m, 2H, H_{3a}, H_{6a}), 2.36 – 2.16 (m, 2H, H_{3b}, H_{6b}), 2.03 – 1.89 (m, 1H, H_{5a}), 1.79 – 1.59 (m, 1H, H_{5b}).

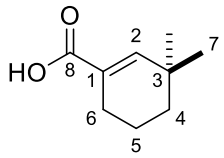
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C_7), 148.0 (ArC), 141.4 (C_2), 134.5 (C_1), 130.0 (ArC), 129.8 (ArC), 127.2 (ArC), 126.7 (ArC), 125.2 (ArC), 39.0 (C_4), 33.8 (C_3), 29.3 (C_5), 24.5 (C_6).

HRMS (ESI-): Found $[M-H]^-$ = 235.0531 ; $C_{13}H_{12}O_2Cl$ requires 235.0531, Δ -0.04 ppm

IR (film) ν_{max}/cm^{-1} 2920, 1669, 1638, 1429, 1283, 783

m.p.: 158-160 °C

3,3-Dimethylcyclohex-1-ene-1-carboxylic acid 604



(3,3-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (28.4 mg, 0.100 mmol, 1 eq.) was subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (2→4% MeOH/CH_2Cl_2) as a white solid (15.4 mg, 0.100 mmol, 100% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H, OH), 6.82 (t, *J* = 2.0 Hz, 1H, H_2), 2.20 (td, *J* = 6.0, 2.0 Hz, 2H, H_6 x 2), 1.72 – 1.62 (m, 2H, H_4 x 2), 1.47 – 1.41 (m, 2H, H_5 x 2), 1.05 (s, 6H, H_7 x 6).

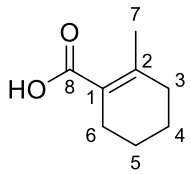
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (C_8), 151.2 (C_2), 127.6 (C_1), 36.3 (C_5), 32.8 (C_3), 29.1 (C_7 x 2), 24.1 (C_6), 19.3 (C_4).

HRMS (ESI-): Found $[M-H]^-$ = 153.0919 ; $C_9H_{13}O_2$ requires 153.0921, Δ -1.06 ppm

IR (film) ν_{max}/cm^{-1} 2935, 2853, 1687, 1641, 1423, 1286

m.p.: 76-78 °C

2-Methylcyclohex-1-ene-1-carboxylic acid 605



(2-Methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (27.4 mg, 0.100 mmol, 1 eq.) was subjected to **General Procedure 6**, heating for 1.5 h at 65 °C. The title compound was afforded after purification by FCC (2% MeOH/CH_2Cl_2) as a white solid (8.5 mg, 0.060 mmol, 60% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H, OH), 2.30 (tt, *J* = 4.5, 2.0 Hz, 2H, H_6 x 2), 2.21 – 2.11 (m, 2H, H_3 x 2), 2.11 – 2.01 (m, 3H, H_7 x 3), 1.66 – 1.53 (m, 4H, H_4 x 2, H_5 x 2).

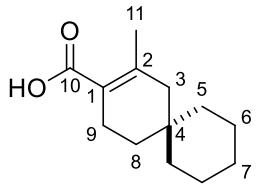
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C_8), 150.7 (C_2), 123.4 (C_1), 34.6 (C_3), 26.3 (C_6), 22.6 (C_7), 22.4 (C_5), 22.4 (C_4).

HRMS (ESI-): Found $[M-H]^-$ = 139.0763 ; $C_8H_{11}O_2$ requires 139.0765, Δ -1.19 ppm

IR (film) ν_{max}/cm^{-1} 2933, 1858, 1678, 1622, 1418, 1282, 1261, 940, 739

m.p.: 78-80 °C

2-Methylspiro[5.5]undec-2-ene-3-carboxylic acid 606



(2-Methylspiro[5.5]undec-2-en-3-yl)(2,3,4,5,6-pentamethylphenyl)methanone (33.8 mg, 0.100 mmol, 1 eq.) was subjected to **General Procedure 6**. The title compound was afforded after purification by FCC (2% MeOH/CH_2Cl_2) as a white solid (15 mg, 0.072 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (S, 1H, OH), 2.24 (tq, *J* = 6.5, 2.0 Hz, 2H, H_9 x 2), 2.00 (s, 3H, H_{11} x 3), 1.95 – 1.89 (m, 2H, H_3 x 2), 1.48 – 1.28 (m, 8H, H_6 x 4, H_7 x 2, H_8 x 2), 1.28 – 1.11 (m, 4H, H_5 x 4).

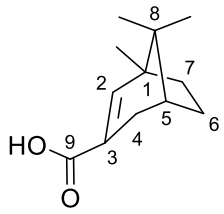
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (C_{10}), 149.7 (C_2), 122.2 (C_1), 46.7 (C_3), 36.5 (C_5 x 2), 32.2 (C_8), 31.5 (C_4), 26.8 (C_7), 23.2 (C_9), 22.9 (C_{11}), 21.9 (C_6 x 2).

HRMS (ESI-): Found $[M-H]^-$ = 207.1388; $C_{13}H_{19}O_2$ requires 207.1380, Δ 4.07 ppm

IR (film) ν_{max}/cm^{-1} 2930, 2847, 1679, 1619, 1441, 1284, 959

m.p.: 133-135 °C

(1*S*,5*S*)-1,8,8-Trimethylbicyclo[3.2.1]oct-2-ene-3-carboxylic acid 607



(2,3,4,5,6-Pentamethylphenyl)((1*S*,5*S*)-1,8,8-trimethylbicyclo[3.2.1]oct-2-en-3-yl)methanone (52 mg, 0.10 mmol, 1 eq., 1:1 with 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one) was subjected to **General Procedure 6.** The title compound was afforded after purification by FCC (2→4% MeOH/CH_2Cl_2) as a white solid (19.0 mg, 0.098 mmol, 98% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H, OH), 6.91 (dd, *J* = 2.0, 1.0 Hz, 1H, H_2), 2.50 (ddq, *J* = 18.0, 4.0, 2.0 Hz, 1H, H_{4a}), 2.18 – 2.09 (m, 1H, H_{4b}), 2.02 – 1.90 (m, 1H, H_{6a}), 1.89 – 1.79 (m, 2H, H_5, H_{7a}), 1.78 – 1.67 (m, 1H, H_{7b}), 1.32 (ddd, *J* = 13.5, 9.5, 6.0 Hz, 1H, H_{6b}), 1.02 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1 (C_9), 154.1 (C_2), 126.5 (C_3), 45.8 (C_1), 43.8 (C_5), 42.2 (C_8), 41.0 (C_7), 33.5 (C_4), 28.9 (C_6), 23.3 (CH_3), 19.2 (CH_3), 17.9 (CH_3).

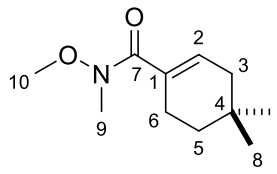
HRMS (ESI-): Found $[M-H]^-$ = 193.1232 ; $C_{12}H_{17}O_2$ requires 193.1234, Δ -1.16 ppm

IR (film) ν_{max}/cm^{-1} 2950, 2872, 1683, 1637, 1422, 1286

m.p.: 106-108 °C

$[\alpha]^{25}_{589}$= −122.8 (c=1.0, $CHCl_3$)

_N_-methoxy-N,4,4-trimethylcyclohex-1-ene-1-carboxamide 608



A 5mL microwave vial was charged with (4,4-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (50.0 mg, 0.175 mmol, 1 eq.), 2M HCl in HFIP (1.75 mL), then sealed and heated at 65 °C for 15 h. The reaction was then cooled to RT, and concentrated *in vacuo*, azeotroping with toluene. EDCI (50 mg, 0.26 mmol, 1.5 eq), DIPEA (0.15 mL ml, 0.88 mmol, 5 eq), HOBT (36 mg, 0.26 mmol, 1.5 eq), DMF (1 mL, 0.175 M) and N,O(dimethyl)hydroxylamine hydrochloride (26 mg, 0.26 mmol, 1.5 eq.) were added, stirring at RT for 15 h. the reaction mixture was diluted with sat. aq. Na_2CO_3 (5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The title compound was afforded after purification by FCC (30% Et_2O/pentane) as a colourless oil (26 mg, 0.13 mmol, 75% yield).

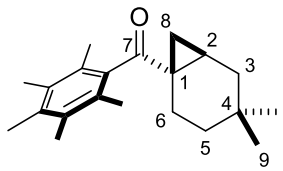
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (tt, *J* = 4.0, 2.0 Hz, 1H, H_2), 3.63 (s, 3H, H_{10} x 3), 3.21 (s, 3H, H_9 x 3), 2.28 (ttd, *J* = 6.5, 2.5, 2.0 Hz, 2H, H_6 x 2), 1.90 (dt, *J* = 4.0, 2.5 Hz, 2H, H_3 x 2), 1.41 (t, *J* = 6.5 Hz, 2H, H_5), 0.93 (s, 6H, H_8 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C_7), 132.7 (C_1), 130.1 (C_2), 61.2 (C_{10}), 39.1 (C_3), 35.1 (C_5), 33.8 (C_9), 28.4 (C_4), 28.3 (C_8 x 2), 23.5 (C_6).

HRMS (ESI+): Found $[M+H]^+$ = 198.1490 ; $C_{11}H_{20}O_2N$ requires 198.1489, Δ 0.51 ppm

IR (film) ν_{max}/cm^{-1} 2926, 2868, 1660, 1631, 1457, 1377, 974

(4,4-dimethylbicyclo[4.1.0]heptan-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 609



A 5mL RBF was charged with trimethylsulfoxonium iodide (58.0 mg, 0.264 mmol, 1.5 eq.) (4,4-dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone (50.0 mg, 0.175 mmol, 1 eq.), NaH (60% wt, 11.0 mg, 0.275 mmol, 1.6 eq.) and DMSO (0.5 mL). The reaction was heated at 50 °C under an Argon atmosphere for 48 hours. The reaction mixture was then cooled to RT, diluted with 3M HCl (3 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (65% CH_2Cl_2/pentane) as a white solid (37.0 mg, 1.23 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 – 2.05 (m, 16H, H_{6a} and $ArCH_3$ x 5), 1.85 – 1.72 (m, 2H, H_{3a} and H_{6b}), 1.68 – 1.56 (m, 1H, H_2), 1.40 (dd, *J* = 9.5, 3.5 Hz, 1H, H_{8a}), 1.33 – 1.24 (m, 1H, H_{3b}), 1.24 – 1.16 (m, 1H, H_{5a}), 0.99 (td, *J* = 13.5, 5.5 Hz, 1H, H_{5b}), 0.86 (s, 3H, H_{9a} x 3), 0.83 (s, 3H, H_{9b} x 3), 0.75 (dd, *J* = 6.5, 3.5 Hz, 1H, H_{8b}).

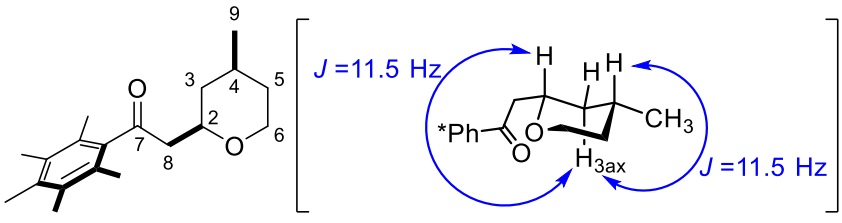
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.4 (C_7), 138.5 (ArC), 135.0 (ArC), 133.0 (ArC), 132.9 (ArC), 128.1 (ArC), 127.9 (ArC), 38.1 (C_3), 33.1 (C_5), 32.0 (C_1), 31.9 (C_{9b}), 27.8 (C_4), 25.7 (C_{9a}), 23.7 (C_8), 23.1 (C_2), 20.4 (C_6), 18.1 ($ArCH_3$), 17.8 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$), 16.1 ($ArCH_3$). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the aryl-C(O) axis.

HRMS (ESI+): Found $[M+H]^+$ = 299.2370; $C_{21}H_{31}O$ requires 299.2369, Δ 0.09 ppm

IR (film) ν_{max}/cm^{-1} 2949, 2806, 1669, 1457, 1384, 1127, 878, 809

m.p.: 80-82 °C

***rac*-2-((2*R*,4*S*)-4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one 631**



Method 1: A 20mL Biotage® microwave vial was charged with 4-methyltetrahydro-2*H*-pyran-2-ol (278 mg, 2.40 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (234 mg, 1.20 mmol, 1 eq.), KOH (269 mg, 4.80 mmol, 4 eq.) and toluene (4.8 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 115 °C for 30 minutes. After cooling to RT, the reaction mixture was filtered through a silica plug, washing with Et_2O and concentrated in

vacuo. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a white solid (83 mg, 0.29 mmol, 23% yield, >95:5 d.r.). The relative stereochemistry was determined by *J*-coupling constant analysis.

Method 2: A flame-dried 2-5 mL Biotage® microwave vial was charged with Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate (600 mg, 1.84 mmol, 1.2 eq.), 60% wt. NaH (72 mg, 1.84 mmol, 1.2 eq), and then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (3 mL, 0.5 M) was then added, stirring the solution for 1h at RT. 4-Methyltetrahydro-2*H*-pyran-2-ol (178 mg, 1.53 mmol, 1 eq.) was then added by syringe, the balloon was removed, and the reaction was heated at 110 °C for 15 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a white solid (418 mg, 1.45 mmol, 95% yield, cis:trans ratio 82:18 dr by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 4.04 – 3.93 (m, 2H, H_{2ax} and H_{6eq}), 3.52 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, H_{6ax}), 3.01 (dd, *J* = 18.0, 7.0 Hz, 1H, H_{8a}), 2.73 (dd, *J* = 18.0, 5.5 Hz, 1H, H_{8b}), 2.26 (s, 3H, $ArCH_3$), 2.21 (s, 6H, $ArCH_3$ x 2), 2.16 (s, 6H, $ArCH_3$ x 2), 1.82 (ddt, *J* = 13.0, 4.0, 2.0 Hz, 1H, H_{3eq}), 1.79 – 1.66 (m, 1H, H_{4ax}), 1.58 (ddq, *J* = 13.5, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.25 (qd, *J* = 12.5, 4.5 Hz, 1H, H_{5ax}), 0.99 (q, *J* = 11.5 Hz, 1H, H_{3ax}), 0.98 (d, *J* = 6.5 Hz, 3H, H_9 x 3).

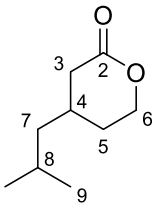
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7 (C_7), 140.5 (ArC), 135.5 (ArC), 133.2 (ArC x 2), 127.6 (ArC x 2), 72.9 (C_2), 68.2 (C_6), 52.3 (C_8), 40.6 (C_3), 34.5 (C_5), 30.3 (C_4), 22.4 (C_9), 17.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.0 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 289.2163; $C_{19}H_{29}O_2$ requires 289.2162, Δ 0.35 ppm

IR (film) ν_{max}/cm^{-1} 2924, 1690, 1655, 1455, 1382, 1306, 1195, 1093, 915, 732

m.p.: 246-248 °C

4-Isobutyltetrahydro-*2H*-pyran-2-one 635



A flame dried 3-neck flask fitted with a reflux condenser was charged with 3-isobutylpentane-1,5-diol (3.00 g, 18.7 mmol, 1 eq.) and copper chromite (117 mg, 0.374 mmol, 0.02 eq.). The reaction was heated to 200 °C for 41 hours and then cooled to RT. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (2.70 g, 17.3 mmol, 92% yield).

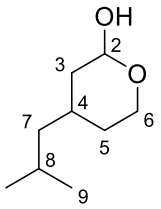
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (ddd, *J* = 11.5, 5.0, 4.0 Hz, 1H, H_{6a}), 4.25 (ddd, *J* = 11.5, 10.5, 4.0 Hz, 1H, H_{6b}), 2.72 – 2.62 (m, 1H, H_{3a}), 2.15 – 1.97 (m, 2H, H_4 and H_{3b}), 1.97 – 1.87 (m, 1H, H_{5a}), 1.72 – 1.58 (m, 1H, H_8), 1.56 – 1.43 (m, 1H, H_{5b}), 1.29 – 1.14 (m, 2H, H_7 x 2), 0.89 (d, *J* = 6.5 Hz, 3H, H_{9a} x 3), 0.89 (d, *J* = 6.5, 3H, H_{9b} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C_2), 68.7 (C_6), 45.7 (C_7), 36.9 (C_3), 29.3 (C_4), 29.3 (C_5), 24.8 (C_8), 22.7 (C_{9a}), 22.7 (C_{9b}).

HRMS (ESI+): Found $[M+H]^+$ = 157.1223; $C_9H_{17}O_2$ requires 157.1223, Δ -0.24 ppm

IR (film) ν_{max}/cm^{-1} 2967, 2911, 1732, 1386, 1254, 1167, 1070, 972

4-Isobutyltetrahydro-*2H*-pyran-2-ol 636



4-Isobutyltetrahydro-*2H*-pyran-2-one (1.0 g, 6.4 mmol, 1 eq.), CH_2Cl_2 (13 mL, 0.5M) and DIBAL-H in hexanes (9 mL, 1M, 1.4 eq.) were subjected to **General procedure 2**. The title compound was afforded after purification by FCC (100% Et_2O) as a colourless oil (1.01 g, 16.4 mmol, 100% yield, 52:48 anomeric mixture by ^{1}H NMR).

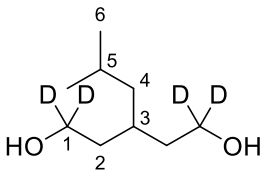
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 – 5.20 (m, 1H, major H_2), 4.66 (ddd, *J* = 9.5, 6.5, 2.0 Hz, 1H, minor H_2), 4.06 – 3.92 (m, 2H, major H_{6a} and minor H_{6a}), 3.68 – 3.57 (m, 2H, major $H_{6b,}$ and minor OH), 3.48 (td, *J* = 12.0, 2.5 Hz, 1H minor H_{6b}), 3.04 (dd, *J* = 3.0, 2.0 Hz, 1H, major OH), 2.04 – 1.93 (m, 1H, major H_4), 1.90 (ddt, *J* = 12.5, 4.0, 2.0 Hz, 1H, minor H_{3a}), 1.79 – 1.55 (m, 5H, major $H_{3a,}$ major H_{5a} and major H_8, minor H_4 and, minor H_8), 1.50 (ddq, *J* = 13.5, 4.0, 2.0 Hz, 1H, minor H_{5a}), 1.31 – 0.93 (m, 8H, major $H_{3b,}$ major H_{5b} and major H_7 x 2, minor $H_{3b,}$ minor H_{5b} and minor H_7 x 2), 0.90 – 0.83 (m, 12H major H_9 x 6 and minor H_9 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 96.4 (minor C_2), 91.9 (major C_2), 65.8 (minor C_6), 59.9 (major C_6), 46.4 (minor C_7), 46.1 (major C_7), 40.2 (minor C_3), 37.3 (major C_3), 32.5 (major C_5), 32.1 (minor C_5), 32.1 (minor C_4), 26.1 (major C_4), 24.5 (minor C_8), 24.4 (major C_8), 23.1 (C_{9a}), 22.9 (C_{9b}), 22.8 (C_{9a}), 22.8 (C_{9b}). n.b C_{9a} and C_{9b} could not be assigned to major or minor anomer.

HRMS (ESI+): Found $[M+Na]^+$ = 181.1201 ; $C_9H_{18}O_2Na$ requires 181.1199, Δ 1.10 ppm

IR (film) ν_{max}/cm^{-1} 3380, 2953, 2870, 1467, 1370, 1070, 898

3-Isobutylpentane-1,1,5,5-*d*$_4$-1,5-diol, *d*$_4$-509



Iodine (12.1 g, 47.8 mmol 1.2 eq) in dry THF (200 mL) was added dropwise *via* dropping funnel to a 1 litre three necked flask at 0 °C under argon atmosphere charged with 3-isobutylglutaric acid (7.49 g, 39.8 mmol, 1 eq.), $NaBD_4$ (5.00 g, 120 mmol, 3 eq.) and dry THF (200 mL). The reaction mixture was then warmed to RT and stirred for 48 hours. The reaction was quenched with MeOH (30 mL) at 0 °C, and then concentrated *in vacuo*. The resulting residue was diluted with water (100 mL), extracted with EtOAc (3x 200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after three purifications by FCC (5% MeOH/CH_2Cl_2, then 3% MeOH/CH_2Cl_2, and 3% MeOH/CH_2Cl_2,) as a colourless oil (3.9 g, 23.9 mmol, 60% yield, >95% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR).

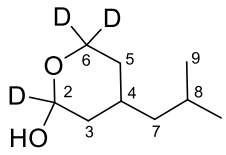
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 2H, OH x 2), 1.77 – 1.61 (m, 2H, H_3, H_5), 1.60 – 1.47 (m, 4H, H_2 x 4), 1.15 (t, *J* = 7.0 Hz, 2H, H_4 x 2), 0.90 (d, *J* = 6.5 Hz, 6H, H_6 x 6). [N.B. in the absence of any deuteration, the peak for H_1 (δ = 3.74-3.64 ppm) would be 4.00, the measured integral by quantitative ^{1}H NMR was 0.14 thus indicating that overall 3.86 D was incorporated across the four symmetrical positions, i.e. >95% D at each position].

^{13}C NMR (101 MHz, $CDCl_3$) δ 60.2 (1:2:3:2:1 quintet, *J* = 21.5 Hz, C_1 x 2), 44.8 (C_4), 36.8 (C_2 x 2), 29.1 (C_3), 25.4 (C_5), 23.0 (C_{6a} and C_{6b}).

^{2}H NMR (77 MHz, $CHCl_3$) δ 3.7 (s, $^2H_1$ x 4).

Apart from deuterium incorporation at C_1, the spectral data of ***d*$_4$-509** was consistent with that of **509** (see above)**.**

4-Isobutyltetrahydro-*2H*-pyran-2,6,6-*d*$_3$-2-ol, *d*$_3$-636



A 25 mL RBF under argon atmosphere was charged with IBX (30% wt. with stabilizer, 2.68 g, 2.88 mmol, 1.2 eq.), dry DMSO (2.8 mL) and acetone (10 mL), and stirred for 40 min at RT. 3-isobutylpentane-1,1,5,5-*d*$_4$-1,5-diol (400 mg, 2.40 mmol, 1 eq.) was added, stirring for 5 hours at RT. The reaction was then diluted with water (10 mL) and filtered. The resulting aqueous solution was extracted with Et_2O (4 x 20 mL). The organic phase was then washed with sat. aq. Na_2CO_3 (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→30% Et_2O/pentane) as a colourless oil (232 mg, 1.44 mmol, 60% yield, 51:49 mixture of anomers ^{1}H NMR, >95% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR).

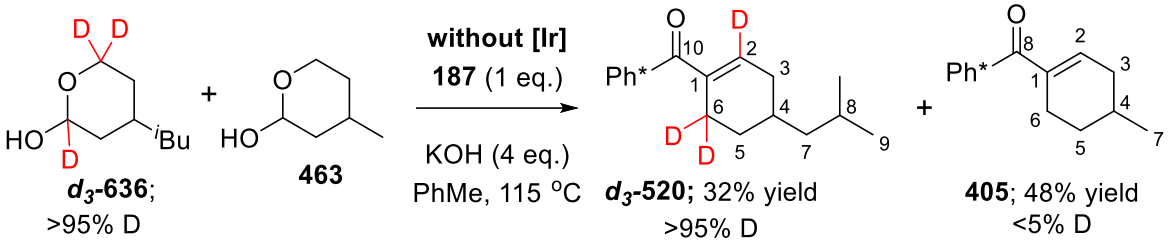
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 1H, minor OH), 2.91 (d, *J* = 2.0 Hz, 1H, major OH), 2.04 – 1.93 (m, 1H, major H_4) 1.90 (ddd, *J* = 12.5, 4.0, 2.0 Hz, 1H, minor H_{3a}), 1.78 – 1.54 (m, 5H, major H_{3a}, major H_{5a} and major H_8, minor H_4 and minor H_8), 1.49 (ddd, *J* = 13.5, 4.0, 2.0 Hz, 1H, minor H_{5a}), 1.31 –0.93 (m, 8H, major $H_{3b,}$ major H_{5b} and major H_7 x 2, minor $H_{3b,}$ minor H_{5b} and minor H_7 x 2), 0.91 – 0.83 (m, 12H, major H_9 x 6 and minor anomer H_9 x 6). [N.B. in the absence of any deuteration, the peaks for H_2, H_{6a} and H_{6b} (see spectra) should each integrate to 1.00. Integration of the quantitative ^{1}H NMR spectrum showed an integral for each of these peaks of 0.02 thus indicating 0.98 D incorporation at each position, i.e. >95% D at each position].

^{13}C NMR (101 MHz, $CDCl_3$) δ 95.9 (1:1:1 t, *J* = 32 Hz, minor anomer C_2), 91.5 (1:1:1 t, *J* = 33 Hz, major anomer C_2), 46.5 (minor anomer C_7), 46.1 (major anomer C_7), 40.1 (minor anomer C_3), 37.2 (major anomer C_3), 32.3 (major anomer C_5), 32.1 (minor anomer C_4), 31.8 (minor anomer C_5), 26.1 (major anomer C_4), 24.5 (minor anomer C_8), 24.4 (major anomer C_8), 23.1 (C_{9a}), 22.9 (C_{9a}), 22.8 (C_{9b}), 22.8 (C_{9b}). n.b $C_{9a\ and}$ C_{9b} could not be assigned to major or minor anomer. C_6 for major and minor anomer not observed.

^{2}H NMR (77 MHz, $CHCl_3$) δ 5.3 (major anomer $^2H_2$), 4.7 (minor anomer $^2H_2$), 4.0 (major anomer $^2H_{6a}$ and minor anomer $^2H_{6a)}$, 3.6 (major anomer $^2H_{6b}$), 3.5 (minor anomer $^2H_{6b}$).

The spectral data of ***d*$_3$-636** was consistent with that of **636** (see above) with >95% incorporation of deuterium at C_2 and C_6.

Lactol crossover experiment



A 2-5mL Biotage® microwave vial was charged with 4-isobutyltetrahydro-2*H*-pyran-2,6,6-*d*$_3$-2-ol (97 mg, 0.60 mmol, 1 eq.), 4-methyltetrahydro-2*H*-pyran-2-ol (70 mg, 0.60 mmol, 1 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (114 mg, 0.600 mmol, 1 eq.), KOH (134 mg, 2.40 mmol, 4 eq.) and toluene (2.4 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with 3M aq. HCl (6 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by FCC (3% Et_2O/pentane) afforded a mixture of ***d*$_3$-520** (>95% D incorporation by quantitative ^{1}H NMR, ^{2}H and ^{13}C NMR) and **405** (<5% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR) as a white solid (140 mg, 0.480 mmol, 80% yield, 60:40 ratio **405**:***d*$_3$-520** by quantitative ^{1}H NMR). An analytical sample of each compound was obtained by preparative TLC (10% EtOAc/Pentane).

Data for *d*$_3$-520 from lactol crossover experiment:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 – 2.12 (m, 10H, $ArCH_3$ x 3, H_{3a}), 2.02 (s, 3H, $ArCH_3$), 2.01 (s, 3H, $ArCH_3$), 1.91 – 1.81 (m, 1H, H_{5a}), 1.81 – 1.56 (m, 3H, H_{3b}, H_4 and H_8), 1.34 – 1.06 (m, 3H, H_{5b}, H_7 x 2), 0.88 (d, *J* = 6.5 Hz, 6H, H_9 x 6). Peaks at 6.46 ppm (H_2) and 2.61 ppm (H_6) integrate to <5% implying >95% D incorporation at each position.

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6 (C_{10}), 145 (1:1:1 triplet, *J* = 24 Hz, C_2), 140.6 (C_1), 138.4 (ArC), 135.1 (ArC), 132.7 (ArC), 132.7 (ArC), 129.3 (ArC), 129.2 (ArC), 45.8 (C_7), 33.2 (C_3), 30.5 (C_4), 28.4 (C_5), 25.1 (C_8), 23.1 (C_{9a}), 22.9 (C_{9b}), 21.8 (1:2:3:2:1 pentet, *J* = 20 Hz, C_6), 17.6 ($ArCH_3$), 17.6 ($ArCH_3$), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). Reduced intensity ^{13}C peak corresponding to C_6 and C_2 due to $^2J_{CD}$ coupling.

^{2}H NMR (77 MHz, $CHCl_3$) δ 6.51 (s, 1 x ^{2}H, $^2H_2$), 2.61 (s, 1 x ^{2}H, $^2H_{6eq}$), 2.24 (s, 1 x ^{2}H, $^2H_{6ax}$).

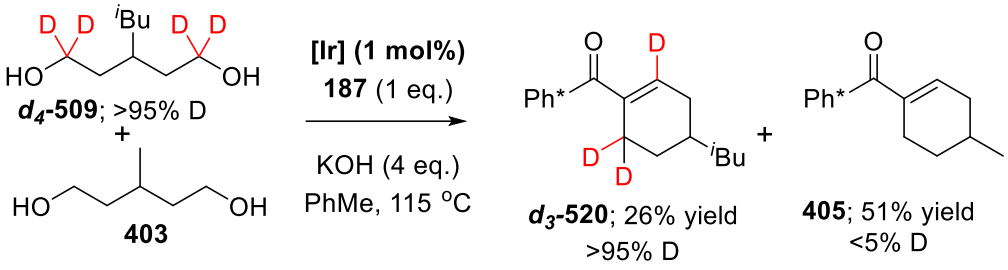
Apart from deuterium incorporation at C2 and C6, the spectral data of ***d*$_3$-520** was consistent with that of **520** (see data above for **520**)

Data for 405 from lactol crossover experiment:

<5% D incorporation at the 2- and 6-positions by quantitative ^{1}H NMR and ^{13}C NMR.

The ^{1}H NMR data was identical to that described previously for non-deuterated **405** and the peaks corresponding to H_2 and H_6 integrated to >95% implying <5% D incorporation at these positions:

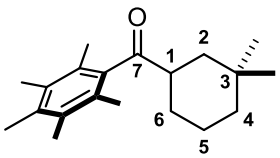
Diol Crossover Experiment



A 2-5mL Biotage® microwave vial was charged with CataCXium® A (4.3 mg, 0.012 mmol, 2 mol%), 3-isobutylpentane-1,1,5,5-*d*$_4$-1,5-diol (99 mg, 0.60 mmol, 1 eq.), 3-methylpentane-1,5-diol (71 mg, 0.60 mmol, 1 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (114 mg, 0.600 mmol, 1 eq.), $[Ir(cod)Cl]_2$ (2 mg, 0.003 mmol, 0.5 mol% dimer), KOH (134 mg, 2.40 mmol, 4 eq.) and toluene (2.4 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (3% Et_2O/pentane) afforded a mixture of ***d*$_3$-520** (>95% D incorporation by quantitative ^{1}H NMR, ^{2}H and ^{13}C NMR) and **405** (<5% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR) as a white solid (135 mg, 0.462 mmol, 77% yield, 64:34 ratio **405**:***d*$_3$-520** by quantitative ^{1}H NMR). An analytical sample of each compound was obtained by preparative TLC (10% EtOAc/Pentane).

The spectral data for both ***d*$_3$-520** and **405** were identical to that described in the lactol cross over experiment.

(3,3-dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone 655



A 2–5 mL Biotage(R) microwave vial was charged with 2,2-dimethylpentane-1,5-diol (79.3 mg, 0.6 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (57 mg, 0.3 mmol, 1 eq.), $[IrCp^*Cl_2]_2$ (4.8 mg, 0.006 mmol, 2 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) toluene (0.075 mL, 4 M). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), fitted with an argon balloon, and the vial was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with HCl (3M, 5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (68 mg, 0.24 mmol, 79% yield).

^{1}H NMR (700 MHz, CD_2Cl_2) δ 2.78 (tt, J = 12.5, 3.5 Hz, 1H, H_1), 2.24 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.05 (s, 6H, $ArCH_3$ x 2), 1.90 – 1.82 (m, 1H, H_{6eq}), 1.64 – 1.59 (m, 1H, H_{5eq}), 1.57 – 1.52 (m, 1H, H_{2eq}), 1.43 (qt, J = 13.5, 3.5 Hz, 1H, H_{5ax}), 1.39 – 1.34 (m, 1H, H_{4eq}), 1.30 (t, J = 13.0 Hz, 1H, H_{2ax}), 1.23 (qd, J = 13.0, 4.0 Hz, 1H, H_{6ax}), 1.14 (td, J = 13.5, 3.5 Hz, 1H, H_{4ax}), 0.95 (s, 3H, CH_3), 0.86 (s, 3H, CH_3).

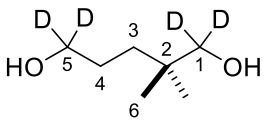
^{13}C NMR (101 MHz, CD_2Cl_2) δ 215.3 (C_7), 140.9 (ArC), 135.8 (ArC), 133.5 (ArC x 2), 128.5 (ArC x 2), 49.7 (C_1), 41.2 (C_2), 39.2 (C_4), 33.6 (CH_3), 31.1 (C_3), 28.9 (C_6), 24.6 (CH_3), 22.5 (C_5), 18.2 ($ArCH_3$ x 2), 17.0($ArCH_3$), 16.3 ($ArCH_3$ x 2).

^{1}H NMR (400 MHz, Tol) δ 2.85 (tt, *J* = 12.0, 3.5 Hz, 1H, H_1), 2.13 (s, 6H, $ArCH_3$ x 2), 2.08 (s, 3H, $ArCH_3$), 2.03 (s, 6H, $ArCH_3$ x 2), 2.01 – 1.95 (m, 1H, H_{6eq}), 1.72 (ddt, *J* = 13.5, 4.0, 2.0 Hz, 1H, H_{2eq}), 1.58 – 1.47 (m, 2H, H_{2ax}, H_{5eq}), 1.45 – 1.23 (m, 3H, H_{4eq}, H_{5ax}, H_{6ax}), 1.14 – 1.02 (m, 1H, H_{4ax}), 0.95 (s, 3H, CH_3), 0.81 (s, 3H, CH_3).

^{13}C NMR (101 MHz, Tol) δ 212.6 (C_7), 141.3 (ArC), 134.9 (ArC), 132.9 (ArC x 2), 128.4 (ArC x 2), 49.4 (C_1), 41.0 (C_2), 39.0 (C_4), 33.4 (CH_3), 30.6 (C_3), 28.7 (C_6), 24.2 (CH_3), 22.3 (C_5), 18.0 ($ArCH_3$ x 2), 16.5 ($ArCH_3$), 15.9 ($ArCH_3$ x 2).

The spectroscopic data matched that previously reported in the literature.[84]

2,2-Dimethylpentane-1,1,5,5-*d*$_4$-1,5-diol, *d*$_4$-514



Iodine (12.1 g, 47.8 mmol 1.2 eq) in dry THF (200 mL) was added dropwise *via* dropping funnel to a 1 litre three necked flask at 0 °C under argon atmosphere charged with 2,2-dimethylglutaric acid (6.37 g, 39.8 mmol, 1 eq.), $NaBD_4$ (5.00 g, 120 mmol, 3 eq.) and dry THF (200 mL). The reaction mixture was then warmed to RT and stirred for 24 hours. The reaction was quenched with MeOH (30 mL) at 0 °C,

and then concentrated *in vacuo*. The resulting residue was diluted with water (100 mL), extracted with EtOAc (3 x 200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after two purifications by FCC (3→5% MeOH/CH_2Cl_2, then 100% EtOAc) as a colourless oil (1.04 g, 7.63 mmol, 19% yield, >95% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR).

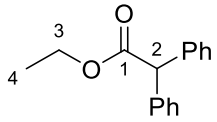
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 2H, OH x 2), 1.62 – 1.40 (m, 2H, H_4 x 2), 1.37 – 1.22 (m, 2H, H_3 x 2), 0.86 (s, 6H, H_6 x 6). [N.B. in the absence of any deuteration, the peak for H_5 (δ = 3.63 ppm) would be 2.00, and the peak for H_1 (δ = 3.32 ppm) would be 2.00. The measured integral by quantitative ^{1}H NMR was for H_5 was 0.07 and for H_1 was 0.09, thus indicating 1.93 D at H_5 and 1.91 D at H_1, i.e. >95% D at each position].

^{13}C NMR (101 MHz, $CDCl_3$) δ 70.5 (1:2:3:2:1 quintet, *J* = 21.5 Hz, C_1), 62.9 (1:2:3:2:1 quintet, *J* = 21.5 Hz, C_5), 34.8 (C_2), 34.3 (C_3), 26.9 (C_4), 24.2 (C_6 x 2).

^{2}H NMR (92 MHz, $CHCl_3$) δ 3.60 (s, $^2H_1$ x 2), 3.29 (s, $^2H_5$ x 2).

Apart from deuterium incorporation at C_1 and C_5, the spectral data of ***d*$_4$-514** was consistent with that of **514**.

Ethyl 2,2-diphenylacetate 657



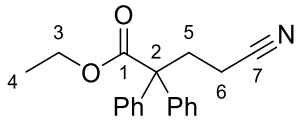
A 250 mL RBF was charged with diphenyl acetic acid (20 g, 94 mmol, 1 eq.), 100 proof ethanol (60 mL, 1.6 M), conc. sulphuric acid (1.5 mL, 8 mmol, 0.09 eq.) and refluxed overnight under argon. The reaction mixture diluted with water 100 mL, and then the ethanol was removed *in* vacuo. The product was extracted with EtOAc (2 x 250 mL), and washed with sat. aq. Na_2CO_3 (100 mL), brine (100 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded as a white solid (22g, 91.5 mmol 97% yield) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.38 (m, 10H, ArCH x 10), 5.18 (s, 1H, H_2), 4.38 (q, J = 7.0 Hz, 2H, H_3 x 2), 1.42 (t, J = 7.0 Hz, 3H, H_4 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C_1), 138.9 (ArC x 2), 128.7 (ArC x 4), 128.7 (ArC x 4), 127.3 (ArC x 2), 61.3 (C_3), 57.3 (C_2), 14.3 (C_4).

The spectroscopic data matched that previously reported in the literature.[166]

Ethyl 4-cyano-2,2-diphenylbutanoate 659



Ethyl 2,2-diphenylacetate (1 g, 4.16 mmol, 1eq.) was added to a suspension of 60 % wt. NaH (200 mg, 5 mmol, 1.2 eq.) in dry THF (50 mL) at 0 °C under argon. After stirring for 30 minutes, acrylonitrile (0.33 mL, 5 mmol, 1.2 eq.) was added and allowed to warm to RT over 4h. The reaction mixture was diluted with sat. aq. Ammonium chloride (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (5→20% EtOAc/pentane) afforded the title compound as a colourless oil (800 mg, 2.73 mmol, 66% yield).

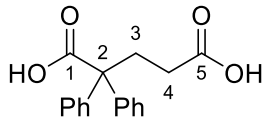
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.11 (m, 10H, ArCH x 10), 4.19 (q, J = 7.0 Hz, 2H, H_3 x 2), 2.83 – 2.69 (m, 2H, H_5 x 2), 2.18 – 2.08 (m, 2H, H_6 x 2), 1.17 (t, J = 7.0 Hz, 3H, H_4 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.13 (C_1), 141.4 (ArC x 2), 128.7 (ArCH x 4), 128.5 (ArCH x 4), 127.6 (ArCH x 2), 119.8 (C_7), 61.8 (C_3), 59.7 (C_2), 34.5 (C_5), 14.0 (C_6), 14.0 (C_4).

HRMS (ESI+): Found $[M+Na]^+$ = 316.13068; $C_{19}H_{19}O_2N_1Na_1$ requires 316.13080, Δ -0.39 ppm

IR (film) ν_{max}/cm^{-1} 3000, 1724, 1446, 1221, 763, 700

2,2-diphenylpentanedioic acid 660



Ethyl 4-cyano-2,2-diphenylbutanoate (400 mg, 1.36 mmol, 1 eq.), dissolved in EtOH (8 mL) was added to a solution of 50% wt. NaOH in EtOH (10 mL), and refluxed for 1h. After cooling to 0 °C the reaction was diluted with water (50 mL), and acidified to pH = 1 with 12 M HCl. The product was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded as a white solid (386 mg, 1.36 mmol, 100% yield) and used without further purification.

^{1}H NMR (400 MHz, DMSO) δ 7.50 – 7.13 (m, 10H, ArCH x 10), 2.74 – 2.41 (m, 2H, H_4 x 2), 2.13 – 1.81 (m, 2H, H_3 x 2).

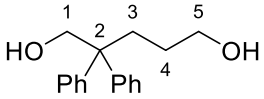
^{13}C NMR (101 MHz, DMSO) δ 174.8 (C_5), 174.0 (C_1), 142.7 (ArC x 2), 128.5 (ArCH x 4), 128.0 (ArCH x 4), 126.7 (ArCH x 2), 59.0 (C_2), 32.9 (C_4), 30.4 (C_3).

HRMS (ESI+): Found $[M-H]^-$ = 283.09748; $C_{17}H_{15}O_4$ requires 283.09649, Δ 3.52 ppm

IR (film) ν_{max}/cm^{-1} 3059, 1700, 1495, 1445, 1413, 1266, 1217, 699

m.p.: 199-200 °C

2,2-diphenylpentane-1,5-diol 661



A suspension of $LiAlH_4$ (400 mg, 10.5 mmol, 3 eq.) in dry THF (20 mL, 0.2 M) was cooled to 0 °C, followed by the portionwise addition of a solution of 2,2-diphenylpentanedioic acid (1 g, 3.5 mmol, 1 eq.) in THF (20 mL). The reaction was then fitted with an air condenser and heated at reflux for 3 hours. The reaction was then cooled to 0 °C, diluted with Et_2O (50 mL) and quenched by sequential addition of water (0.4 mL), aq. NaOH (15% w/v, 0.4 mL), and water (1.2 mL), and stirred vigorously for 15 minutes. $MgSO_4$ was then added, stirred for 15 minutes, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a white solid (340 mg, 1.32 mmol, 38% yield). 4,4-diphenylbutan-1-ol was also isolated as a colourless oil (58 mg, 0.26 mmol, 7% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 6.95 (m, 10H), 4.10 (d, *J* = 6.5 Hz, 2H, H_1 x 2), 3.53 (t, *J* = 5.5 Hz, 2H, H_5 x 2), 2.26 – 2.10 (m, 2H, H_3 x 2), 1.93 – 1.43 (m, 2H, OH x 2), 1.39 – 1.18 (m, 2H, H4 x 2).

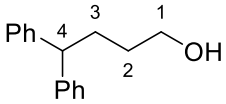
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (ArC x 2), 128.4 (ArCH x 4), 128.3 (ArCH x 4), 126.5 (ArCH x 2), 68.2 (C_1), 63.4 (C_5), 51.8 (C_2), 32.4 (C_3), 27.8 (C_4).

HRMS (ESI+): Found $[M+Na]^+$ = 279.1355; $C_{17}H_{20}O_2Na$ requires 279.1356, Δ -0.30 ppm

IR (film) ν_{max}/cm^{-1} 3345, 2946, 1495, 1445, 1054, 755, 699

m.p.: 127-128 °C

4,4-diphenylbutan-1-ol 662

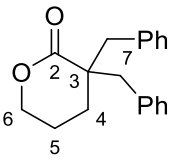


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.01 (m, 10H, ArCH x 10), 3.82 (t, *J* = 8.0 Hz, 1H, H_4), 3.54 (t, *J* = 6.5 Hz, 2H, H_1 x 2), 2.09 – 1.94 (m, 2H, H_3 x 2), 1.51 – 1.37 (m, 2H, H_2 x 2). 1.32 (br s, 1H, OH)

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (ArC x 2), 128.6 (ArCH x 4), 128.0 (ArCH x 4), 126.3 (ArCH x 2), 62.9 (C_1), 51.2 (C_4), 32.0 (C_3), 31.4 (C_2).

The spectroscopic data matched that previously reported in the literature.[167]

3,3-dibenzyltetrahydro-*2H*-pyran-2-one 664



*n*BuLi in hexanes (8.8 mL, 2.5 M, 22 mmol, 2.2 eq.) was added dropwise to a solution of hexamethyldisilazane (4.33 mL, 22 mmol, 2.2 eq) in dry THF (50 mL) cooled to -78 °C under argon. After stirring for 30 minutes, δ-Valerolactone (1 g, 9.98 mmol, 1 eq.) was added dropwise to the solution, and stirred for a further 30 minutes at -78 °C. benzyl bromide (3.7 g, 22 mmol, 2.2 eq.) was added dropwise, warmed to 0 °C and stirred for 2 hours. The reaction was then quenched with sat. aq. Ammonium chloride (20 mL). The product was extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (25% Et_2O/pentane) as a white solid (2.7 g, 9.64 mmol, 97% yield).

1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.08 (m, 10H, ArCH x 10), 3.67 (t, J = 5.5 Hz, 2H, H_6 x 2), 3.40 (d, J = 13.0 Hz, 2H, H_{7a} x 2), 2.56 (d, J = 13.0 Hz, 2H, H_{7b} x 2), 1.83 – 1.63 (m, 2H, H_4 x 2), 1.27 – 1.12 (m, 2H, H_5 x 2).

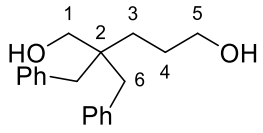
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C_2), 137.1 (ArC x 2), 130.7 (ArCH x 4), 128.6 (ArCH x 4), 127.1 (ArCH x 2), 70.1 (C_6), 49.6 (C_3), 46.9 (C_7 x 2), 27.3 (C_4), 21.3 (C_5).

HRMS (ESI+): Found $[M+H]^+$ = 281.15369; $C_{19}H_{21}O_2$ requires 281.15361, Δ 0.28 ppm

IR (film) ν_{max}/cm^{-1} 2950, 1717, 1496, 1454, 1155, 751, 703

m.p.: 84-85 °C

2,2-dibenzylpentane-1,5-diol 665



A suspension of $LiAlH_4$ (407 mg, 10.7 mmol, 3 eq.) in dry THF (18 mL) was cooled to 0 °C, followed by the portionwise addition of 3,3-dibenzyltetrahydro-2H-pyran-2-one (1.00 g, 3.57 mmol, 1 eq.). The reaction was then heated at reflux for 15 hours and then cooled to 0 °C, diluted with Et_2O (20 mL) and quenched by sequential dropwise addition of water (0.41 mL), aq. NaOH (15% w/v, 0.41 mL), and water (1.23 mL), and stirred vigorously for 15 minutes. $MgSO_4$ was then added, stirred for 15 minutes, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a white solid (1.14 g, 3.57 mmol, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.19 (m, 10H, ArCH x 10), 3.62 (t, *J* = 5.5 Hz, 2H, H_5 x 2), 3.35 (d, *J* = 4.0 Hz, 2H, H_1 x 2), 2.77 (d, *J* = 13.5 Hz, 2H, H_{6a} x 2), 2.65 (d, *J* = 13.5 Hz, 2H, H_{6b} x 2), 1.81 – 1.69 (m, 2H, H_4 x 2), 1.48 (br s, 1H, OH), 1.37 (br s, 1H, OH), 1.28 – 1.19 (m, 2H, H_3 x 2).

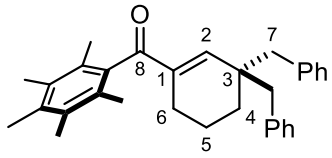
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5 (ArC x 2), 130.6 (ArCH x 4), 128.3 (ArCH x 4), 126.4 (ArCH x 2), 66.4 (C_1), 63.6 (C_5), 42.7 (C_2), 41.3 (C_6), 28.9 (C_3), 26.8 (C_4).

HRMS (ESI+): Found $[M+Na]^+$ = 307.16678; $C_{19}H_{24}O_2Na$ requires 307.16685, Δ -0.24 ppm

IR (film) ν_{max}/cm^{-1} 3340, 2953, 2877, 1386, 114, 982, 760, 701

mp: 109-110 °C

(3,3-dibenzylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 666



Method 1: A 2–5 mL Biotage® microwave vial was charged with CataCXium® A (2.2 mg, 0.0060 mmol, 2 mol%), 2,2-dibenzylpentane-1,5-diol (170 mg, 0.600 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (57 mg, 0.30 mmol, 1 eq), $[Ir(cod)Cl]_2$ (1.0 mg, 0.0015 mmol, 0.5 mol% dimer), KOH (67 mg, 1.2 mmol, 4 eq.) and toluene (1.2 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL), extracted with CH_2Cl_2 (4 x

10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (4-5% Et_2O/pentane) as a white solid (90.0 mg, 0.206 mmol, 69% yield).

Method 2: A 2–5 mL Biotage® microwave vial was charged with 2,2-dibenzylpentane-1,5-diol (170 mg, 0.600 mmol, 2 eq.), 1-(2,3,4,5,6- pentamethylphenyl)ethan-1-one (57 mg, 0.30 mmol, 1 eq), $[IrCp^*Cl_2]_2$ (4 mg, 0.006 mmol, 2 mol% dimer), KOH (67 mg, 1.2 mmol, 4 eq.) and toluene (0.075 mL, 4 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum), fitted with an argon balloon and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL), extracted with CH_2Cl_2 (4 x 10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (112 mg, 0.256 mmol, 86% yield).

Method 3: A 2–5 mL Biotage®microwave vial was charged with 2,2-dibenzylpentane-1,5-diol (170 mg, 0.600 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (57 mg, 0.30 mmol, 1 eq), [Ir(cod)acac] (4.8 mg, 0.012 mmol, 4 mol%), (*R*)-DTBM SEGPHOS (18 mg, 0.015 mmol, 5 mol%) KO*t*Bu (135 mg, 1.2 mmol, 4 eq.) and *t*BuOH (0.1 mL, 3 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum),and heated at 110 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL), extracted with CH_2Cl_2 (4 x 10 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (111 mg, 0.254 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.11 (m, 6H, ArCH x 6), 7.04 – 6.89 (m, 4H, ArCH x 4), 6.50 – 6.28 (m, 1H, H_2), 2.69 (d, *J* = 13.0 Hz, 2H, H_{7a} x 2), 2.62 (d, *J* = 13.0 Hz, 2H, H_{7b} x 2), 2.29 (s, 3H, $ArCH_3$), 2.24 (s, 6H, $ArCH_3$ x 2), 2.22 – 2.16 (m, 2H, H_6 x 2), 2.02 (s, 6H, $ArCH_3$ x 2), 1.66 – 1.48 (m, 4H, H_4 x 2, H_5 x 2).

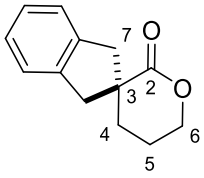
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C_8), 151.1 (C_2), 141.0 (C_1), 138.3 (ArC), 137.8 (ArC x 2), 135.2 (ArC), 132.7 (ArC x 2), 130.7 (ArC x 4), 129.0 (ArC x 2), 128.0 (ArC x 4), 126.4 (ArC x 2), 46.8 (C_7 x 2), 41.5 (C_3), 30.6 (C_4), 22.4 (C_6), 18.6 (C_5), 17.7 ($ArCH_3$ x 2), 16.9 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 437.28326; $C_{32}H_{37}O$ requires 437.28389, Δ -1.44 ppm

IR (film) ν_{max}/cm^{-1} 3027, 2933, 1654, 1495, 1453, 1192, 755, 702

m.p.: 119-120 °C

1,3,5',6'-tetrahydro-2'H,4'H-spiro[indene-2,3'-pyran]-2'-one 668



A flame-dried 100 mL three-necked flask was charged with Hexamethyldisilazane (4.33 mL, 22 mmol, 2.2 eq.), dry THF (40 mL) and cooled to -78 °C under Argon. *n*BuLi in hexanes (8.8 mL, 2.5 M, 22 mmol, 2.2 eq.) was added dropwise, and stirred for 10 minutes at -78 °C. δ-Valerolactone (1g, 9.98 mmol, 1 eq.) dissolved in dry THF (5 mL) was added dropwise, and stirred for 30 minutes at -78 °C. α,α'-Dibromo-o-xylene (2.9g, 11 mmol, 1.1 eq.) dissolved in dry THF (5 mL) was added dropwise, and stirred for 10 minutes at -78 °C. The reaction mixture was then warmed to 0 °C and stirred for 3 hours. The reaction was quenched by the dropwise addition of sat. aq. NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→40% Et_2O/pentane) as a white solid (820 mg, 4.06 mmol, 41% yield).

1H NMR (400 MHz, CDCl3) δ 7.21 – 7.14 (m, 4H, ArCH x 4), 4.44 (t, J = 6.0 Hz, 2H, H_6 x 2), 3.64 (d, J = 15.5 Hz, 2H, H_7 x 2), 2.97 (d, J = 15.5 Hz, 2H, $H_{7'}$ x 2), 2.04 – 1.87 (m, 4H, H_4 x 2 and H_5 x 2).

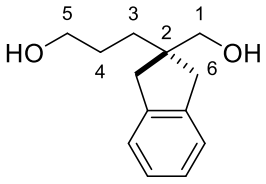
13C NMR (101 MHz, CDCl3) δ 176.5 (C_2), 140.5 (ArC x 2), 127.0 (ArC x 2), 124.7 (ArC x 2), 70.2 (C_6), 49.7 (C_3), 45.8 (C_7 x 2), 33.1 (C_4), 21.1 (C_5).

HRMS (ESI+): Found $[M+H]^+$ = 203.10686; $C_{13}H_{15}O_2$ requires 203.10666, Δ 0.99 ppm

IR (film) ν_{max}/cm^{-1} 2932, 2854, 1717, 1441, 1411, 1292, 1170, 975, 727

m.p.: 99-100 °C

3-(2-(hydroxymethyl)-2,3-dihydro-1H-inden-2-yl)propan-1-ol 669



A suspension of $LiAlH_4$ (580 mg, 12 mmol, 3 eq.) in dry THF (20 mL) was cooled to 0 °C, followed by the portionwise addition of 1,3,5',6'-tetrahydro-2'H,4'H-spiro[indene-2,3'-pyran]-2'-one (800 mg, 4 mmol, 1 eq.). The reaction was then fitted with an air condenser and heated at reflux for 15 hours. The reaction was then cooled to 0 °C, diluted with Et_2O (20 mL) and quenched by sequential addition of water (0.4 mL), aq. NaOH (15% w/v, 0.4 mL), and water (1.2 mL), and stirred vigorously for 15 minutes.

$MgSO_4$ was then added, stirred for 15 minutes, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% MeOH/CH_2Cl_2) as a white solid (633 mg, 3.07 mmol, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 4H, ArCH x 4), 3.66 (t, J = 6.0 Hz, 2H, H_5 x 2), 3.60 – 3.46 (m, 2H, H_1 x 2), 2.86 (d, J = 16.0 Hz, 2H, H_6 x 2), 2.75 (d, J = 16.0 Hz, 2H, H_6 x 2), 2.05 (s, 1H, OH), 1.72 (s, 1H, OH), 1.69 – 1.54 (m, 4H, H_3 x 2, H_4 x 2).

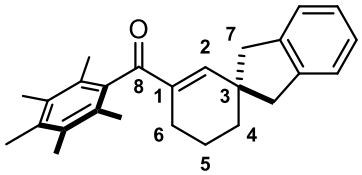
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (ArC x 2), 126.4 (ArC x 2), 124.9 (ArC x 2), 67.9 (C_1), 63.6 (C_2), 47.8 (C_2), 41.5 (C_6 x 2), 32.8 (C_3), 27.8 (C_4).

HRMS (ESI+): Found $[M+Na]^+$ = 229.12004; $C_{13}H_{19}O_2Na$ requires 229.11990, Δ 0.61 ppm

IR (film) ν_{max}/cm^{-1} 3334, 2940, 2845, 1485, 1051, 740

m.p.: 96-97 °C

(1',3'-dihydrospiro[cyclohexane-1,2'-inden]-2-en-3-yl)(2,3,4,5,6-pentamethylphenyl)methanone 670



3-(2-(hydroxymethyl)-2,3-dihydro-1H-inden-2-yl)propan-1-ol (123 mg, 0.6 mmol, 2 eq.) was subjected to **General Procedure 1**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a white solid (94 mg, 0.261 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 4H, ArCH x 4), 6.48 (t, J = 1.5 Hz, 1H, H_2), 2.91 (d, J = 16.0 Hz, 2H, H_7 x 2), 2.81 (d, J = 16.0 Hz, 2H, H_7 x 2), 2.46 (td, J = 6.0, 1.5 Hz, 2H, H_6 x 2), 2.22 (s, 3H, $ArCH_3$), 2.17 (s, 6H, $ArCH_3$ x 2), 2.04 (s, 6H, $ArCH_3$ x 2), 1.81 – 1.73 (m, 2H, H_5 x 2), 1.69 – 1.64 (m, 2H, H_4 x 2).

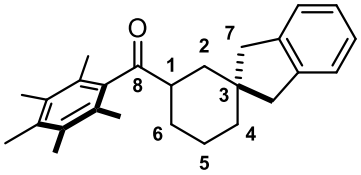
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.0 (C_8), 152.3 (C_2), 141.9 (ArC x 2), 139.4 (C_1), 138.1 (ArC), 135.2 (ArC), 132.7 (ArC x 2), 129.2 (ArC x 2), 126.5 (ArC x 2), 124.7 (ArC x 2), 46.6 (C_7 x 2), 45.0 (C_3), 35.0 (C_4), 22.9 (C_6), 20.0 (C_5), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 359.23666; $C_{26}H_{31}O$ requires 359.23694, Δ -0.77 ppm

IR (film) ν_{max}/cm^{-1} 3021, 2928, 1651, 1632, 1458, 1379, 1278, 1189, 1023, 911, 731

m.p.: 172-173 °C

(1',3'-dihydrospiro[cyclohexane-1,2'-inden]-3-yl)(2,3,4,5,6-pentamethylphenyl)methanone 671



A 2–5 mL Biotage® microwave vial was charged with 3-(2-(hydroxymethyl)-2,3-dihydro-1H-inden-2-yl)propan-1-ol (123 mg, 0.6 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (57 mg, 0.3 mmol, 1 eq.), $[Cp^*IrCl_2]_2$ (4.8 mg, 0.006 mmol, 2 mol%), KOH (67 mg, 1.2 mmol, 4 eq.) toluene (0.075 mL, 4 M). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), fitted with an Ar balloon, and the vial was heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with HCl (3M, 5 mL), extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC (5% Et_2O/pentane) afforded the title compound as a white solid (108 mg, 0.3 mmol, 100% yield).

