The α-Alkylation of Ketones Using Hydrogen Borrowing Catalysis

A thesis submitted to the Board of the Faculty of the Mathematical, Physical and Life Sciences Division for the degree of

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by

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and

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Dedication

I would like to dedicate this thesis to the loving memory of my mother, Naseem Akhtar, who has been a constant source of inspiration and strength.

Declaration

This thesis describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2014 and August 2018. The work it describes is entirely my own except where specifically indicated in the text.

Wasim M. Akhtar

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Acknowledgments

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Glossary of Abbreviations and Acronyms

°C	Degrees Celsius
Ar	Argon/Aryl
aq.	Aqueous
BAIB	Bis(acetoxy)iodobenzene
BArF	Tetrakris(3,5-bis(trifluoromethyl)phenyl)borate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
CataCXium A	Di-(1-adamantyl)-*n*-butylphosphine
cod	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
dba	Dibenzylideneacetone
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppbenz	1,2-Bis(diphenylphosphino)benzene
dppe	Ethylenebis(diphenylphosphine)
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
e.g.	*Exempli gratia* (Latin: for example)
EI^+	Electron ionisation (positive ion detection)
equiv	Equivalent (unit)
e.r.	Enantiomeric ratio
ESI^+	Electrospray ionisation (positive ion detection)
Et	Ethyl
h	Hour(s)
HB	Hydrogen borrowing
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry

HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
Ip-foxap	2-(4-Isopropyl-Δ^2-oxazolin-2-yl)-ferrocenyl(diphenyl)phosphine
*i*Pr	Isopropyl
IPr	*N*,*N*′-Diisopropylimidazolium
J	Coupling constant (NMR)
L	Ligand
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
M	Molar
Me	Methyl
MeO-BIPHEP	2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
min	Minute(s)
mL	Millilitre(s)
mol%	Molar percent
m.p.	Melting point
MPV	Meerwein-Ponndorf-Verley
MW	Microwave
n-	*Primary*-
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
PDC	Pyridinium dichromate
Ph*	Pentamethylphenyl
Ph	Phenyl
pKa	Logarithmic acid dissociation constant
PMP	*Para*-methoxybenzyl
ppm	Parts per million
Pr	Propyl
RSM	Recovered starting material
RT	Room temperature
sat.	Saturated
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
t/tert	tertiary

TFP	Tri(2-furyl)phosphine
TLC	Thin layer chromatography
TOCSY	Total correlated spectroscopy
Tol	Tolyl
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
δ	Chemical shift
μ	Micro (prefix: 10^{-6})
ν_{max}	Infra-red absorption maximum

Abstract

The α-Alkylation of Ketones Using Hydrogen Borrowing Catalysis

A thesis submitted for the degree of **Doctor of Philosophy**
Wasim M. Akhtar, Wolfson College and The Chemistry Research Laboratory, Trinity Term 2018

Introduction – Hydrogen Borrowing Alkylation Reactions Using Alcohols

The introduction reviews the origins of hydrogen borrowing catalysis and how it has been applied to utilise alcohols as alkylating agents. The predominant focus is on highlighting the scope for the use of primary alcohols in the α-alkylation of ketones. Other nucleophiles are discussed with respect to the use of secondary alcohols as alkylating agents. Examples of related methodologies are also briefly discussed.

Results and Discussion – Formation of α-Branched Products Using Primary Alcohols

This chapter explores the alkylation of several ketone substrates and identifies cyclopropyl ketones as key structural motifs that facilitate the formation of α-branched products using primary alcohols. The development of an iridium–catalysed protocol for this reaction is described, including the optimisation of reaction conditions and investigation of the substrate scope with respect to the ketone and alcohol. The derivatisation of the resulting α-branched cyclopropyl ketones is also explored through utilisation of several ring-opening reactions.

Results and Discussion – Formation of β-Branched Products Using Secondary Alcohols

This chapter focuses on the development of an Ir-catalysed procedure for the alkylation of methyl ketones using secondary alcohols to form β-branched products. In developing this procedure, *ortho*-disubstituted aryl ketones were identified as key structural motifs that facilitated the reaction due to the unique properties they possessed. An overview of the optimisation of reaction conditions is provided, followed by exploration of the substrate scope with respect to the methyl ketone and the secondary alcohol. Derivatisation of the resulting β-branched products through bromine-initiated release of the aryl group, followed by trapping with several nucleophiles led to the formation of carboxylic acid derivatives. The final part of the chapter introduces preliminary studies towards the development of an asymmetric route to β-branched products.

Results and Discussion – Formation of Cyclic Products Using Diols

This chapter explores the development of an unprecedented Ir-catalysed procedure for alkylation of a methyl ketone using diols to form five-, six- and seven-membered carbocyclic rings. The optimisation of the reactions conditions is described followed by a systematic investigation into the diastereoselectivity observed in the formation of the carbocyclic rings. With the formation of cyclohexane rings identified as being most effective under the reaction conditions, these were then explored further in a more general substrate scope. The derivatisation of the cyclic products was also explored through a bromine-mediated release of the aryl group followed by trapping with a variety of nucleophiles.

Experimental Section

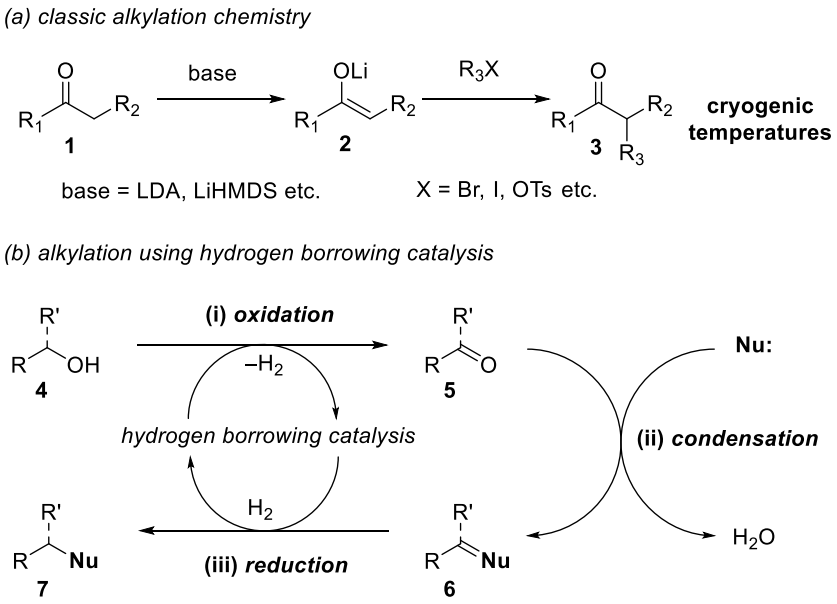
Experimental procedures are provided along with full spectroscopic characterisation of the compounds synthesised.

Chapter 1: Introduction – Hydrogen Borrowing Alkylation Reactions of Alcohols

1.1 The Concept of Hydrogen Borrowing Catalysis

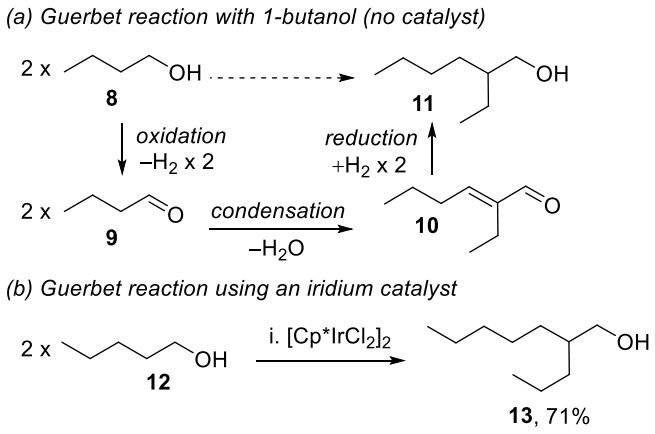
The dehydrogenation of alcohols can be exploited within organic synthesis for the construction of C-C and C-N bonds. As an activation tactic, dehydrogenation of alcohols plays an important role in a strategy commonly called "hydrogen borrowing" (HB) catalysis. This is also often referred to as the "borrowing hydrogen" approach or "hydrogen autotransfer". This process facilitates the use of alcohols in important bond forming reactions. The importance of the strategy can be exemplified by initially considering the classic α-alkylation of ketone **1** *via* enolate **2** (**Scheme 1.1a**). Typically, the alkylation would be achieved through reaction with an alkyl halide or pseudohalide, often require cryogenic reaction temperatures, and the use of strong high molecular weight bases that are air sensitive (e.g. LDA, LHMDS). This forms significant amounts of inorganic waste and hence lowers the overall atom economy of the reaction (**Scheme 1.1a**).[1]

If an alcohol could be employed as the alkylating reagent, the only stoichiometric by-product would be water, which is benign. Due to the strength of the C-O bond in alcohols, typically around 90 kcal mol^{-1}, however, it is unfeasible for them to be used directly as alkylating agents, particularly as deprotonation under the basic reaction media further hinders displacement of hydroxide.[2] Conversely, hydrogen borrowing catalysis can activate the alcohol through oxidation, bypassing this limitation. The general process is thought to occur through the following key steps (**Scheme 1.1b**): (i) metal-mediated oxidation of an alcohol (**4**) to the corresponding carbonyl species (**5**), (ii) reaction with a nucleophile to, typically, form a C-C/C-N followed by elimination of water to afford unsaturated compound **6**, and (iii) return of the 'borrowed' hydrogen from the metal to the unsaturated compound **6** to afford alkylated product **7**.



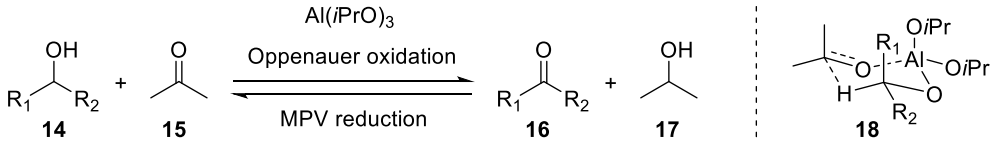
Scheme 1.1 Classic alkylation methods vs. alkylation using hydrogen borrowing catalysis

The developments leading up to this methodology go back over a century, predominantly being driven by the need to circumvent disadvantages with classic oxidation methods such as the use of chromium reagents which are toxic and often result in stoichiometric waste generation.[3] The Guerbet reaction, first reported in 1899[4], demonstrated that dehydrogenation of 1-butanol (**8**) in the presence of base, followed by self-condensation of the resulting aldehydes (**9**) lead to the formation of α-branched aldehyde **10** (**Scheme 1.2a**). Reduction of **10** afforded the corresponding β-branched primary alcohol **11**. The dimerised and branched products resulting from this reaction are often referred to as Guerbet alcohols. Conducted at temperatures of up to 200°C or higher[5], the reaction does not require a hydrogen-transfer catalyst, but can often result in side reactions such as the Cannizzaro reaction and the Tishchenko reaction. The drawbacks with the Guerbet reaction prompted new catalytic systems to be developed, allowing milder reaction temperatures and limiting undesired reaction pathways. One example, reported by Ishii and co-workers[6] utilises an iridium catalyst with 1-pentanol (**12**) to afford dimerised alcohol **13** in 71% yield (**Scheme 1.2b**).



Scheme 1.2 Guerbet reaction. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (1 mol%), 1,7-octadiene (10 mol%), and KO*t*Bu (40 mol%), *p*-xylene, 120 °C, 4 h

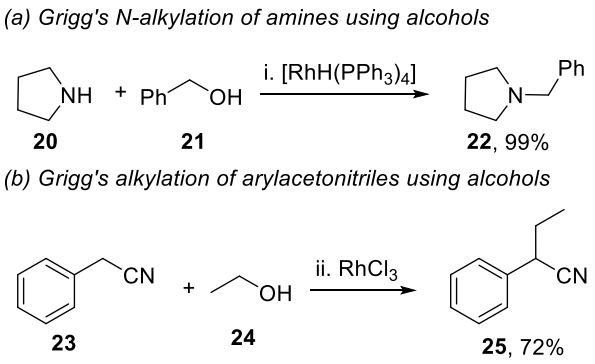
The notion of homogenous transfer hydrogenation, or indeed, dehydrogenation, did not come until 1925 when Meerwein[7] and Verley[8] independently reported what is now widely known as the Meerwein-Ponndorf-Verley (MPV) reduction. The dehydrogenation reaction, which is the reverse of the MPV reduction, was reported later by Oppenauer[9] in 1937 (**Scheme 1.3**). Both reactions are typically catalysed by aluminium alkoxides such as Al(O*i*Pr)$_3$. The equilibrium can be shifted towards oxidation product **16** by using an excess of a sacrificial ketone such as acetone (**15**), and towards reduction product **14** by using an excess of a sacrificial alcohol such as isopropanol (**17**). The reaction is thought to proceed through a direct hydrogen transfer mechanism involving a concerted six-membered chair-like transition state (**18**).[10]



Scheme 1.3 MPV reduction and Oppenauer oxidation

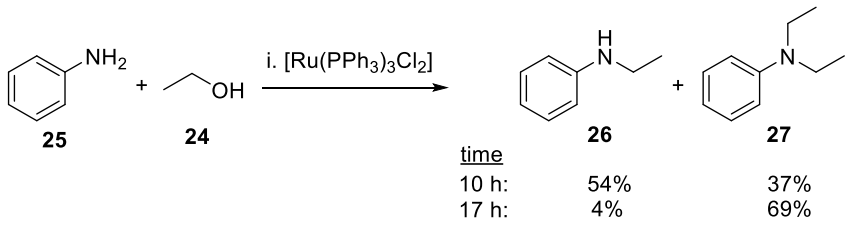
The next key development was driven by reports of a plethora of late transition-metal catalysts, effective at facilitating transfer hydrogenation reactions, were reported from the 1960s onwards.[11] With respect to HB catalysis, one of the first homogenous transition metal-catalysed protocols demonstrating C-C bond formation was reported by Grigg and co-workers in 1981 and

described the N-alkylation of primary and secondary amines using both primary and secondary alcohols.[12] For example, pyrrolidine (**20**) could be alkylated using benzyl alcohol (**21**) in 99% yield (**Scheme 1.4a**). Shortly after, they also reported a rhodium-catalysed alkylation of arylacetonitriles with primary alcohols.[13] In a representative example, using ethanol (**24**) and a catalyst derived *in situ* from rhodium trichloride, triphenylphosphine and sodium carbonate, aryl acetonitrile **23** could be alkylated to form **25** in 72% yield (**Scheme 1.4b**).



Scheme 1.4 Grigg's alkylation of amines and arylacetonitriles. Reagents and conditions: (i) $[RhH(PPh_3)_4]$ (1 mol%), BnOH, 100 °C, 4 h, (ii) $RhCl_3 \cdot 3H_2O$ (5 mol%), PPh_3 (25 mol%), Na_2CO_3 (1.1 equiv), EtOH, 78 °C, 48 h

As well as Grigg and co-workers, the group of Watanabe reported another piece of work describing the N-alkylation of aniline using primary alcohols.[14] Although certain alcohols and conditions (typically shorter reaction times), allowed the predominant isolation of the monoalkylated product, typically the reactions tended towards the dialkylated products. For example, aniline (**25**) reacted with ethanol to give the corresponding monoalkylated (**26**) and dialkylated (**27**) products in 54% and 37% (**Scheme 1.5**).



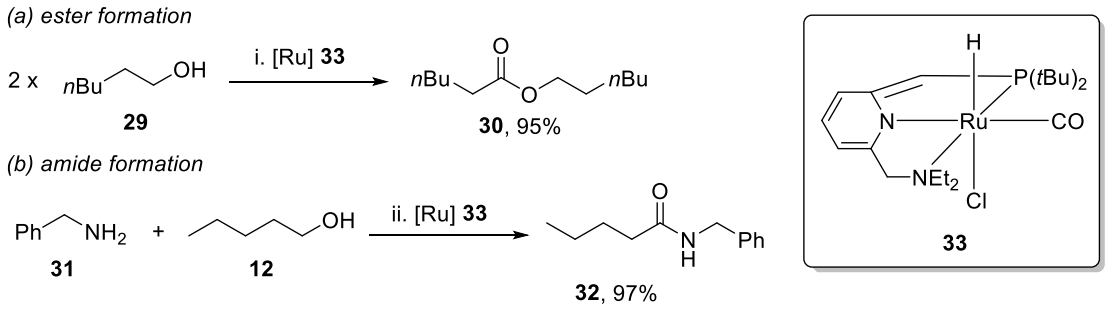
Scheme 1.5 Watanabe's N-alkylation of aniline. Reagents and conditions: $[Ru(PPh_3)_3Cl_2]$ (0.5 mol%), EtOH, 180 °C, 10 h or 17 h

Since the publication of these seminal pieces of work, the field of hydrogen borrowing catalysis has flourished, both in terms of the alcohols that can be utilised as the alkylating agent, as well as the substrates that can be alkylated. Primary alcohols have found widespread use in the alkylation of a range of substrates, whereas the use of secondary alcohols has generally been much more limited.

1.2 Related Methodologies

It is worth noting that there are related strategies to hydrogen borrowing catalysis that also involve the dehydrogenative activation of alcohols, but that are not strictly classified as 'hydrogen borrowing'. These reactions can broadly be termed dehydrogenative couplings and are overall oxidative in nature, typically extruding H_2 rather than 'returning' it to the back into the catalytic cycle. Notably, this process can be employed for the synthesis of esters and amides.

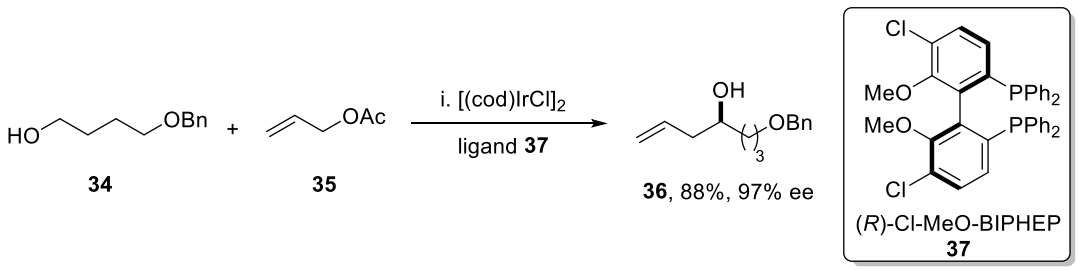
In an example of ester formation, Milstein and co-workers reported a ruthenium PNN pincer complex **33** which was able to catalyse the dehydrogenative coupling of primary alcohols into the corresponding esters.[15] In a representative example, 1-hexanol (**29**) could be converted into hexyl hexanoate (**30**) in 95% yield with the liberation of 2 equivalents of H_2 (**Scheme 1.6a**). The reaction is thought to proceed through initial oxidation of the alcohol to the aldehyde, followed by hemiacetal formation between the aldehyde and the alcohol. Oxidation of the hemiacetal then leads to the desired ester product.



Scheme 1.6 Milstein's Ru-catalysed ester and amide formation. Reagents and conditions: (i) [Ru] **33** (0.1 mol%), KOH (1 equiv), toluene, 115 °C, 24 h, (ii) [Ru] **33** (0.1 mol%), amine (1 equiv), alcohol (1 equiv), toluene, 115 °C, 7 h

Conceptually, the formation of an amide can be thought to proceed through a similar pathway, except that addition of the amine into the aldehyde would result in a hemiaminal, which on dehydrogenation gives the amide product. Milstein and co-workers were able to employ the same ruthenium PNN pincer complex in a protocol which demonstrated that a wide range of primary amines could be coupled with different primary alcohols to afford the corresponding amides.[16] For example, benzylamine (**31**) and 1-pentanol (**12**) could be coupled to form amide **32** in 97% yield (**Scheme 1.6b**). Several other groups have also reported extensively on the area, including, but not limited to, Williams,[17,18] Grützmacher,[19] Murashi,[20] Madsen[21] and Ishii.[22]

Another related strategy to hydrogen borrowing catalysis, developed by Krische and co-workers, exploits the dehydrogenative activation of alcohols in several transition metal-mediated carbonyl addition reactions. Unsaturated compounds can react with an aldehyde generated *in situ* (through oxidation) in C-C bond forming reactions that are ultimately redox neutral. A wide variety of π-unsaturated compounds have been reacted with carbonyl species using this methodology, with examples including propargylations,[23] crotylations[24] and allylations.[25] In a representative protocol, Krische and co-workers were able to employ $[(cod)IrCl]_2$ with chiral phosphine ligand **37** in an enantioselective hydrogenative coupling of allyl acetate (**35**) with a wide range of carbonyl substrates derived from the corresponding alcohol *via* oxidation. A variety of alcohols bearing functionality such as alkenes, benzyl ethers and alkyl chains could be accommodated in the procedure, affording good to excellent yields. For example, alcohol **34** could be allylated to form corresponding alcohol **36** in 88% yield and 97% enantiomeric excess (**Scheme 1.7**).



Scheme 1.7 Krische's enantioselective Ir-catalysed allylation of alcohols. Reagents and conditions: (i) $[(cod)IrCl]_2$ (2.5 mol%), (*R*)-Cl-MeO-BIPHEP (5 mol%), Cs_2CO_3 (20 mol%), *m*-NO_2BzOH (10 mol%), *i*PrOH (2 equiv), THF, 100 °C, 20 h

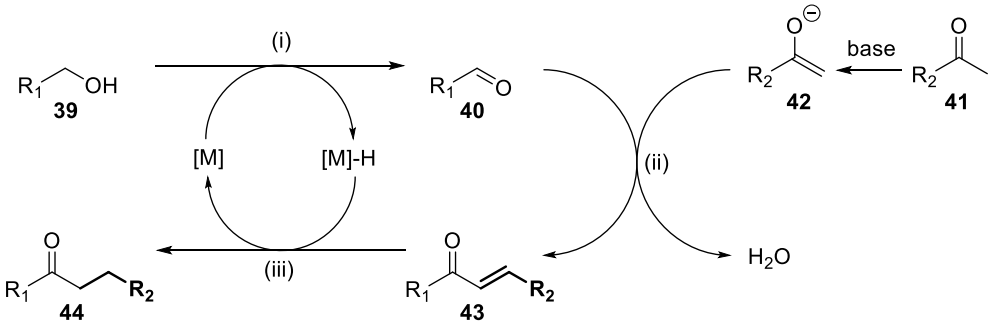
1.3 Hydrogen Borrowing Alkylation Reactions Using Primary Alcohols

Primary alcohols have found widespread use as alkylating agents for a variety of substrates under hydrogen borrowing catalysis conditions. Areas of key importance include: (i) the N-alkylation of amines, (ii) the α-alkylation of ketones and (iii) the alkylation of nitriles.[26,27] Many of the earlier reports within the area of hydrogen borrowing catalysis involved the development of methodology for the N-alkylation of amines and the alkylation of nitrile substrates. The focus herein will principally be on the alkylation of ketone substrates, with the alkylation of nitriles discussed briefly within the context of C-C bond forming reaction of activated methylene compounds (see **Chapter 1.3.2**). Reports relating to the N-alkylation of amines with respect to primary alcohols will not be discussed, but examples of this methodology will be covered within the context of the use of secondary alcohols in hydrogen borrowing catalysis (see **Chapter 1.4.2**).

1.3.1 Alkylation of Ketones

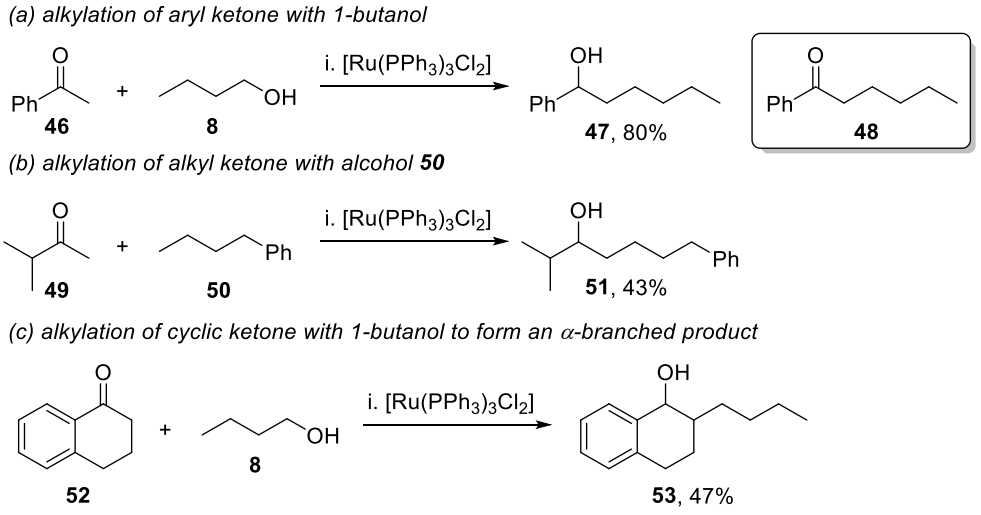
The alkylation of ketone substrates using alcohols *via* hydrogen borrowing catalysis has garnered a high level of interest. The use of hydrogen borrowing methodology for the construction of C-C bonds between ketones and alcohols has several advantages over conventional alkylation methods which typically involve the formation of an enolate, often using strong lithium bases, followed by reaction with alkylating agents such as alkyl halides. As well as the relatively high toxicity of alkyl halides when compared to alcohols, conventional alkylation methods also result in the formation of stoichiometric amounts of waste. In contrast, the alkylation of ketones using

alcohols results only in the formation of water as the stoichiometric by-product. The reaction is thought to proceed through (i) metal-mediated oxidation of an alcohol (**39**) to the aldehyde (**40**) (ii) enolate formation of ketone **41** and subsequent reaction with aldehyde **40** resulting in formation of corresponding enone **43** after elimination of water and (iii) reduction of the enone by the metal hydride species formed earlier, returning the 'borrowed' hydrogen and completing the catalytic cycle to afford alkylated ketone **44** (**Scheme 1.8**).



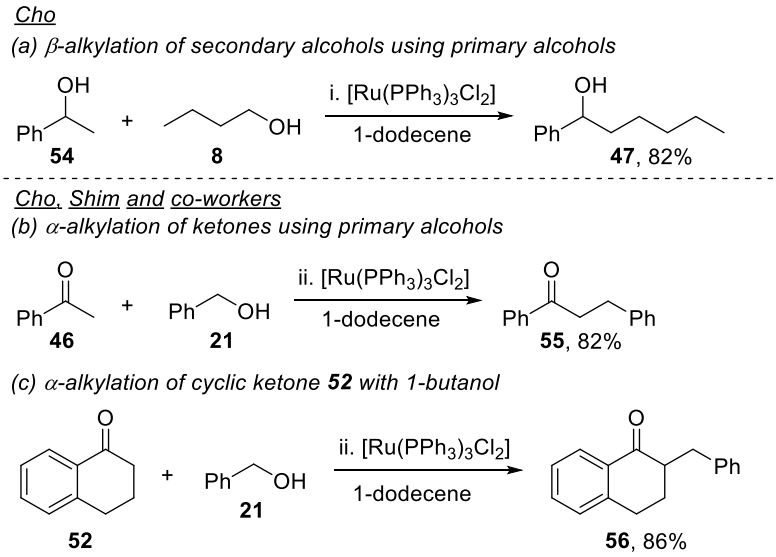
Scheme 1.8 α-Alkylation of ketones with alcohols using hydrogen borrowing catalysis

An influential publication came from the group of Cho, Shim and co-workers in 2001 when they attempted to conduct transfer hydrogenations of methyl substituted ketones using alcohols as the sacrificial source of hydrogen; instead they noted the formation of C-C coupled alcohol products.[28] Optimisation revealed ruthenium catalyst, $Ru(PPh_3)_3Cl_2$, to be the best at conducting the reaction. It was observed that aryl ketones, exemplified by the reaction of acetophenone (**46**), with 1-butanol (**8**) to yield alcohol **47** in 80% yield (**Scheme 1.9a**), typically resulted in higher yields than the reaction with alkyl ketones such as **49** (**Scheme 1.9b**). The oxidation level of the products is interesting as the authors use a three-equivalent excess of the primary alcohol. This, perhaps, leads to an abundance of metal hydride and therefore affords products at the alcohol oxidation level. On decreasing the amount of alcohol to one equivalent, an increased amount of ketone **48** was isolated. In addition, as the only example of the formation of an α-branched product, cyclic ketone **52** could be alkylated with 1-butanol (**8**) to afford **53** in 47% yield (**Scheme 1.9c**).



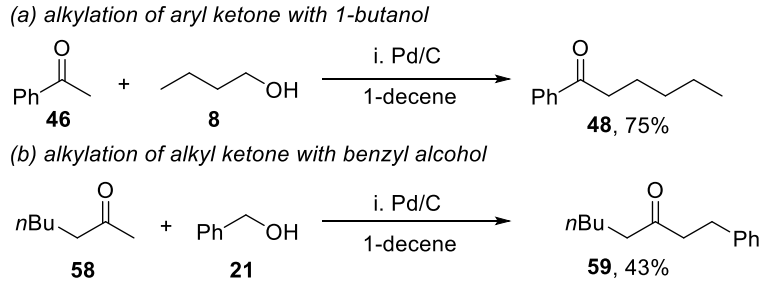
Scheme 1.9 Cho & Shim's alkylation of ketones. Reagents and conditions: (i) $Ru(PPh_3)_3Cl_2$ (5 mol%), alcohol (3 equiv), KOH (3 equiv), dioxane, 80 °C, Ar, 40 h

In another publication by Cho it was demonstrated that the same ruthenium based catalyst could facilitate the alkylation of secondary alcohols at the β-position using primary alcohols.[29] Using two alcohols as starting materials causes an imbalance in the oxidation and reduction steps, with two oxidations and one reduction required en-route to the desired alcohol product. Therefore, fundamental to the success of the reaction was the addition of 1-dodecene as a sacrificial hydride acceptor, which presumably aids turnover of the catalyst. Under these modified conditions, 1-phenylethanol (**54**) could be alkylated with 1-butanol (**8**) in 82% yield (**Scheme 1.10a**). In a separate report, when Cho, Shim and co-workers added 1-dodecene to their procedure for the alkylation of methyl ketones with alcohols, over-reduction of the products was avoided, this time affording the corresponding α-alkylated ketone products rather than the alcohol products as they had done so previously.[30] In representative examples, acetophenone (**46**) could be benzylated in 82% yield (**Scheme 1.10b**), and α-branched ketone **56** could be isolated in an 86% yield (**Scheme 1.10c**). Notably, the α-alkylation of aryl ketones proceeded in good to excellent yields, whereas the alkylation of alkyl ketones generally resulted in lower yields.



Scheme 1.10 (a) Cho's β-alkylation of secondary alcohols using primary alcohols (b) Cho and Shim's α-alkylation of ketones using primary alcohols. Reagents and conditions: (i) $Ru(PPh_3)_3Cl_2$ (5 mol%), primary alcohol (2 equiv), KOH (3 equiv), 1-dodecene (5 equiv), dioxane, 80 °C, Ar, 40 h, (ii) $Ru(PPh_3)_3Cl_2$ (2 mol%), primary alcohol (1 equiv), KOH (1 equiv), 1-dodecene (1 equiv), dioxane, 80 °C, Ar, 20 h

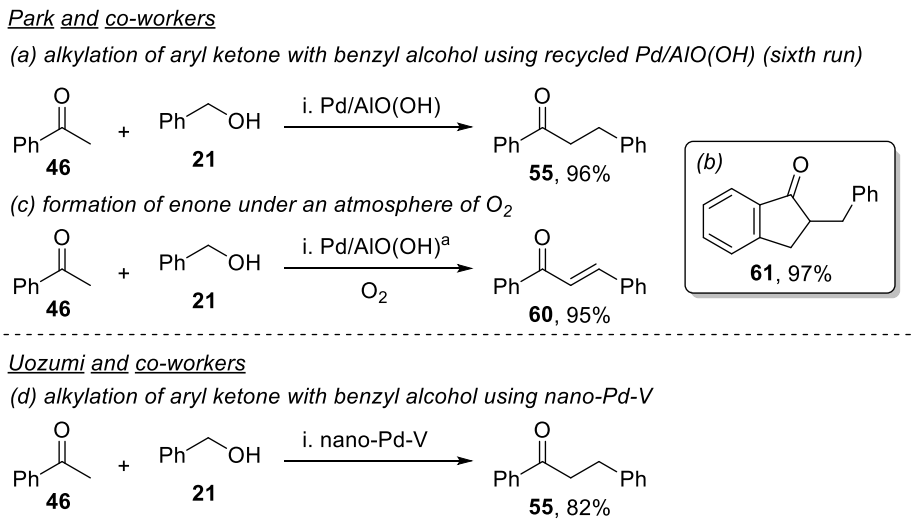
In addition to the Ru-catalysed protocol, Cho demonstrated that Pd/C was also capable of effectively catalysing the α-alkylation of methyl ketones with alcohols under an otherwise similar set of conditions.[31] Using 1-decene as a hydride scavenger instead of 1-dodecene, in a representative example, acetophenone (**46**) could be alkylated with 1-butanol (**8**) to afford **48** in 75% yield (**Scheme 1.11a**). Interestingly, alkyl ketones generally afforded relatively lower yields of the corresponding α-alkylated products in comparison to aryl ketones. As previously, it was interesting to note that only a single example of an α-branched product was given, resulting from α-benzylation of cyclic ketone 1-tetralone (**52**) in a moderate 46% yield.



Scheme 1.11 Cho's Pd-catalysed α-alkylation of ketones. Reagents and conditions: (i) 5% Pd/C (5 mol%), alcohol (2 equiv), KOH (3 equiv), 1-decene (4 equiv), dioxane, 100 °C, Ar, 40 h

Consistent with their Ru-catalysed protocol, the authors note that the alkylation is regioselective, as when both methyl and methylene sites are available, only the methyl site is alkylated; no α-branched products were observed. This is exemplified by the reaction of alkyl ketone **58** with benzyl alcohol (**21**) to provide **59** in 43% yield (**Scheme 1.11b**).

A heterogenous palladium catalyst, Pd/AlO(OH), composed of palladium nanoparticles entrapped in aluminium hydroxide, was reported by Park and co-workers as the first recyclable catalyst for the α-alkylation of ketones with alcohols.[32] Recovering the catalyst by filtration or decantation and recharging the reaction with the required equivalents of base, Pd/AlO(OH) was able to catalyse the alkylation of acetophenone (**46**) with benzyl alcohol to afford **55** in 96% yield even after six consecutive runs (**Scheme 1.12a**). Both electron-rich and electron-poor aryl, and alkyl, methyl ketones could be alkylated using benzylic and alkyl alcohols in excellent yields. The only example of an α-branched compound being formed was the α-alkylation of 1-indanone to give compound **61** (**Scheme 1.12b**).



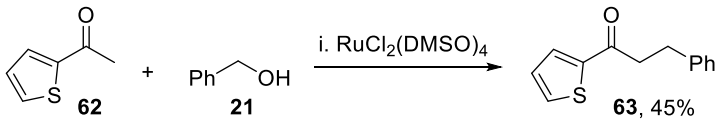
Scheme 1.12 Park's and Uozumi's Pd-catalysed α-alkylation of ketones using alcohols. Reagents and conditions: (i) Pd/AlO(OH) (0.2 mol%), K_3PO_4 (3 equiv), BnOH (1.2 equiv), toluene, 110 °C, Ar, 3 h, [a] under an O_2 atmosphere, 20 h. (ii) nano-Pd-V (5 mol%), BnOH (2 equiv), $Ba(OH)_2{\cdot}H_2O$ (1 equiv), H_2O (7 equiv), 80 °C, 12 h

Interestingly, when the reaction atmosphere was switched to oxygen, enone intermediate could **60** be isolated in 95% yield (**Scheme 1.12c**). The authors also noted that the reactions proceeded

much more slowly under oxygen. Presumably under this set of conditions, the metal hydride is sequestered by O_2, preventing the reduction of the α,β-unsaturated ketone.

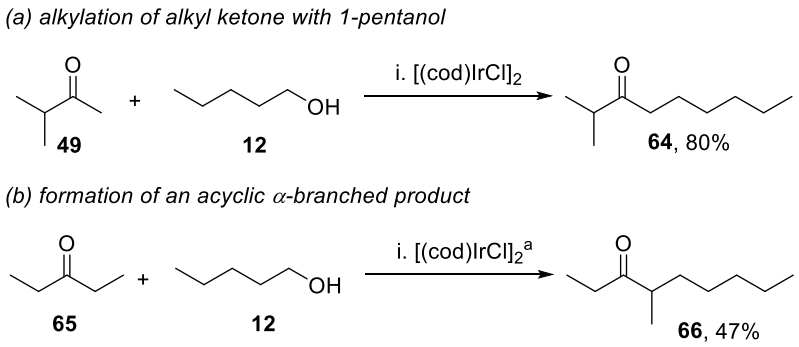
Another heterogenous palladium catalyst, nano-Pd-V, reported by Uozumi and co-workers consisted of palladium nanoparticles supported on viologen polymers assembled *via* a self-organisation process.[33] Also recyclable, this catalyst was shown to catalyse the α-alkylation of both alkyl and aryl ketones using a range of alkyl and benzylic alcohols in excellent yields. A representative example shows the alkylation of acetophenone (**46**) with benzyl alcohol, affording alkylated ketone **55** in 82% yield (**Scheme 1.12d**).

The group of Yus introduced another ruthenium catalyst, $RuCl_2(DMSO)_4$, which was demonstrated to be effective at performing the α-alkylation of methyl substituted ketones with primary alcohols.[34,35] Using their Ru-catalysed protocol, Yus and co-workers expanded the scope of ketone alkylation to include heteroaromatic methyl ketones, such as 2-thienyl ketone **62**, which could be alkylated with benzyl alcohol (**21**) to afford **63** in a moderate 45% yield (**Scheme 1.13**). In addition, both electron-rich and electron-poor aryl methyl ketones could be alkylated in moderate to excellent yields. This could be achieved without the use of a hydride scavenger such as 1-dodecene or 1-decene, which was vital in Cho and Shim's catalytic systems to afford good yields of the desired ketone products. With respect to the scope of the alcohols that could be utilised as alkylating agents, it was interesting to note that they predominantly consisted of primary benzylic alcohols. The only attempted reaction of acetophenone with an alkyl alcohol, 1-butanol, led to < 5% of the desired α-alkylated ketone being observed.



Scheme 1.13 Yus' α-alkylation of methyl ketones. Reagents and conditions: $RuCl_2(DMSO)_4$ (2 mol%), BnOH (1 equiv), KOH (1 equiv), 80°C, Ar, 24 h,

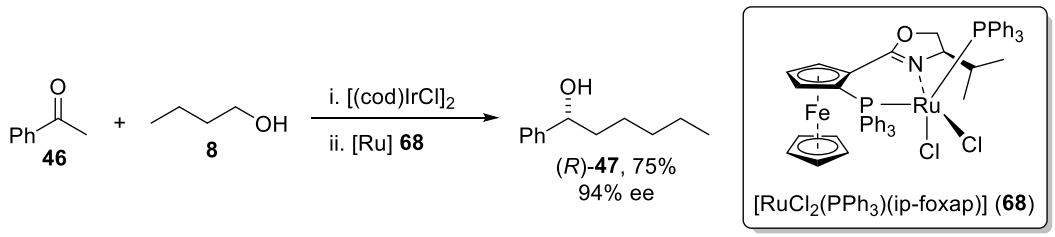
The group of Ishii were able to use their solvent-free, $[(cod)IrCl]_2/PPh_3$ system to effect the α-alkylation of both alkyl and aryl methyl ketones using benzylic and alkyl alcohols in excellent yields.[36] It was interesting to note that this methodology did not suffer from impaired yields when attempting the alkylation of alkyl ketones relative to aryl ketones. For example, alkyl ketone **49** could be alkylated with 1-pentanol (**12**) in 80% yield (**Scheme 1.14a**). In a rare example of the formation of an α-branched ketone from the alkylation of an acyclic methylene centre, branched product **66** could be isolated in a moderate 47% (**Scheme 1.14b**). In addition, no sacrificial hydride acceptor was required to prevent over-reduction of the ketone products, with the authors noting only trace amount of 1,2-reduction occurred in any particular example.



Scheme 1.14 Ishii's Ir-catalysed α-alkylation of ketones using alcohols. Reagents and conditions: (i) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (8 mol%), KOH (10 mol%), alcohol (2 equiv), 100 °C, Ar, 4 h, [a] using KOH (30 mol%)

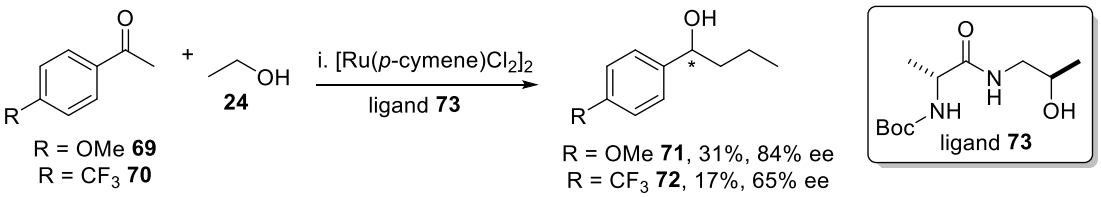
Another interesting report came from the Nishibayashi group, in which they had successfully coupled Ishii's $[(cod)IrCl]_2/PPh_3$ catalysed α-alkylation of ketones with a tandem ruthenium-catalysed asymmetric reduction of the ketone products to form enantiopure alcohols.[37] In a representative example, acetophenone (**46**) could be alkylated with 1-butanol, followed by an asymmetric Ru-catalysed reduction of the ketone to yield enantioenriched α-alkylated alcohol (*R*)-**47** in 75% yield and a 94% enantiomeric excess (**Scheme 1.15**). With respect to the scope of the ketones, it was interesting to note that only acetophenones, featuring both electron-poor and electron-rich aromatic rings, could be alkylated and reduced successfully under this protocol. No examples of alkyl ketones were demonstrated by the authors. In addition, the scope of the

alcohols was limited to alkyl, as an attempt at using benzylic alcohols resulted in no conversion to the desired products.



Scheme 1.15 Nishibayashi's tandem Ir-catalysed α-alkylation followed by Ru-catalysed asymmetric reduction. Reagents and conditions: (i) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (5 mol%), BuOH (3 equiv), 100 °C, 4 h, (ii) $[RuCl_2(PPh_3)(ip\text{-}foxap)]$ **68**(1 mol%), NaO*i*Pr (4 mol%), *i*PrOH, RT, 2 h

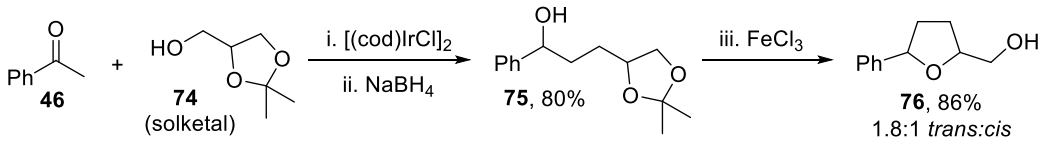
In an attempt to unify the hydrogen borrowing alkylation reaction and the asymmetric 1,2-reduction of the ketone under a single catalytic system, Adolfsson and co-workers had limited success using $[Ru(p\text{-cymene})Cl_2]_2$ with ligand **73**.[38] As the first example of such a process, they were able to show that their catalytic system was capable of carrying out both steps, although the yields of the enantioenriched alcohols achieved were low, and their enantiomeric excess generally moderate. The substrate scope was limited to aryl methyl ketones, but it was also interesting to note that electron-rich aryl ketones generally gave slightly higher yields and enantiomeric excesses. This can be highlighted by comparing the alkylation/reduction to form electron-rich aryl ketone **71**, isolated in 31% yield with 84% enantiomeric excess, whereas electron-poor aryl ketone **72** was formed in a lower 17% yield with only 65% enantiomeric excess (**Scheme 1.16**).



Scheme 1.16 Adolfsson's unified α-alkylation/reduction to form enantioenriched alcohols. Reagents and conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (0.5 mol%), ligand **73** (1 mol%), LiCl (10 mol%), KO*t*Bu (50 mol%), alcohol (3 equiv), DMSO, 65 °C to 40 °C, 5 h

Interestingly, the authors noted that addition of 10 mol% of LiCl had a positive effect on the catalytic activity and enantioselectivity of asymmetric transfer hydrogenations, though no discussion as to the origin of this effect was provided.

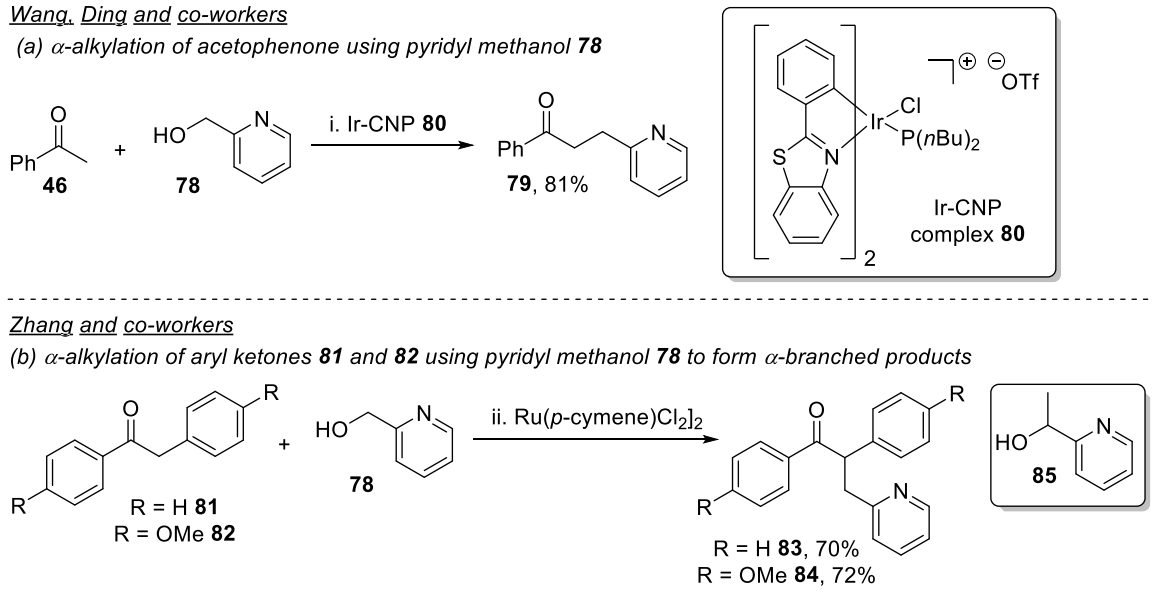
In a further adaption of Ishii's $[(cod)IrCl]_2/PPh_3$ protocol, the group of Rueping were able to employ the α-alkylation of methyl ketones in a sequential one-pot synthesis of tetrahydrofuran derivatives.[39] Using solketal (**74**), which could be synthesised by protection of glycerol with acetone, a range of both electron-poor and electron-rich aryl substituted methyl ketones could be alkylated. In a representative sequence, α-alkylated alcohol **75** could be formed in a two-step protocol, first undergoing Ir-catalysed alkylation with solketal (**74**) then reduction with $NaBH_4$, in 80% yield. Following deprotection and $FeCl_3$-mediated cyclisation, tetrahydrofuran **76** could be isolated in 86% yield as a 1.8:1 *trans*:*cis* mixture of diastereoisomers (**Scheme 1.17**).



Scheme 1.17 Rueping's sequential Ir-catalysed α-alkylation followed by cyclisation to form THFs. Reagents and conditions: : (i) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (6 mol%), $LiOH·H_2O$ (40 mol%), solketal (**74**) (1.8 equiv), toluene, 110 °C, 17 h, (ii) $NaBH_4$ (1 equiv), MeOH, 10 °C, 2 h, (iii) anhydrous $FeCl_3$ (1 equiv), CH_2Cl_2, RT, 45 mins

Wang, Ding and co-workers have reported an iridium CNP complex (**80**) which could catalyse the α-alkylation of a range of alkyl and aryl methyl ketones using both alkyl and benzylic alcohols in moderate to excellent yields.[40] Their protocol constituted one of the first methods to utilise pyridyl methanols as the alkylating agent for the α-alkylation of methyl ketones. In a representative example, acetophenone (**46**) could be alkylated using pyridyl methanol **78** to afford **79** in 81% yield (**Scheme 1.18a**). In a separate report, the group of Zhang also reported the α-alkylation of ketones using pyridyl methanols, though they utilised a ruthenium based catalyst, $[Ru(p\text{-cymene})Cl_2]_2$/Xantphos for the transformation.[41] Using their Ru-catalysed protocol, they successfully alkylated acetophenones featuring both electron-rich and electron-poor aromatic

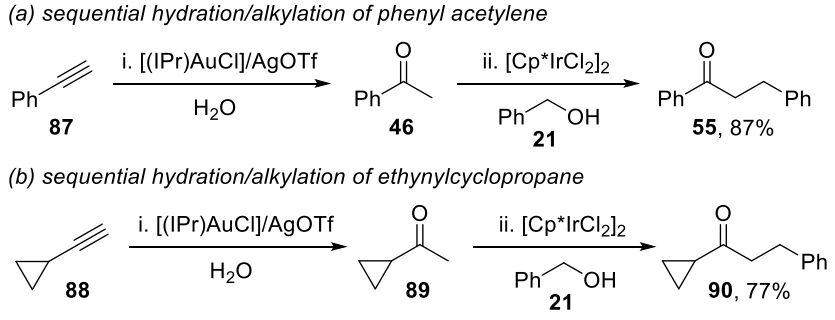
rings in moderate to good yields. Interestingly, they were able to form two α-branched products from acyclic methylene ketones, a type of transformation that is rarely observed in ketone alkylation chemistry. Acyclic methylene ketones **81** and **82** could be alkylated using pyridyl methanol **78** to form the corresponding α-branched products **83** and **84** in 70% and 72% yields respectively (**Scheme 1.18b**). Their protocol was, however, limited to the alkylation of aryl ketones, with no examples of alkyl ketones demonstrated. In addition, it was important to note that their attempt at the alkylation of acetophenone with secondary alcohol **85** did not result in any of the desired β-branched product.



Scheme 1.18 Wang & Ding's and Zhang's α-alkylation of ketones using pyridyl methanols. Reagents and conditions: Ir-CNP **80** (1 mol%), Cs_2CO_3 (1 equiv), alcohol (1.1 equiv), *t*-amyl alcohol, 120 °C, 24 h, (ii) $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%), Xantphos (1 mol%), KO*t*Bu (40 mol%), alcohol (1.2 equiv), 120 °C, 10 h

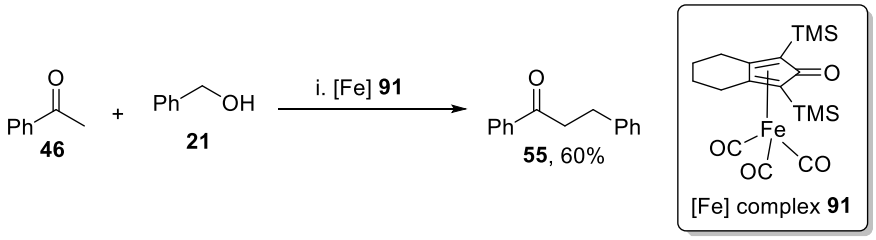
In a report by Li and co-workers, a sequential strategy involving the initial catalytic hydration of alkynes to methyl ketones using [(IPr)AuCl]/AgOTf, followed by the Ir-catalysed alkylation with alcohols was accomplished using microwave irradiation.[42] A wide range of substituted phenyl acetylenes underwent hydration to the corresponding methyl ketones followed by alkylation with both benzylic and alkyl alcohols in good to excellent yields. Although the majority of the starting materials consisted of substituted phenyl acetylenes, such as **87** (**Scheme 1.19a**), interestingly ethynylcyclopropane (**88**) could also be converted into the corresponding cyclopropyl methyl

ketone (**89**) (**Scheme 1.19b**). Using $[Cp^*IrCl_2]_2$, both the resulting acetophenone (**46**) and cyclopropyl methyl ketone (**89**) could be alkylated with benzyl alcohol to afford α-alkylated products **55** and **90** in 87% and 77% yields respectively. The authors noted that although they utilised $[Cp^*IrCl_2]$ for the α-alkylation step, $[(cod)IrCl]_2$ was just as effective, affording ketone product **55** in 85% yield.



Scheme 1.19 Li's hydration/alkylation sequence. Reagents and conditions: (i) [(IPr)AuCl]/AgOTf (1 mol%), H_2O (2 equiv), 1,4-dioxane, MW, 120 °C, 1 h, (ii) $[Cp^*IrCl_2]_2$ (1 mol%), alcohol (1.2 equiv), KO*t*Bu (30 mol%), MW, 130 °C, 2 h

All the catalysts discussed thus far, including ruthenium, palladium, iridium and rhodium, are based on expensive metals, owing to their low abundance in the Earth's crust. In terms of environmental sustainability, a move to cheaper, more abundant metals such as iron would be preferred. With respect to hydrogen borrowing catalysis and the alkylation of ketones, a key recent publication comes from Beller and co-workers who reported an iron-complex able to catalyse the α-alkylation of ketones using alcohols.[43] A wide range of substituted acetophenones, featuring both electron-rich and electron-poor aromatic rings could be alkylated using both benzylic and alkyl alcohols in moderate to good isolated yields. Using a Knölker-type iron complex, **91**, acetophenone (**46**) could be alkylated with benzyl alcohol in 60% yield (**Scheme 1.20**). Furthermore, in another example of the formation of an α-branched product from a cyclic ketone, 1-tetralone could be alkylated with benzyl alcohol under the protocol in 50% yield, though it required the use of KO*t*Bu instead of Cs_2CO_3 and a longer reaction time of 48 h.



Scheme 1.20 Beller's Fe-catalysed α-alkylation of ketones using alcohols. Reagents and conditions: [Fe] **91** (1 mol%), PPh_3 (2 mol%), Cs_2CO_3 (10 mol%), alcohol (1.3 equiv), toluene, 140 °C, 24 h

1.3.1.1 Using Methanol

As has been highlighted in the previous section, the vast majority of α-alkylation reactions of ketones using primary alcohols result in the formation of linear products of type **92**. Conversely, the α-alkylation of methylene ketones to form α-branched centres (**94**) using primary alcohols is very limited, with most examples pertaining to the alkylation of cyclic ketones 1-tetralone or 1-indanone **93** (**Figure 1.1**). Though this appears to be the case with long chain alcohols, methanol may be uniquely placed to form α-branched products, perhaps due to the small and reactive nature of the aldehyde produced upon oxidation. Indeed, reports from several groups have shown how methanol can be utilised to good effect in this regard, examples of which are discussed below.

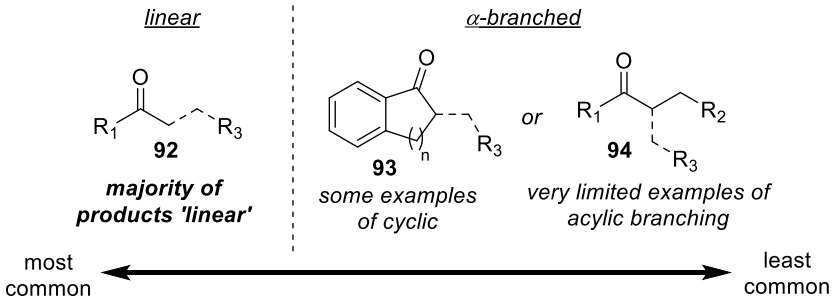
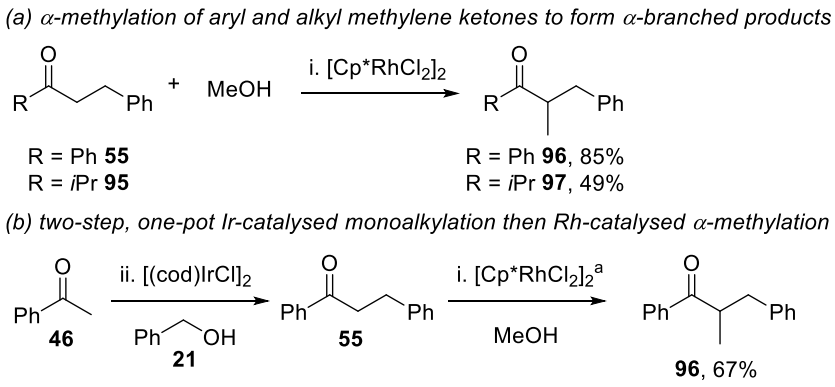


Figure 1.1 Relative prevalence of the types of motifs generated through the α-alkylation of ketones using primary alcohols *via* hydrogen borrowing catalysis

Donohoe and co-workers have recently demonstrated the use of a rhodium catalyst for the α-methylation of a range of aryl and alkyl methylene ketones using methanol as the alkylating agent in moderate to excellent yields.[44] Aryl ketones featuring both electron-rich and electron-poor rings were accommodated under the protocol. In representative examples, using

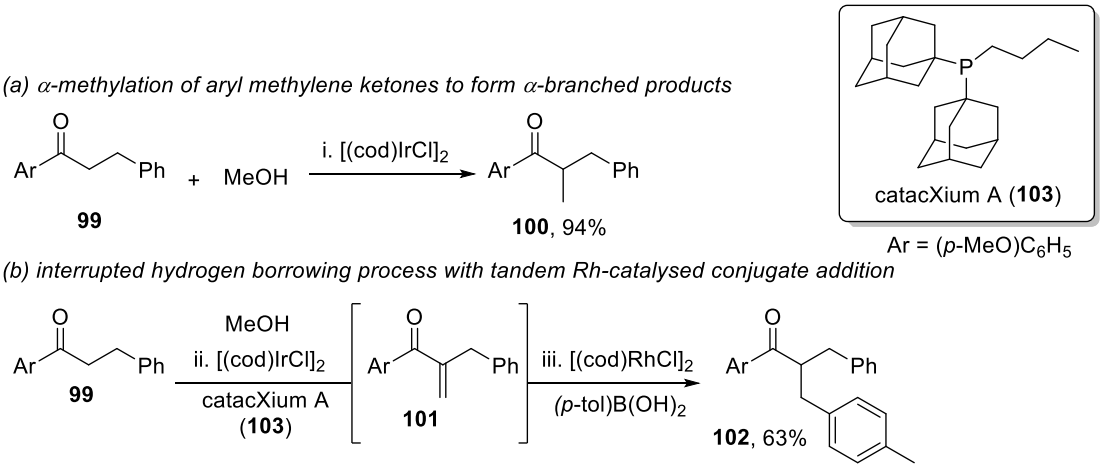
$[Cp^*RhCl_2]_2$, aryl ketone **55** could be methylated in 85% yield and alkyl ketone **95** in 49% yield (**Scheme 1.21a**). In addition, they were able to demonstrate a two-step, one-pot catalytic procedure for the double sequential alkylation of methyl ketones, first with a long chain primary alcohol then with methanol under their developed protocol. The first step involving the α-alkylation of the methyl ketone with a long chain primary alcohol was adapted from Ishii and co-workers and utilised their $[(cod)IrCl]_2/PPh_3$ system,[36] exploiting the fact that double alkylation to form an α-branched centre would not occur under these conditions. An example highlighting this two-step procedure began with the reaction of acetophenone and benzyl alcohol, followed by α-methylation with methanol to give α-branched product **96** in 67% yield over two-steps (**Scheme 1.21b**). Unusually, the Rh-catalysed protocol is conducted under an atmosphere of oxygen as it was found to be beneficial for the reaction.



Scheme 1.21 Donohoe's α-methylation of methylene ketones to form α-branched products. Reagents and conditions: (i) $[Cp^*RhCl_2]_2$ (5 mol%), Cs_2CO_3 (5 equiv), MeOH, O_2, 65 °C, 48 h, [a] 12 h (ii) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (10 mol%), BnOH (2 equiv), 100 °C, 4 h

In a later report, Donohoe and co-workers showed that methylation of *p*-methoxyphenyl substituted aryl ketones could also be conducted with $[(cod)IrCl]_2/PPh_3$ to form the corresponding α-methylated products,[45] for example, methylene ketone **99** could be α-alkylated in an excellent 94% yield (**Scheme 1.22a**). Interestingly, by varying the phosphine ligand utilised with the iridium catalyst from PPh_3 to the sterically bulkier catacXium A (**103**), the reduction of the enone intermediate could be prevented, thus allowing it to be interrupted with a nucleophile in a tandem

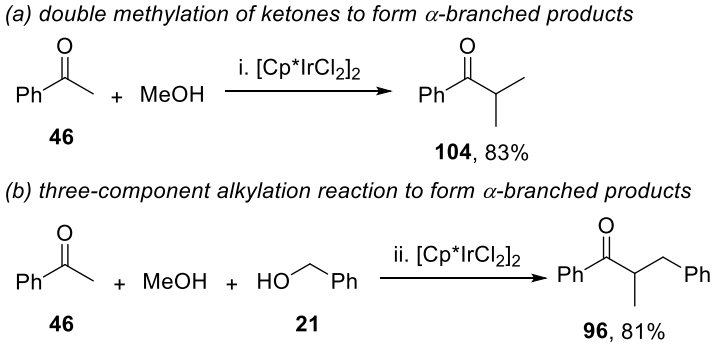
conjugate addition sequence. Driven by the desire to overcome the limited scope of α-branched products that could be formed (i.e. with cyclic ketones or using MeOH), a range of nucleophiles were successfully employed to 'interrupt' the process. In a representative procedure, aryl ketone **99** could be subjected to the interrupted hydrogen borrowing process, with the intermediate enone **101** intercepted with a rhodium-catalysed conjugate addition of (*p*-tol)$B(OH)_2$ to form the resulting doubly benzylated, α-branched ketone **102** in 63% yield (**Scheme 1.22b**).



Scheme 1.22 Donohoe's Ir-catalysed α-methylation and tandem interrupted/conjugate addition procedure. Reagents and conditions: (i) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (2 equiv), MeOH, 65 °C, 48 h, (ii) $[(cod)IrCl]_2$ (2 mol%), catacXium A (**103**) (8 mol%), KOH (3 equiv), MeOH, 65 °C, 48 h, (iii) $[(cod)RhCl]_2$ (2.5 mol%), 1,5-cyclooctadiene (10 mol%), KOH (3 equiv), *p*-tolylboronic acid (5 equiv), 100 °C, 6 h

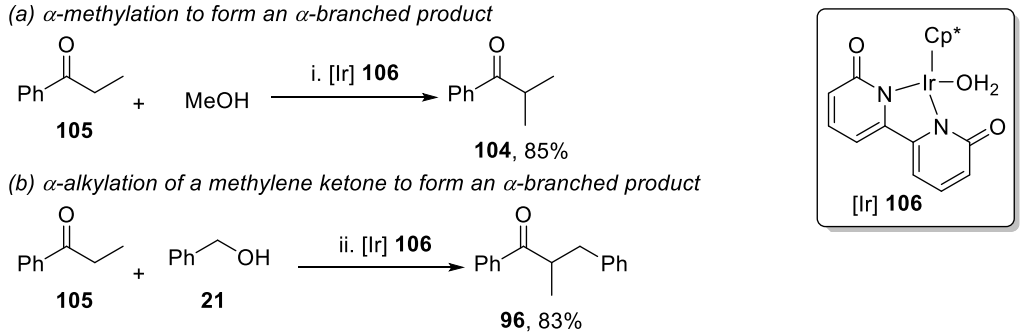
Obora and co-workers have also reported an Ir-catalysed protocol for the methylation of ketones to form α-branched products.[46] Using $[Cp^*IrCl_2]_2$, they were able to α-methylate several aryl and alkyl methylene ketones. Although most starting materials were methyl ketones, α-branched centres were often formed from double methylation reactions, e.g. compound **104** (**Scheme 1.23a**). In addition, similar to the Donohoe group, the authors could perform sequential alkylation reactions with both a long chain primary alcohol and methanol. In contrast to the procedure by Donohoe and co-workers, which required sequential addition of the two alcohols, this protocol allowed all three components (ketone, long chain primary alcohol, and methanol), to be added together at the beginning of the reaction. An example highlighting this involved the

reaction of acetophenone with benzyl alcohol and methanol to afford α-branched compound **96** in 81% yield (**Scheme 1.23b**). It was interesting to note that in the three-component reaction, the long chain alcohol was used as the limiting reagent with the ketone used in a two-fold excess.



Scheme 1.23 Obora's Ir-catalysed α-methylation reaction to form branched products. Reagents and conditions: $[Cp^*IrCl_2]_2$ (5 mol%), KOH (50 mol%), MeOH, 120 °C, 15 h, (ii) $[Cp^*IrCl_2]_2$ (5 mol%), KOH (50 mol%), BnOH (1 equiv), acetophenone (2 equiv), 140 °C, 15 h

Li and co-workers were able to apply a Cp*Ir complex featuring a functional bypyridonate ligand **106** to the α-alkylation of methylene aryl ketones with methanol to form α-branched centres, as well as alkylation of methyl ketones with long chain alcohols to form linear products.[47] Ethyl substituted aryl ketone **105** could be methylated to form α-branched compound **104** in 85% yield (**Scheme 1.24a**).

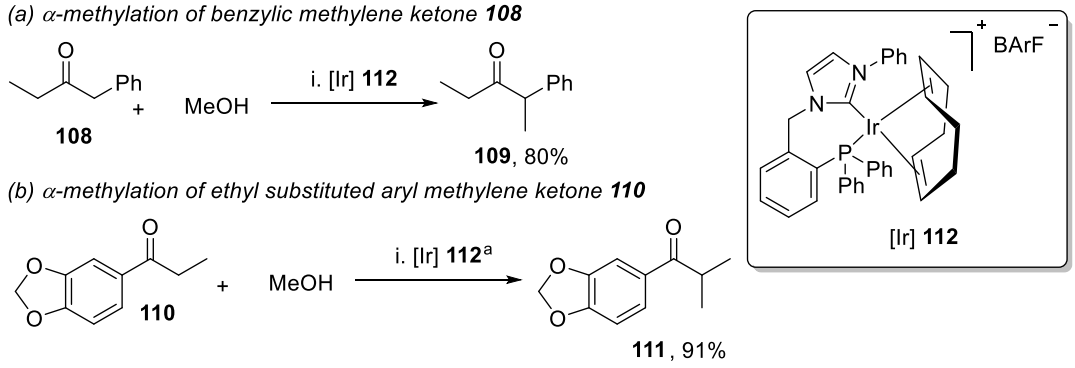


Scheme 1.24 Li's Ir-catalysed α-alkylation reaction to form branched products. Reagents and conditions: [Ir] **106** (2 mol%), Cs_2CO_3 (30 mol%), MeOH, 65 °C, 12 h, (ii) [Ir] **106** (1 mol%), Cs_2CO_3 (10 mol%), BnOH (1.1 equiv), *t*-amyl alcohol, 100 °C, 6 h

In a rare example of the formation of an α-branched centre from an acyclic methylene ketone, ketone **105** could also be alkylated with benzyl alcohol to afford product **96** in 83% yield (**Scheme**

1.24b). The authors propose that bypyridonate ligand **106** plays a functional role in the reaction mechanism by shuttling a proton between the alcohol during oxidation and the enone on reduction.