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.20 – 7.02 (m, 4H, ArCH x 4), 2.88 – 2.66 (m, 5H, H_1, H_7 x 4), 2.23 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.06 (s, 6H, $ArCH_3$ x 2), 1.93 (dtq, J = 10.5, 3.5, 2.0 Hz, 1H, H_{6eq}), 1.87 (dq, J = 13.0, 2.5 Hz, 1H, H_{2eq}), 1.75 – 1.69 (m, 1H, H_{5eq}), 1.67 – 1.62 (m, 1H, H_{4eq}), 1.60 (t, J = 13.0 Hz, 1H, H_{2ax}), 1.47 (qt, J = 13.5, 3.5 Hz, 1H, H_{5ax}), 1.38 – 1.29 (m, 2H, H_{4ax}, H_{7ax}).

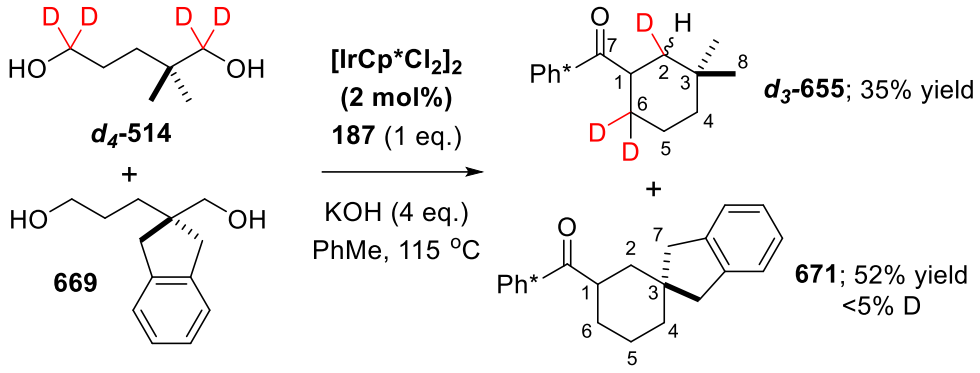
^{13}C NMR (101 MHz, CD_2Cl_2) δ 214.8 (C_8), 143.1 (ArC), 143.0 (ArC), 140.7 (ArC), 135.9 (ArC), 133.6 (ArC x 2), 128.5 (ArC x 2), 126.7 (ArC), 126.6 (ArC), 125.3 (ArC), 125.2 (ArC), 50.8 (C_1), 49.4 (C_7), 44.2 (C_3), 42.4 (C_7), 39.5 (C_2), 37.4 (C_4), 28.8 (C_6), 23.4 (C_5), 18.3 ($ArCH_3$ x 2), 17.0 ($ArCH_3$), 16.3 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+Na]^+$ = 383.23480; $C_{26}H_{32}ONa$ requires 383.23454, Δ 0.69 ppm

IR (film) vmax/cm-1 2925, 1689, 1448, 1382, 1306, 911, 733.

m.p.: 157-158 °C

Reductive crossover experiment with $[IrCp^*Cl_2]_2$:



A 2-5mL Biotage® microwave vial was charged with 2,2-dimethylpentane-1,1,5,5-d_4-1,5-diol (82 mg, 0.60 mmol, 1 eq.), 3-(2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl)propan-1-ol (124 mg, 0.60 mmol, 1 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (114 mg, 0.60 mmol, 1 eq.), $[IrCp^*Cl_2]_2$ (9.6 mg, 0.012 mmol, 2 mol% dimer), KOH (134 mg, 2.40 mmol, 4 eq.) and toluene (0.15 mL, 4 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and fitted with an argon balloon and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (3→4% Et_2O/pentane) afforded ***d*$_3$-655** as a white solid (see assignment for details of deuterium incorporation, 61 mg, 0.21 mmol, 35% yield, ~1:1 d.r.) and **671** as a white solid (<5% D incorporation by quantitative ^1H NMR and ^{13}C NMR, 112 mg, 0.31 mmol, 52% yield).

Data for *d*$_3$-655 from reductive crossover experiment:

^1H NMR (700 MHz, CD_2Cl_2) δ 2.79 – 2.74 (1H, m, 0.91 H, H_1), 2.23 (3H, s, $ArCH_3$), 2.18 (6H, s, $ArCH_3$), 2.05 (6H, s, $ArCH_3$), 1.84 (0.12H, br s, H_{6eq}), 1.63 – 1.57 (1H, m, 1H, H_{5eq}), 1.52 (0.48H, s, H_{2eq}), 1.45 – 1.38 (1H, m, H_{5ax}), 1.38 – 1.34 (1H, m, H_{4eq}), 1.28 (0.47H, br d, J = 12.5 Hz, H_{2ax}), 1.24 – 1.18 (0.13H, m, H_{6ax}), 1.13 (1H, td, J = 13.4, 4.2 Hz, H_{4ax}), 0.95 (3H, s, 3 x H_{8a}), 0.86 (3H, s, 3 x H_{8b}).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 215.2 (C_7), 140.7 (ArC), 135.6 (ArC), 133.3 (ArC x 2), 128.4 (ArC x 2), 49.3 (C_1), 49.2 ($C_{1'}$), 40.5 (1:1:1 triplet, J = 19.5 Hz, C_2), 40.5 (1:1:1 triplet, J = 19.5 Hz, $C_{2'}$), 39.0 (C_4), 33.4 (C_{8a}), 33.4 ($C_{8a'}$), 30.8 (C_3), 28.5 – 27.5 (m, C_6), 24.4 (C_{8b}), 24.3 ($C_{8b'}$), 22.1 (C_5), 18.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

^2H NMR (92 MHz, CH_2Cl_2) δ 2.77 (s, $^2H_1$), 1.85 (s, $^2H_{6eq}$), 1.54 (s, $^2H_{2eq}$), 1.29 (s, $^2H_{2ax}$), 1.21 (s, $^2H_{6ax}$).

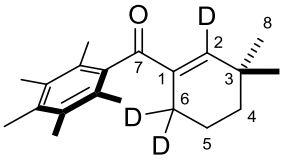
Apart from deuterium incorporation at C2 and C6, the spectral data of ***d₃*-655** was consistent with that of **655** (see data above for **655**)

Data for 671 from reductive crossover experiment:

<5% D incorporation at the 2- and 6-positions by quantitative ^{1}H NMR and ^{13}C NMR.

The ^{1}H NMR data was identical to that described previously for non-deuterated **671** and the peaks corresponding to H_2 and H_6 integrated to >95% implying <5% D incorporation at these positions.

(3,3-Dimethylcyclohex-1-en-1-yl-2,6,6-*d₃*)(2,3,4,5,6-pentamethylphenyl)methanone, *d₃*-541



2,2-Dimethylpentane-1,1,5,5-*d₄*-1,5-diol (164 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 1.** The title compound was afforded after purification by FCC (2→3% Et_2O/pentane) as a white solid (130 mg, 0.450 mmol, 75% yield, >95% D incorporation by quantitative ^{1}H NMR).

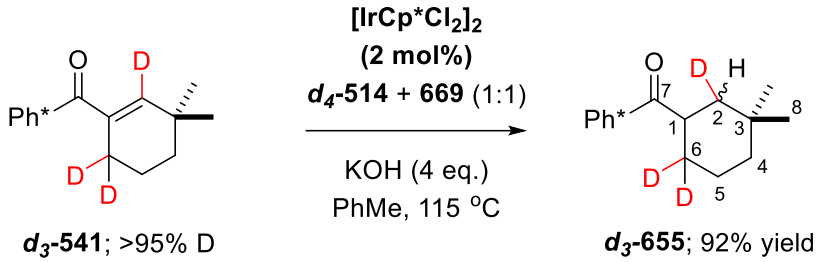
^{1}H NMR (700 MHz, $CDCl_3$) δ 2.24 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.00 (s, 6H, $ArCH_3$ x 2), 1.78 – 1.62 (m, 2H, H_5 x 2), 1.54 – 1.38 (m, 2H, H_4 x 2), 0.96 (s, 6H, H_8 x 6). [N.B. in the absence of any deuteration, the integral for H_2 (δ = 6.19 ppm) would be 1.00, and the integral for H_6 (δ = 2.36 ppm) would be 2.00. The measured integral by quantitative ^{1}H NMR was for H_2 was 0.03 and for H_6 was <0.10 (n.b. peak overlaps with ^{13}C satellite peak for $ArCH_3$ peak), thus indicating 0.97 D at H_2 and >1.90 D at H_6, i.e. >95% D at each position].

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_7), 154.0 (1:1:1 triplet, 23.5 Hz, C_2), 138.4 (ArC), 138.0 (C_1), 135.1 (ArC), 132.7 (ArC x 2), 129.3 (ArC x 2), 36.7 (C_4), 32.9 (C_3), 28.9 (C_8 x 2), 22.2 (1:2:3:2:1 quintet, *J* =22.0 Hz, C_6), 19.1 (C_5), 17.5 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

^{2}H NMR (92 MHz, $CHCl_3$) δ 6.19, (s, $^{2}H_2$), 2.32 (s, $^{2}H_6$ x 2).

Apart from deuterium incorporation at C_2 and C_6, the spectral data of ***d₃*-541** was consistent with that of **541** (see data above for **541**).

Transfer hydrogenation of deuterated enone



***d*$_3$-541**; >95% D

***d*$_3$-655**; 92% yield

A 2-5mL Biotage® microwave vial was charged with 2,2-dimethylpentane-1,1,5,5-*d*$_4$-1,5-diol (16 mg, 0.12 mmol, 1 eq.), 3-(2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl)propan-1-ol (25 mg, 0.12 mmol, 1 eq.), (3,3-dimethylcyclohex-1-en-1-yl-2,6,6-*d*$_3$)(2,3,4,5,6-pentamethylphenyl)methanone (35 mg, 0.12 mmol, 1 eq.), $[IrCp^*Cl_2]_2$ (1.9 mg, 0.0026 mmol, 2 mol% dimer), KOH (27 mg, 0.48 mmol, 4 eq.) and toluene (0.03 mL, 4 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and fitted with an argon balloon and heated at 115 °C for 24 hours. After cooling to RT, the reaction mixture was diluted with aq. HCl (3 M, 5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (3% Et_2O/pentane) afforded ***d*$_3$-655** as a white solid (see assignment for details of deuterium incorporation, 32 mg, 0.11 mmol, 92% yield, ~1:1 d.r.).

The spectral data for ***d*$_3$-655** was very similar to that described in the reductive cross over experiment.

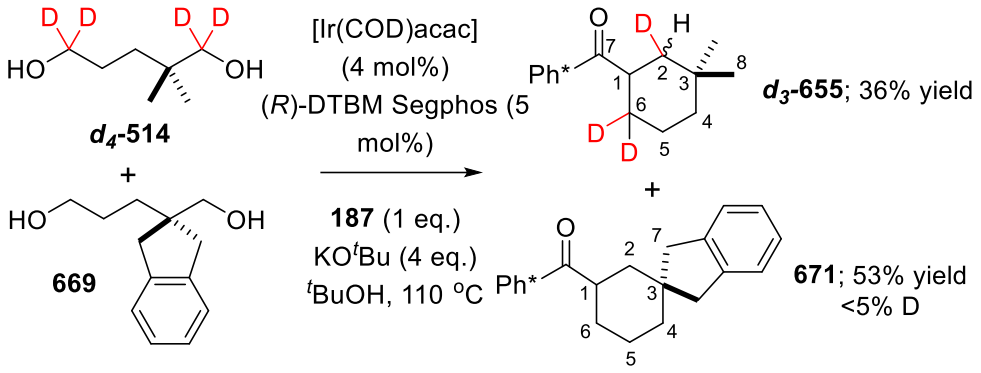
^{1}H NMR (700 MHz, CD_2Cl_2) δ 2.79 – 2.74 (1H, m, 0.90 H, H_1), 2.23 (3H, s, $ArCH_3$), 2.18 (6H, s, $ArCH_3$), 2.05 (6H, s, $ArCH_3$), 1.84 (0.07H, br s, H_{6eq}), 1.63 – 1.57 (1H, m, 1H, H_{5eq}), 1.52 (0.51H, s, H_{2eq}), 1.45 – 1.38 (1H, m, H_{5ax}), 1.38 – 1.34 (1H, m, H_{4eq}), 1.28 (0.50 H, br d, J = 12.5 Hz, H_{2ax}), 1.24 – 1.18 (0.11H, m, H_{6ax}), 1.13 (1H, td, J = 13.4, 4.2 Hz, H_{4ax}), 0.95 (3H, s, 3 x H_{8a}), 0.86 (3H, s, 3 x H_{8b}).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 215.2 (C_7), 140.7 (ArC), 135.6 (ArC), 133.3 (ArC x 2), 128.4 (ArC x 2), 49.3 (C_1), 49.2 ($C_{1'}$), 40.5 (1:1:1 triplet, J = 19.5 Hz, C_2), 40.5 (1:1:1 triplet, J = 19.5 Hz, $C_{2'}$), 39.0 (C_4), 33.4 (C_{8a}), 33.4 ($C_{8a'}$), 30.8 (C_3), 28.5 – 27.5 (m, C_6), 24.4 (C_{8b}), 24.3 ($C_{8b'}$), 22.1 (C_5), 18.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

^{2}H NMR (92 MHz, CH_2Cl_2) δ 2.77 (s, $^2H_1$), 1.85 (s, $^2H_{6eq}$), 1.54 (s, $^2H_{2eq}$), 1.29 (s, $^2H_{2ax}$), 1.21 (s, $^2H_{6ax}$).

Apart from deuterium incorporation at C2 and C6, the spectral data of ***d*$_3$-655** was consistent with that of **655** (see data above for **655**).

Reductive crossover experiment with Ir(COD)acac and *(R)*-DTBM Segphos:



A 2-5mL Biotage® microwave vial was charged with 2,2-dimethylpentane-1,1,5,5-d_4-1,5-diol (82 mg, 0.60 mmol, 1 eq.), 3-(2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl)propan-1-ol (124 mg, 0.60 mmol, 1 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (114 mg, 0.60 mmol, 1 eq.), [Ir(COD)acac] (9.6 mg, 0.024 mmol, 4 mol%), (*R*)-DTBM SEGPHOS (35.4 mg, 0.03 mmol, 5 mol%), ^{t}BUOH (0.2 mL, 3 M) and KO*t*Bu (270 mg, 2.5 mmol, 4eq.). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 110 °C for 24 hours. After cooling to RT, the reaction mixture was filtered through silica (eluting with Et_2O). The crude ethereal solution was treated with tert-butyl hydroperoxide (5-6 M in decane, 100 µL, ~0.56 mmol), swirled and allowed to stand at RT for 10 min, and then dry loaded onto silica gel Purification by FCC (3-4% Et_2O/pentane) afforded ***d*$_3$-655** as a white solid (see assignment for details of deuterium incorporation, 62 mg, 0.22 mmol, 36% yield, ~1:1 d.r.) and **671** as a white solid (<5% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR, 115 mg, 0.32 mmol, 53% yield).

Data for *d*$_3$-655 from reductive crossover experiment:

^{1}H NMR (700 MHz, CD_2Cl_2) δ 2.79 – 2.74 (1H, m, 0.93 H, H_1), 2.23 (3H, s, $ArCH_3$), 2.18 (6H, s, $ArCH_3$), 2.05 (6H, s, $ArCH_3$), 1.84 (0.09H, br s, H_{6eq}), 1.63 – 1.57 (1H, m, 1H, H_{5eq}), 1.52 (0.48H, s, H_{2eq}), 1.45 – 1.38 (1H, m, H_{5ax}), 1.38 – 1.34 (1H, m, H_{4eq}), 1.28 (0.47H, br d, *J* = 12.5 Hz, H_{2ax}), 1.24 – 1.18 (0.1 H, m, H_{6ax}), 1.13 (1H, td, *J* = 13.4, 4.2 Hz, H_{4ax}), 0.95 (3H, s, 3 x H_{8a}), 0.86 (3H, s, 3 x H_{8b}).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 215.2 (C_7), 140.7 (ArC), 135.6 (ArC), 133.3 (ArC x 2), 128.4 (ArC x 2), 49.3 (C_1), 49.2 ($C_{1'}$), 40.5 (1:1:1 triplet, *J* = 19.5 Hz, C_2), 40.5 (1:1:1 triplet, *J* = 19.5 Hz, $C_{2'}$), 39.0 (C_4), 33.4 (C_{8a}), 33.4 ($C_{8a'}$), 30.8 (C_3), 28.5 – 27.5 (m, C_6), 24.4 (C_{8b}), 24.3 ($C_{8b'}$), 22.1 (C_5), 18.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

^{2}H NMR (92 MHz, CH_2Cl_2) δ 2.77 (s, $^2H_1$), 1.85 (s, $^2H_{6eq}$), 1.54 (s, $^2H_{2eq}$), 1.29 (s, $^2H_{2ax}$), 1.21 (s, $^2H_{6ax}$).

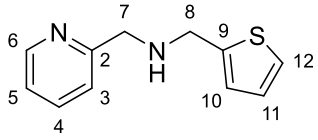
Apart from deuterium incorporation at C2 and C6, the spectral data of ***d₃*-655** was consistent with that of **655** (see data above for **655**).

Data for 671 from reductive crossover experiment:

<5% D incorporation at the 2- and 6-positions by quantitative ^{1}H NMR and ^{13}C NMR.

The ^{1}H NMR data was identical to that described previously for non-deuterated **671** and the peaks corresponding to H_2 and H_6 integrated to >95% implying <5% D incorporation at these positions

1-(Pyridin-2-yl)-N-(thiophen-2-ylmethyl)methanamine 678



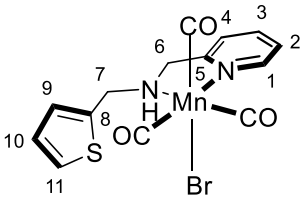
A round bottom flask under an argon atmosphere was charged with 2-(aminomethyl)-pyridine (476 mg, 4.4 mmol, 1.1 eq.), dry methanol (40 mL, 0.1 M), 2-thiophenecarboxyladehyde (449 mg, 4 mmol, 1 eq.) and oven dried Na_2SO_4 (1.42 g, 10 mmol, 2.5 eq.). The flask was then wrapped in foil, and stirred for 16 h at RT. The reaction mixture was then filtered, and $NaBH_4$ (151 mg, 4 mmol, 1 eq.) was added to the solution and heated at 50 °C for 1h. The reaction mixture was then concentrated *in vacuo*. The resulting residue was diluted with water (5 mL), extracted with CH_2Cl_2 (3 x 20 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (80% EtOAc/pentane) as a colourless oil (554 mg, 2.71 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 5, 2, 1.0 Hz, 1H, H_6), 7.64 (td, *J* = 7.5, 2.0 Hz, 1H, H_4), 7.32 (dt, *J* = 8.0, 1.0 Hz, 1H, H_3), 7.25 – 7.19 (m, 1H, H_{12}), 7.19 – 7.12 (m, 1H, H_5), 6.98 – 6.91 (m, 2H, H_{10}, H_{11}), 4.04 (s, 2H, H_7 x 2), 3.96 (s, 2H, H_8 x 2), 2.16 (s, 1H, NH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C_2), 149.5 (C_6), 144.1 (C_9), 136.6 (C_4), 126.8 (C_{11}), 125.1 (C_{10}), 124.6 (C_{12}), 122.5 (C_5), 122.1 (C_3), 54.32 (C_8), 48.1 (C_7).

The spectroscopic data matched that previously reported in the literature.[111]

Mn I Complex 340



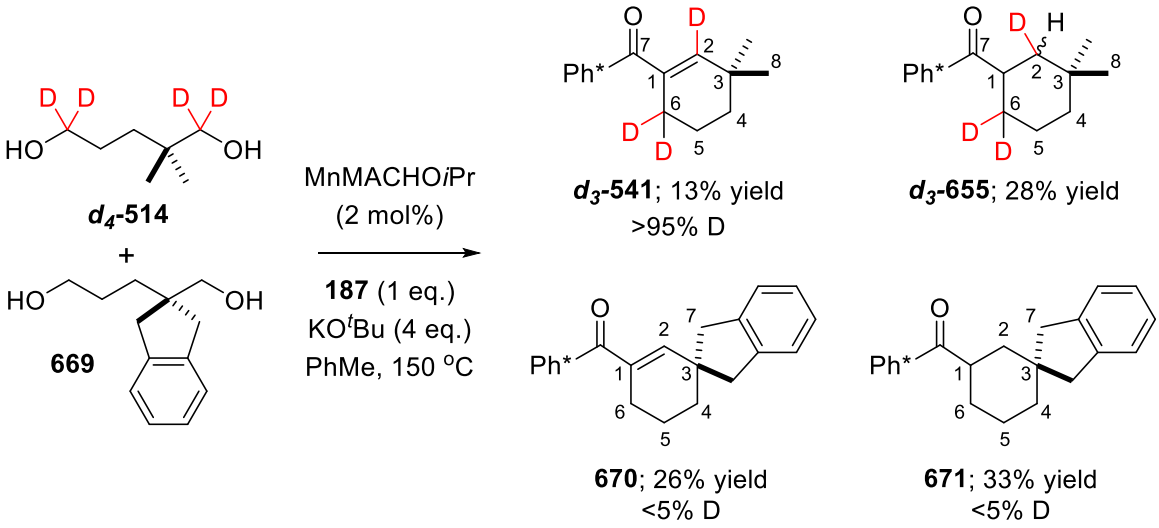
A 2-5 mL Biotage® microwave vial was charged with 1-(Pyridin-2-yl)-N-(thiophen-2-ylmethyl)methanamine (40.8 mg, 0.2 mmol, 1 eq.) $Mn(CO)_5Br$ (56 mg, 0.204 mmol, 1.02 eq.), and sealed with a microwave vial cap (containing a Reseal® septum). The vial was degassed and backfilled with argon, and then dry THF (4 mL, 0.05M) was added *via* syringe. The vial was then sealed with Parafilm® and heated at 90 °C for 5 hours. The solvent was then removed under argon, and then the resulting solid was washed with hexane (3 x 2 mL) and dried. The title compound was used without further purification as a brown solid (40 mg, 0.095 mmol, 47% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (br s, 1H, H_1), 7.77 (br s, 1H, H_3), 7.58 – 6.76 (m, 5H, H_2, H_4, H_9, H_{10}, H_{11}), 5.15 – 4.70 (m, 1H, NH), 4.43 – 3.43 (m, 4H, H_6 x 2, H_7 x 2).

^{13}C NMR (126 MHz, $CDCl_3$) δ 222.4 (CO), 221.4 (CO), 221.0 (CO), 158.4 (C_5), 154.1 (C_1), 138.3 (C_8), 137.7 (C_3), 128.9 (ArCH), 127.7 (ArCH), 127.0 (ArCH), 125.0 (ArCH), 121.5 (ArCH), 57.3 (C_6), 53.6 (C_7).

The spectroscopic data matched that previously reported in the literature.[111]

Reductive crossover experiment with Mn MACHO *i*Pr:



A 35mL ACE Pressure was charged with 2,2-dimethylpentane-1,1,5,5-d_4-1,5-diol (68 mg, 0.5 mmol, 2 eq.), 3-(2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl)propan-1-ol (103 mg, 0.5 mmol, 2 eq.), 1-

(2,3,4,5,6-pentamethylphenyl)ethan-1-one (48 mg, 0.25 mmol, 1 eq.), MnMACHO^{i}Pr complex (2.5 mg, 2mol%) and KO^{t}Bu (112 mg, 1 mmol, 4eq.). The vial was then degassed and backfilled with argon three times, and then dry PhMe (1 mL, 0.25M) was added. The vial was then sealed and heated at 150 ^{o}C for 32 hours. After cooling to RT, the reaction mixture was diluted with 3M HCl (3 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$ and concentrated Purification by FCC (2-5% Et_2O/pentane) afforded ***d*$_3$-655** as a white solid (see assignment for details of deuterium incorporation, 20 mg, 0.07 mmol, 28% yield, ~1:1 d.r.), enone **670** as a white solid (<5% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR, 23 mg, 0.065 mmol, 26% yield) and a mixture of enone **d$_3$-541** and cyclohexane **671** (39 mg, 0.115 mmol). This mixture was fully separated by preparative reverse phase HPLC (95% MeCN/H_2O) to give cyclohexane **671** (<5% D incorporation by quantitative ^{1}H NMR and ^{13}C NMR, 30 mg, 0.083 mmol, 33% yield) and deuterated enone **d$_3$-541** (>95% D incorporation by quantitative ^{1}H NMR, ^{2}H NMR and ^{13}C NMR, 9 mg, 0.033 mmol, 13% yield).

Data for cyclohexane *d*$_3$-655 from Mn MACHO ^{i}Pr crossover experiment:

^{1}H NMR (700 MHz, CD_2Cl_2) δ 2.79 – 2.74 (1H, m, 0.93 H, H_1), 2.23 (3H, s, $ArCH_3$), 2.18 (6H, s, $ArCH_3$), 2.05 (6H, s, $ArCH_3$), 1.84 (0.09H, br s, H_{6eq}), 1.63 – 1.57 (1H, m, 1H, H_{5eq}), 1.52 (0.3H, s, H_{2eq}), 1.45 – 1.38 (1H, m, H_{5ax}), 1.38 – 1.34 (1H, m, H_{4eq}), 1.28 (~0.3H, br d, *J* = 12.5 Hz, H_{2ax}), 1.24 – 1.18 (0.15 H, m, H_{6ax}), 1.13 (1H, td, *J* = 13.4, 4.2 Hz, H_{4ax}), 0.95 (3H, s, 3 x H_{8a}), 0.86 (3H, s, 3 x H_{8b}). Due to an unknown impurity at 1.26 ppm, the deuterium incorporation for H_{2eq} and H_{2ax} were confirmed in deuterated toluene.

^{1}H NMR (400 MHz, Tol) δ 2.85 (tt, *J* = 12.0, 3.5 Hz, 1H, H_1), 2.13 (s, 6H, $ArCH_3$ x 2), 2.08 (s, 3H, $ArCH_3$), 2.03 (s, 6H, $ArCH_3$ x 2), 2.01 – 1.95 (m, 0.1H, H_{6eq}), 1.66 – 1.59 (m, 0.3H, H_{2eq}), 1.58 – 1.47 (m, 1.3H, H_{2ax}, H_{5eq}), 1.45 – 1.23 (m, 3H, H_{4eq}, H_{5ax}, H_{6ax} + unknown impurity), 1.14 – 1.02 (m, 1H, H_{4ax}), 0.95 (s, 3H, CH_3), 0.81 (s, 3H, CH_3).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 215.2 (C_7), 140.7 (ArC), 135.6 (ArC), 133.3 (ArC x 2), 128.4 (ArC x 2), 49.3 (C_1), 49.2 ($C_{1'}$), 40.5 (1:1:1 triplet, *J* = 19.5 Hz, C_2), 40.5 (1:1:1 triplet, *J* = 19.5 Hz, $C_{2'}$), 39.0 (C_4), 33.4 (C_{8a}), 33.4 ($C_{8a'}$), 30.8 (C_3), 28.5 – 27.5 (m, C_6), 24.4 (C_{8b}), 24.3 ($C_{8b'}$), 22.1 (C_5), 18.1 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

^{2}H NMR (92 MHz, CH_2Cl_2) δ 2.77 (s, $^{2}H_1$), 1.85 (s, $^{2}H_{6eq}$), 1.54 (s, $^{2}H_{2eq}$), 1.29 (s, $^{2}H_{2ax}$), 1.21 (s, $^{2}H_{6ax}$).

Apart from deuterium incorporation at C_2 and C_6, the spectral data of ***d*$_3$-655** was consistent with that of **655** (see data above for **655**).

Data for cyclohexene *d*$_3$-541 from Mn MACHO *i*Pr crossover experiment:

^{1}H NMR (700 MHz, $CDCl_3$) δ 2.24 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.00 (s, 6H, $ArCH_3$ x 2), 1.78 – 1.62 (m, 2H, H_5 x 2), 1.54 – 1.38 (m, 2H, H_4 x 2), 0.96 (s, 6H, H_8 x 6). [N.B. in the absence of any deuteration, the integral for H_2 (δ = 6.19 ppm) would be 1.00, and the integral for H_6 (δ = 2.36 ppm) would be 2.00. The measured integral by quantitative ^{1}H NMR was for H_2 was 0.03 and for H_6 was <0.10 (n.b. peak overlaps with ^{13}C satellite peak for $ArCH_3$ peak), thus indicating 0.97 D at H_2 and >1.90 D at H_6, i.e. >95% D at each position].

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9 (C_7), 154.0 (1:1:1 triplet, 23.5 Hz, C_2), 138.4 (ArC), 138.0 (C_1), 135.1 (ArC), 132.7 (ArC x 2), 129.3 (ArC x 2), 36.7 (C_4), 32.9 (C_3), 28.9 (C_8 x 2), 22.2 (1:2:3:2:1 quintet, *J* =22.0 Hz, C_6), 19.1 (C_5), 17.5 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

^{2}H NMR (92 MHz, $CHCl_3$) δ 6.19, (s, $^2H_2$), 2.32 (s, $^2H_6$ x 2).

Apart from deuterium incorporation at C_2 and C_6, the spectral data of ***d*$_3$-541** was consistent with that of **541** (see data above for **541**).

Data for Cyclohexane 671 from Mn MACHO *i*Pr crossover experiment:

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.20 – 7.02 (m, 4H, ArCH x 4), 2.88 – 2.66 (m, 5H, H_1, H_7 x 4), 2.23 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.06 (s, 6H, $ArCH_3$ x 2), 1.93 (dtq, J = 10.5, 3.5, 2.0 Hz, 1H, H_{6eq}), 1.87 (dq, 0.86H, J = 13.0, 2.5 Hz, H_{2eq}), 1.75 – 1.69 (m, 1H, H_{5eq}), 1.67 – 1.62 (m, 1H, H_{4eq}), 1.60 (t, 0.88H, J = 13.0 Hz, H_{2ax}), 1.47 (qt, J = 13.5, 3.5 Hz, 1H, H_{5ax}), 1.38 – 1.29 (m, 2H, H_{4ax}, H_{7ax}). See <5% D incorporation at each position, except at H_{2eq} and H_{2ax}, which have partial D incorporation (0.12-14D).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 214.8 (C_8), 143.1 (ArC), 143.0 (ArC), 140.7 (ArC), 135.9 (ArC), 133.6 (ArC x 2), 128.5 (ArC x 2), 126.7 (ArC), 126.6 (ArC), 125.3 (ArC), 125.2 (ArC), 50.8 (C_1), 49.4 (C_7), 44.2 (C_3), 42.4 (C_7), 39.5 (C_2), 39.1 (1:1:1 t, J = 20.0 Hz, C_2), 39.1 (1:1:1 t, J = 20. Hz, $C_{2'}$), 37.4 (C_4), 28.8 (C_6), 23.4 (C_5), 18.3 ($ArCH_3$ x 2), 17.0 ($ArCH_3$), 16.3 ($ArCH_3$ x 2).

^{2}H NMR (92 MHz, CH_2Cl_2) δ 1.87 (s, $^2H_{2eq}$), 1.60 (s, $^2H_{2ax}$).

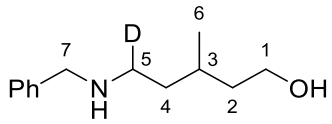
Apart from deuterium incorporation at C_2, the spectral data of **671** was consistent with that of **671** (see data above for **671**).

Data for Cyclohexene 670 from Mn MACHO *i*Pr crossover experiment:

<5% D incorporation at the 2- and 6-positions by quantitative ^{1}H NMR and ^{13}C NMR.

The ^{1}H NMR data was identical to that described previously for non-deuterated **670** and the peaks corresponding to H_2 and H_6 integrated to >95% implying <5% D incorporation at these positions.

5-(Benzylamino)-3-methylpentan-5-d-1-ol 700



A 2-5 mL Biotage® microwave vial was charged with $NaHCO_3$ (1.7 mg, 0.02 mmol, 0.02 eq.), 4-Methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 mmol, 1.0 eq.), and then sealed with a microwave vial cap (containing a Reseal™ septum) and degassed and backfilled with argon. Dry toluene (0.5 mL, 2 M) and benzylamine (0.16 mL, 1.5 mmol, 1.5 eq.) was then added by syringe. The vial was sealed with Parafilm®, and heated 110 °C for 16 hours. The reaction was then cooled to 0 °C, diluted with methanol (1 mL, 1M) and $NaBD_4$ was added (84 mg, 2 mmol, 2 eq.). The reaction was resealed with a microwave vial cap, fitted with an argon balloon and stirred for 1h at RT. The reaction was then quenched with water (2 mL), extracted with EtOAc (4 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% $MeOH/CH_2Cl_2$) as a colourless oil (110 mg, 0.528 mmol 53% yield, 1:1 d.r, >95% D incorporation at C_5 by quantitative ^{1}H, ^{2}H and ^{13}C NMR). The

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 5H, ArCH x 5), 3.80 – 3.75 (m, 2H, H_7 x 2), 3.73 – 3.57 (m, 2H, H_1 x 2), 2.73 – 2.66 (m, 0.54H, H_{5a}), 2.65 – 2.58 (m, 0.50H, H_{5b}), 2.16 (s, 2H, H_1 x 2), 1.77 – 1.61 (m, 1H, H_3), 1.62 – 1.48 (m, 2H, H_{2a}, H_{4a}), 1.49 – 1.30 (m, 2H, H_{2b}, H_{4b}), 0.91 (d, *J* = 6.5 Hz, 3H, H_6 x 3). Integral of peaks for H_5 1.04, indicating a deuterium incorporation of >95%.

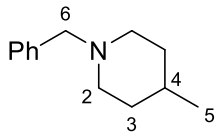
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 (ArC), 128.6 (ArCH x 2), 128.4 (ArCH x 2), 127.2 (ArCH), 60.9 (C_1), 54.2 (C_7), 46.8 (1:1:1 t, 20.0 Hz, H_5), 39.8 (C_2), 36.9 (C_4), 27.8 (C_3), 20.5 (C_6).

^{2}H NMR (77 MHz, $CDCl_3$) δ 2.92 – 2.34 (m, 1H, $^{2}H_5$).

HRMS (ESI+): Found $[M+H]^+$ = 209.1758; $C_{13}H_{21}{}^{2}HON$ requires 209.1759, Δ -0.34 ppm

IR (film) ν_{max}/cm^{-1} 3298, 2956, 2922, 2870, 1454, 1061, 737

1-Benzyl-4-methylpiperidine 701



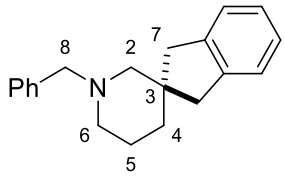
A 2-5 mL Biotage® microwave vial was charged with 3-methyl pentane-1,5-diol (118 mg, 1 mmol, 1.0 eq.), $[IrCp^*Cl_2]_2$ (8 mg, 1.0 mol%) and $NaHCO_3$ (1.7 mg, 2.0 mol%). The vial was sealed with a microwave vial cap (containing a Reseal® septum), degassed and backfilled with argon. Dry toluene (0.5 mL, 2 M) and dry benzylamine (0.16 mL, 1.5 mmol, 1.5 eq.) were then added *via* syringe. The vial was sealed with Parafilm®, and heated at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. The title compound was afforded after purification by FCC (1:1 Et_2O/pentane) as a yellow oil (180 mg, 0.95 mmol, 95% yield)

^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.03 (m, 5H, ArCH x 5), 3.39 (s, 2H, H_6 x 2), 2.85 – 2.63 (m, 2H, H_{2a} x 2), 1.90 – 1.79 (m, 2H, H_{2b} x 2), 1.55 – 1.39 (m, 2H, H_3 x 2), 1.41 – 1.09 (m, 3H, H_3 x 2, H_4), 0.83 (d, *J* = 6.0 Hz, 3H, H_5 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (ArC), 129.3 (ArCH x 2), 128.2 (ArCH x 2), 126.9 (ArCH), 63.7 (C_6), 54.1 (C_2 x 2), 34.5 (C_3 x 2), 30.9 (C_4), 22.0 (C_5).

The spectroscopic data matched that previously reported in the literature.[112]

1'-Benzyl-1,3-dihydrospiro[indene-2,3'-piperidine] 708



A 2-5 mL Biotage® microwave vial was charged with 3-(2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl)propan-1-ol (206 mg, 1 mmol, 1.0 eq.), $[IrCp^*Cl_2]_2$ (8 mg, 1.0 mol%) and $NaHCO_3$ (1.7 mg, 2.0 mol%). The vial was sealed with a microwave vial cap (containing a Reseal® septum), degassed and backfilled with argon. Dry toluene (0.5 mL, 2 M) and dry benzylamine (0.16 mL, 1.5 mmol, 1.5 eq.) were then added *via* syringe. The vial was sealed with Parafilm®, and heated at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (148 mg, 0.535 mmol, 54% yield).

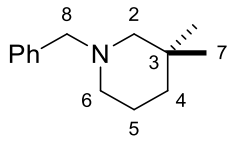
^1H NMR (400 MHz, $CDCl_3$) δ 7.51 – 6.86 (m, 9H, ArCH x 9), 3.48 (s, 2H, H_8 x 2), 2.96 (d, *J* = 16.0 Hz, 2H, H_{7a} x 2), 2.78 (d, *J* = 16.0 Hz, 2H, H_{7b} x 2), 2.51 – 2.20 (m, 4H, H_2 x 2, H_6 x 2), 1.67 (p, *J* = 5.5 Hz, 2H, H_5 x 2), 1.61 – 1.51 (m, 2H, H_4 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8 (ArC x 2), 139.3 (ArC), 128.9 (ArCH x 2), 128.2 (ArCH x 2), 126.9 (ArCH), 126.2 (ArCH x 2), 125.0 (ArCH x 2), 64.2 (C_2), 63.3 (C_8), 54.1 (C_6), 44.3 (C_7 x 2), 43.7 (C_3), 36.4 (C_4), 23.6 (C_5).

HRMS (ESI+): Found $[M+H]^+$ = 278.1904; $C_{20}H_{24}N$ requires 278.1903, Δ 0.37 ppm

IR (film) ν_{max}/cm^{-1} 2927, 2792, 2755, 1453, 1124, 1027, 736, 698

1-Benzyl-3,3-dimethylpiperidine 709



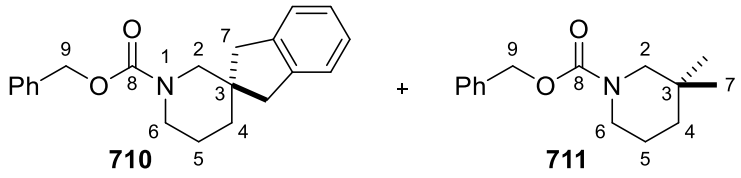
A 2-5 mL Biotage® microwave vial was charged with 2,2-dimethylpentane-1,5-diol (132 mg, 1 mmol, 1.0 eq.), $[IrCp^*Cl_2]_2$ (8 mg, 1.0 mol%) and $NaHCO_3$ (1.7 mg, 2.0 mol%). The vial was sealed with a microwave vial cap (containing a Reseal® septum), degassed and backfilled with argon. Dry toluene (0.5 mL, 2 M) and dry benzylamine (0.16 mL, 1.5 mmol, 1.5 eq.) were then added *via* syringe. The vial was sealed with Parafilm®, and heated at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (158 mg, 0.778 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.17 (m, 5H, ArCH x 5), 3.47 (s, 2H, H_8 x 2), 2.36 (Br s, 2H, H_6 x 2), 2.04 (Br s, 2H, H_2 x 2), 1.63 (p, *J* = 6.0 Hz, 2H, H_5 x 2), 1.26 (t, *J* = 6.0 Hz, 2H, H_4 x 2), 0.96 (s, 6H, H_7 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (ArC), 128.8 (ArCH x 2), 128.2 (ArCH x 2), 126.8 (ArCH), 66.1 (C_2), 63.5 (C_8), 54.8 (C_6), 37.8 (C_4), 31.1 (C_3), 27.5 (C_7 x 2), 22.9 (C_5).

The spectroscopic data matched that previously reported in the literature.[112]

Benzyl 1,3-dihydrospiro[indene-2,3'-piperidine]-1'-carboxylate 710 and benzyl 3,3-dimethylpiperidine-1-carboxylate 711



A 2-5 mL Biotage® microwave vial was charged with a mixture of 1-Benzyl-3,3-dimethylpiperidine (10 mg, 0.05 mmol, 1 eq.) and 1'-Benzyl-1,3-dihydrospiro[indene-2,3'-piperidine] (14 mg, 0.05 mmol,

1eq.) and benzyl chloroformate in toluene (0.2 mL, 3M, 0.6 mmol, 12 eq.). The vial was sealed with a microwave vial cap (containing a Reseal® septum), fitted with an argon balloon and heated at 80 °C for 15 hours. The reaction was then cooled to RT, and quenched with 3M HCl (3 mL). The product was extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by FCC (5-10% Et_2O/pentane) afforded benzyl 1,3-dihydrospiro[indene-2,3'-piperidine]-1'-carboxylate **710** (10 mg, 0.04 mmol, 80% yield), and benzyl 3,3-dimethylpiperidine-1-carboxylate **711** (14 mg, 0.044 mmol, 87% yield) as colourless oils.

Benzyl 1,3-dihydrospiro[indene-2,3'-piperidine]-1'-carboxylate 710

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.18 (m, 5H, ArCH x 5), 7.14 (s, 4H, ArCH x 4), 5.28 – 4.87 (m, 2H, H_9 x 2), 3.50 (t, *J* = 5.5 Hz, 2H, H_6 x 2), 3.33 (s, 2H, H_2 x 2), 2.92 – 2.64 (m, 4H, H_7 x 4), 1.89 – 1.52 (m, 4H, H_4 x 2, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (ArC x 2), 136.95 (ArC), 128.41 (ArCH x 2), 127.8 (ArCH x 2), 127.6 (ArCH), 126.3 (ArCH x 2), 124.9 (ArCH x 2), 66.8 (C_9), 53.2 (C_2), 44.4 (C_6), 43.6 (C_3), 42.7 (C_7 x 2), 36.2 (C_4), 23.0 (C_5). C_8 not observed.

HRMS (ESI+): Found $[M+H]^+$ = 322.1803; $C_{21}H_{24}O_2N$ requires 322.1802, Δ 0.37 ppm

IR (film) ν_{max}/cm^{-1} 2927, 2849, 1698, 1431, 1249, 1177, 738, 698

Benzyl 3,3-dimethylpiperidine-1-carboxylate 711

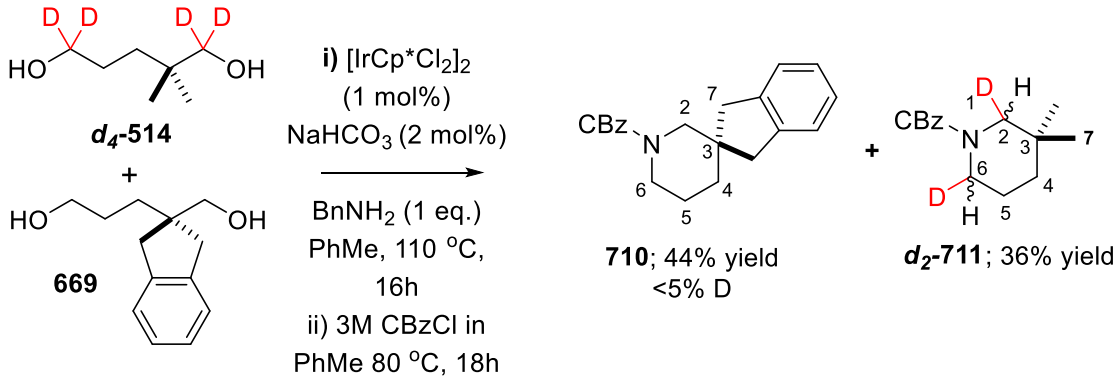
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H, ArCH x 5), 5.13 (s, 2H, H_9 x 2), 3.41 (t, *J* = 5.5 Hz, 2H, H_6 x 2), 3.14 (s, 2H, H_2 x 2), 1.66 – 1.48 (m, 2H, H_5 x 2), 1.40 – 1.32 (m, 2H, H_4 x 2), 0.99 – 0.80 (m, 6H, H_7 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C_8), 137.3 (ArC), 128.6 (ArCH x 2), 128.0 (ArCH), 127.9 (ArCH x 2), 67.0 (C_9), 55.7 (br s, C_2), 44.6 (C_6), 37.9 (C_4), 31.0 (C_3), 26.1 (C_7 x 2), 21.8 (br s, C_5). N.b broad signals at 55.7 and 21.8 observed due to rotamers.

HRMS (ESI+): Found $[M+H]^+$ = 248.1646; $C_{15}H_{22}O_2N$ requires 248.1645, Δ 0.38 ppm

IR (film) ν_{max}/cm^{-1} 2950, 2862, 1699, 1431, 1272, 1193, 984, 764

Piperidine reductive crossover experiment:



A 2-5 mL Biotage® microwave vial was charged with 2,2-dimethylpentane-1,1,5,5-d_4-1,5-diol (69 mg, 0.5 mmol, 0.5 eq.), 3-(2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl)propan-1-ol (103 mg, 0.5 mmol, 0.5 eq.), $[IrCp^*Cl_2]_2$ (8 mg, 1.0 mol%) and $NaHCO_3$ (1.7 mg, 2.0 mol%). The vial was sealed with a microwave vial cap (containing a Reseal® septum), degassed and backfilled with argon. Dry toluene (0.5 mL, 2 M) and dry benzylamine (0.16 mL, 1.5 mmol, 1.5 eq.) were then added *via* syringe. The vial was sealed with Parafilm®, and heated at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. An inseparable mixture of **708** and **709** was afforded after purification by FCC (10% Et_2O/pentane, deactivated silica) as a colourless oil (195 mg, 0.8 mmol, 80% yield, 55:45 ratio by Q ^1H NMR).

To determine deuterium incorporation, a portion of the mixture (195 mg, 0.8 mmol) and benzyl chloroformate in toluene (3.2 mL, 3M, 9.6 mmol, 12 eq.) was then added to a 2-5 mL Biotage® microwave vial. The vial was sealed with a microwave vial cap (containing a Reseal® septum), fitted with an argon balloon and heated at 80 °C for 15 hours. The reaction was then cooled to RT, and quenched with 3M HCl (3 mL).The product was extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by FCC (5→10% Et_2O/pentane) afforded **710** (87 mg, 0.287 mmol, 36% yield, <5% D by ^1H and ^{13}C NMR), and D_2-**711** (65 mg, 0.281 mmol, 35% yield, for details of deuterium incorporation, see assignment) as colourless oils.

Data for d_2-711 from crossover experiment:

^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H, ArCH x 5), 5.13 (s, 2H, H_9 x 2), 3.43 – 3.30 (m, 1.03H, H_6 x 2), 3.10 (Br d, *J* = 17.5 Hz, 1.07H, H_2 x 2), 1.66 – 1.48 (m, 2H, H_5 x 2), 1.40 – 1.32 (m, 2H, H_4 x 2), 0.99 – 0.80 (m, 6H, H_7 x 6). The integrals for H_2 and H_6 were both 1 instead of 2, indicating a 1:1 D:H at both positions.

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C_8), 137.2 (ArC), 128.6 (ArCH x 2), 128.0 (ArCH), 127.9 (ArCH x 2), 67.0 (C_9), 55.2 (m, C_2), 44.2 (1:1:1 triplet, *J*=21.5 Hz, C_6), 37.9 (C_4), 30.9 (C_3), 26.3 (C_7), 26.0 ($C_{7'}$), 26.0 ($C_{7''}$), 25.9, ($C_{7'''}$) 21.7 (br s, C_5). N.b broad peaks at 55.2 and 21.7 ppm observed due to rotamers.

^{2}H NMR (92 MHz, $CHCl_3$) δ 3.43 (s, 1H, $^2H_6$), 3.16 (s, 1H, $^2H_2$).

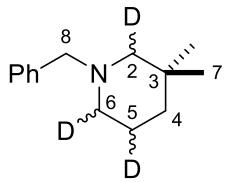
Apart from deuterium incorporation at C_2 and C_6, the spectral data of ***d*$_2$-711** was consistent with that of **711** (see data above for **711**).

Data for 710 from crossover experiment:

<5% D incorporation at the 2- and 6-positions by quantitative ^{1}H NMR and ^{13}C NMR.

The ^{1}H NMR data was identical to that described previously for non-deuterated **710** and the peaks corresponding to H_2 and H_6 integrated to >95% implying <5% D incorporation at these positions.

***D*$_3$-1-Benzyl-3,3-dimethylpiperidine d$_3$-709**



A 2-5 mL Biotage® microwave vial was charged with 2,2-dimethylpentane-1,5-diol (132 mg, 1 mmol, 1.0 eq.), $[IrCp^*Cl_2]_2$ (8 mg, 1.0 mol%) and $NaHCO_3$ (1.7 mg, 2.0 mol%). The vial was sealed with a microwave vial cap (containing a Reseal® septum), degassed and backfilled with argon. D_2O (0.5 mL, 2 M) and dry benzylamine (0.16 mL, 1.5 mmol, 1.5 eq.) were then added *via* syringe. The vial was sealed with Parafilm®, and heated at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (101 mg, 0.5 mmol, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.08 (m, 5H, ArCH x 5), 3.35 (s, 2H, H_8 x 2), 2.24 (1.5 H, Br s, 2H, H_6 x 2), 2.06 – 1.78 (1.63 H, m, 2H, H_2 x 2), 1.58 – 1.42 (1.03 H, m, 1H, H_5 x 2), 1.23 – 1.06 (m, 2H, H_4 x 2), 0.85 (s, 6H, H_7 x 6). Peak at 2.24 integrated to 1.5 H, indicating 0.5 D incorporation. Similarly, peak at 2.06-1.78 integrated to 1.63 H indicating 0.37 D incorporation and peak at 1.58-1.42 integrated to 1.03 H suggesting 0.97 D incorporation.

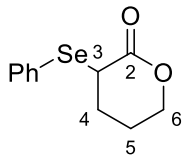
^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7 (ArC), 128.8 (ArCH x 2), 128.2 (ArCH x 2), 126.8 (ArCH), 66.1 (C_2), 66.1 ($C_{2'}$) 65.6 (1:1:1 t, *J* = 20.5 Hz, C_2), 63.49 (C_8), 63.46 ($C_{8'}$), 54.8 (C_6), 54.8 ($C_{6'}$), 54.7 ($C_{6''}$), 54.2 (1:1:1

t, *J* = 25.0 Hz, C_6) 37.8 (C_4), 37.8 ($C_{4'}$), 37.7 ($C_{4''}$), 37.6 ($C_{4'''}$), 31.1 (C_3), 31.0 ($C_{3'}$), 27.5 (Br s, C_7 x 2), 22.85 (C_5), 22.74 ($C_{5'}$), 22.48 (1:1:1 t, *J* = 20.0 Hz, C_5)

^{2}H NMR (92 MHz, $CHCl_3$) δ 2.24 (s, 0.5 x ^{2}H, $^2H_6$), 1.92 (s, 0.5 x ^{2}H, $^2H_2$), 1.50 (s, 1 x ^{2}H, $^2H_5$).

Apart from deuterium incorporation at C_2, C_5 and C_6, the spectral data of ***d*$_3$-709** was consistent with that of **709** (see data above for **709**).

3-(phenylselanyl)tetrahydro-*2H*-pyran-2-one 740



A flame dried three-necked flask under Argon was charged with freshly distilled DIPA (8.05 mL, 57.4 mmol, 1.15 eq.), dry THF (25 mL) and cooled to -78 °C. *n*BuLi (22 mL, 2.5 M in hexanes, 55 mmol, 1.1 eq.) was added dropwise and stirred for 30 minutes. A solution of tetrahydro-*2H*-pyran-2-one (5 g, 49.94 mmol, 1 eq.) in THF (50 mL) was added dropwise and stirred for a further 1 h. The resulting solution was then cannulated into a stirred solution of PhSeCl (11.5 g, 60 mmol 1.2 eq.) in THF (75 mL) at -78 °C, and stirred for 1 h. The reaction was quenched with sat. aq. Ammonium chloride (50 mL), warmed to RT and stirred overnight. The mixture was then extracted with CH_2Cl_2 (3 x 100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (50% Et_2O/pentane) as a white solid (7 g, 27.4 mmol, 55% yield).

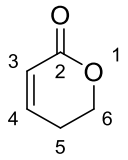
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 2H, ArCH x 2), 7.40 – 7.28 (m, 3H, ArCH x 3), 4.45 – 4.28 (m, 2H, H_6 x 2), 4.02 (dd, *J* = 6.5, 5.5 Hz, 1H, H_3), 2.38 – 2.25 (m, 1H, H_{4a}), 2.16 – 1.95 (m, 2H, H_{4b}, H_{5a}), 1.82 (dddd, *J* = 12.5, 10.5, 6.0, 3.0 Hz, 1H, H_{5b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (C_2), 135.8 (ArCH x 2), 129.4 (ArCH x 2), 129.0 (ArCH), 128.1 (ArC), 69.4 (C_6), 39.2 (C_3), 27.4 (C_4), 21.5 (C_5).

HRMS (ESI+): Found $[M+H]^+$ = 251.01372; $C_{11}H_{13}O_2Se$ requires 251.01348, Δ 0.94 ppm

Due to the high toxicity of organoselenium compounds, IR and melting point was not obtained.

5,6-dihydro-2H-pyran-2-one 741



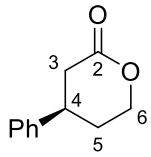
30% aq. H_2O_2 (0.4 mL, 4 mmol, 1 eq.) was added dropwise to a 25 mL RBF charged with 3-(phenylselanyl)tetrahydro-2H-pyran-2-one (1g, 4 mmol, 1 eq.), dry THF (10 mL, 0.4 M) and glacial acetic acid (0.22 mL, 4 mmol) at 0 °C under argon. The reaction was stirred for 30 minutes at 0 °C, warmed to RT and stirred for a further 30 minutes. The reaction mixture was then poured into cold sat. aq. Sodium bicarbonate (10 mL), extracted with diethyl ether (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (30→50% Et_2O/pentane) as a colourless oil (275 mg, 2.8 mmol, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.86 (m, 1H, H_4), 6.03 (dt, *J* = 10.0, 2.0 Hz, 1H, H_3), 4.42 (td, *J* = 6.5, 0.5 Hz, 2H, H_6 x 2), 2.45 (tdd, *J* = 6.5, 4.0, 2.0 Hz, 2H, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8 (C_2), 145.7 (C_4), 121.9 (C_3), 66.6 (C_6), 24.2 (C_5).

The spectroscopic data matched that previously reported in the literature.[168]

***(R)*-4-phenyltetrahydro-2*H*-pyran-2-one 742**



A 5 mL microwave vial was charged with Rh(acac)(C_2H_4) (3.1 mg, 12 mmol, 3 mol%), *(R)*-BINAP (9 mg, 14 mmol, 4 mol%), phenyl boronic acid (244 mg, 2 mmol, 5 eq.), and dry 1,4 dioxane (2 mL, 0.2 M). The vial was then flushed with argon, followed by the addition of water (0.2 mL, 2 M) and 5,6-dihydro-*2H*-pyran-2-one (39 mg, 0.4 mmol, 1 eq.). The resulting mixture was heated at 100 °C for 3 h. After removal of the solvent, the residue was diluted with sat. aq. Sodium bicarbonate (10 mL), extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20% EtOAc/pentane) as a colourless oil (69 mg, 0.39 mmol, 98% yield, 99:1 e.r.).

Racemate: The racemic compound was prepared following the same procedure using racemic BINAP (9 mg, 14 mmol, 4 mol%). 4-phenyltetrahydro-*2H*-pyran-2-one was isolated as a colourless oil (42 mg, 0.24 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H, ArCH x 2), 7.33 – 7.27 (m, 1H, ArCH), 7.27 – 7.21 (m, 2H, ArCH x 2), 4.53 (ddd, J = 11.5, 5.0, 4.0 Hz, 1H, H_{6a}), 4.42 (ddd, J = 11.5, 10.5, 4.0 Hz, 1H, H_{6b}), 3.27 (tdd, J = 10.5, 6.0, 4.5 Hz, 1H, H_4), 2.95 (ddd, J = 17.5, 6.0, 1.5 Hz, 1H, H_{3a}), 2.66 (dd, J = 17.5, 10.5 Hz, 1H, H_{3b}), 2.21 (dqd, J = 14.0, 4.0, 1.5 Hz, 1H, H_{5a}), 2.07 (dtd, J = 14.0, 10.5, 5.0 Hz, 1H, H_{5b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C_2), 142.9 (ArC), 129.1 (ArC x 2), 127.4 (ArC), 126.6 (ArC x 2), 68.8 (C_6), 37.6 (C_3), 37.6 (C_4), 30.5 (C_5).

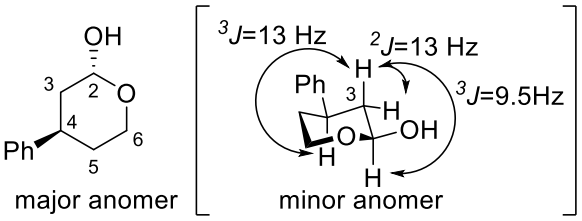
HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (90:10 hexane:IPA, 1.0 mL min-1, 210 nm, room temperature),; t_r (major) = 27.6 min, t_r (minor) = 29.2 min, 99:1 er.

a_{25}^{D}= -5.0 (c=1.0, $CHCl_3$).