The group of Andersson introduced an NHC-phosphine iridium complex (**112**) which was also very active in the α-methylation of methylene ketones with methanol to form α-branched centres.[97] The vast majority of the ketones that underwent alkylation were acetophenones or substituted acetophenones, with only two examples of alkyl ketones being methylated. The majority of the methylene side chains being methylated were either benzylic positions, as demonstrated by the methylation of ketone **108** to afford **109** in 80% yield (**Scheme 1.25a**) or methylation of ethyl chains, as exemplified by the alkylation of ketone **110** to provide **111** in 91% yield (**Scheme 1.25b**).



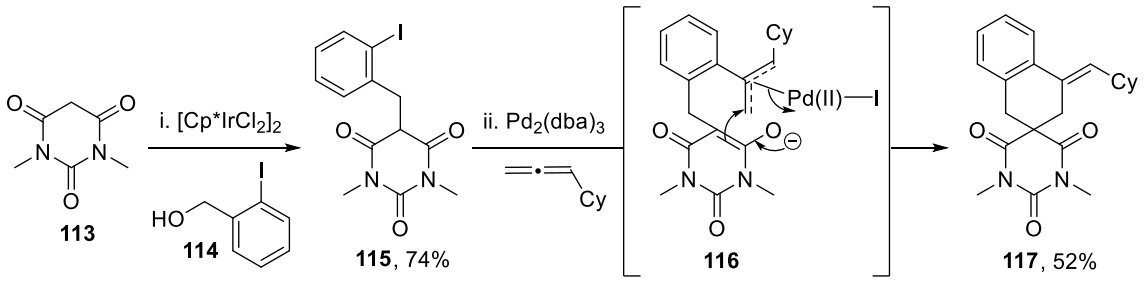
Scheme 1.25 Anderrson's Ir-catalysed α-alkylation reaction to form branched ketones. Reagents and conditions: (i) [Ir] **112** (1 mol%), Cs_2CO_3 (5 equiv), MeOH, 65 °C, 24 h, [a]using Cs_2CO_3 (4 equiv)

1.3.2 Alkylation of Activated Methylene Centres to Form Branched Products

As discussed in the previous section, the α-alkylation of ketones to afford α-branched products is fairly limited. Where α-branched ketones have been formed with long chain alcohols, the ketone starting materials have usually been cyclic in nature. Methodologies that have, on the rare occasion, accommodated the formation of acyclic α-branched ketones using long chain alcohols, are highlighted in the previous section. Indeed, the majority of α-branched products formed have resulted from the use of methanol as the alkylating agent.

Aside from ketones, it is worth noting that hydrogen borrowing methodologies for the alkylation of compounds featuring activated methylene groups to form branched centres with long chain primary alcohols have also been reported by several authors. The reactions typically follow an analogous mechanism to that of the alkylation of ketones. After deprotonation of the activated methylene centre, addition to the aldehyde (formed *via* oxidation) through a Knoevenagel condensation reaction and reduction of the unsaturated compound results in the alkylated product. Reports of this type are discussed below.

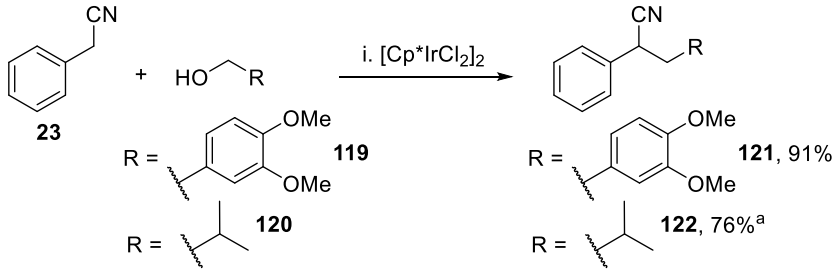
One such example reported by Grigg and co-workers demonstrated that 1,3-dimethylbarbituric acid could be alkylated *via* an Ir-catalysed microwave assisted protocol using both benzylic and alkyl primary alcohols to afford the corresponding 5-monoalkylated barbituric acid derivatives.[48] For example, derivative **115** could be isolated in 74% following alkylation with benzyl alcohol **114** using $[Cp^*IrCl_2]_2$. In addition, certain products from the alkylation reaction were amenable to a sequential one-pot procedure which involved a second palladium-catalysed reaction with an allene to afford spirocyclic products, such as **117** which could be isolated in 52% yield (**Scheme 1.26**). The Pd-catalysed step was thought to proceed *via* allene insertion to the arylpalladium(II) iodide species to generate a π-allyl intermediate **116**, followed by cyclisation to afford the spirocyclic compound.



Scheme 1.26 Grigg's alkylation of 1,3-dimethylbarbituric acid. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2.5 mol%), KOH (15 mol%), alcohol (1.5 equiv), PhMe, 110 °C, MW, 10 min, (ii) Pd_2dba_3 (5 mol%), TFP (20 mol%), K_2CO_3 (2 equiv), allene (1.2 equiv), CH_3CN, MW, 110 °C, 20 min

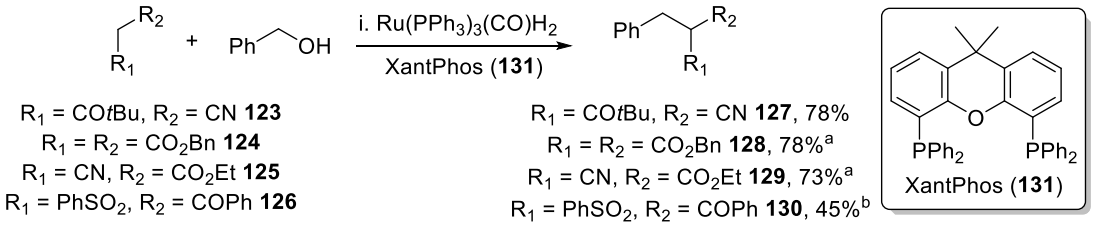
Using the same catalytic system, the group of Grigg have also reported the alkylation of arylacetonitrile substrates with primary alcohols to form branched centres using microwave

irradiation.[49] Arylacetonitriles featuring both electron-poor and electron-rich aromatic rings could be alkylated using predominantly benzylic alcohols, though two alkyl alcohols were also included within the scope. As well as phenyl rings, the acetonitrile compound could also accommodate pyridyl rings without loss of yield for the alkylation step. In representative examples, arylacetonitrile **23** could be alkylated with benzylic alcohol **119** to afford **121** in 91% yield, and with alkyl alcohol **120** to provide **122** in 76% yield (**Scheme 1.27**).



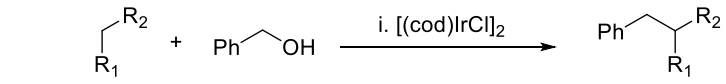
Scheme 1.27 Grigg's alkylation of arylacetonitriles. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2.5 mol%), KOH (15 mol%), alcohol (3 equiv), 100 °C, MW, 14 h, [a]alcohol used as solvent

Williams and co-workers have reported the alkylation of several activated methylene compounds using $Ru(PPh_3)_3(CO)H_2$/Xantphos as the catalyst.[50] The majority of the examples feature the alkylation of ketonitrile substrates, which underwent the oxidation-Knoevenagel-reduction process with several benzylic and aliphatic alcohols to provide the corresponding alkylated products. In a representative example, ketonitrile **123** could be alkylated with benzyl alcohol in 78% yield. In addition, dibenzyl malonate **124** could be alkylated in 78% yield, cyanoester **125** in 73% yield and sulfone **126** in a moderate 45% yield (**Scheme 1.28**).



Scheme 1.28 Williams' alkylation of activated methylene compounds. Reagents and conditions: (i) $Ru(PPh_3)_3(CO)H_2$ (0.5 mol%), XantPhos (0.5 mol%), piperidinium acetate (5 mol%), PhMe, 110 °C, 4 h, [a] using $Ru(PPh_3)_3(CO)H_2$ (5 mol%), XantPhos (5 mol%), piperidinium acetate (25 mol%), 24 h, [b] using $Ru(PPh_3)_3(CO)H_2$ (2 mol%), XantPhos (2 mol%), piperidinium acetate (25 mol%)

Ishii and co-workers were able to apply their $[(cod)IrCl]_2/PPh_3$ system to a similar set of activated methylene substrates.[51] Choosing to optimise their system on butyl cyanoacetate, many of the examples demonstrate the alkylation of this methylene compound with both aliphatic and benzylic alcohols in good to excellent yields. Whereas Williams' protocol required piperidinium acetate to catalyse the condensation step, the procedure from Ishii and co-workers required no additive for the majority of the transformations. Alkylation of dibutyl malonate **134**, however, required the addition of Cs_2CO_3. In examples showing the alkylation of a variety of activated methylene substrates, ethylcyanoacetate (**125**) could be alkylated with 1-butanol in 75% yield, ketonitrile **133** in 66% yield and dibutyl malonate (**134**) in 80% yield (**Scheme 1.29**).

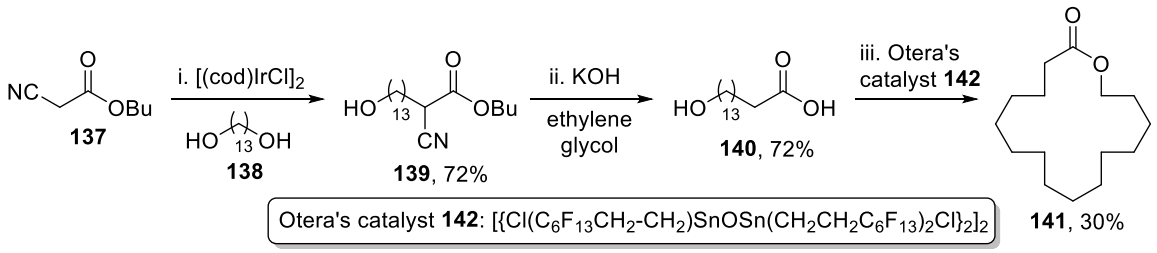


$R_1 = CO_2Et$, $R_2 = CN$ **125**
$R_1 = COPh$ $R_2 = CN$ **133**
$R_1 = R_2 = CO_2Bu$ **134**

$R_1 = CO_2Et$, $R_2 = CN$ **129**, 75%
$R_1 = COPh$ $R_2 = CN$ **135**, 66%
$R_1 = R_2 = CO_2Bu$ **136**, 80%[a]

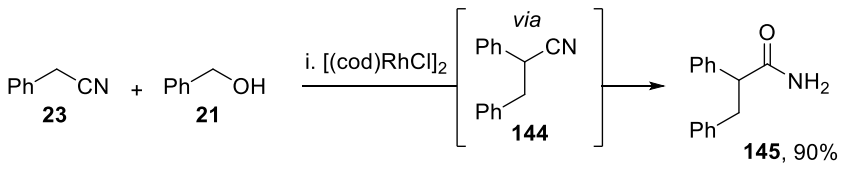
Scheme 1.29 Ishii's alkylation of activated methylene compounds. Reagents and conditions: $[(cod)IrCl]_2$ (5 mol%), PPh_3 (20 mol%), alcohol (2 equiv), *p*-xylene, 130 °C, 15 h, [a] using dibutyl malonate (**134**) (4 equiv), $[(cod)IrCl]_2$ (5 mol%), dppe (10 mol%), Cs_2CO_3

With some optimisation to incorporate diols as alkylating agents for butyl cyanoacetate, Ishii and co-workers were able to use their methodology and apply it to the synthesis of cyclopentadecanolide (CPDL), also known as synthetic musk.[52] Using $[(cod)IrCl]_2/PPh_3$, butyl cyanoacetate **137** could be reacted with diol **138** to afford the α-branched compound **139** in 72% yield. Subjection of **139** to KOH in ethylene glycol led to formation of hydroxy acid **140** which could be cyclised to form CPDL (**141**) in 30% yield using Otera's catalyst (**142**) (**Scheme 1.30**).



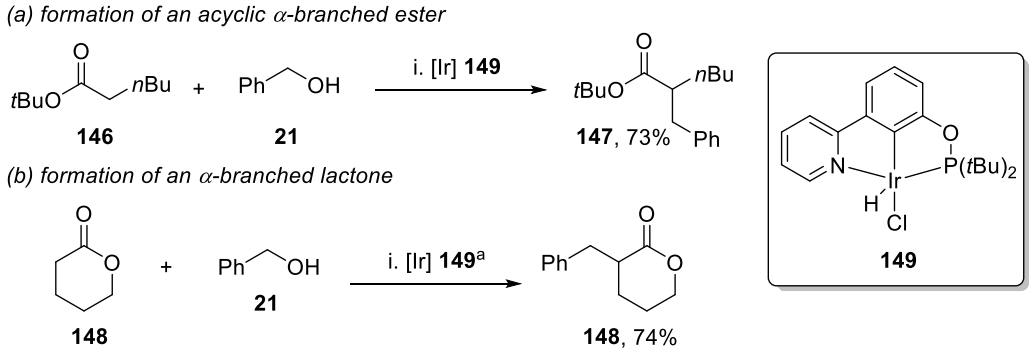
Scheme 1.30 Ishii's synthesis of CPDL *via* alkylation of butyl cyanoacetate using a diol. Reagents and conditions: (i) $[(cod)IrCl]_2$ (5 mol%), PPh_3 (20 mol%), diol (3 equiv), dioxane, 120 °C, 20 h, (ii) KOH (4 equiv), ethylene glycol, 200 °C, 6 h, (iii) Otera's catalyst **142** (10 mol%), perfluorohexane/decane, 150 °C, 5 h

Another interesting report came from Li and co-workers where they successfully employed a $[(cod)RhCl]_2/PPh_3$ system in the alkylation of arylacetonitriles with primary alcohols using microwave irradiation.[53] Unlike the method reported by Grigg and co-workers (discussed above), the products resulting from the reaction were α-alkylated arylacetamides. The authors propose that after initial alkylation of the arylacetonitriles with primary alcohols, the water generated from the Knoevenagel condensation step leads to hydrolysis of the nitrile groups and therefore results in arylacetamides as the products. A range of arylacetontriles featuring both electron-poor and electron-rich aromatic rings could be tolerated in the procedure. The scope with respect to the alcohols included both aliphatic and benzylic alcohols, resulting in good to excellent yields of the products. In a representative example phenylacetonitrile (**23**) could be alkylated with benzyl alcohol, presumably *via* the alkylated arylacetonitrile species **144**, to the α-benzylated arylacetamide **145** in 90% yield (**Scheme 1.31**). When the reaction was conducted in the presence of 4Å molecular sieves, the alkylated arylacetonitrile compound **144** and arylacetamide **145** were formed in a reversed 93:7 ratio, indicating that water generated by the reaction may indeed be of importance for the hydrolysis of the nitrile.



Scheme 1.31 Li's Rh-catalysed alkylation of arylacetonitriles to form α-alkylated arylacetamides. Reagents and conditions: (i) $[(cod)RhCl]_2$ (1 mol%), PPh_3 (10 mol%), KOH (40 mol%), BnOH (1.1 equiv), *t*-amyl alcohol, MW, 130 °C, 2 h

In a key recent publication by Huang and co-workers, the α-alkylation of unactivated esters with primary alcohols was reported using an iridium/NCP pincer complex **149**.[54] Interestingly, the alkylation of methylene *t*butyl esters to form α-branched esters was demonstrated (four examples), as exemplified by the alkylation of ester **146** using benzyl alcohol to afford **147** in 73% yield (**Scheme 1.32a**). The majority of examples reported, however, involved the α-alkylation of lactones, such as lactone **148** with benzyl alcohol (**Scheme 1.32b**). The scope with respect to the alcohols was predominantly limited to benzylic alcohols (three examples of alkyl alcohols reported). Notably, acyclic α-branched products were only formed from *t*butyl esters, with other esters affording 'linear' products. In addition, it was interesting to note that the reaction is conducted at 60 °C, which is on the low end of the scale for hydrogen borrowing alkylation reactions.



Scheme 1.32 Huang's Ir-catalysed alkylation of unactivated esters to form α-branched products. Reagents and conditions: (i) [Ir] **149** (0.5 mol%), KO*t*Bu (1.5 equiv), ester (1.2 equiv), toluene, 60 °C, 12 h, [a] [Ir] **149** (2 mol%), LiO*t*Bu (2 equiv) instead of KO*t*Bu

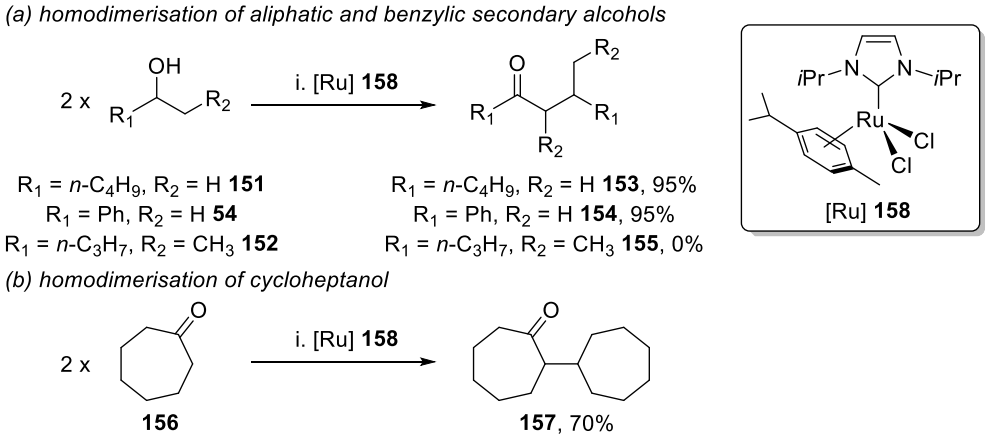
1.4 Alkylation Reactions Using Secondary Alcohols

While the use of primary alcohols in alkylation reactions has been widespread, the use of secondary alcohols has been much more limited. Secondary alcohols have predominantly been utilised in Guerbet-type dimerisation processes, a methodology related to hydrogen borrowing catalysis. In hydrogen borrowing catalysis, the use of secondary alcohols has centred around the N-alkylation of amines, N-heterocyclisation reactions and the alkylation of nitriles. Examples pertaining to the use of secondary alcohols under these methodologies will be discussed below.

1.4.1 Guerbet-type Dimerisations

The Guerbet reaction, which was introduced previously (see **Chapter 1.1**), involves the homodimerisation of primary and secondary alcohols and has been known for more than a century.[4] Typically conducted in the presence of metal alkoxides and requiring elevated temperatures, often exceeding 200-250 °C, hydrogen transfer leads to the β-branched alcohols. More recently, many heterogenous and homogenous catalytic systems have been reported, allowing the reaction to proceed at lower temperatures 100–150 °C.[5] The majority of the reports concern either the homodimerisation of primary alcohols, or the β-alkylation of secondary alcohols using primary alcohols (some examples of which are discussed in **Chapter 1.3.1**).[29] In what can be thought of as a dehydrogenative Guerbet reaction, the ketone can be isolated as the major product as opposed to the branched alcohol that is typically isolated. Conceptually, two molecules of alcohol are oxidised to produce two equivalents of H_2, one equivalent of which is 'returned' the to α,β-unsaturated ketone, whereas the other is given off as H_2 gas. Examples of heterogenous catalysts that can achieve this have been reported, though predominantly concern the reaction of 1-phenylethanol with primary alcohols.[55–57] Examples highlighted in this section use secondary alcohols as the alkylating agent using homogenous catalytic systems in dehydrogenative couplings that furnish ketones as the major products.

The first homogenous catalytic system for the homodimerisation of secondary alcohols *via* this methodology was reported by Madsen and co-workers, who were able to employ their Ru-catalysed protocol to furnish β-branched ketones.[58] A wide range of secondary alcohols, both benzylic and aliphatic were accommodated under the reaction conditions. For example, both the dimerisation of 1-phenylethanol (**54**) and dimerisation of aliphatic secondary alcohol **151** resulted in the corresponding β-branched ketones **153** and **154**, both in 95% yields (**Scheme 1.33a**). Interestingly, when at least either one of the R_1 and R_2 substituents was not a methyl group (i.e. both featured a longer chain alkyl group or an aromatic ring e.g. alcohol **152**), the reaction did not proceed at all. Cycloalkanols reacted under the conditions but both cyclopentanol and cyclohexanol resulted in mixtures of α-monosubstituted and α,α-disubstituted products. However, cycloheptanol (**156**) could react to give the corresponding monoalkylated product (**157**) in 70% yield (**Scheme 1.33b**).



Scheme 1.33 Madsen's Ru-catalysed homodimerisation of aliphatic and benzylic secondary alcohols. Reagents and conditions: [Ru] **158** (2 mol%), $PCy_3{\cdot}HBF_4$ (2 mol%), KOH (1.1 equiv), toluene, 110 °C, 24 h

Gelman and co-workers reported iridium and ruthenium based PC(sp^3)P pincer complexes **159** and **160** (**Figure 1.2a**) which were also able to catalyse the homodimerisation of secondary alcohols, affording β-branched ketones in excellent yields.[59] A key limitation of this methodology, however, was that the scope of the secondary alcohols was limited to the use of 1-phenylethanols,

containing both electron-rich and electron-poor aromatic rings. For example, 1-phenylethanol could be homodimerised to give β-branched ketone **154** in 94% yield.

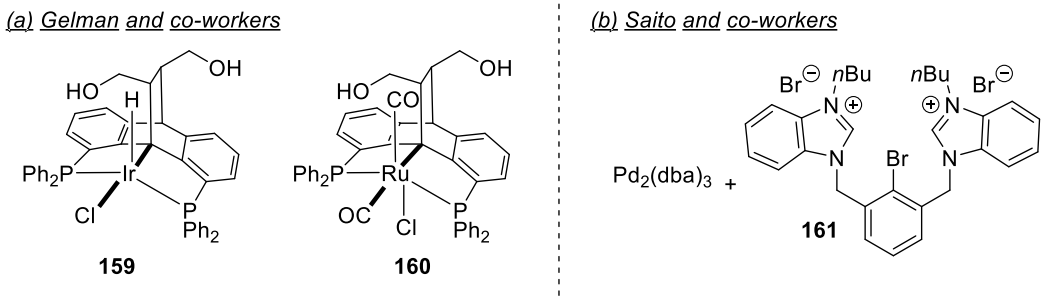


Figure 1.2 Homodimerisation of secondary alcohols: (a) Gelman's iridium and ruthenium catalysts (b) Saito's palladium catalyst

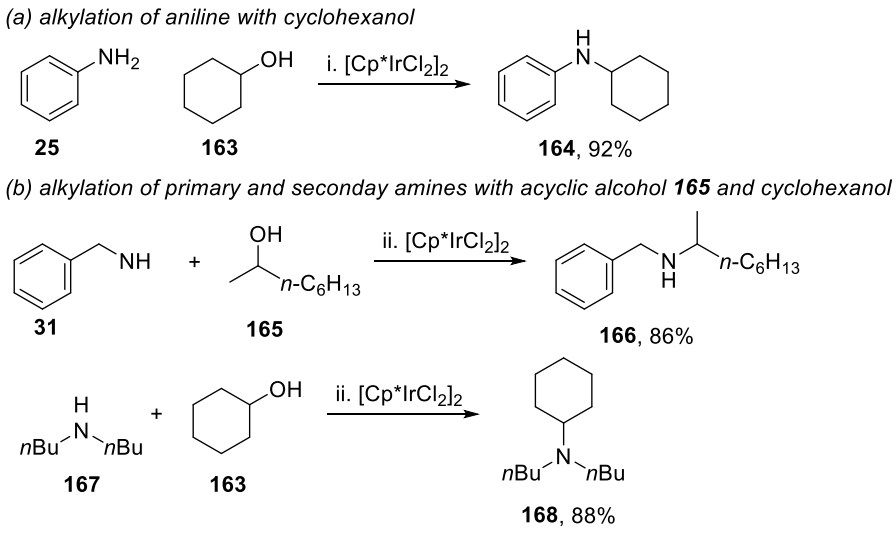
Saito and co-workers reported a $Pd_2(dba)_3$/ligand **161**, NHC pincer-type complex, (**Figure 1.2b**) which catalysed the homodimerisation of alcohols, though they were only able to a demonstrate a single example pertaining to secondary alcohols. This involved the homodimerisation of 1-phenylethanol, affording corresponding ketone **154** product in 70% yield.[60]

1.4.2 Alkylation of Amines Using Hydrogen Borrowing Catalysis

C-N bond formation *via* N-alkylation of amines using alcohols under hydrogen borrowing catalysis conditions has garnered widespread attention since the seminal publications of the groups of Grigg and Watanabe in 1981[12,14] and is perhaps one of the most extensively reported on areas of hydrogen borrowing catalysis alongside the alkylation of ketones.[61] The mechanism is thought to be analogous to the α-alkylation of ketones, where the nucleophile is an amine instead of a ketone enolate. On condensation of an amine with an aldehyde or ketone (produced *in situ* from the oxidation of an alcohol precursor), the resulting imine can be reduced by the 'borrowed' hydrogen to furnish the alkylated amine product. Much of the earlier work predominantly focused on the alkylation of amines using primary alcohols, though more recently, general methods for the alkylation of both primary and secondary amines using secondary alcohols have been reported by several groups and some examples are highlighted below.

Fujita and co-workers, who have published extensively in this area, reported an early example of the alkylation of primary amines with cyclopentanol and cyclohexanol using $[Cp^*IrCl_2]_2$ as the catalyst.[62] For example, aniline (**25**) could be alkylated with cyclohexanol (**163**) to afford **164** in an excellent yield of 92% (**Scheme 1.34a**).

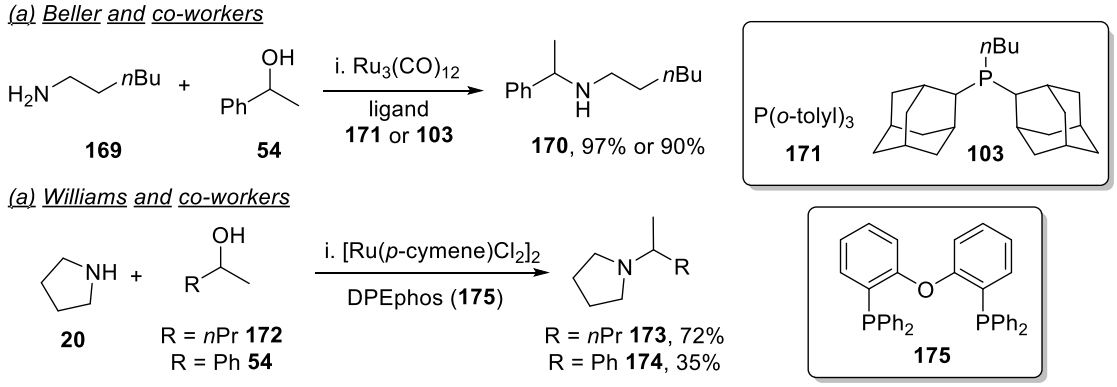
In a later report, the authors were able to extend this methodology under a slightly modified set of conditions utilising $[Cp^*IrCl_2]_2$ to incorporate acyclic secondary alcohols such as **165** as the alkylating agent.[63] Secondary amines could also be accommodated under these conditions. In a representative examples, benzylamine (**31**) could be alkylated by acyclic alcohol **165** in 86% yield and dibutylamine (**167**) could be alkylated with cyclohexanol (**163**) in 88% yield (**Scheme 1.34b**).



Scheme 1.34 Fujita's Ir-catalysed alkylation of amines using secondary alcohols. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2.5 mol%), K_2CO_3 (5 mol%), alcohol (1 equiv), toluene, 110 °C, 17 h, (ii) $[Cp^*IrCl_2]_2$ (3 mol%), $NaHCO_3$ (3 mol%), alcohol (1 equiv), toluene, 110 °C, 17 h

Beller and co-workers reported a ruthenium-catalysed protocol for the alkylation of primary amines with several secondary alcohols. [64] Utilising $Ru_3(CO)_{12}$ with either tri-*o*-tolylphosphine **171** or *n*-butyl-di-1-adamantylphosphine (also known as catacXium A) **103**, alkylation of *n*-hexylamine (**169**) using 1-phenylethanol (**54**) could be achieved in 97% and 90% respectively (**Scheme 1.35a**). In addition, several other alkyl and benzylic secondary alcohols could be used to afford the

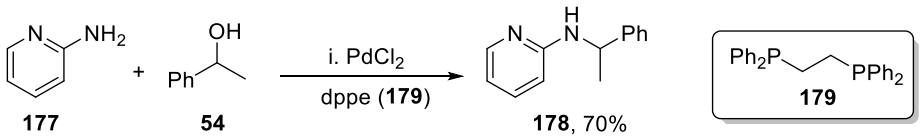
N-alkylated amine in moderate to good yields. Unlike the protocol by Fujita and co-workers, this procedure required a 5-fold excess of the secondary alcohol.



Scheme 1.35 Alkylation of amines using secondary alcohols: (a) Beller's Ru-catalysed protocol (b) Williams' Ru-catalysed protocol. Reagents and conditions: (i) $Ru_3(CO)_{12}$ (2 mol%), ligand (6 mol%), alcohol (5 equiv), toluene, 110 °C, 24 h (ii) [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), DPEphos (5 mol%), alcohol (1.2 equiv), xylene, 150 °C, 24 h

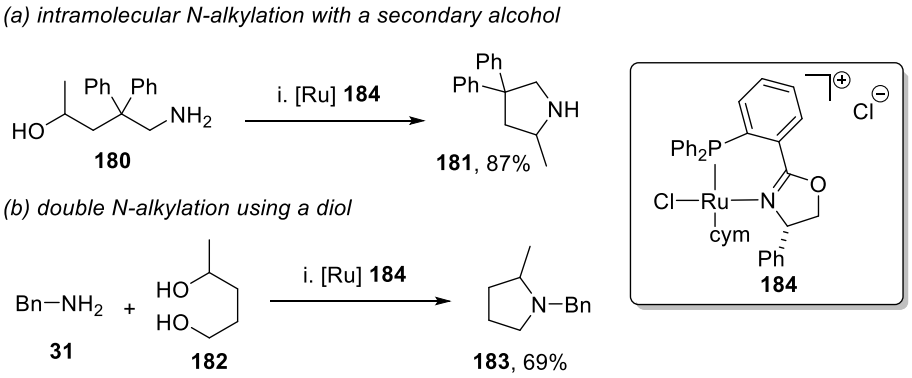
The group of Williams also demonstrated the use of another ruthenium catalyst, [Ru(*p*-cymene)Cl_2]$_2$ with DPEphos (**175**), which was effective at catalysing the alkylation of several secondary amines using secondary alcohols.[65] The scope was relatively limited and an elevated temperature of 150 °C was required for the reaction to proceed. Aliphatic secondary alcohols generally provided higher yields than the benzylic 1-phenylethanol (**54**), which was found to be the least reactive under their set of conditions. For example, pentan-2-ol (**172**) could be used to alkylate pyrrolidine (**20**) to afford **173** in 72% yield, whereas alkylation with 1-phenylethanol (**54**) resulted in a much lower 35% yield of the corresponding N-alkylated amine **174** (**Scheme 1.35b**).

A palladium based catalyst, $PdCl_2$/dppe, was also found to be effective at catalysing the alkylation of primary and secondary amines by Seayad and co-workers under a solvent-free protocol.[66] An interesting example demonstrated the alkylation of 2-aminopyridine (**177**) using 1-phenylethanol (**54**) to afford the N-alkylated amine **178** in 70% yield (**Scheme 1.36**). However, lengthy reaction times of 48 h and elevated temperatures of 130-150 °C were required to achieve the desired alkylation reactions.



Scheme 1.36 Seayad's Pd-catalysed alkylation of amines using secondary alcohols. Reagents and conditions: (i) $PdCl_2$ (2 mol%), dppe (2 mol%), LiOH (20 mol%), alcohol (3 equiv), 130 °C, 48 h

Although only intermolecular examples of amine N-alkylation using secondary alcohols is described here, there are several intramolecular examples that also involve the reaction of secondary alcohol centres with amines and lead to the formation of N-heterocyclic ring systems. Several groups, including that of Fujita,[67,68] have published methodologies towards the formation of such ring systems. A recent example comes from Takacs and co-workers who reported the intramolecular cyclisations of aminoalcohols, diols and diamines leading to the formation of heterocyclic ring systems using a ruthenium catalyst.[69]



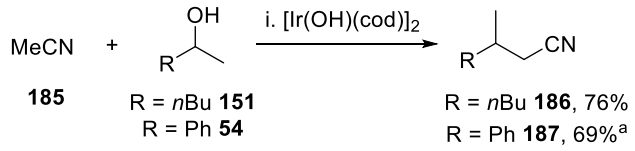
Scheme 1.37 Takacs' Ru-catalysed protocol for the formation of N-heterocyclic rings. Reagents and conditions: (i) [Ru] **184** (2 mol%), KO*t*Bu (50 mol%), toluene, 110 °C, 24 h

For example, amino alcohol **180** could undergo intramolecular C-N bond formation under the reaction conditions to afford the corresponding pyrrolidine **181** in 87% yield (**Scheme 1.37a**). In addition, benzylamine could also be reacted under the same protocol with a diol containing a secondary alcohol centre (**182**) which led to N-heterocyclic compound **183** in 69% yield (**Scheme 1.37b**).

1.4.3 Alkylation of Nitriles Using Hydrogen Borrowing Catalysis

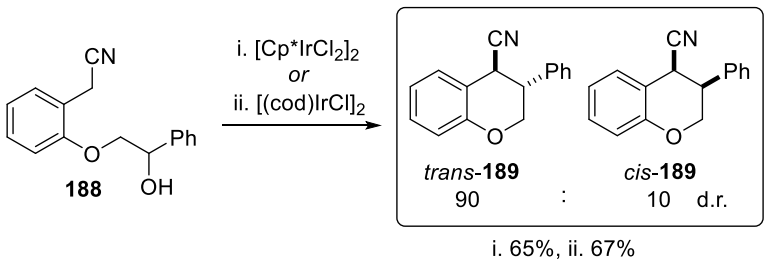
Several examples for the alkylation of nitrile compounds with primary alcohols have previously been discussed (see **Chapter 1.3.2**). In comparison to primary alcohols, the use of secondary alcohols to alkylate nitrile compounds *via* hydrogen borrowing catalysis has been very limited.

A key contribution to the area came from Obora and co-workers who reported the alkylation of acetonitrile with several secondary alcohols using $[Ir(OH)(cod)]_2/PPh_3$.[70] The scope of the secondary alcohols included both benzylic and aliphatic alcohols, as well as cyclohexanol. In representative examples, acetonitrile could be alkylated with 2-hexanol (**151**) and 1-phenylethanol (**54**) in 76% and 69% yields respectively (**Scheme 1.38**). Interestingly, the conditions utilise acetonitrile in a 10-fold excess, with the alcohol being set as the limiting reagent.



Scheme 1.38 Obora's Ir-catalysed alkylation of acetonitrile using secondary alcohols. Reagents and conditions: (i) $[Ir(OH)(cod)]_2$ (10 mol%), PPh_3 (40 mol%), KO*t*Bu (20 mol%), MeCN (10 equiv), 1,4-dioxane, 130 °C, 24 h [a]using KO*t*Bu (30 mol%), 48 h

Another report, from Cossy and co-workers, investigated the feasibility of an intramolecular alkylation reaction of hydroxynitriles.[71] Using either $[Cp^*IrCl_2]_2$ or $[(cod)IrCl]_2$ under microwave irradiation they found that a range of hydroxynitriles could undergo cyclisation to give the corresponding bicyclic product, although most of the reactions involved a primary alcohol centre. In the only example of the cyclisation of a secondary alcohol centre, hydroxynitrile **188** led to bicyclic product **189** in 65% or 67% yield using either $[Cp^*IrCl_2]_2$ or $[(cod)IrCl]_2$ respectively (**Scheme 1.39**). The product was isolated as a thermodynamic mixture in a 90:10 *trans*:*cis* ratio.



Scheme 1.39 Cossy's Ir-catalysed intramolecular alkylation of hydoxynitriles. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2.5 mol%), Cs_2CO_3 (20 mol%), 1,4-dioxane, 110 °C, MW, 15 h, (ii) $[(cod)IrCl]_2$ (2.5 mol%), PPh_3 (10 mol%), Cs_2CO_3 (20 mol%), 1,4-dioxane, 110 °C, MW, 15 h

1.5 Project Aims

Having explored the use of primary alcohols as alkylating agents in hydrogen borrowing catalysis it was apparent that the formation of acyclic α-branched products from methylene ketones was a difficult transformation, with only a very limited number of examples reported. An exception was methanol, which appeared to be uniquely placed to form α-branched products. Several general methods using it to form α-branched products had been reported, including protocols developed within the Donohoe group.

In addition, it was noted that despite several examples pertaining to the use of secondary alcohols in hydrogen borrowing alkylation reactions of amines and nitriles, their use in ketone alkylation was generally limited to Guerbet-type homodimerisation reactions.

We envisaged that in developing a general hydrogen borrowing alkylation protocol to address these issues, value could be added by allowing access to motifs which currently relied upon the use of stoichiometric amount of toxic reagents for their syntheses. In this regard, our aims for the project were to:

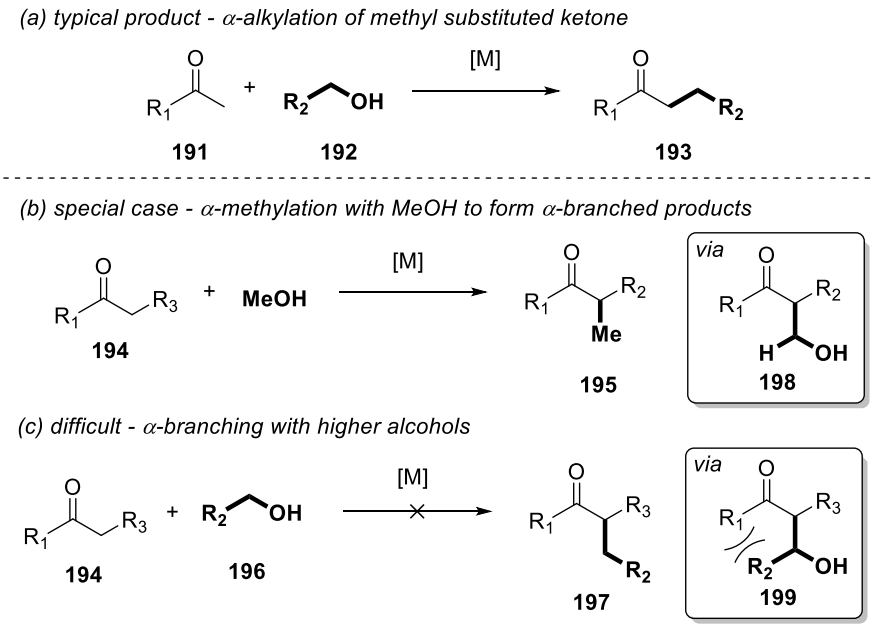
1. Investigate the possibility of a mild and general protocol for the alkylation of ketones using long chain alcohols to form α-branched ketone products, whilst keeping synthetic utility of the products in mind.
2. Explore the scope of the methodology with respect to the ketone as well as the alcohol.

3. Consider how the methodology could be extended to incorporate secondary alcohols as alkylating reagents.

Chapter 2: Results & Discussion – α-Branched Products Using Primary Alcohols

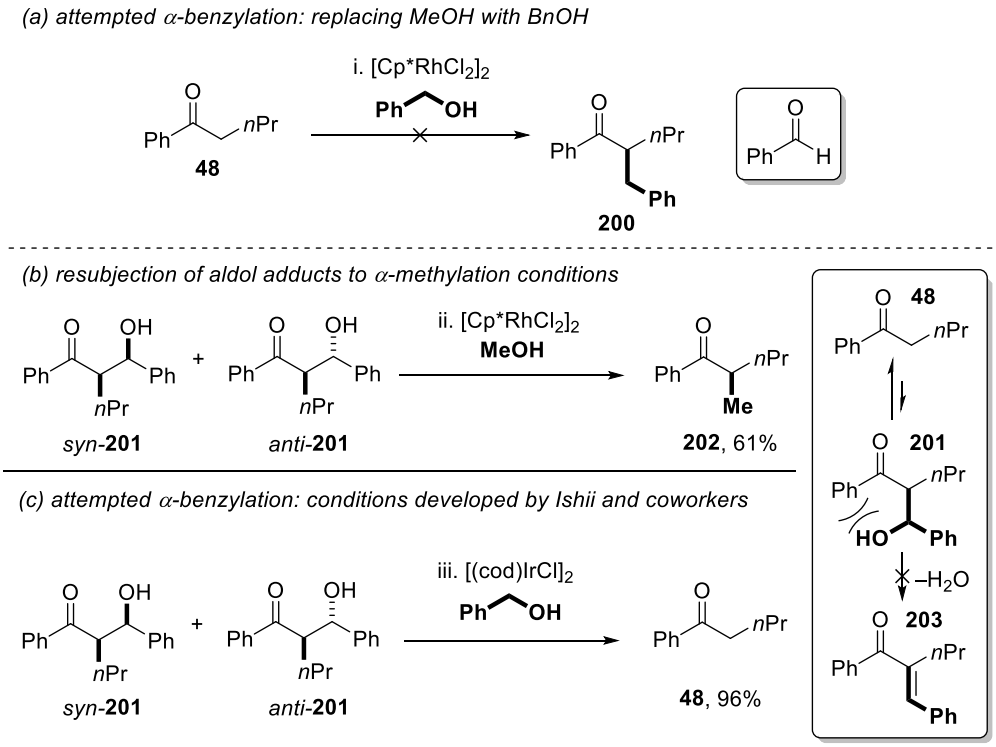
2.1 Introduction

As illustrated in **Chapter 1**, hydrogen borrowing methodologies for the alkylation of ketones have steadily evolved in recent years. Despite strides forward, it is clear that the majority of the existing methodologies are limited to the monoalkylation of methyl-substituted ketones **(191**) with primary alcohols to produce 'linear' products, **193** (**Scheme 2.1a**). In contrast, the monoalkylation of methylene ketones (**194**) to form α-branched products remains relatively underdeveloped. A key exception, highlighted in the previous discussion, was the α-alkylation of ketones using methanol to form branched products, **195** (**Scheme 2.1b**).[44] The use of methanol as an alkylating reagent is unique, as the aldehyde generated from its oxidation, formaldehyde, is small and highly reactive. In contrast, aldehydes generated from higher alcohols are much less electrophilic[72] and the resulting aldol adduct (**199**) generated during the formation of α-branched products are thought to be more sterically encumbered, leading to an increase in strain (**Scheme 2.1c**).[73]



Scheme 2.1 Limitations in the formation of α-branched products

The strained adduct was hypothesised to facilitate a retro-aldol process to relieve strain, as opposed to an E1cB mechanism which would lead to the desired enone that could undergo reduction to provide the desired α-branched product.



Scheme 2.2 Previous failed attempts at benzylation to form branched products by Dr Darren Poole. Reagents and conditions: (i) $[Cp^*RhCl_2]_2$ (5 mol%), Cs_2CO_3 (5 equiv), BnOH (0.2 M) 65-100 °C, O_2/Ar, (ii) $[Cp^*RhCl_2]_2$ (5 mol%), Cs_2CO_3 (5 equiv), MeOH (0.2 M) 65 °C, O_2, (iii) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (10 mol%), 2 equiv BnOH, 100 °C. Reactions conducted by Dr Darren Poole

Previous attempts by Dr Darren Poole[73] to adapt the α-methylation conditions developed in the Donohoe group[44] by replacing methanol with benzyl alcohol resulted only in the isolation of unreacted starting material, **48**, and benzaldehyde (**Scheme 2.2a**). When the corresponding aldol adducts, **201**, were synthesised independently and subjected to the developed α-methylation conditions, it resulted only in the formation of α-methylated product **202** in 61% yield (**Scheme 2.2b**). Product **202** was thought to be formed through initial retro-aldol reactions of β-hydroxy ketones **201**, followed by trapping of the resulting enolate with formaldehyde (generated from the oxidation of methanol) to give the corresponding enone. Reduction of the enone would afford α-methylated product **202**. Subjection of the aldol adducts, **201**, to

benzylation conditions developed by Ishii and coworkers[36] resulted in a 96% yield of the ketone **48** (**Scheme 2.2c**). These results suggest that the deprotonation of alcohol **201** followed by a retro-aldol reaction is faster than the corresponding elimination of water to give enone **203**. This pathway is presumably facilitated by a destabilising steric interaction in the aldol adduct (**201**).

We hypothesised that replacing the phenyl substituent (R_1) on the parent ketone with a smaller, less sterically demanding group would alleviate the strain in the aldol adduct (**204**) and enable the elimination of water to occur more readily (**Figure 2.1**).

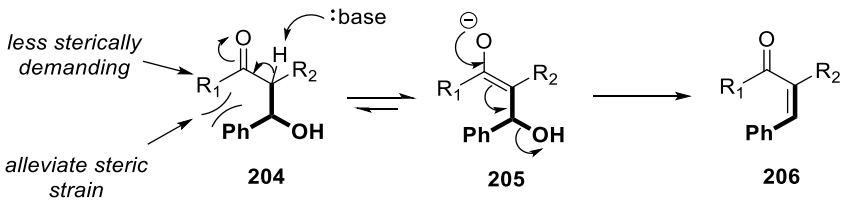


Figure 2.1 Stabilisation of aldol adduct by making R_1 less sterically demanding

Taking these observations and thoughts into consideration we set out to explore and identify potential substrates that fit this criterion and would allow us to test our hypothesis.

2.2 Substrate Exploration: Ynones

Ynones (**207**) were identified as potential targets on which to begin testing our hypothesis (**Figure 2.2**). The alkyne motif, which has an A-value of 0.52[74] kcal mol^{-1}, is sterically much smaller than a phenyl group, with an A-value of 3.0[75] kcal mol^{-1} and we envisaged this smaller size would provide the relief of steric strain required to allow the reaction to proceed forwards.

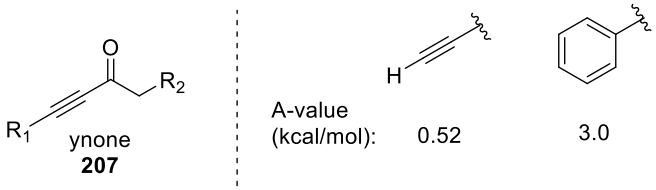
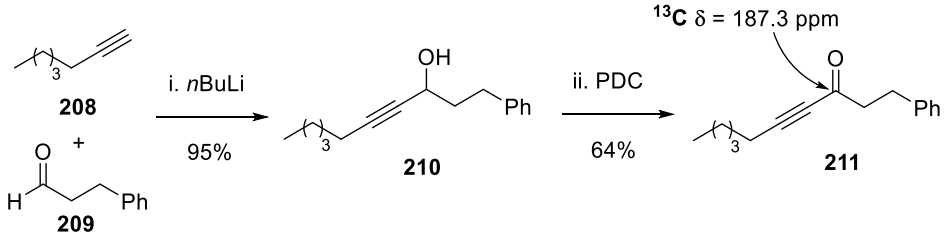


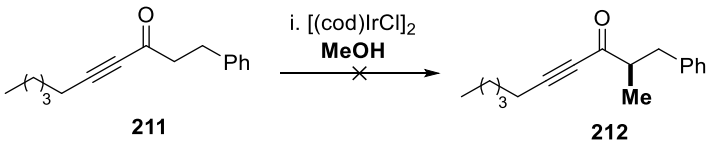
Figure 2.2 Ynone structure and comparison to Ph group

We began by synthesising ynone **211** (**Scheme 2.3**) starting from the addition of terminal alkyne **208** into hydrocinnamaldehyde **209** to give alcohol **210**. Initially we followed a protocol by Aggarwal and co-workers[76], where the terminal alkyne was deprotonated using *n*BuLi at –78 °C, followed by addition of the aldehyde at the same temperature. Unfortunately, under these conditions, the reaction gave a complex mixture. We suspected this may be due to incomplete deprotonation of the terminal alkyne at –78 °C. The procedure was repeated but with the mixture of *n*BuLi and terminal alkyne **208** warmed to –40 °C for 30 minutes before re-cooling to –78 °C and addition of hydrocinnamaldehyde. We were pleased to find that this modification resolved the issue and the desired alcohol **210** was isolated in 95% yield. Oxidation[76] of **210** with pyridinium dichromate provided desired ynone **211** in 64% yield.



Scheme 2.3 Synthesis of ynone **211**. Reagents and conditions: (i) hydrocinnamaldehyde **209** (1.1 equiv), *n*BuLi (1.05 equiv), THF, –78 to –40 to –78 °C, 1 h (ii) PDC (1.1 equiv), CH_2Cl_2, 0 °C, 16 h

Before attempting to develop an α-alkylation protocol for ynone **211** with higher alcohols, we first decided to try and methylate it under iridium-catalysed methylation conditions previously developed in the Donohoe group.[45]



Scheme 2.4 Attempted Ir-catalysed α-methylation of ynone **211**. Reagents and conditions: (i) $[(cod)IrCl]_2$ (1.0 mol%), PPh_3 (4.0 mol%), KOH (2 equiv), MeOH, O_2, 65 °C, 1 h

On subjection of ynone **211** to these conditions (**Scheme 2.4**), consumption of starting material occurred within 1 h, as indicated by TLC analysis. On purification, however, it was clear that the

desired methylation product had not been formed. Instead, single and double conjugate addition products **213** and **214** were formed in 65% and 28% yield, respectively (**Figure 2.3**). The *E* double bond geometry of methoxy enone **213** was confirmed using an nOe observed between the methoxy group and the alkenyl proton.

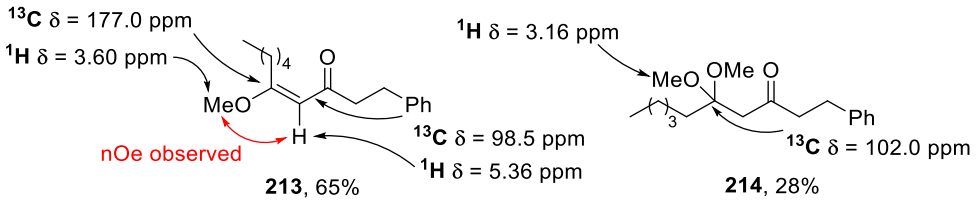
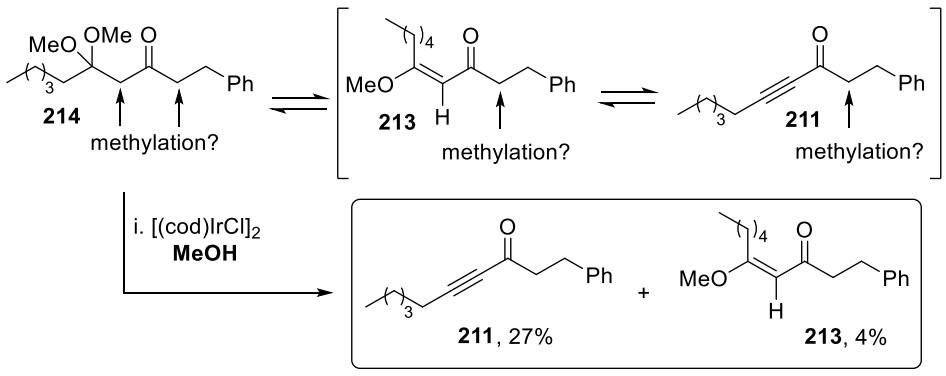


Figure 2.3 Isolated products from attempts to α-methylate ynone **211**

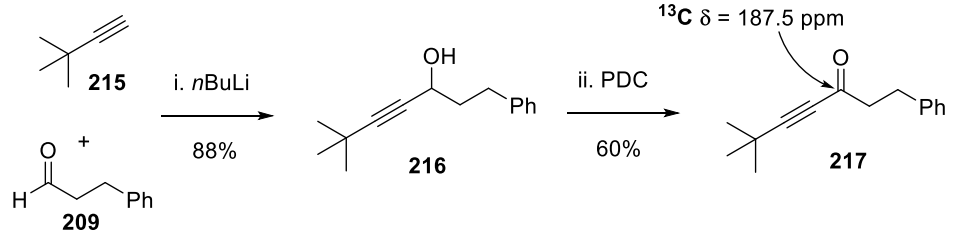
Indeed, the conjugate addition of methoxide, which is generated under these conditions, into an α,β-unsaturated compound is well known in the literature.[77] A control reaction was conducted whereby ynone **211** was subjected to KOH and methanol, with the catalyst omitted, at 65 °C. This returned the same conjugate addition products in an identical ratio to that observed under the methylation conditions.

Assuming that the conjugate addition products would all be in equilibrium, we decided to re-subject double conjugate addition product **214** to the methylation conditions for 48 h to determine if any α-alkylation would occur (**Scheme 2.5**).



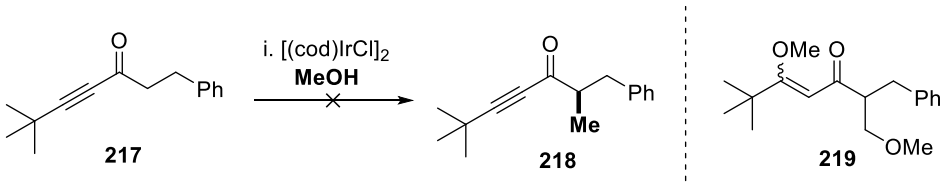
Scheme 2.5 Re-subjection of double conjugate addition product **214** to α-methylation conditions. Reagents and conditions: (i) [(cod)IrCl]$_2$ (1.0 mol%), PPh_3 (4.0 mol%), KOH (2 equiv), MeOH, O_2, 65 °C, 48 h

Unfortunately, no methylation was observed. Instead ynone **211** and methoxy enone **213** were isolated in 27% and 4% yield, respectively, demonstrating that **211**, **213** and **214** are indeed, interconvertible. With ynone **211** proving to be troublesome under the reaction conditions, we turned our attention towards the synthesis of sterically bulkier ynone **217**. Using the same modified protocol, alcohol **216** was synthesised in 88%, followed by a PDC oxidation, providing desired ynone **217** in 60% yield (**Scheme 2.6**).



Scheme 2.6 Synthesis of ynone **217**. Reagents and conditions: (i) hydrocinnamaldehyde **209** (1.1 equiv), *n*BuLi (1.1 equiv), THF, –78 to –40 to –78 °C, 1 h, 95%, (ii) PDC (1.1 equiv), CH_2Cl_2, 0 °C, 16 h

We hoped that the introduction of a bulky *tert*-butyl group would act as a steric shield for the conjugate addition reaction and provide a greater window for α-methylation to occur.



Scheme 2.7 Attempted Ir-catalysed α-methylation of ynone **217**. Reagents and conditions: (i) $[(cod)IrCl]_2$ (1.0 mol%), PPh_3 (4.0 mol%), KOH (2 equiv), MeOH, O_2, 65 °C, 48 h

Despite the increased steric bulk, subjection of ynone **217** to the methylation conditions lead to a complex mixture and no observation of α-alkylated compound **218**. ^{1}H NMR analysis of the crude material revealed trace amounts of compound **219**, but despite multiple purification attempts this could not be isolated or fully characterised.

It was clear from these results that the alkyne functionality was not well tolerated under the reaction conditions, and therefore these substrates were not pursued further.

2.3 Substrate Exploration: Cyclopropyl Ketones

Cyclopropyl ketones have previously been alkylated *via* hydrogen borrowing catalysis to form α-branched products using methanol in the Donohoe group[44]. Although an A-value has not been measured for a cyclopropane ring, we assumed the value would be related to, and possibly slightly smaller, than the A-value of the isopropyl group which is 2.15[75] kcal mol^{-1}. This value is smaller than that for the phenyl group of 3.0[75] kcal mol^{-1}. We hypothesised the 'small' size of the cyclopropane group may facilitate alkylation with higher alcohols. In addition, we hoped the unique reactivity of cyclopropyl ketones would offer a synthetic handle for further derivatisation.

2.3.1 Reactivity

The reactivity of cyclopropane rings has been likened to that of a C=C double bond due to similarities in their behaviour.[78] Cyclopropanes are able to undergo many of the same transformations, such as, catalytic hydrogenations. Cyclopropanes feature a type of strain called small-angle strain, which arises as the angles within the ring are forced to be smaller than those that would typically be expected from a sp^3 hybridised carbon atom with normal orbital overlap. A consequence of this strain is that cyclopropanes are cleaved more easily than what would be expected for the corresponding alkane. Unlike a normal carbon atom which typically features four approximately equal sp^3 hybridised bonds, the bonds in a cyclopropane carbon atom are not equal. The bonds directed outside the ring feature more *s* character and tend towards sp^2 hybridisation, whereas those directed into the ring feature more *p* character. As the preferred bond angle for *p* orbitals is 90° rather than 109.5°, the higher *p* character relieves some of the strain in the cyclopropane ring. Whereas the overlap of sp^3 hybridised bonds in normal C-C bonds occur in such a way that the electron density is distributed symmetrically around an axis between the two bonded nuclei, in cyclopropanes, the electron density is directed outwards, leading to 'bent bonds' (**Figure 2.4a**). The character of these bonds is somewhere between σ and π. This allows them to behave similar to double bonds.[79] Conjugation between an adjacent π-system and

the *p*-like orbitals of the cyclopropane ring is therefore possible and is greatest in the configurations depicted (**Figure 2.4b**).[79,80]

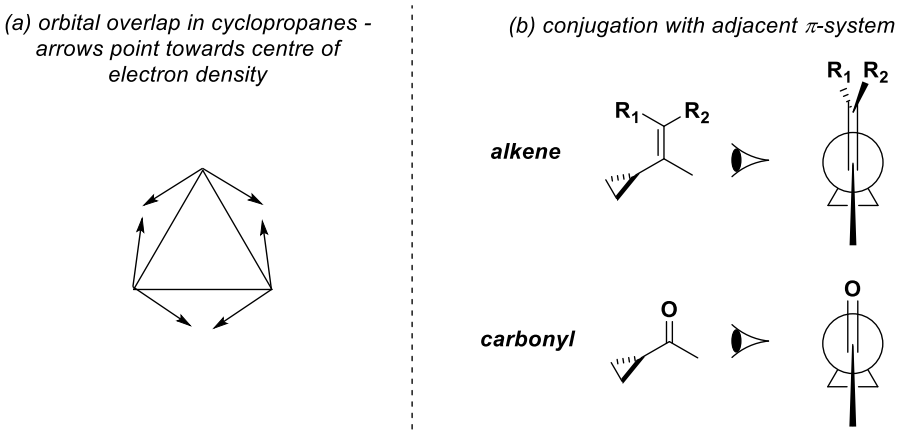


Figure 2.4 Bonding in cyclopropanes and conjugation with adjacent systems

The effects of this conjugation can be seen in the spectroscopic properties of molecules. Spectroscopic data of structurally similar ketones **95**, **90**, **220** and **55** suggests that the conjugation in cyclopropyl ketone **90** may sit somewhere between that of enone **220**[81] or aromatic ketone **55**[82], and isopropyl ketone **95**[83] (**Figure 2.5**).

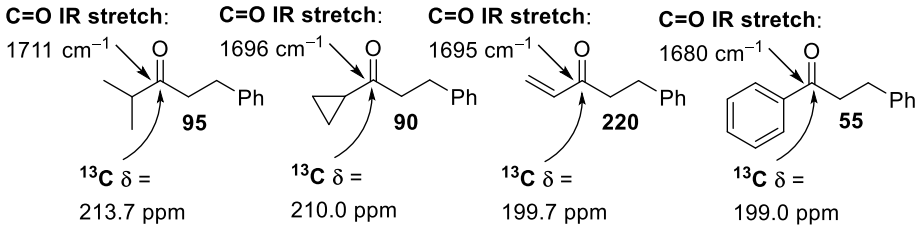


Figure 2.5 A comparison of the C=O IR stretch and ^{13}C chemical shift (C=O) of compounds **95**, **90**, **220** and **55**

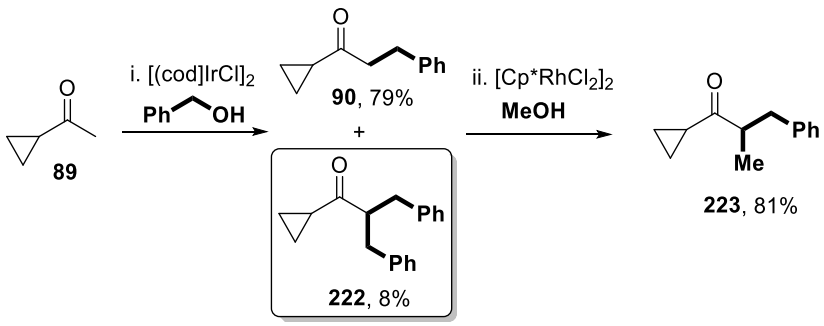
Analysis of IR spectroscopy data shows that cyclopropyl ketone **90** exhibits a C=O stretch at 1696 cm^{-1}, lower than the corresponding peak for isopropyl ketone **95** (1711 cm^{-1}) and similar to that of enone **220** (1695 cm^{-1}) and aromatic ketone **55** (1680 cm^{-1}). This suggests that a degree of conjugation may certainly exist between the cyclopropyl moiety and the carbonyl group, weakening the C=O bond and hence lowering the wavenumber at which the C=O stretch appears. Further evidence for conjugation is provided by ^{13}C NMR data, where the C=O peak for cyclopropyl

ketone **90** appears at 210.0 ppm, whereas for isopropyl ketone **95** it appears at 213.7 ppm. Much like enone **220** (199.7 ppm) and aromatic ketone **55** (199.0 ppm), a lower chemical shift indicates a more shielded carbon, which would be expected from a delocalised system.

The implication of conjugation on the ability of cyclopropyl ketones to undergo alkylation *via* hydrogen borrowing catalysis could therefore be two-fold. Firstly, the ketone may be less-susceptible to over-reduction to the corresponding alcohol. Secondly, as discussed earlier, the cyclopropyl group is relatively 'small', which, in line with our hypothesis, would alleviate steric strain in the aldol adduct and facilitate elimination over a retro-aldol reaction. Furthermore, cyclopropanes hold the potential to be derivatised through a plethora of ring-opening reactions and would serve as a valuable functional handle post-alkylation.

2.3.2 Lead Results

Cyclopropyl methyl ketone **89** and cyclopropyl ketone **90** have been used in hydrogen borrowing alkylation reactions previously to form linear product **90** and α-branched product **223** (**Scheme 1.8**).[44]

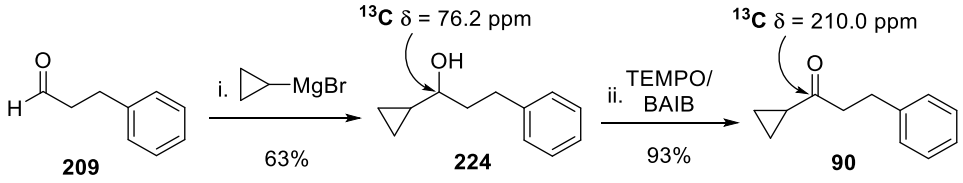


Scheme 2.8 Formation of debenzylated ketone **222** as a by-product. Reagents and conditions: (i) $[(cod)IrCl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (10 mol%), BnOH (2 equiv), Ar, 100 °C, 4 h, (ii) $[Cp^*RhCl_2]_2$ (5 mol%), Cs_2CO_3 (5 equiv), MeOH (0.2 M), O_2, 65 °C, 48 h. Reactions conducted by Dr Di Shen

Interestingly, when step (i) was carried out using a 2-fold excess of benzyl alcohol by Dr Di Shen, debenzylated product **222** was isolated in 8% yield.[84] It was hypothesised that this α-branched product was formed from two subsequent hydrogen borrowing alkylation reactions starting from

cyclopropyl methyl ketone **89**. This was a promising sign that cyclopropyl ketones could indeed form branched products using long chain primary alcohols. With this result in hand, we set out to optimise the reaction parameters.

2.3.3 Optimisation



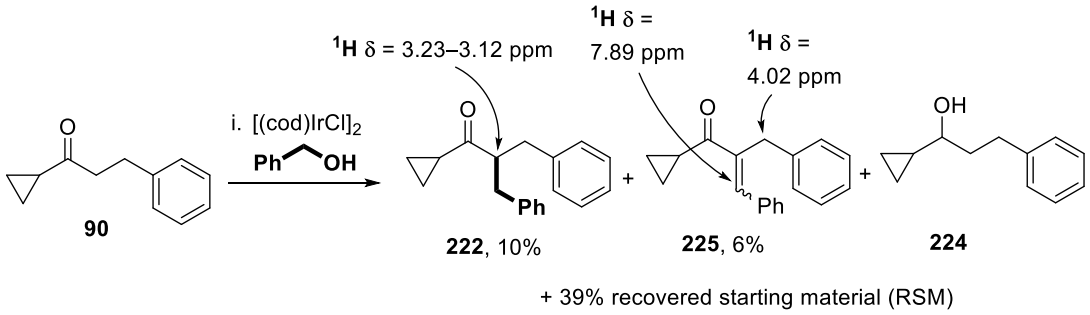
Scheme 2.9 Synthesis of cyclopropyl ketone **90**. Reagents and conditions: (i) cyclopropyl magnesium bromide (1.2 equiv), THF, –78 °C to RT, 24 h, (ii) TEMPO (10 mol%), BAIB (1.1 equiv), CH_2Cl_2, RT, 48 h

Cyclopropyl ketone **90** was chosen as the model substrate on which to begin our optimisation. The synthesis began with Grignard addition of cyclopropyl magnesium bromide into hydrocinnamaldehyde (**209**) affording cyclopropyl alcohol **224** in 63% yield (**Scheme 2.9**). The alcohol was then oxidised using a TEMPO/BAIB protocol[85] to the provide desired cyclopropyl ketone **90** in 93% yield.

The decision was made to begin the optimisation using benzyl alcohol. This was based on the positive lead result discussed earlier (see **Chapter 2.3.2**) where debenzylated ketone **222** was isolated in small quantities following an α-alkylation reaction of cyclopropyl methyl ketone using benzyl alcohol. Pleasingly, under a starting set of conditions* using $[(cod)IrCl]_2$ as the catalyst with (±)-BINAP as the ligand, desired α-branched ketone **222** was formed in 12% yield† (**Scheme 2.10**).

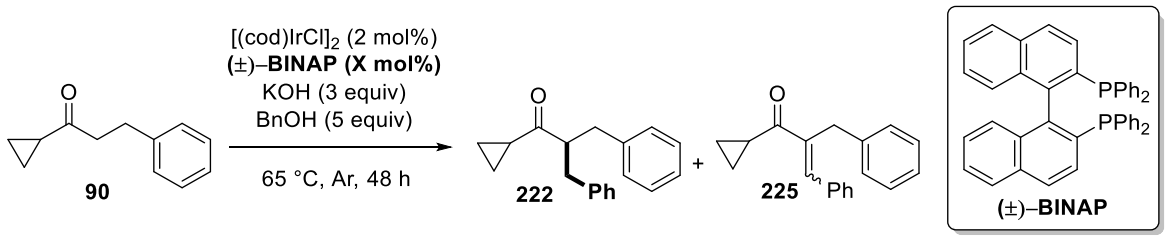
* Conditions obtained from Choon Boon Cheong.