HRMS (ESI+): Found $[M+H]^+$ = 177.0910 ; $C_{12}H_{13}O_2$ requires 166.0910, Δ 0.16 ppm

The spectroscopic data matched that previously reported in the literature.[147]

(4*R*)-4-phenyltetrahydro-2*H*-pyran-2-ol 743



A flame dried 3-neck flask under argon was charged with *(R)*-4-phenyltetrahydro-2*H*-pyran-2-one (700 mg, 4 mmol, 1 eq.), dry CH_2Cl_2 (8 mL, 0.5 M), and cooled to -78 °C. DIBAL-H in hexanes (1M, 5.6 mL, 5.6 mmol, 14 eq.) was added dropwise and stirred at -78 °C for 2 hours. Sat. aq. Rochelle salt (20 mL) was added, warmed to RT and stirred vigorously overnight. The aqueous phase was then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was afforded after purification by FCC (40% Et_2O/hexane) as a white solid (706 mg, 3.96 mmol, 99% yield, 99:1 e.r., 66:34 mixture of anomers by ^{1}H NMR). n.b anomeric ratio varies between experiments, ranging between 1:1 and 3:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.15 (m, 10H minor ArCH x 5 and major ArCH x 5), 5.54 – 5.39 (m, 1H, major H_2), 4.86 (ddd, *J* = 9.5, 6.5, 2.0 Hz, 1H, minor H_2), 4.30 – 4.10 (m, 2H, major H_{6ax} and minor H_{6eq}), 3.79 (ddd, *J* = 11.5, 4.5, 2.0 Hz, 1H, major H_{6eq}), 3.74 – 3.62 (m, 1H, minor H_{6ax}), 3.41 (d, *J* = 6.5 Hz, 1H, minor OH), 3.25 (tt, *J* = 12.2, 4.1 Hz, 1H, major H_4), 2.95 – 2.78 (m, 2H, minor H_4, major OH), 2.24 – 2.12 (m, 1H, minor H_{3eq}), 2.02 (ddt, *J* = 13.5, 3.5, 1.5 Hz, 1H, major H_{3eq}), 1.96 – 1.73 (m, 5H, major H_{3ax}, major $H_{5eq,}$ major $H_{5ax,}$ minor $H_{5eq,}$ minor H_{5ax}), 1.62 (td, *J* = 12.5, 9.5 Hz, 1H, minor H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (major Arc), 144.6 (minor Arc), 128.8 (minor Arc x 2), 128.7 (major Arc x 2), 126.9 (major Arc x 2), 126.9 (minor Arc x 2), 126.7 (minor Arc), 126.5 (major Arc), 96.5 (minor C_2), 91.9 (major C_2), 66.0 (minor C_6), 66.0 major C_6), 40.7 (minor C_4), 40.5 (minor C_3), 37.7 (major C_3), 34.7 (major C_4), 33.2 (minor C_5), 32.9 (major C_5).

HRMS (ESI+): Found $[M+H]^+$ = 201.0888 ; $C_{11}H_{14}O_2{}^{23}Na$ requires 201.0886, Δ 1.15 ppm

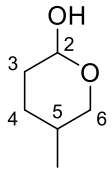
IR (film) ν_{max}/cm^{-1} 3338, 2954, 2877, 1386, 1252, 1140, 874, 760, 701

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (95:5 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature),; major anomer t_r (minor) = 13.4 min, t_r (major)= 15.3 min, minor anomer t_r (major)= 27.7 min, t_r (minor)= 31.1 min. 99:1 er.

$a_{25}{}^{D}$= −42.4 (c=1.0, $CHCl_3$).

m.p.: 128-129 °C

5-Methyltetrahydro-*2H*-pyran-2-ol 745



DIBAL-H in hexanes (1M, 2.8 mL, 2.8 mmol, 1.4 eq.), 3-methyltetrahydro-*2H*-pyran-2-one (233 mg, 2.00 mmol, 1 eq.) and CH_2Cl_2 (4 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (35→50% Et_2O/pentane) as a colourless oil (184 mg, 1.58 mmol, 79% yield, 53:47 mixture of anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (q, *J* = 3.0 Hz, 1H, minor H_2), 4.68 (ddd, *J* = 8.5, 6.0, 2.0 Hz, 1H, major H_2), 3.94 – 3.84 (m, 1H, major H_{6a}), 3.64 – 3.55 (m, 1H, minor H_{6a}), 3.55 – 3.45 (m, 2H, minor H_{6b} and major OH), 3.16 – 3.07 (m, 1H, major H_{6b}), 3.07 – 2.98 (m, 1H, minor OH), 1.92 – 1.35 (m, 9H, major H_3

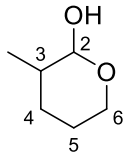
x 2, minor H_3 x 2, major H_{4a}, minor H_4 x 2, major H_5, minor H_5), 1.26 – 1.11 (m, 1H, major H_{4b}), 0.85 (d, *J* = 6.5 Hz, 3H, minor CH_3), 0.81 (d, *J* = 6.5 Hz, 3H, major CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 96.3 (major C_2), 91.6 (minor C_2), 72.2 (major C_6), 66.5 (minor C_6), 32.6 (major C_3), 30.6 (major C_4), 30.3 (major C_5), 30.0 (minor C_5), 30.0 (minor C_3), 26.2 (minor C_4), 17.5 (minor CH_3), 16.6 (major CH_3).

HRMS (ESI+): Found $[M+Na]^+$ = 139.0731; $C_6H_{12}O_2Na$ requires 139.0730, Δ 1.01 ppm

IR (film) ν_{max}/cm^{-1} 3376, 2952, 2931, 2873, 1458, 1059, 1033, 867

3-Methyltetrahydro-*2H*-pyran-2-ol 747



DIBAL-H in hexanes (1M, 2.4 mL, 2.4 mmol, 1.4 eq.), 3-methyltetrahydro-*2H*-pyran-2-one (194 mg, 1.67 mmol, 1 eq.) and CH_2Cl_2 (3 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (35→50% Et_2O/pentane) as a colourless oil (138 g, 1.19 mmol, 70% yield, 2:1 mixture of anomers by ^1H NMR).

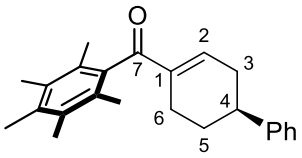
^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (t, *J* = 3.5 Hz, 1H, minor H_2), 4.32 (dd, *J* = 7.5, 6.0 Hz, 1H, major H_2), 4.04 – 3.89 (m, 2H, major H_{6a}, minor H_{6a}), 3.59 – 3.45 (m, 2H, major H_{6b}, minor H_{6b}), 3.30 – 3.14 (m, 1H, major OH), 2.87 – 2.70 (m, 1H, minor OH), 1.88 – 1.41 (m, 9H,major H_3, minor H_3, minor H_4 x 2, major H_{4a}, major H_5 x 2, minor H_5 x 2), 1.27 – 1.14 (m, 1H, major H_{4b}), 0.97 (d, *J* = 6.5 Hz, 3H, major CH_3), 0.92 (d, *J* = 7.0 Hz, 3H, minor CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 101.0 (major C_2), 95.2 (minor C_2), 66.1 (major C_6), 60.3 (minor C_6), 37.3 (major C_3), 34.7(minor C_3), 30.5 (major C_4), 25.9 (minor C_4), 25.3 (major C_5), 25.1 (minor C_5), 17.0 (major CH_3), 16.3 (minor CH_3).

HRMS (ESI+): Found $[M+Na]^+$ = 139.0730; $C_6H_{12}O_2Na$ requires 139.0730, Δ 0.37 ppm

IR (film) ν_{max}/cm^{-1} 3378, 2932, 2852, 1462, 1154, 1067, 1029, 987, 959

***(S)*-(2,3,4,5,6-pentamethylphenyl)(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methanone (-)-387**



Method 1: A flame-dried 2-5 mL Biotage® microwave vial was charged with 1-(2,3,4,5,6-pentamethylphenyl)-2-((2S,4R)-4-phenyltetrahydro-2H-pyran-2-yl)ethan-1-one (52.5 mg, 0.15 mmol, 1 eq., 97:3 e.r.), oven dried Na_2SO_4 (64 mg, 0.45 mmol 3 eq.), 60% wt. NaH (18 mg, 0.45 mmol, 3 eq.), and then sealed with a microwave vial cap (containing a Reseal™ septum) and degassed, and fitted with an argon balloon. Dry toluene (0.5 mL, 0.3 M) was then added, and once the effervescence had stopped, the balloon was removed and the reaction was heated at 110 ^oC for 5h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (38 mg, 0.114 mmol, 76% yield, 97:3 e.r, 100% e.s).

Method 2: (4R)-4-phenyltetrahydro-2H-pyran-2-ol (214 mg, 1.20 mmol, 2 eq.) was subjected to **General Procedure 3**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (140 mg, 0.42 mmol, 70% yield, 58:42 e.r).

^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H, ArCH x 2), 7.25 – 7.18 (m, 3H, ArCH x 3), 6.62 – 6.54 (m, 1H, H_2), 2.91 – 2.80 (m, 1H, H_4), 2.80 – 2.69 (m, 1H, H_{6a}), 2.54 – 2.36 (m, 2H, H_{6b}, H_{3a}), 2.37 – 2.26 (m, 1H, H_{3b}), 2.25 (s, 3H, $ArCH_3$), 2.20 (s, 6H, $ArCH_3$ x 2), 2.12 (dddt, *J* = 11.5, 5.5, 2.5, 1.5 Hz, 1H, H_{5a}), 2.08-2.03 (m, 6H, $ArCH_3$ x 2), 1.86 – 1.72 (m, 1H, H_{5b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3 (C_7), 146.1 (ArC), 144.6 (C_2), 140.6 (C_1), 138.3 (ArC), 135.2 (ArC), 132.8 (ArC x 2), 129.3 (ArC), 129.2 (ArC), 128.7 (ArC x 2), 127.0 (ArC x 2), 126.5 (ArC), 39.6 (C_4), 34.4 (C_3), 29.5 (C_5), 23.2 (C_6), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2). N.B. additional peaks for C_6Me_5 were observed due to restricted rotation about the Ar-C(O) axis

HRMS (ESI+): Found $[M+H]^+$ = 333.2214; $C_{24}H_{29}O$ requires 333.2213, Δ 0.30 ppm

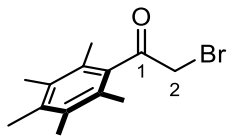
IR (film) ν_{max}/cm^{-1} 2931, 1650, 1635, 1451, 1428, 1379, 1311, 1265, 1181, 852, 756, 699

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IA column (99:1 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature),; t_r (minor) = 7.7 min, t_r (major)= 8.5 min.

$a_{25}{}^D$= −50.0 (c=1.0, CHCl3).

m.p.: 187-188 °C

2-Bromo-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one 755



$AlCl_3$ (12 g, 87.8 mmol, 1.3 eq.) was added portionwise to a stirred solution of pentamethylbenzene (10 g, 67.5 mmol, 1 eq.), bromoacetyl bromide (6.44 mL, 74.3 mmol, 1.1 eq.) in dry CH_2Cl_2 (350 mL, 0.2 M) at 0 °C. The reaction was warmed to RT and stirred for 3 hours. The reaction mixture was then poured onto crushed ice and once melted, extracted with CH_2Cl_2 (3 x 200 mL), dried over $MgSO_4$ and concentrated *in* vacuo. The title compound was afforded after purification by FCC (7% Et_2O/pentane) as a white solid (15 g, 55.7 mmol, 83% yield.

^1H NMR (400 MHz, $CDCl_3$) δ 4.28 (s, 2H, H_2 x 2), 2.25 (s, 3H, $ArCH_3$), 2.19 (s, 6H, $ArCH_3$ x 2), 2.12 (s, 6H, $ArCH_3$ x 2).

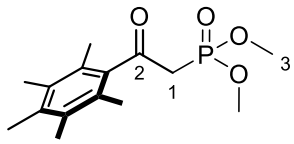
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2 (C_1), 137.1 (ArC), 136.9 (ArC), 133.5 (ArC x 2), 128.3 (ArC x 2), 38.2 (C_2), 17.7 ($ArCH_3$), 16.9 ($ArCH_3$ x 2), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 291.0356; $C_{13}H_{37}{}^{79}BrO^{23}Na$ requires 291.0355, Δ 0.34 ppm

IR (film) ν_{max}/cm^{-1} 2997, 2935, 1717, 1446, 1396, 1306, 1270, 1234, 1101

m.p.: 109-110 °C

Dimethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate 756



A 5 mL RBF was charged with 2-bromo-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (1 g, 3.71 mmol, 1 eq.) and trimethyl phosphite (0.6 mL, 1.3 eq., 4.82 mmol). The flask was fitted with a reflux condenser and heated at reflux 24 h. The title compound was afforded by purification by FCC (20→60→100% EtOAc/pentane) as a white solid (140 mg, 0.47 mmol, 13% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (d, *J* = 11.2 Hz, 6H, H_3 x 6), 3.40 (d, *J* = 20.4 Hz, 2H, H_1 x 2), 2.23 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.16 (s, 6H, $ArCH_3$ x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (d, *J* = 7.0 Hz, C_2), 140.0 (ArC), 136.4 (ArC), 133.4 (ArC x 2), 127.8 (ArC x 2), 53.0 (d, *J* = 6.5 Hz, C_3 x 2), 43.5 (d, *J* = 134.0 Hz, C_1), 17.5 ($ArCH_3$), 16.9 ($ArCH_3$ x 2), 16.1 ($ArCH_3$ x 2).

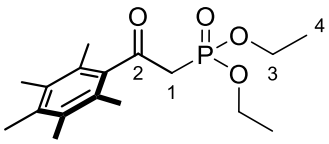
^{31}P NMR (162 MHz, $CDCl_3$) δ 22.6.

HRMS (ESI+): Found $[M+H]^+$ = 299.1405; $C_{15}H_{24}O_4P$ requires 299.1407, Δ -0.45 ppm

IR (film) ν_{max}/cm^{-1} 2954, 1698, 1456, 1259, 1056, 1030, 813

m.p.: 107-108 °C

Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate 757



A 50 mL RBF was charged with 2-bromo-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (15.8 g, 59 mmol, 1 eq.) and triethyl phosphite (11.3 mL, 1.1 eq., 65 mmol). The flask was fitted with a reflux condenser and heated at 140 °C for 24 h. The title compound was afforded by purification by FCC (40→60% EtOAc/pentane) as a white solid (11.4 g, 34.9 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.08 (m, 4H, H_3 x 4), 3.41 (d, J = 20.5 Hz, 2H, H_1 x 2), 2.25 (s, 3H, $ArCH_3$), 2.20 (s, 6H, $ArCH_3$ x 2), 2.19 (s, 6H, $ArCH_3$ x 2), 1.32 (td, J = 7.0 Hz, 0.5 Hz, 6H, H_4 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (d, J = 7.0 Hz, C_2), 134.0 (ArC), 136.1 (ArC), 133.2 (ArC x 2), 127.8 (ArC x 2), 62.4 (d, J = 6.5 Hz, C_3 x 2), 44.2 (d, J = 133.0 Hz, C_1), 17.5 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.3 (d, J = 6.5 Hz, C_4 x 2), 16.0 ($ArCH_3$ x 2).

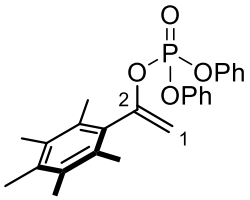
^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8.

HRMS (ESI+): Found $[M+H]^+$ = 327.1721; $C_{17}H_{28}O_4P$ requires 327.1720, Δ 0.26 ppm

IR (film) ν_{max}/cm^{-1} 2982, 2908, 1698, 1256, 1022, 965

m.p.: 89-90 °C

1-(2,3,4,5,6-Pentamethylphenyl)vinyl diphenyl phosphate 760



EtMgBr in Et_2O (1.2 mL, 3 M, 3.6 mmol, 1.2 eq.) was added to a solution of (2,3,4,5,6-pentamethylphenyl)ethan-1-one (570 mg, 3 mmol, 1 eq.) in dry Et_2O (10 mL, 0.3 M) under argon. The flask was fitted with a condenser and heated at 40 °C for 30 minutes. Diphenyl phosphoryl chloride (0.62 mL, 3 mmol, 1 eq.) was added and heated at 40 °C for a further 3 h. The reaction was cooled to 0 °C and quenched with sat. aq. Ammonium chloride (10 mL). The biphasic mixture was then extracted with CH_2Cl_2 (3 x20 mL), dried over $MgSO_4$ and concentrated *in* vacuo. Purification by FCC (20→100% EtOAc/pentane) afforded the title compound as a white solid (312 mg, 0.74 mmol, 25% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H, ArCH x 4), 7.21 – 7.11 (m, 6H, ArCH x 6), 5.51 (t, *J* = 2.5 Hz, 1H, H_1), 4.76 (dd, *J* = 2.5, 1.0 Hz, 1H, H_1), 2.27 (s, 6H, $ArCH_3$ x 2), 2.25 (s, 3H, $ArCH_3$), 2.19 (s, 6H, $ArCH_3$ x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.80 (d, *J* = 9.5 Hz, ArC x 2), 150.65 (d, *J* = 7.5 Hz, C_2), 136.18 (ArC x 2), 132.66 (d, *J* = 1.5 Hz, ArC x 2), 132.55 (d, *J* = 5.5 Hz, ArC), 129.75 (ArC x 5), 125.37 (ArC x2), 120.10 (d, *J* = 5.0 Hz, ArC x 4), 103.35 (d, *J* = 5.0 Hz, C_1). 17.99 ($ArCH_3$ x 2), 16.97 ($ArCH_3$), 16.61 ($ArCH_3$ x 2).

^{31}P NMR (162 MHz, $CDCl_3$) δ -18.6.

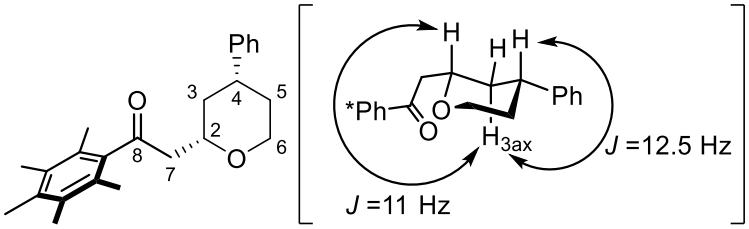
LRMS (ESI+): Found $[M+H]^+$= 423.2; $C_{25}H_{27}O_4P$, requires $[M+H]^+$= 423.2

Acceptable Ionisation not observed by ESI method (>5 ppm error).

IR (film) ν_{max}/cm^{-1} 3026, 2927, 1700, 1654, 1637, 1420, 1217, 814

m.p.: 193-194 °C

1-(2,3,4,5,6-pentamethylphenyl)-2-((*2S,4R*)-4-phenyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 748



A flame-dried 2-5 mL Biotage® microwave vial was charged with Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate (700 mg, 2.25 mmol, 1.3 eq.), 60% wt. NaH (83 mg, 2.08 mmol, 1.2 eq), and then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (3.5 mL, 0.5 M) was then added, stirring the solution for 1 h at RT. (4*R*)-4-Phenyltetrahydro-2*H*-pyran-2-ol (309 mg, 1.73 mmol, 1 eq.) was then added, the balloon was removed, and the reaction was heated at 110 °C for 15 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a white solid (515 mg, 1.47 mmol, 85% yield, cis:trans ratio 90:10 dr by ^1H NMR, 97:3 e.r). The major diastereomer was assigned by coupling constant analysis.

Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, *J* = 7.0, 1.5 Hz, 2H, ArCH x 2), 7.28 – 7.17 (m, 3H, ArCH x 3), 4.20 – 4.01 (m, 2H, H_2, H_{6eq}), 3.71 – 3.59 (m, 1H, H_{6ax}), 3.04 (dd, *J* = 18.0, 7.0 Hz, 1H, H_{7a}), 2.89 (tdd, *J* = 12.5, 8.0, 3.5 Hz, 1H, H_4), 2.75 (dd, *J* = 18.0, 5.0 Hz, 1H, H_{7b}), 2.23 (s, 3H, $ArCH_3$), 2.18 (s, 6H, $ArCH_3$ x 2), 2.12 (s, 6H, $ArCH_3$ x 2), 2.01 (dq, *J* = 12.5, 2.0 Hz, 1H, H_{3eq}), 1.85 – 1.74 (m, 2H, H_5 x 2), 1.50 (td, *J* = 12.5, 11.0 Hz, 1H, H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C_8), 145.7 (ArC), 140.4 (ArC), 135.7 (ArC), 133.3 (ArC x 2), 128.7 (ArCH x 2), 127.7 (ArC x 2), 126.9 (ArCH x 2), 126.5 (ArCH), 73.3 (C_2), 68.4 (C_6), 52.3 (C_7), 41.8 (C_4), 39.6 (C_3), 33.3 (C_5), 17.2 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

Diagnostic peaks for minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 – 4.57 (m, 1H, H_2), 3.81 – 3.75 (m, 2H, H_6 x 2), 3.20 (dd, *J* = 18.0, 6.5 Hz, 1H, H_{7a}), 2.94 (dd, *J* = 18.0, 6.5 Hz, 1H, H_{7b}).

HRMS (ESI+): Found $[M+H]^+$ = 351.2318; $C_{24}H_{31}O_2$ requires 351.2319, Δ -0.21 ppm

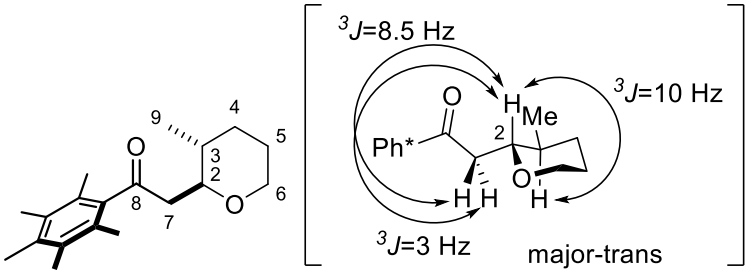
IR (film) ν_{max}/cm^{-1} 3027, 2932, 2848, 1699, 1452, 1380, 1054, 757, 699

a_{25}^D= +2.0 (c=1.0, CHCl3).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® ID column (97:3 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature),; t_r (minor) = 9.6 min, t_r (major)= 10.3 min.

m.p.: 90-91 °C

2-(3-Methyltetrahydro-*2H*-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one 762



A flame-dried 2-5 mL Biotage® microwave vial was charged with diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate (212 mg, 0.65 mmol, 1.3 eq.), 60% wt. NaH (24 mg, 0.6 mmol, 1.2 eq), and then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (3.5 mL, 0.5 M) was then added, stirring the solution for 1 h at RT. 3-Methyltetrahydro-2H-pyran-2-ol (58 mg, 0.5 mmol, 1 eq.) was then added, the balloon was removed, and the reaction was heated at 110 °C for 15 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a white solid (110 mg, 0.381 mmol, 76% yield, cis:trans ratio 66:34 d.r). The major diastereomer was assigned by coupling constant analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (ddd, *J* = 8.5, 3.5, 2.0 Hz, 1H, minor H_2), 3.98 – 3.86 (m, 2H, major H_{6eq}, minor H_{6eq}), 3.60 (ddd, *J* = 10.0, 8.5, 3 Hz, 1H, major H_2), 3.55 – 3.47 (m, 1H, minor H_{6ax}), 3.42 (td, *J* = 12.0, 2.5 Hz, 1H, major H_{6ax}), 2.99 – 2.76 (m, 5H, major H_7 x 2, minor H_{7a}), 2.56 (dd, *J* = 17.5, 3.5 Hz, 1H, minor H_{7b}), 2.24 – 2.21 (m, 6H, major $ArCH_3$, minor $ArCH_3$), 2.20 – 2.15 (m, 12H, major $ArCH_3$ x 2, minor $ArCH_3$ x 2), 2.15 – 2.10 (m, 12H, major $ArCH_3$ x 2, minor $ArCH_3$ x 2), 1.87 – 1.74 (m, 4H, minor H_3, minor $H_{4eq,}$ minor $H_{5eq,}$ major H_{4eq}), 1.73 – 1.60 (m, 2H, minor H_{4ax}, major H_{5ax}), 1.53 (dp, *J* = 13.5, 2.0 Hz, 1H, major H_{5eq}), 1.49 – 1.35 (m, 1H, major H_3), 1.34 – 1.14 (m, 2H, minor $H_{5ax,}$ major H_{4ax}), 0.97 (d, *J* = 7.0 Hz, 1H, minor H_9 x 3), 0.84 (d, *J* = 6.5 Hz, 3H, major H_9 x 3).

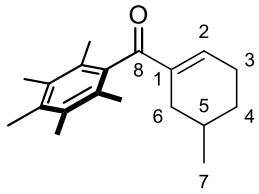
^{13}C NMR (101 MHz, $CDCl_3$) δ 210.4 (major C_8), 210.0 (minor C_8), 140.8 (major ArC), 140.7 (minor ArC), 135.6 (minor ArC x 2), 135.5 (major ArC x 2), 133.2 (minor ArC x 2), 133.2 (major ArC x 2), 127.8 (major ArC), 127.7 (major ArC), 79.3 (major C_2), 75.3 (minor C_2), 68.9 (minor C_6), 68.3 (major C_6), 49.6 (major C_7), 49.5 (minor C_7), 35.1 (major C_3), 32.8 (major C_4), 31.5 (minor C_3), 30.8 (minor C_4), 26.6 (major C_5), 20.9 (minor C_5), 18.3 (major C_9), 17.3 (major $ArCH_3$ x 2, minor $ArCH_3$ x 2), 16.8 (major $ArCH_3$, minor $ArCH_3$), 16.1 (major $ArCH_3$ x 2, minor $ArCH_3$ x 2), 12.4 (minor C_9).

HRMS (ESI+): Found $[M+H]^+$ = 289.2162; $C_{19}H_{29}O_2$ requires 289.2162 Δ -0.08 ppm

IR (film) ν_{max}/cm^{-1} 2929, 2850, 1704, 1460, 1381, 1097,

m.p.: 72-73 °C

(5-Methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone 536



A flame-dried 2-5 mL Biotage® microwave vial was charged with 2-(3-Methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (43.2 mg, 0.15 mmol, 1 eq.), oven dried Na_2SO_4 (64 mg, 0.45 mmol 3 eq.), 60% wt. NaH (18 mg, 0.45 mmol, 3 eq.), and then sealed with a microwave vial cap (containing a Reseal™ septum) and degassed, and fitted with an argon balloon. Dry toluene (0.5 mL, 0.3 M) was then added, and once the effervescence had stopped, the balloon was removed and the reaction was heated at 110 °C for 5h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a white solid (23 mg, 0.085 mmol, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 – 6.34 (m, 1H, H_2), 2.68 (ddt, *J* = 17.5, 4.5, 1.5 Hz, 1H, H_{6a}), 2.26 – 2.13 (m, 11H, H_3 x 2, $ArCH_3$ x 3), 2.01 (s, 6H, $ArCH_3$ x 2), 1.88 (dddt, *J* = 17.5, 9.5, 3.5, 2.5 Hz, 1H, H_{6b}), 1.80 – 1.65 (m, 2H, H_5, H_{4a}), 1.32 – 1.15 (m, 1H, H_{4b}), 1.06 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

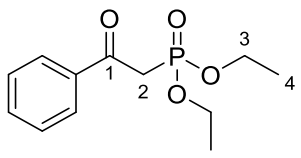
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C_8), 145.2 (C_2), 140.5 (C_1), 138.5 (ArC), 135.0 (ArC), 132.7 (ArC), 132.6 (ArC), 129.3 (ArC), 129.2 (ArC), 30.8 (C_6), 29.9 (C_4), 28.3 (C_5), 26.4 (C_3), 21.7 (C_7), 17.6 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 271.2056; $C_{19}H_{27}O$ requires 271.2056, Δ -0.09 ppm

IR (film) ν_{max}/cm^{-1} 2948, 2924, 1654, 1637, 1455, 1191, 881, 698

m.p.: 94-95 °C

Diethyl (2-oxo-2-phenylethyl)phosphonate 764



A 25 mL RBF was charged with 2-bromo acetophenone (4g, 20 mmol, 1 eq.), triethyl phosphite (3.6 g, 22 mmol, 1.1 eq.) and then fitted with a reflux condenser and heated to 160 °C for 24 h. The reaction mixture was then cooled to RT and purified by FCC (50→100% Et_2O/pentane) to afford the title compound as a colourless oil (4.9g, 19.2 mmol, 96% yield).

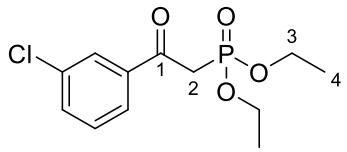
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H, ArCH x 2), 7.65 – 7.56 (m, 1H, ArCH), 7.55 – 7.45 (m, 2H, ArCH x 2), 4.22 – 4.07 (m, 4H, H_3 x 4), 3.65 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.30 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.9.

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1 (d, *J* = 7.0 Hz, C_1), 136.7 (d, *J* = 1.5 Hz, ArC), 133.8 (ArC), 129.2 (ArC x 2), 128.7 (ArC x 2), 62.8 (d, *J* = 6.5 Hz, C_3 x 2), 38.6 (d, *J* = 130.0 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[169]

Diethyl (2-(3-chlorophenyl)-2-oxoethyl)phosphonate 767



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 3-chlorobenzoate (1.23 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50% EtOAc/pentane) as a colourless oil (1.55 g, 5.33 mmol, 74% yield).

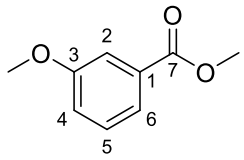
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, *J* = 2.0 Hz, 1H, ArCH), 7.89 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, ArCH), 7.55 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, ArCH), 7.42 (t, *J* = 8.0 Hz, 1H, ArCH), 4.22 – 4.03 (m, 4H, H_3 x 4), 3.59 (d, *J* = 22.5 Hz, 2H, H_2 x 2), 1.28 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.2.

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9 (d, *J* = 6.5 Hz, C_1), 138.1 (d, *J* = 2.0 Hz, ArC), 135.1 (ArC), 133.7 (ArC), 130.1 (ArC), 129.2 (ArC), 127.4 (ArC), 62.9 (d, *J* = 6.5 Hz, C_3 x 2), 38.9 (d, *J* = 129.5 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[170]

Methyl 3-methoxybenzoate 769



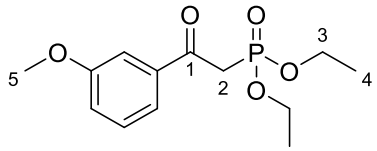
3-methoxy benzoic acid (2.16 g, 14.2 mmol), concentrated sulphuric acid (1 mL) and MeOH (28.4 mL, 0.5 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a white solid (2.22 g, 13.36 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dt, J = 8.0, 1.5 Hz, 1H, H_6), 7.55 (dd, J = 3.0 1.5 Hz, 1H, H_2), 7.34 (t, *J* = 8.0 Hz, 1H, H_5), 7.09 (ddd, J = 8.0, 3.0, 1.0 Hz, 1H, H_4), 3.91 (s, 3H, CH_3), 3.84 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1 (C_7), 159.7 (C_3), 131.6 (C_1), 129.5 (C_5), 122.1 (C_6), 119.6 (C_4), 114.1 (C_2), 55.5 (CH_3), 52.3 (CH_3).

The spectroscopic data matched that previously reported in the literature.[171]

Diethyl (2-(3-methoxyphenyl)-2-oxoethyl)phosphonate 770



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 3-methoxybenzoate (1.2 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a colourless oil (1.9 g, 6.62 mmol, 92% yield).

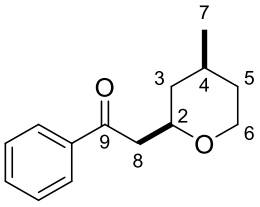
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, ArCH), 7.52 (dd, *J* = 2.5, 1.5 Hz, 1H, ArCH), 7.37 (t, *J* = 8.0 Hz, 1H, ArCH), 7.12 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H, ArCH), 4.27 – 4.03 (m, 4H, H_3 x 4), 3.84 (s, 3H, H_5 x 3), 3.61 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.27 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.9.

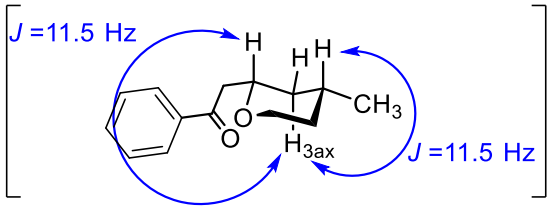
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (d, *J* = 6.5 Hz, C_1), 159.9 (ArC), 138.0 (d, *J* = 2.0 Hz, ArC), 129.7 (ArC), 122.0 (ArC), 120.5 (ArC), 112.9 (ArC), 62.8 (d, *J* = 6.65 Hz, C_3 x 2), 55.6 (C_5), 38.7 (d, *J* = 130.0 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[172]

2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one 775



major *(cis)*



Method 1: Diethyl (2-(phenyl)-2-oxoethyl)phosphonate (356 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (201 mg, 0.92 mmol, 92% yield, 94:6 cis/trans ratio determined by Q ^{1}H NMR).

Method 2: A solution of trimethylsilyl trifluoromethanesulfonate (7 mg, 0.03 mmol, 0.1 eq.) in CH_2Cl_2 (1 mL) was added dropwise to a Schlenk tube charged with 4-Methyltetrahydro-2H-pyran-2-yl acetate (52 mg, 0.33 mmol, 1.1 eq.), trimethyl((1-phenylvinyl)oxy)silane (58 mg, 0.3 mmol, 1 eq.) and CH_2Cl_2 (0.5 mL) cooled to -78 °C under argon. The reaction mixture was stirred for 3 hours, and then quenched with sat. aq. $NaHCO_3$. The reaction mixture was then warmed to RT, extracted with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (59 mg, 0.246 mmol, 82% yield, >95:5 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.92 (m, 2H, ArCH x 2), 7.61 – 7.51 (m, 1H, ArCH), 7.50 – 7.41 (m, 2H, ArCH x 2), 4.01 – 3.89 (m, 2H, H_2, H_{6eq}), 3.46 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, H_{6ax}), 3.30 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{8a}), 2.93 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{8b}), 1.81 – 1.60 (m, 2H, H_{3eq}, H_4), 1.54 (ddq, *J* = 13.5, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.32 – 1.15 (m, 1H, H_{5ax}), 1.00 (dt, *J* = 12.5, 11.5 Hz, 1H, H_{3ax}), 0.94 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C_9), 137.4 (ArC), 133.2 (ArC), 128.7 (ArC x 2), 128.4 (ArC x 2), 74.2 (C_2), 68.4 (C_6), 45.4 (C_8), 40.8 (C_3), 34.6 (C_5), 30.3 (C_4), 22.4 (C_7).

Diagnostic peaks observed for *trans*-2-(4-Methyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one:

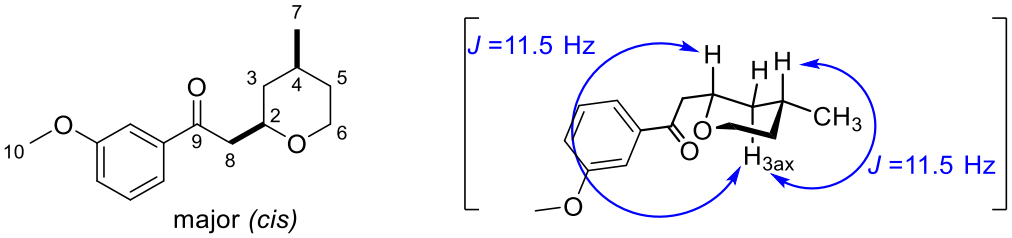
303

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (dtd, *J* = 9.5, 6.5, 3.0 Hz, 1H, H_2), 3.77 – 3.68 (m, 2H, H_6 x 2), 2.13 – 2.00 (m, 1H, H_4), 1.10 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.0 (C_6), 44.3 (C_8), 37.7 (C_3), 32.2 (C_5), 25.1 (C_4), 18.7 (C_7)**.**

HRMS (ESI+): Found $[M+H]^+$ = 219.1381; $C_{14}H_{19}O_2$ requires 219.1380, Δ 0.69 ppm

IR (film) ν_{max}/cm^{-1} 2978, 2842, 1683, 1597, 1489, 1382, 1079, 750, 689.

1-(3-Methoxyphenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 776



Diethyl (2-(3-methoxyphenyl)-2-oxoethyl)phosphonate (400 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (235 mg, 0.58 mmol, 95% yield, 85:15 cis/trans ratio determined by Q ^{1}H NMR).

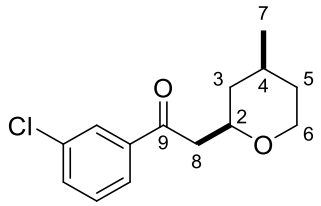
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.46 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.36 (t, *J* = 8.0 Hz, 2H, major ArCH, minor ArCH), 7.10 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 2H, major ArCH, minor ArCH), 4.29 (dtd, *J* = 9.5, 6.5, 3.0 Hz, 1H, minor H_2), 4.01 – 3.89 (m, 2H, major H_2, major H_{6eq}), 3.87 – 3.82 (m, 6H, major H_{10} x 3, minor H_{10} x 3), 3.76 – 3.69 (m, 2H, minor H_6 x 2), 3.45 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, major H_{6ax}), 3.34 – 3.22 (m, 2H, major H_{8a}, minor H_{8a}), 2.99 – 2.85 (m, 2H, major H_{8b}, minor H_{8b}), 2.06 (qp, *J* = 7.0, 4.5 Hz, 1H, minor H_4), 1.88 – 1.58 (m, 4H, major H_{3eq}, major H_4, minor H_{3eq}, minor H_{5eq}), 1.58 – 1.46 (m, 2H, major H_{5eq}, minor H_{3ax}), 1.31 – 1.15 (m, 2H, major H_{5ax}, minor H_{5ax}), 1.10 (d, *J* = 7.0 Hz, 3H, minor H_7 x 3), 0.99, (dt, *J* = 12.5, 11.5 Hz, 1H, major H_{3ax}), 0.94 (d, *J* = 6.5 Hz, 3H, major H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (minor C_9), 198.3 (major C_9), 159.9 (minor ArC), 159.9 (major ArC), 138.8 (major ArC, minor ArC), 129.7 (major ArC, minor ArC), 121.1 (minor ArC), 121.1 (major ArC), 119.8 (major ArC, minor ArC), 112.5 (major ArC, minor ArC), 74.1 (major C_2), 69.1 (minor C_2), 68.4 (major C_6), 62.9 (minor C_6), 55.6 (major C_{10}, minor C_{10}), 45.6 (major C_8), 44.4 (minor C_8), 40.7 (major C_3), 37.7 (minor C_3), 34.6 (major C_5), 32.2 (minor C_5), 30.3 (major C_4), 25.1 (minor C_4), 22.4 (major C_7), 18.7 (minor C_7).

HRMS (ESI+): Found $[M+H]^+$ = 249.1486; $C_{15}H_{21}O_3$ requires 249.1485, Δ 0.40 ppm

IR (film) ν_{max}/cm^{-1} 3003, 2837, 1683, 1597, 1430, 1262, 1090, 826, 686.

1-(3-Chlorophenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 777



major *(cis)*

Diethyl (2-(3-chlorophenyl)-2-oxoethyl)phosphonate (407 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (4→10% Et_2O/pentane) as a colourless oil (215 mg, 0.85 mmol, 85% yield, 94:6 cis/trans ratio determined by Q ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 2.0 Hz, 1H, ArCH), 7.83 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, ArCH), 7.52 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, ArCH), 7.40 (t, *J* = 8.0 Hz, 1H, ArCH), 3.99 – 3.87 (m, 2H, H_2, H_{6eq}), 3.44 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, H_{6ax}), 3.25 (dd, *J* = 16.0, 7.0 Hz, 1H, H_{8a}), 2.87 (dd, *J* = 16.0, 5.5 Hz, 1H, H_{8b}), 1.80 – 1.50 (m, 3H, H_{3eq}, H_4, H_{5eq}), 1.27 – 1.14 (m, 1H, H_{5ax}), 1.05 – 0.95 (m, 1H, H_{3ax}), 0.94 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

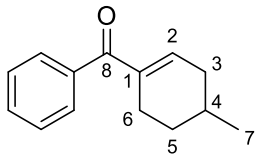
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4 (C_9), 139.2 (ArC), 135.1 (ArC), 133.1 (ArC), 130.0 (ArC), 128.5 (ArC), 126.5 (ArC), 74.1 (C_2), 68.4 (C_6), 45.5 (C_8), 40.7 (C_3), 34.5 (C_5), 30.3 (C_4), 22.4 (C_7).

Diagnostic peaks observed for 1-(3-Chlorophenyl)-*trans*-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one: ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 – 4.24 (m, 1H, H_2), 3.74 – 3.68 (m, 2H, H_6 x 2), 2.11 – 2.02 (m, 1H, H_4), 1.10 (d, *J* = 7.1 Hz, 3H, H_7 x 3).

HRMS (ESI+): Found $[M+H]^+$ = 253.0990; $C_{14}H_{18}O_2Cl$ requires 253.0990, Δ 0.12 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2841, 1689, 1572, 1423, 1206, 1090, 785, 681.

(4-Methylcyclohex-1-en-1-yl)(phenyl)methanone 753



Method 1: 2-(4-Methyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (65.4 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq. 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (57.7 mg, 0.288 mmol, 96% yield).

Method 2: A solution of trimethylsilyl trifluoromethanesulfonate (7 mg, 0.03 mmol, 0.1 eq.) in CH_2Cl_2 (1 mL) was added dropwise to a Schlenk tube charged with 4-Methyltetrahydro-2H-pyran-2-yl acetate (52 mg, 0.33 mmol, 1.1 eq.), trimethyl((1-phenylvinyl)oxy)silane (58 mg, 0.3 mmol, 1 eq.) and CH_2Cl_2 (0.5 mL) cooled to -78 ^oC under argon. The reaction mixture was stirred for 3 hours, and then warmed to RT. Xylene (1.5 mL, 0.2 M), and alumina (600 mg, 6 mmol, 20 eq.) were added, and the then the vessel was heated to 110 ^oC for 15 hours. The reaction mixture was then cooled to RT, filtered through silica, washing with Et_2O and concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (40.3 mg, 0.201 mmol, 67% yield).

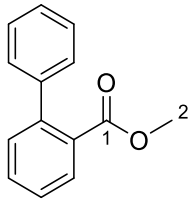
^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2H, ArCH x 2), 7.53 – 7.44 (m, 1H, ArCH), 7.45 – 7.36 (m, 2H, ArCH x 2), 6.59 – 6.51 (m, 1H, H_2), 2.67 – 2.53 (m, 1H, H_6), 2.42 – 2.22 (m, 2H, H_3, H_6), 1.94 – 1.80 (m, 2H, H_3, H_5), 1.82 – 1.66 (m, 1H, H_4), 1.30 (dtd, *J* = 12.0, 10.0, 5.0 Hz, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C_8), 143.7 (C_2), 138.9 (C_1), 138.6 (ArC), 131.4 (ArC), 129.3 (ArC x 2), 128.1 (ArC x 2), 34.7 (C_3), 30.4 (C_5), 27.9 (C_4), 24.2 (C_6), 21.7 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 201.1275; $C_{14}H_{17}O$ requires 201.1274, Δ 0.71 ppm

IR (film) ν_{max}/cm^{-1} 3000, 2886, 1725, 1685, 1380, 1252, 1154, 1088, 954, 752

Methyl [1,1'-biphenyl]-2-carboxylate 792



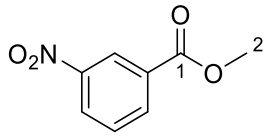
[1,1'-biphenyl]-2-carboxylic acid (2.4 g, 12.1 mmol), concentrated sulphuric acid (1 mL) and MeOH (28.4 mL, 0.5 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a white solid (1.63 g, 7.68 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H, ArCH), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H, ArCH), 7.46 – 7.29 (m, 7H, ArCH x 7), 3.64 (s, 3H, H_2 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (C_1), 142.6 (ArC), 141.4 (ArC), 131.4 (ArC), 131.0 (ArC), 130.8 (ArC), 129.9 (ArC), 128.4 (ArC x 2), 128.2 (ArC x 2), 127.4 (ArC), 127.3 (ArC), 52.1 (C_2).

The spectroscopic data matched that previously reported in the literature.[173]

Methyl 3-nitrobenzoate 793



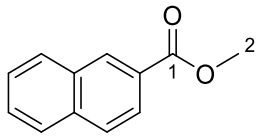
3-Nitrobenzoic acid (6.16 g, 37 mmol), concentrated sulphuric acid (3 mL) and MeOH (80 mL, 0.3 M) were subjected to **general procedure 7**. The title compound was used in the next step without further purification as a white solid (6.23 g, 34.4 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (ddd, *J* = 2.0, 1.5, 0.5 Hz, 1H, ArCH), 8.45 – 8.32 (m, 2H, ArCH x 2), 7.65 (ddd, *J* = 8.0, 7.5, 0.5 Hz, 1H, ArCH), 3.98 (s, 3H, H_2 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (C_1), 148.4 (ArC), 135.4 (ArC), 132.0 (ArC), 129.8 (ArC), 127.5 (ArC), 124.7 (ArC), 52.9 (C_2).

The spectroscopic data matched that previously reported in the literature.[174]

Methyl 2-naphthoate 795



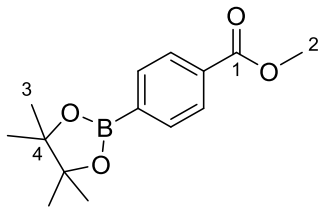
2-Naphthoic acid (1.5 g, 8.72 mmol), concentrated sulphuric acid (1 mL) and MeOH (28.4 mL, 0.5 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a white solid (1.1 g, 5.91 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 1.5, 1.0 Hz, 1H, ArCH), 7.79 (dd, *J* = 8.5, 1.5 Hz, 1H, ArCH), 7.72 – 7.64 (m, 1H, ArCH), 7.64 – 7.54 (m, 2H, ArCH x 2), 7.37 – 7.18 (m, 2H, ArCH x 2), 3.71 (s, 3H, H_2 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (C_1), 135.7 (ArC), 132.6 (ArC), 131.2 (ArC), 129.5 (ArC), 128.4 (ArC), 128.3 (ArC), 127.9 (ArC), 127.5 (ArC), 126.8 (ArC), 125.4 (ArC), 52.4 (C_2).

The spectroscopic data matched that previously reported in the literature.[174]

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate 797



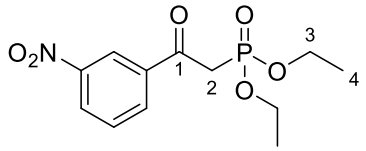
An oven dried 50 mL RBF was charged with (4-(methoxycarbonyl)phenyl)boronic acid (3 g, 16.6 mmol, 1 eq.), pinnacol (2.36 g, 20 mmol, 1.2 eq.) and dry Et_2O (30 mL). The reaction mixture was then stirred for 15 h at RT under an argon atmosphere. The reaction mixture was then concentrated *in vacuo*. The title compound was afforded after purification by FCC (10→25% Et_2O/pentane) as a colourless oil (3.4 g, 12.97 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H, ArCH x 2), 7.31 – 7.24 (m, 2H, ArCH x 2), 3.32 (s, 3H, H_2 x 3), 0.76 (s, 12H, H_3 x 12).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C_1), 134.8 (ArC x 2), 132.5 (ArC), 128.7 (ArC x 2), 84.3 (C_4 x 2), 52.3 (C_2), 25.0 (C_3 x 4). n.b. ArC adjacent to boron was not observed due to quadrapolar relaxation.

The spectroscopic data matched that previously reported in the literature.[175]

Diethyl (2-(3-nitrophenyl)-2-oxoethyl)phosphonate 802



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 3-nitrobenzoate (1.3 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a white solid (1.2 g, 3.98 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (t, *J* = 2.0 Hz, 1H, ArCH), 8.44 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, ArCH), 8.36 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, ArCH), 7.70 (t, *J* = 8.0 Hz, 1H, ArCH), 4.25 – 4.02 (m, 4H, H_3 x 4), 3.68 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.29 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 18.4.

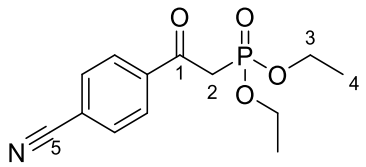
^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (d, *J* = 6.5 Hz, C_1), 148.6 (ArC), 137.8 (ArC), 134.8 (ArC), 130.0 (ArC), 128.0 (ArC), 124.1 (ArC), 63.1 (d, *J* = 6.5 Hz, C_3 x 2), 39.2 (d, *J* = 128.5 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 324.0608; $C_{12}H_{16}O_6NNaP$ requires 324.0607, Δ 0.05 ppm

IR (film) ν_{max}/cm^{-1} 2980, 1689, 1534, 1351, 1265, 1021, 973, 807.

m.p.: 67-68 °C

Diethyl (2-(4-cyanophenyl)-2-oxoethyl)phosphonate 803



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 4-cyanobenzoate (1.16 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a white solid (0.82 g, 2.92 mmol, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.06 (m, 2H, ArCH x 2), 7.79 – 7.73 (m, 2H, ArCH x 2), 4.19 – 4.05 (m, 4H, H_3 x 4), 3.62 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.27 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 18.5.

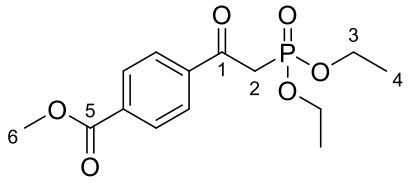
^{13}C NMR (101 MHz, $CDCl_3$) δ 190.9 (d, *J* = 6.5 Hz, C_1), 139.5 (d, *J* = 1.5 Hz, ArC), 132.5 (ArC x 2), 129.6 (ArC x 2), 117.9 (C_5), 116.9 (ArC), 63.0 (d, *J* = 6.5 Hz, C_3 x 2), 39.1 (d, *J* = 128.5 Hz, C_2), 16.3 (d, *J* = 6.5 Hz, C_4 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 282.0890; $C_{13}H_{17}O_4NP$ requires 282.0890, Δ -0.04 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2873, 2840, 1685, 1509, 1360, 1140, 1090, 858.

m.p.: 55-56 °C

Methyl 4-(2-(diethoxyphosphoryl)acetyl)benzoate 804



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), dimethyl terephthalate (1.4 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% Et_2O/pentane) as a colourless oil (960 mg, 3.05 mmol, 42% yield).

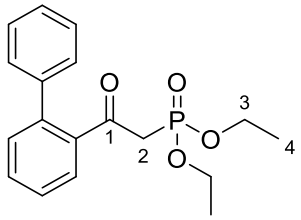
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.01 (m, 4H, ArCH x 4), 4.19 – 4.06 (m, 4H, H_3 x 4), 3.94 (s, 3H, H_6 x 3), 3.64 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.26 (t, *J* = 7.0 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.2.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7 (d, *J* = 6.5 Hz, C_1), 166.2 (C_5), 139.8 (d, *J* = 2.0 Hz, ArC), 134.4 (ArC), 129.9 (ArC x 2), 129.1 (ArC x 2), 62.9 (d, *J* = 6.5 Hz, C_3 x 2), 52.6 (C_6), 39.0 (d, *J* = 129.5 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[176]

Diethyl (2-([1,1'-biphenyl]-2-yl)-2-oxoethyl)phosphonate 805



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl [1,1'-biphenyl]-2-carboxylate (1.53 g, 7.2mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a colourless oil (1.7 g, 5.12 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.48 (m, 2H, ArCH x 2), 7.46 – 7.30 (m, 7H, ArCH x 7), 4.04 – 3.85 (m, 4H, H_3 x 4), 2.91 (d, *J* = 22.5 Hz, 2H, H_2 x 2), 1.16 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (d, *J* = 6.5 Hz, C_1), 140.5 (ArC), 140.3 (ArC), 140.2 (ArC), 131.2 (ArC), 130.2 (ArC), 129.1 (ArC x 2), 129.0 (ArC x 2), 129.00 (ArC), 128.3 (ArC), 127.6 (ArC), 62.4 (d, *J* = 6.5 Hz, C_3 x 2), 42.2 (d, *J* = 126.5 Hz, C_2), 16.2 (d, *J* = 6.5 Hz, C_4 x 2).

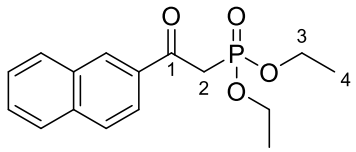
^{31}P NMR (162 MHz, $CDCl_3$) δ 19.70.

HRMS (ESI+): Found $[M+H]^+$ = 333.1249; $C_{18}H_{22}O_4P$ requires 333.1250, Δ -0.43 ppm

IR (film) ν_{max}/cm^{-1} 3058, 1688, 1476, 1255, 1022, 959, 776, 703

m.p.: 68-69 °C

Diethyl (2-(naphthalen-2-yl)-2-oxoethyl)phosphonate 806



Methyl diethyl phosphonate (900 mg, 5.90 mmol, 1.1 eq.), methyl 2-naphthoate (1 g, 5.36 mmol, 1 eq.), diisopropylamine (1.7 mL, 12.1 mmol, 2.25 eq.), *n*BuLi in hexanes (4.7 mL, 2.5 M, 11.8 mmol, 2.2 eq.) and dry THF (30 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was

afforded after purification by FCC (50→100% EtOAc/pentane) as a white solid (1.26 g, 4.11 mmol, 77% yield).

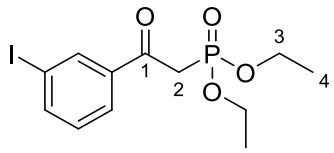
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.49 (m, 1H, ArCH), 8.05 (dd, *J* = 8.5, 2.0 Hz, 1H, ArCH), 7.98 (ddt, *J* = 8.0, 1.5, 0.5 Hz, 1H, ArCH), 7.93 – 7.84 (m, 2H, ArCH x 2), 7.69 – 7.45 (m, 2H, ArCH x 2), 4.24 – 4.04 (m, 4H, H_3 x 4), 3.76 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.27 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 20.0.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (d, *J* = 6.5 Hz, C_1), 135.9 (ArC), 134.0 (d, *J* = 2.0 Hz, ArC), 132.5 (ArC), 131.6 (ArC), 129.9 (ArC), 129.0 (ArC), 128.6 (ArC), 127.9 (ArC), 127.0 (ArC), 124.3 (ArC), 62.8 (d, *J* = 6.5 Hz, C_3 x 2), 38.7 (d, *J* = 130.0 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[176]

Diethyl (2-(3-iodophenyl)-2-oxoethyl)phosphonate 807



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 3-Iodobenzoate (1.88 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50% EtOAc/pentane) as a colourless oil (1.9 g, 4.97 mmol, 69% yield).

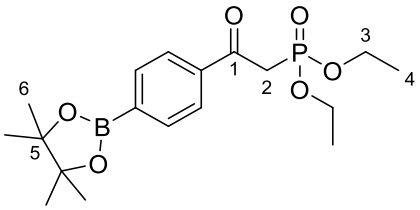
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (t, *J* = 1.5 Hz, 1H, ArCH), 7.97 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, ArCH), 7.90 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, ArCH), 7.22 (t, *J* = 8.0 Hz, 1H, ArCH), 4.24 – 4.01 (m, 4H, H_3 x 4), 3.58 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.28 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.2.

^{13}C NMR (101 MHz, $CDCl_3$) 190.7 (d, *J* = 7.0 Hz, C_1), 142.5 (ArC), 138.3 (d, *J* = 2.0 Hz, ArC), 138.0 (ArC), 130.4 (ArC), 128.4 (ArC), 94.4 (ArC), 62.9 (d, *J* = 6.5 Hz, C_3 x 2) 38.7 (d, *J* = 129.5 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[170]

Diethyl (2-oxo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)phosphonate 808



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.89 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a colourless oil (1.65 g, 4.32 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.83 (m, 4H, ArCH x 4), 4.19 – 4.05 (m, 4H, H_3 x 4), 3.63 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.35 (s, 12H, H_6 x 12), 1.27 (t, *J* = 7.0 Hz, 6H, H_4 x 6).

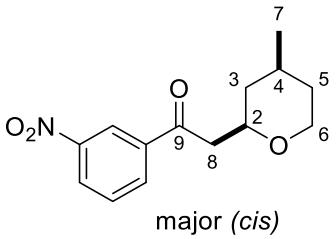
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4 (d, *J* = 6.5 Hz, C_1), 138.5 (d, *J* = 2.0 Hz, ArC), 135.0 (ArC x 2), 128.1 (ArC x 2), 84.4 (C_5 x 2), 62.8 (d, *J* = 6.5 Hz, C_3 x 2), 38.7 (d, *J* = 130.0 Hz, C_2), 25.0 (C_6 x 4), 16.4 (d, *J* = 6.5 Hz, C_4 x 2). n.b. ArC adjacent to boron was not observed due to quadrapolar relaxation.

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.8.

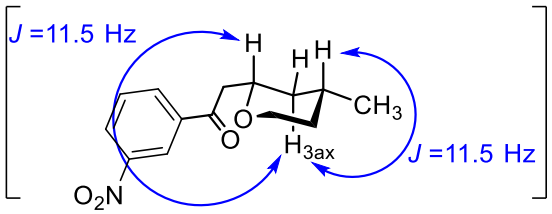
HRMS (ESI+): Found $[M+H]^+$ = 383.1787; $C_{18}H_{29}O_6BP$ requires 383.1790, Δ -0.26 ppm

IR (film) ν_{max}/cm^{-1} 2988, 1681, 1509, 1360, 1275, 1088, 1024, 962, 822

2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(3-nitrophenyl)ethan-1-one 809



major *(cis)*



Diethyl (2-(3-nitrophenyl)-2-oxoethyl)phosphonate (420 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a colourless oil (180 mg, 0.7 mmol, 70% yield, 92:8 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (t, *J* = 2.0 Hz, 1H, ArCH), 8.40 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, ArCH), 8.29 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, ArCH), 7.66 (t, *J* = 8.0 Hz, 1H, ArCH), 3.97 – 3.88 (m, 2H, H_2, H_{6eq}), 3.43 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, H_{6ax}), 3.32 (dd, *J* = 16.0, 7.5 Hz, 1H, H_{8a}), 2.92 (dd, *J* = 16.0, 5.0 Hz, 1H, H_{8b}), 1.81 – 1.60 (m, 2H, H_{3eq}, H_4), 1.54 (ddq, *J* = 13.5, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.28 – 1.15 (m, 1H, H_{5ax}), 1.04 (dt, *J* = 12.5, 11.5 Hz, 1H, H_{3ax}), 0.95 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

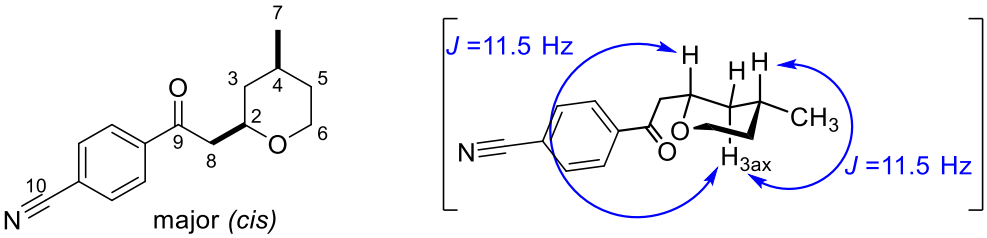
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7 (C_9), 148.6 (ArC), 138.8 (ArC), 134.0 (ArC), 129.9 (ArC), 127.4 (ArC), 123.5 (ArC), 74.1 (C_2), 68.4 (C_6), 45.6 (C_8), 40.7 (C_3), 34.4 (C_5), 30.3 (C_4), 22.4 (C_7).

Diagnostic peaks observed for *trans*-2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(3-nitrophenyl)ethan-1-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (dddd, *J* = 10.0, 7.5, 5.0, 3.0 Hz, 1H, H_2), 3.73 – 3.68 (m, 2H, H_6 x 2), 2.15 – 2.01 (m, 1H, H_4), 1.11 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.1 (C_2), 63.0 (C_6), 44.7 (C_8), 37.7 (C_3), 31.9 (C_5), 25.1 (C_4), 18.5 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 264.1231; $C_{14}H_{18}O_4N$ requires 264.1230, Δ 0.28 ppm

IR (film) ν_{max}/cm^{-1} 2981, 1696, 1533, 1382, 1350, 1256, 1090.

4-(2-(4-Methyltetrahydro-*2H*-pyran-2-yl)acetyl)benzonitrile 810



Diethyl (2-(4-cyanophenyl)-2-oxoethyl)phosphonate (393 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a white solid (243 mg, 1.0 mmol, 100% yield, 91:9 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 2H, ArCH x 2), 7.80 – 7.72 (m, 2H, ArCH x 2), 3.97 – 3.85 (m, 2H, H_2, H_{6eq}), 3.46 – 3.38 (m, 1H, H_{6ax}), 3.28 (dd, *J* = 16.0, 7.5 Hz, 1H, H_{8a}), 2.88 (dd, *J* = 16.0, 5.0 Hz, 1H, H_{8b}), 1.80 – 1.49 (m, 3H, H_{3eq}, H_4, H_{5eq}), 1.27 – 1.14 (m, 1H, H_{5ax}), 1.01 (dt, *J* = 12.5, 11.5 Hz, 1H, H_{3ax}), 0.95 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6 (C_9), 140.5 (ArC), 132.6 (ArC x 2), 128.9 (ArC x 2), 118.1 (C_{10}), 116.4 (ArC), 74.1 (C_2), 68.4 (C_6), 45.7 (C_8), 40.7 (C_3), 34.5 (C_5), 30.3 (C_4), 22.4 (C_7).

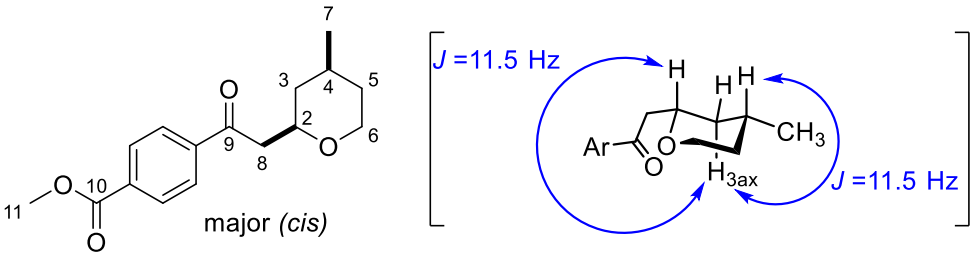
Diagnostic peaks observed for 4-(*trans*-2-(4-Methyltetrahydro-*2H*-pyran-2-yl)acetyl)benzonitrile ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (dddd, *J* = 10.0, 7.5, 5.0, 3.0 Hz, 1H, H_2), 3.73 – 3.66 (m, 2H, H_6 x 2), 2.13 – 2.02 (m, 1H, H_4), 1.11 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.1 (C_2), 63.0 (C_6), 44.8 (C_8), 37.7 (C_3), 31.9 (C_5), 25.1 (C_4), 18.5 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 244.1334; $C_{15}H_{18}O_2N$ requires 244.1332, Δ 0.64 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2952, 1691, 1382, 1258, 1174, 1089, 941, 827.

m.p.: 48-49 °C

Methyl 4-(2-(4-methyltetrahydro-*2H*-pyran-2-yl)acetyl)benzoate 811



Methyl 4-(2-(diethoxyphosphoryl)acetyl)benzoate (440 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a white solid (220 mg, 0.80 mmol, 80% yield, 92:8 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 2H, ArCH x 2), 8.03 – 7.97 (m, 2H, ArCH x 2), 4.01 – 3.87 (m, 5H, H_2, H_{6eq}, H_{11} x 3), 3.44 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, H_{6ax}), 3.30 (dd, *J* = 16.0, 7.0 Hz, 1H, H_{8a}), 2.92 (dd, *J* = 16.0, 5.5 Hz, 1H, H_{8b}), 1.80 – 1.46 (m, 3H, H_{3eq}, H_4, H_{5eq}), 1.28 – 1.18 (m, 1H, H_{5ax}), 1.01 (dt, *J* = 12.5, 11.5 Hz, 1H, H_{3ax}), 0.94 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2 (C_9), 166.4 (C_{10}), 140.7 (ArC), 134.0 (ArC), 129.9 (ArC x 2), 128.3 (ArC x 2), 74.1 (C_2), 68.4 (C_6), 52.6 (C_{11}), 45.8 (C_8), 40.7 (C_5), 34.5 (C_3), 30.3 (C_4), 22.4 (C_7).

Diagnostic peaks observed for Methyl 4-(*trans*-2-(4-methyltetrahydro-*2H*-pyran-2-yl)acetyl)benzoate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.23 (m, 1H, H_2), 3.74 – 3.67 (m, 2H, H_6 x 2),

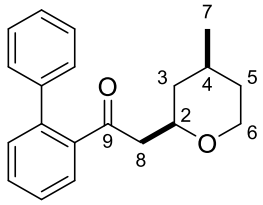
2.13 – 2.01 (m, 1H, H_4), 1.10 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.0 (C_6), 37.7 (C_3), 18.6 (C_7).

HRMS (ESI+): Found $[M+Na]^+$ = 299.1254; $C_{16}H_{20}O_4Na$ requires 299.1254, Δ 0.16 ppm

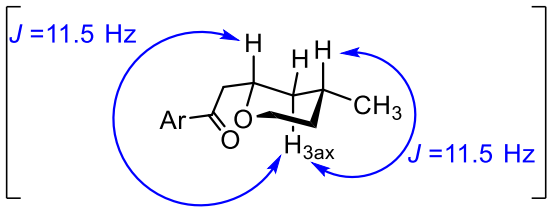
IR (film) ν_{max}/cm^{-1} 2981, 2844, 1726, 1689, 1437, 1378, 1279, 1108, 975, 763.

m.p.: 67-68 °C

1-([1,1'-Biphenyl]-2-yl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 812



major *(cis)*



Diethyl (2-([1,1'-biphenyl]-2-yl)-2-oxoethyl)phosphonate (465 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (303 mg, 1 mmol, 100% yield, 74:26 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.45 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.45 – 7.29 (m, 14H, minor ArCH x 7, minor ArCH x 7), 3.99 (tdd, *J* = 8.0, 5.5, 3.5 Hz, 1H, minor H_2), 3.85 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, major H_{6eq}), 3.60 (dddd, *J* = 11.0, 7.5, 5.5, 2.0 Hz, 1H, major H_2), 3.55 – 3.44 (m, 2H, minor H_6 x 2), 3.29 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, major H_{6ax}), 2.70 – 2.49 (m, 2H, major H_{8a}, minor H_{8a}), 2.34 – 2.22 (m, 2H, major H_{8b}, minor H_{8b}), 1.83 – 1.71 (m, 1H, minor H_4), 1.69 – 1.39 (m, 4H, major H_{3eq}, major H_4, major H_{5eq}, minor H_{5eq}), 1.33 – 1.01 (m, 4H, major H_{5ax}, minor H_3 x 2, minor H_{5ax}), 0.96 (d, *J* = 7.0 Hz, 3H, minor H_7 x 3), 0.85 (d, *J* = 6.5 Hz, 3H, major H_7 x 3), 0.66 (dt, *J* = 13.0, 11.5 Hz, 1H, major H_{3ax}).

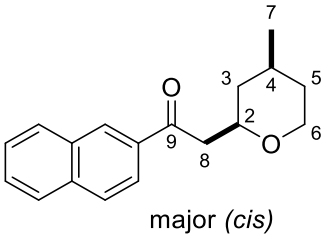
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8 (major C_9, minor C_9), 141.3 (major ArC, minor ArC), 140.7 (major ArC, minor ArC), 140.2 (major ArC) 140.1 (minor ArC), 130.6 (major ArC, minor ArC), 130.3 (major ArC), 130.2 (minor ArC), 129.1 (major ArC x 2), 129.1 (minor ArC x 2), 128.8 (major ArC x 2), 128.8 (minor ArC x 2), 128.0 (minor ArC), 127.9 (major ArC, minor ArC), 127.9 (major ArC), 127.6 (minor ArC), 127.6 (major ArC), 74.4 (major C_2), 69.4 (minor C_2), 68.1 (major C_6), 62.5 (minor C_6), 49.7 (major C_8),

48.1 (minor C_8), 40.3 (major C_3), 37.3 (minor C_3), 34.4 (major C_5), 32.3 (minor C_5), 30.2 (major C_4), 24.9 (minor C_4), 22.3 (major C_7), 19.1 (minor C_7).

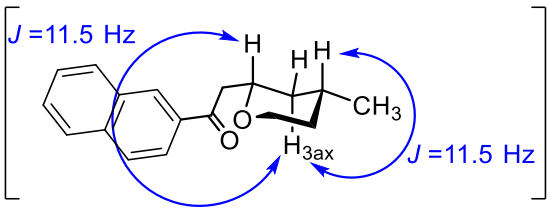
HRMS (ESI+): Found $[M+H]^+$ = 295.1695; $C_{20}H_{23}O_2$ requires 295.1693, Δ 0.91 ppm

IR (film) ν_{max}/cm^{-1} 2979, 1687, 1381, 1257, 1177, 1089, 744, 701

4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(naphthalen-2-yl)ethan-1-one 813



major *(cis)*



Diethyl (2-(naphthalen-2-yl)-2-oxoethyl)phosphonate (428 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (268 mg, 1 mmol, 100% yield, 83:17 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 2.0 Hz, 2H, major ArCH, minor ArCH), 8.04 (dd, *J* = 8.5, 2.0 Hz, 2H, major ArCH, minor ArCH), 8.00 – 7.93 (m, 2H, major ArCH, minor ArCH), 7.93 – 7.84 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.66 – 7.47 (m, 4H, major ArCH x 2, minor ArCH x 2), 4.37 (dtd, *J* = 9.5, 6.5, 3.0 Hz, 1H, minor H_2), 4.09 – 3.92 (m, 2H, major H_2, major H_{6eq}), 3.81 – 3.71 (m, 2H, minor H_6 x 2), 3.54 – 3.39 (m, 3H, major H_{6ax}, major H_{8a}, minor H_{8a}), 3.15 – 2.97 (m,2H, major H_{8b}, minor H_{8b}), 4.44 – 4.30 (m, 1H, minor H_4), 1.88 – 1.77 (m, 2H, major H_{3eq}, minor H_{5eq}), 1.76 – 1.61 (m, 2H, major H_4, minor H_{3eq}), 1.60 – 1.50 (m, 2H, major H_{5eq}, minor H_{3ax}), 1.35 – 1.16 (m, 2H, major H_{5ax}, minor H_{5ax}), 1.12 (d, *J* = 7.0 Hz, 1H, minor H_7 x 3), 1.05 (dt, *J* = 13.0, 11.5 Hz, 1H, major H_{3ax}), 0.95 (d, *J* = 6.5 Hz, 3H, major H_7 x 3).

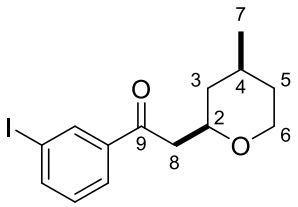
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (minor C_9), 198.5 (major C_9), 135.7 (major ArC, minor ArC), 134.8 (major ArC, minor ArC), 132.7 (major ArC, minor ArC), 130.2 (major ArC), 130.2 (minor ArC), 129.8 (major ArC), 129.8 (minor ArC), 128.6 (major ArC, minor ArC), 128.5 (minor ArC), 128.5 (major ArC), 127.9 (major ArC, minor ArC), 126.9 (major ArC, minor ArC), 124.1 (major ArC, minor ArC), 74.3 (major C_2), 69.2 (minor C_2), 68.4 (major C_6), 63.0 (minor C_6), 45.5 (major C_8), 44.4 (minor C_8), 40.8 (major C_3),

37.8 (minor C_3), 34.6 (major C_5), 32.2 (minor C_5), 30.3 (major C_4), 25.1 (minor C_4), 22.4 (major C_7), 18.7 (minor C_7).

HRMS (ESI+): Found $[M+H]^+$ = 269.1536; $C_{18}H_{21}O_2$ requires 269.1356, Δ -0.16 ppm

IR (film) ν_{max}/cm^{-1} 2998, 2838, 1678, 1469, 1383, 1172, 1088, 817, 744

1-(3-Iodophenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 814



major *(cis)*

Diethyl (2-(3-iodophenyl)-2-oxoethyl)phosphonate (535 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 1 M LDA in THF (1.2 mL, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (4→10% Et_2O/pentane) as a white solid (282 mg, 0.82 mmol, 82% yield, 91:9 cis/trans ratio determined by Q ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.5 Hz, 1H, ArCH), 7.95 – 7.83 (m, 2H, ArCH x 2), 7.19 (t, *J* = 8.0 Hz, 1H, ArCH), 4.01 – 3.87 (m, 2H, H_2, H_{6eq}), 3.44 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, H_{6ax}), 3.24 (dd, *J* = 16.0, 7.0 Hz, 1H, H_{8a}), 2.86 (dd, *J* = 16.0, 5.5 Hz, 1H, H_{8b}), 1.79 – 1.47 (m, 3H, H_{3eq}, H_4, H_{5eq}), 1.27 – 1.13 (m, 1H, H_{5ax}), 1.06 – 0.96 (m, 1H, H_{3ax}), 0.94 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2 (C_9), 141.9 (ArC), 139.2 (ArC), 137.4 (ArC), 130.4 (ArC), 127.6 (ArC), 94.6 (ArC), 74.0 (C_2), 68.3 (C_6), 45.4 (C_8), 40.7 (C_3), 34.5 (C_5), 30.3 (C_4), 22.4 (C_7).

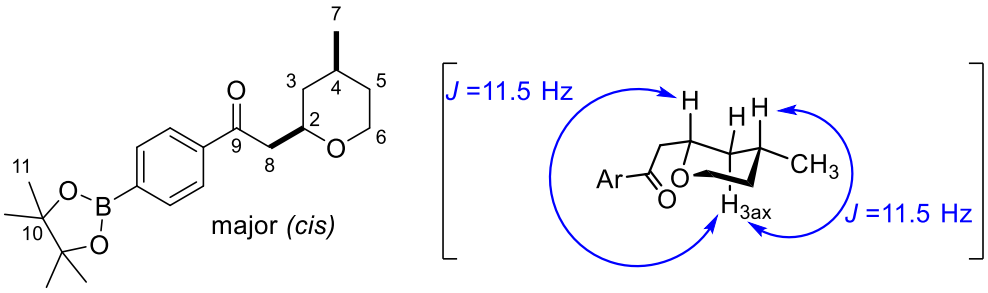
Diagnostic peaks observed for 1-(3-Iodophenyl)-*trans*-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one: ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (dddd, *J* = 9.0, 7.0, 5.5, 3.0 Hz, 1H, H_2), 3.74 – 3.67 (m, 2H, H_6 x 2), 2.12 – 1.99 (m, 1H, H_4), 1.10 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.0 (C_2), 62.9 (C_6), 44.3 (C_8), 37.7 (C_3), 32.1 (C_5), 25.1 (C_4), 18.7 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 345.0345; $C_{14}H_{18}O_2I$ requires 345.0346, Δ -0.42 ppm

IR (film) ν_{max}/cm^{-1} 2997, 2886, 1394, 1252, 1151, 1071, 954.

m.p.: 44-45 °C

2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one 815



Diethyl (2-oxo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)phosphonate (535 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (15% Et_2O/pentane) as a white solid (325 mg, 0.94 mmol, 94% yield, 92:8 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.83 (m, 4H, ArCH x 4), 4.01 – 3.87 (m, 2H, H_2, H_{6eq}), 3.53 – 3.41 (m, 1H, H_{6ax}), 3.29 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{8a}), 2.94 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{8b}), 1.81 – 1.59 (m, 2H, H_{3eq}, H_4), 1.53 (ddq, *J* = 13.5, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.35 (s, 12H, H_{11} x 12), 1.27 – 1.18 (m, 1H, H_{5ax}), 0.99 (dt, *J* = 13.0, 11.5 Hz, 1H, H_{3ax}), 0.93 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8 (C_9), 139.3 (ArC), 135.0 (ArC x 2), 127.4 (ArC x 2), 84.3 (C_{10} x 2), 74.1 (C_2), 68.3 (C_6), 45.6 (C_8), 40.7 (C_3), 34.6 (C_5), 30.3 (C_4), 25.0 (C_{11} x 4), 22.4 (C_7). n.b. ArC adjacent to boron was not observed due to quadrapolar relaxation.

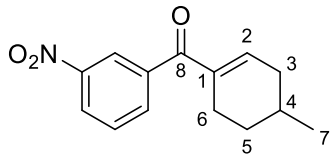
Diagnostic peaks observed for *trans*-2-(4-methyltetrahydro-*2H*-pyran-2-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (dtd, *J* = 9.5, 6.5, 3.0 Hz, 1H, H_2), 3.75 – 3.69 (m, 2H, H_6 x 2), 2.12 – 2.00 (m, 1H, H_4), 1.09 (d, *J* = 7.0 Hz, 3H, H_7 x 3).

HRMS (ESI+): Found $[M+H]^+$ = 345.2230; $C_{20}H_{30}O_4B$ requires 345.2232, Δ -0.51 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2873, 2840, 1685, 1509, 1360, 1140, 1090, 858.

m.p.: 73-74 °C

(4-Methylcyclohex-1-en-1-yl)(3-nitrophenyl)methanone 816



2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(3-nitrophenyl)ethan-1-one (79mg, 0.3 mmol, 1 eq.), Al(O^{t}Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (55 mg, 0.224 mmol, 75% yield).

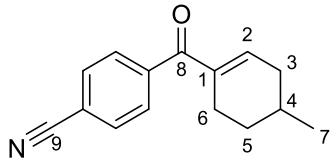
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (t, *J* = 2.0 Hz, 1H, ArCH), 8.35 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, ArCH), 7.94 (dt, *J* = 7.5, 1.5 Hz, 1H, ArCH), 7.62 (t, *J* = 7.9 Hz, 1H, ArCH), 6.62 – 6.50 (m, 1H, H_2), 2.68 – 2.55 (m, 1H, H_6), 2.45 – 2.28 (m, 2H, H_3, H_6), 1.98 – 1.83 (m, 2H, H_3, H_5), 1.82 – 1.69 (m, 1H, H_4), 1.39 – 1.23 (m, 1H, H_5), 1.03 (d, *J* = 6.5 Hz, 3H, H_7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4 (C_8), 148.0 (ArC), 145.6 (C_2), 140.4 (C_1), 138.4 (ArC), 134.9 (ArC), 129.5 (ArC), 125.8 (ArC), 124.0 (ArC), 34.8 (C_3), 30.2 (C_5), 27.9 (C_4), 24.0 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 246.1127; $C_{14}H_{16}O_3N$ requires 246.1125 Δ 0.75 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2886, 1650, 1531, 1381, 1253, 1152, 1073, 954.

4-(4-Methylcyclohex-1-ene-1-carbonyl)benzonitrile 817



4-(2-(4-Methyltetrahydro-*2H*-pyran-2-yl)acetyl)benzonitrile (73 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**.The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (50 mg, 0.222 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.63 (m, 4H, ArCH x 4), 6.57 – 6.48 (m, 1H, H_2), 2.66 – 2.53 (m, 1H, H_3), 2.48 – 2.24 (m, 2H, H_3, H_6), 1.95 – 1.82 (m, 2H, H_5, H_6), 1.81 – 1.67 (m, 1H, H_4), 1.37 – 1.23 (m, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

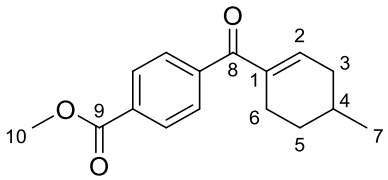
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3 (C_8), 145.8 (C_2), 142.9 (C_1), 138.5 (ArC), 132.1 (ArC x 2), 129.5 (ArC x 2), 118.3 (C_9), 114.7 (ArC), 34.8 (C_3), 30.2 (C_5), 27.8 (C_4), 23.8 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 226.1228; $C_{15}H_{16}ON$ requires 226.1226 Δ 0.72 ppm

IR (film) ν_{max}/cm^{-1} 2998, 2981, 2886, 2230, 1648, 1381, 1263, 1154, 1082, 942, 878.

m.p.: 94-95 °C

Methyl 4-(4-methylcyclohex-1-ene-1-carbonyl)benzoate 818



Methyl 4-(2-(4-methyltetrahydro-*2H*-pyran-2-yl)acetyl)benzoate (83 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a white solid (70 mg, 0.27 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.03 (m, 2H, ArCH x 2), 7.69 – 7.60 (m, 2H, ArCH x 2), 6.58 – 6.52 (m, 1H, H_2), 3.94 (s, 3H, H_{10} x 3), 2.66 – 2.54 (m, 1H, H_6), 2.42 – 2.25 (m, 2H, H_3, H_6), 1.94 – 1.82 (m, 2H, H_3, H_5), 1.82 – 1.66 (m, 1H, H_4), 1.37 – 1.22 (m, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

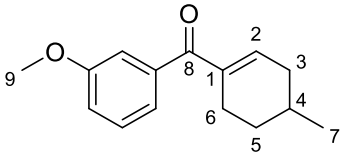
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4 (C_8), 166.6 (C_9), 145.2 (C_2), 143.0 (C_1), 138.7 (ArC), 132.4 (ArC), 129.4 (ArC x 2), 129.0 (ArC x 2), 52.5 (C_{10}), 34.8 (C_3), 30.3 (C_5), 27.9 (C_4), 23.9 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 259.1330; $C_{16}H_{19}O_3$ requires 259.1329 Δ 0.48 ppm

IR (film) ν_{max}/cm^{-1} 2948, 2923, 1725, 1632, 1279, 1107, 747, 719.

m.p.: 94-95 °C

(3-Methoxyphenyl)(4-methylcyclohex-1-en-1-yl)methanone 781



1-(3-Methoxyphenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (74.5 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**.The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (59 mg, 0.256 mmol, 85% yield).

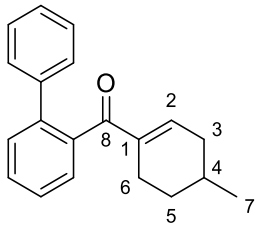
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 1H, ArCH), 7.21 – 7.13 (m, 2H, ArCH x 2), 7.03 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, ArCH), 6.61 – 6.53 (m, 1H, H_2), 3.84 (s, 3H, H_9 x 3), 2.65 – 2.52 (m, 1H, H_6), 2.41 – 2.24 (m, 2H, H_3, H_6), 1.94 – 1.82 (m, 2H, H_3, H_5), 1.80 – 1.67 (m, 1H, H_4), 1.29 (dtd, *J* = 13.0, 11.0, 5.5 Hz, 1H, H_5), 1.01 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (C_8), 159.5 (ArC), 143.8 (C_2), 140.2 (C_1), 138.5 (ArC), 129.1 (ArC), 121.8 (ArC), 117.5 (ArC), 114.0 (ArC), 55.5 (C_9), 34.7 (C_3), 30.4 (C_5), 27.9 (C_4), 24.2 (C_6), 21.7 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 231.1380; $C_{15}H_{19}O_2$ requires 231.1380 Δ 0.26 ppm

IR (film) ν_{max}/cm^{-1} 2952, 2870, 1647, 1579, 1430, 1268, 1233, 1048, 803.

[1,1'-Biphenyl]-2-yl(4-methylcyclohex-1-en-1-yl)methanone 819



1-([1,1'-Biphenyl]-2-yl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (88 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a white solid (73 mg, 0.264 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.09 (m, 9H, ArCH x 9), 6.12 – 5.99 (m, 1H, H_2), 2.23 (ddtd, *J* = 17.5, 5.5, 2.5, 1.0 Hz, 1H, H_6), 2.00 – 1.85 (m, 2H, H_3, H_6), 1.57 – 1.34 (m, 2H, H_3, H_5), 1.34 – 1.22 (m, 1H, H_4), 0.83 (dtd, *J* = 13.0, 10.5, 5.5 Hz, 1H, H_5), 0.71 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

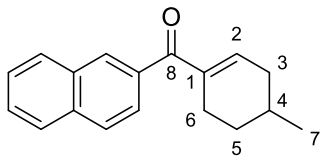
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7 (C_8), 144.7 (C_2), 141.4 (C_1), 140.9 (ArC), 140.0 (ArC), 139.7 (ArC), 129.9 (ArC), 129.5 (ArC), 128.8 (ArC x 2), 128.5 (ArC), 128.5 (ArC x 2), 127.3 (ArC), 127.3 (ArC) 34.4 (C_3), 30.0 (C_5), 27.5 (C_4), 23.1 (C_6), 21.3 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 277.1859 $C_{20}H_{21}O$ requires 277.1857 Δ 0.77 ppm

IR (film) ν_{max}/cm^{-1} 2951, 1651, 1636, 1474, 1275, 1078, 747, 699.

m.p.: 90-91 °C

(4-Methylcyclohex-1-en-1-yl)(naphthalen-2-yl)methanone 820



4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(naphthalen-2-yl)ethan-1-one (80.5 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a colourless oil (49 mg, 0.196 mmol, 65% yield).

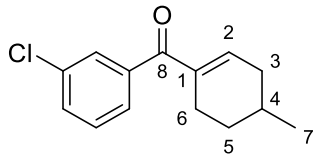
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 1.5, 0.5 Hz, 1H, ArCH), 7.95 – 7.83 (m, 3H, ArCH x 3), 7.75 (dd, *J* = 8.5, 1.5 Hz, 1H, ArCH), 7.60 – 7.50 (m, 2H, ArCH x 2), 6.61 (qd, *J* = 3.1, 1.2 Hz, 1H, H_2), 2.72 – 2.60 (m, 1H, H_6), 2.49 – 2.31 (m, 2H, H_3, H_6), 1.98 – 1.85 (m, 2H, H_3, H_5), 1.85 – 1.71 (m, 1H, H_4), 1.41 – 1.28 (m, 1H, H_5), 1.04 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C_8), 143.6 (C_2), 138.8 (C_1), 136.1 (ArC), 134.9 (ArC), 132.4 (ArC), 130.2 (ArC), 129.2 (ArC), 128.1 (ArC), 127.9 (ArC), 127.8 (ArC), 126.7 (ArC), 125.9 (ArC), 34.7 (C_3), 30.5 (C_5), 28.0 (C_4), 24.3 (C_6), 21.7 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 251.1431; $C_{18}H_{19}O_2$ requires 251.1430 Δ 0.28 ppm

IR (film) ν_{max}/cm^{-1} 3057, 2950, 2870, 1647, 1453, 1381, 1277, 1135, 817, 755.

(3-Chlorophenyl)(4-methylcyclohex-1-en-1-yl)methanone 782



1-(3-Chlorophenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (76 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure**

10. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a colourless oil (49 mg, 0.209 mmol, 70% yield).

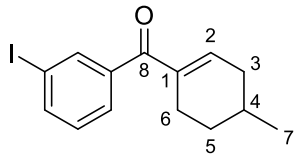
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, *J* = 2.0 Hz, 1H, ArCH), 7.50 – 7.43 (m, 2H, ArCH x 2), 7.34 (t, *J* = 8.0 Hz, 1H, ArCH), 6.55 (ddd, *J* = 5.0, 2.5, 1.5 Hz, 1H, H_2), 2.64 – 2.51 (m, 1H, H_6), 2.43 – 2.23 (m, 2H, H_3, H_6), 1.96 – 1.82 (m, 2H, H_3, H_5), 1.81 – 1.67 (m, 1H, H_4), 1.36 – 1.22 (m, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6 (C_8), 144.6 (C_2), 140.6 (C_1), 138.4 (ArC), 134.3 (ArC), 131.3 (ArC), 129.5 (ArC), 129.2 (ArC), 127.3 (ArC), 34.7 (C_3), 30.3 (C_5), 27.9 (C_4), 24.0 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 235.0885 $C_{14}H_{16}OCl$ requires 235.0884 Δ 0.28 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2926, 2871, 1648, 1566, 1418, 1255, 1078, 736, 709.

(3-Iodophenyl)(4-methylcyclohex-1-en-1-yl)methanone 821



1-(3-Iodophenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (103 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a white solid (80 mg, 0.245 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (t, *J* = 1.5 Hz, 1H, ArCH), 7.81 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, ArCH), 7.55 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H, ArCH), 7.15 (t, *J* = 8.0 Hz, 1H, ArCH), 6.58 – 6.51 (m, 1H, H_2), 2.64 – 2.50 (m, 1H, H_6), 2.43 – 2.19 (m, 2H, H_3, H_6), 1.95 – 1.82 (m, 2H, H_3, H_5), 1.81 – 1.65 (m, 1H, H_4), 1.28 (dtd, *J* = 13.0, 10.5, 5.5 Hz, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

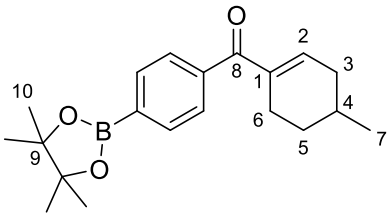
^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4 (C_8), 144.7 (C_2), 140.9 (C_1), 140.1 (ArC), 138.4 (ArC), 137.8 (ArC), 129.9 (ArC), 128.3 (ArC), 93.9 (ArC), 34.7 (C_3), 30.3 (C_5), 27.9 (C_4), 24.0 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 327.0239; $C_{14}H_{16}OI$ requires 327.0240 Δ -0.33 ppm

IR (film) ν_{max}/cm^{-1} 2950, 2925, 2869, 1647, 1558, 1378, 1256, 1062, 728.

m.p.: 63-64 °C

(4-Methylcyclohex-1-en-1-yl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone 822



2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (103 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a white solid (72 mg, 0.221 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H, ArCH x 2), 7.62 – 7.54 (m, 2H, ArCH x 2), 6.58 – 6.46 (m, 1H, H_2), 2.67 – 2.51 (m, 1H, H_6), 2.42 – 2.23 (m, 2H, H_3, H_6), 1.93 – 1.79 (m, 2H, H_3, H_5), 1.79 – 1.68 (m, 1H, H_4), 1.35 (s, 13H, H_5, H_{10} x 12), 1.01 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

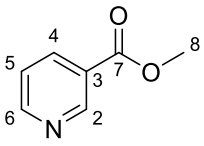
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (C_8), 144.3 (C_2), 141.3 (C_1), 138.7 (ArC), 134.5 (ArC x 2), 128.3 (ArC x 2), 84.2 (C_9 x 2), 34.7 (C_3), 30.4 (C_5), 28.0 (C_4), 25.0 (C_{10} x 4), 24.1 (C_6), 21.7 (C_7). *n.b. ArC adjacent to boron was not observed due to quadrapolar relaxation.*

HRMS (ESI+): Found $[M+H]^+$ = 327.2129; $C_{20}H_{28}O_3B$ requires 327.2126 Δ 0.98 ppm

IR (film) ν_{max}/cm^{-1} 2980, 2886, 1647, 1397, 1356, 1260, 1144, 1088, 964, 878

m.p.: 88-89 °C

Methyl nicotinate 824



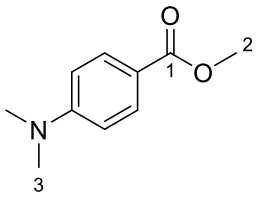
Nictonic acid (5 g, 40 mmol), concentrated sulphuric acid (13.5 mL) and MeOH (80 mL, 0.5 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a white solid (5.27 g, 38.4 mmol, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, J = 2.0 Hz, 1H, H_2), 8.76 (dd, J = 5.0, 2.0 Hz, 1H, H_6), 8.28 (dt, J = 8.0, 2.0 Hz, 1H, H_4), 7.38 (dd, J = 8.0, 5.0 Hz, 1H, H_5), 3.94 (s, 3H, H_8 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (C_7), 153.5 (C_6), 151.0 (C_2), 137.2 (C_4), 126.2 (C_3), 123.4 (C_5), 52.5 (C_8).

The spectroscopic data matched that previously reported in the literature.[177]

Methyl 4-(dimethylamino)benzoate 826



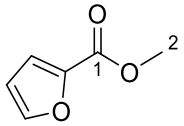
4-(Dimethylamino)benzoic acid (5 g, 30 mmol), concentrated sulphuric acid (3 mL) and MeOH (80 mL, 0.4 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a white solid (3.6 g, 20 mmol, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.86 (m, 2H, ArCH x 2), 6.71 – 6.59 (m, 2H, ArCH x 2), 3.85 (s, 3H, H_2 x 3), 3.04 (s, 6H, H_3 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C_1), 153.4 (ArC), 131.4 (ArC x 2), 117.2 (ArC), 111.0 (ArC x 2), 51.62 (C_2), 40.2 (C_3 x 2).

The spectroscopic data matched that previously reported in the literature.[178]

Methyl furan-2-carboxylate 828



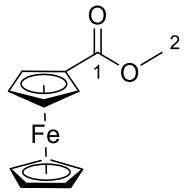
Furyoic acid (4.5 g, 40 mmol), concentrated sulphuric acid (13.5 mL) and MeOH (80 mL, 0.5 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a colourless oil (4.4 g, 34.8 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.5, 1.0 Hz, 1H, ArCH), 7.17 (dd, *J* = 3.5,1.0 Hz, 1H, ArCH), 6.50 (dd, *J* = 3.5, 1.5 Hz, 1H, ArCH), 3.89 (s, 3H, H_2 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C_1), 146.4 (ArC), 144.8 (ArC), 118.1 (ArC), 112.0 (ArC), 52.0 (C_2).

The spectroscopic data matched that previously reported in the literature.[179]

Methyl ferrocene carboxylate 830



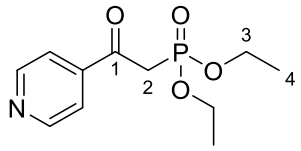
Ferrocene carboxylic acid (3 g, 13.2 mmol), concentrated sulphuric acid (2 mL) and MeOH (30 mL, 0.4 M) were subjected to **general procedure 7**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a red oil (2 g, 8.2 mmol, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 2H, ArCH x 2), 4.39 (s, 2H, ArCH x 2), 4.20 (s, 5H, ArCH x 5), 3.80 (s, 3H, H_2 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C_1), 71.4 (ArC x 2), 71.2 (ArC), 70.3 (ArC x 2), 69.9 (ArC x 5), 51.7 (C_2).

The spectroscopic data matched that previously reported in the literature.[180]

Diethyl (2-oxo-2-(pyridin-4-yl)ethyl)phosphonate 833



Methyl diethyl phosphonate (0.6 g, 4 mmol, 1.1 eq.), methyl isonicotinate (0.5 g, 3.6 mmol, 1 eq.), diisopropylamine (1.14 mL, 8.1 mmol, 2.25 eq.), *n*BuLi in hexanes (3.15 mL, 2.5 M, 7.92 mmol, 2.2 eq.) and dry THF (18 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50% EtOAc/pentane) as a colourless oil (0.55 g, 2.13 mmol, 59% yield).

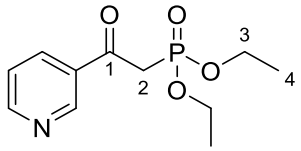
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 – 8.68 (m, 2H, ArCH x 2), 7.93 – 7.59 (m, 2H, ArCH x 2), 4.23 – 4.07 (m, 4H, H_3 x 4), 3.61 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.46 – 1.12 (m, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 18.4.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7 (d, *J* = 7.0 Hz, C_1), 151.1 (ArC x 2), 142.4 (d, *J* = 2.0 Hz, ArC), 121.82 (ArC x 2), 63.0 (d, *J* = 6.5 Hz, C_3 x 2), 39.0 (d, *J* = 129.0 Hz, C_2), 16.3 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[181]

Diethyl (2-oxo-2-(pyridin-3-yl)ethyl)phosphonate 834



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl nicotinate (0.99 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (2% MeOH, CH_2Cl_2) as a colourless oil (0.62 g, 2.41 mmol, 33% yield).

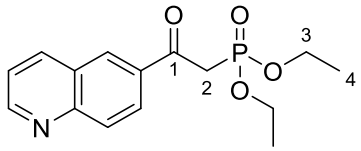
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 2.0 Hz, 1H, ArCH), 8.79 (dd, *J* = 5.0, 1.5 Hz, 1H, ArCH), 8.30 (dt, *J* = 8.0, 2.0 Hz, 1H, ArCH), 7.43 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, ArCH), 4.21 – 4.05 (m, 4H, H_3 x 4), 3.63 (d, *J* = 23.0 Hz, 2H, H_2 x 2), 1.28 (t, *J* = 7.0 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 18.8.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0 (d, *J* = 7.0 Hz, C_1), 153.9 (ArC), 150.5 (ArC), 136.5 (ArC), 132.0 (ArC), 123.7 (ArC), 63.0 (d, *J* = 6.5 Hz, C_3 x 2), 39.1 (d, *J* = 129.0 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[182]

Diethyl (2-oxo-2-(quinolin-6-yl)ethyl)phosphonate 835



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl quinoline-6-carboxylate (1.35 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (30→100% EtOAc/pentane) as a colourless oil (2.1 g, 6.83 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, J = 4.5, 1.5 Hz, 1H, ArCH), 8.55 (d, J = 2.0 Hz, 1H, ArCH), 8.34 – 8.23 (m, 2H, ArCH x 2), 8.14 (dt, J = 9.0, 0.5 Hz, 1H, ArCH), 7.47 (dd, J = 8.5, 4.5 Hz, 1H, ArCH), 4.24 – 4.02 (m, 4H, H_3 x 4), 3.74 (d, J = 23.0 Hz, 2H, H_2 x 2), 1.26 (td, J = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.49.

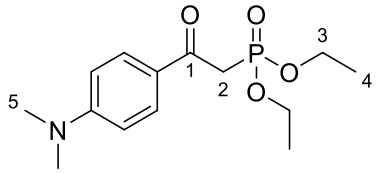
^{13}C NMR (101 MHz, $CDCl_3$) δ191.3 (d, J = 6.5 Hz, C_1), 152.9 (ArC), 150.3 (ArC), 137.8 (ArC), 134.30 (d, J = 2.0 Hz, ArC), 131.3 (ArC), 130.1 (ArC), 128.0 (ArC), 127.4 (ArC), 122.08 (ArC), 62.8 (d, J = 6.5 Hz, C_3 x 2), 38.9 (d, J = 129.0 Hz, C_2), 16.3 (d, J = 6.5 Hz, C_4 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 308.1042; $C_{15}H_{19}O_4NP$ requires 308.1046, Δ -1.41 ppm

IR (film) ν_{max}/cm^{-1} 2982, 2908, 1678, 1621, 1249, 1055, 1022, 827

m.p.: 47-48 °C

diethyl (2-(4-(dimethylamino)phenyl)-2-oxoethyl)phosphonate 836



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 4-(dimethylamino)benzoate (1.29 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a colourless oil (1.0 g, 3.34 mmol, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H, ArCH x 2), 6.67 – 6.57 (m, 2H, ArCH x 2), 4.20 – 4.02 (m, 4H, H_3 x 4), 3.51 (d, *J* = 22.5 Hz, 2H, H_2 x 2), 3.04 (s, 6H, H_5 x 6), 1.26 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

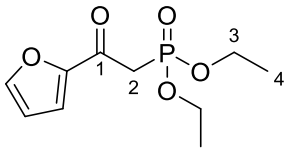
^{31}P NMR (162 MHz, $CDCl_3$) δ 21.4.

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.4 (d, *J* = 6.5 Hz, C_1), 153.8 (ArC), 131.5 (ArC x 2), 124.6 (d, *J* = 2.0 Hz, ArC), 110.7 (ArC x 2), 62.5 (d, *J* = 6.5 Hz, C_3 x 2), 40.1 (C_5 x 2), 37.9 (d, *J* = 129.5 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 300.1355; $C_{14}H_{23}O_4NP$ requires 300.1359, Δ -1.41 ppm

IR (film) ν_{max}/cm^{-1} 2986, 1657, 1593, 1369, 1521, 1025, 941, 791.

Diethyl (2-(furan-2-yl)-2-oxoethyl)phosphonate 837



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl furan-2-carboxylate (907 mg, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (100% EtOAc/pentane) as a colourless oil (1.45g, 5.9 mmol, 82% yield

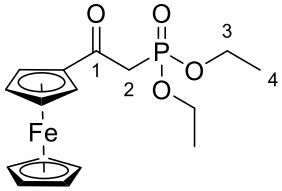
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 1.5, 1.0 Hz, 1H, ArCH), 7.32 (dd, *J* = 3.5, 1.0 Hz, 1H, ArCH), 6.58 (dd, *J* = 3.5, 1.5 Hz, 1H, ArCH), 4.31 – 3.97 (m, 4H, H_3 x 4), 3.51 (d, *J* = 22.5 Hz, 2H, H_2 x 2), 1.30 (td, *J* = 7.0, 0.5 Hz, 6H, H_4 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.5.

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1 (d, *J* = 7.0 Hz, C_1), 152.4 (d, *J* = 2.5 Hz, ArC), 147.2(ArC), 119.0 (ArC), 112.9 (ArC), 62.8 (d, *J* = 6.5 Hz, C_3 x 2), 38.4 (d, *J* = 130.0 Hz, C_2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[183]

Diethyl (2-oxo-2-ferrocene ethyl)phosphonate 838



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl ferrocene carboxylate (1.76 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a red oil (2.6 g, 7.14 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (t, *J* = 2.0 Hz, 2H, ArCH x 2), 4.55 (t, *J* = 2.0 Hz, 2H, ArCH x 2), 4.24 (s, 5H, ArCH x 5), 4.22 – 4.12 (m, 4H, H_3 x 4), 3.39 (d, *J* = 22.0 Hz, 2H, H_2 x 2), 1.32 (t, *J* = 7.0 Hz, 6H, H_4 x 6).

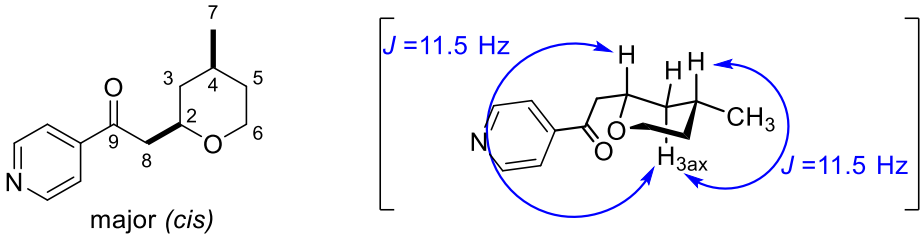
^{31}P NMR (162 MHz, $CDCl_3$) δ 20.7.

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4 (C_1), 79.1 (ArC), 73.1 (ArC x 2), 70.2 (ArC x 2), 70.2 (ArC x 5), 62.6 (d, *J* = 6.0 Hz, C_3 x 2), 39.7 (d, *J* = 132.0 Hz, C_2), 16.5 (d, *J* = 6.0 Hz, C_4 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 365.0608; $C_{16}H_{21}FeO_4P$ requires 365.0600, Δ 2.94 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2901, 1659, 1452, 1250, 1019, 967, 823, 782.

2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(pyridin-4-yl)ethan-1-one 839



Diethyl (2-oxo-2-(pyridin-4-yl)ethyl)phosphonate (360 mg, 1.4 equiv., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 equiv., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (40→70% Et_2O/pentane) as a colourless oil (201 mg, 0.92 mmol, 92% yield, 94:6 cis/trans ratio determined by Q ^{1}H NMR).

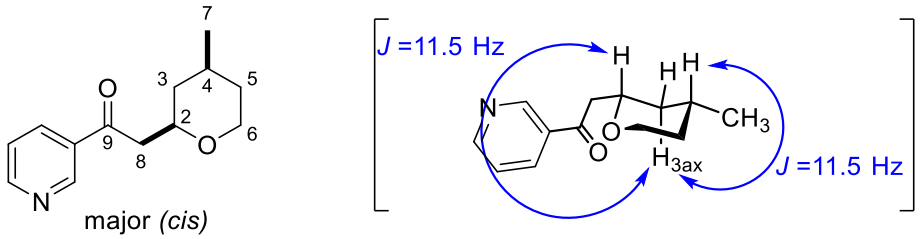
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 – 8.74 (m, 4H, Major ArCH x 2, minor ArCH x 2), 7.81 – 7.69 (m, 4H, Major ArCH x 2, minor ArCH x 2), 4.26 (dddd, *J* = 10.0, 8.0, 5.0, 3.0 Hz, 1H, minor H_2), 3.96 – 3.87 (m, 2H, major H_2, major H_{6eq}), 3.74 – 3.66 (m, 2H, minor H_6 x 2), 3.42 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, major H_{6ax}), 3.33 – 3.21 (m, 2H, major H_{8a}, minor H_{8a}), 2.95 – 2.80 (m, 2H, major H_{8b}, minor H_{8b}), 2.14 – 2.00 (m, 1H, minor H_4), 1.88 – 1.58 (m, 4H, major H_{3eq}, major H_4, minor H_{3eq}, minor H_{5eq}), 1.59 – 1.44 (m, 2H, major H_{5eq}, minor H_{3ax}), 1.33 – 1.13 (m, 2H, major H_{5ax}, minor H_{5eq}), 1.11 (d, *J* = 7.0 Hz, 3H, minor H_7 x 3), 1.01 (dt, *J* = 12.5, 11.5 Hz, 1H, major H_{3ax}), 0.95 (d, *J* = 6.5 Hz, 3H, major H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (major C_9, minor C_9), 150.9 (major ArC), 150.9 (minor ArC), 143.4 (major ArC x 2, minor ArC x 2), 121.5 (major ArC x 2), 121.4 (minor ArC x 2), 74.0 (major C_2), 68.9 (minor C_2), 68.4 (major C_6), 63.0 (minor C_6), 45.7 (major C_8), 44.8 (minor C_8), 40.7 (major C_3), 37.7 (minor C_3), 34.5 (major C_5), 31.9 (minor C_5), 30.3 (major C_4), 25.1 (minor C_4), 22.4 (major C_7), 18.5 (minor C_7).

HRMS (ESI+): Found $[M+H]^+$ = 220.1333; $C_{13}H_{18}O_2N$ requires 220.1332, Δ 0.29 ppm

IR (film) ν_{max}/cm^{-1} 2952, 2925, 2840, 1696, 1556, 1408, 1258, 1090, 810.

4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(pyridin-3-yl)ethan-1-one 840



Diethyl (2-oxo-2-(pyridin-3-yl)ethyl)phosphonate (360 mg, 1.4 equiv., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 equiv., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (70% Et_2O/pentane) as a colourless oil (215 mg, 0.98 mmol, 98% yield, 74:26 cis/trans ratio determined by Q ^1H NMR).

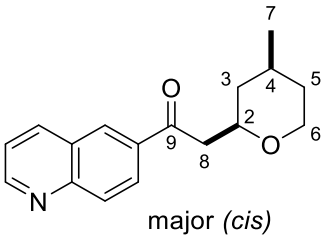
^1H NMR (400 MHz, $CDCl_3$) δ 9.27 – 9.12 (m, 2H, major ArCH, minor ArCH), 8.85 – 8.66 (m, 2H, major ArCH, minor ArCH), 8.37 – 8.18 (m, 2H, major ArCH, minor ArCH), 7.52 – 7.33 (m, 2H, major ArCH, minor ArCH), 4.28 (dddd, *J* = 9.9, 7.5, 5.0, 3.0 Hz, 1H, minor H_2), 4.01 – 3.85 (m, 2H, major H_2, major H_{6eq}), 3.75 – 3.64 (m, 2H, minor H_6 x 2), 3.50 – 3.37 (m, 1H, major H_{6ax}), 3.35 – 3.23 (m, 2H, major H_{8a}, minor H_{8a}), 2.95 – 2.84 (m, 2H, major H_{8b}, minor H_{8b}), 2.16 – 1.92 (m, 1H, minor H_4), 1.87 – 1.58 (m, 4H, major H_{3eq}, major H_4, minor H_{3eq}, minor H_{5eq}), 1.58 – 1.45 (m, 2H, major H_{5eq}, minor H_{3ax}), 1.31 – 1.14 (m, 2H, major H_{5ax}, minor H_{5ax}), 1.10 (d, *J* = 7.0 Hz, 3H, minor H_7 x 3), 1.02 (dt, *J* = 12.5, 11.5 Hz, 1H, major H_{3ax}), 0.94 (d, *J* = 6.5 Hz, 3H, major H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7 (minor C_9), 197.6 (major C_9), 153.5 (major ArC, minor ArC), 150.0 (major ArC), 149.9 (minor ArC), 135.8 (major ArC, minor ArC), 132.7 (major ArC, minor ArC), 123.7 (major ArC, minor ArC), 74.0 (major C_2), 69.0 (minor C_2), 68.3 (major C_6), 63.0 (minor C_6), 45.7 (major C_8), 44.8 (minor C_8), 40.7 (major C_3), 37.7 (minor C_3), 34.5 (major C_5), 31.9 (minor C_5), 30.3 (major C_4), 25.1 (minor C_4), 22.4 (major C_7), 18.5 (minor C_7).

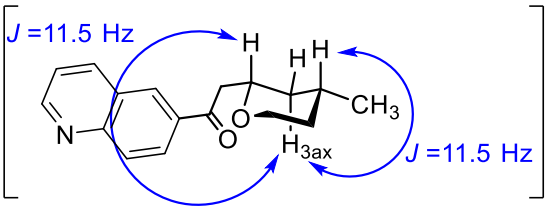
HRMS (ESI+): Found $[M+H]^+$ = 220.1332; $C_{13}H_{18}O_2N$ requires 220.1332, Δ -0.19 ppm

IR (film) ν_{max}/cm^{-1} 2999, 2886, 1689, 1585, 1380, 1259, 1089, 971, 703.

4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(quinolin-6-yl)ethan-1-one 841



major *(cis)*



Diethyl (2-oxo-2-(quinolin-6-yl)ethyl)phosphonate (430 mg, 1.4 equiv., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 equiv., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (80% Et_2O/pentane) as a colourless oil (241 mg, 0.90 mmol, 90% yield, 64:36 cis/trans ratio determined by Q ^{1}H NMR).

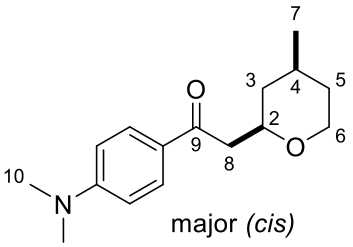
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 4.5, 1.5 Hz, 2H, major ArCH, minor ArCH), 8.46 (d, *J* = 2.0 Hz, 2H, major ArCH, minor ArCH), 8.34 – 8.23 (m, 4H, major ArCH x 2, minor ArCH x 2), 8.16 (dt, *J* = 9.0, 1.0 Hz, 2H, major ArCH, minor ArCH), 7.48 (dd, *J* = 8.5, 4.0 Hz, 2H, major ArCH, minor ArCH), 4.34 (dddd, *J* = 9.0, 7.0, 5.5, 3.0 Hz, 1H, minor H_2), 4.04 – 3.91 (m, 2H, major H_2 major H_{6eq}), 3.78 – 3.68 (m, 2H, minor H_6 x 2), 3.54 – 3.37 (m, 3H, major H_{6ax}, major H_{8b}, minor H_{8b}), 3.13 – 2.94 (m, 2H, major H_{8b}, minor H_{8b}), 2.17 – 2.02 (m, 1H, minor H_4), 1.90 – 1.75 (m, 2H, major H_{3eq}, minor H_{5ax}), 1.75 – 1.61 (m, 2H, major H_4, minor H_{3eq}), 1.60 – 1.49 (m, 2H, major H_{5eq}, minor H_{3ax}), 1.34 – 1.15 (m, 2H, major H_{5ax}, minor H_{5ax}), 1.12 (d, *J* = 7.2 Hz, 3H, minor H_7 x 3), 1.05 (dt, *J* = 13.0, 11.5 Hz, 1H, major H_{3ax}), 0.95 (d, *J* = 6.5 Hz, 3H, major H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (minor C_9), 198.0 (major C_9), 152.5 (major ArC, minor ArC), 150.0 (major ArC, minor ArC), 138.0 (major ArC, minor ArC), 135.4 (major ArC, minor ArC), 130.0 (minor ArC), 130.0 (major arC), 129.9 (major ArC), 129.9 (minor ArC), 128.1 (major ArC), 128.1 (minor ArC), 127.7 (major ArC, minor ArC), 122.0 (major ArC, minor ArC), 74.3 (major C_2), 69.2 (minor C_2), 68.4 (major C_6), 63.0 (minor C_6), 45.6 (major C_8), 44.6 (minor C_8), 40.8 (major C_3), 37.8 (minor C_3), 34.5 (major C_5), 32.1 (minor C_5), 30.3 (major C_4), 25.1 (minor C_4), 22.4 (major C_7), 18.6 (minor C_7).

HRMS (ESI+): Found $[M+H]^+$ = 270.1488; $C_{17}H_{20}O_2N$ requires 270.1489, Δ -0.08 ppm

IR (film) ν_{max}/cm^{-1} 2952, 2925, 1673, 1459, 1168, 1089, 839

1-(4-(Dimethylamino)phenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 842



major *(cis)*

Diethyl (2-(4-(dimethylamino)phenyl)-2-oxoethyl)phosphonate (418 mg, 1.4 equiv., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 equiv., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (25% Et_2O/pentane) as a white solid (261 mg, 1.0 mmol, 100% yield, 91:9 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.83 (m, 2H, ArCH x 2), 6.74 – 6.58 (m, 2H, ArCH x 2), 4.03 – 3.85 (m, 2H, H_2, H_{6eq}), 3.46 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, H_{6ax}), 3.21 (dd, *J* = 15.5, 6.0 Hz, 1H, H_{8a}), 3.05 (s, 6H, H_{10} x 6), 2.85 (dd, *J* = 15.5, 6.5 Hz, 1H, H_{8b}), 1.76 (ddt, *J* = 13.0, 4.0, 2.0 Hz, 1H, H_{3eq}), 1.73 – 1.57 (m, 1H, H_4), 1.52 (ddq, *J* = 13.0, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.27 – 1.14 (m, 1H, H_{5ax}), 1.03 – 0.95 (m, 1H, H_{3ax}), 0.92 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4 (C_9), 153.5 (ArC), 130.7 (ArC x 2), 125.6 (ArC), 110.8 (ArC x 2), 74.7 (C_2), 68.4 (C_6), 44.7 (C_8), 40.8 (C_3), 40.2 (C_{10} x 2), 34.7 (C_5), 30.3 (C_4), 22.4 (C_7).