† Despite several attempts, ketone **222**, enone **225** and starting material **90** could not be separated cleanly. As a result, the ratios were assessed by ^{1}H NMR



Scheme 2.10 Initial attempt at the alkylation of cyclopropyl ketone **90**. Reagents and conditions: (i) [(cod)IrCl]$_2$ (2 mol%), (±)-BINAP (3 mol%), KOH (3 equiv), BnOH (5 equiv), 65 °C, Ar, 48 h

Also formed in the reaction was enone **225** in 6% yield and 1,2-reduction product **224**[*]. Starting ketone **90** was also recovered in a 39% yield. Building on these conditions, we initially decided to look at amount of bidentate phosphine ligand, (±)-BINAP. Unfortunately, changing the loading of (±)-BINAP had little to no effect on the distribution of products in the reaction, within experimental error (**Table 2.1**).



Entry	BINAP (mol%)	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	2	11	5	41
2	3	10	6	39
3	**4**	**12**	**7**	**47**
4	6	9	5	44
5	8	9	6	43

Table 2.1 Screen of varying mol% of (±)-BINAP. [a]yields based on ^{1}H NMR analysis

We therefore decided to proceed with 4 mol% of the bidentate ligand, preserving the 1:2 ratio of iridium to phosphine utilised previously in the Donohoe group in hydrogen borrowing catalysis.[45]

[*] Could not be separated from benzyl alcohol but was identified by ^{1}H and ^{13}C NMR.

Next, we focused our attention on varying the phosphine ligand. The bite angle of diphosphine ligands is known to have an effect on the catalytic activity of metal complexes[86] therefore a range of bite angles[87] were covered when selecting ligands to screen (**Figure 2.6**).

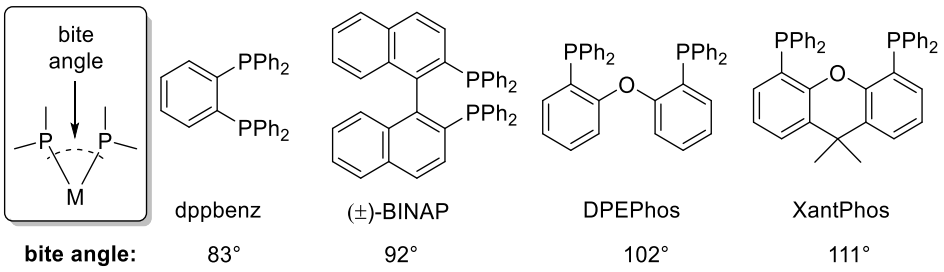
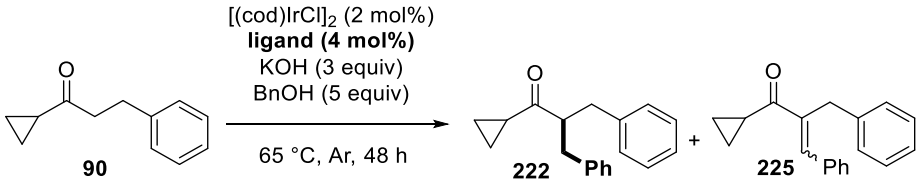


Figure 2.6 Bidentate phosphine ligands and their bite angles

Disappointingly, changing the phosphine ligand offered no improvement on the yield of branched ketone **222**. Notably, XantPhos and the monodentate triphenylphosphine provided a slightly decreased yield of the desired ketone (**Table 2.2, Entry 4 and 5**), whereas dppbenz, (±)-BINAP and DPEPhos were almost indistinguishable, within experimental error (**Entries 1-3**). The decision was made to proceed with (±)-BINAP.

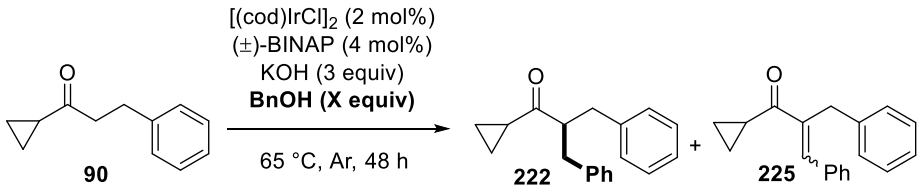


Entry	Ligand	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	dppbenz	12	4	38
2	**(±)-BINAP**	**12**	**7**	**47**
3	DPEPhos	12	8	47
4	XantPhos	6	12	35
5	PPh_3	7	8	42

Table 2.2 Phosphine ligand screen. [a]yields based on ^{1}H NMR analysis

Having looked at both the loading and type of phosphine ligand, we turned our focus to the stoichiometry of benzyl alcohol. Lowering the amount of benzyl alcohol to 2 equivalents (**Table 2.3, Entry 1**) had a negligible effect on the distribution of products, though it is important

to note that there was difficulty in getting the reaction mixture to stir uniformly under magnetic stirring, most likely due to the small amount of solvent available.

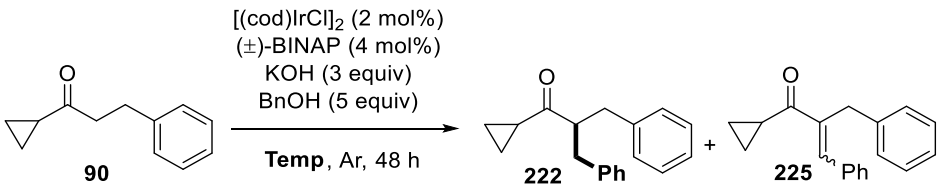


Entry	BnOH (equiv)	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	2	11	4	38
2	**5**	**12**	**7**	**47**
3	10	6	10	48
4	25	4	6	67

Table 2.3 Screen of benzyl alcohol equivalents. [a]yields based on ^{1}H NMR analysis

Using 10 equivalents of benzyl alcohol (**Entry 3**) did little to improve the yield of the desired ketone and diluting the reaction further with 25 equivalents (**Entry 4**) seemed to hinder it, with 67% recovered starting material. Due to the physical issues encountered when using 2 equivalents, we decided to move forward and keep the stoichiometry of benzyl alcohol at 5 equivalents.

Aware that a temperature of 65°C was on the lower end of the scale for hydrogen borrowing catalysis, with reactions typically carried out at temperatures over 100 °C, we decided to explore this parameter next. We were pleased to find the increasing the temperature to 85 °C provided desired ketone **222** in 41% yield, although 8% of enone **225** was still present as well as 20% RSM.

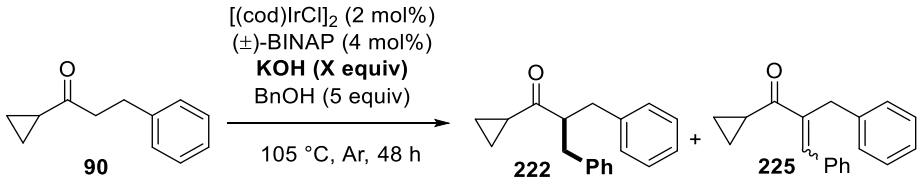


Entry	Temp (°C)	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	65	12	7	47
2	85	41	8	20
3	**105**	**74**[b]	-	-

Table 2.4 Temperature screen. [a]yields based on ^{1}H NMR analysis, [b]isolated yield

Gratifyingly, when the temperature was increased to 105 °C, ketone **222** could be isolated cleanly in 74% yield, with no enone or starting material observed.

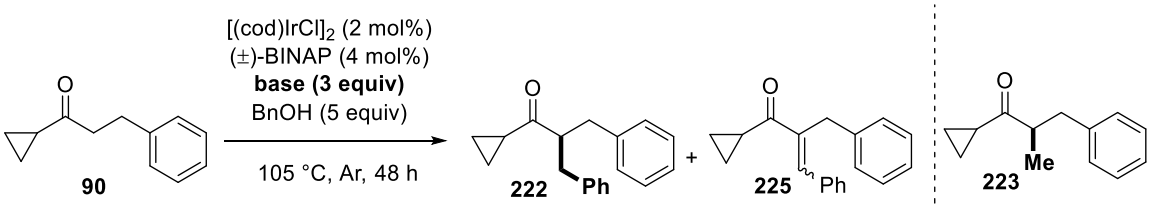
With this result in hand, we wanted to investigate whether the stoichiometry and type of base, as well as the loading and type of catalyst were optimal for this reaction. We began by looking at the stoichiometry of KOH.



Entry	KOH (equiv)	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	1	20	10	48
2	2	71	6	2
3	**3**	**74**[b]	-	-
4	5	57	4	13

Table 2.5 Screen of equivalents of KOH . [a]yields based on ^{1}H NMR analysis, [b]isolated yield

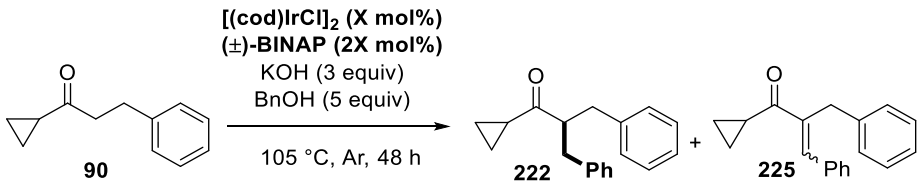
The use of 1 equivalent of KOH appeared to hinder the reaction significantly, with only 20% of desired ketone **222** formed and 48% RSM (**Table 2.5, Entry 1**). Moving up to 2 equivalents of KOH fared much better resulting in a 71% yield of desired ketone **222** (**Entry 2**), almost comparable to the distribution achieved using 3 equivalents of KOH (**Entry 3**). Increasing the loading of KOH further still to 5 equivalents did not provide any further improvement, but was instead detrimental, with the yield of α-branched ketone **222** lowered to 57%. Due to small amounts of enone **225** and traces of starting material recovered when using 2 equivalents of KOH, the decision was made to continue to use 3 equivalents to ensure the reaction would consistently proceed to completion.



Entry	Base	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	**KOH**	**74**[b]	-	-
2[c]	NaOMe	20	-	-
3	K_2CO_3	-	-	94
4	KO*t*Bu	50[b]	-	-

Table 2.6 A brief look at other bases. [a]yields based on ^{1}H NMR analysis, [b]isolated yield, [c]methylated ketone **223** also formed in 34% yield

Next, we briefly explored other bases to determine whether the use of KOH was optimal. Interestingly, as well at 20% of desired ketone **222**, 34% of methylated ketone **223** was also formed when NaOMe was used (**Table 2.6, Entry 2**). This is perhaps not so surprising, as upon protonation NaOMe would generate methanol. Methanol can then enter the hydrogen borrowing catalytic cycle, leading to the formation of methylated ketone **223**. The use of milder, K_2CO_3 (**Entry 3**), lead to no observed reaction with 94% RSM. We suspected this may be due to its inability to form the enolate efficiently, as well as difficultly in completing the required E1cB elimination to form the enone. KO*t*Bu gave a moderate yield of 50% (**Entry 4**), with no enone or starting material observed. It was clear that KOH was the optimal base out of those screened.



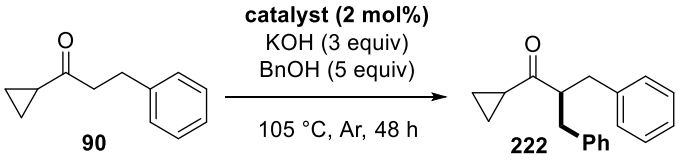
Entry	Catalyst (mol%)[c]	222 (%)[a]	225 (%)[a]	RSM (%)[a]
1	1	58	11	6
2	**2**	**74**[b]	-	-
3	4	82[b]	-	-
4	8	84[b]	-	-

Table 2.7 Screen of catalyst mol%. [a]yields based on ^{1}H NMR analysis, [b]isolated yield, [c]metal to ligand ratio, 1:2

We then turned our attention to the loading of catalyst in the reaction, keeping the ratio of iridium to phosphine at 1:2 in all cases. Unfortunately, lowering the catalyst loading to 1 mol% (**Table 2.7, Entry 1**) lead to a corresponding drop in yield of desired ketone **222** to 58%, with 11% enone **225** and 6% RSM. Although increasing the catalyst loading to 4 mol% (**Entry 3**) and 8 mol% (**Entry 4**) lead to reasonable increases in the yield, with product **222** isolated in 82% and 84% respectively, the increase was deemed too little to warrant an increased loading of $[(cod)IrCl]_2$. We therefore decided to proceed with 2 mol% of the catalyst.

Finally, we decided to explore other catalysts previously investigated in the Donohoe group[73,84], focusing on those which did not necessarily require additional ligand to be added. Pleasingly, $[Cp^*IrCl_2]_2$ gave α-benzylated ketone **222** in 73% yield (**Table 2.8, Entry 2**). Switching to the rhodium analogue of the catalyst (**Entry 4**), the reaction also proceeded to completion, but afforded a slightly lower 64% yield of desired ketone **222**. In addition, we were pleased to find that reducing the reaction time from 48 h to 24 h led to no loss in yield (**Entry 3**).

Based on the final round of optimisation, we decided to adopt $[IrCp^*Cl_2]_2$ as the catalyst, as although it gave a similar yield to $[(cod)IrCl]_2$/BINAP, the elimination of the need to add a ligand to the reaction was preferred. Furthermore, the decision was made to reduce the reaction time from 48 h to 24 h.

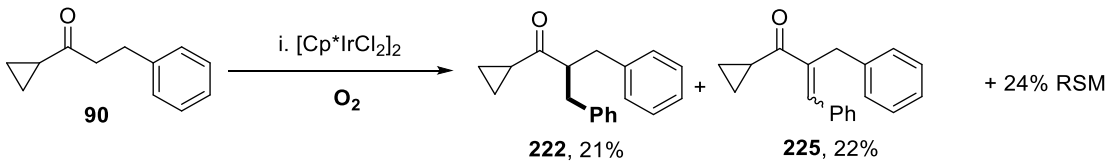


Entry	Catalyst (ligand)	222 (%)
1	$[(cod)IrCl]_2$ (BINAP)	74[b]
2	$[Cp^*IrCl_2]_2$	73[b]
3[a]	$[Cp^*IrCl_2]_2$	**73[b]**
4	$[Cp^*RhCl_2]_2$	64[b]

Table 2.8 A brief look at other catalysts. [a]24 h, [b]isolated yield

2.3.4 Control Experiments

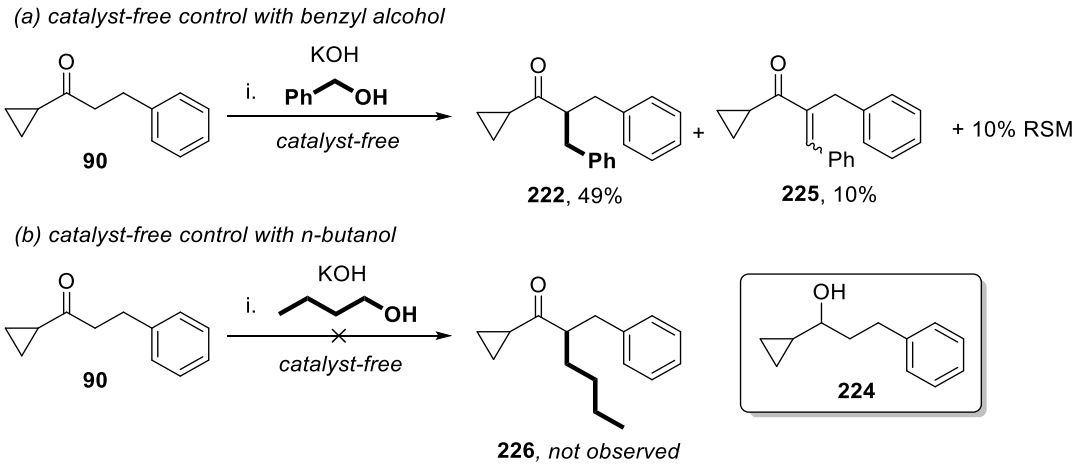
With the optimised conditions for the alkylation of ketones with higher alcohols to form α-branched products in hand, it was important to carry out a series of control reactions to provide further insight into the reaction. Although the optimised conditions were developed under an atmosphere of argon, the α-methylation chemistry reported by the Donohoe group[44,45] was conducted under an atmosphere of O_2. An atmosphere of O_2 was beneficial and provided higher yields of α-methylated ketones when compared to an atmosphere of argon. To test whether our optimised conditions where susceptible to any such effect, a reaction under an atmosphere of O_2 was conducted (**Scheme 2.11**).



Scheme 2.11 Subjection of ketone **90** to the optimised condition under an atmosphere of O_2. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), BnOH (5 equiv), 105 °C, O_2, 24 h.

The yield of α-benzylated ketone **222** was reduced to 21% under O_2, showing the atmosphere switch was detrimental to the reaction, having no beneficial effect as it had done previously. Interestingly, enone **225** was formed in an improved yield of 22%. Previous work has demonstrated that switching the atmosphere of a related alkylation reaction from argon to O_2 can indeed promote olefin formation.[88] It is proposed that O_2 may do this by hindering the final reduction step in the hydrogen borrowing catalytic cycle, perhaps by reacting with the metal hydride species in preference to the enone, recycling the catalyst and therefore promoting a dehydrogenative coupling pathway leading to accumulation of enone.

To confirm that $[Cp^*IrCl_2]_2$ was playing a vital role in the reaction, it was important to run the reaction in absence of the catalyst. On subjection of ketone **90** to the reaction conditions with $[Cp^*IrCl_2]_2$ omitted, surprisingly branched ketone **222** was formed in 49% yield, along with 10% of enone **225** and 10% RSM (**Scheme 2.12a**).



Scheme 2.12 Catalyst-free control reactions with benzyl alcohol and *n*-butanol. Reagents and conditions: (i) KOH (3 equiv), BnOH (5 equiv), 105 °C, Ar, 24 h, (ii) KOH (3 equiv), *n*BuOH (5 equiv), 105 °C, Ar, 24 h

Catalyst-free autocatalysed hydrogen borrowing alkylation reactions are known in the literature[89,90] and are thought to proceed through Meerwein-Pondorf-Verley-Oppenauer (MPV-O) type processes (**Figure 2.7**). Benzylic alcohols are most suited to undergo this process, presumably because they undergo facile oxidation when compared to their alkyl counterparts.

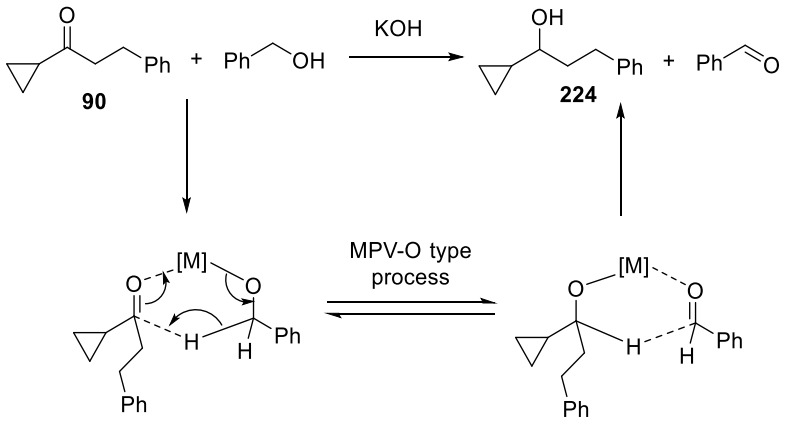


Figure 2.7 Possible mechanism for oxidation of benzyl alcohol in an MPV-O type process

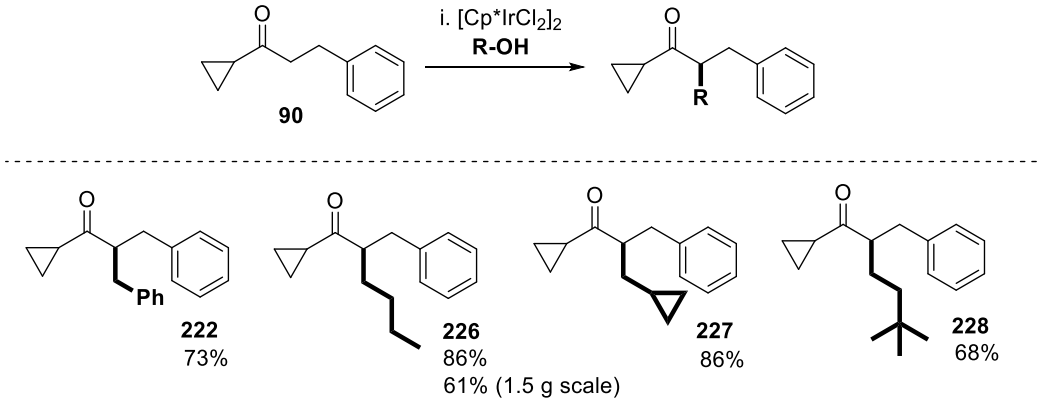
It is therefore perhaps unsurprising that most examples using catalyst-free methodology involve benzylic alcohols, with alkyl alcohols often performing poorly in comparison. It quickly became evident that the catalyst-free result using benzyl alcohol under our optimised conditions also fit this trend, with no conversion to α-branched ketone **222** observed when the catalyst-free control

was repeated with 1-butanol (**Scheme 2.12b**). Analysis of the ^{1}H NMR spectrum of the crude material revealed only small amounts of reduced starting material, alcohol **224**, to be present.

2.3.5 Substrate Scope

With a protocol for the alkylation of ketones using higher alcohols optimised, our attention turned to the exploration of the substrate scope for this reaction. The aims of the substrate screen were three-fold: (i) explore the scope of primary alcohols that can be used as the alkylation source (ii) determine limitations in terms of the steric bulk that can be tolerated using a combination of alcohols and ketones (iii) demonstrate that the alkylation conditions are applicable to a range of ketones.

2.3.5.1 Scope of Primary Alcohols



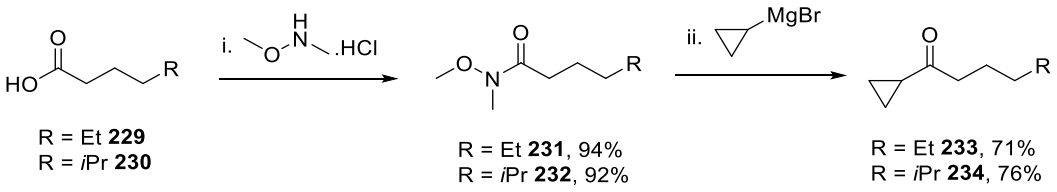
Scheme 2.13 Alcohol substrate scope for α-alkylation of cyclopropyl ketone **90**. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), alcohol (5 equiv), 105 °C, Ar, 24 h

Pleasingly, cyclopropyl ketone **90** underwent facile alkylation with a range of primary alcohols (**Scheme 2.13**). The α-branched ketones formed in this reaction could be easily identified in the ^{1}H NMR spectrum by the appearance of a 1H multiplet in the region of 3.0 ppm corresponding to the single α-proton adjacent to the newly alkylated centre. This 1H multiplet had a HSQC correlation to a peak in region of 50 ppm in the ^{13}C NMR spectrum corresponding to CO*C*H. Alkylation with 1-butanol and cyclopropyl carbinol afforded both alkylated ketones **226** and **227** in excellent yields of 86%. Despite the steric bulk of 3,3-dimethylbutan-1-ol, alkylated ketone **228**

was isolated in a good yield of 68%. We were pleased to find that when the alkylation of ketone **90** using 1-butanol was scaled up to a 1.5 g scale, the corresponding alkylated ketone **226** was formed in a slightly reduced, but still respectable, yield of 61%.

2.3.5.2 Scope of Ketones

With a range of alcohols demonstrated to work well under our designed protocol, we turned our focus to exploring the scope of ketones that could be alkylated with them. We began by preparing ketones **233** and **234** (**Scheme 2.14**).



Scheme 2.14 Synthesis of ketones **233** and **234**. Reagents and conditions: (i) Et_3N (1.4 equiv), DMAP (14 mol%), DCC (1.4 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride (1.4 equiv), CH_2Cl_2, 0 °C to RT, 16 h, (ii) cyclopropyl magnesiumbromide (1.2 equiv), THF, 0 °C to RT, 16 h

Carboxylic acids **229** and **230** were reacted with *N*,*O*-dimethylhydroxyamine hydrochloride to form Weinreb amides **231** and **232** in 94% and 92% yields respectively.[91] Cyclopropyl magnesiumbromide was then added to Weinreb amides **231** and **232**, to provide desired ketones **233** and **234** in 71% and 76% yield respectively. Formation of ketones **233** and **234** was confirmed by the observation of peaks at 211.5 ppm and 211.4 ppm in their ^{13}C NMR spectra, respectively, corresponding to *C*=O. Furthermore, a 1H multiplet in their 1H spectrum in the region of 1.9 ppm relating to the cyclopropyl C-*H* proton further confirmed the formation of the desired cyclopropyl ketones.

A range of other ketones were also prepared to test under our α-alkylation conditions (**Figure 2.8**). The ketones prepared covered a range of functionalities, including an electron-withdrawing CF_3 group, unsaturation, an acetal, and several heterocyclic ring systems.

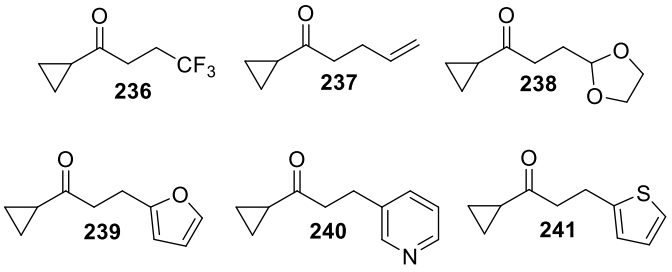
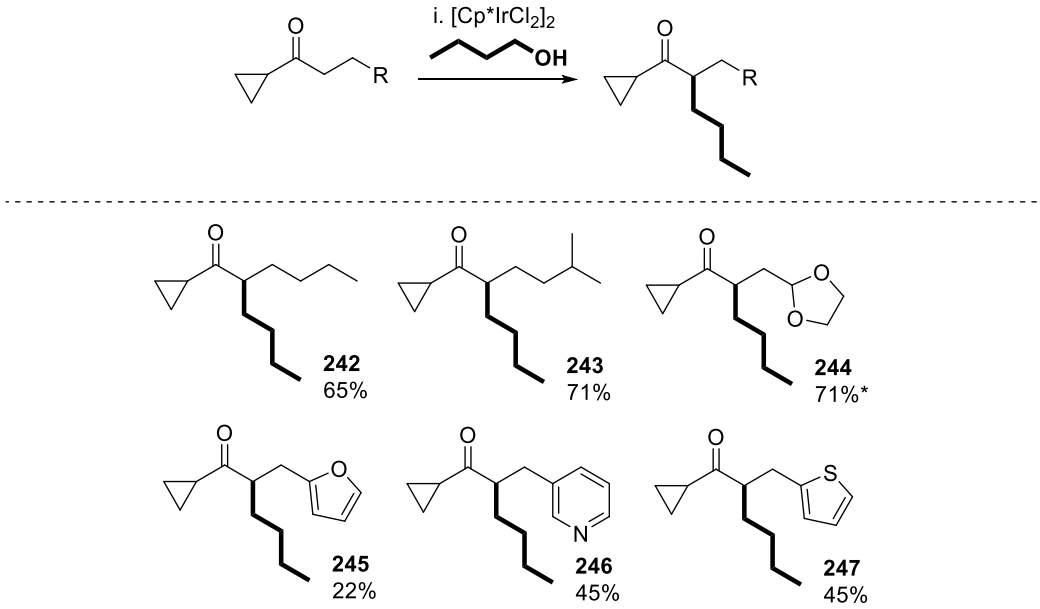


Figure 2.8 Ketones prepared to test under the developed α-alkylation conditions. Synthesised by Dr James Frost

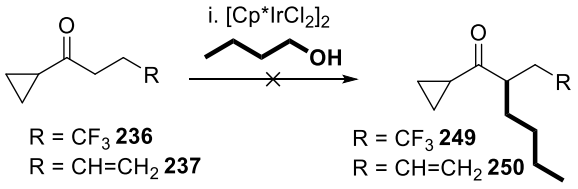
Aware of the MPV-O type process which was observed to occur in absence of catalyst with benzyl alcohol (see **Chapter 2.3.4**), we decided to initially explore the alkylation of the prepared ketones using 1-butanol which was shown to not undergo this process. We were pleased to find that a range of ketones underwent α-alkylation providing the desired branched products in moderate to good yields (**Scheme 2.15**).



Scheme 2.15 Ketones successfully alkylated using 1-butanol. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), 1-butanol (5 equiv), 105 °C, Ar, 24 h

The α-butylated ketones generated in this reaction were easily identified by a 1H multiplet in the region of 2.5–3.0 ppm in the ^{1}H NMR spectrum corresponding to the α-proton adjacent to the alkylated centre. Additionally, a 3H triplet corresponding to the terminal CH_3 group of the added butyl chain was easily identified in the region of 0.9 ppm in the ^{1}H NMR spectrum of the alkylated

products. Pleasingly, alkyl ketones **233** and **234** underwent alkylation with 1-butanol to afford **242** an **243** in good yields of 65% and 71%, respectively, while acetal substituted ketone was also successfully alkylated to form **244**[*] in 71% yield. Ketones bearing heterocyclic rings generally gave moderate yields, with both pyridyl ketone **240** and thiophenyl ketone **241** providing both desired α-alkylated products **246** and **247** in 45% yield, whereas furanyl ketone **239** was alkylated in a reduced yield of 22%. Unfortunately, subjection of ketone **236** to the conditions resulted in no desired reaction (**Scheme 2.16**).



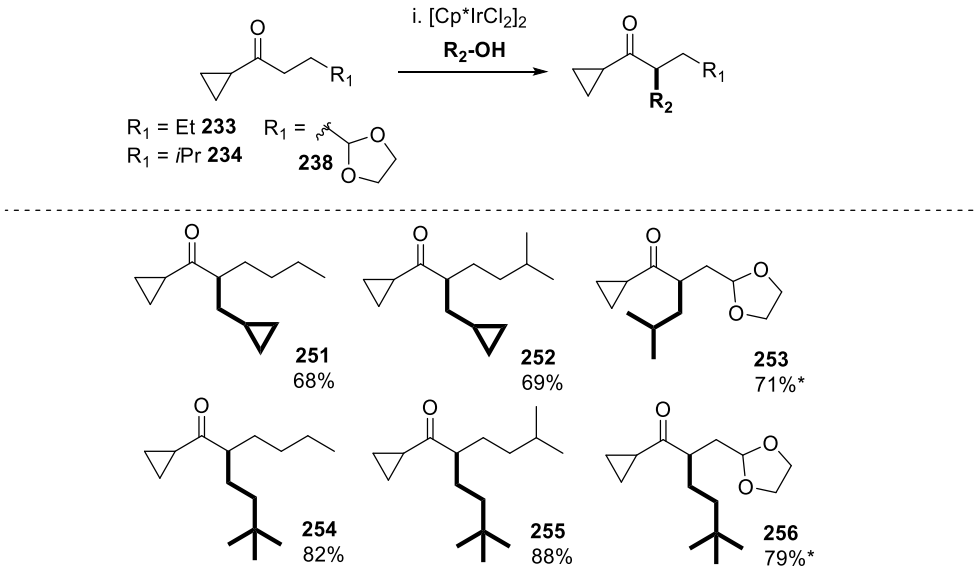
Scheme 2.16 Ketones that failed to alkylate using *n*-butanol. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), 1-butanol (5 equiv), 105 °C, Ar, 24 h

^{1}H NMR analysis of the crude reaction mixture showed a complex mixture, with no sign of starting material. We suspected this may be partially due to the extreme volatility of ketone **236**, not tolerating the elevated reaction temperature. Subjection of alkenyl ketone **237** also returned a complex mixture as indicated by ^{1}H NMR analysis of the crude material. The lack of alkene signals in the NMR spectrum lead us to believe that the double bond had reduced under the reactions conditions and was therefore not tolerated.

2.3.5.3 Further Alkylation Examples: Alcohols and Ketones

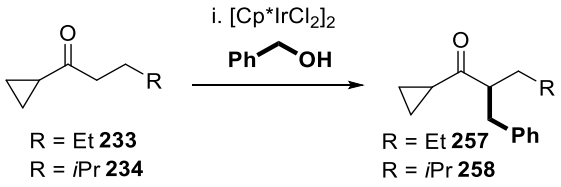
With a greater understanding of the cyclopropyl ketones accommodated under our developed conditions, we set out to test these with primary alcohols other than 1-butanol.

[*] compound **244** synthesised by Dr James Frost



Scheme 2.17 Ketones **233**, **234** and **238** successfully alkylated with a range of primary alcohols. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), alcohol (5 equiv), 105 °C, Ar, 24 h

Gratifyingly, alkyl ketones **233** and **234** were successfully alkylated with cyclopropyl carbinol to form **251** and **252** in good yields of 68% and 69%. In addition, these ketones underwent facile reaction with sterically bulky primary alcohol 3,3-dimethylbutan-1-ol to afford **254** and **255** in excellent yields of 82% and 88%, respectively. We were pleased to find ketone **238** could also be alkylated with *sec*-butanol in 71% yield (**253**)* and 3,3-dimethylbutan-1-ol in 79% (**256**)*.



Scheme 2.18 Ketones that failed to alkylate using BnOH. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), BnOH (5 equiv), 105 °C, Ar, 24 h

Unfortunately, alkyl ketones **233** and **234** reacted poorly with benzyl alcohol (**Scheme 2.18**). Although the formation of small amounts of desired α-branched ketones **257** and **258** were identified by ^{1}H NMR analysis of the crude material, they could not be isolated cleanly despite several purification attempts.