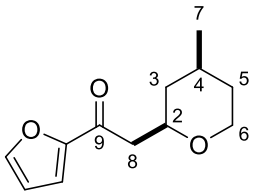
Diagnostic peaks observed for 1-(4-(Dimethylamino)phenyl)-*trans*-2-(4-methyltetrahydro-2H-pyran-2-yl)ethan-1-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (dtd, *J* = 9.5, 6.5, 3.0 Hz, 1H, H_2), 3.76 – 3.70 (m, 2H, H_6 x 2), 2.12 – 1.98 (m, 1H, H_4), 1.08 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.5 (C_2), 62.9 (C_6), 43.6 (C_8), 37.8 (C_3), 32.3 (C_5), 25.1 (C_4), 18.8 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 262.1803; $C_{16}H_{24}O_2N$ requires 262.1802, Δ 0.52 ppm

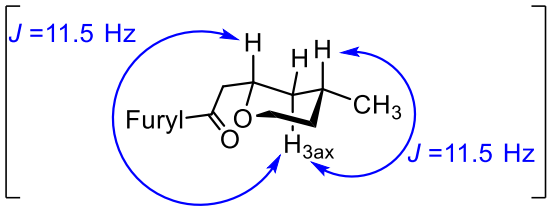
IR (film) ν_{max}/cm^{-1} 2949, 2921, 2839, 1659, 1598, 1370, 1189, 1167, 1089, 818.

m.p.: 59-60 °C

1-(Furan-2-yl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 843



major *(cis)*



Diethyl (2-(furan-2-yl)-2-oxoethyl)phosphonate (344 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a white solid (201 mg, 0.97 mmol, 97% yield, 72:28 cis/trans ratio determined by Q ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 1.5, 0.5 Hz, 2H, major ArCH, minior ArCH), 7.20 (dt, *J* = 3.5, 0.5 Hz, 2H, major ArCH, minior ArCH), 6.52 (ddd, *J* = 3.5, 2.0, 1.0 Hz, 2H, major ArCH, minior ArCH), 4.27 (tdd, *J* = 8.5, 5.5, 3.0 Hz, 1H, minor H_2), 3.98 – 3.85 (m, 2H, major H_2, major H_{6eq}), 3.77 – 3.63 (m, 2H, minor H_6 x 2), 3.43 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, major H_{6ax}), 3.24 – 3.05 (m, 2H, major H_{8a}, minor H_{8a}), 2.84 – 2.70 (m, 2H, major H_{8b}, minor H_{8b}), 2.05 (qp, *J* = 7.0, 4.5 Hz, 1H, minor H_4), 1.85 – 1.55 (m, 4H, major H_3, major H_4, minor H_{3eq}, minor H_{5eq}), 1.56 – 1.39 (m, 2H, major H_{5eq}, minor H_{3ax}), 1.32 – 1.13 (m, 2H, major H_{5ax}, minor H_{5ax}), 1.08 (d, *J* = 7.0Hz, 3H, minor H_7 x 3), 1.00 (dt, *J* = 12.5, 11.5 Hz, 1H, major H_{3ax}), 0.93 (d, *J* = 6.5 Hz, 3H, major H_7 x 3).

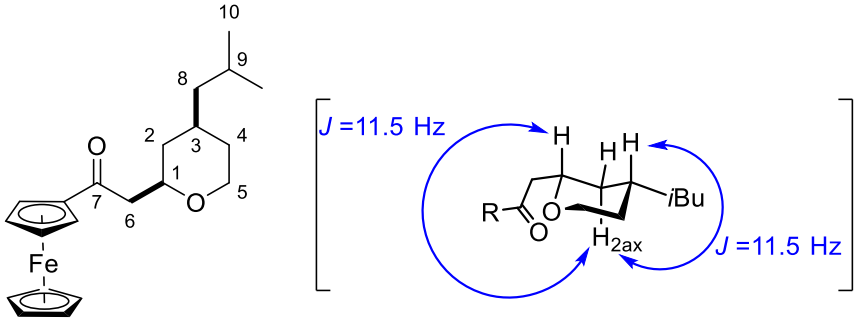
^{13}C NMR (101 MHz, $CDCl_3$) δ 187.6 (minor C_9), 187.4 (major C_9), 153.2 (major ArC, minor ArC), 146.7 (major ArC), 146.6 (minor ArC), 117.8 (major ArC), 117.7 (minor ArC), 112.4 (minor ArC), 112.4 (major ArC), 74.1 (major C_2), 69.2 (minor C_2), 68.3 (major C_6), 62.8 (minor C_6), 45.4 (major C_8), 44.2 (minor C_8), 40.6 (major C_3), 37.7 (minor C_3), 34.5 (major C_5), 32.1 (minor C_5), 30.3 (major C_4), 25.0 (minor C_4), 22.4 (major C_7), 18.8 (minor C_7).

HRMS (ESI+): Found $[M+Na]^+$ = 231.0992; $C_{12}H_{16}O_3Na$ requires 231.0992, Δ 0.14 ppm

IR (film) ν_{max}/cm^{-1} 2997, 2886, 1673, 1381, 1265, 1165, 1090, 954

mp: 70-71 °C

2-(4-isobutyltetrahydro-*2H*-pyran-2-yl)-1-ferrocene ethan-1-one 844



Diethyl (2-oxo-2-ferrocene ethyl)phosphonate (509 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (25% Et_2O/pentane) as a white solid (387 mg, 1.0 mmol, 100% yield, > 95:5 cis/trans ratio by Q ^1H NMR).

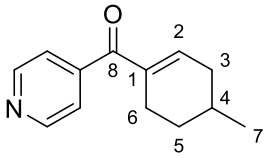
^1H NMR (400 MHz, $CDCl_3$) δ 4.83 – 4.78 (m, 1H, ArCH), 4.78 – 4.74 (m, 1H, ArCH), 4.53 – 4.46 (m, 2H, ArCH x 2), 4.22 (s, 5H, ArCH x 5), 4.05 – 3.87 (m, 2H, H_1, H_{5eq}), 3.54 – 3.42 (m, 1H, H_{5ax}), 3.02 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{6a}), 2.67 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{6b}), 1.85 – 1.49 (m, 4H, H_{2eq}, H_3, H_{4eq}, H_9), 1.30 – 1.14 (m, 1H, H_{4ax}), 1.14 – 1.05 (m, 2H, H_8 x 2), 0.94 (q, *J* = 11.5 Hz, 1H, H_{2ax}), 0.89 – 0.85 (m, 6H, H_{10} x 6)

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3 (C_7), 79.6 (ArC), 74.0 (C_1), 72.5 (ArC), 72.4 (ArC), 70.0 (ArC x 5), 69.6 (ArC), 69.5 (ArC), 68.3 (C_5), 46.7 (C_6, C_8), 39.3 (C_2), 33.1 (C_4), 32.8 (C_3), 24.4 (C_9), 23.0 (C_{10}), 22.9 (C_{10}).

HRMS (ESI+): Found $[M+H]^+$ = 369.1506; $C_{21}H_{29}O_2Fe$ requires 369.1511, Δ -0.50 ppm

IR (film) ν_{max}/cm^{-1} 2924, 2838, 1670, 1454, 1094, 1026, 820.

(4-Methylcyclohex-1-en-1-yl)(pyridin-4-yl)methanone 845



Method 1: 2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(pyridin-4-yl)ethan-1-one (65.7 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**, heating for 24 hours. The title compound was afforded after purification by FCC (50→100% Et_2O/pentane) as a colourless oil (5 mg, 0.025 mmol, 8% yield) and recovered starting material (39 mg, 0.18 mmol, 60% yield).

Method 2: 2-(4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(pyridin-4-yl)ethan-1-one (65.7 mg, 0.3 mmol, 1 eq.), alumina (600 mg, 20 eq., 6.0 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**, heating for 48 hours. The title compound was afforded after purification by FCC (50→100% Et_2O/pentane) as a colourless oil (18 mg, 0.09 mmol, 30% yield).

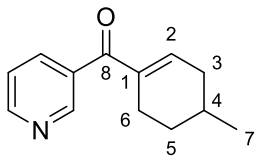
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.68 (m, 2H, ArCH x 2), 7.45 – 7.38 (m, 2H, ArCH x 2), 6.58 (dq, *J* = 5.0, 1.5 Hz, 1H, H_2), 2.66 – 2.54 (m, 1H, H_6), 2.43 – 2.23 (m, 2H, H_3, H_6), 1.96 – 1.81 (m, 2H, H_3, H_5), 1.81 – 1.67 (m, 1H, H_4), 1.29 (dtd, *J* = 13.0, 11.0, 5.5 Hz, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2 (C_8), 149.8 (ArC x 2), 146.7 (C_2), 146.4 (C_1), 138.4 (ArC), 122.7 (ArC x 2), 34.9 (C_3), 30.2 (C_5), 27.8 (C_4), 23.6 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 202.1128 $C_{13}H_{16}ON$ requires 202.1126 Δ 0.95 ppm

IR (film) ν_{max}/cm^{-1} 2998, 2886, 1650, 1630, 1380, 1153, 1088, 954, 819.

(4-Methylcyclohex-1-en-1-yl)(pyridin-3-yl)methanone 846



4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(pyridin-3-yl)ethan-1-one (65.8 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (60→70% Et_2O/pentane) as a colourless oil (33 mg, 0.165 mmol, 55% yield).

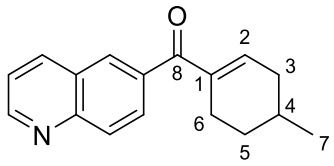
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 2.0, 1.0 Hz, 1H, ArCH), 8.70 (dd, *J* = 5.0, 2.0 Hz, 1H, ArCH), 7.92 (dt, *J* = 8.0, 2.0 Hz, 1H, ArCH), 7.42 – 7.27 (m, 1H, ArCH), 6.61 – 6.54 (m, 1H, H_2), 2.65 – 2.53 (m, 1H, H_6), 2.42 – 2.25 (m, 2H, H_3, H_6), 1.96 – 1.80 (m, 2H, H_3, H_5), 1.80 – 1.67 (m, 1H, H_4), 1.29 (dtd, *J* = 13.0, 11.0, 5.5 Hz, 1H, H_5), 1.01 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0 (C_8), 152.0 (ArC), 150.0 (ArC), 145.3 (C_2), 138.8 (C_1), 136.6 (ArC), 134.4 (ArC), 123.3 (ArC), 34.8 (C_3), 30.2 (C_5), 27.8 (C_4), 23.9 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 202.1226 $C_{13}H_{16}ON$ requires 202.1226 Δ -0.10 ppm

IR (film) ν_{max}/cm^{-1} 2999, 2886, 1646, 1583, 1380, 1268, 1153, 1071, 954, 719.

(4-Methylcyclohex-1-en-1-yl)(quinolin-6-yl)methanone 847



4-Methyltetrahydro-*2H*-pyran-2-yl)-1-(quinolin-6-yl)ethan-1-one (80.8 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (50% Et_2O/pentane) as a white solid (62 mg, 0.247 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 4.0, 2.0 Hz, 1H, ArCH), 8.24 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, ArCH), 8.19 – 8.07 (m, 2H, ArCH x 2), 7.96 (dd, *J* = 8.5, 2.0 Hz, 1H, ArCH), 7.47 (dd, *J* = 8.5, 4.5 Hz, 1H, ArCH), 6.66 – 6.56 (m, 1H, H_2), 2.71 – 2.59 (m, 1H, H_6), 2.46 – 2.31 (m, 2H, H_3, H_6), 1.97 – 1.84 (m, 2H, H_3, H_5), 1.85 – 1.70 (m, 1H, H_4), 1.34 (dtd, *J* = 13.0, 11.0, 5.5 Hz, 1H, H_5), 1.04 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

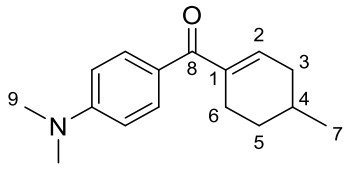
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4 (C_8), 151.9 (ArC), 149.3 (ArC), 144.5 (C_2), 138.8 (ArC), 137.4 (ArC), 136.9 (C_1), 129.7 (ArC), 129.6 (ArC), 129.5 (ArC), 127.4 (ArC), 121.9 (ArC), 34.8 (C_3), 30.4 (C_5), 27.9 (C_4), 24.2 (C_6), 21.7 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 252.1383 $C_{17}H_{18}ON$ requires 252.1383 Δ -0.12 ppm

IR (film) ν_{max}/cm^{-1} 2999, 2886, 1642, 1380, 1251, 1152, 1089, 954.

m.p.: 80-81 °C

(4-(Dimethylamino)phenyl)(4-methylcyclohex-1-en-1-yl)methanone 848



1-(4-(Dimethylamino)phenyl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (78.4 mg, 0.3 mmol, 1 eq.), Al(O^{t}Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (15% Et_2O/pentane) as a colourless oil (55.5 mg, 0.228 mmol, 76% yield).

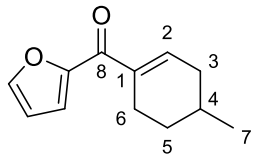
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.66 (m, 2H, ArCH x 2), 6.69 – 6.61 (m, 2H, ArCH x 2), 6.36 (tdd, *J* = 3.5, 2.5, 1.5 Hz, 1H, H_2), 3.04 (s, 6H, H_9 x 6), 2.61 – 2.46 (m, 1H, H_6), 2.43 – 2.26 (m, 2H, H_3, H_6), 1.93 – 1.69 (m, 3H, H_3, H_4, H_5), 1.31 (dtd, *J* = 13.0, 10.5, 5.5 Hz, 1H, H_5), 1.02 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (C_8), 153.0 (ArC), 138.6 (C_1), 138.3 (C_2), 132.0 (ArC x 2), 125.8 (ArC), 110.7 (ArC x 2), 40.3 (C_9 x 2), 34.3 (C_3), 30.7 (C_5), 28.1 (C_4), 25.0 (C_6), 21.8 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 244.1698; $C_{16}H_{22}ON$ requires 244.1696 Δ 0.92 ppm

IR (film) ν_{max}/cm^{-1} 2995, 2921, 2877, 1631, 1593, 1526, 1366, 1271, 1189, 1122, 821.

Furan-2-yl(4-methylcyclohex-1-en-1-yl)methanone 849



1-(Furan-2-yl)-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (80.8 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**, heating for 8 hours. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (48 mg, 0.253 mmol, 84% yield).

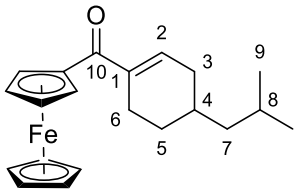
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 1.5, 1.0 Hz, 1H, ArCH), 7.06 (dd, *J* = 3.5, 1.0 Hz, 1H, ArCH), 6.92 (ddt, *J* = 5.0, 3.0, 1.0 Hz, 1H, H_2), 6.49 (dd, *J* = 3.5, 1.5 Hz, 1H, ArCH), 2.60 – 2.49 (m, 1H, H_6), 2.44 – 2.22 (m, 2H, H_3, H_6), 1.95 – 1.65 (m, 3H, H_3, H_4, H_5), 1.27 (dtd, *J* = 13.0, 11.0, 5.5 Hz, 1H, H_5), 1.00 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 183.9 (C_8), 152.4 (ArC), 146.3 (ArC), 140.5 (C_2), 138.1 (C_1), 118.7 (ArC), 111.7 (ArC), 34.6 (C_3), 30.3 (C_5), 27.9 (C_4), 24.2 (C_6), 21.7 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 191.1067 $C_{12}H_{15}O_2$ requires 191.1067 Δ 0.41 ppm

IR (film) ν_{max}/cm^{-1} 2999, 2886, 1634, 1380, 1252, 1152, 1072, 953, 831.

(4-Isobutyllcyclohex-1-en-1-yl)(ferrocene)methanone 850



Method 1: 2-(4-Isobutyltetrahydro-*2H*-pyran-2-yl)-1-ferrocene ethan-1-one (110 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (52.5 mg, 0.15 mmol, 50% yield).

Method 2: 2-(4-Isobutyltetrahydro-*2H*-pyran-2-yl)-1-ferrocene ethan-1-one (110 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (62 mg, 0.177 mmol, 59% yield).

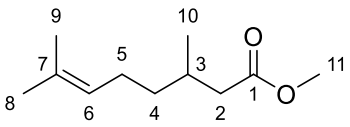
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (p, *J* = 2.5 Hz, 1H, H_2), 4.80 (t, *J* = 2.0 Hz, 2H, ArCH x 2), 4.47 (t, *J* = 2.0 Hz, 2H, ArCH x 2), 4.18 (s, 5H, ArCH x 5), 2.60 – 2.47 (m, 1H, H_6), 2.40 – 2.26 (m, 2H, H_3, H_6), 1.95 – 1.54 (m, 4H,H_3, H_4, H_5, H_8), 1.34 – 1.12 (m, 3H, H_5, H_7 x 2,), 0.94 – 0.88 (m, 6H, H_9 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C_{10}), 139.8 (C_1), 136.0 (C_2), 78.9 (ArC), 71.8 (ArC x 2), 71.2 (ArC), 71.2 (ArC), 70.1 (ArC x 5), 46.0 (C_7), 32.8 (C_3), 30.6 (C_4), 28.9 (C_5), 25.1 (C_8), 24.9 (C_6), 23.1 (C_9), 22.9 (C_9).

HRMS (ESI+): Found $[M+H]^+$ = 351.1406 $C_{21}H_{27}OFe$ requires 351.1406 Δ 0.81 ppm

IR (film) ν_{max}/cm^{-1} 2953, 2868, 1625, 1443 1276, 821.

Methyl 3,7-dimethyloct-6-enoate 852



Dimethyl sulfate (1.32 mL, 1.2 eq., 14 mmol) was added to a 50 mL RBF charged with citronellic acid (2.0 g, 1 eq., 11.7 mmol), acetone (22 mL, 0.5 M) and potassium carbonate (2 g, 1.2 eq., 14 mmol). The reaction vessel was then fitted with a reflux condenser and refluxed for 2 hours. The reaction mixture was then cooled to RT, diluted with water (50 mL), extracted with diethyl ether (3 x 50 mL),

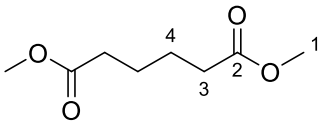
dried over Na_2SO_4, and then concentrated *in vacuo*. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (1.95 g, 10.5 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 – 5.03 (m, 1H, H_6), 3.66 (s, 3H, H_{11} x 3), 2.32 (dd, *J* = 14.5, 6.0 Hz, 1H, H_{2a}), 2.11 (dd, *J* = 14.0, 8.0 Hz, 1H, H_{2b}), 2.05 – 1.88 (m, 3H, H_3, H_5 x 2), 1.67 (s, 3H, H_8 x 3 or H_9 x 3), 1.60 (s, 3H, H_8 x 3 or H_9 x 3), 1.41 – 1.28 (m, 1H, H_{4a}), 1.27 – 1.15 (m, 1H, H_{4b}), 0.94 (d, *J* = 6.5 Hz, 3H, H_{10} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C_1), 131.7 (C_7), 124.4 (C_6), 51.5 (C_{11}), 41.7 (C_2), 36.9 (C_4), 30.2 (C_3), 25.8 (C_8 or C_9), 25.6 (C_5), 19.8 (C_{10}), 17.8 (C_8 or C_9).

The spectroscopic data matched that previously reported in the literature.[184]

Dimethyl adipate 854



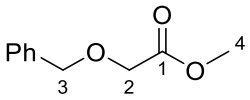
Adipic acid (5.84 g, 40 mmol), concentrated sulphuric acid (13.5 mL) and MeOH (80 mL, 0.5 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a colourless oil (4.2 g, 24.1 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 6H, H_1 x 6), 2.45 – 2.21 (m, 4H, H_3 x 4), 1.83 – 1.49 (m, 4H, H_4 x 4).

^{13}C NMR (101 MHz, CDCl3) δ 173.9 (C_2 x 2), 51.7 (C_1 x 2), 33.8 (C_3 x 2), 24.5 (C_4 x 2).

The spectroscopic data matched that previously reported in the literature.[185]

Methyl 2-(benzyloxy)acetate 856



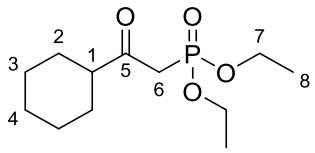
2-(Benzyloxy)acetic acid (3 g, 23.8 mmol), concentrated sulphuric acid (3 mL) and MeOH (80 mL, 0.3 M) were subjected to **general procedure 7**. The title compound was used in the next step without purification as a colourless oil (2.9 g, 16.1 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H, ArCH x 5), 4.64 (s, 2H, H_3 x 2), 4.11 (s, 2H, H_2 x 2), 3.77 (s, 3H, H_4 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C_1), 137.2 (ArC), 128.7 (ArC x 2), 128.2 (ArC x 2), 128.2 (ArC), 73.5 (C_3), 67.3 (C_2), 52.0 (C_4).

The spectroscopic data matched that previously reported in the literature.[186]

Diethyl (2-cyclohexyl-2-oxoethyl)phosphonate 859



Methyl diethyl phosphonate (1.18 g, 7.7 mmol, 1.1 eq.), methyl cyclohexanecarboxylate (1 g, 7 mmol, 1 eq.), LDA in THF (2M, 7.7 mL, 15.4 mmol) and dry THF (15 mL, 0.47 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (60% Et_2O/pentane) as a colourless oil (1.4 g, 5.34 mmol, 76% yield).

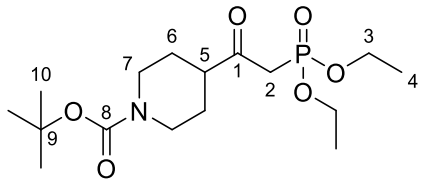
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.06 (m, 4H, H_7 x 4), 3.11 (d, *J* = 22.5 Hz, 2H, H_6 x 2), 2.59 (tt, *J* = 11.0, 3.5 Hz, 1H, H_1), 1.95 – 1.59 (m, 5H, H_2 x 2, H_3 x 2, H_4) 1.36 – 1.13 (m, 11H, H_2 x 2, H_3 x 2, H_4, H_8 x 6).

^{31}P NMR (162 MHz, $CDCl_3$) δ 20.4.

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6 (d, *J* = 6.0 Hz, C_5), 62.6 (d, *J* = 6.5 Hz, C_7 x 2), 51.6 (C_1), 40.4 (d, *J* = 128.5 Hz, C_6), 28.4 (C_2 x 2), 25.9 (C_4), 25.7 (C_3 x 2), 16.5 (d, *J* = 6.5 Hz, C_7 x 2).

The spectroscopic data matched that previously reported in the literature.[181]

Tert-butyl 4-(2-(diethoxyphosphoryl)acetyl)piperidine-1-carboxylate 860



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), 1-(tert-butyl) 4-methyl piperidine-1,4-dicarboxylate (1.75 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50→100% EtOAc/pentane) as a colourless oil (2.1 g, 5.78 mmol, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 – 3.98 (m, 6H, H_3 x 4, H_7 x 2), 3.10 (d, *J* = 23.0 Hz, 2H, H_2), 2.82 – 2.68 (m, 3H, H_5, H_7 x 2), 1.90 – 1.77 (m, 2H, H_6 x 2), 1.57 – 1.39 (m, 11H, H_6 x 2, H_{10} x 9), 1.36 – 1.26 (m, 6H, H_4 x 6).

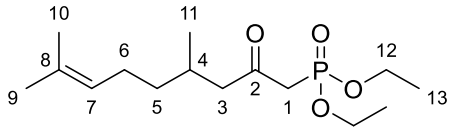
^{31}P NMR (162 MHz, $CDCl_3$) δ 19.7.

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (d, *J* = 6.0 Hz, C_1), 154.7 (C_8), 79.7 (C_9), 62.7 (d, *J* = 6.5 Hz, C_3 x 2), 49.3 (C_5), 43.2 (br S, C_7 x 2), 40.6 (d, *J* = 128.0 Hz, C_2), 28.5 (C_{10} x 3), 27.4 (C_6 x 2), 16.4 (d, *J* = 6.5 Hz, C_4 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 364.1884; $C_{16}H_{31}O_6NP$ requires 364.1884, Δ 0.10 ppm

IR (film) ν_{max}/cm^{-1} 2931, 1689, 1422, 1238, 1160, 1012, 963, 770.

Diethyl (4,8-dimethyl-2-oxonon-7-en-1-yl)phosphonate 861



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), Methyl 3,7-dimethyloct-6-enoate (1.33 mg, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (50% EtOAc/pentane) as a colourless oil (1.95 g, 6.41 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (tp, *J* = 7.0, 1.5 Hz, 1H, H_7), 4.20 – 4.06 (m, 4H, H_{12} x 4), 3.15 – 2.94 (m, 2H, H_1 x 2), 2.59 (dd, *J* = 17.0, 5.5 Hz, 1H, H_{3a}), 2.44 (dd, *J* = 17.0, 8.0 Hz, 1H, H_{3b}), 2.14 – 1.84 (m, 3H, H_4, H_6 x 2), 1.66 (s, 3H, H_9 x 3 or H_{10} x 3), 1.58 (s, 3H, H_9 x 3 or H_{10} x 3), 1.38 – 1.12 (m, 8H, H_5 x 2, H_{13} x 6), 0.90 (d, *J* = 6.5 Hz, 3H, H_{11} x 3).

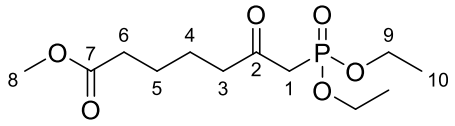
^{31}P NMR (162 MHz, $CDCl_3$) δ 20.0.

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0 (d, *J* = 6.0 Hz, C_2), 131.7 (C_8), 124.4 (C_7), 62.6 (d, *J* = 6.5 Hz, C_{12} x 2), 51.5 (C_3), 42.8 (d, *J* = 127.0 Hz, C_1), 36.9 (C_5), 28.7 (C_4), 25.8 (C_9 or C_{10}), 25.6 (C_6), 19.7 (C_{11}), 17.8 (C_9 or C_{10}), 16.4 (d, *J* = 6.5 Hz, C_{13} x 2).

HRMS (ESI+): Found $[M+H]^+$ = 305.1876; $C_{15}H_{30}O_4P$ requires 305.1874, Δ -0.74 ppm

IR (film) ν_{max}/cm^{-1} 2973, 2937, 1713, 1465, 1365, 1254, 1018, 966

Methyl 7-(diethoxyphosphoryl)-6-oxoheptanoate 862



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), dimethyl adipate (1.15 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (30→100% EtOAc/pentane) as a colourless oil (330 mg, 1.13 mmol, 16% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 – 4.03 (m, 4H, H_9 x 4), 3.64 (s, 3H, H_8 x 3), 3.05 (d, J = 22.7 Hz, 2H, H_1 x 2), 2.73 – 2.54 (m, 2H, H_3 x 2), 2.40 – 2.23 (m, 2H, H_6 x 2), 1.68 – 1.56 (m, 4H, H_4 x 2, H_5 x 2), 1.32 (t, J = 7.0 Hz, 6H, H_{10} x 6).

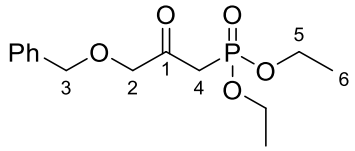
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7 (d, *J* = 6.0 Hz, C_2), 173.9 (C_7), 62.7 (d, *J* = 6.5 Hz, C_9 x 2), 51.6 (C_8), 43.7 (C_3), 42.6 (d, *J* = 127.0 Hz, C_1), 33.9 (C_6), 24.3 (C_4 or C_5), 22.9 (C_4 or C_5), 16.4 (d, *J* = 6.5 Hz, C_{10} x 2).

^{31}P NMR (162 MHz, $CDCl_3$) δ 19.5.

HRMS (ESI+): Found $[M+H]^+$ = 295.1303; $C_{12}H_{24}O_6P$ requires 295.1305, Δ -0.68 ppm

IR (film) ν_{max}/cm^{-1} 2984, 1736, 1713, 1438, 1252, 1164, 1015, 968, 800

Diethyl (3-(benzyloxy)-2-oxopropyl)phosphonate 863



Methyl diethyl phosphonate (1.2 g, 8 mmol, 1.1 eq.), methyl 2-(benzyloxy)acetate (1.3 g, 7.2 mmol, 1 eq.), diisopropylamine (2.28 mL, 16.2 mmol, 2.25 eq.), *n*BuLi in hexanes (6.3 mL, 2.5 M, 15.8 mmol, 2.2 eq.) and dry THF (36 mL, 0.2 M) were subjected to **general procedure 8**. The title compound was afforded after purification by FCC (20→100% EtOAc/pentane) as a colourless oil (1.2 g, 4 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H, ArCH x 5), 4.60 (s, 2H, H_3 x 2), 4.19 (s, 2H, H_2 x 2), 4.17 – 4.08 (m, 4H, H_5 x 4), 3.15 (d, *J* = 23.0 Hz, 2H, H_4 x 2), 1.31 (t, *J* = 7.0 Hz, 6H, H_6 x 6).

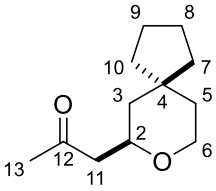
^{31}P NMR (162 MHz, $CDCl_3$) δ 19.2.

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (d, *J* = 6.5 Hz, C_1), 137.1 (ArC), 128.6 (ArC x 2), 128.2 (ArC), 128.1 (ArC x 2), 75.2 (d, *J* = 1.5 Hz, C_2), 73.5 (C_3), 62.8 (d, *J* = 6.5 Hz, C_5 x 2), 38.6 (d, *J* = 128.0 Hz, C_4), 16.4 (d, *J* = 6.0 Hz, C_6 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 301.1197; $C_{14}H_{22}O_5P$ requires 301.1199, Δ -0.72 ppm

IR (film) ν_{max}/cm^{-1} 1728, 1246, 1133, 1015, 962, 786, 699.

1-(8-Oxaspiro[4.5]decan-7-yl)propan-2-one 866



Diethyl (2-oxopropyl)phosphonate (272 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 8-oxaspiro[4.5]decan-7-ol (156 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a colourless oil (196 mg, 1 mmol, 100% yield).

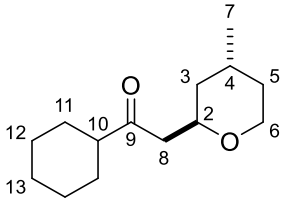
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 – 3.77 (m, 2H, H_2, H_{6eq}), 3.52 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, H_{6ax}), 2.64 (dd, *J* = 15.5, 8.0 Hz, 1H, H_{11a}), 2.36 (dd, *J* = 15.5, 4.5 Hz, 1H, H_{11b}), 2.17 (s, 3H, H_{13} x 3), 1.71 – 1.47 (m, 7H, H_{5eq}, H_8 x 2, H_9 x 2, H_7 x 2 or H_{10} x 2), 1.44 – 1.20 (m, 5H, H_3 x 2, H_{5ax}, H_7 x 2 or H_{10} x 2).

13C NMR (101 MHz, CDCl3) δ 207.7 (C_{12}), 71.5 (C_2), 65.8 (C_6), 50.5 (C_{11}), 43.9 (C_3), 42.6 (C_7 or C_{10}), 41.1 (C_4), 37.6 (C_5), 34.5 (C_7 or C_{10}), 31.2 (C_{13}), 24.9 (C_8 or C_9), 23.7 (C_8 or C_9).

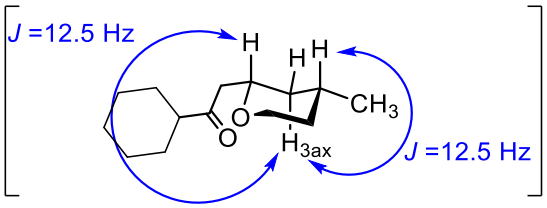
HRMS (ESI+): Found $[M+H]^+$ = 197.1539; $C_{12}H_{21}O_2$ requires 197.1536, Δ 1.57 ppm

IR (film) ν_{max}/cm^{-1} 2998, 2867, 1715, 1381, 1357, 1253, 1167, 1102, 954.

1-Cyclohexyl-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one 867



major (*trans*)



minor (*cis*)

Diethyl (2-oxo-2-(quinolin-6-yl)ethyl)phosphonate (550 mg, 1.4 eq., 2.1 mmol), dry toluene (7.5 mL), 60% wt. NaH (72 mg, 1.2 eq., 1.8 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (174 mg, 1 eq., 1.5 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (284 mg, 1.23 mmol, 85% yield, 29:71 cis/trans ratio determined by Q ^{1}H NMR).

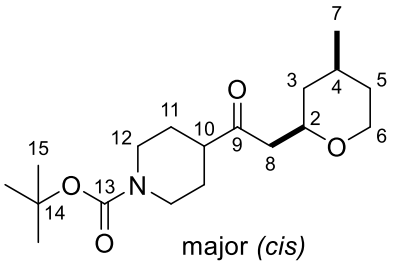
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 – 4.05 (m, 1H, major H_2), 3.92 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, minor H_{6eq}), 3.75 (dddd, *J* = 11.0, 7.0, 5.5, 2.0 Hz, 1H, minor H_2), 3.71 – 3.65 (m, 2H, major H_6 x 2), 3.41 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, minor H_{6ax}), 2.72 (ddd, *J* = 16.1, 11.0, 7.2 Hz, 2H, major $_{H8a}$, minor H_{8a}), 2.47 – 2.29 (m, 4H, major $_{H8a}$ major H_{10}, minor $H_{8a,}$ minor H_{10}), 2.01 (qp, *J* = 6.8, 4.6 Hz, 1H, major H_4), 1.91 – 1.71 (m, 9H, major $H_{5eq,}$ major H_{11} x 2 major H_{12} x 2, minor H_{11} x 2, minor H_{12} x 2), 1.69 – 1.59 (m, 4H, major $H_{13,}$ minor H_{3eq}, minor $H_{4,}$ minor H_{13}), 1.55 – 1.46 (m, 2H, major H_{3eq}, minor H_{5eq}), 1.44 – 1.35 (m, 1H, major H_{3ax}), 1.35 – 1.11 (m, 12H, major H_{5ax}, major H_{11} x 2, major H_{12} x 2, major $H_{13,}$ minor $H_{5ax,}$ minor H_{11} x 2, minor H_{12} x 2, minor H_{13}), 1.07 (d, *J* = 7.0 Hz, 3H, major H_7 x 3), 0.91 (d, *J* = 6.5 Hz, 3H, minor H_7 x 3) 0.88, (q, *J* = 12.5 Hz, 1H minor H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5 (major C_9, minor C_9), 73.9 (minor C_2), 68.8 (major C_2), 68.3 (minor C_6), 62.9 (major C_6), 51.6 (minor C_{10}), 51.5 (major C_{10}), 47.5 (minor C_8), 46.4 (major C_8), 40.6 (minor C_3), 37.6 (major C_3), 34.6 (minor C_5), 32.1 (major C_5), 30.3 (minor C_4), 28.4 (major C_{11} x 2), 28.2 (minor C_{11} x 2), 26.0 (major C_{12} x 2), 25.8 (major C_{13}, and minor C_{12} x 2), 25.7 (minor C_{13}), 25.1 (major C_4), 22.4 (minor C_7), 18.7 (major C_7).

HRMS (ESI+): Found $[M+H]^+$ = 225.1850; $C_{14}H_{25}O_2$ requires 225.1849, Δ 0.34 ppm

IR (film) ν_{max}/cm^{-1} 2927, 2853, 1708, 1449, 1315, 1080, 1003

***Tert*-butyl 4-(2-(4-methyltetrahydro-*2H*-pyran-2-yl)acetyl)piperidine-1-carboxylate 868**



major *(cis)*

Tert-butyl 4-(2-(diethoxyphosphoryl)acetyl)piperidine-1-carboxylate (509 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (50% Et_2O/pentane) as a white solid (325 mg, 1 mmol, 100% yield, 88:12 cis/trans ratio determined by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.01 (m, 2H, H_{12eq} x 2), 3.91 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, H_{6eq}), 3.81 – 3.70 (m, 1H, H_2), 3.40 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, H_{6ax}), 2.86 – 2.62 (m, 3H, H_{12ax} x 2, H_{8a}), 2.48 (tt, *J* = 11.5, 3.5 Hz, 1H, H_{10}), 2.40 (dd, *J* = 16.0, 5.0 Hz, 1H, H_{8b}), 1.86 – 1.76 (m, 2H, H_{11eq} x 2), 1.70 – 1.40 (m, 14H, H_{3eq}, H_4, H_{5eq}, H_{11ax} x 2, H_{15} x 9), 1.25 – 1.11 (m, 1H, H_{5ax}), 0.96 – 0.83 (m, 4H, H_7 x 3, H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7 (C_9), 154.8 (C_{13}), 79.7 (C_{14}), 74.0 (C_2), 68.3 (C_6), 49.4 (C_{10}), 47.4 (C_8), 43.4 (br, s, C_{11} x 2), 40.6 (C_3), 34.5 (C_5), 30.3 (C_4), 28.6 (C_{15} x 3), 27.4 (C_{12}), 27.2 (C_{12}), 22.4 (C_7). *n.b broad singlet observed at 43.4 ppm (C_{11}) and two peaks at 27.4 (C_{12}) and 27.2 (C_{12}) due to N-Boc romaters.*

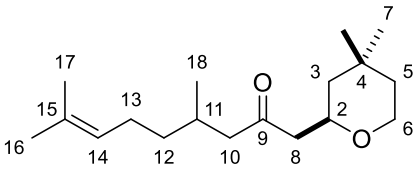
Diagnostic peaks observed for Tert-butyl 4-(*trans*-2-(4-methyltetrahydro-2H-pyran-2-yl)acetyl)piperidine-1-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 – 3.63 (m, 2H, H_6 x 2), 2.08 – 1.96 (m, 1H, H_4), 1.08 (d, *J* = 7.0 Hz, 3H, H_7 x 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.9 (C_6), 46.5 (C_8), 37.6 (C_3), 32.0 (C_5), 25.1 (C_4) 18.5 (C_7).

HRMS (ESI+): Found $[M+Na]^+$ = 348.2146; $C_{18}H_{31}O_4NNa$ requires 348.2145, Δ 0.26 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2859, 1693, 1422, 1276, 1165, 1091, 1016.

m.p.: 40-41 °C

1-(4,4-Dimethyltetrahydro-*2H*-pyran-2-yl)-4,8-dimethylnon-7-en-2-one 869



Diethyl (4,8-dimethyl-2-oxonon-7-en-1-yl)phosphonate (426 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4,4-dimethyltetrahydro-*2H*-pyran-2-ol (130 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (280 mg, 1.0 mmol, 100% yield, inconsequential 1:1 mixture of diastereomers).

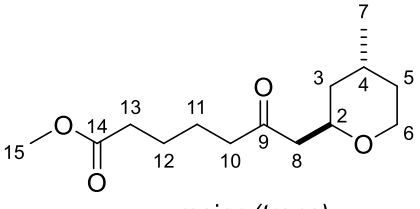
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (ddq, *J* = 8.5, 5.75, 1.5 Hz, 1H, H_{14}), 3.91 (ddddd, *J* = 11.0, 8.0, 5.0, 2.0, 1.0 Hz, 1H, H_2), 3.77 (ddd, *J* = 12.0, 5.0, 1.5 Hz, 1H, H_{6eq}), 3.58 (ddd, *J* = 13.0, 12.0, 2.5 Hz, 1H, H_{6ax}), 2.61 (ddd, *J* = 15.5, 7.5, 1.0 Hz, 1H, H_{8a}), 2.42 (dt, *J* = 16.0, 5.5 Hz, 1H, H_{10a}), 2.34 – 2.18 (m, 2H, H_{8b}, H_{10b}), 2.07 – 1.87 (m, 3H, H_{11}, H_{13} x 2), 1.67 (s, 3H, H_{16} x 3, or H_{17} x 3), 1.59 (s, 3H, H_{16} x 3, or H_{17} x 3), 1.51 – 1.38 (m, 1H, H_{5eq}), 1.35 – 1.08 (m, 5H, H_{5ax}, H_3 x 2, H_{12} x 2), 1.02 (s, 3H, H_7 x 3), 0.93 (s, 3H, H_7 x 3), 0.88 (d, *J* = 6.5Hz, 3H, H_{18} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C_{9a}), 209.4 (C_{9b}), 131.6 (C_{15}), 124.6 (C_{14}), 70.1 (C_{2a}), 70.0 (C_{2b}), 64.5 (C_6), 51.5 (C_{10}), 50.1 (C_{8a}), 50.1 (C_{8b}), 45.0 (C_3), 38.7 (C_5), 37.1 (C_{12a}), 37.1 (C_{12b}), 33.3 (C_7), 29.1 (C_4), 28.8 (C_{11a}), 28.8 (C_{11b}), 25.8 (C_{16} or C_{17}), 25.6 (C_{13a}), 25.6 (C_{13b}), 24.1 (C_7), 19.9 (C_{18a}), 19.9 (C_{18b}), 17.8 (C_{16} or C_{17}). C4

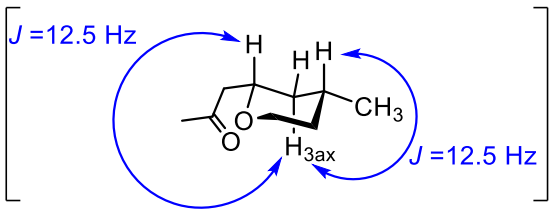
HRMS (ESI+): Found $[M+H]^+$ = 281.2475; $C_{18}H_{33}O_2$ requires 281.2474, Δ 0.81 ppm

IR (film) ν_{max}/cm^{-1} 2972, 2900, 1714, 1469, 1364, 1190, 1084.

Methyl 7-(4-methyltetrahydro-*2H*-pyran-2-yl)-6-oxoheptanoate 870



major *(trans)*



minor *(cis)*

Methyl 7-(diethoxyphosphoryl)-6-oxoheptanoate (307 mg, 1.4 eq., 1.07 mmol), dry toluene (4 mL), 60% wt. NaH (36 mg, 1.2 eq., 0.9 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (89 mg, 1 eq., 348

0.77 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5-10% Et_2O/pentane) as a colourless oil (183 mg, 0.76 mmol, 99% yield, 38:62 cis/trans ratio determined by Q ^1H NMR).

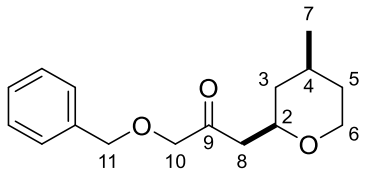
^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (tdd, *J* = 8.5, 5.0, 3.0 Hz, 1H, major H_2), 3.91 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, minor H_{6eq}), 3.77 – 3.59 (m, 9H, major H_6 x 2, major H_{15} x 3, minor H_2, minor H_{15} x 3), 3.39 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, minor H_{6ax}), 2.72 – 2.58 (m, 2H, major H_{8a}, minor H_{8a}), 2.52 – 2.41 (m, 4H, major H_{10} x 2, minor H_{10} x 2), 2.40 – 2.26 (m, 6H, major H_{8b}, major H_{13} x 2, minor H_{8b}, minor H_{13} x 2), 2.07 – 1.94 (m, 1H, major H_4), 1.75 (dddd, *J* = 13.5, 9.0, 6.0, 5.0 Hz, 1H, major H_{5eq}), 1.68 – 1.55 (m, 10H, major H_{11} x 2, major H_{12} x 2, minor H_{3eq}, minor H_4, minor H_{11} x 2, minor H_{12} x 2), 1.55 – 1.46 (m, 2H, major $H_{3eq,}$ minor H_{5eq}), 1.41 – 1.32 (m, 1H, major H_{3ax}), 1.29 – 1.09 (m, 2H, major $H_{5ax,}$ minor H_{5ax}), 1.06 (d, *J* = 7.5 Hz, 3H, major H_7 x 3), 0.91 (d, *J* = 6.5 Hz, 3H, minor H_7 x 3), 0.89 (q, *J* = 12.5 Hz, minor H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (major C_9), 209.1 (minor C_9), 174.0 (major C_{14}, minor C_{14}), 74.0 (minor C_2), 68.9 (major C_2), 68.2 (minor C_6), 62.8 (major C_6), 51.6 (major C_{15}, minor C_{15}), 49.6 (minor C_8), 48.6 (major C_8), 43.5 (minor C_{10}), 43.4 (major C_{10}), 40.6 (minor C_3), 37.6 (major C_3), 34.4 (minor C_5), 34.0 (major C_{13}, minor C_{13}), 32.0 (major C_5), 30.3 (minor C_4), 25.0 (major C_4), 24.5 (major C_{12}, minor C_{12}), 23.0 (major C_{11}, minor C_{11}), 22.4 (minor C_7), 18.6 (major C_7).

HRMS (ESI+): Found $[M+H]^+$ = 257.1748; $C_{14}H_{25}O_4$ requires 257.1747, Δ 0.38 ppm

IR (film) ν_{max}/cm^{-1} 2978, 2929, 1736, 1711, 1381, 1256, 1169, 1076, 970

1-(Benzyloxy)-3-(4-methyltetrahydro-*2H*-pyran-2-yl)propan-2-one 871



major *(cis)*

Diethyl (3-(benzyloxy)-2-oxopropyl)phosphonate (420 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a colourless oil (220 mg, 0.84 mmol, 84% yield, 75:25 cis/trans ratio determined by Q ^1H NMR).

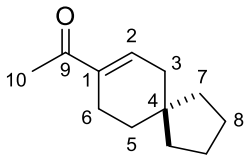
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H, major ArCH x 5, minor ArCH x 5), 4.59 (s, 4H, major H_{11} x 2, minor H_{11} x 2), 4.21 – 4.04 (m, 5H, major H10 x 2, minor H_2 minor H10 x 2), 3.91 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, major H_{6eq}), 3.74 (dddd, *J* = 11.0, 8.0, 4.5, 2.0 Hz, 1H, major H_2), 3.69 – 3.62 (m, 2H, minor H_6 x 2), 3.39 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, major H_{6ax}), 2.77 – 2.61 (m, 2H, major H_{8a}, minor H_{8a}), 2.46 – 2.35 (m, 2H, major H_{8b}, minor H_{8b}), 2.02 (qp, *J* = 7.0, 4.5 Hz, 1H, minor H_4), 1.81 – 1.71 (m, 1H, minor H_{5eq}), 1.70 – 1.46 (m, 4H, major H_{3eq}, major H_4, major H_{5eq}, minor H_{3eq}), 1.43 – 1.35 (m, 1H, minor H_{3ax}), 1.30 – 1.10 (m, 2H, major H_{5ax}, minor H_{5eq}), 1.07 (d, *J* = 7.0 Hz, 3H, minor H_7 x 3), 0.98 – 0.85 (m, 4H, major H_{3ax}, major H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2 (minor C_9), 207.0 (major C_9), 137.4 (major ArC, minor ArC), 128.6 (major ArC x 2, minor ArC x 2), 128.1 (major ArC x 2, minor ArC x 2), 128.1 (major ArC, minor ArC), 75.8 (major C_{10}), 75.8 (minor C_{10}), 73.8 (major C_2), 73.4 (minor C_{11}), 73.4 (major C_{11}), 68.8 (minor C_2), 68.2 (major C_6), 62.8 (minor C_6), 46.0 (major C_8), 45.0 (minor C_8), 40.6 (major C_3), 37.7 (minor C_3), 34.4 (major C_4), 32.0 (minor C_4), 30.3 (major C_4), 25.0 (minor C_4), 22.4 (major C_7), 18.6 (minor C_7).

HRMS (ESI+): Found $[M+H]^+$ = 263.1643; $C_{16}H_{23}O_3$ requires 263.1642, Δ 0.40 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2885, 1719, 1381, 1252, 1152, 1087, 955

1-(Spiro[4.5]dec-7-en-8-yl)ethan-1-one 873



1-(8-Oxaspiro[4.5]decan-7-yl)propan-2-one (58 mg, 0.3 mmol, 1 eq.), Alumina (150 mg, 5 eq. 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (49 mg, 0.275 mmol, 92% yield).

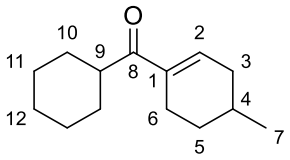
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (tt, *J* = 4.0, 1.5 Hz, 1H, H_2), 2.32 – 2.23 (m, 5H, H_6 x 2, H_{10} x 3), 2.13 (dt, *J* = 4.0, 2.5 Hz, 2H, H_3 x 2), 1.70 – 1.59 (m, 4H, H_7 x 4), 1.50 (t, *J* = 6.5 Hz, 2H, H_5 x 2), 1.46 – 1.31 (m, 4H, H_8 x 4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4 (C_9), 140.7 (C_2), 139.4 (C_1), 40.5 (C_4), 39.0 (C_3), 38.3 (C_8 x 2), 33.3 (C_5), 25.4 (C_{10}), 24.5 (C_7 x 2), 21.7 (C_6).

HRMS (ESI+): Found $[M+H]^+$ = 179.1432; $C_{12}H_{19}O$ requires 179.1430 Δ 0.90 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2856, 1665, 1639, 1385, 1248, 1074, 953, 807.

Cyclohexyl(4-methylcyclohex-1-en-1-yl)methanone 874



1-Cyclohexyl-2-(4-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (67.3 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a colourless oil (58 mg, 0.281 mmol, 94% yield).

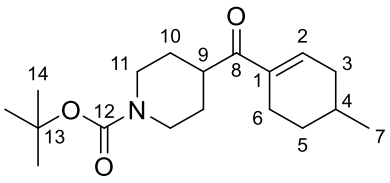
^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (dt, *J* = 5.0, 2.0 Hz, 1H, H_2), 2.96 (tt, *J* = 11.5, 3.5 Hz, 1H, H_9), 2.49 – 2.26 (m, 2H, H_3, H_6), 2.19 – 1.99 (m, 1H, H_6), 1.94 – 1.55 (m, 8H, H_3, H_4, H_5 H_{10} x 2, H_{11} x 2, H_{12}), 1.48 – 1.08 (m, 6H, H_5, H_{10} x 2, H_{11} x 2, H_{12}), 0.98 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.1 (C_8), 138.6 (C_2), 138.0 (C_1), 44.4 (C_9), 34.7 (C_3), 30.5 (C_5), 29.9 (C_{10} x 2), 27.9 (C_4), 26.1 (C_{11} x 2), 26.1 (C_{12}), 23.6 (C_6), 21.6 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 207.1744 $C_{14}H_{23}O$ requires 207.1743 Δ 0.25 ppm

IR (film) ν_{max}/cm^{-1} 2998, 2929, 1709, 1663, 1450, 1382, 1248, 1151, 954.

***Tert*-butyl 4-(4-methylcyclohex-1-ene-1-carbonyl)piperidine-1-carboxylate 875**



Tert-butyl 4-(2-(4-methyltetrahydro-*2H*-pyran-2-yl)acetyl)piperidine-1-carboxylate (98 mg, 0.3 mmol, 1 eq.), $Al(O^tBu)_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**, and heated for 48 hours. The title compound was afforded after purification by FCC (10→20% Et_2O/pentane) as a colourless oil (69 mg, 0.224 mmol, 75% yield).

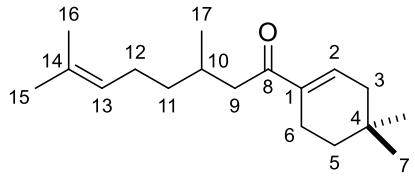
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 – 6.81 (m, 1H, H_2), 4.22 – 4.00 (m, 2H, H_{11} x 2), 3.11 (tt, *J* = 10.5, 4.5 Hz, 1H, H_9), 2.98 – 2.60 (m, 2H, H_{11} x 2), 2.49 – 2.26 (m, 2H, H_3, H_6), 2.21 – 2.03 (m, 1H, H_6), 1.93 – 1.73 (m, 2H, H_3, H_5), 1.72 – 1.52 (m, 5H, H_4, H_{10} x 4), 1.45 (s, 9H, H_{14} x 9), 1.26 – 1.11 (m, 1H, H_5), 0.98 (d, *J* = 6.5 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0 (C_8), 154.7 (C_{12}), 139.1 (C_2), 137.8 (C_1), 79.5 (C_{13}), 43.4 (C_{11} x 2), 42.1 (C_9), 34.5 (C_3), 30.2 (C_5), 28.8 (C_{10} x 2), 28.5 (C_{14} x 3), 27.7 (C_4), 23.4 (C_6), 21.5 (C_7).

HRMS (ESI+): Found $[M+Na]^+$ = 330.2039; $C_{18}H_{29}O_3NNa$ requires 330.2040 Δ -0.23 ppm

IR (film) ν_{max}/cm^{-1} 2951, 2927, 1682, 1659, 1635, 1423, 1160, 906.

3,7-Dimethyl-1-(4-methylcyclohex-1-en-1-yl)oct-6-en-1-one 876



1-(4,4-Dimethyltetrahydro-*2H*-pyran-2-yl)-4,8-dimethylnon-7-en-2-one (84 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (2→5% Et_2O/pentane) as a colourless oil (75 mg, 0.286 mmol, 95% yield).

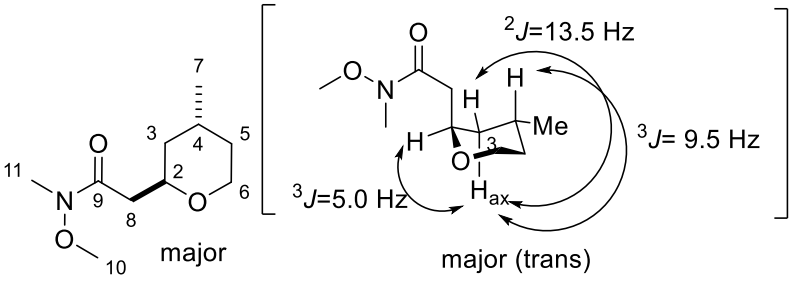
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (tt, *J* = 4.0, 1.5 Hz, 1H, H_2), 5.08 (dddd, *J* = 7.0, 5.5, 3.0, 1.5 Hz, 1H, H_{13}), 2.61 (dd, *J* = 15.0, 5.5 Hz, 1H, H_{9a}), 2.42 (dd, *J* = 15.0, 8.0 Hz, 1H, H_{9b}), 2.31 – 2.21 (m, 2H, H_6 x 2), 2.10 – 1.90 (m, 5H, H_3 x 2, $H_{10,}$ H_{12} x 2), 1.68 (s, 3H, H_{15} x 3 or H_{16} x 3), 1.59 (s, 3H, H_{15} x 3 or H_{16} x 3), 1.44 – 1.13 (m, 4H, H_5 x 2, H_{11} x 2), 0.91 (s, 6H, H_7 x 6), 0.89 (d, *J* = 6.5 Hz, 3H, H_{17} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7 (C_8), 138.9 (C_2), 138.7 (C_1), 131.5 (C_{14}), 124.7 (C_{13}), 44.6 (C_9), 40.2 (C_3), 37.4 (C_{11}), 35.1 (C_5), 30.1 (C_{10}), 28.6 (C_4), 28.2 (C_7 x 2), 25.9 (C_{12}), 25.7 (C_{15} or C_{16}), 21.2 (C_6), 20.1 (C_{17}), 17.8 (C_{15} or C_{16}).

HRMS (ESI+): Found $[M+H]^+$ = 263.2370 $C_{18}H_{31}O$ requires 263.2369 Δ 0.33 ppm

IR (film) ν_{max}/cm^{-1} 2980, 2867, 1667, 1639, 1460, 1381, 1363, 1170, 1085, 733.

***N*-Methoxy-*N*-methyl-2,4-methyltetrahydro-2H-pyran-2-yl)acetamide 880**



A flame-dried 2-5 mL Biotage® microwave vial was charged with Diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (155 mg, 0.65 mmol, 1.2 eq.), 60% wt. NaH (24 mg, 0.6 mmol, 1.2 eq.), and then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (1 mL, 0.5 M) was then added, stirring the solution for 1h at RT. 4-Methyltetrahydro-*2H*-pyran-2-ol (58 mg, 0.5 mmol, 1 eq.) was then added, the balloon was removed, and the reaction was heated at 110 °C for 15 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (50→70% Et_2O/pentane) as a colourless oil (48 mg, 0.238 mmol, 48% yield, cis:trans ratio 36:64 d.r.). The major diastereomer was assigned by coupling constant analysis.

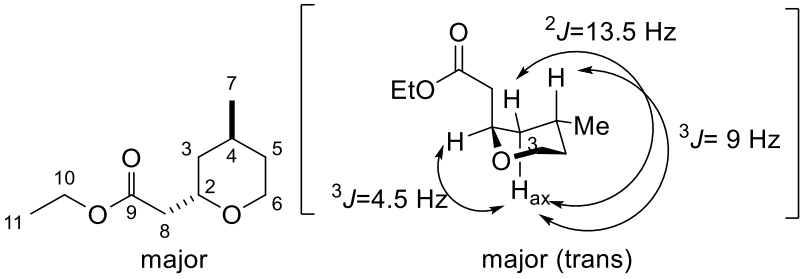
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.08 (m, 1H, major H_2), 3.94 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, minor H_{6eq}), 3.79 (dddd, *J* = 11.0, 7.5, 5.5, 2.0 Hz, 1H, minor H_2), 3.74 – 3.61 (m, 8H, major H_6 x 2, major H_{10} x 3, minor H_{10} x 3), 3.43 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, minor H_{6ax}), 3.18 (s, 6H, major H_{11} x 3, minor H_{11} x 3), 2.86 – 2.69 (m, 2H, major H_{8a}, minor H_{8a}), 2.43 – 2.32 (m, 2H, major H_{8b}, minor H_{8b}), 2.03 (qp, *J* = 7.0, 4.5 Hz, 1H, major H_4), 1.82 – 1.74 (m, 1H, major H_{5eq}), 1.70 (ddt, *J* = 12.5, 4.0, 2.0, Hz, 1H, minor H_{3eq}), 1.65 – 1.60 (m, 1H, minor H_4) 1.57 (ddd, *J* = 13.5, 9.5, 5.0 Hz, 1H, major H_{3ax}), 1.54 – 1.39 (m, 2H, minor H_{5eq}, major H_{3eq}), 1.29 – 1.20 (m, 1H, major H_{5ax}), 1.20 – 1.12 (m, 1H, minor H_{5ax}), 1.07 (d, *J* = 7.0 Hz, 3H, major H_7 x 3), 1.00 – 0.87 (m, 4H, minor H_7 x 3, minor H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (major C_9), 172.1 (minor C_9), 74.0 (minor C_2), 68.9 (major C_2), 68.1 (minor C_6), 62.7 (major C_6), 61.3 (C_{10} x 2), 40.5 (minor C_3), 38.7 (minor C_8), 37.7 (major C_8), 37.5 (major C_3), 34.4 (minor C_5), 32.0 (C_{11} x 2, major C_5), 30.1 (minor C_4), 25.0 (major C_4), 22.3 (minor C_7), 18.5 (major C_7).

HRMS (ESI+): Found $[M+H]^+$ = 202.1438; $C_{10}H_{20}O_3N$ requires 202.1438, Δ 0.37 ppm

IR (film) ν_{max}/cm^{-1} 2923, 2874, 2846, 1662, 1441, 1386, 1080, 1002

Ethyl 2-(4-methyltetrahydro-*2H*-pyran-2-yl)acetate 883



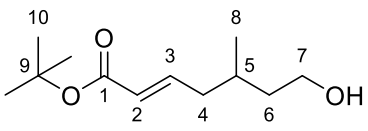
60% wt. NaH (77 mg, 2 mmol, 2eq.) was added to a stirred solution of ethyl 2-(diethoxyphosphoryl)acetate (448 mg, 2 mmol, 2 eq.) in THF (5 mL, 0.2 M) at 0 °C under nitrogen. After 30 minutes, 4-methyltetrahydro-*2H*-pyran-2-ol (116 mg, 1 mmol, 1 eq.) was added, and stirred for 48 h at RT. The solvent was then removed *in vacuo*. The title compound was afforded after purification by FCC (10% EtOAc/pentane) as a colourless oil (115 mg, 0.62 mmol, 62% yield, 80:20 trans:cis by Q ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 – 3.96 (m, 5H, major H_2, major H_{10} x 2, minor H_{10} x 2), 3.90 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, minor H_{6eq}), 3.73 – 3.56 (m, 3H, minor H_2, major H_{6eq}, major H_{6ax}), 3.37 (ddd, *J* = 12.5, 11.5, 2.0 Hz, 1H, minor H_{6ax}), 2.58 – 2.39 (m, 2H, major $H_{8a,}$ minor H_{8a}), 2.36 – 2.23 (m, 2H, major $H_{8b,}$ minor H_{8b}), 1.95 (qp, *J* = 7.0, 5.0 Hz, 1H, major H_4), 1.70 (ddt, *J* = 14.0, 9.5, 5.0 Hz, 1H, major H_{5eq}), 1.63 – 1.54 (m, 2H, minor H_4, minor H_{3eq}), 1.49 (ddd, *J* = 13.5, 9.0, 4.5 Hz, 1H, major H_{3ax}), 1.48 – 1.42 (m, 1H, minor H_{5eq}), 1.35 (dddd, *J* = 13.5, 5.0, 3.0, 1.5 Hz, 1H, major H_{3eq}), 1.24 – 1.10 (m, 8H, major H_{11} x 3, minor H_{11} x 3, major H_{5ax}, minor H_{5ax}), 1.00 (d, *J* = 7.0 Hz, 3H, major H_7 x 3), 0.91 – 0.83 (m, 4H, minor H_7 x 3, minor H_{3ax})

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7 (major C_9), 171.6 (minor C_9), 74.2 (minor C_2), 69.2 (major C_2), 68.3 (minor C_6), 62.7 (major C_6), 60.6 (major C_{10}, minor C_{10}), 41.8 (minor C_8), 40.6 (major C_8), 40.3 (minor C_3), 37.3 (major C_3), 34.4 (minor C_5), 32.1 (major C_5), 30.3 (minor C_4), 24.9 (major C_4), 22.4 (minor C_7), 18.9 (major C_7), 14.3 (major C_{11}, minor C_{11}).

The spectroscopic data matched that previously reported in the literature.[187]

***Tert*-butyl *(E)*-7-hydroxy-5-methylhept-2-enoate 886**



4-Methyltetrahydro-*2H*-pyran-2-ol (400 mg, 3.44 mmol, 1 eq.) was added to a stirred solution of (*tert*-Butoxycarbonylmethylene)triphenylphosphorane (3.88 g, 3 eq., 10.32 mmol) in toluene (15 mL, 0.22 M) under argon. The reaction was stirred for 48 hours at RT. The solvent was then removed *in vacuo*. The title compound was afforded after purification by FCC (25% EtOAc/pentane) as a colourless oil (516 mg, 2.38 mmol, 70% yield, 88:12 E/Z mixture by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dt, *J* = 15.0, 7.5 Hz, 1H, H_3), 5.68 (dt, *J* = 15.0, 1.5 Hz, 1H, H_2), 3.73 – 3.49 (m, 2H, H_7 x 2), 2.14 (dddd, *J* = 14.5, 7.5, 6.0, 1.5 Hz, 1H, H_{4a}), 2.05 – 1.92 (m, 1H, H_{4b}), 1.81 – 1.65 (m, 1H, H_5), 1.62 – 1.30 (m, 11H, H_{10} x 9, H_6 x 2), 0.87 (d, *J* = 6.5 Hz, 3H, H_8 x 3). *n.b OH peak not observed.*

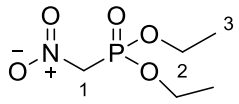
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (C_1), 145.8 (C_3), 124.6 (C_2), 81.0 (C_9), 61.0 (C_7), 39.7 (C_4), 39.5 (C_6), 29.4 (C_5), 28.3 (C_{10} x 3), 19.7 (C_8).

Diagnostic peaks for *(Z)*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dt, *J* = 11.5, 7.5 Hz, 1H, H_3), 2.64 (dddd, *J* = 15.0, 7.5, 5.5, 2.0 Hz, 1H, H_{4a}), 2.35 (dtd, *J* = 15.0, 7.5, 1.5 Hz, 1H, H_{4b}), 0.82 (d, *J* = 6.5 Hz, 3H, H_8 x 3). Smaller alkene coupling of ^{3}J=11.5 Hz indicates the minor compound is the *(Z)* isomer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (C_3), 122.6 (C_2).

HRMS (ESI+): Found $[M+Na]^+$ = 237.14624; $C_{12}H_{22}O_3{}^{23}Na$ requires 237.14612, Δ 0.52 ppm

IR (film) ν_{max}/cm^{-1} 3401, 2975, 2929, 1713, 1651, 1368, 1324, 1154, 983

Diethyl (nitromethyl)phosphonate 888



Diethyl (2-oxopropyl)phosphonate (4 g, 20.6 mmol, 1 eq.) was added to acetic anhydride (2 mL) and warmed to 30 °C. A stirred solution of 90% HNO_3 (1.07 mL, 22.7 mmol, 1.1 eq.) and acetic anhydride (1.31 mL) was then added dropwise, with care taken for the temperature to not rise above 35 °C. The reaction was then stirred for 1h and cooled to RT. Water (15 mL) was then added, and stirred for a 1 h. The product was then extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→60% EtOAc/pentane) as a pale yellow oil (2.14 g, 10.8 mmol, 42% yield).

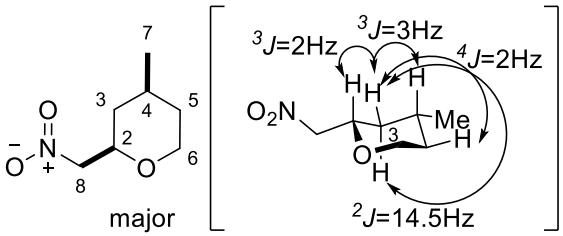
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, *J* = 15.5 Hz, 2H, H_1 x 2), 4.26 (dq, *J* = 8.5, 7.1 Hz, 4H, H_2 x 4), 1.38 (td, *J* = 7.1, 0.5 Hz, 6H, H_3 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 72.20 (d, *J* = 142 Hz, C_1), 64.49 (d, *J* = 6.5 Hz, C_2 x 2), 16.37 (d, *J* = 6.0 Hz, C_3 x 2).

^{31}P NMR (162 MHz, $CDCl_3$) δ 9.20.

The spectroscopic data matched that previously reported in the literature.[188]

4-Methyl-2-(nitromethyl)tetrahydro-*2H*-pyran 889



A flame-dried 2-5 mL Biotage® microwave vial was charged with Diethyl (nitromethyl)phosphonate (256 mg, 1.3 mmol, 1.3 eq.), dry toluene (3 mL, 0.3 M), and 60% wt. NaH (48 mg, 1.2 mmol, 1.2 eq), and then sealed with a microwave vial cap (containing a Reseal™ septum), and fitted with an argon balloon. The solution was stirred for 1 h at RT. 4-Methyltetrahydro-*2H*-pyran-2-ol (111 mg, 1 mmol, 1 eq.) was then added, the balloon was removed, and the reaction was heated at 70 °C for 15 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (56 mg, 0.352 mmol, 35% yield, cis:trans ratio 72:28 d.r by ^{1}H NMR). The major diastereomer was assigned by coupling constant analysis

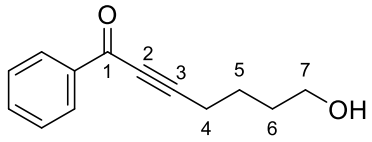
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, *J* = 12.0, 9.5 Hz, 1H, minor H_{8a}), 4.45 – 4.35 (m, 2H, major H_{8a}, minor H_2), 4.35 – 4.25 (m, 2H, major H_{8b}, minor H_{8b}), 4.09 – 3.96 (m, 2H, major H_{6eq}, major H_2), 3.82 – 3.66 (m, 2H, minor H_6 x 2), 3.43 (ddd, *J* = 12.5, 11.5, 2.5 Hz, 1H, major H_{6ax}), 2.11 – 1.99 (m, 1H, minor H_4), 1.88 – 1.74 (m, 1H, minor H_{5eq}), 1.73 – 1.66 (m, 1H, major H_4), 1.63 (ddt, *J* = 14.5, 3.0, 2.0 Hz, 1H, major H_{3eq}), 1.57 (ddt, *J* = 13.5, 4.0, 2.0 Hz, 1H, major H_{5eq}), 1.47 – 1.38 (m, 1H, minor H_{3eq}), 1.37 – 1.14 (m, 3H, minor H_{3ax}, minor $H_{5ax,}$ major H_{5ax}), 1.10 (d, *J* = 7.0 Hz, 3H, minor H_7 x 3), 1.02 – 0.92 (m, 4H, major H7 x 3, major H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 80.0 (major C_8), 79.2 (minor C_8), 74.2 (major C_2), 69.6 (minor C_2), 68.2 (major C_6), 62.7 (minor C_6), 36.9 (major C_3), 34.3 (minor C_3), 34.0 (major C_5), 31.6 (minor C_5), 30.0 (major C_4), 24.8 (minor C_4), 22.2 (major C_7), 18.6 (minor C_7).

HRMS (ESI+): Found $[M+H]^+$ = 160.0967; $C_7H_{14}O_3N$ requires 160.0968, Δ -0.67 ppm

IR (film) ν_{max}/cm^{-1} 2926, 2847, 1550, 1217, 1096, 1037

7-Hydroxy-1-phenylhept-2-yn-1-one 894



A solution of *n*BuLi in hexanes (23 mL, 2.5M, 57.6 mmol, 2.4 eq.) was added dropwise to a solution of 5-hexyn-1-ol (2.83 g, 1.2 eq., 28.8 mmol) in dry THF (100 mL, 0.25M) cooled to -78 °C under nitrogen atmosphere. The resulting solution was stirred for 1 hour, and then a solution of *N*-methoxy-*N*-methylbenzamide (3.39 g, 1 eq., 24 mmol) in dry THF (10 mL) was added dropwise by syringe. The reaction mixture was then warmed to RT and stirred for 1 hour. The reaction was then quenched with sat. aq. ammonium chloride (50 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were then dried over $MgSO_4$, and concentrated *in vacuo.* The title compound was afforded after purification by FCC (combiflash rf, 10→50% EtOAc/cyclohexane) as a yellow oil (4.15 g, 20.5 mmol, 86% yield).

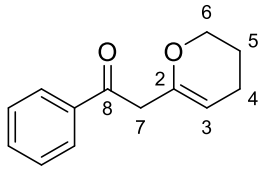
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 2H, ArCH x 2), 7.65 – 7.53 (m, 1H, ArCH), 7.53 – 7.41 (m, 2H, ArCH x 2), 3.72 (t, *J* = 6.0, Hz, 2H, H_7 x 2), 2.56 (t, *J* = 6.5 Hz, 1H, H_4 x 2), 1.92 – 1.69 (m, 4H, H_5 x 2, H_6 x 2), 1.60 (s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4 (C_1), 137.0 (ArC), 134.1 (ArC), 129.7 (ArC x 2), 128.7 (ArC x 2), 96.4 (C_3), 80.0 (C_2), 62.3 (C_7), 31.9 (C_6), 24.4 (C_5), 19.2 (C_4).

HRMS (ESI+): Found $[M+H]^+$ = 203.1067; $C_{13}H_{15}O_2$ requires 203. 1067 Δ 0.20 ppm

IR (film) ν_{max}/cm^{-1} 3389, 2938, 2869, 2236, 2200, 1639, 1449, 1265, 701.

2-(3,4-Dihydro-*2H*-pyran-6-yl)-1-phenylethan-1-one 895



7-Hydroxy-1-phenylhept-2-yn-1-one (60.7 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title

compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (24 mg, 0.12 mmol, 40% yield).

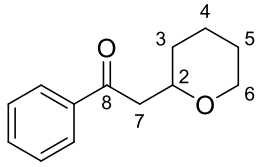
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H, ArCH x 2), 7.59 – 7.50 (m, 1H, ArCH), 7.50 – 7.40 (m, 2H, ArCH x 2), 4.75 – 4.61 (m, 1H, H_3), 4.03 – 3.93 (m, 2H, H_6 x 2), 3.69 – 3.57 (m, 2H, H_7 x 2), 2.08 – 1.99 (m, 2H, H_4 x 2), 1.85 – 1.72 (m, 2H, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C_8), 148.8 (C_2), 136.9 (ArC), 133.2 (ArC), 128.7 (ArC x 2), 128.6 (ArC x 2), 99.8 (C_3), 66.6 (C_6), 44.7 (C_7), 22.2 (C_5), 20.5 (C_4).

HRMS (ESI+): Found $[M+H]^+$ = 203.1066; $C_{13}H_{15}O_2$ requires 203.1067 Δ -0.36 ppm

IR (film) ν_{max}/cm^{-1} 2930, 2849, 1683, 1448, 1271, 1061, 754, 720.

1-Phenyl-2-(tetrahydro-*2H*-pyran-2-yl)ethan-1-one 910



Diethyl (2-oxo-2-phenylethyl)phosphonate (358 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and tetrahydro-*2H*-pyran-2-ol (102 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (194 mg, 0.95 mmol, 95% yield).

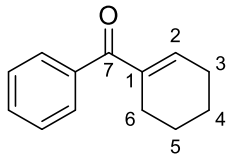
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 2H, ArCH x 2), 7.60 – 7.52 (m, 1H, ArCH), 7.50 – 7.41 (m, 2H, ArCH x 2), 4.01 – 3.90 (m, 2H, H_2, H_{6eq}), 3.48 (td, *J* = 11.5, 3.0 Hz, 1H, H_{6ax}), 3.29 (dd, *J* = 16.0, 6.5 Hz, 1H, H_{7a}), 2.92 (dd, *J* = 16.0, 5.5 Hz, 1H, H_{7b}), 1.89 – 1.79 (m, 1H, H_{4eq}), 1.75 (ddt, *J* = 12.5, 4.5, 2.0 Hz, 1H, H_{3eq}), 1.65 – 1.47 (m, 3H, H_{4ax}, H_5 x 2), 1.45 – 1.29 (m, 1H, H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C_8), 137.5 (ArC), 133.2 (ArC), 128.7 (ArC x 2), 128.4 (ArC x 2), 74.5 (C_2), 68.8 (C_6), 45.6 (C_7), 32.2 (C_3), 26.0 (C_5), 23.5 (C_4).

HRMS (ESI+): Found $[M+H]^+$ = 205.1225; $C_{13}H_{17}O_2$ requires 205.1223, Δ 0.81 ppm

IR (film) ν_{max}/cm^{-1} 2998, 2886, 1682, 1380, 1154, 1044, 941, 751, 690.

Cyclohex-1-en-1-yl(phenyl)methanone 911



1-Phenyl-2-(tetrahydro-*2H*-pyran-2-yl)ethan-1-one (61.5 mg, 0.3 mmol, 1 eq.), $Al(O^tBu)_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**.The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (45 mg, 0.241 mmol, 80% yield).

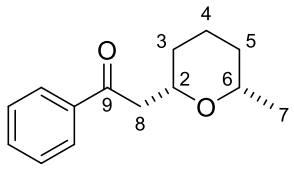
^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H, ArCH x 2), 7.53 – 7.45 (m, 1H, ArCH), 7.45 – 7.36 (m, 2H, ArCH x 2), 6.57 (tt, *J* = 4.0, 1.5 Hz, 1H, H_2), 2.47 – 2.38 (m, 2H, H_6 x 2), 2.31 – 2.21 (m, 2H, H_3 x 2), 1.79 – 1.60 (m, 4H, H_4 x 2, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (C_7), 144.1 (C_2), 138.9 (C_1, ArC), 131.4 (ArC), 129.3 (ArC x 2), 128.1 (ArC x 2), 26.3 (C_3), 24.1 (C_6), 22.2 (C_5), 21.8 (C_4).

HRMS (ESI+): Found $[M+H]^+$ = 187.1118; $C_{13}H_{15}O$ requires 187.1117 Δ 0.15 ppm

IR (film) ν_{max}/cm^{-1} 2998, 1649, 1277, 1014, 886, 749.

2-(6-Methyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one 915



Diethyl (2-(phenyl)-2-oxoethyl)phosphonate (356 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 6-methyltetrahydro-2H-pyran-2-ol (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (10→15% Et_2O/pentane) as a colourless oil (200 mg, 0.92 mmol, 92% yield, >95:5 cis/trans by Q ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 2H, ArCH x 2), 7.59 – 7.51 (m, 1H, ArCH), 7.49 – 7.41 (m, 2H, ArCH x 2), 4.05 – 3.91 (m, 1H, H_6), 3.56 – 3.41 (m, 1H, H_2), 3.31 (dd, *J* = 16.0, 6.0 Hz, 1H, H_{8a}), 2.97

(dd, *J* = 16.0, 6.5 Hz, 1H, H_{8b}), 1.88 – 1.77 (m, 1H, H_{4eq}), 1.74 (dtd, *J* = 10.5, 4.0, 2.5 Hz, 1H, H_{5eq}), 1.65 – 1.50 (m, 2H, H_{3eq}, H_{4ax}), 1.30 – 1.16 (m, 2H, H_{3ax}, H_{5ax}), 1.14 (d, *J* = 6.2 Hz, 3H, H_7 x 3).

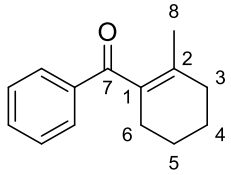
^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C_9), 137.5 (ArC), 133.1 (ArC), 128.6 (ArC x 2), 128.4 (ArC x 2), 74.3 (C_6), 74.2 (C_2), 45.8 (C_8), 33.3 (C_3), 31.6 (C_5), 23.7 (C_4), 22.3 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 219.1380; $C_{14}H_{19}O_2$ requires 219.1381, Δ 0.69 ppm

IR (film) ν_{max}/cm^{-1} 2971, 2861, 1686, 1449, 1216, 1068, 751, 691.

The spectroscopic data matched that previously reported in the literature.[189]

(2-Methylcyclohex-1-en-1-yl)(phenyl)methanone 914



2-(6-Methyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one (84 mg, 0.3 mmol, 1 eq.), aluminium *tert*-butoxide (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (48 mg, 0.240 mmol, 80% yield).

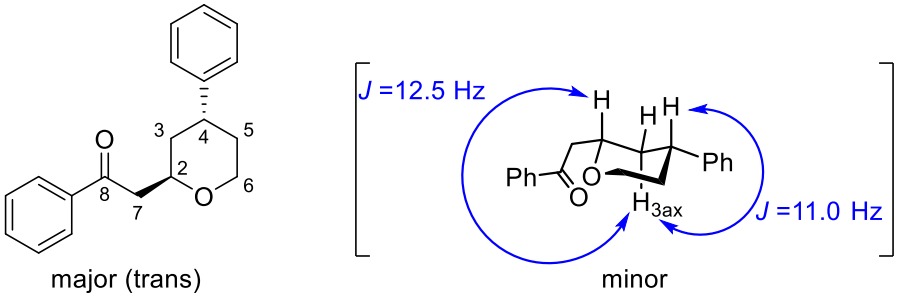
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 2H, ArCH x 2), 7.59 – 7.50 (m, 1H, ArCH), 7.50 – 7.41 (m, 2H, ArCH x 2), 2.22 (ddp, *J* = 5.5, 4.0, 2.0 Hz, 2H, H_6 x 2), 2.16 – 2.06 (m, 2H, H_3 x 2), 1.79 – 1.66 (m, 4H, H_4 x 2, H_5 x 2), 1.54 (dt, *J* = 2.0, 1.0 Hz, 3H, H_8 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7 (C_7), 137.1 (C_2), 134.9 (ArC), 133.1 (ArC), 132.5 (C_1), 129.4 (ArC x 2), 128.8 (ArC x 2), 31.3, (C_3) 27.6 (C_6), 22.7 (C_4), 22.4 (C_5), 21.3 (C_8).

HRMS (ESI+): Found $[M+H]^+$ = 201.1275; $C_{14}H_{17}O$ requires 201.1274, Δ 0.40 ppm

IR (film) ν_{max}/cm^{-1} : 2972, 2931, 1663, 1448, 1244, 936, 709.

1-Phenyl-2-*((2R,4R)*-4-phenyltetrahydro-2H-pyran-2-yl)ethan-1-one 921



Diethyl (2-oxo-2-phenylethyl)phosphonate (358 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL) 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and (4*R*)-4-phenyltetrahydro-2*H*-pyran-2-ol (178 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (233 mg, 1.0 mmol, 83% yield, 43:57 cis/trans ratio by Q ^1H NMR, 99:1 e.r determined by chiral HPLC).

^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 7.5, 6.5, 1.5 Hz, 4H, major ArCH x 2, minor ArCH x 2), 7.65 – 7.55 (m, 2H, major ArCH, minor ArCH), 7.51 (dd, *J* = 8.0, 6.5 Hz, 4H, major ArCH x 2, minor ArCH x 2), 7.41 – 7.30 (m, 6H, major ArCH x 3, minor ArCH x 3), 7.30 – 7.18 (m, 4H, major ArCH x 2, minor ArCH x 2), 4.57 (td, *J* = 6.5, 4.5 Hz, 1H, major H_2), 4.21 – 4.09 (m, 2H, minor H_2, minor H_6), 3.92 – 3.73 (m, 2H, major H_6 x 2), 3.73 – 3.61 (m, 1H, minor H_6), 3.50 (dd, *J* = 16.0, 6.5 Hz, 1H, major H_{7a}), 3.40 (dd, *J* = 16.0, 6.5 Hz, 1H, minor H_{7a}), 3.27 – 3.12 (m, 2H, major H_{7b}, major H_4), 3.02 (dd, *J* = 16.0, 5.5 Hz, 1H, minor H_{7b}), 2.89 (ddt, *J* = 12.0, 9.0, 4.0 Hz, 1H, minor H_4), 2.23 (ddd, *J* = 12.5, 8.0, 4.0 Hz, 1H, major H_{3eq}), 2.08 – 1.76 (m, 5H, major H_{3ax}, minor H_{3eq}, major H_5 x 2, minor H_5 x 2), 1.57 (td, *J* = 12.5, 11.0 Hz, 1H, minor H_{3ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (major C_8), 198.3 (minor C_8), 145.6 (minor ArC), 144.5 (major ArC), 137.4 (minor ArC), 137.3 (major ArC), 133.3 (major ArC), 133.3 (minor ArC), 128.8 (major ArC x 2), 128.7 (minor ArC x 2), 128.7 (minor ArC x 2), 128.7 (major ArC x 2), 128.4 (minor ArC x 2), 128.3 (major ArC x 2), 127.4 (major ArC x 2), 126.9 (minor ArC x 2), 126.5 (major ArC), 126.3 (minor ArC), 74.4 (minor C_2), 69.8 (major C_2), 68.5 (minor C_6), 62.9 (major C_6), 45.3 (minor C_7), 42.4 (major C_7), 41.7 (minor C_4), 39.7 (minor C_3), 35.9 (major C_3), 35.3 (major C_4), 33.4 (minor C_5), 32.3 (major C_5).

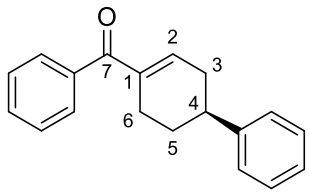
HRMS (ESI+): Found $[M+H]^+$ = 281.1537; $C_{19}H_{21}O_2$ requires 281.1536, Δ 0.45 ppm

IR (film) ν_{max}/cm^{-1}: 2955, 2921, 2870, 2842, 1683, 1586

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IC column (97:3 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature),; major diastereomer t_r (minor) = 10.18min, minor diastereomer t_r (minor)= 16.77 min, minor diastereomer t_r (major)= 19.00 min, major diastereomer t_r (major)= 19.73 min.

α_{25}^{D}= −8.5 (c=1.0, CHCl3).

***(S)*-Phenyl(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methanone 922**



1-Phenyl-2-*((2R,4R)*-4-phenyltetrahydro-*2H*-pyran-2-yl)ethan-1-one (84 mg, 0.3 mmol, 1 eq.), aluminium *tert*-butoxide (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (75 mg, 0.286 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H, ArCH x 2), 7.43 (t, *J* = 7.5 Hz, 1H, ArCH), 7.35 (t, *J* = 7.5 Hz, 2H, ArCH x 2), 7.25 (t, *J* = 7.5 Hz, 2H, ArCH x 2), 7.17 (dd, *J* = 7.9, 4.0 Hz, 3H, ArCH x 3), 6.58 (dt, *J* = 5.0, 2.5 Hz, 1H, H_2), 2.88 – 2.70 (m, 1H, H_4), 2.70 – 2.56 (m, 1H, H_6), 2.56 – 2.23 (m, 3H, H_3 x 2, H_6), 2.05 (ddq, *J* = 13.0, 5.0, 2.5 Hz, 1H, H_5), 1.76 (qd, *J* = 12.0, 5.0 Hz, 1H, H_5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (C_7), 146.1 (ArC), 143.1 (C_2), 138.7 (C_1), 138.7 (ArC), 131.5 (ArC), 129.3 (ArC x 2), 128.7 (ArC x 2), 128.2 (ArC x 2), 126.9 (ArC x 2), 126.5 (ArC), 39.5 (C_4), 34.3 (C_3), 29.5 (C_5), 24.9 (C_6).

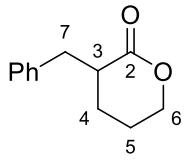
HRMS (ESI+): Found $[M+H]^+$ = 263.3597; $C_{19}H_{19}O$ requires 263.3595, Δ -0.56 ppm

IR (film) ν_{max}/cm^{-1} : 2927, 2868, 1672, 1640, 1579, 1479

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IH column (99:1 hexane:IPA, 1.0 mL min^{-1}, 254 nm, room temperature),; t_r (minor)= 9.59 min, t_r (major)= 11.03 min. 99:1 er.

α_{25}^{D}= −70.8 (c=1.0, $CHCl_3$).

3-Benzyltetrahydro-*2H*-pyran-2-one 923



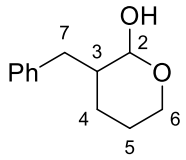
*n*BuLi in hexanes (21 mL, 2.5 M, 52.5 mmol, 1.1 eq.) was added dropwise to a solution of di-*iso*propylamine (7.7 mL, 55 mmol, 1.15 eq.) in dry THF (80 mL) at -78 ^{o}C under argon. After stirring for 30 minutes, δ-valerolactone (4.43 mL, 47.7 mmol, 1 eq.) in dry THF (20 mL) was added dropwise. After 30 minutes, benzyl bromide (11.3 mL, 95.4 mmol, 2 eq.) was added dropwise and stirred for 3h. The reaction was then quenched with sat. aq. Ammonium chloride (200 mL). The mixture was warmed to RT, extracted with Et_2O (3 × 200 mL dried over $MgSO_4$, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (25% Et_2O/pentane) as a white solid (4.3 g, 22.6 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.07 (m, 5H, ArCH x 5), 4.44 – 3.99 (m, 2H, H_6 x 2), 3.41 – 3.31 (m, 1H, H_{7a}), 2.78 – 2.65 (m, 2H, H_{7b}, H_3), 1.99 – 1.71 (m, 3H, H_5 x 2, H_4), 1.59 – 1.40 (m, 1H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C_2), 139.0 (ArC), 129.3 (2 × ArCH), 128.6 (2 × ArCH), 126.6 (ArCH), 68.6 (C_6), 41.6 (C_3), 37.3 (C_7), 24.2 (C_4), 22.0 (C_5).

The spectroscopic data matched that previously reported in the literature.[74]

3-Benzyltetrahydro-*2H*-pyran-2-ol 924



DIBAL-H in hexanes (1M, 7.3 mL, 7.3 mmol, 1.4 eq.), 3-benzyltetrahydro-*2H*-pyran-2-one (1 g, 5.26 mmol, 1 eq.) and CH_2Cl_2 (20 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a colourless oil (1 g, 5.2 mmol, 99% yield, 52:48 mixture of anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 4H, ArCH x 4), 7.26 – 7.15 (m, 6H, ArCH x 6), 4.99 (d, J = 3.0 Hz, 1H, minor H_2), 4.55 (d, J = 7.0 Hz, 1H, major H_2), 4.13 – 3.88 (m, 2H, major H_{6a} and minor H_{6a}), 3.67

– 3.43 (m, 3H, major H_{6b}, minor H_{6b} and OH), 3.19 – 3.01 (m, 2H, major H_{7a} and OH), 2.74 (dd, J = 13.5, 7.5 Hz, 1H, minor H_{7a}), 2.54 (dd, J = 13.5, 8.0 Hz, 1H, minor H_{7b}), 2.43 (dd, J = 13.5, 9.5 Hz, 1H, major H_{7b}), 2.05 – 1.91 (m, 1H, minor H_3), 1.86 – 1.40 (m, 8H, major H_3, major H_{4a}, major H_5 x 2, minor H_4 x 2, minor H_5 x 2), 1.33 – 1.13 (m, 1H, major H_{4b}).

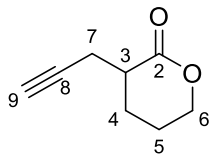
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (minor ArC), 139.9 (major ArC), 129.5 (major ArC x 2), 129.2 (minor ArC x 2), 128.4 (major ArC x 2, minor ArC x 2), 126.1 (major ArC), 126.0 (minor ArC), 99.0 (major C_2), 93.6 (minor C_2), 65.4 (major C_6), 59.9 (minor C_6), 43.5 (major C_3), 41.9 (minor C_3), 38.1 (minor C_7), 37.5 (major C_7), 26.6 (major C_4), 25.5 (minor C_4), 24.7 (major C_5), 23.5 (minor C_5).

Acceptable ionization could not be obtained by EI, CI or ESI methods.

IR (film) ν_{max}/cm^{-1} 3381, 2941, 1496, 1454, 1290, 1128, 1073, 985, 748, 700

m.p.: 73-74 °C

3-(Prop-2-yn-1-yl)tetrahydro-*2H*-pyran-2-one 925



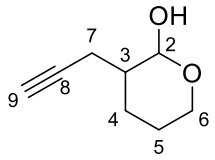
A flame-dried RBF under argon was charged with di-*iso*propylamine (4.6 g, 33 mmol, 2.2 eq.), dry THF (150 mL, 0.2M) and cooled to -78 °C. *n*BuLi in hexanes (12 mL, 2.5M, 30 mmol, 2 equiv.) was added dropwise, and the resulting solution was stirred for 30 minutes at 0 °C. The solution was then cooled to -78 °C and δ-valeralactone (3g, 30 mmol, 2 eq.) was added dropwise and stirred for 1 hour, followed by the addition of propargyl bromide in toluene (1.61 mL, 80% wt., 15 mmol, 1 eq.). The reaction mixture was stirred at -78 ^{0}C for 20 hours, and then warmed to RT and quenched with sat. aq. Ammonium chloride (50 mL). The layers were then separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were then dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (30-50% Et_2O/ pentane) and then distillation by Kugelrohr (180 °C, 5 mbar) as a colourless oil (630 mg, 4.56 mmol, 30% yield)

1H NMR (400 MHz, $CDCl_3$) δ 4.45 – 4.20 (m, 2H, H_6 x 2), 2.72 (ddd, J = 16.5, 4.5, 2.5 Hz, 1H, H_{7a}), 2.68 – 2.60 (m, 1H, H_3), 2.50 (ddd, J = 16.5, 8.0, 2.5 Hz, 1H, H_{7b}), 2.36 – 2.22 (m, 1H, H_{4a}), 2.01 (t, J = 2.5 Hz, 1H, H_9), 1.99 – 1.89 (m, 2H, H_5 x 2), 1.81 – 1.62 (m, 1H, H_{4b}).

13C NMR (101 MHz, $CDCl_3$) δ 172.8 (C_2), 81.2 (C_8), 70.5 (C_9), 68.9 (C_6), 39.1 (C_3), 24.3 (C_4), 22.2 (C_5), 20.9 (C_7).

The spectroscopic data matched that previously reported in the literature.[190]

3-(Prop-2-yn-1-yl)tetrahydro-*2H*-pyran-2-ol 926



DIBAL-H in hexanes (1M, 4 mL, 4 mmol, 1.4 eq.), 3-(prop-2-yn-1-yl)tetrahydro-*2H*-pyran-2-one (400 mg, 2.89 mmol, 1 eq.) and CH_2Cl_2 (10 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a colourless oil (381 mg, 2.72 mmol, 94% yield, 58:42 mixture of anomers).

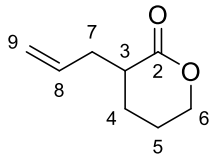
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, J = 3.0 Hz, 1H, minor H_2), 4.56 (d, J = 7.5 Hz, 1H, major H_2), 4.08 – 3.87 (m, 2H, major H_{6a}, minor H_{6a}), 3.65 – 3.43 (m, 2H, major H_{6b}, minor H_{6b}), 3.39 (s, 1H, minor OH), 2.88 (s, 1H, major OH), 2.43 (ddd, J = 17.0, 45, 2.5 Hz, 1H, major H_{7a}), 2.34 – 2.23 (m, 2H, major $H_{7b,}$ minor H_{7a}), 2.13 (ddd, J = 17.0, 7.5, 2.5 Hz, 1H, minor H_{7b}), 2.06 – 1.95 (m, 3H, major H_{4a}, major H_9, minor H_9), 1.94 – 1.86 (m, 1H, minor H_3), 1.74 – 1.54 (m, 7H, major H_3, minor H_4 x 2, minor H_5 x 2, major H_5 x 2), 1.54 – 1.37 (m, 1H, major H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 98.3 (minor C_2), 93.1 (major C_2), 82.8 (minor C_8), 82.0 (major C_8), 70.0 (major C_9), 69.3 (minor C_9), 65.7 (major C_6), 60.1 (minor C_6), 40.6 (major C_3), 39.3 (minor C_3), 26.8 (major C_4), 25.0 (minor C_4), 24.8 (major C_5), 23.5 (minor C_5), 20.8 (minor C_7), 20.6 (major C_7).

HRMS (ESI+): Found $[M+H]^+$ = 141.0910; $C_8H_{13}O_2$ requires 141.0910, Δ -0.22 ppm

IR (film) ν_{max}/cm^{-1} 3373, 3292, 2942, 1432, 1277, 1075, 988, 895, 622

3-Allyltetrahydro-*2H*-pyran-2-one 927



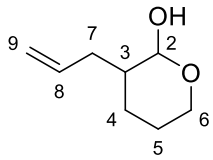
*n*BuLi in hexanes (21 mL, 2.5 M, 52.5 mmol, 1.1 eq.) was added dropwise to a solution of hexamethyldisilazane (11.5 mL, 54.9 mmol, 1.15 eq.) in dry THF (100 mL) at -78 °C under argon. After stirring for 30 minutes, δ-valerolactone (4.43 mL, 47.7 mmol, 1 eq.) in dry THF (50 mL) was added dropwise. After 30 minutes allyl bromide (4.54 mL, 52.5 mmol, 1.1 eq.) was added dropwise and stirred for 3 h. The reaction was then quenched with sat. aq. ammonium chloride (200 mL). The mixture was warmed to RT, extracted with Et_2O (3 × 200 mL dried over $MgSO_4$, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (20→40% Et_2O/pentane) and then vacuum distillation (180 °C, 7 mbar) as a colourless oil (2.84 g, 20.3 mmol, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.70 (m, 1H, H_8), 5.18 – 4.97 (m, 2H, H_9 x 2), 4.42 – 4.13 (m, 2H, H_6 x 2), 2.66 – 2.56 (m, 1H, H_{7a}), 2.56 – 2.48 (m, 1H, H_3), 2.35 – 2.22 (m, 1H, H_{7b}), 2.05 (dh, *J* = 13.5, 6.5 Hz, 1H, H_{4a}), 1.97 – 1.78 (m, 2H, H_5 x 2), 1.55 (ddt, *J* = 13.5, 11.0, 7.5 Hz, 1H, H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C_2), 135.3 (C_8), 117.6 (C_9), 68.7 (C_6), 39.5 (C_3), 35.7 (C_7), 24.3 (C_4), 22.1 (C_5).

The spectroscopic data matched that previously reported in the literature.[191]

3-Allyltetrahydro-*2H*-pyran-2-ol 928



DIBAL-H in hexanes (1M, 7.3 mL, 7.3 mmol, 1.4 eq.), 3-allyltetrahydro-*2H*-pyran-2-one (730 mg, 5.2 mmol, 1 eq.) and CH_2Cl_2 (20 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (20% Et_2O/pentane) as a colourless oil (682 mg, 4.8 mmol, 92% yield, 57:43 mixture of anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 – 5.67 (m, 2H, major H_8 and minor H_8), 5.16 – 4.91 (m, 5H, minor H_2, major H_9 x 2, minor H_9 x 2), 4.46 (d, J = 7.0 Hz, 1H, major H_2), 4.10 – 3.86 (m, 2H, major H_{6a}, minor H_{6a}),

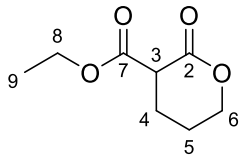
3.60 – 3.44 (m, 2H, major H_{6b}, minor H_{6b}), 3.34 (s, 1H, major OH), 2.91 (s, 1H, minor OH), 2.41 (dddt, J = 14.0, 6.5, 4.5, 1.5 Hz, 1H, major H_{7a}), 2.17 (dtt, J = 14.0, 7.0, 1.5 Hz, 1H, minor H_{7a}), 2.03 – 1.85 (m, 3H, major H_{4b}, major $H_{7b,}$ minor H_{7b}), 1.73 (pd, J = 7.5, 3.0 Hz, 1H, minor H_3), 1.67 – 1.40 (m, 7H, major H_3, minor H_4 x 2, major H_5 x 2, minor H_5 x 2), 1.29 – 1.11 (m, 1H, major H_{4b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (minor C_8), 136.3 (minor C_8), 116.5 (major C_9), 116.3 (minor C_9), 99.1 (major C_2), 93.9 (minor C_2), 65.4 (major C_6), 60.1 (minor C_6), 41.6 (major C_3), 39.8 (minor C_3), 36.1 (minor C_7), 35.7 (major C_7), 26.9 (major C_4), 25.4 (minor C_4), 24.8 (major C_5), 23.6 (minor C_5).

HRMS (ESI+): Found $[M+Na]^+$ = 165.0888 $C_8H_{14}O_2{}^{23}Na$ requires 165.0886, Δ 1.21 ppm

IR (film) ν_{max}/cm^{-1} 3373, 2940, 2851, 1641, 1439, 1276, 1062, 983, 910

Ethyl 2-oxotetrahydro-*2H*-pyran-3-carboxylate 929



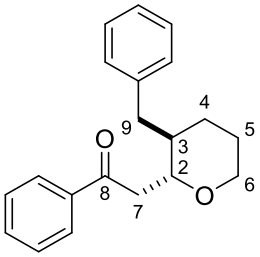
δ-valeralactone (1g, 10 mmol, 1 eq.) and diethyl carbonate (1.3 mL, 11 mmol, 1.1 eq.) in dry THF (5 mL) was added dropwise to a solution of LiHMDS (3.43 g, 20 mmol, 2 eq.) in dry THF (20 mL, 0.5M) at -78 ^oC under argon. The reaction mixture was then warmed to RT and stirred for 15 h. The reaction mixture was quenched with glacial acetic acid (5 mL) and diluted with Et_2O (20 mL), which resulted in the precipitation of a white solid. The precipitate was removed by filtration, and the resulting solution was concentrated *in vacuo*. The title compound was afforded after purification by FCC (50% Et_2O/pentane) as a colourless oil (1.23 g, 7.14 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (4.42 – 4.31 (m, 2H, H_6 x 2), 4.23 (q, 2H, 7.0 Hz, H_8 x 2), 3.54 (t, *J* = 7.5 Hz, 1H, H_3), 2.36 – 2.09 (m, 2H, H_4 x 2), 2.04 – 1.79 (m, 2H, H_5 x 2), 1.29 (t, *J* = 7.0 Hz, 3H, H_9 x 3).

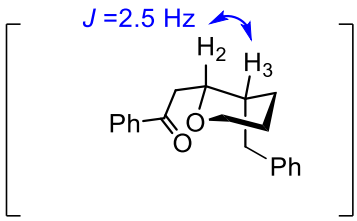
13C NMR (101 MHz, $CDCl_3$) δ 169.2 (C_2), 167.5 (C_7), 69.5 (C_6), 62.0 (C_8), 47.5 (C_3), 22.9 (C_4), 21.0 (C_5), 14.1 (C_9).

The spectroscopic data matched that previously reported in the literature.[192]

2-(3-Benzyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one 931



major *(trans)*



minor (*cis*)

Diethyl (2-(phenyl)-2-oxoethyl)phosphonate (356 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 3-benzyltetrahydro-*2H*-pyran-2-ol (192 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (10→15% Et_2O/pentane) as a colourless oil (294 mg, 1.0 mmol, 100% yield, 44:56 cis/trans ratio determined by Q ^1H NMR).

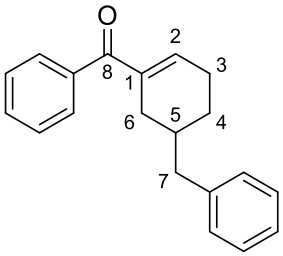
^1H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.91 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.62 – 7.54 (m, 2H, major ArCH, minor ArCH), 7.52 – 7.44 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.36 – 7.27 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.26 – 7.14 (m, 6H, major ArCH x 3, minor ArCH x 3), 4.29 (ddd, *J* = 8.0, 5.0, 2.5 Hz, 1H, minor H_2), 4.02 (ddt, *J* = 11.5, 4.0, 2.0 Hz, 1H, minor H_{6eq}), 3.95 – 3.82 (m, 2H, major H_2, major H_{6eq}), 3.58 (td, *J* = 11.5, 3.0 Hz, 1H, minor H_{6ax}), 3.45 – 3.35 (m, 2H, major H_{6ax}, minor H_{7a}), 3.33 – 3.19 (m, 2H, major H_7 x 2), 2.98 (dd, *J* = 16.0, 5.0 Hz, 1H, minor H_{7b}), 2.93 – 2.76 (m, 3H, major H_{9a}, minor H_9 x 2), 2.30 (dd, *J* = 13.5, 10.0 Hz, 1H, major H_{9b}), 2.11 (ddq, *J* = 12.0, 6.0, 2.5 Hz, 1H, minor H_3), 1.97 – 1.67 (m, 3H, major H_3, major H_{4eq}, minor H_{5eq}), 1.68 – 1.49 (m, 4H, major H_5 x 2, minor H_4 x 2), 1.41 – 1.31 (m, 1H, minor H_{5ax}), 1.31 – 1.11 (m, 1H, major H_{4ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (major C_8), 198.6 (minor C_8), 141.0 (minor ArC), 139.9 (major ArC), 137.7 (major ArC), 137.3 (minor ArC), 133.2 (minor ArC), 133.1 (major ArC), 129.3 (major ArC x 2), 129.1 (minor ArC x 2), 128.7 (minor ArC x 2), 128.6 (major ArC x 2), 128.5 (minor ArC x 2), 128.5 (major ArC x 2), 128.5 (major ArC x 2), 128.3 (minor ArC x 2), 126.2 (major ArC), 126.0 (minor ArC), 79.3 (major C_2), 76.6 (minor C_2), 68.7 (minor C_6), 68.3 (major C_6), 43.2 (major C_7), 42.5 (major C_3), 41.8 (minor C_7), 38.9 (major C_9), 38.2 (minor C_3), 32.4 (minor C_9), 29.5 (major C_4), 26.4 (minor C_4), 26.3 (major C_5), 21.3 (minor C_5).

HRMS (ESI+): Found $[M+H]^+$ = 295.1693; $C_{20}H_{23}O_2$ requires 295.1693, Δ 0.29 ppm

IR (film) ν_{max}/cm^{-1} 3061, 2939, 2850, 1685, 1450, 1092, 751, 701.

(5-Benzylcyclohex-1-en-1-yl)(phenyl)methanone 932



2-(3-Benzyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one (88.3 mg, 0.3 mmol, 1 eq.), aluminium *tert*-butoxide (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a colourless oil (60 mg, 0.217 mmol, 72% yield, >95:5 r.r by Q^{1}H NMR).

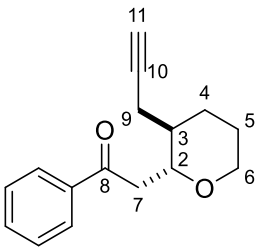
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 2H, ArCH x 2), 7.53 – 7.46 (m, 1H, ArCH), 7.44 – 7.37 (m, 2H, ArCH x 2), 7.34 – 7.27 (m, 2H, ArCH x 2), 7.25 – 7.17 (m, 3H, ArCH x 3), 6.61 – 6.52 (m, 1H, H_2), 2.76 (dd, *J* = 13.5, 6.5 Hz, 1H, H_7), 2.69 – 2.57 (m, 2H, H_6, H_7), 2.43 – 2.16 (m, 2H, H_3 x 2), 2.13 – 2.00 (m, 1H, H_6), 2.00 – 1.86 (m, 1H, H_5), 1.87 – 1.75 (m, 1H, H_4), 1.36 – 1.23 (m, 1H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C_8), 143.8 (C_2), 140.6 (ArC), 138.9 (C_1), 138.3 (ArC), 131.4 (ArC), 129.3 (ArC x 2), 129.2 (ArC x 2), 128.4 (ArC x 2), 128.1 (ArC x 2), 126.1 (ArC), 42.9 (C_7), 35.5 (C_5), 30.6 (C_6), 27.5 (C_4), 26.3 (C_3).

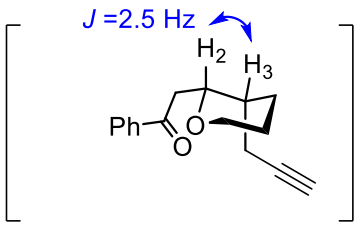
HRMS (ESI+): Found $[M+H]^+$ = 277.1586 $C_{20}H_{21}O$ requires 277.1587 Δ -0.22 ppm

IR (film) ν_{max}/cm^{-1} 2916, 1642, 1494, 1279, 745, 663.

1-Phenyl-2-(3-(prop-2-yn-1-yl)tetrahydro-*2H*-pyran-2-yl)ethan-1-one 933



major *(trans)*



minor (*cis*)

Diethyl (2-(phenyl)-2-oxoethyl)phosphonate (356 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 3-(Prop-2-yn-1-yl)tetrahydro-*2H*-pyran-2-ol (140 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (242 mg, 1.0 mmol, 100% yield, 37:63 cis/trans ratio determined by Q ^{1}H NMR).

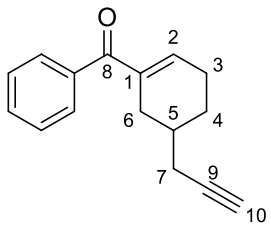
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.90 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.59 – 7.51 (m, 2H, major ArCH, minor ArCH), 7.50 – 7.40 (m, 4H, major ArCH x 2, minor ArCH x 2), 4.22 (ddd, *J* = 7.5, 5.0, 2.5 Hz, 1H, minor H_2), 3.98 – 3.79 (m, 3H, major H_2, major H_{6eq}, minor H_{6eq}), 3.51 (td, *J* = 11.0, 2.5 Hz, 1H, minor H_{6ax}), 3.36 (td, *J* = 11.5, 3.0 Hz, 1H, major H_{6ax}), 3.28 (dd, *J* = 16.5, 7.5 Hz, 1H, minor H_{7a}), 3.24 – 3.11 (m, 2H, major H_7 x 2), 2.97 (dd, *J* = 16.5, 5.0 Hz, 1H, minor H_{7b}), 2.51 – 2.36 (m, 2H, minor H_9 x 2), 2.31 – 2.15 (m, 2H, major H_9 x 2), 2.08 (dtd, *J* = 11.5, 3.5, 2.0 Hz, 1H, minor H_{4eq}), 2.04 – 1.96 (m, 3H, major H_{4eq}, major H_{11}, minor H_3), 1.93 (t, *J* = 2.5 Hz, 1H, minor H_{11}), 1.83 – 1.55 (m, 5H, major H_3, major H_5 x 2, minor H_{4ax}, minor H_{5eq}), 1.53 – 1.40 (m, 1H, major H_{4ax}), 1.39 – 1.31 (m, 1H, minor H_{5ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8 (major C_8), 198.1 (minor C_8), 137.5 (major ArC), 137.3 (minor ArC), 133.2 (minor ArC), 133.1 (major ArC), 128.7 (minor ArC x 2), 128.6 (major ArC x 2), 128.5 (major ArC x 2), 128.3 (minor ArC x 2), 83.7 (minor C_{10}), 81.8 (major C_{10}), 78.2 (major C_2), 75.7 (minor C_2), 70.4 (major C_{11}), 69.7 (minor C_{11}), 68.9 (minor C_6), 68.3 (major C_6), 42.9 (major C_7), 41.8 (minor C_7), 39.6 (major C_3), 36.2 (minor C_3), 29.6 (major C_4), 27.8 (minor C_4), 26.3 (major C_5), 22.0 (major C_9), 20.9 (minor C_5), 16.4 (minor C_9).

HRMS (ESI+): Found $[M+H]^+$ = 243.1380; $C_{16}H_{19}O_2$ requires 243.1380, Δ 0.24 ppm

IR (film) ν_{max}/cm^{-1} 3650, 3292, 2981, 2851, 1685, 1449, 1379, 1090, 968, 751, 691, 634.

Phenyl(5-(prop-2-yn-1-yl)cyclohex-1-en-1-yl)methanone 934



1-Phenyl-2-(3-(prop-2-yn-1-yl)tetrahydro-*2H*-pyran-2-yl)ethan-1-one (72.6 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**.

The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a colourless oil (54mg, 0.24 mmol, 80% yield, >95:5 r.r by Q ^1H NMR).

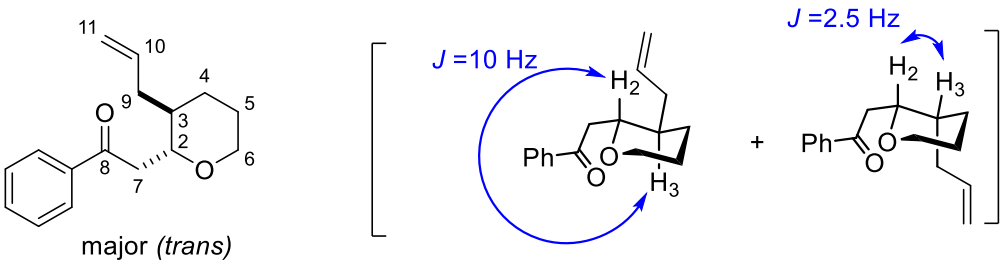
^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2H, ArCH x 2), 7.54 – 7.45 (m, 1H, ArCH), 7.46 – 7.36 (m, 2H, ArCH x 2), 6.61 – 6.53 (m, 1H, H_2), 2.73 (dddd, *J* = 17.5, 5.0, 2.0, 1.0 Hz, 1H, H_6), 2.46 – 2.19 (m, 4H, H_3 x 2, H_7 x 2), 2.10 (dddt, *J* = 17.5, 10.0, 3.5, 2.5 Hz, 1H, H_6), 2.01 (t, *J* = 2.5 Hz, 1H, H_{10}), 1.99 – 1.81 (m, 2H, H_4, H_5), 1.42 (dddd, *J* = 13.0, 11.0, 10.0, 6.5 Hz, 1H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 (C_8), 143.6 (C_2), 138.8 (C_1), 138.0 (ArC), 131.5 (ArC), 129.3 (ArC x 2), 128.2 (ArC x 2), 82.7 (C_9), 69.7 (C_{10}), 32.9 (C_5), 29.9 (C_6), 27.1 (C_4), 26.1 (C_3), 25.2 (C_7).

HRMS (ESI+): Found $[M+H]^+$ = 225.1275; $C_{16}H_{17}O$ requires 225.1274, Δ 0.49 ppm

IR (film) ν_{max}/cm^{-1} 2941, 2918, 1666, 1642, 1279, 1260, 748, 707.

2-(3-Allyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one 935



Diethyl (2-(phenyl)-2-oxoethyl)phosphonate (356 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 3-allyltetrahydro-*2H*-pyran-2-ol (142 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (240 mg, 0.98 mmol, 98% yield, 25:75 cis/trans ratio determined by Q ^1H NMR).

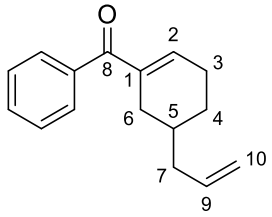
^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.61 – 7.51 (m, 2H, major ArCH, minor ArCH), 7.49 – 7.40 (m, 4H, major ArCH x 2, minor ArCH x 2), 5.87 – 5.65 (m, 2H, major H_{10}, minor H_{10}), 5.16 – 4.96 (m, 4H, major H_{11} x 2, minor H_{11} x 2), 4.20 (ddd, *J* = 7.5, 5.0, 2.5 Hz, 1H, minor H_2), 3.99 – 3.83 (m, 2H, major H_{6eq}, minor H_{6eq}), 3.75 (ddd, *J* = 10.0, 7.5, 4.0 Hz, 1H, major H_2), 3.51 (td, *J* = 11.0, 2.5 Hz, 1H, minor H_{6ax}), 3.40 – 3.32 (m, 1H, major H_{6ax}) 3.31 (dd, *J* = 16.0, 7.5 Hz, 1H, minor H_{7a}), 3.22 – 3.09 (m, 2H, major H_7 x 2), 2.89 (dd, *J* = 16.0, 5.0 Hz, 1H, minor H_{7b}), 2.32 – 2.24 (m, 2H, minor H_9 x 2), 2.24 – 2.13 (m, 1H, major H_{9a}), 1.97 – 1.46 (m, 9H, major H_3, major H_{4eq}, major H_5 x 2, major H_{9b}, minor H_3, minor H_4 x 2, minor H_{5eq}), 1.37 – 1.14 (m, 2H, major H_{4ax}, minor H_{5ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (major C_8), 198.6 (minor C_8), 137.7 (minor C_{10}), 137.7 (major ArC), 137.4 (minor ArC), 136.0 (major C_{10}), 133.2 (minor ArC), 133.0 (major ArC), 128.7 (minor ArC x 2), 128.6 (major ArC x 2), 128.5 (major ArC x 2), 128.4 (minor ArC x 2), 116.8 (major C_{11}), 116.1 (minor C_{11}), 78.9 (major C_2), 76.5 (minor C_2), 68.6 (minor C_6), 68.3 (major C_6), 43.1 (major C_7), 41.7 (minor C_7), 40.5 (major C_3), 37.0 (major C_9), 36.4 (minor C_3), 30.9 (minor C_9), 29.5 (major C_4), 26.9 (minor C_4), 26.4 (major C_5), 21.1 (minor C_5).

HRMS (ESI+): Found $[M+H]^+$ = 245.1537; $C_{16}H_{21}O_2$ requires 245.1536, Δ 0.45 ppm

IR (film) ν_{max}/cm^{-1} 3006, 2848, 1686, 1448, 1269, 1094, 996, 911, 750, 690.

(5-Allylcyclohex-1-en-1-yl)(phenyl)methanone 936



2-(3-Allyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one (73 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (74 mg, 1 eq. 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (4% Et_2O/pentane) as a colourless oil (56 mg, 0.25 mmol, 83% yield, >95:5 r.r by Q ^{1}H NMR).

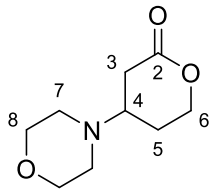
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H, ArCH x 2), 7.55 – 7.45 (m, 1H, ArCH), 7.45 – 7.36 (m, 2H, ArCH x 2), 6.62 – 6.51 (m, 1H, H_2), 5.86 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, H_9), 5.17 – 4.94 (m, 2H, H_{10} x 2), 2.66 (dddt, *J* = 17.5, 5.0, 2.5, 1.5 Hz, 1H, H_6), 2.42 – 2.05 (m, 4H, H_3 x 2, H_7 x 2), 1.99 (dddt, *J* = 17.5, 10.0, 3.5, 2.5 Hz, 1H, H_6), 1.84 (ddt, *J* = 12.0, 3.5, 2.0 Hz, 1H, H_4), 1.78 – 1.64 (m, 1H, H_5), 1.27 (dddd, *J* = 13.0, 11.0, 10.0, 6.0 Hz, 1H, H_4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2 (C_8), 143.8 (C_2), 138.9 (C_1), 138.4 (ArC), 136.8 (C_9), 131.4 (ArC), 129.3 (ArC x 2), 128.2 (ArC x 2), 116.3 (C_{10}), 40.7 (C_7), 33.4 (C_5), 30.4 (C_6), 27.5 (C_4), 26.3 (C_3).

HRMS (ESI+): Found $[M+H]^+$ = 227.1429; $C_{16}H_{19}O$ requires 227.1430 Δ -0.50 ppm

IR (film) ν_{max}/cm^{-1} 2917, 2859, 1641, 1636, 1446, 1277, 911, 701.