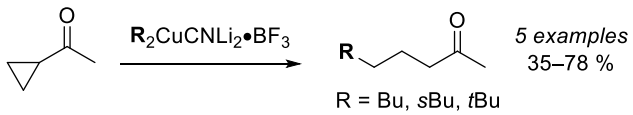
* Compounds **253** and **256** synthesised by Dr James Frost

2.3.6 Ring-opening of α-Alkylated Cyclopropyl Ketones

With the substrate scope completed, we turned our attention to highlighting the synthetic utility of the cyclopropane ring as a versatile handle for further derivatisation. Mono-activated cyclopropanes are known to undergo homoconjugate 1,5-addition reactions under a range of different conditions such as cuprate addition and the addition of hydrogen halides.

2.3.6.1 Addition of Lewis Acid Complexed Cyanocuprates

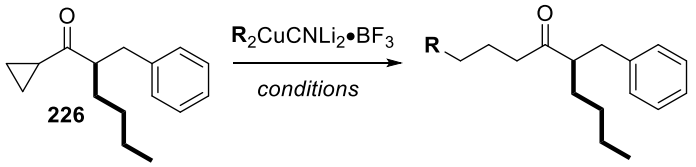
One such method for derivatisation, first reported by Falck and co-workers[92], uses Lewis acid complexed cyanocuprates to add to mono-activated cyclopropyl ketones, opening the cyclopropane ring with concomitant C-C bond formation (**Scheme 2.19**). The addition of Lewis acid is essential, as without it, the system is low yielding and also has an increased propensity for undesired 1,2-addition.[93]

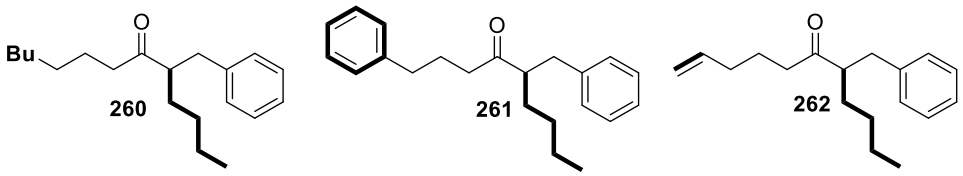


Scheme 2.19 Falck's homoconjugate addition of Lewis acid complexed cyanocuprates to cyclopropyl ketones

We wondered whether the cyclopropyl ketones generated in our reaction would undergo this type of process and whether it could be extended to utilise other organolithiums. α-Branched cyclopropyl ketone **226** was chosen as a model substrate for our studies.

Directly following the protocol by Falck and co-workers[92] using *n*BuLi (**Table 2.9, Entry 1**), lead to some formation of desired ketone **260**, but the reaction did not proceed to completion. Unfortunately, the starting material could not be separated from the desired product. When the reaction was repeated with 3 equivalents of the cyanocuprate (**Entry 2**) to drive the reaction to completion, we were pleased to find desired ketone **260** could be isolated in 63% yield with no trace of starting material.





Entry	R	Conditions	Temp (°C)	Time (h)	Yield (%)
1	Bu	CuCN (2 equiv), *n***Bu**Li (4 equiv), $BF_3{\cdot}Et_2O$ (2 equiv)	–78	1	-
2	Bu	CuCN (3 equiv), *n***Bu**Li (6 equiv), $BF_3{\cdot}Et_2O$ (3 equiv)	–78	1	63 (**260**)
3	Ph	CuCN (3 equiv), *n***Ph**Li (6 equiv), $BF_3{\cdot}Et_2O$ (3 equiv)	–78	1	70 (**261**)
4	$CH{=}CH_2$	$Sn(\mathbf{CH{=}CH_2})_4$ (1.6 equiv), CuCN (3 equiv), *n*BuLi (6.1 equiv), $BF_3{\cdot}Et_2O$ (3 equiv)	–30 to –78	1	46 (**262**)
5	$CH{=}CH_2$	$Sn(\mathbf{CH{=}CH_2})_4$ (3.2 equiv), CuCN (6 equiv), *n*BuLi (12.2 equiv), $BF_3{\cdot}Et_2O$ (6 equiv)	–30 to –78	1	22 (**262**)
6	$CH{=}CH_2$	$Sn(\mathbf{CH{=}CH_2})_4$ (0.8 equiv), CuCN (1.5 equiv), *n*BuLi (3.1 equiv), $BF_3{\cdot}Et_2O$ (1.5 equiv)	–30 to –78	1	43 (**262**)

Table 2.9 Homoconjugate addition of $BF_3{\cdot}Et_2O$ complexed cyanocuprates to cyclopropyl ketone **226**

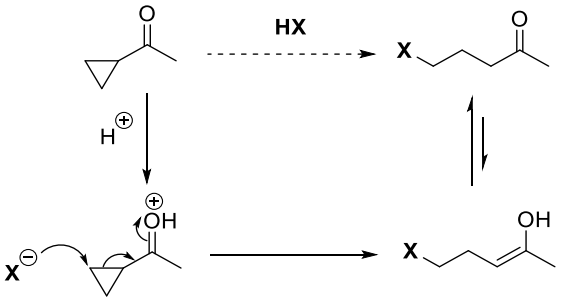
The formation of the product was confirmed by the loss of the characteristic 1H multiplet corresponding to the cyclopropyl C-H proton in the region of 1.9 ppm in the ^{1}H NMR spectrum. A diastereotopic pair of protons corresponding to the newly generated methylene group were observed at 2.32–2.22 ppm and 2.15–2.05 ppm.

Using our modified procedure, we were also able to successfully extend the methodology to incorporate usage of PhLi, affording desired ketone **261** in an excellent yield of 70%. The formation of the product was confirmed by the replacement of the characteristic cyclopropyl C-H proton peak in the ^{1}H NMR spectrum by a pair of (1H, dt) diastereotopic protons at 2.30 ppm and 2.11 ppm corresponding to the new methylene centre adjacent to the carbonyl group.

We then turned our focus to generating a vinyl cuprate species, hoping to form ketone **262**. As vinyl lithium is not available as a commercial solution, this was generated from tetravinyltin prior to forming the cyancuprate species. In our first attempt, desired ketone **262** was isolated cleanly in a moderate yield of 46% (**Entry 3**). The formation of the product was confirmed by observation of a (1H, ddt) proton at 5.61 corresponding to CH_2=C*H* and a 2H multiplet at 4.89–4.83 corresponding to CH_2=CH in the ^{1}H NMR spectrum. It was noted that unreacted starting material remained, though this was not isolated. In an attempt to increase the yield further, the equivalents of cuprate in the reaction were doubled (**Entry 4**). Unfortunately, this led to isolation of ketone **262** in a reduced yield of 22%. In a final attempt to improve the yield, the equivalents of cuprate were halved from the original conditions (**Entry 5**), which also failed to improve the yield but returned a moderate 43% yield.

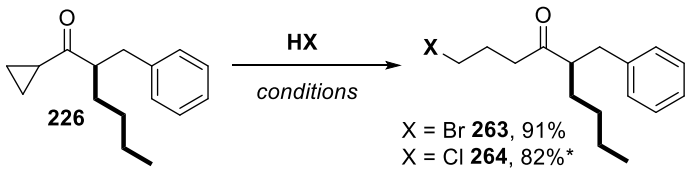
2.3.6.2 Brønsted and Lewis Acid Promoted Addition

A common method for the ring-opening of mono-activated cyclopropanes involves homoconjugate 1,5-addition of hydrogen halides to cyclopropyl ketones (**Scheme 2.20**). This is thought to proceed through initial protonation of the carbonyl oxygen followed by nucleophilic attack by halide, X, and tautomerization to the product.[94]



Scheme 2.20 1,5 homoconjugate addition of HX to cyclopropyl methyl ketone

On subjection of model substrate **226** to aq. HBr, we were pleased to find that ketone **263** could be isolated in an excellent yield of 91% (**Table 2.10, Entry 1**). Additionally, when ketone **226** was treated with HCl/dioxane, chlorinated ketone **264**[*] could also be isolated in 82% yield (**Entry 2**).

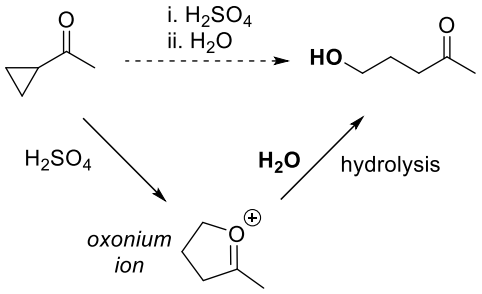


Entry	Conditions	Temp (°C)	Time (h)	Yield (%)
1	aq. HBr (48%)	40	16	91 (**263**)
2[*]	4 N HCl, dioxane	RT	24	82 (**264**)

Table 2.10 Homoconjugate addition of HX to cyclopropyl ketone **226**

Formation of ketone **263** was confirmed by the observation of a peak at 311.1006 in the HRMS corresponding to $C_{16}H_{24}O^{79}Br$, showing that bromine had indeed been incorporated into the product. Furthermore, a characteristic peak at 33.4 ppm in the ^{13}C NMR spectrum was observed which corresponded to CH_2Br.

In related protocols, cyclopropyl ketones have been shown to rearrange to form oxonium ions when subjected to concentrated sulfuric acid[95,96] (**Scheme 2.21**). On hydrolysis, these were converted to the corresponding γ-hydroxyketones.

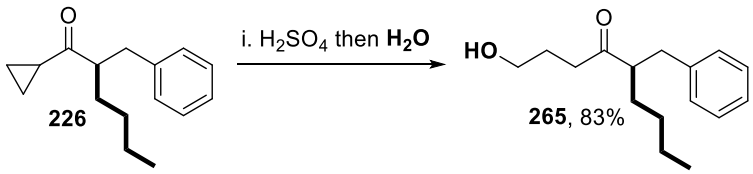


Scheme 2.21 Formation of γ-hydroxypentan-2-one from cyclopropyl methyl ketone

Pleasingly, on subjection of α-alkylated cyclopropyl ketone **226** to concentrated sulfuric acid, γ-hydroxyketone **265** was formed in an excellent yield of 83% (**Scheme 2.22**). Formation of the

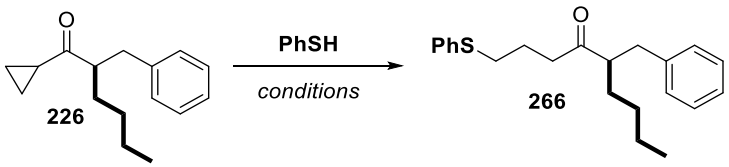
[*] Compound **264** synthesised by Dr James Frost

product was confirmed by observation of a characteristic peak at 62.3 ppm in the ^{13}C NMR spectrum corresponding to *C*H_2OH. A broad peak in the IR spectrum corresponding to an O-H stretch was also observed a 3411 cm^{-1}.



Scheme 2.22 Subjection of cyclopropyl ketone **226** to conc. H_2SO_4. Reagents and conditions: (i) conc. H_2SO_4, 80 °C, 1 h *then* H_2O

Next, we turned our attention to nucleophilic opening of cyclopropyl ketone **226** using thiophenol. Despite its high nucleophilicity, simply heating sodium thiophenolate with cyclopropyl ketone **226** resulted in no reaction (**Table 2.11, Entry 1**). ^1H NMR analysis of the crude material indicated that unreacted starting material remained. We theorised that cyclopropyl ketone **226** required further activation despite the high nucleophilicity of PhSH. Knowing that cyclopropyl ketone **226** was reactive towards Lewis acid $BF_3{\cdot}OEt_2$ from previous studies, we hoped addition of this would help the reaction proceed. Indeed, on addition of Lewis acid, desired ketone **266** could be isolated in a 36% yield (**Entry 2**).



Entry	Conditions	Temp (°C)	Time (h)	Yield (%)
1	NaSPh (1.2 equiv), 0.2 M EtOH	85	17	-
2	PhSH (10 equiv), $BF_3{\cdot}OEt_2$ (15 equiv)	0 °C to RT	24	36
3	PhSH (3.7 equiv), $BF_3{\cdot}OEt_2$ (5 equiv)	0 °C to RT	24	78
4	PhSH (2 equiv), $BF_3{\cdot}OEt_2$ (3 equiv)	0 °C to RT	24	80

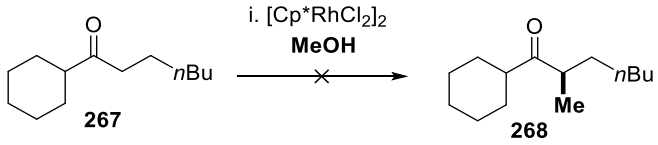
Table 2.11 Optimisation of the addition of PhSH to cyclopropyl ketone **226**

Concerned about the large excess of reagents used in our preliminary attempt with $BF_3{\cdot}OEt_2$, we reduced the equivalents by a factor of 3. Pleasingly, the reduction lead to isolation of ketone **266** in 78% yield (**Entry 3**). Reducing the quantities further still gave ketone **266** in an excellent yield of

80% (**Entry 4**). The formation of product was confirmed by a characteristic peak at 32.9 ppm in the ^{13}C NMR spectrum corresponding to *C*H_2SPh. A peak at 341.1945 was also observed in the HRMS corresponding to the $[M+H]^+$ ion, showing that PhSH had indeed been incorporated into the product.

2.4 Substrate Exploration: Cyclobutyl, Cyclopentyl and Cyclohexyl Ketones

One of the key hypotheses underpinning our decision to pursue cyclopropyl ketones stemmed from the small size of the cyclopropane group. We hoped its small size would prevent the aldol adduct undergoing retro-aldol due to steric strain and facilitate the desired forward reaction. With a protocol for the α-alkylation of cyclopropyl ketones with higher alcohols now in hand, we wondered if the procedure could be extended to related cyclobutyl, cyclopentyl and cyclohexyl ketones. When cyclohexyl ketone **267** was previously subjected to the α-methylation conditions developed in the Donohoe group by Dr. Darren Poole[73], minimal reactivity was reported with almost complete starting material observed by ^1H NMR analysis (**Scheme 2.23**).

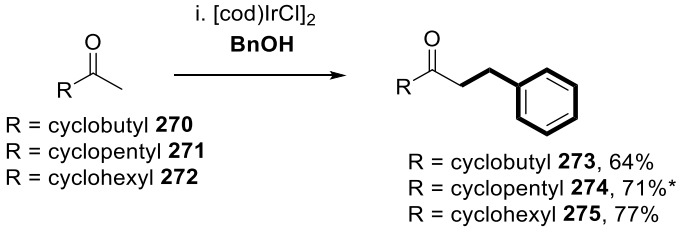


Scheme 2.23 Attempted α-methylation of cyclohexyl ketone **267**. Reagents and conditions: (i) $[Cp^*RhCl_2]_2$ (5 mol%), Cs_2CO_3 (5 equiv), MeOH (0.2 M) 65 °C, O_2. Reaction conducted by Dr Darren Poole

Despite this discouraging result, the A-values for a cyclohexyl group and *i*Pr (a proxy for the cyclopropyl group) are in fact the same, at 2.15[75] kcal mol^{-1}. It would therefore transgress that the A-value for cyclobutyl and cyclopentyl groups would be similar. Consequently, we wondered if our procedure would in fact be able to α-alkylate this related family of compounds.

To test our hypothesis, we began by synthesising the desired cyclobutyl, cyclopentyl and cyclohexyl ketones from the corresponding methyl ketones, **270**, **271** and **272** using hydrogen

borrowing catalysis to form the monoalkylated products (**Scheme 2.24**).[84] Ketones **273**, **274** and **275** were successfully isolated in 64%, 71%* and 77% yields respectively.

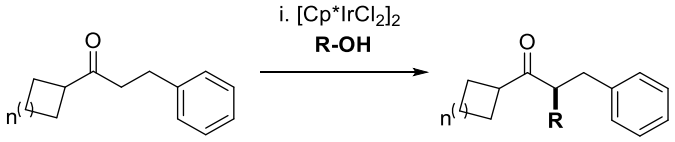


Scheme 2.24 Synthesis of ketones **273**, **274** and **275**. Reagents and conditions: $[(cod)IrCl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (10 mol%), BnOH (1.2 equiv), Ar, 100 °C, 24 h

Three representative primary alcohols, identified from our screen (see **Chapter 2.3.5.1**), were chosen to alkylate newly synthesised ketones **273**, **274** and **275** (**Table 2.12**). Pleasingly, the reaction proceeded in all cases to generate the desired α-alkylated ketone, albeit in varying yields. The formation of α-branched products was confirmed by appearance of a 1H multiplet in the region of 3.0 ppm corresponding to the α-proton adjacent to the newly formed branched centre. It was clear that the yields were generally poorer than those observed with cyclopropyl ketone **90** (see **Chapter 2.3.5**).

Alkylations of all three ketones with benzyl alcohol (**Table 2.12, Entry 1, 4, 7**), were notably poorer. Yields for the alkylation of cyclobutyl ketone **273** (**Entries 1-3**) were also notably poorer than those for cyclopentyl ketone **274** and cyclohexyl ketone **275**. We were pleased to find that alkylation of cyclopentyl ketone **274** and cyclohexyl ketone **275** with butanol and cyclopropyl carbinol provided the desired α-alkylated ketones in moderate to good yields (**Entries 5, 6, 8, 9**).

* ketone **274** synthesised by Dr James Frost



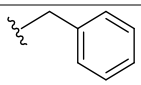
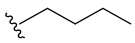
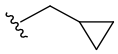
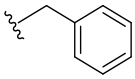
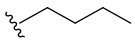
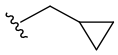
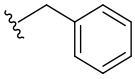
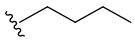
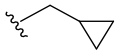
Ketone	Entry	n	R	Yield (%)
Cyclobutyl (273)	1	1		13[a] (**276**)
	2	1		27 (**277**)
	3	1		34 (**278**)
Cyclopentyl (274)	4	2		18 (**279**)
	5	2		40 (**280**)
	6	2		60 (**281**)
Cyclohexyl (275)	7	3		11[a] (**282**)
	8	3		45(**283**)
	9	3		62 (**284**)

Table 2.12 Summary of the alkylation of ketones **273**, **274** and **275**. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv), alcohol (5 equiv), 105 °C, Ar, 24 h [a]contained traces of enone

Despite the conditions being optimised for a different system, we were pleased ketones **273**, **274**, and **275** underwent alkylation under our protocol. This was particularly interesting in the case of cyclohexyl ketone **275**, an analogue of which had previously failed to undergo α-methylation (**Scheme 2.24**). The generally lower yields observed for the alkylation of these ketones compared to cyclopropyl ketone **90** may suggest that steric factors, although important, are only part of the reason that makes cyclopropyl ketones particularly amenable to our methodology. Indeed, as previously discussed, cyclopropanes display a unique reactivity (see **Chapter 2.3.1**), which ketones **273**, **274** and **275** either do not possess or possess to a lesser extent, despite potentially having similar A-values.

2.5 Conclusion

We have extended the scope of α-alkylation chemistry to form branched products using higher alcohols *via* hydrogen borrowing catalysis. In doing so we have developed a procedure for the α-alkylation of cyclopropyl ketones using a range of higher alcohols.

After initial investigation of ynones, which were not tolerated even under α-methylation conditions, cyclopropyl ketones were recognised as key structural motifs that facilitated α-alkylation under hydrogen borrowing conditions to form branched centres. In optimising the alkylation of cyclopropyl ketones, several parameters were investigated, with an increased temperature being recognised as crucial to improving the yield and $[Cp^*IrCl_2]_2$ proving optimal in catalysing the reaction. The optimised procedure was shown to be applicable to a range of cyclopropyl ketones using a variety of primary alcohols.

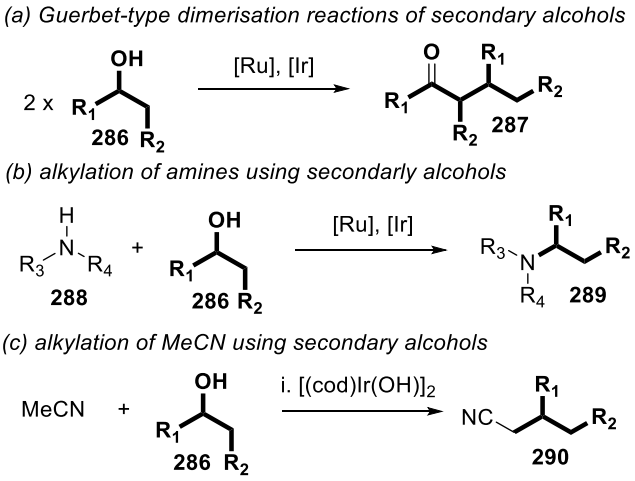
The synthetic utility of the cyclopropane motif as a handle for further functionalisation was then demonstrated through derivatisation of a representative α-alkylated cyclopropyl ketone. The cyclopropyl ketone was successfully ring-opened through a range of homoconjugate 1,5-addition reactions.

Finally, using our optimised protocol for the alkylation of ketones, we attempted to alkylate related cyclobutyl, cyclopentyl and cyclohexyl ketones with primary alcohols. This afforded the desired α-alkylated ketone in all cases, though in varying and lower yields than those observed with cyclopropyl ketones.

Chapter 3: Results & Discussion – β-Branched Products Using Secondary Alcohols

3.1 Introduction

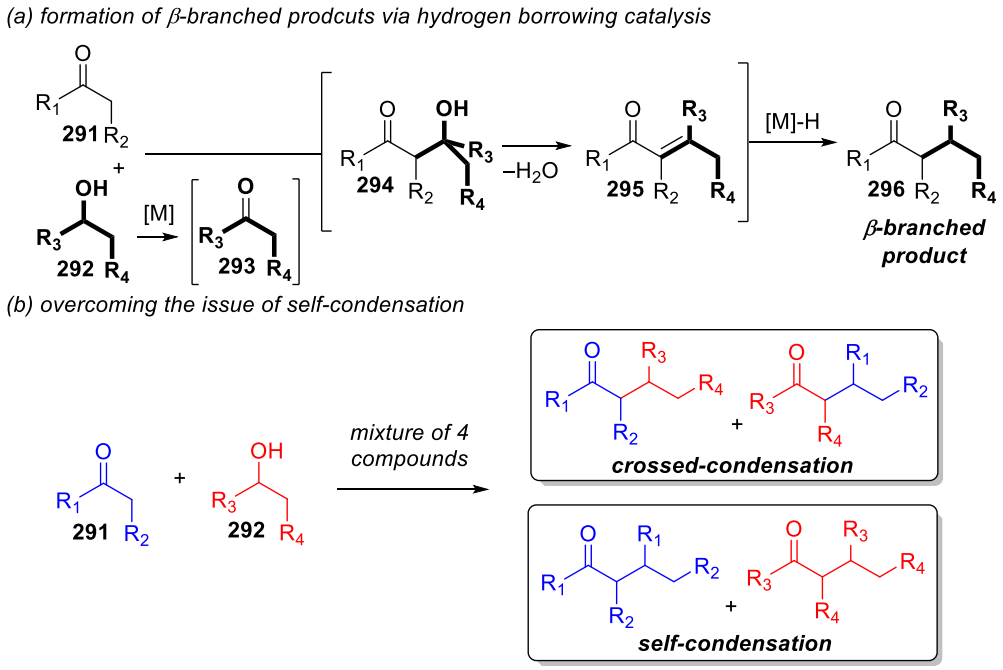
While the alkylation of ketones using primary alcohols has been widely explored, the use of secondary alcohols in similar processes has been much more limited. As discussed in **Chapter 1**, the use of secondary alcohols as alkylating agents has mostly centred around Guerbet-type dimerization reactions to form self-condensation products (**287**) (**Scheme 3.1a**) with the processes typically using ruthenium[58] and iridium[59] based catalytic systems. Additionally, secondary alcohols have also found use in the N-alkylation of amines (**289**) (**Scheme 3.1b**), commonly employing ruthenium[64,65] and iridium[68] based catalysts. In a key contribution to the use of secondary alcohols as alkylating agents, Obora and co-workers[70] demonstrated that acetonitrile could be alkylated with several secondary alcohols (**290**) using $[(cod)Ir(OH)]_2/PPh_3$, though a 10-fold excess of acetonitrile was required at elevated temperatures of 130 °C (**Scheme 3.1c**).



Scheme 3.1 Limited use of secondary alcohols in alkylation reactions: Reagents and conditions: (i) $[(cod)Ir(OH)]_2$ (1 mol%), PPh_3 (4 mol%), KO*t*Bu (2–4 mol%), MeCN (10 equiv), 1,4-dioxane, 130 °C, 24–48 h

Despite this precedent, we were unaware of any methods for the alkylation of carbonyl substrates that involved crossed-condensation with a secondary alcohol to form β-branched products **296** (**Scheme 3.2a**). It was clear that for this transformation to be successful, the issues of

self-condensation of starting ketone **291** as well the ketone derived from the secondary alcohol after oxidation, **292**, needed to be resolved (**Scheme 3.2b**).

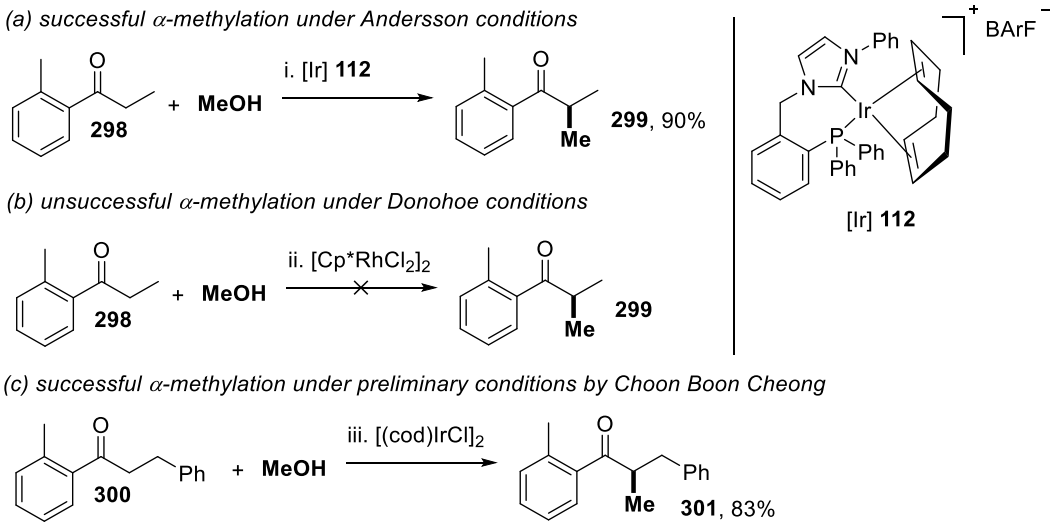


Scheme 3.2 Formation of β-branched products *via* hydrogen borrowing catalysis and the issue of self-condensation and crossed-condensation products forming

3.2 Lead Results – Obtained by Choon Boon Cheong

Choon Boon Cheong, a PhD student within the Donohoe group, had obtained an interesting set of results that formed the foundation upon which this project was built. These results are described within this section.

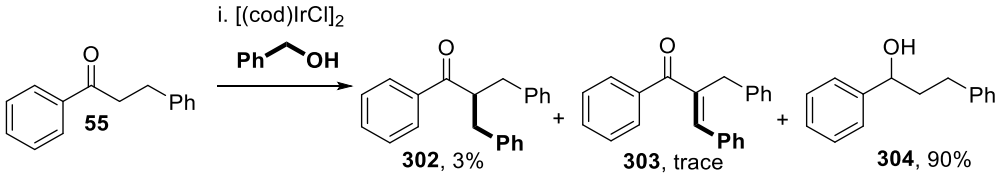
While the work on α-alkylation of cyclopropyl ketones using higher alcohols *via* hydrogen borrowing catalysis was being conducted (see **Chapter 2.3**), Andersson and co-workers reported a procedure for the α-methylation of ketones to form branched products.[97] Interestingly, they were able to methylate phenyl ketone **298** to form the corresponding α-branched ketone **299** (**Scheme 3.3a**), a substrate which Dr Darren Poole in the Donohoe group had been unable to alkylate under the methylation conditions developed within the Donohoe group (**Scheme 3.3b**).[73]



Scheme 3.3 α-methylation of *ortho*-methyl substituted phenyl ketones using methanol. Reagents and conditions: (i) [Ir] **112** (1.0 mol%), Cs_2CO_3 (4 equiv), MeOH (0.2 M), 65 °C, 24 h, (ii) $[Cp^*RhCl_2]_2$ (5 mol%), Cs_2CO_3 (5 equiv), MeOH (0.2 M) 65 °C, O_2, (iii) $[(cod)IrCl]_2$ (2 mol%), (±)-BINAP (3 mol%), KOH (3 equiv), MeOH (0.2 M), 65 °C, Ar, 48 h

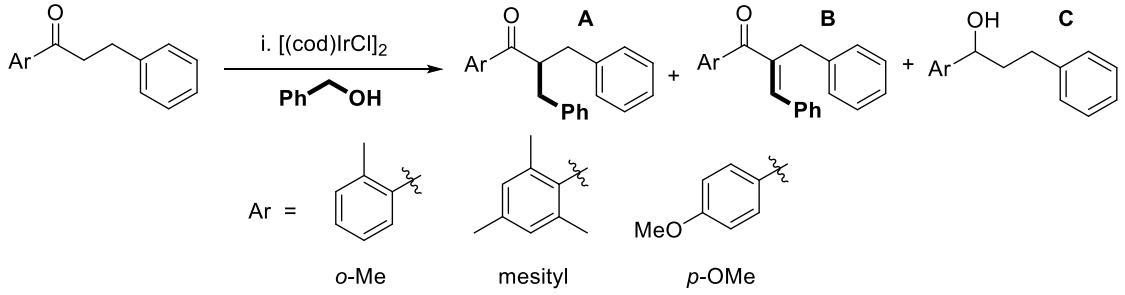
The failure of ketone **298** to methylate under these Rh-catalysed conditions was thought to be due to an excessively strained aldol adduct due to extra steric bulk added by the *ortho*-methyl group on the phenyl ring, leading to a retro-aldol process. It was hypothesised whether the result from Andersson and co-workers suggested that it was not, in fact, the substrate that resulted in a more sterically encumbered aldol adduct, but simply that the Rh-catalysed system was ineffective at alkylating ketone **298.** Reverting to an Ir-based system, as Andersson and co-workers had shown to be effective, was potentially thought to be relevant. To test this hypothesis, *ortho*-methyl substituted methylene ketone **300** was subjected to a set of preliminary conditions (**Scheme 3.3c**). Surprisingly, α-methylated product **301** could be isolated in 83% yield.

Alongside the optimisation of conditions for the alkylation of cyclopropyl ketones with higher alcohols (see **Chapter 2.3.3**), Choon Boon Cheong had also investigated the α-alkylation chemistry of ketones with higher alcohols *via* hydrogen borrowing catalysis, although with a focus on aromatic ketones. Initially, little success was found in attempting to form α-branched compounds from aromatic ketones.



Scheme 3.4 Attempted benzylation of methylene ketone **55**. Reagents and conditions: $[(cod)IrCl]_2$ (2 mol%), (±)-BINAP (3 mol%), KOH (3 equiv), BnOH (7 equiv), 65 °C, Ar, 48 h. Reaction conducted by Choon Boon Cheong

When methylene ketone **55**, a substrate which had undergone facile α-methylation, was subjected to alkylation with benzyl alcohol, the major product formed was alcohol **304** in 90% yield, resulting from direct 1,2-reduction of starting ketone **55** (**Scheme 3.4**). The desired α-benzylated compound, **302**, was only formed in 3% yield. Interestingly, when *ortho*-methyl phenyl ketone **300** was subjected to the same benzylation conditions, desired α-benzylated ketone **305** was isolated in 40% yield (**Table 3.1, Entry 1**). The major side product was alcohol **307**, as before, generated by direct 1,2-reduction of starting methylene ketone **300**.



Entry	Ar	A (%)	B (%)	C (%)	RSM (%)
1	*o*-Me (**300**)	40 (**305**)	trace (**306**)	60 (**307**)	trace
2	Mesityl (**308**)	75 (**309**)	20 (**310**)	- (**311**)	4
3	*p*-OMe (**312**)	< 3 (**313**)	trace (**314**)	60 (**315**)	40

Table 3.1 Alkylation of aryl methylene ketones with benzyl alcohol. Reagents and conditions: (i) $[(cod)IrCl]_2$ (2 mol%), (±)-BINAP (3 mol%), KOH (3 equiv), BnOH (7 equiv), 65 °C, Ar, 48 h. Reactions conducted by Choon Boon Cheong

To understand why the presence of an *ortho*-methyl substituent was proving beneficial to this reaction, the alkylation of other aryl methylene ketones was studied. When mesityl ketone **308**, featuring a di-*ortho*-methyl substitution pattern was subjected to the reaction conditions, desired α-benzylated ketone **309** was formed in a good yield of 75%, alongside 20% of corresponding

enone intermediate **310**, with no 1,2-reduction product **311** observed (**Entry 2**). To probe whether this effect was a consequence of sterics or electronics, *p*-OMe phenyl ketone **312** was also tested (**Entry 3**). Interestingly, only trace conversion to desired ketone **313** was observed, with the main product of reaction being alcohol **315**. It was suspected that the *ortho*-methyl groups on the phenyl ring were resultin in the aromatic ring twisting out of plane of the carbonyl group and therefore out of conjugation. Indeed, when the C=O IR stretches for aryl ketones **55**, **300** and **308** were compared (**Figure 3.1**), the presence of *ortho*-methyl groups shifted this signal to a higher wavenumber, indicating a stronger C=O bond and hence a lower degree of conjugation. This effect was particularly pronounced in the case of mesityl ketone **308**, for which the C=O stretch was observed at 1697 cm^{-1}. This was reinforced by the observation that the ^{13}C NMR signal for C=O in mesityl ketone **308** was shifted downfield to 209.8 ppm, in contrast to that for unsubstituted phenyl ketone **55** at 199.0 ppm. Again, this indicated a more deshielded carbon, as would be expected from a system with a lower degree of conjugation.