4-Morpholinotetrahydro-2H-pyran-2-one 939



Morpholine (87 mg, 1 mmol, 1 eq.) was added to a 5 mL RBF charged with 5,6-Dihydro-*2H*-pyran-2-one (100 mg, 1 mmol, 1 eq.) and dry CH_2Cl_2 (2 mL, 0.5 M), and stirred for 15 hours at room temperature. The reaction mixture was then concentrated *in vacuo*. The title compound was afforded after purification by FCC (2→5% MeOH/CH_2Cl_2) as a white solid (180 mg, 0.97 mmol, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (dt, *J* = 11.5, 5.0 Hz, 1H, H_{6a}), 4.21 (ddd, *J* = 11.5, 9.5, 3.5 Hz, 1H, H_{6b}), 3.78 – 3.65 (m, 4H, H_8 x 4), 2.85 (tt, *J* = 8.5, 5.5 Hz, 1H, H_4), 2.76 (ddd, *J* = 17.0, 6.0, 1.5 Hz, 1H, H_{3a}), 2.60 – 2.46 (m, 5H, H_{3b}, H_7 x 4), 2.08 (dtdd, *J* = 14.0, 5.0, 3.5, 1.5 Hz, 1H, H_{5a}), 1.83 (dtd, *J* = 14.0, 9.5, 4.5 Hz, 1H, H_{5b})

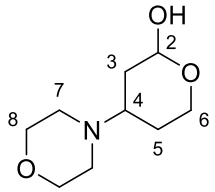
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9 (C_2), 67.0 (C_8 x 2), 66.7 (C_6), 57.1 (C_4), 49.8 (C_7 x 2), 34.0 (C_3), 26.0 (C_5).

HRMS (ESI+): Found $[M+H]^+$ = 186.1126; $C_9H_{16}O_3N$ requires 186.1125, Δ 0.51 ppm

IR (film) ν_{max}/cm^{-1} 2856, 1730, 1453, 1273, 1151, 1069, 887.

m.p.: 95-96 °C

4-Morpholinotetrahydro-*2H*-pyran-2-ol 940



DIBAL-H in hexanes (1M, 1.7 mL, 1.7 mmol, 1.4 eq.), 4-Morpholinotetrahydro-*2H*-pyran-2-one (225 mg, 1.2 mmol, 1 eq.) and CH_2Cl_2 (6 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (100% acetone) as a white solid (191 mg, 1 mmol, 83% yield, 51:49 mixture of anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H, OH), 5.40 (dd, *J* = 3.5, 2.0 Hz, 1H, minor anomer H_2), 4.95 (dd, *J* = 4.5, 3.0 Hz, 1H, major anomer H_2), 4.11 – 3.95 (m, 2H, major anomer H_{6a}, minor anomer H_{6a}), 3.77 – 3.68 (m, 9H, minor anomer H_{6b}, major anomer H_7 x 4, minor anomer H_7 x 4), 3.54 (ddd, *J* = 12.0, 5.5, 4.5 Hz, 1H, major anomer H_{6b}), 2.92 (s, 1H, OH), 2.81 (tt, *J* = 11.5, 4.0 Hz, 1H, minor anomer H_4), 2.70 – 2.45 (m, 10H, major anomer H_4, major anomer H_8 x 4, minor anomer H_8 x 4), 2.06 – 1.73 (m, 6H, major anomer H_{3a}, minor anomer H_{3a}, major anomer H_5 x 2, minor anomer H_5 x 2), 1.66 – 1.48 (m, 2H, major anomer H_{3b}, minor anomer H_{3b}).

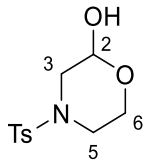
^{13}C NMR (101 MHz, $CDCl_3$) δ 94.0 (major anomer C_2), 92.4 (minor anomer C_2), 67.3 (minor anomer C_7 x 2), 67.2 (major anomer C_7 x 2), 59.3 (minor anomer C_6), 58.1 (major anomer C_6), 57.9 (major anomer C_4), 55.3 (minor anomer C_4), 50.8 (major anomer C_8 x 2), 49.6 (minor anomer C_8 x 2), 33.2 (major anomer C_3, minor anomer C_5), 29.0 (minor anomer C_3), 27.7 (major anomer C_5).

HRMS (ESI+): Found $[M+H]^+$ = 188.1282; $C_9H_{18}O_3N$ requires 188.1281, Δ 0.37 ppm

IR (film) ν_{max}/cm^{-1} 3365, 2962, 2855, 1453, 1269, 1112, 979, 878.

m.p.: 95-96 °C

4-Tosylmorpholin-2-ol 942



A 50 mL RBF under argon atmosphere was charged with IBX (30% wt. with stabilizer, 4.3 g, 4.63 mmol, 1.2 eq.), dry DMSO (4.5 mL) and acetone (16 mL), and stirred for 40 min at RT. *N,N*-Bis(2-hydroxyethyl)-4-methylbenzenesulfonamide (1 g, 3.86 mmol, 1 eq.) was added, stirring for 18 hours at RT. The reaction was then diluted with water (10 mL) and filtered. The resulting aqueous solution was extracted with Et_2O (4 x 20 mL). The organic phase was then washed with sat. aq. Na_2CO_3 (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (70% Et_2O/pentane) as a white solid (809 mg, 3.14 mmol, 81% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H, ArCH x 2), 7.34 (d, *J* = 8.5 Hz, 2H, ArCH x 2), 4.96 (dd, *J* = 5.5, 2.5 Hz, 1H, H_2), 4.02 (ddd, *J* = 12.0, 5.5, 3.0 Hz, 1H, H_{6eq}), 3.68 (ddd, *J* = 12.0, 7.5, 3.0 Hz, 1H, H_{6ax}), 3.47 (s, 1H, OH), 3.27 (ddd, *J* = 11.5, 2.5, 1.0 Hz, 1H, H_{3eq}), 3.10 (dddd, *J* = 11.5, 5.5, 3.0, 1.0 Hz, 1H, H_{5eq}), 2.91 – 2.80 (m, 1H, H_{5ax}), 2.70 (ddd, *J* = 11.5, 5.5, 1.0 Hz, 1H, H_{3ax}), 2.44 (s, 3H, CH_3).

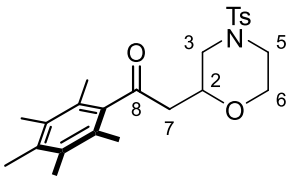
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (ArC), 132.3 (ArC), 130.0 (ArCH x 2), 128.0 (ArCH x 2), 91.2 (C_2), 61.7 (C_6), 50.4 (C_3), 45.2 (C_5), 21.7 (CH_3).

HRMS (ESI+): Found $[M+Na]^+$ = 280.0614; $C_{11}H_{15}O_4N^{23}Na^{32}S$ requires 280.0614, Δ 0.01 ppm

IR (film) ν_{max}/cm^{-1} 3432, 2857, 1345, 1054, 926, 759

m.p.: 127-128 °C

1-(2,3,4,5,6-Pentamethylphenyl)-2-(4-tosylmorpholin-2-yl)ethan-1-one 943



A flame-dried 2-5 mL Biotage® microwave vial was charged with Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate (212 mg, 0.6 mmol, 1.2 eq.), 60% wt. NaH (24 mg, 0.6 mmol, 1.2 eq), and then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (1 mL, 0.5 M) was then added, stirring the solution for 1 h at RT. 4-Tosylmorpholin-2-ol (129 mg, 0.5 mmol, 1 eq.) was then added, the balloon was removed, and the reaction was heated at 110 °C for 15 h. The reaction was then cooled to RT, filtered through a silica plug with Et_2O, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (40→70% Et_2O/pentane) as a white solid (64 mg, 0.149 mmol, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 7.34 (d, *J* = 8.0 Hz, 2H, ArCH x 2), 4.25 – 4.15 (m, 1H, H_2), 3.88 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H, H_{6eq}), 3.72 (ddd, *J* = 11.5, 11.0, 2.5 Hz, 1H, H_{6ax}), 3.61 (dt, *J* = 11.0, 2.0 Hz, 1H, H_{3eq}), 3.47 (dq, *J* = 11.5, 2.2 Hz, 1H, H_{5eq}), 2.87 (dd, *J* = 17.5, 7.5 Hz, 1H, H_{7a}), 2.68 (dd, *J* = 17.5, 4.5 Hz, 1H, H_{7b}), 2.49 (td, *J* = 11.3, 3.4 Hz, 1H, H_{5ax}), 2.44 (s, 3H, $ArCH_3$), 2.26 (dd, *J* = 11.0, 10 Hz, 1H, H_{3ax}), 2.22 (s, 3H, $ArCH_3$), 2.17 (s, 6H, $ArCH_3$ x 2), 2.08 (s, 6H, $ArCH_3$ x 2).

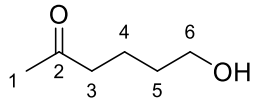
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (C_8), 144.1 (ArC), 139.9 (ArC), 135.9 (ArC), 133.3 (ArC x 2), 132.6 (ArC), 129.9 (ArCH x 2), 128.0 (ArCH x 2), 127.6 (ArC x 2), 70.8 (C_2), 65.8 (C_6), 49.8 (C_3), 48.6 (C_7), 45.5 (C_5), 21.7 ($ArCH_3$), 17.2 ($ArCH_3$ x 2), 16.8 ($ArCH_3$), 16.1 ($ArCH_3$ x 2).

HRMS (ESI+): Found $[M+H]^+$ = 430.2040; $C_{24}H_{32}O_4N^{32}S$ requires 430.2047, Δ -1.43 ppm

IR (film) ν_{max}/cm^{-1} 2915, 2862, 1700, 1347, 1166, 1069, 980, 756

m.p.: 221-222 °C

6-Hydroxyhexan-2-one 945



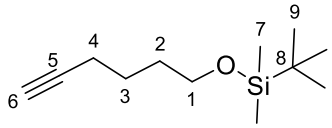
A 50 mL RBF was charged with 5-Hexyn-1-ol (500 mg, 5.09 mmol, 1 eq.), ethyl acetate (15 mL, 0.3M), Silver triflate (131 mg, 0.51 mmol, 0.1 eq.), and water (275 mg, 15.27 mmol, 3 eq.), fitted with a reflux condenser and heated to 90 °C for 8 hours. The reaction mixture was then cooled to room temperature, the concentrated *in vacuo*. The title compound was afforded after purification by FCC (30% EtOAc/pentane) as a colourless oil (180 mg, 1.55 mmol, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 – 3.98 (m, 2H, H_6 x 2), 2.53 – 2.39 (m, 2H, H_3 x 2), 2.13 (s, 3H, H_1 x 3), 1.74 – 1.53 (m, 4H, H_4 x 2, H_5 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5 (C_2), 64.2 (C_6), 43.1 (C_3), 30.0 (C_1), 28.2 (C_4 or C_5), 20.3 (C_4 or C_5).

The spectroscopic data matched that previously reported in the literature.[193]

Tert-butyl(hex-5-yn-1-yloxy)dimethylsilane 947



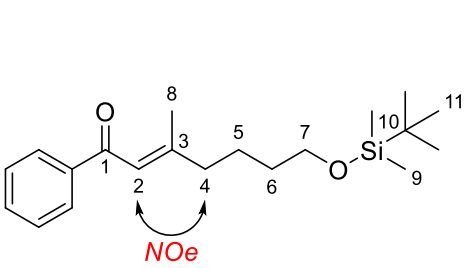
TBSCl (4.57 g, 1.1 eq., 30.3 mmol) was added to a RBF charged with trimethylamine (4.6 mL, 1.2 eq., 33 mmol), DMAP (330 mg, 0.1 eq., 2.7 mmol), 5-hexyn-1-ol (2.7 g, 1 eq., 27.5 mmol) in CH_2Cl_2 (100 mL, 0.3 M) at 0 °C under an argon atmosphere. The reaction mixture was then warmed to RT and stirred for 15 hours. The reaction mixture was then diluted with sat. aq. ammonium chloride (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were then dried over $MgSO_4$, and concentrated *in vacuo*. The title compound was afforded after purification by FCC (100% pentane) as a colourless oil (5.83 g, 27.5 mmol, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.0 Hz, 2H, H_1 x 2), 2.21 (td, *J* = 7.0, 2.5 Hz, 2H, H_4 x 2), 1.94 (t, *J* = 2.5 Hz, 1H, H_6), 1.71 – 1.50 (m, 4H, H_2 x 2, H_3 x 2), 0.89 (s, 9H, H_9 x 9), 0.05 (s, 6H, H_7 x 6).

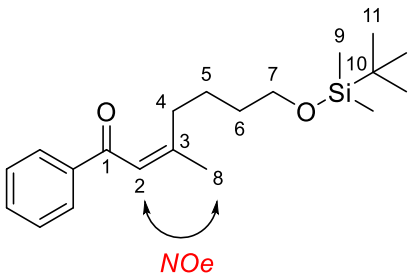
^{13}C NMR (101 MHz, $CDCl_3$) δ 84.7 (C_5), 68.4 (C_6), 62.7 (C_1), 32.0 (C_2 or C_3), 26.1 (C_9 x 3), 25.1 (C_2 or C_3), 18.5 (C_8), 18.4 (C_4), -5.2 (C_7).

The spectroscopic data matched that previously reported in the literature.[194]

7-((Tert-butyldimethylsilyl)oxy)-3-methyl-1-phenylhept-2-en-1-one 948



Major (E)



Minor (Z)

Method 1: A solution of MeLi in diethyl ether (2.5 mL, 4 mmol, 1.6M, 4 eq.) was added slowly to a solution of CuI (381 mg, 2 mmol, 2 eq.) in dry THF (5 mL, 0.1 M) cooled to -78 °C under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 1 hour, which resulted in the formation of a colourless solution. The solution was cooled to -78 °C and a solution of 7-((tert-butyldimethylsilyl)oxy)-1-phenylhept-2-yn-1-one (317 mg, 1 mmol, 1 eq.) in dry THF (5 mL) was added dropwise, and stirred for thirty minutes. The reaction was then quenched by the addition of sat. aq. ammonium chloride (10 mL), and then warmed to room temperature. The reaction mixture was then treated with 20% aq. ammonium hydroxide, which resulted in the formation of clear blue aqueous phase. The reaction mixture was then extracted with EtOAc (3 x 20 mL), and the organic phases were combined and dried over $MgSO_4$. The title compound was afforded after purification by FCC (combiflash rf, 0→10% TBME/cyclohexane) as an inconsequential mixture of E/Z stereoisomers as a colourless oil (179 mg, 0.54 mmol, 54% yield, 59:41 E/Z ratio measured by Q ^{1}H NMR).

Method 2: A solution of $AlMe_3$ in toluene (2 M, 5 mL, 10 mmol, 3 eq.) was added dropwise to an RBF charged with Cp_2ZrCl_2 (973 mg, 3.33 mmol, 1 eq.) and CH_2Cl_2 (17 mL, 0.2M) cooled to -23 °C and then warmed to room temperature and stirred for 2 hours. The resulting solution was then cooled to -23 °C and tert-butyl(hex-5-yn-1-yloxy)dimethylsilane (710 mg, 3.33 mmol, 1 eq.) in a solution of CH_2Cl_2 (5 mL) was added dropwise and then warmed to room temperature and stirred for 2 hours. The reaction was then cooled to -23 °C and benzoyl chloride (562 mg, 4 mmol, 1.2 eq.) was added dropwise and then warmed to room temperature and stirred for 30 minutes. The reaction was then quenched with the addition of water (10 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (combiflash rf, 3% Et_2O/pentane) as an inconsequential mixture of E/Z stereoisomers as a colourless oil (312 mg, 0.93 mmol, 28% yield, 71:29 E/Z ratio measured by Q ^{1}H NMR).

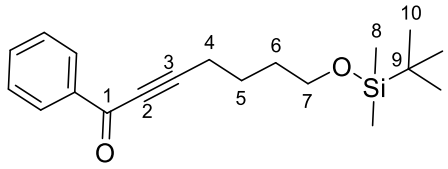
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.84 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.65 – 7.38 (m, 6H, major ArCH x 3, minor ArCH x 3), 6.94 – 6.61 (m, 2H, major H_2, minor H_2), 3.77 – 3.55 (m, 4H, major H_7 x 2, minor H_7 x 2), 2.67 – 2.62 (m, 2H, minor H_4 x 2), 2.32 – 2.25 (m, 2H, major H_4 x 2), 2.20 (d, *J* = 1.5 Hz, 3H, major H_8 x 3), 2.00 (d, *J* = 1.5 Hz, 3H, minor H_8 x 3), 1.73 – 1.48 (m, 8H, major H_5 x 2, major H_6 x 2, minor H_5 x 2, minor H_6 x 2), 0.96 – 0.83 (m, 18H, major H_{11} x 9, minor H_{11} x 9), 0.18 –0.00 (m, 12H, major H_9 x 6, minor H_9 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8 (major C_1), 191.5 (minor C_1), 160.6 (minor C_3), 160.3 (major C_3), 139.5 (major ArC), 139.4 (minor ArC), 133.2 (major ArC), 132.4 (minor ArC), 128.7 (major ArC x 2), 128.6 (minor ArC x 2), 128.5 (major ArC x 2), 128.3 (minor ArC x 2), 121.6 (minor C_2), 120.7 (major C_2), 63.1 (minor C_7), 62.9 (major C_7), 41.3 (major C_4), 33.9 (minor C_4), 33.0 (minor C_6), 32.5 (major C_6), 26.1 (major C_{11} x 3, minor C_{11} x 3), 25.7 (minor C_8), 24.6 (major C_5), 24.1 (minor C_5), 19.9 (major C_8), 18.5 (major C_{10}, minor C_{10}) -5.1 (major C_9 x 2, minor C_9 x2).

HRMS (ESI+): Found $[M+H]^+$ = 333.2245; $C_{20}H_{33}O_2Si$ requires 333.2244 Δ 0.07 ppm

IR (film) ν_{max}/cm^{-1} 3000, 2886, 2852, 1662, 1612, 1474, 1395, 1252, 1152, 1072, 954, 833

7-((Tert-butyldimethylsilyl)oxy)-1-phenylhept-2-yn-1-one 949



Method 1: A Biotage® microwave vial was charged with $PdCl_2(PPh_3)_2$ (10 mg, 0.01 eq., 0.025 mmol), CuI (10 mg, 0.05 eq., 0.125 mmol), tert-butyl(hex-5-yn-1-yloxy)dimethylsilane (500 mg, 1 eq., 2.5 mmol), sealed with a microwave vial cap (containing a Reseal™ septum) and then degassed with argon. Dry triethylamine (5 mL, 0.5M) and benzoyl chloride (457 mg, 1.3 eq., 3.25 mmol) were added by syringe and the reaction mixture was stirred at RT for 15 hours. The reaction mixture was then diluted with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (2% Et_2O/pentane) as a colourless oil (658 mg, 2.08 mmol, 84% yield).

Method 2: A solution of *n*BuLi in hexanes (1.92 mL, 2.5M, 1.2 equiv.) was added dropwise to a solution of tert-butyl(hex-5-yn-1-yloxy)dimethylsilane (1.02 g, 1.2 eq., 4.8 mmol) in dry THF (20 mL, 0.2M) cooled to -78 °C under nitrogen atmosphere. The resulting solution was stirred for 30 minutes, and

then N-methoxy-N-methylbenzamide (661 mg, 1 eq., 4 mmol) was added dropwise by syringe. The reaction mixture was then warmed to RT and stirred for 1 hour. The reaction was then quenched with sat. aq. ammonium chloride (20 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were then dried over $MgSO_4$, and concentrated *in vacuo.* The title compound was afforded after purification by FCC (combiflash rf, 0→5% EtOAc/cyclohexane) as a colourless oil (1.12 g, 3.55 mmol, 89% yield).

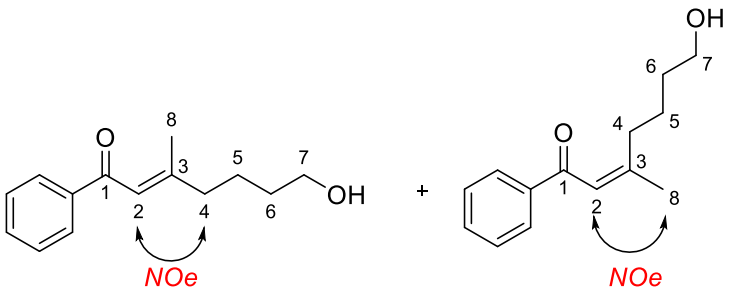
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.08 (m, 2H, ArCH x 2), 77.64 – 7.56 (m, 1H, ArCH), 7.52 – 7.42 (m, 2H, ArCH x 2), 3.67 (t, *J* = 6.0 Hz, 2H, H_7 x 2), 2.54 (t, *J* = 7.0 Hz, 2H, H_4 x 2), 1.86 – 1.64 (m, 4H, H_5 x 2, H_6 x 2), 0.90 (s, 9H, H_{10} x 9), 0.06 (s, 6H, H_8 x 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4 (C_1), 137.1 (ArC), 134.0 (ArC), 129.7 (ArC x 2), 128.6 (ArC x 2), 96.8 (C_3), 79.9 (C_2), 62.5 (C_7), 32.1 (C_6), 26.1 (C_{10} x 3), 24.6 (C_5), 19.2 (C_4), 18.5 (C_9), -5.2 (C_8 x 2).

HRMS (ESI+): Found $[M+H]^+$ = 317.1930; $C_{19}H_{29}O_2Si$ requires 317.1931 Δ -0.35 ppm

IR (film) ν_{max}/cm^{-1} 2999, 2885, 1644,1473, 1394, 1263, 1088, 834, 700

7-Hydroxy-3-methyl-1-phenylhept-2-en-1-one 950



Major (E) *Minor (Z)*

A solution of MeLi (11.25 mL, 18 mmol, 1.6M, 6 eq.) was added slowly to a solution of CuI (1.43 g, 9 mmol, 3 eq.) in dry THF (30 mL, 0.1 M) cooled to -78 °C under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 1 hour, which resulted in the formation of a colourless solution. The solution was cooled to -78 °C and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one (606 mg, 3 mmol, 1 eq.) in dry THF (5 mL) was added dropwise, and stirred for thirty minutes. The reaction was then quenched by the addition of sat. aq. ammonium chloride (30 mL), and then warmed to room temperature. The reaction mixture was then treated with 20% aq. ammonium hydroxide, which resulted in the formation of clear blue aqueous phase. The reaction mixture was then extracted with EtOAc (3 x 50 mL), and the organic phases were combined and dried over $MgSO_4$. The title compound

was afforded after purification by FCC (combiflash rf, 10→30% EtOAc/cyclohexane) as an inconsequential mixture of E/Z stereoisomers as a yellow oil (588 mg, 2.69 mmol, 90% yield, 67:33 E/Z ratio measured by Q ^{1}H NMR).

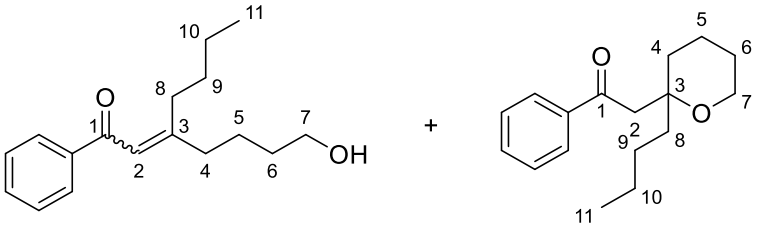
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.88 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.56 – 7.49 (m, 2H, major ArCH, minor ArCH), 7.49 – 7.39 (m, 4H, major ArCH x 2, minor ArCH x 2), 6.79 – 6.69 (m, 2H, major H_2, minor H_2), 3.83 – 3.60 (m, 4H, major H_7 x 2, minor H_7 x 2), 2.62 (t, *J* = 8.0 Hz, 2H, minor H_4 x 2), 2.29 (t, *J* = 7.0 Hz, 2H, major H_4 x 2), 2.20 (s, 3H, major H_8 x 3), 2.03 (s, 3H, minor H_8 x 3), 1.78 – 1.55 (m, 8H, major H_5 x 2, major H_6 x 2, minor H_5 x 2, minor H_6 x 2). *n.b. the enone isomers were determined by 1D NOe experiments.* OH signal was not observed

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9 (major C_1), 191.4 (minor C_1), 161.6 (minor C_3), 159.9 (major C_3), 139.5 (major ArC), 139.3 (minor ArC), 132.5 (minor ArC), 132.4 (major ArC), 128.6 (major ArC x 2, minor ArC x 2), 128.4 (minor ArC x 2), 128.3 (major ArC x 2), 121.1 (minor C_2), 120.9 (major C_2), 62.7 (major C_7), 62.1 (minor C_7), 41.3 (major C_4), 33.7 (minor C_4), 32.4 (major C_6), 32.3 (minor C_6), 26.1 (minor C_8), 24.4 (minor C_5), 24.0 (major C_5), 19.9 (major C_8).

HRMS (ESI+): Found $[M+Na]^+$ = 241.1199; $C_{14}H_{18}O_2Na$ requires 241.1199 Δ 0.20 ppm

IR (film) ν_{max}/cm^{-1} 2934, 2864, 1674, 1448, 1083, 1047, 751, 690.

3-Butyl-7-hydroxy-1-phenylhept-2-en-1-one 951 and 2-(2-butyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one



A solution of *n*BuLi (1.2 mL, 3 mmol, 2.5M, 6 equiv.) was added slowly to a solution of CuI (286 mg, 1.5 mmol, 3 eq.) in dry THF (5 mL, 0.1 M) cooled to -78 °C under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 1 hour, which resulted in the formation of a grey precipitate. The solution was cooled to -78 °C and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one (101 mg, 0.5 mmol, 1 eq.) in dry THF (2 mL) was added dropwise, and stirred for thirty minutes. The reaction was then quenched by the addition of sat. aq. ammonium chloride (10 mL), and then warmed to room temperature. The reaction mixture was then treated with 20% aq. ammonium hydroxide, which

resulted in the formation of clear blue aqueous phase. The reaction mixture was then extracted with EtOAc (3 x 30 mL), and the organic phases were combined and dried over $MgSO_4$. The title compound was afforded after purification by FCC (combiflash rf, 0→30% EtOAc/cyclohexane) as an inconsequential mixture of E/Z stereoisomers (66:34) and 2-(2-butyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one (101 mg, 0.39 mmol, 77% yield). The title compounds were then separated for characterisation and then recombined before subjecting to the next step of the synthesis. *n.b*. we were unable to determine whether the major compound was *E* or *Z* due to completely overlapping signals in ^{1}H NMR.

3-Butyl-7-hydroxy-1-phenylhept-2-en-1-one 951

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.85 (m, 4H, Major ArCH x 2, minor ArCH x 2), 7.57 – 7.41 (m, 6H, Major ArCH x 3, minor ArCH x 3), 6.81 – 6.62 (m, 2H, major H_2, minor H_2), 3.83 – 3.61 (m, 4H, major H_7 x 2, minor H_7 x 2), 2.72 – 2.51 (m, 4H, major H_8 x 2, minor H_8 x 2), 2.41 – 2.21 (m, 4H, major H_4 x 2, minor H_4 x 2), 1.72 – 1.59 (m, 8H, major H_5 x 2, major H_6 x 2, minor H_5 x 2 minor H_6 x 2), 1.60 – 1.33 (m, 8H, major H_8 x 2, major H_9 x 2, minor H_8 x 2 minor H_9 x 2), 1.05 – 0.82 (m, 6H, major H_{11} x 3, minor H_{11} x 3*). n.b. OH peak not observed.*

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6 (major C_1), 191.6 (minor C_1), 165.9 (minor C_3), 164.4 (major C_3), 139.5 (minor ArC), 139.5 (major ArC), 132.5 (minor ArC), 132.4 (major ArC), 128.6 (minor ArC x 2), 128.6 (major ArC x 2), 128.4 (minor ArC x 2), 128.3 (major ArC x 2), 120.6 (major C_2), 120.1 (minor C_2), 62.8 (major C_7), 61.9 (minor C_7), 39.2 (minor C_4), 38.7 (major C_4), 32.8 (major C_8), 32.6 (minor C_8 and major C_6), 32.3 (minor C_6), 31.0 (major C_9), 30.1 (minor C_9), 24.7 (minor C_5), 24.2 (major C_5), 23.2 (major C_{10}) 22.7 (minor C_{10}), 14.1 (major C_{11} and minor C_{11}).

HRMS (ESI+): Found $[M+H]^+$ = 261.1847; $C_{17}H_{25}O_2$ requires 261.1849 Δ -0.77 ppm

IR (film) ν_{max}/cm^{-1} 2933, 2861, 1677, 1448, 1349, 1084, 752, 690.

2-(2-Butyltetrahydro-*2H*-pyran-2-yl)-1-phenylethan-1-one

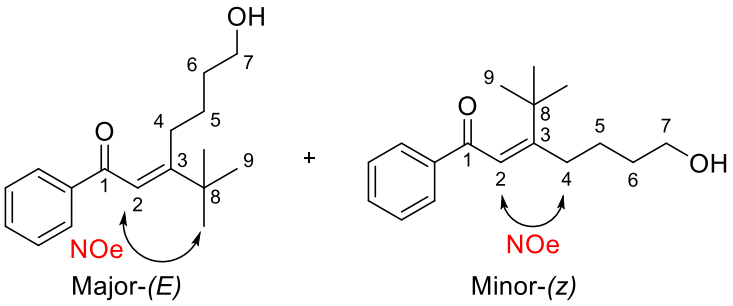
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H, ArCH x 2), 7.58 – 7.50 (m, 1H, ArCH), 7.49 – 7.40 (m, 2H, ArCH x 2), 3.66 (dd, *J* = 6.0, 5.0 Hz, 2H, H_7 x 2), 3.24 (d, *J* = 15.5 Hz, 1H, H_{2a}), 3.14 (d, *J* = 15.5 Hz, 1H, H_{2b}), 1.91 – 1.56 (m, 6H, H_4 x 2, H_5 x 2, H_8 x 2), 1.55 – 1.45 (m, 2H, H_6 x 2), 1.41 – 1.13 (m, 4H, H_9 x 2, H_{10} x 2), 0.86 (t, *J* = 7.0 Hz, 3H, H_{11} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3 (C_1), 138.6 (ArC), 132.9 (ArC), 128.6 (ArC x 2), 128.4 (ArC x 2), 75.4 (C_3), 61.5 (C_7), 44.8 (C_2), 34.3 (C_8), 33.7 (C_4), 25.9 (C_6), 25.4 (C_9), 23.3 (C_{10}), 19.2 (C_5), 14.2 (C_{11}).

HRMS (ESI+): Found $[M+H]^+$ = 261.1848; $C_{17}H_{25}O_2$ requires 261.1849 Δ -0.38 ppm

IR (film) ν_{max}/cm^{-1} 2933, 2860, 1677, 1448, 1350, 1085, 1000, 752, 690.

3-(*Tert*-butyl)-7-hydroxy-1-phenylhept-2-en-1-one 952



Major-*(E)* Minor-*(z)*

A solution of *t*BuLi in pentane (3.5 mL, 6 mmol, 1.7M, 6 equiv.) was added slowly to a solution of CuI (572 mg, 3 mmol, 3 eq.) in dry THF (10 mL, 0.1 M) cooled to -78 °C under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 1 hour, which resulted in the formation of a grey precipitate. The solution was cooled to -78 °C and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one (202 mg, 1 mmol, 1 eq.) in dry THF (2 mL) was added dropwise, and stirred for thirty minutes. The reaction was then quenched by the addition of sat. aq. ammonium chloride (10 mL), and then warmed to room temperature. The reaction mixture was then treated with 20% aq. ammonium hydroxide, which resulted in the formation of clear blue aqueous phase. The reaction mixture was then extracted with EtOAc (3 x 30 mL), and the organic phases were combined and dried over $MgSO_4$. The title compound was afforded after purification by FCC (combiflash rf, 0→40% EtOAc/cyclohexane) as an inconsequential mixture of E/Z stereoisomers (215 mg, 0.83 mmol, 83% yield, 68:32 E:Z ratio).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.79 (m, 4H, ArCH x 4), 7.68 – 7.34 (m, 6H, ArCH x 6), 6.87 (s, 1H, major H_2), 6.20 – 5.92 (m, 1H, minor H_2), 3.98 – 3.52 (m, 4H, major H_7 x 2, minor H_7 x 2), 2.79 – 2.54 (m, 2H, major H_4 x 2), 2.40 – 2.18 (m, 2H, minor H_4 x 2), 1.88 – 1.47 (m, 8H, major H_5 x 2, major H_6 x 2, minor H_5 x 2, major H_6 x 2), 1.22 (s, 9H major H_9 x 9), 1.13 (s, 9H, minor H_9 x 9). *n.b. OH signal was not observed*

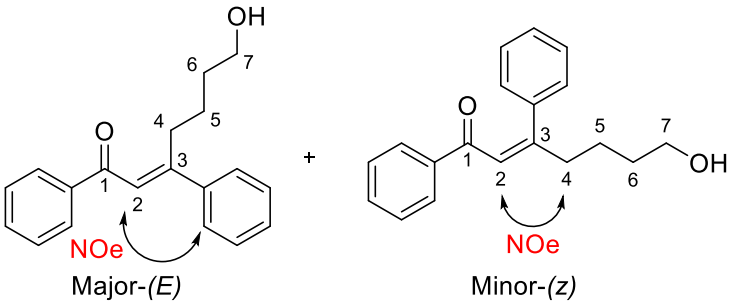
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 (minor C_1), 192.2 (major C_1), 173.6 (major C_3), 158.2 (minor C_3), 140.0 (minor ArC), 138.0 (major ArC), 133.1 (major ArC), 132.4 (minor ArC), 129.2 (minor ArC x 2), 128.6 (major ArC x 2, minor ArC x 2), 128.3 (major ArC x 2), 123.0 (minor C_2), 117.1 (major C_2), 62.9

(major C_7), 61.4 (minor C_7), 39.0 (major C_8), 37.6 (minor C_8), 34.6 (minor C_4), 32.9 (major C_6), 32.7 (minor C_6), 30.1 (major C_9 x 3), 29.5 (major C_4), 29.0 (minor C_9 x 3), 26.3 (minor C_5), 26.2 (major C_5).

HRMS (ESI+): Found $[M+H]^+$ = 261.1847; $C_{17}H_{25}O_2$ requires 261.1849 Δ -0.80 ppm

IR (film) ν_{max}/cm^{-1} 3442, 2957, 2872, 1703, 1658, 1599, 1227, 1014, 844, 700.

7-Hydroxy-1,3-diphenylhept-2-en-1-one 953



Major-*(E)* Minor-*(z)*

A solution of PhLi in dibutyl ether (3.16 mL, 6 mmol, 1.9M, 6 eq.) was added slowly to a solution of CuCN (269 mg, 3 mmol, 3 eq.) in dry THF (10 mL, 0.1 M) cooled to -78 °C under nitrogen. The reaction mixture was warmed to 0 °C and stirred for 30 minutes, which resulted in the formation of a clear solution. The solution was cooled to -78 °C and a solution of 7-hydroxy-1-phenylhept-2-yn-1-one (202 mg, 1 mmol, 1 eq.) in dry THF (2 mL) was added dropwise, and stirred for thirty minutes. The reaction was then quenched by the addition of methanol (5 mL), and then water (20 mL) and warmed to room temperature. The reaction mixture was then treated with 20% aq. ammonium hydroxide, which resulted in the formation of clear blue aqueous phase. The reaction mixture was then extracted with EtOAc (3 x 30 mL), and the organic phases were combined and dried over $MgSO_4$. The title compound was afforded after purification by FCC (combiflash rf, 0→40% EtOAc/cyclohexane) as an inconsequential mixture of E/Z stereoisomers (272 mg, 0.97 mmol, 97% yield, 60:40 E:Z ratio).

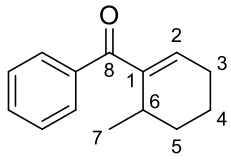
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H, major ArCH x 2), 7.85 – 7.79 (m, 2H, minor ArCH x 2), 7.59 – 7.50 (m, 3H, major ArCH x 3), 7.50 – 7.38 (m, 6H, major ArCH x 5, minor ArCH), 7.37 – 7.30 (m, 2H, minor ArCH x 2), 7.25 – 7.17 (m, 3H, minor ArCH x 3), 7.16 – 7.12 (m, 2H, minor ArCH x 2), 7.10 (s, 1H, major H_2), 6.67 (t, *J* = 1.0 Hz, 1H, minor H_2), 3.70 (t, *J* = 6.0 Hz, 2H, major H_7 x 2), 3.65 (t, *J* = 6.5 Hz, 2H, minor H_7 x 2), 3.16 – 3.02 (m, 2H, major H_4 x 2), 2.63 (td, *J* = 7.5, 1.0 Hz, 2H, minor H_4 x 2), 2.13 (s, 1H, major OH), 1.73 – 1.50 (m, 8H, major H_5 x 2, major H_6 x 2, minor H_5 x 2, minor H_6 x 2), 1.45 (s, 1H, minor OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4 (minor C_1), 191.6 (major C_1), 160.8 (major C_2), 156.6 (minor C_2), 141.9 (major ArC), 139.9 (minor ArC), 139.4 (major ArC), 138.2 (minor ArC), 132.8 (major ArC), 132.6 (minor ArC), 129.3 (major ArC), 128.9 (major ArC x 2, minor ArC x 2), 128.7 (major ArC x 2), 128.5 (major ArC x 2), 128.4 (minor ArC x 2),, 128.2 (minor ArC x 2),, 128.0 (minor ArC), 127.8 (minor ArC x 2), 126.9 (major ArC x 2), 124.0 (minor C_3), 122.2 (major C_3), 62.7 (minor C_7), 62.1 (major C_7), 39.7 (minor C_4), 32.3 (minor C_6), 32.3 (major C_6), 31.3 (major C_4), 25.2 (major C_5), 24.2 (minor C_5).

HRMS (ESI+): Found $[M+H]^+$ = 281.1537; $C_{19}H_{21}O_2$ requires 281.1536 Δ 0.39 ppm

IR (film) ν_{max}/cm^{-1} 3411, 2936, 2864, 1655, 1598, 1448, 1224, 1052, 763, 697.

(6-methylcyclohex-1-en-1-yl)(phenyl)methanone 956



Chemglass Life Sciences® Vial, 2 Dram, 17 x 60mm, 15-425 Thread, with Red Pressure Relief Cap was charged with 7-Hydroxy-3-methyl-1-phenylhept-2-en-1-one (65.4 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (74 mg, 0.3 mmol, 1 eq.) and then degassed with nitrogen. Dry toluene (1.5 mL, 0.2M) was added by syringe and the reaction mixture was heated at 110 °C for 15 hours. The reaction mixture was then cooled to room temperature and filtered through a silica plug, washing with TBME (50 mL), and then concentrated *in vacuo*. The title compound was afforded after purification by FCC (0→10% TMBE/cyclohexane) as a colourless oil (50 mg, 0.25 mmol, 83% yield).

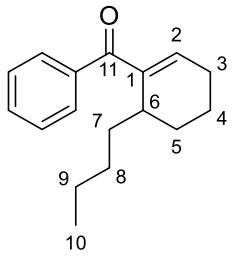
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.62 (m, 2H, ArCH x 2), 7.55 – 7.47 (m, 1H, ArCH), 7.45 – 7.37 (m, 2H, ArCH x 2), 6.40 (td, *J* = 4.0, 1.5 Hz, 1H, H_2), 3.09 – 2.88 (m, 1H, H_6), 2.37 – 2.05 (m, 2H, H_3 x 2), 1.86–1.50 (m, 4H, H_4 x 2, H_5 x 2), 1.07 (d, *J* = 7.0 Hz, 3H, H_7 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C_8), 144.1 (C_1), 141.8 (C_2), 139.2 (ArC), 131.7 (ArC), 129.5 (ArC x 2), 128.2 (ArC x 2), 30.2 (C_5), 28.1 (C_6), 26.3 (C_3), 19.9 (C_7), 18.6 (C_4).

HRMS (ESI+): Found $[M+H]^+$ = 201.1273; $C_{14}H_{17}O$ requires 201.1274 Δ -0.45ppm

IR (film) ν_{max}/cm^{-1} 2929, 2869, 1646, 1447, 1267, 721, 699.

(6-butylcyclohex-1-en-1-yl)(phenyl)methanone 957



Chemglass Life Sciences® Vial, 2 Dram, 17 x 60mm, 15-425 Thread, with Red Pressure Relief Cap was charged with 3-butyl-7-hydroxy-1-phenylhept-2-en-1-one (78 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (75 mg, 0.3 mmol, 1 eq.) and then degassed with nitrogen. Dry toluene (1.5 mL, 0.2 M) was added by syringe and the reaction mixture was heated at 110 °C for 15 hours. The reaction mixture was then cooled to room temperature and filtered through a silica plug, washing with TBME (50 mL), and then concentrated *in vacuo*. The title compound was afforded after purification by FCC (0→10% TMBE/cyclohexane) as a colourless oil (48 mg, 0.2 mmol, 67% yield).

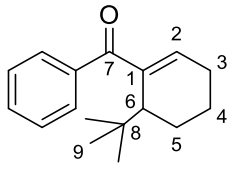
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H, ArCH x 2), 7.54 – 7.46 (m, 1H, ArCH), 7.46 – 7.36 (m, 2H, ArCH x 2), 6.38 (td, *J* = 4.0, 1.0 Hz, 1H, H_2), 3.08 – 2.75 (m, 1H, H_6), 2.39 – 2.02 (m, 2H, H_3 x 2), 1.80 – 1.54 (m, 4H, H_4 x 2, H_5 x 2), 1.53 – 1.39 (m, 1H, H_{7a}), 1.42 – 1.13 (m, 5H, H_{7b}, H_8 x 2, H_9 x 2), 0.85 (t, *J* = 7.0 Hz, 3H, H_{10} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C_{11}), 143.7 (C_1), 141.8 (C_2), 139.0 (ArC), 131.8 (ArC), 129.6 (ArC x 2), 128.2 (ArC x 2), 33.5 (C_7), 32.8 (C_6), 29.8 (C_9), 26.4 (C_5), 26.3 (C_3), 22.9 (C_8), 18.4 (C_4), 14.2 (C_{10}).

HRMS (ESI+): Found $[M+H]^+$ = 243.1741; $C_{17}H_{23}O$ requires 243.1743 Δ -0.82ppm

IR (film) ν_{max}/cm^{-1} 2929, 2858, 1648, 1447, 1267, 902, 719.

(6-(tert-butyl)cyclohex-1-en-1-yl)(phenyl)methanone 958



Chemglass Life Sciences® Vial, 2 Dram, 17 x 60mm, 15-425 Thread, with Red Pressure Relief Cap was charged with 3-(tert-butyl)-7-hydroxy-1-phenylhept-2-en-1-one (78 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (74 mg, 0.3 mmol, 1 eq.) and then degassed with nitrogen. Dry toluene (1.5 mL, 0.2 M)

was added by syringe and the reaction mixture was heated at 110 °C for 15 hours. The reaction mixture was then cooled to room temperature and filtered through a silica plug, washing with TBME (50 mL), and then concentrated *in vacuo*. The title compound was afforded after purification by FCC (0→10% TMBE/cyclohexane) as a colourless oil (15 mg, 0.06 mmol, 21% yield).

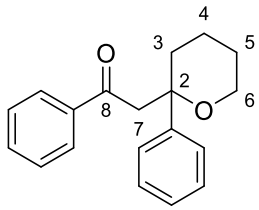
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H, ArCH x 2), 7.57 – 7.49 (m, 1H, ArCH), 7.48 – 7.39 (m, 2H, ArCH x 2), 6.44 (ddd, *J* = 4.5, 3.5, 1.0 Hz, 1H, H_2), 3.09 – 2.95 (m, 1H, H_6), 2.32 – 2.05 (m, 2H, H_3 x 2), 2.00 – 1.78 (m, 2H, H_{4a}, H_{5a}), 1.77 – 1.60 (m, 1H, H_{5b}), 1.57 – 1.47 (m, 1H, H_{4b}), 0.93 (s, 9H, H_9 x 9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9 (C_7), 142.5 (C_1), 142.0 (C_2), 137.7 (ArC), 132.2 ArC), 130.2 (ArC x 2), 128.3 (ArC x 2), 41.9 (C_6), 35.9 (C_8), 29.5 (C_9 x 3), 25.5 (C_3), 24.5 (C_5), 20.3 (C_4).

HRMS (ESI+): Found $[M+H]^+$ = 243.1741; $C_{17}H_{23}O$ requires 243.1743 Δ -0.82ppm

IR (film) ν_{max}/cm^{-1} 2958, 2868, 1653, 1252, 728.

1-Phenyl-2-(2-phenyltetrahydro-2H-pyran-2-yl)ethan-1-one 960



7-Hydroxy-1,3-diphenylhept-2-en-1-one (84 mg, 0.3 mmol, 1 eq.), Al(O*t*Bu)$_3$ (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (3→5% Et_2O/pentane) as a colourless oil (30 mg, 0.107 mmol, 36% yield).

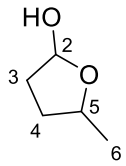
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H, ArCH x 2), 7.42 – 7.36 (m, 3H, ArCH x 3), 7.30 – 7.05 (m, 5H, ArCH x 5), 3.63 (ddt, *J* = 11.5, 4.0, 2.0 Hz, 1H, H_{6eq}), 3.40 (td, *J* = 11.5, 2.5 Hz, 1H, H_{6ax}), 3.24 (s, 2H, H_7 x 2), 2.64 – 2.52 (m, 1H, H_{3eq}), 1.93 (ddd, *J* = 14.0, 12.5, 3.5 Hz, 1H, H_{3ax}), 1.68 – 1.25 (m, 4H, H_5 x 2, H_4 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C_8), 142.3 (ArC), 138.3 (ArC), 132.7 (ArC), 128.6 (ArC x 2), 128.5 (ArC x 2), 128.3 (ArC x 2), 127.2 (ArC x 2), 127.1 (ArC), 77.9 (C_2), 62.8 (C_6), 53.3 (C_7), 32.5 (C_3), 26.0 (C_5), 19.8 (C_4).

HRMS (ESI+): Found $[M+Na]^+$ = 303.1357; $C_{19}H_{20}O_2Na$ requires 303.1356 Δ 0.33 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2889, 1673, 1448, 1157, 1079, 956, 701.

5-Methyltetrahydrofuran-2-ol 971



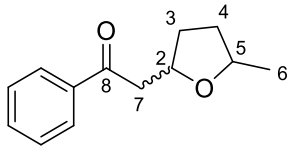
DIBAL-H in hexanes (1M, 28 mL, 28 mmol, 1.4 eq.), γ-valeralactone (2 g,20 mmol, 1 eq.) and CH_2Cl_2 (60 mL) were subjected to **General Procedure 2**. The title compound was afforded after purification by FCC (30% Et_2O/pentane) as a colourless oil (2 g, 19.6 mmol, 98% yield, 61:39 mixture of anomers).

^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (dt, J = 5.0, 2.5 Hz, 1H, major H_2), 5.45 (td, J = 3.5, 1.0 Hz, 1H, minor H_2), 4.41 – 4.27 (m, 1H, major H_5), 4.22 – 4.05 (m, 1H, minor H_5), 3.59 – 3.38 (m, 2H, OH x 2), 2.20 – 2.03 (m, 2H, major $H_{3a,}$ major H_{4a}), 2.04 – 1.77 (m, 4H, minor $H_{3a,}$ minor H_4 x 2, major H_{4b}), 1.78 – 1.64 (m, 1H, minor H_{3b}), 1.48 – 1.35 (m, 1H, major H_{3b}), 1.34 (d, J = 6.0 Hz, 3H, minor H_6 x 3), 1.21 (d, J = 6.0 Hz, 3H, major H_6 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 98.6 (major C_2), 98.6 (minor C_2), 77.1 (minor C_5), 74.4 (major C_5), 34.4 (minor C_4), 33.4 (major C_4), 31.4 (major C_3), 31.1 (minor C_3), 23.0 (minor C_6), 21.0 (major C_6).

The spectroscopic data matched that previously reported in the literature.[195]

2-(5-Methyltetrahydrofuran-2-yl)-1-phenylethan-1-one 972



Diethyl (2-(phenyl)-2-oxoethyl)phosphonate (356 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 5-methyltetrahydrofuran-2-ol (102 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (200 mg, 0.98 mmol, 98% yield, 57:43 d.r. ratio determined by Q ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 4H, major ArCH x 2, minor ArCH x 2), 7.60 – 7.51 (m, 2H, major ArCH, minor ArCH), 7.50 – 7.39 (m, 4H, major ArCH x 2, minor ArCH x 2), 4.58 (tt, *J* = 7.5, 6.0 Hz, 1H, minor H_2), 4.40 (qd, *J* = 7.0, 5.5 Hz, 1H, major H_2), 4.14 (dp, *J* = 8.0, 6.0 Hz, 1H, minor H_5), 3.98 (dp, *J* = 7.5, 6.0 Hz, 1H, major H_5), 3.52 – 3.34 (m, 2H, major H_{7a}, minor H_{7a}), 3.16 – 2.94 (m, 2H, major H_{7b},

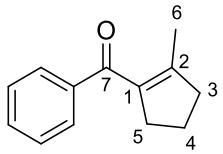
minor H_{7b}), 2.33 – 2.12 (m, 2H, major H_{3a}, minor H_{3a}), 2.12 – 1.96 (m, 2H, major H_{4a}, minor H_{4a}), 1.69 – 1.42 (m, 4H, major H_{3b}, minor $H_{3b,}$ major H_{4b}, minor H_{4b}), 1.24 (d, *J* = 6.0 Hz, 3H, major H_6 x 3), 1.22 (d, *J* = 6.0 Hz, 3H, minor H_6 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (minor C_8), 198.5 (major C_8), 137.3 (minor ArC), 137.2 (major ArC), 133.2 (major ArC, minor ArC), 128.7 (minor ArC x 2), 128.7 (major ArC x 2), 128.4 (major ArC x 2), 128.3 (minor ArC x 2), 75.6 (major C_5), 75.5 (major C_2), 75.0 (minor C_5), 75.0 (minor C_2), 45.4 (major C_7), 45.2 (minor C_7), 33.9 (minor C_4), 33.0 (major C_4), 32.7 (minor C_3), 31.8 (major C_3), 21.5 (major C_6), 21.4 (minor C_6).

HRMS (ESI+): Found $[M+H]^+$ = 205.1224; $C_{13}H_{17}O_2$ requires 205.1223, Δ 0.49 ppm

IR (film) ν_{max}/cm^{-1} 2968, 2869, 1681, 1448, 1210, 1082, 752, 690.

(2-Methylcyclopent-1-en-1-yl)(phenyl)methanone 973



Method 1: 2-(5-Methyltetrahydrofuran-2-yl)-1-phenylethan-1-one (61.2 mg, 0.3 mmol, 1 eq.), alumina (150 mg, 5 eq., 1.5 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (1 mg, 0.005 mmol,2% yield).

Method 2: 2-(5-Methyltetrahydrofuran-2-yl)-1-phenylethan-1-one (61.2 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (75 mg, 1 eq., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (5% Et_2O/pentane) as a colourless oil (7 mg, 0.038 mmol,13% yield).

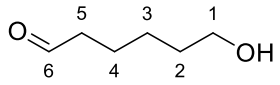
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H, ArCH x 2), 7.49 – 7.41 (m, 1H, ArCH), 7.40 – 7.33 (m, 2H, ArCH x 2), 2.69 (ddq, *J* = 9.5, 6.0, 2.0 Hz, 2H, H_5 x 2), 2.46 (dddq, *J* = 9.0, 7.0, 2.0, 1.0 Hz, 2H, H_3 x 2), 1.85 (p, *J* = 7.5 Hz, 2H, H_4 x 2), 1.61 (tt, *J* = 2.0, 1.0 Hz, 3H, H_6 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3 (C_7), 150.2 (C_2), 139.3 (C_1), 136.3 (ArC), 132.4 (ArC), 129.0 (ArC x 2), 128.5 (ArC x 2), 40.6 (C_3), 35.9 (C_5), 22.3 (C_4), 16.9 (C_6).

HRMS (ESI+): Found $[M+H]^+$ = 187.1118 $C_{13}H_{15}O$ requires 187.1117 Δ 0.48 ppm

IR (film) ν_{max}/cm^{-1} 2999, 2886, 1639, 1380, 1252, 1152, 1072, 954.

6-Hydroxyhexanal 975



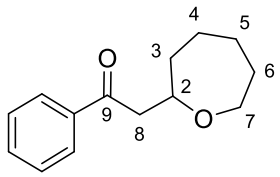
DIBAL-H in hexanes (1 M, 14 mL, 14 mmol, 1.4 eq.), ε-caprolactone (1.14 g, 10 mmol, 1 eq.) and CH_2Cl_2 (50 mL) were subjected to **General Procedure 2.** The title compound was used without further purification as a colourless oil (1.02 g, 8.78 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 – 9.67 (m, 1H, H_6), 3.66 (dt, *J* = 8.0, 4.0 Hz, 2H, H_1 x 2), 2.50 – 2.34 (m, 2H, H_5 x 2), 1.77 – 1.24 (m, 6H, H_2 x 2, H_3 x 2, H_4 x 2). N.b. OH peak not observed.

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7 (C_6), 62.8 (C_1), 44.0 (C_5), 32.5 (C_2), 25.5 (C_3), 21.9 (C_4).

The spectroscopic data matched that previously reported in the literature.[196]

2-(Oxepan-2-yl)-1-phenylethan-1-one 976



Diethyl (2-oxo-2-phenylethyl)phosphonate (358 mg, 1.4 eq., 1.4 mmol), dry toluene (5 mL), 60% wt. NaH (48 mg, 1.2 eq., 1.2 mmol) and 6-Hydroxyhexanal (116 mg, 1 eq., 1 mmol) were subjected to **general procedure 9**. The title compound was afforded after purification by FCC (5→10% Et_2O/pentane) as a colourless oil (21 mg, 0.096 mmol, 10% yield).

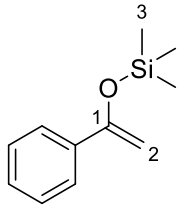
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H, ArCH x 2), 7.58 – 7.50 (m, 1H, ArCH), 7.50 – 7.40 (m, 2H, ArCH x 2), 4.17 (dddd, *J* = 9.0, 7.5, 5.0, 3.5 Hz, 1H, H_2), 3.80 (ddd, *J* = 12.5, 6.5, 5.0 Hz, 1H, H_{7a}), 3.58 (ddd, *J* = 12.5, 7.5, 4.5 Hz, 1H, H_{7b}), 3.32 (dd, *J* = 16.0, 7.5 Hz, 1H, H_{8a}), 2.89 (dd, *J* = 16.0, 5.0 Hz, 1H, H_{8b}), 1.94 – 1.47 (m, 8H, H_3 x 2, H_4 x 2, H_5 x 2, H_6 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9 (C_9), 137.6 (ArC), 133.1 (ArC), 128.7 (ArC x 2), 128.4 (ArC x 2), 76.0 (C_2), 69.1 (C_7), 45.8 (C_8), 36.1 (C_3), 31.1 (C_6), 26.4 (C_4 or C_5), 26.2 (C_4 or C_5).

HRMS (ESI+): Found $[M+Na]^+$ = 241.1201; $C_{14}H_{18}O_2Na$ requires 241.1199 Δ 0.64 ppm

IR (film) ν_{max}/cm^{-1} 2981, 2930, 2890, 1684, 1381, 1250, 1114, 955.

Trimethyl((1-phenylvinyl)oxy)silane 992



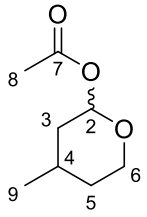
TMSCl (3.35g, 31 mmol, 1.24 eq.) and NaI (4.65 g, 31 mmol, 1.24 eq.) were added sequentially to a 100 mL RBF under argon charged with acetophenone (3 g, 25 mmol, 1 eq.), trimethylamine (3.15 mL, 31 mmol, 1.24 eq.) and MeCN (31 mL, 0.8 M) at RT. The reaction mixture was stirred for three hours and then poured onto ice-cold water, and extracted with hexane (3 x 100 mL). The combined organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was afforded after purification by vacuum distillation (1 mbar, 80 °C) as a colourless oil (3.9 g, 20.3 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H, ArCH x 2), 7.23 – 7.10 (m, 3H, ArCH x 3), 4.77 (d, *J* = 1.5 Hz, 1H, H_2), 4.28 (d, *J* = 1.5 Hz, 1H, H_2), 0.12 (s, 9H, H_3 x 9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C_1), 137.7 (ArC), 128.4 (ArC), 128.2 (ArC x 2), 125.4 (ArC x 2), 91.2 (C_2), 0.2 (C_3 x 3).

The spectroscopic data matched that previously reported in the literature.[197]

4-Methyltetrahydro-*2H*-pyran-2-yl acetate 995



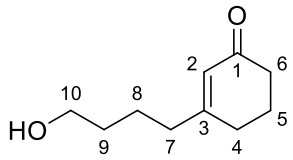
KHMDS in toluene (0.5 M, 9 mL, 4.5 mmol, 1.05 eq.) was added dropwise to an RBF charged with 4-methyltetrahydro-*2H*-pyran-2-ol (500 mg, 4.3 mmol, 1 eq.) in dry THF (20 mL, 0.2 M) cooled to -78 °C under argon and stirred for 30 minutes. Acetic anhydride (1.22 mL, 12.9 mmol, 3 eq.) was added, stirring at -78 °C for two hours. The reaction mixture was then quenched with sat. aq. ammonium chloride (20 mL) and warmed to RT. Distilled water was then added (20 mL), and extracted with diethyl ether (3 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10→20% Et_2O/pentane) as a colourless oil (547 mg, 3.45 mmol, 80% yield, >95:5 d.r. by ^{1}H NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dd, *J* = 9.5, 2.5 Hz, 1H, H_2), 4.03 (ddd, *J* = 12.0, 4.5, 2.0 Hz, 1H, H_{6eq}), 3.57 (td, *J* = 12.0, 2.5 Hz, 1H, H_{6ax}), 2.09 (s, 3H, H_8 x 3), 1.88 – 1.67 (m, 2H, H_{3eq}, H_4), 1.55 (ddq, *J* = 13.5, 4.0, 2.0 Hz, 1H, H_{5eq}), 1.30 – 1.15 (m, 2H, H_{3ax}, H_{5ax}), 1.00 (d, *J* = 6.5 Hz, 3H, H_9 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C_7), 94.5 (C_2), 66.1 (C_6), 38.5 (C_3), 33.3 (C_5), 29.0 (C_4), 21.8 (C_9), 21.3 (C_8).

The spectroscopic data matched that previously reported in the literature.[198]

3-(4-Hydroxybutyl)cyclohex-2-en-1-one 1024



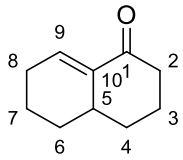
A solution of MeMgBr in THF (11.9 mL, 3M, 35.6 mmol, 1.5 eq.) was added to a solution of 4-chloro-1-butanol (3.86 g, 35.6 mmol, 1.5 eq.) in THF (10 ml) at -78 °C under an argon atmosphere. The resulting solution was warmed to RT, and then magnesium turnings (0.92 g, 38 mmol, 1.6 eq.) were added and then mixture was heated under reflux for three hours. The reaction mixture was then cooled to -10 °C and 3-ethylcyclohex-2-en-1-one (3.34 g, 23.8 mmol, 1 eq.) was added dropwise, and stirred for 1.5 hours. The reaction was mixture was then quenched with sat. aq. ammonium chloride (10 mL), and then diluted with 2M HCl (50 mL). The organic phase was extracted with TBME (3 x 50 mL), combined and dried over $MgSO_4$, and concentrated *in vacuo.* The title compound was afforded after purification by FCC (combiflash rf 20→70% EtOAc/cyclohexane) followed by a second purification by reverse phase chromatography (combiflash rf C18 column, 10→40% water/MeCN) as a colourless oil (540 mg, 3.21 mmol, 13% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5 6.05 – 5.72 (m, 1H, H_2), 3.79 – 3.56 (m, 2H, H_{10} x 2), 2.37 (t, *J* = 6.5 Hz, 2H, H_6 x 2), 2.31 – 2.19 (m, 4H, H_4 x 2, H_7 x 2), 1.99 (p, *J* = 6.5 Hz, 2H, H_5 x 2), 1.89 – 1.47 (m, 5H, OH, H_8 x 2, H_9 x 2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5 (C_1), 166.9 (C_3), 125.8 (C_2), 62.4 (C_{10}), 37.8 (C_7), 37.4 (C_6), 32.2 (C_9), 29.7 (C_4), 23.3 (C_8), 22.8 (C_5).

The spectroscopic data matched that previously reported in the literature.[199]

3,4,4a,5,6,7-Hexahydronaphthalen-1(*2H*)-one 1025



3-(4-Hydroxybutyl)cyclohex-2-en-1-one (50.5 mg, 0.3 mmol, 1 eq.), aluminium tert-butoxide (75 mg, 1 equiv., 0.3 mmol), dry PhMe (1.5 mL, 0.2 M) were subjected to **general procedure 10**. The title compound was afforded after purification by FCC (10→20% Et_2O/pentane) as a colourless oil (9 mg, 0.06 mmol, 20% yield).

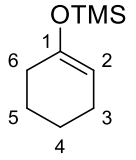
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 – 6.62 (m, 1H, H_9), 2.49 (ddt, *J* = 17.5, 4.7, 2.0 Hz, 1H, H_8), 2.34 – 2.08 (m, 4H, H_2 x 2, H_5 , H_8), 1.96 – 1.79 (m, 3H, H_4, H_6 H_7), 1.77 – 1.61 (m, 2H, H_3, H_7), 1.44 (dtdd, *J* = 16.5, 13.5, 6.5, 3.0 Hz, 1H, H_3), 1.29 – 1.09 (m, 2H, H_4, H_6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (C_1), 140.1 (C_{10}), 136.0 (C_9), 40.4 (C_8), 38.0 (C_5), 31.7 (C_4 or C_6), 30.5 (C_4 or C_6), 26.3 (C_2), 22.7 (C_7), 21.6 (C_3).

HRMS (ESI+): Found $[M+H]^+$ = 151.1117; $C_{10}H_{15}O$ requires 151.1117 Δ -0.31 ppm

IR (film) ν_{max}/cm^{-1} 3023, 2925, 1656, 1617, 1452, 1262, 863.

(Cyclohex-1-en-1-yloxy)trimethylsilane 1036



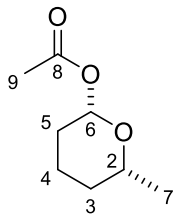
A flame dried RBF was charged with *N,N*-diisopropylamine (2 ml, 14 mmol, 1.2 eq.) and dry THF (20 mL) under argon and cooled to 0 °C. *n*BuLi (5.28 mL, 2.5M, 13.2 mmol, 1.1 eq.) was added dropwise and stirred for 30 minutes. The reaction mixture was then cooled to -78 °C and 2-cyclohexen-1-one (1.2 mL, 12 mmol, 1 eq.) was added dropwise followed by trimethylsilyl chloride (2.2 mL, 17 mmol, 1.5 eq.). The reaction mixture was stirred for 15 minutes and then warmed to RT. After 1 hour, the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with hexanes (3 x 20 mL). The combined organic layers were then washed with water (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was afforded after purification by FCC (100% pentane) as a colourless oil (1.04 g, 6.13 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (tt, *J* = 3.5, 1.0 Hz, 1H, H_2), 2.04 – 1.93 (m, 4H, H_3 x 2, H_6 x 2), 1.70 – 1.58 (m, 2H, H_4 x 2), 1.54 – 1.45 (m, 2H, H_5 x 2), 0.17 (s, 9H, CH_3 x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (C_1), 104.4 (C_2), 30.1 (C_6), 24.0 (C_3), 23.3 (C_4), 22.5 (C_5), 0.5 (CH_3 x 3).

The spectroscopic data matched that previously reported in the literature.[200]

6-Methyltetrahydro-*2H*-pyran-2-yl acetate 1037



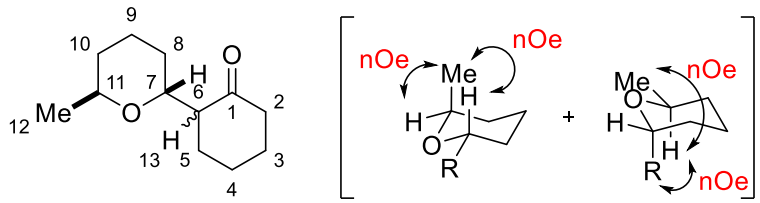
KHMDS in toluene (0.5M, 6.3 mL, 3.15 mmol, 1.05 eq.) was added dropwise to an RBF charged with 4-methyltetrahydro-*2H*-pyran-2-ol (348 mg, 3.0 mmol, 1 eq.) in dry THF (15 mL, 0.2 M) cooled to -78 °C under argon and stirred for 30 minutes. Acetic anhydride (0.85 mL, 9 mmol, 3 eq.) was added, stirring at -78 °C for two hours. The reaction mixture was then quenched with sat. aq. ammonium chloride (20 mL) and warmed to RT. Distilled water was then added (20 mL) and extracted with diethyl ether (3 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10% Et_2O/pentane) as a colourless oil (309 mg, 1.95 mmol, 65% yield, >95:5 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dd, *J* = 10.0, 2.0 Hz, 1H, H_6), 3.67 (dqd, *J* = 11.0, 6.0, 2.0 Hz, 1H, H_2), 2.09 (s, 3H, H_9 x 3), 1.93 – 1.82 (m, 1H, H_{4a}), 1.84 – 1.74 (m, 1H, H_{5a}), 1.66 – 1.38 (m, 3H, H_{3a}, H_{4b}, H_{5b}), 1.29 – 1.11 (m, 4H, H_7 x 3, H_{3b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (C_8), 95.0 (C_6), 73.5 (C_2), 32.1 (C_3), 29.9 (C_5), 21.9 (C_4), 21.7 (C_7), 21.4 (C_9).

The spectroscopic data matched that previously reported in the literature.[201]

2-(6-Methyltetrahydro-2H-pyran-2-yl)cyclohexan-1-one 1027



A solution of trimethylsilyl trifluoromethanesulfonate (22 mg, 0.1 mmol, 0.1 eq.) in CH_2Cl_2 (2 mL) was added dropwise to a 5 mL microwave vial charged with 6-methyltetrahydro-*2H*-pyran-2-yl acetate (174 mg, 1.1 mmol, 1.1 eq.), (Cyclohex-1-en-1-yloxy)trimethylsilane (170 mg, 1.0 mmol, 1 eq.) and CH_2Cl_2 (3 mL) cooled to -78 °C under argon. The reaction mixture was stirred for 3 hours, and then quenched with sat. aq. $NaHCO_3$. The reaction mixture was then warmed to RT, extracted with CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was afforded after purification by FCC (10→20% Et_2O/pentane) as a colourless oil (181 mg, 0.92 mmol, 92% yield, inconsequential 68:32 mixture of diastereomers by ^1H NMR)

^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (ddd, *J* = 9.5, 5.5, 4.0 Hz, 1H, H_7), 3.74 (pd, *J* = 6.5, 3.0 Hz, 1H, H_{11}), 2.67 (td, *J* = 9.0, 5.0 Hz, 1H, H_6), 2.40 – 2.23 (m, 2H, H_2 x 2), 2.14 (dtt, *J* = 10.5, 6.5, 2.5 Hz, 1H, H_{5a}), 2.04 – 1.93 (m, 1H, H_{3a}), 1.93 – 1.83 (m, 1H, H_{4a}), 1.82 – 1.50 (m, 7H, H_{3b}, H_{4b}, H_{5b}, H_{8a}, H_9 x 2, H_{10a}), 1.46 – 1.35 (m, 1H, H_{8b}), 1.34 – 1.23 (m, 1H, H_{10b}), 1.17 (d, *J* = 6.5 Hz, 3H, H_{12} x 3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7 (C_1), 69.3 (C_7), 67.5 (C_{11}), 52.3 (C_6), 42.7 (C_2), 31.8 (C_{10}), 29.9 (C_5), 28.4 (C_3), 28.3 (C_8), 24.2 (C_4), 20.1 (C_{12}), 18.7 (C_9).

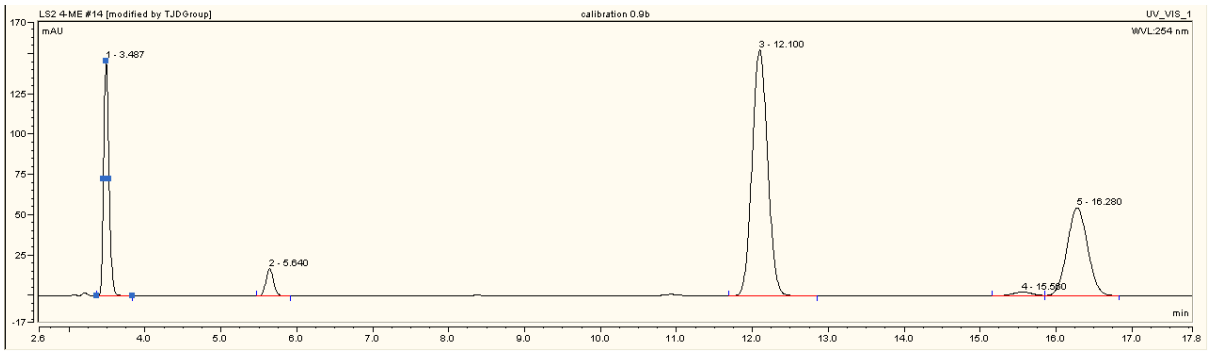
HRMS (ESI+): Found $[M+H]^+$ = 197.1538; $C_{12}H_{21}O_2$ requires 197.1536 Δ 0.87 ppm

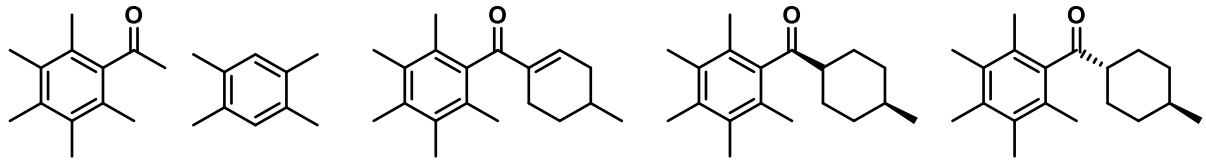
IR (film) ν_{max}/cm^{-1} 2931, 2861, 1707, 1448, 1380, 1203, 1040.

Chapter 6: Appendix

6.1 HPLC Calibration

6.1.1 Calibration Data for HPLC with 1,2,4,5-tetramethylbenzene at 254 nm





187 **1038** **405** ***cis*-404** ***trans*-404**

Figure 1. Illustrative HPLC trace. 187. 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one elutes at 3.5 minutes. **1038.** 1,2,4,5-tetramethylbenzene elutes at 5.6 minutes. **405.** (4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone elutes at 12.1 minutes. ***Cis*-404.** (*cis*-4-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone elutes at 15.6 minutes. ***Trans*-404.** (*trans*-4-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone elutes at 16.3 minutes.

Mol Equivalents w.r.t standard	**1**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**	**0.4**	**0.3**	**0.2**	**0.1**
187	13.9733	12.5052	11.9138	10.1605	8.5462	6.7892	5.5433	4.5526	2.6606	1.5475
1038	1.9306	1.9764	2.1709	2.1161	2.0459	1.9961	2.0485	2.118	1.9115	1.9647
405	41.0396	39.4159	37.3627	31.7767	26.5086	21.7666	18.0436	14.9875	9.0936	4.6313
***Cis*-404**	0.7549	0.7431	0.6895	0.5689	0.4656	0.3751	0.3252	0.2533	0.1532	0.0615
***Trans*-404**	19.3695	18.8629	17.6924	15.1451	12.2346	10.028	8.5404	6.6741	4	2.1206
404 Total	20.1244	19.606	18.3819	15.714	12.7002	10.4031	8.8656	6.9274	4.1532	2.1821

Table 1. Peak areas from HPLC calibration with durene at 254 nm

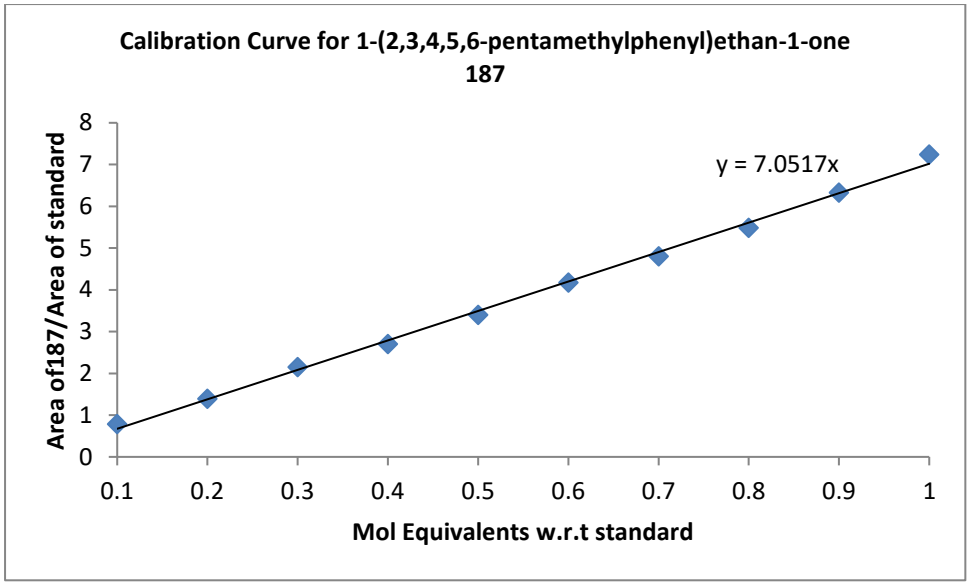


Figure 2. Calibration Curve for 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one. Gradient on the trend used to find the yield **187** of based on the ratio of peak area between its absorption and 1,2,4,5-tetramethylbenzene **1038** at 254 nm.

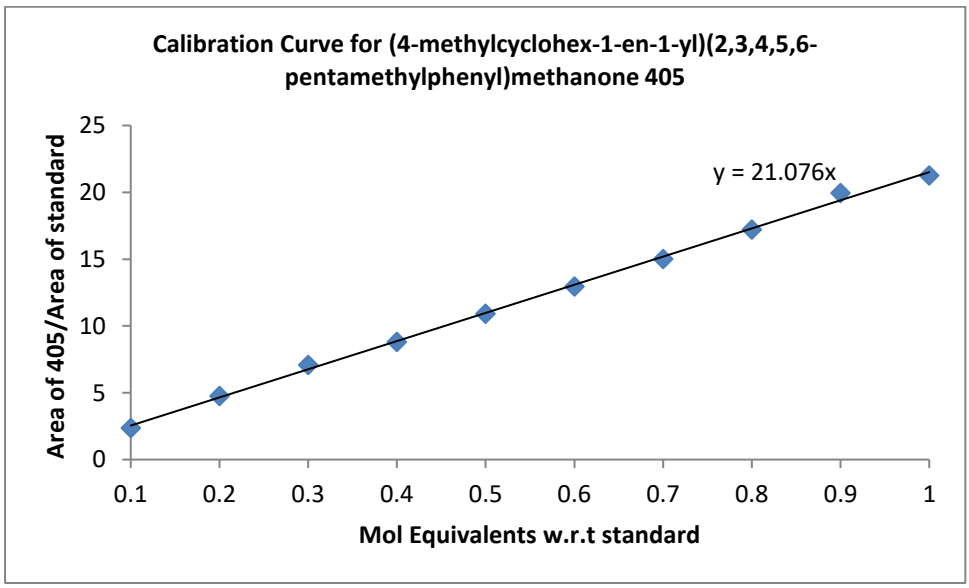


Figure 3. Calibration Curve for (4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)-methanone. Gradient on the trend used to find the yield **405** of based on the ratio of peak area between its absorption and 1,2,4,5-tetramethylbenzene **1038** at 254 nm.

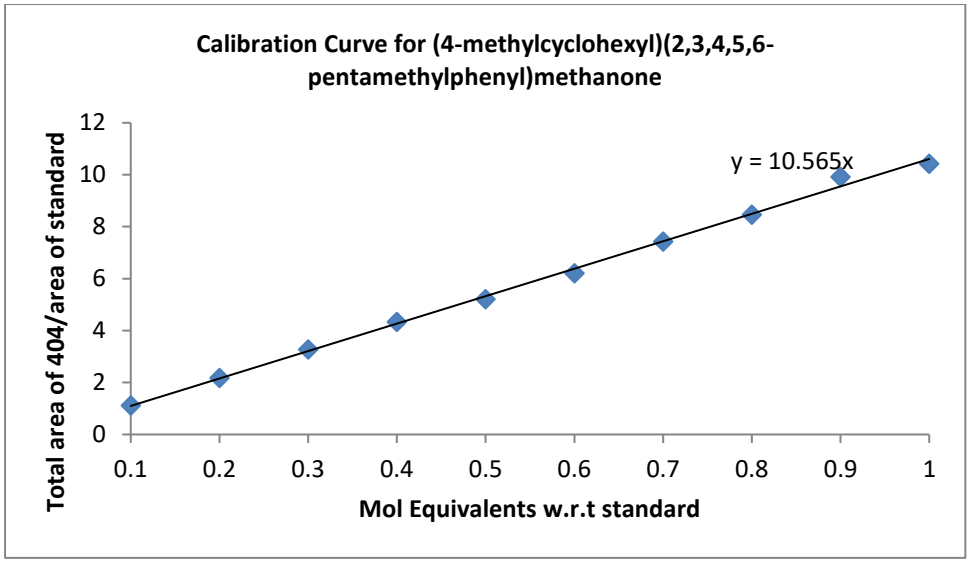
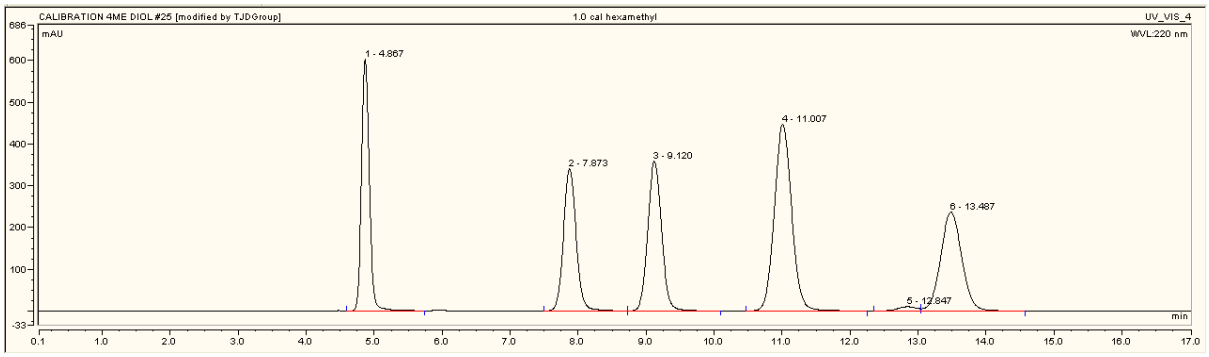
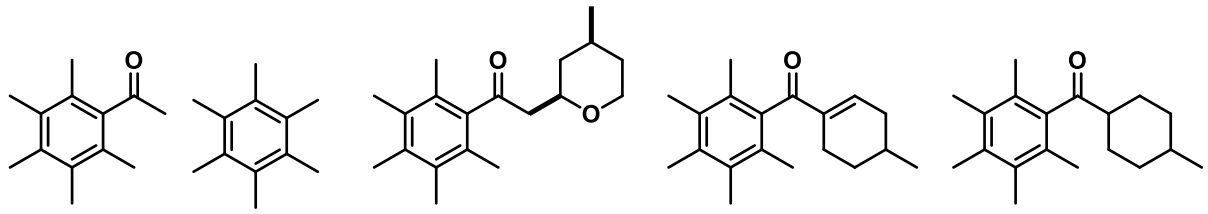


Figure 4. Calibration Curve for (4-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone. Gradient on the trend used to find the combined yield of **404** of based on the ratio of peak area between its absorption and 1,2,4,5-tetramethylbenzene **1038** at 254 nm.

6.1.2 Calibration Data for HPLC with hexamethylbenzene at 220 nm





187 **1039** **631** **405** **404**

Figure 5. Illustrative HPLC trace. 187. 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one elutes at 4.9 minutes. **1039.** hexamethylbenzene elutes at 7.9 minutes. **631.** 2-((*cis*)-4-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **405.** (4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-

pentamethylphenyl)methanone elutes at 11.0 minutes. **404.** (4-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone elutes at 12.8 and 13.5 minutes.

Mol Equivalents w.r.t standard	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1
187	79.6919	80.9975	66.6406	61.415	53.5845	45.4827	34.7654	26.9443	19.5018	9.9529
631	73.6279	76.5343	61.9016	57.768	50.0388	42.6311	35.8186	26.1201	18.089	9.1264
1039	84.2014	94.7386	86.6098	92.897	91.7205	92.9495	99.3746	100.5317	101.5103	100.532
405	131.9355	132.6366	105.1597	102.0856	86.5798	73.7923	62.8381	48.1688	33.738	17.976
404 total	88.5613	92.119	73.9612	67.9204	59.269	50.3833	39.4641	31.8277	21.8383	10.373

Table 2. Peak areas from HPLC calibration with hexamethylbenzene at 220 nm

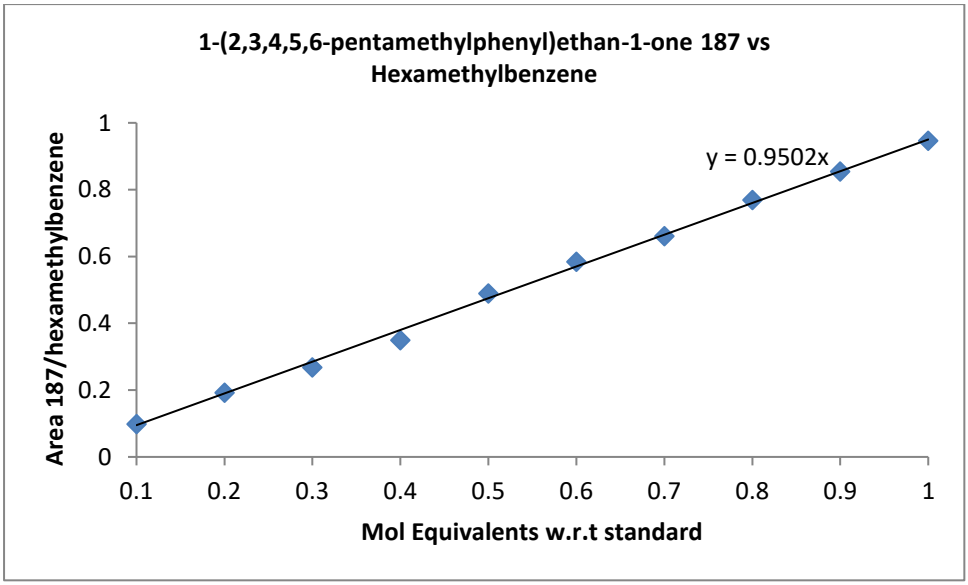


Figure 6. Calibration Curve for 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one. Gradient on the trend used to find the yield **187** of based on the ratio of peak area between its absorption and hexamethylbenzene **1039** at 220 nm.

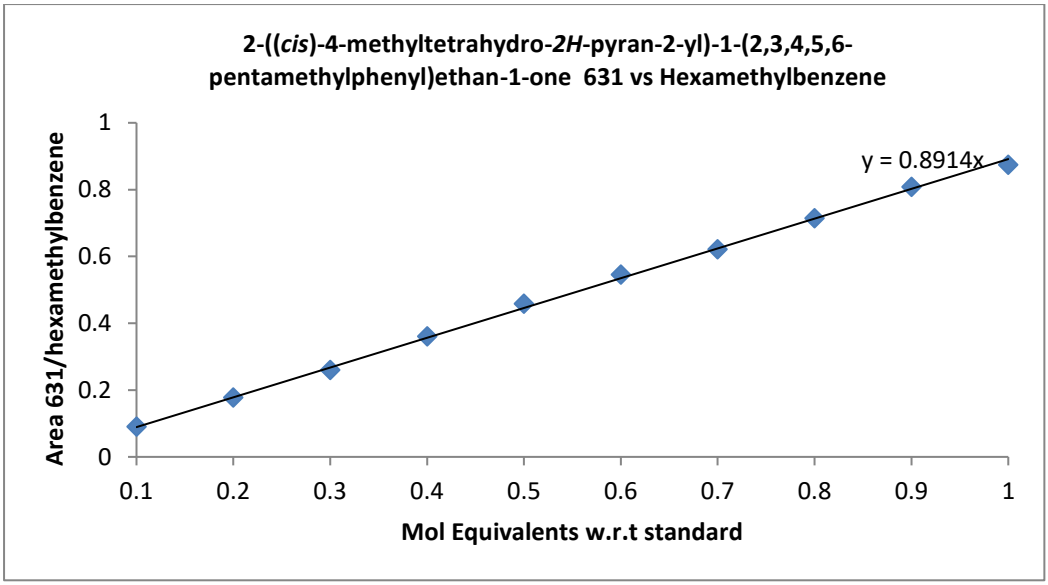


Figure 7. Calibration Curve for 2-((*cis*)-4-methyltetrahydro-*2H*-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one. Gradient on the trend used to find the yield of **631** of based on the ratio of peak area between its absorption and hexamethylbenzene **1039** at 220 nm.

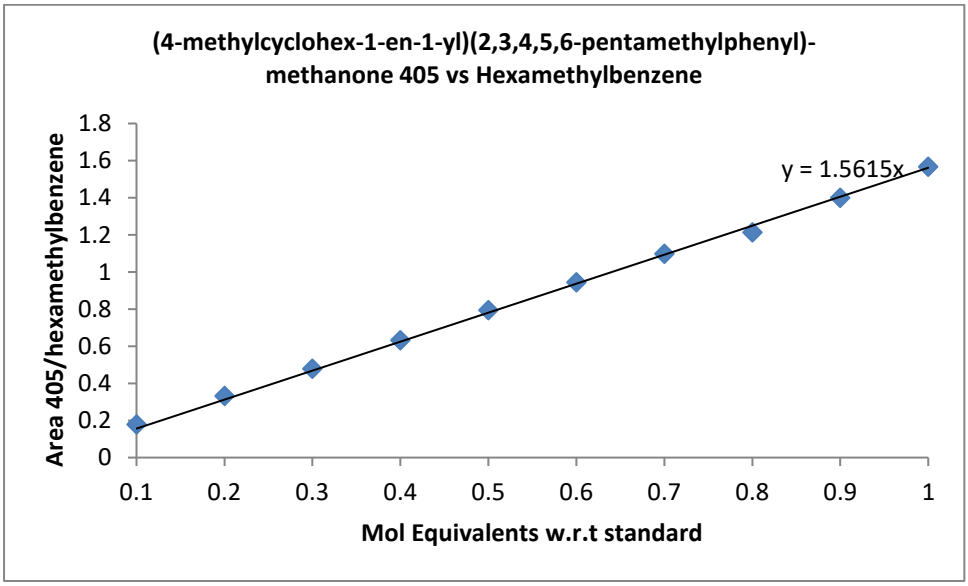


Figure 8. Calibration Curve for (4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)-methanone. Gradient on the trend used to find the yield **405** of based on the ratio of peak area between its absorption and hexamethylbenzene **1039** at 220 nm.

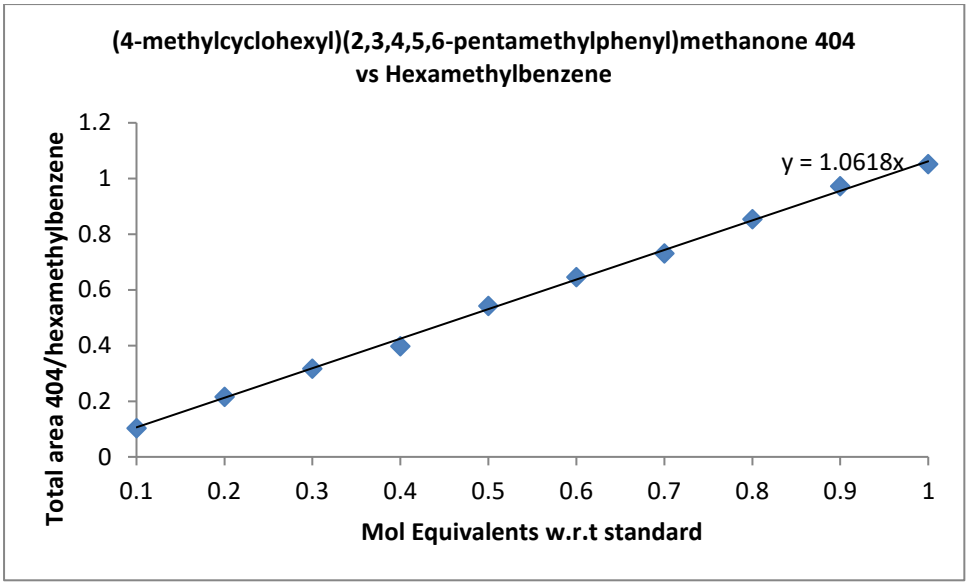


Figure 9. Calibration Curve for (4-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone. Gradient on the trend used to find the combined yield of **404** of based on the ratio of peak area between its absorption and hexamethylbenzene **1039** at 220 nm.

HPLC calibration for Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate **757** with hexamethylbenzene **1039** and 2-4-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **631** (67:33 cis/trans ratio) against hexamethylbenzene **1039** at 220 nm. The HPLC calibration was performed up to 1.3 equivalents, as this was the stoichiometry of the HWE reagent in the reaction. The HPLC calibration for 2-4-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one was repeated from chapter 2 on a mixture of cis and trans tetrahydropyran, as this reaction produced both diastereomers.

Mol Equivalents w.r.t standard	**1.3**	**1.2**	**1.1**	**1.0**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**	**0.4**	**0.3**	**0.2**	**0.1**
757	115.8091	101.0376	95.1558	85.4528	77.5584	68	64.5884	54.5291	46.2766	34.2891	27.6374	15.6176	7.5889
1039	106.4478	101.8808	98.5955	97.4643	98.3611	96.2603	103.3854	105.4155	102.9875	98.0066	105.1789	98.9345	84.5402

Table 3: Peak areas for Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate from HPLC calibration with hexamethylbenzene at 220 nm

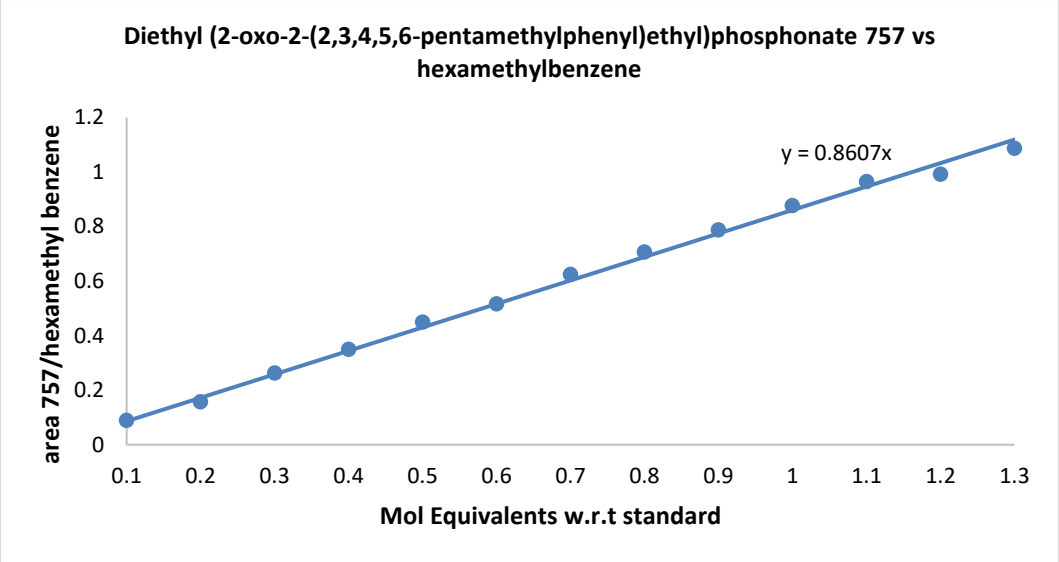


Figure 10. Calibration Curve for Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate Gradient on the trend used to find the yield of **757** of based on the ratio of peak area between its absorption and hexamethylbenzene **1039** at 220 nm.

Mol eq. WRT standard	**1.3**	**1.2**	**1.1**	**1.0**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**	**0.4**	**0.3**	**0.2**	**0.1**
631 67:33 *d.r.*	96.186	109.2044	102.9118	96.6502	81.3133	81.1961	69.2324	52.6333	49.6541	38.036	28.659	19.3134	8.4925
1039	77.2159	95.2584	94.9105	98.7806	89.5832	103.5006	98.9775	89.4656	98.5122	92.8378	93.3912	94.4132	79.3139

Table 4: Peak areas for 2-4-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (67:33 cis/trans ratio) against hexamethylbenzene at 220 nm

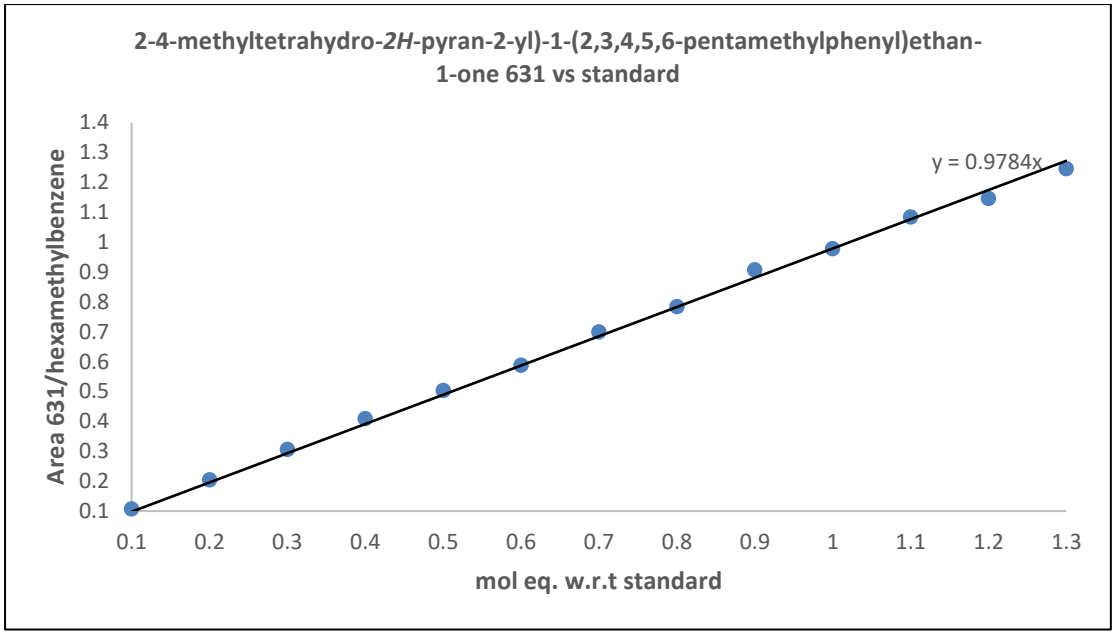
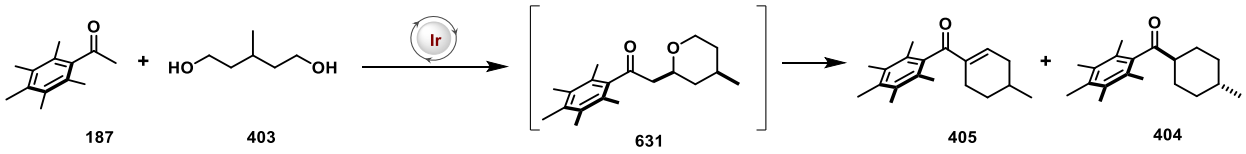


Figure 10. Calibration Curve for 2-4-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one Gradient on the trend used to find the yield of **631** based on the ratio of peak area between its absorption and hexamethylbenzene **1039** at 220 nm.

6.1.3 Time Course Experiments

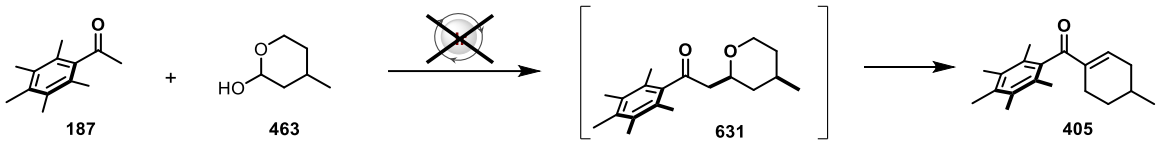
Reaction Profile of Iridium-Catalysed Reaction



A 20 mL Biotage® microwave vial was charged with CataCXium® A (17 mg, 0.048 mmol, 2 mol%), 3-methylpentane-1,5-diol (567 mg, 4.80 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (456 mg, 2.40 mmol, 1 eq), $[Ir(cod)Cl]_2$ (8.0 mg, 0.012 mmol, 0.5 mol% dimer), KOH (538 mg, 9.60 mmol, 4 eq.), hexamethylbenzene (389.5 mg, 2.40 mmol, 1 eq.) and toluene (9.6 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 115 °C for 24 hours, taking 0.1 mL aliquots at the times listed below. The aliquot was filtered through silica, washing with Et_2O and the solvent was removed *in vacuo*. The sample was diluted with 5 mL of MeCN and analysed by reverse phase HPLC analysis (Agilent InfinityLab Poroshell 120 EC-C18 column with guard, 75% MeCN, 25% H_2O, 1.0 mL/min, 25 °C, λ = 220 nm, 5 µL injection). The mmol of **187**, **631**, **405** and **404** were determined by relative peak area to a calibrated absorption of the internal standard hexamethylbenzene at 220 nm.

Time (h)	mmol of **187**	mmol of **631**	mmol of **405**	mmol of **404**
0.5	2.4	0	0	0
0.75	2.29	0.15	0.11	0
1	2.19	0.22	0.20	0
2	2.15	0.28	0.30	0
3	1.63	0.27	0.54	0.01
4	1.41	0.30	0.87	0.02
5	1.17	0.29	1.12	0.03
6	1.02	0.27	1.29	0.03
7	0.89	0.23	1.30	0.04

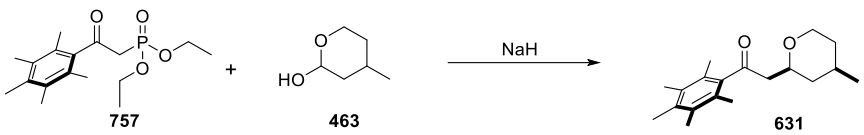
Reaction Profile of Iridium-Free Reaction



A 20 mL Biotage® microwave vial was charged with 4-methyltetrahydro-2*H*-pyran-2-ol (558 mg, 4.80 mmol, 1 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (456 mg, 2.40 mmol, 1 eq), KOH (538 mg, 9.60 mmol, 4 eq.), hexamethylbenzene (390 mg, 2.40 mmol, 1 eq.) and toluene (9.6 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 115 °C for 24 hours, taking 0.1 mL aliquots at the times listed below. The aliquot was filtered through silica, washing with Et_2O and the solvent was removed *in vacuo*. The sample was diluted with 5 mL of MeCN and analysed by reverse phase HPLC analysis (Agilent InfinityLab Poroshell 120 EC-C18 column with guard, 75% MeCN, 25% H_2O, 1.0 mL/min, 25 °C, λ = 220 nm, 5 µL injection). The mmol of **187**, **631**, **405** and **404** were determined by relative peak area to a calibrated absorption of the internal standard hexamethylbenzene at 220 nm.

Time (h)	mmol of **187**	mmol of **631**	mmol of **405**	mmol of **404**
0.5	2.4	0	0	0
0.75	0.26	1.42	0.91	0
1	0.20	1.31	1.10	0
2	0.18	1.09	1.13	0
3	0.14	0.81	1.43	0
4	0.14	0.53	1.60	0
5	0.13	0.41	1.76	0
6	0.12	0.34	1.79	0
7.16	0.12	0.26	1.81	0

Reaction Profile for HWE Reaction

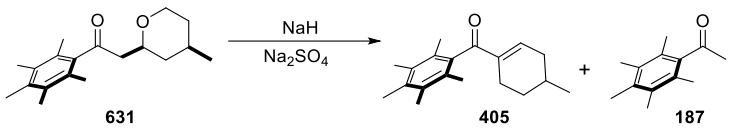


A flame-dried 2-5 mL Biotage® microwave vial was charged with Diethyl (2-oxo-2-(2,3,4,5,6-pentamethylphenyl)ethyl)phosphonate (242mg, 0.78 mmol, 1.3 eq.), 60% wt. NaH (28.8 mg, 0.72 mmol, 1.2 eq), oven dried Na_2SO_4 (256 mg, 1.8 mmol, 3eq.) and hexamethylbenzene (97.4 mg, 0.6 mmol, 1 eq.) then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (1.2 mL, 0.5 M) was then added, stirring the solution for 1 h at RT. -4-Methyltetrahydro-2*H*-pyran-2-ol (70 mg, 0.6 mmol, 1 eq.) was then added by syringe, the balloon was removed, and the reaction was heated at 110 °C for 15 h, taking 0.1 mL aliquots at the times listed below. The aliquot was filtered through silica, washing with Et_2O and the solvent was removed *in vacuo*. The sample was diluted with 5 mL of MeCN and analysed by reverse phase HPLC analysis (Agilent InfinityLab Poroshell 120 EC-C18 column with guard, 75% MeCN, 25% H_2O, 1.0 mL/min, 25 °C, λ = 220 nm, 5 µL injection). The mmol of **757** and **631** were determined by relative peak area to a calibrated absorption of the internal standard hexamethylbenzene at 220 nm.

Time (h)	Mmol of 757	Mmol of 631	Cis/trans ratio
0.5	0.45	0.35	54.46
1	0.28	0.47	61:39
1.5	0.2	0.53	65:35
2	0.16	0.55	67:33
2.5	0.14	0.57	69:31
3	0.11	0.59	71:29
3.5	0.11	0.63	72:28
4	0.11	0.6	71:29
4.5	0.09	0.59	74:26
5	0.09	0.61	75:25
5.5	0.1	0.62	75:25
6	0.1	0.63	76:24

n.b yield of pyran exceeds 100%, however as the limiting reagent (lactol) was added by syringe, a 5% error in the mass added would be expected, and would account for the overestimation.

Reaction Profile for [1,5]-H Shift Reaction under Basic Conditions

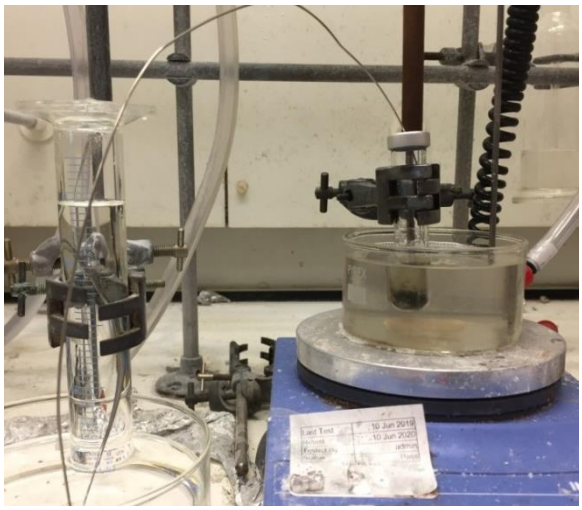


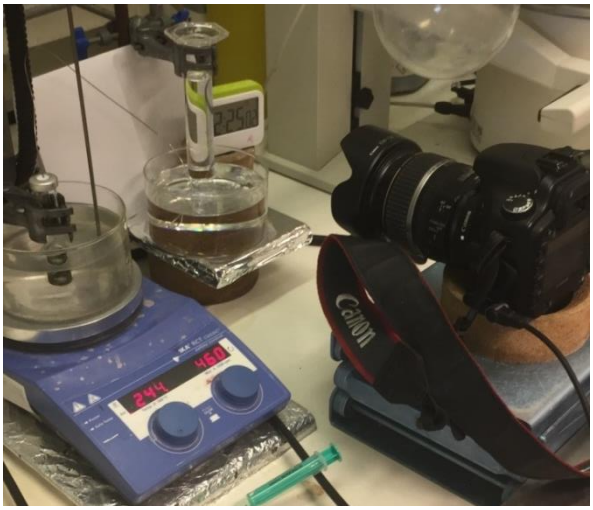
A flame-dried 2-5 mL Biotage® microwave vial was charged 2-4-methyltetrahydro-*2H*-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (173 mg, 0.6 mmol, 1 eq.), 60% wt. NaH (72 mg, 1.8 mmol, 3 eq), oven dried Na_2SO_4 (256 mg, 1.8 mmol, 3eq.) and hexamethylbenzene (97.4 mg, 0.6 mmol, 1 eq.) then sealed with a microwave vial cap (containing a Reseal™ septum), degassed, and fitted with an argon balloon. Dry toluene (1.2 mL, 0.5 M) was then added, and once the effervesence had stopped, the argon balloon was removed and the reaction was heated at 110 °C for 15 h, taking 0.1 mL aliquots at the times listed below. The aliquot was filtered through silica, washing with Et_2O and the solvent was removed *in vacuo*. The sample was diluted with 5 mL of MeCN and analysed by reverse phase HPLC analysis (Agilent InfinityLab Poroshell 120 EC-C18 column with guard, 75% MeCN, 25% H_2O, 1.0 mL/min, 25 °C, λ = 220 nm, 5 µL injection). The mmol of **187**, **631** and **405** were determined by relative peak area to a calibrated absorption of the internal standard hexamethylbenzene at 220 nm.

time	mmol 631	Cis/trans ratio of 631	mmol 405	mmol 187
0.5	0.54	82:18	0.1	0
1	0.32	75:25	0.3	0.01
1.5	0.13	73:27	0.43	0.02
2	0.04	69:31	0.49	0.04
2.5	0.01	69:31	0.5	0.06
3	0.01	-	0.49	0.08
3.5	0	-	0.49	0.08
4	0	-	0.47	0.1
4.5	0	-	0.44	0.13
5	0	-	0.44	0.14
5.5	0	-	0.42	0.16
6	0	-	0.44	0.15
24	0	-	0.09	0.33

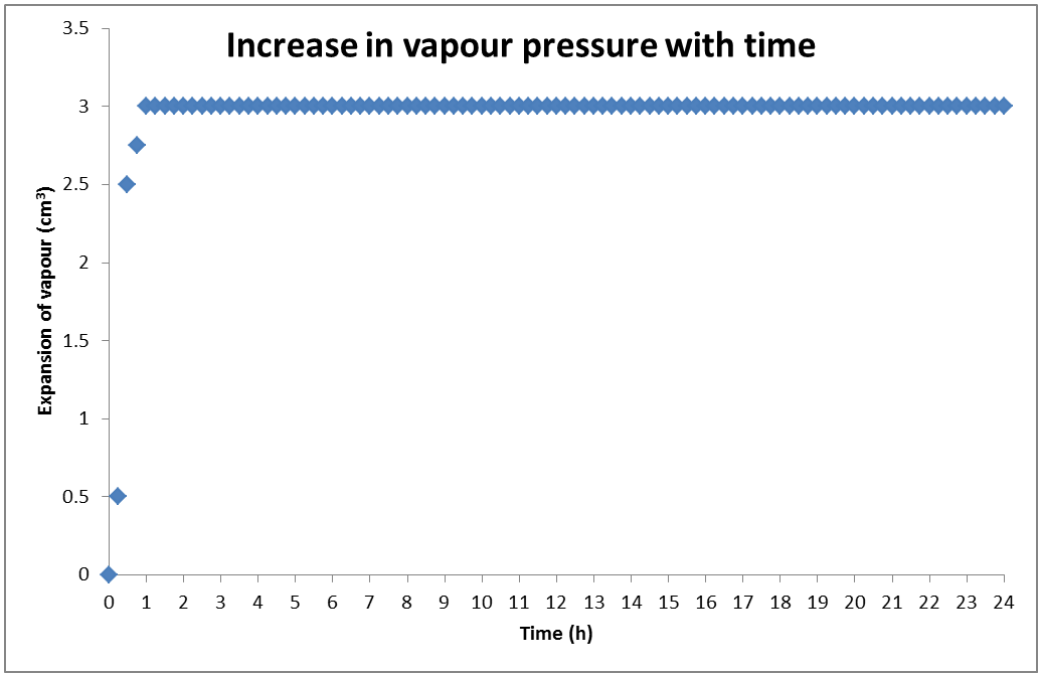
6.1.4 Method for Measuring Hydrogen Evolution

Apparatus: A 50 mL measuring cylinder filled with toluene was inverted and submerged in a bath of toluene and a cannula was inserted into the cylinder. The other end of the cannula was then placed into the neck of the Biotage® microwave vial by piercing the septum. A Canon EOS 30D camera fitted with Canon TC-80N3 Timer Remote Control was set up to take photos of the measuring cylinder and a clock at 15 minute intervals for 24 hours. See photographs below:

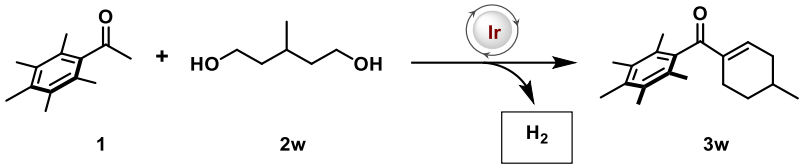




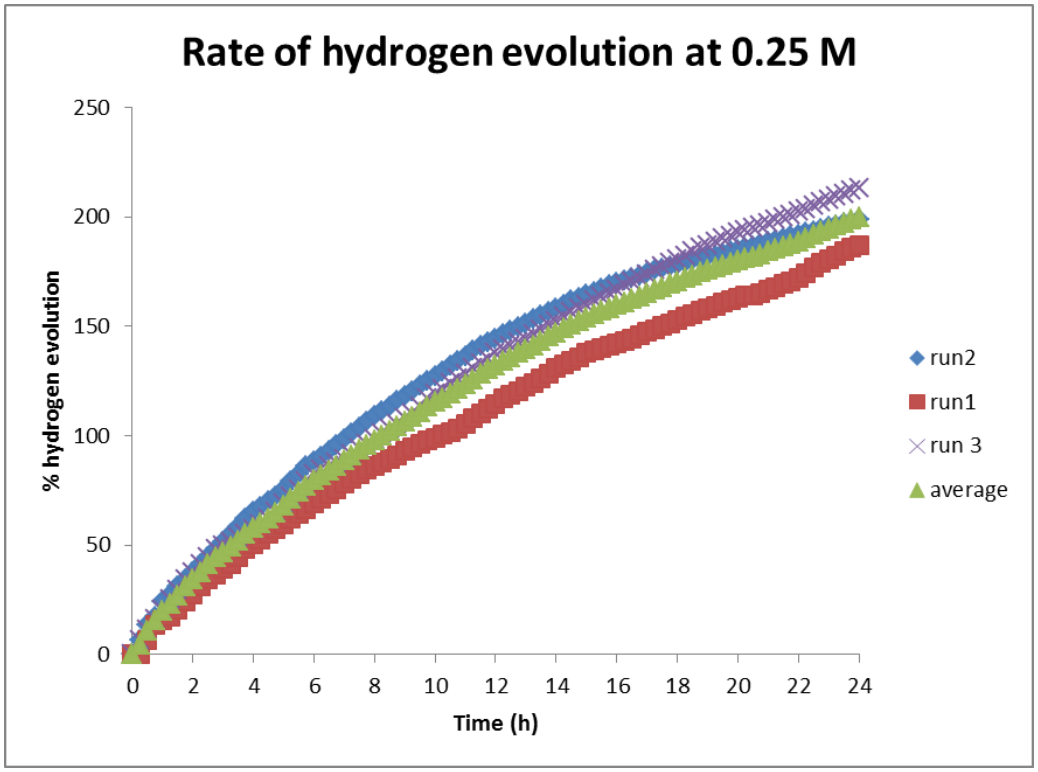
N.B. Heating 2.4 mL of toluene in a Biotage® microwave vial at 115 ^{o}C caused an increase in the vapour pressure within the reaction vessel. To account for this in our measurements, toluene (2.4 mL) was heated at 115 ^{O}C for 24 hours in a sealed 2-5 mL Biotage® microwave vial using the apparatus described above to measure the increase in volume. The observed expansion of the headspace amounted to approximately 3 mL and was deducted from all subsequent hydrogen evolution experiments – the data for this control experiment is plotted overleaf for reference.

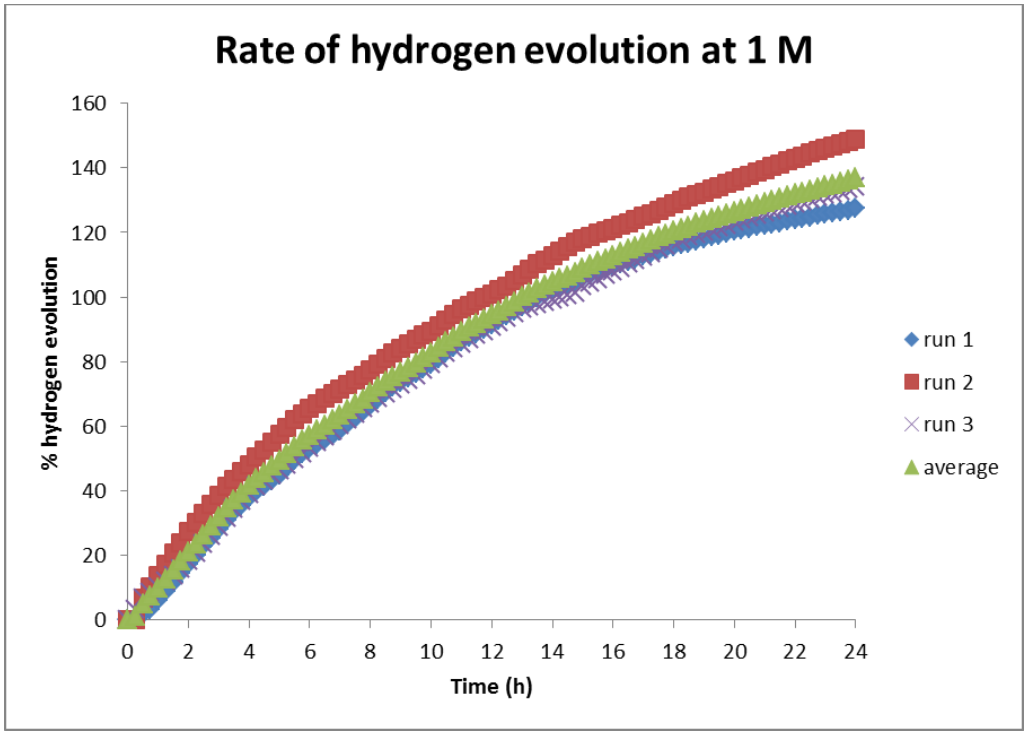


Measurement of Hydrogen Evolution in Iridium Catalyzed Annulation



A 2-5mL Biotage® microwave vial was charged with CataCXium® A (4.3 mg, 0.012 mmol, 2 mol%), 3-methylpentane-1,5-diol **2w** (143 mg, 1.20 mmol, 2 eq.), 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **1** (114 mg, 0.600 mmol, 1 eq.), $[Ir(cod)Cl]_2$ (2 mg, 0.003 mmol, 0.5 mol% dimer), KOH (134 mg, 2.40 mmol, 4 eq.) and toluene (2.4 mL, 0.25 M). The vial was then sealed with a microwave vial cap (containing a Reseal™ septum) and connected to the cannula from the hydrogen collection apparatus. The reaction was heated at 115 °C for 24 hours, with a photograph taken of the cylinder at 15 minute intervals. Volume was converted to mmol using the ideal gas equation, with 1 mmol of H_2 at 298 K assumed to be 24.2 dm^3.


Rate of hydrogen evolution at 0.25 M
% hydrogen evolution
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
run2
run1
run 3
average


Rate of hydrogen evolution at 1 M
% hydrogen evolution
160
140
120
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (h)
run 1
run 2
run 3
average

Chapter 7: References

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