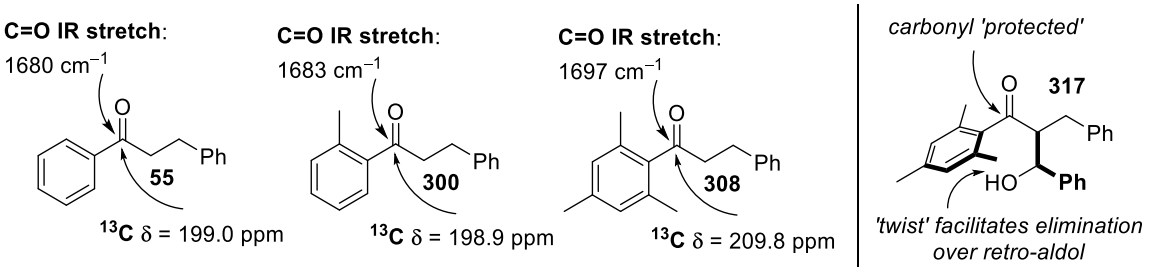
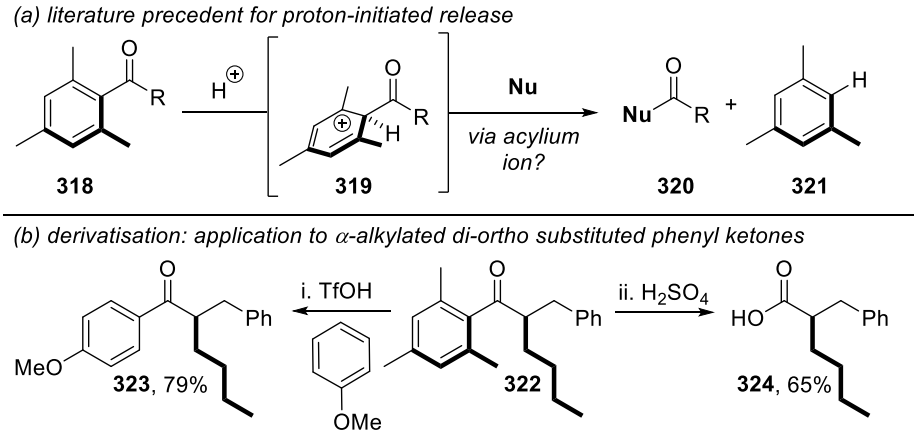


Figure 3.1 Comparison of IR stretches and ^{13}C NMR peaks for C=O in aryl methylene ketones

We theorised that the benefits of di-*ortho*-methyl substituted phenyl rings in this reaction were two-fold: (i) the *ortho*-methyl groups protect the carbonyl from undesired 1,2-reduction, and (ii) twisting out of the plane reduces steric hindrance around the α-carbon, attenuating the rate of retro-aldol of β-hydroxy ketone **317** (**Figure 3.1**) and allowing facile elimination to the enone.

Next, the α-alkylation of aryl ketones with higher alcohols using *ortho*-methyl phenyl ketone **300** as a model substrate was optimised and it was demonstrated that the protocol could be applied to a range of *ortho*-substituted aryl ketones, including mesityl ketone **308**. Meanwhile, a

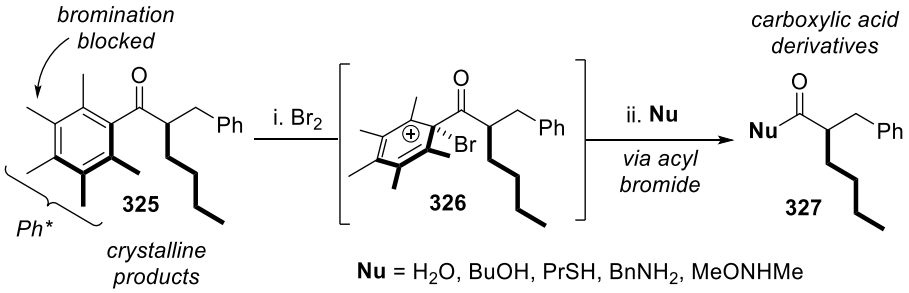
precedent for the derivatisation of *ortho*-substituted aromatic ketones was discovered by Dr James Frost. Di-*ortho* substituted aromatic ketones were known to undergo *ipso*-protonation, followed by a retro-Friedel–Crafts acylation reaction to form an acylium ion.[98,99] Notably, this was only observed to occur when *ortho*-substitution on the aromatic ring was present, which, through the lack of planarity imposed, was thought to facilitate *ipso*-reaction. The reactive intermediate **319** could then be trapped to form a variety of products **320** with release of mesitylene **321** (**Scheme 3.5a**).



Scheme 3.5 Proton-initiated release of mesityl ketones *via ipso*-protonation and a retro-Friedel–Crafts acylation reaction. Reagents and conditions: (i) H_2SO_4 (15.5 M), 65 °C, 30 mins, (ii) anisole (3.0 equiv.), TfOH (1.2 equiv.), 100 °C, 1.5 h. Reactions conducted by Dr James Frost

This procedure was successfully applied to α-alkylated mesityl ketone **322**, with the reactive intermediate trapped with anisole to provide aromatic ketone **323,** and water to provide carboxylic acid **324** (**Scheme 3.5b**). In searching for milder and a more versatile set of conditions, it was discovered that treatment of *ortho*-disubstituted aryl ketones with Br_2 at low temperatures was particularly effective. This was thought to proceed through *ipso*-bromination to give **326**, followed by generation of the corresponding acid bromide which could subsequently be trapped with a range of nucleophiles to give carboxylic acid derivatives (**327**) (**Scheme 3.6**). Although mesityl ketones underwent this reaction, a large excess of bromine was required as bromination at the unsubstituted positions of the mesityl group occurred. To prevent this unwanted reaction, the pentamethylphenyl (Ph*) group was utilised (**325**), effectively blocking bromination of the

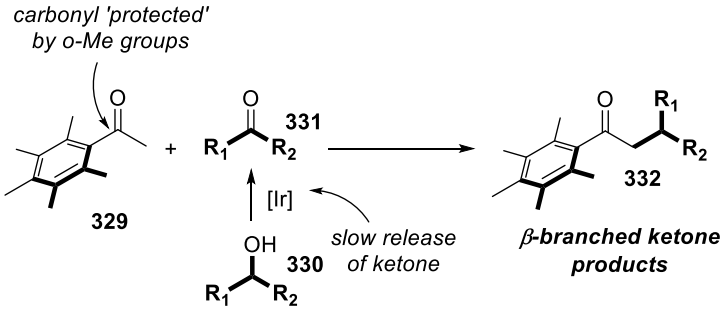
aromatic ring and lowering the equivalents of bromine required. Pleasingly, pentamethylphenyl ketones also underwent facile α-alkylation with higher alcohols under the conditions optimised by Choon Boon Cheong.



Scheme 3.6 Bromine-initiated release of α-alkylated pentamethylphenyl ketones. Reagents and conditions: Br_2 (2 equiv), CH_2Cl_2, –17 °C, *then* Nu (3 equiv), –17 °C to RT

With respect to the alkylation of ketones using secondary alcohols, we wondered if the attributes of di-*ortho*-methyl substituted ketones could be exploited to overcome some of the issues anticipated with their use (see **Chapter 3.1**). We anticipated the protection of the carbonyl group afforded by the di-*ortho*-methyl substitution pattern on the phenyl ring would prevent self-condensation of this starting ketone **329** (**Scheme 3.7**). In addition, we hoped a slow release of partner ketone **331** *via* oxidation of secondary alcohol **330** by the catalyst would prevent self-condensation of this ketone too. The control afforded by the substrate and catalyst could therefore hold the potential to facilitate the formation of cross condensation product **332** as the major product of the reaction.

The following sections describe my efforts at optimisation of the desired reaction, followed by exploration of the substrate scope and related processes.



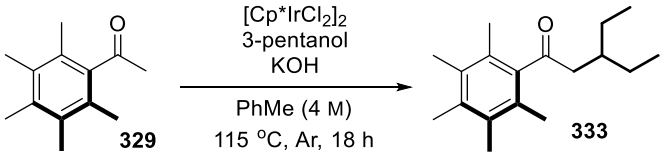
Scheme 3.7 Exploiting attributes of di-*ortho*-methyl phenyl ketones and catalytic control to overcome problems with the use of secondary alcohols in hydrogen borrowing catalysis

3.3 Optimisation

It was clear from the results obtained by Choon Boon Cheong and Dr James Frost in the Donohoe group (see **Chapter 3.2**) that pentamethylphenyl (Ph*) ketones were the best substrate to begin optimisation of a protocol for alkylation using secondary alcohols.

Although $[(cod)IrCl]_2$ had been used as the catalyst in the α-alkylation reactions of Ph* ketones thus far, it had been noted previously that $[Cp^*IrCl_2]_2$ was also effective at performing analogous α-alkylation chemistry on cyclopropyl ketones (see **Chapter 2.3.3**) but did not require any additional ligand. It was therefore decided that initial studies would begin by using $[Cp^*IrCl_2]_2$ as the catalyst. The optimisation studies began by subjecting Ph* methyl ketone **329** and 3-pentanol (**328**) (1.1 equiv), with $[Cp^*IrCl_2]_2$ (2 mol%) and KOH (1 equiv) at 115°C in toluene (**Table 3.2, Entry 1**). Pleasingly, under these conditions, desired β-branched ketone **333** was isolated in a 12% yield as a single product, with no other crossed condensation or self-condensation products observed. Recovered starting material (RSM) accounted for 61% of the isolated material. To address the low yield, adding an excess of KOH (**Entries 2–4**) was investigated. Increasing the amount of base to 2 or 3 equivalents of KOH (**Entries 2 and 3**) significantly increased the conversion to 40% of ketone **333**, whilst 39% starting material was recovered. Increasing the amount of base further did not provide any further benefit (**Entry 4**) therefore 3 equivalents of KOH was deemed optimal. Since starting material had been recovered from each example, we decided to investigate increasing the equivalents of 3-pentanol in the reaction (**Entries 5–7**). When

the amount of 3-pentanol was increased to 1.5 equivalents (**Entry 5**), there was a corresponding increase in yield to 44%. Pleasingly, when this was increased further to 2 equivalents (**Entry 6**), desired ketone **333** was isolated in a good yield of 65%, with 21% recovered starting material.

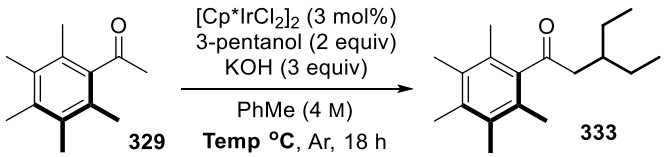


Entry	KOH (equiv)	3-Pentanol (equiv)	$[Cp^*IrCl_2]_2$ (mol%)	333 (%)	RSM (%)
1	1	1.1	2	12	61
2	2	1.1	2	18	53
3	3	1.1	2	40	39
4	4	1.1	2	33	39
5	3	1.5	2	44	40
6	3	2.0	2	65	21
7	3	4.0	2	60	26
8	3	2.0	1	60	21
9	3	2.0	3	70	25
10	3	2.0	4	56	21

Table 3.2 Screen of equivalents of KOH, equivalents of 3-pentanol and loading of $[Cp^*IrCl_2]_2$

Increasing the diol loading further to 4 equivalents (**Entry 7**) did not improve the yield; therefore, the optimisation was taken forward with 2 equivalents of secondary alcohol. Next, we turned our attention to the loading of catalyst $[Cp^*IrCl_2]_2$ (**Entries 8–10**). Lowering the loading to 1 mol% (**Entry 8**) had minimal impact on the yield, with ketone **333** isolated in 60% yield. However, increasing the loading to 3 mol% (**Entry 9**) afforded the desired product in 70% yield, with 25% recovered starting material – a mass recovery of 95%. When the amount of catalyst was increased further to 4 mol% (**Entry 10**), a slightly reduced yield of β-branched ketone **333** was isolated, therefore 3 mol% was decided upon as being optimal.

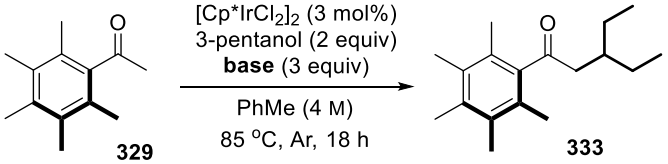
With these conditions in hand, attention was turned to varying the reaction temperature. Initially the study began by increasing the temperature progressively to 125 °C (**Table 3.3, Entries 1–3**), which provided little to no improvement to the yield of desired ketone **333**.



Entry	Temp (°C)	333 (%)	RSM (%)
1	115	70	25
2	120	72	14
3	125	65	18
4	105	80	5
5	95	16	55
6	85	12	61

Table 3.3 Screen of temperatures

Gratifyingly, when the temperature of the reaction was lowered to 105 °C (**Entry 4**), β-branched ketone **333** was isolated in 80% yield, with only 5% recovered starting material. Unfortunately, lowering the temperature to 95 °C (**Entry 5**) and 85 °C (**Entry 6**) resulted in the reaction stalling significantly, returning yields of only 16% and 12% of ketone **333**, respectively. At these lower temperatures, it was observed that after 18 h the KOH pellets had not dissolved and could be recovered almost intact from the reaction vessel. This observation led us to consider whether the reaction was only stalling at lower temperatures due to the solubility of KOH in toluene. In searching for bases with notable solubility in toluene, it was discovered KO*t*Bu may be a suitable candidate with a solubility of 2.27 g per 100 mL toluene at 25-26 °C.[100] In addition, we wondered whether the use of powdered KOH would improve the situation.



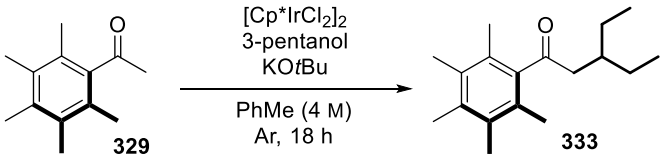
base	333 (%)	RSM (%)
KOH (pellets)	12	61
KOH (powder)	15	60
KO*t*Bu	84	-

Scheme 3.8 Investigation of a more soluble base

Using powdered KOH instead of KOH pellets provided little improvement to the yield at 85 °C (**Scheme 3.8**). Pleasingly, substituting KOH with KO*t*Bu afforded β-branched ketone **333** in an

excellent yield of 84% with full conversion of the starting material (**Scheme 3.8**). Based on this result, it was decided that KOH should be replaced with KO*t*Bu in the protocol.

With the temperature required for reaction lowered to 85 °C and a potential solubility issue addressed, some of the parameters optimised earlier were revisited before moving ahead to ensure they were still optimal after taking the latest results into consideration.



Entry	3-Pentanol (equiv)	$[Cp^*IrCl_2]_2$ (mol%)	KO*t*Bu (equiv)	Temp (°C)	333 (%)	RSM (%)
1	2.0	3	3	85	84	-
2	2.0	2	3	85	86	-
3	2.0	1	3	85	56	25
4	1.1	2	3	85	58	21
5	1.5	2	3	85	55	25
6	2.0	2	1	85	15	65
7	2.0	2	2	85	31	51
8	2.0	2	3	65	33	40
9	2.0	2	3	75	54	19

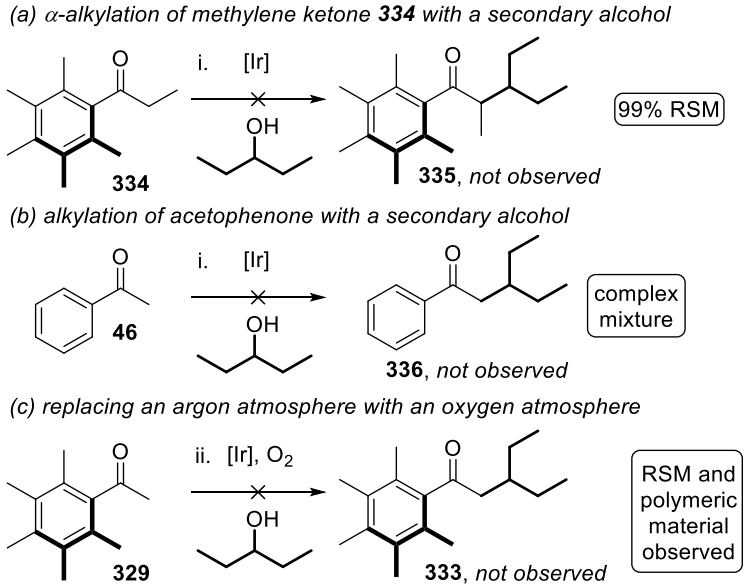
Table 3.4 Second round of optimisation screening equivalents of 3-pentanol, equivalents of KO*t*Bu, loading of $[Cp^*IrCl_2]_2$ and temperature

The catalyst loading could be lowered to 2 mol% without any loss in yield of ketone **333** (**Table 3.4, Entry 2**), though a further reduction (**Entry 3**) led to a reduced yield of 56% and 25% recovered starting material. Adopting 2 mol% as the catalyst loading, the stoichiometry of 3-pentanol required in the reaction were investigated. Reducing the amount of alcohol from 2 equivalents to 1.5 or 1.1 equivalents had a detrimental effect on the yield in both cases (**Entries 4 and 5**). The amount of KO*t*Bu also could not be lowered without causing the reaction to stall, resulting in a reduced yield of ketone **333** and recovered stating material (**Entries 6 and 7**). Finally, we attempted to reduce the reaction temperature to 75 °C (**Entry 8**) and 65 °C (**Entry 9**), though in

both cases after 18 h, the reaction was incomplete and led to reduced yields of desired ketone **333** and significant amounts of recovered starting material.

3.4 Control Experiments

Satisfied that an optimised set of conditions for the alkylation of di-*ortho*-substituted ketones with secondary alcohols were in hand, a set of control experiments were conducted.



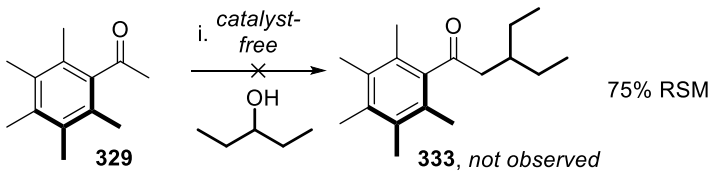
Scheme 3.9 Control experiments: (a) attempted α-alkylation of methylene ketone **334** with 3-pentanol, (b) attempted alkylation of acetophenone with 3-pentanol, (c) attempted alkylation of ketone **329** with 3-pentanol under an atmosphere of O_2. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), 3-pentanol (2 equiv), 85 °C, Ar, 18 h, (ii) $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), 3-pentanol (2 equiv), 85 °C, O_2, 18 h

The investigation began by attempting to α-alkylate methylene ketone **334** with 3-pentanol (**Scheme 3.9a**). Although Ph* methylene ketones had successfully been alkylated with primary alcohols previously in the Donohoe group by Choon Boon Cheong (see **Chapter 3.2**), methylene ketone **334** did not show any conversion to desired ketone **335**, with 99% of starting material recovered. It was suspected this may be due to a very strained aldol adduct preferring to undergo a retro-aldol reaction rather than elimination to give the corresponding enone.

To highlight the crucial role that Ph* methyl ketone **329** plays in facilitating the alkylation process, acetophenone (**46**) was subjected to the optimised procedure (**Scheme 3.9b**). Lacking any

ortho-substitution on its aromatic ring, it was perhaps unsurprising that the reaction with acetophenone led to the formation of a complex mixture. Without protection, the carbonyl would be susceptible to 1,2-reduction, as well as self-condensation, which most likely contributed to its consumption under the reaction conditions.

Though our protocol had been optimised under an atmosphere of argon, we were interested to test the effects of switching this to oxygen (**Scheme 3.9c**). Rh-catalysed α-methylation chemistry developed in the Donohoe group previously had benefitted from improved yields under oxygen.[44,73] In this case, oxygen provided no beneficial effect, returning only traces of starting material and insoluble polymeric material.

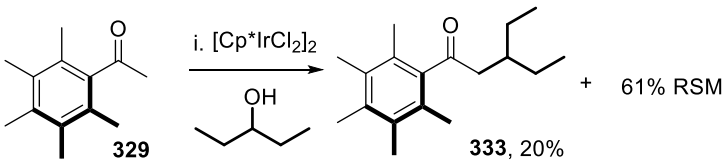


Scheme 3.10 Catalyst-free control experiment. Reagents and conditions: (i) KO*t*Bu (3 equiv), 3-pentanol (2 equiv), 85 °C, Ar, 18 h

Next, ketone **329** was subjected to a control reaction omitting $[Cp^*IrCl_2]_2$ from the procedure to highlight the key role it plays in facilitating the reaction (**Scheme 3.10**). No conversion to β-branched ketone **333** was observed under catalyst-free conditions, with only 75% starting material recovered.

3.4.1 Reproducibility Issues with Potassium tert-Butoxide

Part of the investigation was conducted at GlaxoSmithKline's (GSK) laboratory in Stevenage, UK. It was at this point an unusual reproducibility issue with the optimised protocol was identified. When ketone **329** was subjected to the optimised protocol under identical conditions at this laboratory, the reaction behaved very differently, resulting in only 20% yield of desired ketone **333** with 61% recovered starting material (**Scheme 3.11**).

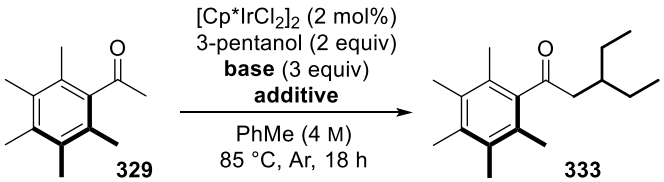


Scheme 3.11 Repeating the optimised procedure in GlaxoSmithKline's laboratory. Reagents and conditions: $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), 3-pentanol (2 equiv), 85 °C, Ar, 18 h

After a thorough investigation, several factors were ruled out, leaving the base, KO*t*Bu, as the source likely to be hindering the reaction. As KO*t*Bu is known to be water and air sensitive[100], it was suspected that the batch being used may have been quenched to some degree. Despite several new commercial bottles of KO*t*Bu being tested, the result repeatedly led to poor conversion to β-branched ketone **333**, typically varying between 20-50%. We were, however, aware, that a 'new' bottle from a commercial supplier did not necessarily constitute a freshly made batch of KO*t*Bu. Next, the reaction was conducted at GSK using the same batch of KO*t*Bu that had been used during the optimisation at our laboratory in Oxford. Pleasingly, the desired ketone could again, be isolated in 86% yield. Interestingly, the base used at our laboratory in Oxford was 95% grade, whereas the grade being used at GSK was 98% grade, both of which were provided by the chemical supplier Sigma Aldrich. On contacting Sigma Aldrich, it was determined that the 95% grade of KO*t*Bu was no longer available, with only 98% or 99.99% sublimed grade now provided. To eliminate the possibility that our 95% grade was unique in composition, several batches of 95% grade KO*t*Bu were sourced from other research groups within the department. The reaction went to completion in all cases, providing a yield of ketone **333** in the vicinity of 85%.

Satisfied that this was indeed an issue relating to the grade of KO*t*Bu, focus was turned to investigating why the 98% grade was behaving differently to the 95% grade. It was hypothesised that the 95% grade KO*t*Bu may contain levels of *t*BuOH, KOH or in fact water. All these factors could potentially effect the reactivity of the base. Investigation of these hypotheses began by looking at the effect of adding *t*BuOH to the reaction. The addition of 0.9 equiv of *t*BuOH appeared to have no impact on the yield (**Table 3.5, Entry 1**) whereas increasing this to 2.8 equiv appeared

to have only a marginally positive effect, leading to 30% yield of ketone **333**. Interestingly, when 2 mol% of water was added into the reaction (**Entry 3**), **333** could be isolated in 40% yield. Intrigued by this observation, the amount of water was increased to 5 mol% which remarkably led to complete reaction and isolation of β-branched ketone **333** in 86% yield (**Entry 4**). This result was repeated several times, with the reaction proceeding to completion in each case.



Entry	Base	Additive	333 (%)	RSM (%)
1	KO*t*Bu (98% grade)	*t*BuOH (0.9 equiv)	21	59
2	KO*t*Bu (98% grade)	*t*BuOH (2.8 equiv)	30	49
3	KO*t*Bu (98% grade)	water (2 mol%)	40	35
4	KO*t*Bu (98% grade)	water (5 mol%)	86	-
5	KO*t*Bu (95% grade)	water (5 mol%)	-	91
6	KOH	water (5 mol%)	trace[a]	-[a]
7	KOH	*t*BuOH (0.9 equiv)	trace[a]	-[a]
8	KO*t*Bu[b]	-	86	-
9	KO*t*Bu (99.99%)[c]	-	16	69

Table 3.5 Investigating the effects of various additives and grades of KO*t*Bu on yield of ketone **333**. [a]observed by ^{1}H NMR analysis of the crude material only, [b]synthesised from *t*BuOH and potassium metal by Dr James Frost, [c]sublimed grade

When 95% grade KO*t*Bu was used instead of 98% grade KO*t*Bu, with 5 mol% of water also added in, no reaction was observed (**Entry 5**). Changing the base to KOH and spiking in 5 mol% water only resulted in trace conversion to desired ketone **333** (**Entry 6**). Using KOH again but with *t*BuOH also only resulted in a trace of product (**Entry 7**). The reason behind the beneficial effect of water in this reaction was not clear to us.

However, we were pleased to find, when KO*t*Bu that had been synthesised* in our lab from *t*BuOH and potassium metal (see **Chapter 5.1** for experimental procedure) was used, desired ketone **333**

* Synthesised by Dr James Frost

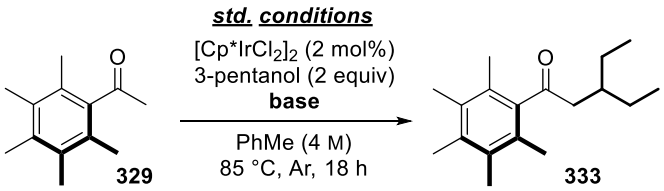
was isolated in an excellent yield of 86% (**Entry 8**). In contrast, when commercially purchased sublimed grade KO*t*Bu (99.99%) was used, ketone **333** was formed in a reduced yield of 16% (**Entry 9**). Trace-metal analysis was conducted on all the grades of KO*t*Bu that had been used but unfortunately this was inconclusive.

On further investigation it was discovered that it is, in fact, known that KO*t*Bu can exist in two distinct structural forms, characteristics of which can differ.[101] As reported by Chisholm and co-workers, the first of these, which is formed from addition of potassium metal to *t*BuOH with no further purification, adopts a one-dimensional ribbon-like chain structure, $[KO\textit{t}Bu{\cdot}\textit{t}BuOH]_{\infty}$, in the solid state. NMR studies in benzene or toluene at room temperature suggest it exists as a trimer or possibly a cyclic trimer in solution. The authors note that in this form, KO*t*Bu is highly soluble. Ribbon-like $[KO\textit{t}Bu{\cdot}\textit{t}BuOH]_{\infty}$ could be converted into its other structural form, the tetramer $[KO\textit{t}Bu]_4$, upon sublimation. This tetrameric form was shown to persist in the solid state, in solution, as well as the gaseous phase. Notably, even in Lewis-basic solvents such as Et_2O and THF the tetrameric species remained intact.

It was therefore hypothesised that the difference in reactivity that had been observed in using different grades of KO*t*Bu was due to difference in solubilities of the two forms, stemming from their structural differences. Though Sigma Aldrich could not confirm the methods through which they had synthesised the, now discontinued, 95% grade KO*t*Bu, it was suspected that it may have been prepared in a similar protocol to that used by Chisholm and co-workers to synthesise $[KO\textit{t}Bu{\cdot}\textit{t}BuOH]_{\infty}$, as well as the method that we had used to synthesise KO*t*Bu. Both the KO*t*Bu synthesised in our lab, and the 95% grade batches were successful at performing the desired reaction. In contrast, it was thought that the preparation of 98% grade and 99.99% grade KO*t*Bu from Sigma Aldrich may involve a sublimation step which results in the formation of the less soluble tetrameric form of the base. One explanation for the beneficial effect of water on the reaction with the poorly performing 98% grade KO*t*Bu may be that is able to break-up the

tetrameric aggregates, aiding solubility of the base and hence facilitating the desired reaction. Due to the discontinuation of the 95% grade KO*t*Bu, it was decided to conduct all future reactions requiring KO*t*Bu using batches synthesised in our laboratory.

Furthermore, in conjunction with Dr James Frost, a variety of other related bases were explored. Unfortunately, LiO*t*Bu resulted in no reaction, with 94% starting material recovered (**Table 3.6, Entry 1**). The use of NaOH resulted in incomplete reaction, offering a moderate yield of 44% of ketone **333** (**Entry 2**). Comparably, when KOH was used under these conditions (see **Chapter 3.3, Table 3.3, Entry 1**), it only resulted in a 12% yield of ketone **333**. Led by this result, we next tested NaO*t*Bu in our protocol. Gratifyingly, this afforded β-branched ketone **333** in an excellent yield of 97%. Dr James Frost in the Donohoe group then proceeded to optimise the conditions utilising NaO*t*Bu further which led to a reduction of Ir-catalyst loading to 0.5 mol% and amount of 3-pentanol to 1.5 equivalents (**Entry 4**).



Entry	Base	Base (equiv)	Deviation from std. conditions	333 (%)	RSM (%)
1[*]	LiO*t*Bu	3	-	-	94
2	NaOH	3	-	44	44
3	NaO*t*Bu	3	-	97	-
4	NaO*t*Bu	2	$[Cp^*IrCl_2]_2$ (0.5 mol%), 3-pentanol (1.5 equiv)	91	-

Table 3.6 Exploring other bases for the formation of β-branched products

Control reactions performed on the KO*t*Bu system (see **Chapter 3.4**), were repeated with the NaO*t*Bu system and returned identical results.

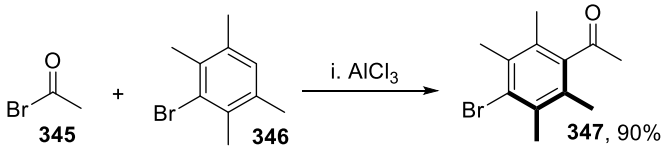
[*] Reaction conducted by Dr James Frost

3.5 Substrate Scope

With two robust protocols using either KO*t*Bu or NaO*t*Bu in-hand, attention was turned to exploring the substrate scope for the reaction.

3.5.1 ortho-Substituted Aryl Ketones

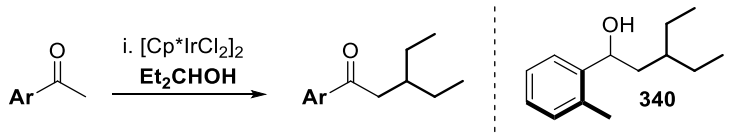
The investigation began by exploring the scope of the aryl group under the optimised protocol. As discussed previously (see **Chapter 3.1**), *ortho*-substitution on the aryl group was deemed to be essential for the successful α-alkylation of methylene ketones. This was thought to be due to the *ortho*-substitution protecting the ketone carbonyl from 1,2-reduction. In addition, in the context of the alkylation of aryl methyl ketones with secondary alcohols, the *ortho*-substitution pattern was considered essential to also prevent self-condensation of the starting ketone itself. No *ortho*-substitution led to a complex mixture, as was demonstrated by the control reaction subjecting acetophenone to the optimised Ir-catalysed alkylation conditions with 3-pentanol (see **Chapter 3.4**). With this in mind, a range of *ortho*-substituted aryl ketones were prepared (**Table 3.7**). Whereas *ortho*-methylphenyl ketone **338,** trimethoxyphenyl ketone **341** and pyridyl ketone **343** were commercially available, *para*-bromophenyl ketone **347** could be synthesised from acetyl bromide (**345**) and **346** *via* a Friedel–Crafts acylation reaction (**Scheme 3.12**).



Scheme 3.12 Synthesis of ketone **347** *via* Friedel–Crafts acylation. Reagents and conditions: acetyl bromide (1.1 equiv), $AlCl_3$ (1.2 equiv), $CHCl_2$, 0 °C, 1 h

On subjection of *ortho*-methylphenyl ketone **338** to the optimised protocol, alkylated ketone **339** was isolated in a low yield of 15% (**Table 3.7, Entry 1**). Although it could not be isolated cleanly, the product was formed alongside what appeared alcohol **340** (**Table 3.7**). Limited protection of the carbonyl by the single *ortho*-methyl substituent on the phenyl ring presumably leads to an increased amount of 1,2-reduction and therefore production of side product **340**. Despite being

di-*ortho* substituted, trimethoxyphenyl ketone **341** resulted in only 32% yield of corresponding ketone **342**. We were pleased to find that subjecting pyridyl ketone **343** to the protocol led to an excellent 78% yield of β-branched ketone **344** (**Entry 3**).



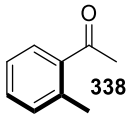
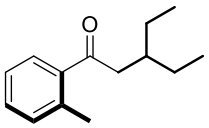
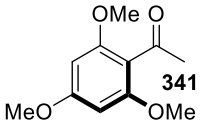
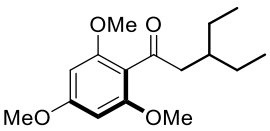
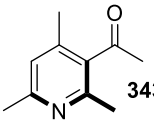
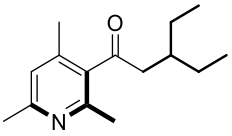
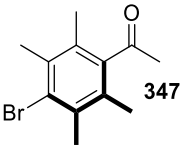
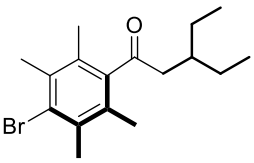
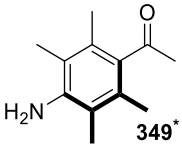
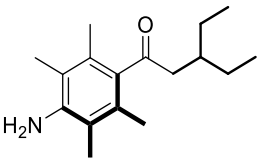
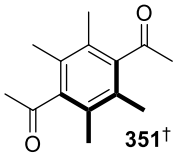
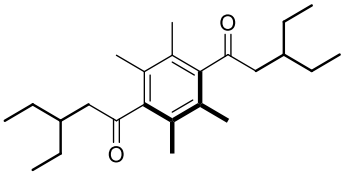
Entry	Aryl Ketone	Product	Yield (%)
1	 **338**		15 (**339**)
2	 **341**		32 (**342**)
3	 **343**		78 (**344**)
4	 **347**		70 (**348**)
5	 **349***		76 (**350**)*
6[a]	 **351**†		88 (**352**)†

Table 3.7 Alkylation of orthro-substituted aryl ketones with 3-pentanol *via* hydrogen borrowing catalysis. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (0.5 mol%), NaO*t*Bu (2 equiv), 3-pentanol (1.5 equiv), 85 °C, Ar, 18 h, [a] using $[Cp^*IrCl_2]_2$ (1 mol%), NaO*t*Bu (4 equiv), 3-pentanol (3 equiv)

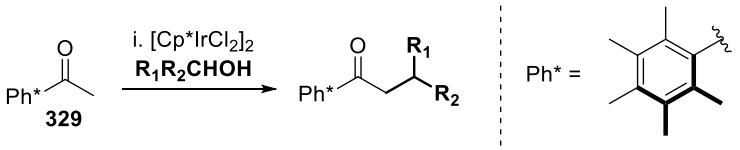
The methodology could also be extended to di-*ortho* substituted ketones **347** and **349** bearing a *para*-substitutions of -Br and -NH_2, leading to good yields of 70% and 76% respectively (**Entries 4**

* Compounds **349** and **350** synthesised by Choon Boon Cheong
† Compounds **351** and **352** synthesised by Dr James Frost

and 5). We were pleased to find that double alkylation of diketone **351** was also possible, affording the corresponding dialkylated product **352** in an excellent yield of 88% (**Entry 6**).

3.5.2 Acyclic Secondary Alcohols

Next, attention was turned to assessing the scope of secondary alcohols with Ph* methyl ketone **329**. Following on from 3-pentanol used in the optimisation of the reaction conditions to form ketone **333**, we began by exploring several acyclic secondary alcohols as the alkylation partner.



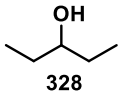
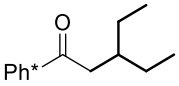
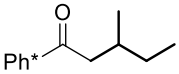
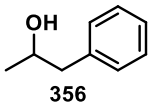
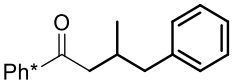
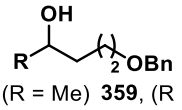
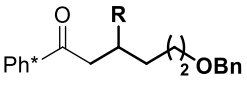
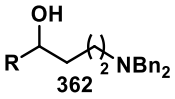
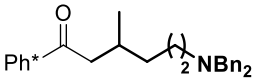
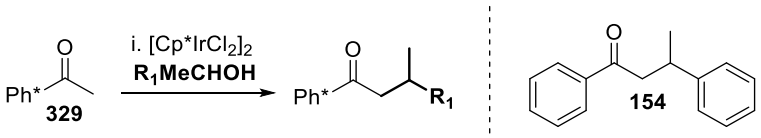
Entry	Secondary Alcohol	Product	Yield (%)
1	 **328**		97 (**333**)
2	 **354**		84 (**355**)
3	 **356**		66 (**357**)*
4	 **358**, (R = Me) **359**, (R = Et)		71 (**360**, R = Me)* 70 (**361**, R = Et)*[a]
5	 **362**		78 (**363**)

Table 3.8 Substrate scope: acyclic secondary alcohols. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (0.5 mol%), NaO*t*Bu (2 equiv), alcohol (1.5 equiv), 85 °C, Ar, 18 h, [a] using $[Cp^*IrCl_2]_2$ (2 mol%), NaO*t*Bu (3 equiv), alcohol (2 equiv), 105 °C

On subjection of non-symmetrical alcohol, 2-butanol **354**, to the reaction conditions, ketone **355** was isolated in an excellent yield of 84% (**Table 3.8, Entry 2**). We were delighted not to find

* Compounds **357**, **360** and **361** synthesised by Dr James Frost

self-condensation products resulting from 2-butanol. Presence of a phenyl group was also accommodated, affording ketone **357** in a good yield of 66% (**Entry 3**). Gratifyingly, the introduction of a benzyl ether did not hinder the reaction, with the methyl variant, **360**, isolated in 70% yield. Replacing the methyl group with an ethyl group required additional quantities of catalyst, base and a slightly elevated temperature of 105 °C to afford β-branched ketone **361** in 70% yield (**Entry 4**). In addition, subjection of related debenzylated amino alcohol **362** to the reaction conditions led to ketone **363** in a good yield of 78% (**Entry 5**).



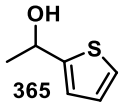
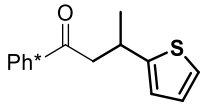
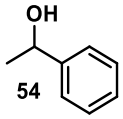
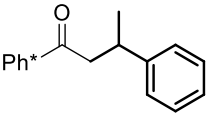
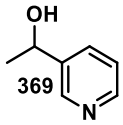
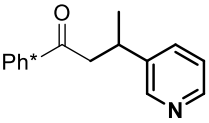
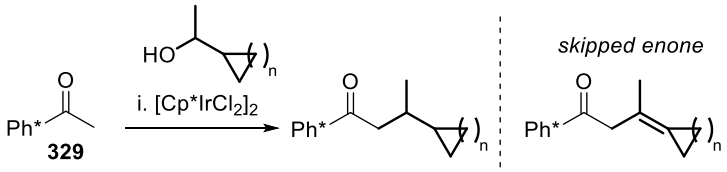
Entry	Secondary Alcohol	Product	Yield (%)
1[a]			82 (**366**)
2			92 (**368**)[b]
3[a]			75 (**370**)*

Table 3.9 Substrate scope: acyclic secondary alcohols. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (0.5 mol%), NaO*t*Bu (2 equiv), 3-pentanol (1.5 equiv), 85 °C, Ar, 18 h, [a] using $[Cp^*IrCl_2]_2$ (2 mol%), NaO*t*Bu (3 equiv), 3-pentanol (2 equiv), [b] along with side product **154**

Next, we subjected a range of benzylic acyclic secondary alcohols to our reaction conditions. Pleasingly, both electron rich (thiophene, **365**) and electron poor (pyridine, **369**) heterocyclic ring systems were tolerated within the secondary alcohol, providing the corresponding products **366** and **370** in 82% and 75% yields respectively (**Table 3.9, Entries 1 and 3**). Through experimentation, we found that these reactions required 2 equivalents of the alcohol and 3 equivalents of the base to push the reaction to completion. Subjection of benzylic alcohol **54** to the reaction conditions

* Compound **370** synthesised by Choon Boon Cheong

resulted in an excellent 92% yield of β-branched ketone **368**. It was interesting to note that small amounts of self-condensation product **154** resulted from this reaction (**Table 3.9**). Presumably, benzylic alcohol **367** undergoes facile oxidation to the resulting ketone at a rate greater than which it is consumed in the desired catalytic pathway. This may therefore lead to a slight accumulation of the ketone, which is then able to self-condense to give side product **154**. This side product was found to co-run with the desired product, though treatment of the crude mixture with $NaBH_4$ allowed isolation of desired ketone **368** cleanly. This exploited the fact that Ph* can prevent reduction of the carbonyl group thereby only side product **154** is reduced to the corresponding alcohol, aiding purification.



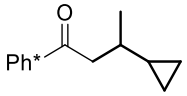
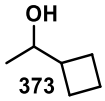
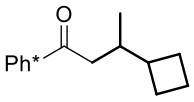
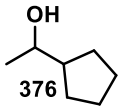
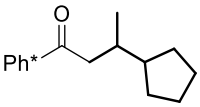
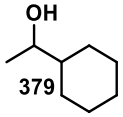
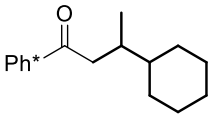
Entry	Secondary Alcohol	Product	Yield (%)	Skipped Enone (%)
1			96 (**372**)	-
2			89 (**374**)	8 (**375**)
3			75 (**377**)	13 (**378**)
4			84 (**380**)	-

Table 3.10 Substrate scope: acyclic secondary alcohols. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), NaO*t*Bu (3 equiv), alcohol (2 equiv), 85 °C, Ar, 18 h

Next, a series of secondary alcohols featuring α-substituted cycloalkanes of various sizes were investigated. The study began by subjecting the alcohol **371**, featuring a cyclopropane, to the

reaction conditions. Pleasingly, the corresponding ketone **372** could be isolated in an excellent yield of 96% (**Table 3.10, Entry 1**). Increasing the ring size to four also provided the desired ketone **374** in a high yield of 89%, as well as 8% of tetrasubstituted skipped enone **375** (**Entry 2**). Secondary alcohol **376**, containing a cyclopentyl group, provided a slightly lower but respectable yield of 75% of β-branched ketone **377** (**Entry 3**). Skipped enone **378** was isolated in an increased amount of 13% in this case. To complete the series, ketone **380**, bearing a cyclohexyl group, could also be isolated in an excellent yield of 84% (**Entry 4**). Through experimentation, it was identified that this series of alcohols required 2 equivalents of the respective alcohol and 3 equivalents of base, as utilising any lower resulted in incomplete reaction and increased amounts of tetrasubstituted skipped enone being observed.

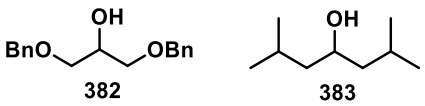
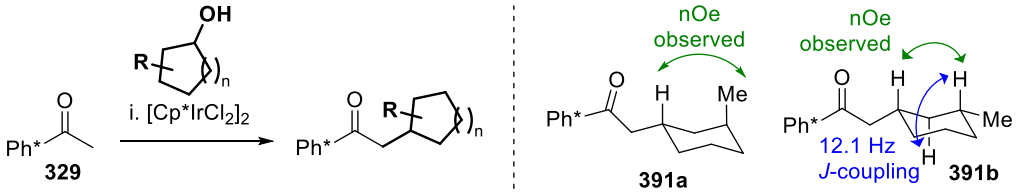


Figure 3.2 Acyclic secondary alcohols that failed to react

It is noteworthy that acyclic secondary alcohols **382** and **383** failed to react under our optimised protocols (**Figure 3.2**). Reaction with alcohol **382** resulted only in the observation of unreacted Ph* ketone **329** and alcohol **382** by ^{1}H NMR analysis of the crude material. We suspected the presence of two electron-withdrawing β-oxygen atoms with respect to the alcohol may disfavour oxidation, a key step on route to forming the desired β-branched product. Similarly, when alcohol **383** was subjected to the reaction conditions, only unreacted ketone **329** and alcohol **383** were observed by ^{1}H NMR analysis of the crude material. It was theorised that the two bulky isopropyl groups may result in a sterically encumbered aldol adduct which favours a retro-aldol process over the desired elimination process.

3.5.3 Cyclic Secondary Alcohols

Next, we turned our attention to investigating the use of cyclic secondary alcohols as alkylating agents under the developed protocol. Experimentation revealed that reactions with cyclic secondary alcohols gave superior yields when KO*t*Bu was used as the base instead of NaO*t*Bu.



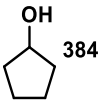
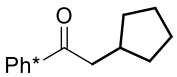
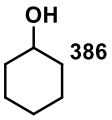
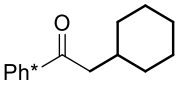
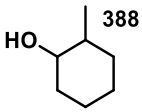
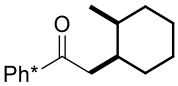
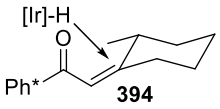
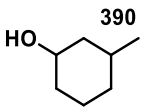
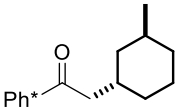
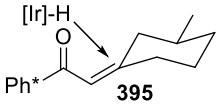
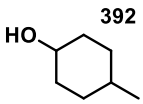
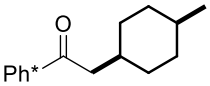
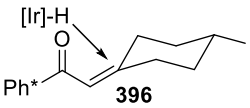
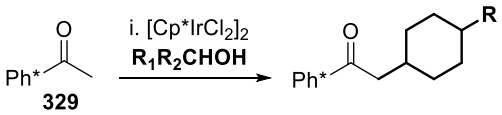
Entry	Secondary Alcohol	Product	Yield (%)	
1			82 (**385**)	
2			86 (**387**)	
3[a,b]			73 (**389a:389b**)* 84:16 d.r.	*equatorial attack* 
4[b]			80 (**391a:391b**) 90:10 d.r.	*equatorial attack* 
5[b]			88 (**393a:393b**)* 79:21 d.r.	*equatorial attack* 

Table 3.11 Substrate scope: cyclic secondary alcohols. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), 3-pentanol (2 equiv), 85 °C, Ar, 18 h, [a]conducted at 105 °C. [b]d.r. determined by ^{1}H NMR analysis of the crude material, major diastereomer shown

We began by looking at cyclopentanol (**384**) and unsubstituted cyclohexanol (**386**). We were pleased to find ketones **385** and **387** could be isolated in excellent yields of 82% and 86% respectively (**Table 3.11, Entries 1 and 2**). Next, we looked at a series of methyl-substituted cyclohexanols. Reaction with substituted cyclohexanol **388** gave ketone **389** in 73% yield and with

* Compounds **389** and **393** synthesised by Dr James Frost

84:16 d.r. (**Entry 3**). This reaction required a slightly higher temperature of 105 °C to push the reaction to completion, presumably due to the proximity of the methyl substituent to the alcohol centre resulting in a sterically encumbered aldol adduct. Pleasingly, 1,3-substituted cyclohexanol **390** reacted smoothly to give desired ketone **391** in 80% yield and 90:10 d.r. (**Entry 4**). Furthermore, ketone **393** could also be isolated in an excellent yield of 88% and 79:21 d.r. (**Entry 5**). The substrate-induced diastereoselectivity observed in the formation of **389**, **391** and **393** could be predicated by an equatorial attack of an [Ir]-H species on an exocyclic enone (**Table 3.11, Entries 3-5**). The relative stereochemistry of the diastereoisomers of **389**, **391** and **393** was determined using observed nOe interactions after running 2D NOESY NMR experiments.



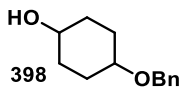
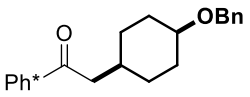
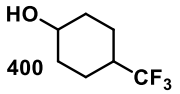
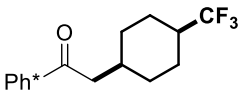
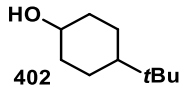
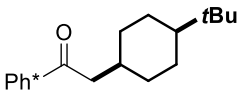
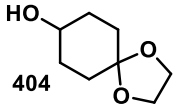
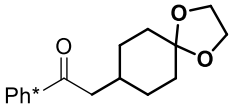
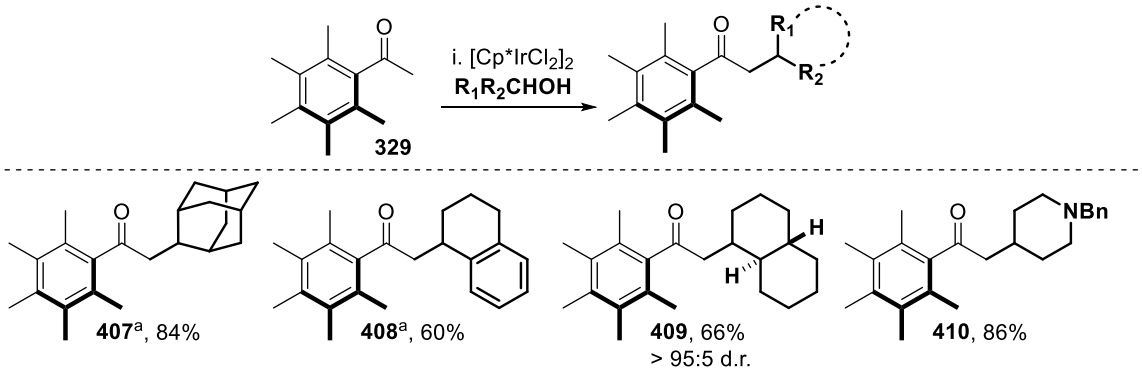
Entry	Secondary Alcohol	Product	Yield (%)
1[a]			81 (**399a:399b**) 70:30 d.r.
2[a]			60 (**401a:401b**)* 89:11 d.r.
3[a]			91 (**403**)* > 95:5 d.r.
4[ii]			99 (**405**)

Table 3.12 Substrate scope: cyclic secondary alcohols [a] d.r. determined by ^{1}H NMR analysis of the crude material, major diastereomer shown. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), 3-pentanol (2 equiv), 85 °C, Ar, 18 h (ii) $[Cp^*IrCl_2]_2$ (0.5 mol%), NaO*t*Bu (2 equiv), 3-pentanol (1.5 equiv), 85 °C, Ar, 18 h

* Compounds **401** and **403** synthesised by Choon Boon Cheong

We were pleased to find that benzyl-ether containing secondary alcohol **398** could be tolerated, with ketone **399** isolated in 81% and 70:30 d.r. (**Table 3.12, Entry 1**). The structure of product **399a** was unambiguously confirmed by single crystal X-ray diffraction (see **Experimental Details**, **Chapter 5.3**). Trifluoromethyl alcohol **400** was also well tolerated, affording desired ketone **401** in 60% yield and 89:11 d.r. (**Entry 2**). The structure of product **401b** was also determined by single crystal X-ray diffraction*. With the trifluoromethyl group replaced with *t*butyl, ketone **403** was isolated in 91% yield and an excellent > 95:5 d.r. (**Entry 3**), the structure of which was also determined by single crystal X-ray diffraction§§§§. With an A-value of > 4.5 kcal mol^{-1} [75] for the *t*butyl group, it is perhaps not too surprising that ketone **403** is isolated with such high diastereoselectivity. As before, the relative stereochemistry for the major diastereoisomer observed in the formation of **399**, **401** and **403** could be predicated by an equatorial attack of a [Ir]-H species on an exocyclic enone. Gratifyingly, cyclic acetal containing alcohol **404** reacted with ketone **329** to form corresponding product **405** in an excellent yield of 99%.

In addition, Choon Boon Cheong from the Donohoe group showed that ketones **407**, **408**, **409** and **410** could also be isolated in good yields from corresponding secondary alcohols (**Scheme 3.13**).



Scheme 3.13 Additional substrate scope: cyclic alcohols – conducted by Choon Boon Cheong. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), alcohol (2 equiv), 85 °C, Ar, 18 h, [a] conducted at 105 °C

* X-ray crystal structure for compounds **401b** and **403** obtained by Choon Boon Cheong

Gratifyingly, many cyclic secondary alcohols with a variety of functional groups and steric requirements were demonstrated to work under our optimised protocol, although there were also several secondary alcohols which failed to react (**Figure 3.3**). Use of tetrahydropyranyl alcohol **411** resulted in a complex mixture with starting ketone **329** only recovered in trace amounts. Unfortunately, 2-indanol (**412**) did not react to give the desired product, with 80% of starting ketone **329** recovered at the end of the reaction. Subjection of fluorenol **413** to our reaction conditions did not deliver the corresponding product with ^{1}H NMR analysis of the crude material revealing unreacted starting ketone **329** and fluorenol **413**. Oxidation of fluorenol would lead to the stable aromatic ketone, fluorenone, which perhaps once formed is unreactive towards the enolate of ketone **329**.

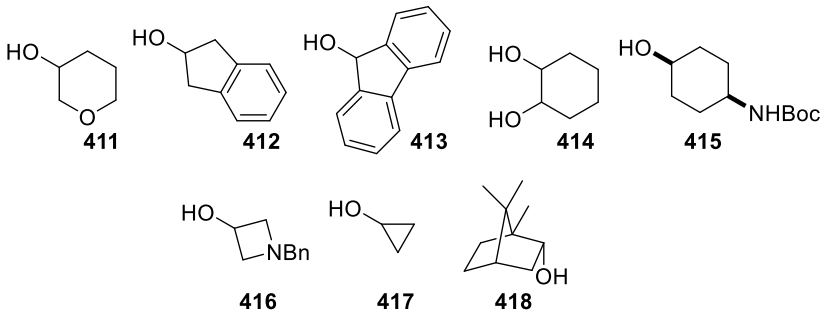
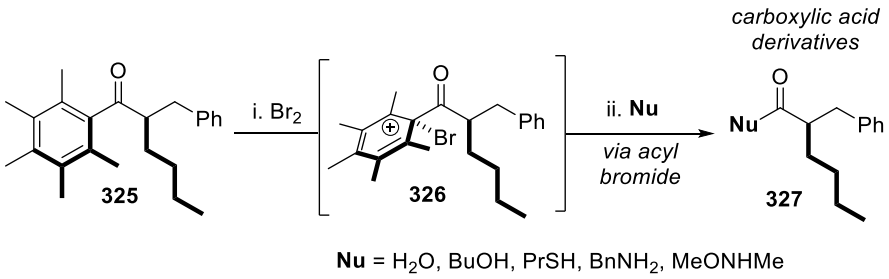


Figure 3.3 Cyclic secondary alcohols that failed to react

Unfortunately, diol **414**, mono-Boc protected amino alcohol **415** and cyclopropanol (**417**) all resulted in complex mixtures on subjection to the reaction conditions. Subjection of N-benzyl azetidinyl alcohol **416** to the reaction conditions resulted in no reaction, with both Ph* methyl ketone **329** and unreacted secondary alcohol **416** observed by ^{1}H NMR analysis of the crude material. One suggestion for the lack of reactivity may be due to the electronegative β-nitrogen atom being present in the alcohol, lowering the ease by which the centre is oxidised. Finally, when (–)-borneol **418** was subjected to our reaction conditions, it did not react, with both starting ketone **329** and alcohol **418** observed by ^{1}H NMR analysis of the crude material.

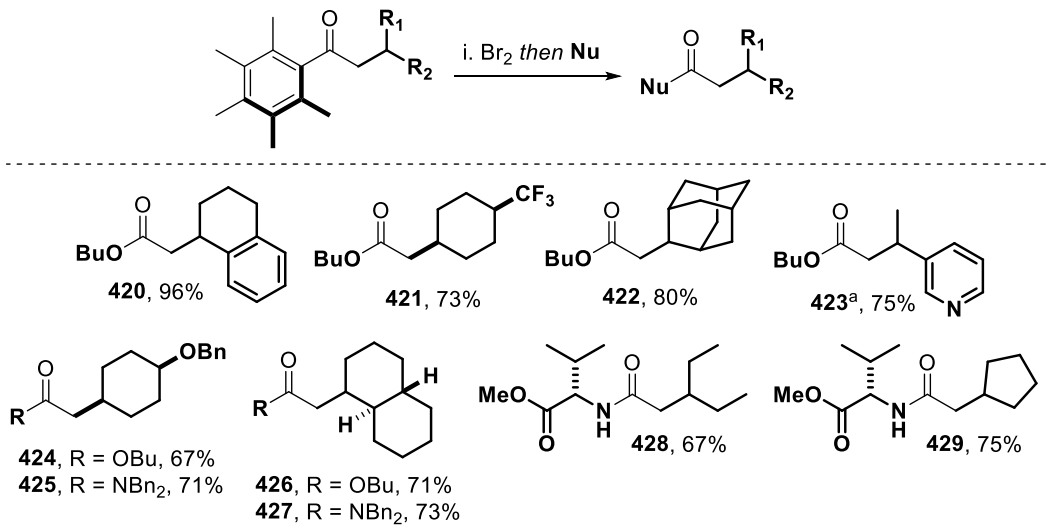
3.6 Derivatisation of Products via Bromine-initiated Ph Release*

With the substrate scope complete and a range of both acyclic and cyclic secondary alcohols found to be effective under our optimised protocol, it was important to demonstrate the utility of the products. As discussed earlier (see **Chapter 3.2**), (Ph*) ketones had been shown to undergo a retro-Friedel–Crafts acylation process, leading to 'release' of the aryl group and trapping with a range of nucleophiles to provide carboxylic acid derivatives.



Scheme 3.14 Work by Dr James Frost demonstrating how bromine-initiated release of α-alkylated Ph* ketones (made by Choon Boon Cheong) could be 'released' and trapped with a nucleophile

As Dr James Frost had demonstrated previously that α-alkylated substrate **325** (synthesised *via* hydrogen borrowing catalysis by Choon Boon Cheong (**Scheme 3.14**)) could be derivatised using our bromine-initiated release protocol, he once again attempted to apply this methodology to the β-branched products synthesised under the newly developed protocol. A selection of β-branched products were selected and treated with Br_2 (**Scheme 3.15**). Gratifyingly, the acid bromide generated *in situ* could be trapped with 1-butanol to form the corresponding butyl esters and dibenzylamine to afford the corresponding amides in good to excellent yields with no stereochemical erosion observed. We were pleased to find that functional groups such as a benzyl ether (**424** & **425**), trifluoromethyl (**421**) and a heterocyclic ring (**423**) were all tolerated under the derivatisation method. The derivatisation method was also shown to be applicable to peptide coupling, with α-amino methyl esters successfully coupled to afford products **428** and **429** in good yields.



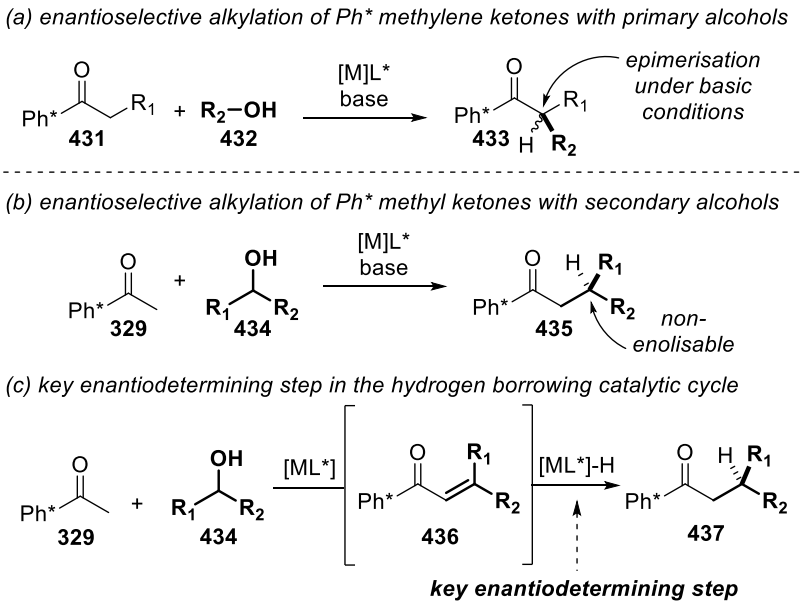
Scheme 3.15 Bromine-initiated release of β-branched Ph* ketones. Reagents and conditions: Br_2 (2 equiv), CH_2Cl_2, –17 °C, *then* Nu (3 equiv), –17 °C to RT, [a] Br_2 (4 equiv) required. Reactions conducted by Dr James Frost

3.7 Preliminary Studies: Enantioselective Route Towards β-Branched Ketones

3.7.1 Introduction

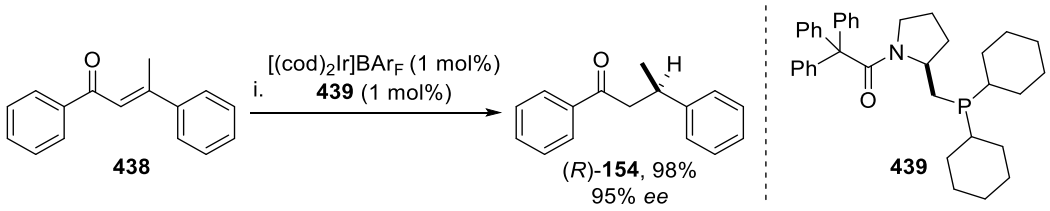
To our knowledge, an asymmetric variant for the alkylation of ketone enolates *via* hydrogen borrowing catalysis using alcohols is unprecedented. The development of such a process would add great value to the chemistry, as methods for access to single enantiomers are highly sought after, particularly in the field of pharmaceuticals. As the methods we have developed thus far afford racemic products, we wondered if it would be possible to extend them to generate single enantiomers.

Work by Choon Boon Cheong in the Donohoe group had already demonstrated that although asymmetric alkylation of methylene ketones (**431**) using primary alcohols would be desirable, the newly generated α-branched stereogenic centre (**433**) would likely be susceptible to racemisation under the strong basic conditions required to conduct the chemistry (**Scheme 3.16a**).



Scheme 3.16 Enantioselective alkylation of Ph* ketones using primary and secondary alcohols *via* hydrogen borrowing catalysis

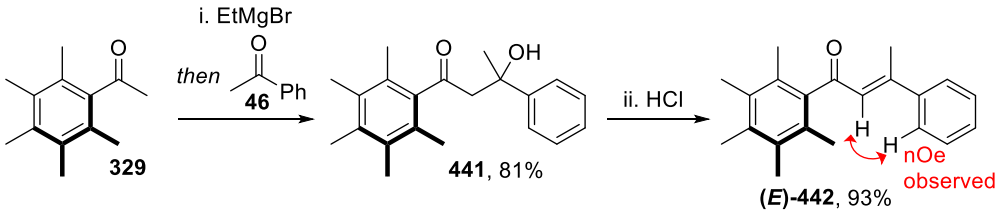
In contrast, the alkylation of Ph* methyl ketone (**329**) using secondary alcohols would generate a β-stereogenic centre (**435**), which would generally be non-enolisable (**Scheme 3.16b**). We therefore identified this as a process which held the potential to be developed further into a catalytic enantioselective process. We theorised that the key enantiodetermining step in this reaction pertained to delivery of the metal hydride to enone **436** (**Scheme 3.16c**). We noted the similarity of this step to enantioselective transition metal catalysed hydrogenation reactions and wondered whether the plethora of ligands that have been developed for this reaction could impart asymmetry on our reaction too. For example, Pfaltz and co-workers have previously reported iridium/proline-based P,O-ligand complexes as highly selective catalysts for the asymmetric hydrogenation of trisubstituted alkenes.[102] They were able to apply this procedure to aryl enone **438**, isolating (*R*)-**154** in an excellent 98% yield and 95% enantiomeric excess (**Scheme 3.17**). Aryl enone **438** is not dissimilar from the types of substrates we would hope to reduce asymmetrically, therefore it was reassuring to see this transformation could be achieved in high yield and high enantiomeric excess, albeit under different conditions.



Scheme 3.17 Example of a substrate shown to undergo catalytic asymmetric hydrogenation under a protocol developed by Pfaltz and co-workers. Reagents and conditions: [(cod)$_2$Ir]BArF (1 mol%), **439** (1 mol%), H_2 (50 bar), CH_2Cl_2, RT, 2 h

3.7.2 Preliminary Studies

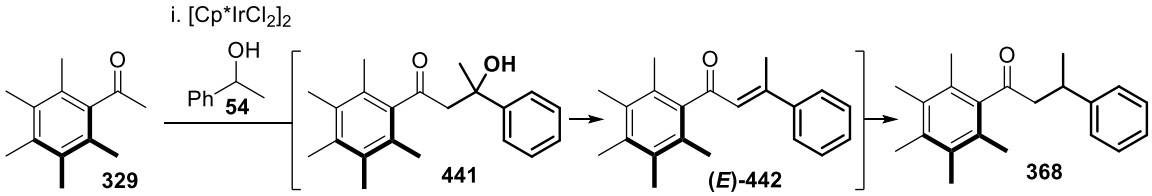
The study began with enone **442** being chosen as a model substrate for a preliminary study. We would initially focus on carrying out an asymmetric transfer hydrogenation of enone **442** which, as highlighted previously was thought to be the key enantiodetermining step, to determine if there was any induction of asymmetry. Any successful leads would then be tested in a full hydrogen borrowing alkylation reaction. Using a protocol adapted from that of Fisher and co-workers[103], Ph* ketone **329** was added to EtMgBr to form the corresponding bromomagnesium enolate, which could subsequently be trapped with acetophenone **46** to provide β-hydroxyketone **441** in 81% yield (**Scheme 3.18**). Subjecting **441** to HCl resulted in elimination to afford the desired enone (*E*)-**442** in 93% yield.



Scheme 3.18 Synthesis of enone **442**. Reagents and conditions: (i) EtMgBr (3 M in Et_2O), Et_2O *then* acetophenone (1.1 equiv), 40 °C, 16 h, (ii) HCl (37%), Et_2O, 40 °C, 24 h

The stereochemistry of enone **442** was identified as (*E*) based upon NMR analysis revealing an nOe interaction between the α-alkenyl proton and an aromatic proton (**Scheme 3.18**). The corresponding (*Z*) isomer would be expected to have a nOe interaction between the α-alkenyl proton and the β-methyl group, which was also absent in this analysis.

Concerned that the relatively high temperatures required for hydrogen borrowing catalysis could potentially become troublesome in garnering asymmetric induction, first, a study of the hydrogen borrowing alkylation reaction of Ph* ketone **329** and 1-phenylethan-1-ol (**54**) over time at a range of temperatures under our optimised protocol[*] was conducted (**Scheme 3.19**). With Ph* ketone **329**, and desired product **368** in hand, as well as intermediates **441** and **442**, HPLC analysis could be utilised to track the formation and/or depletion of these compounds over time vs mesitylene as an internal standard.



Scheme 3.19 Hydrogen borrowing alkylation reaction of Ph* ketone **329** with alcohol **54** to be studied at different temperatures. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KO*t*Bu (3 equiv), water (5 mol%) 1-phenylethan-1-ol **54** (2 equiv), PhMe (4 M), variable temperature, 24 h, N_2

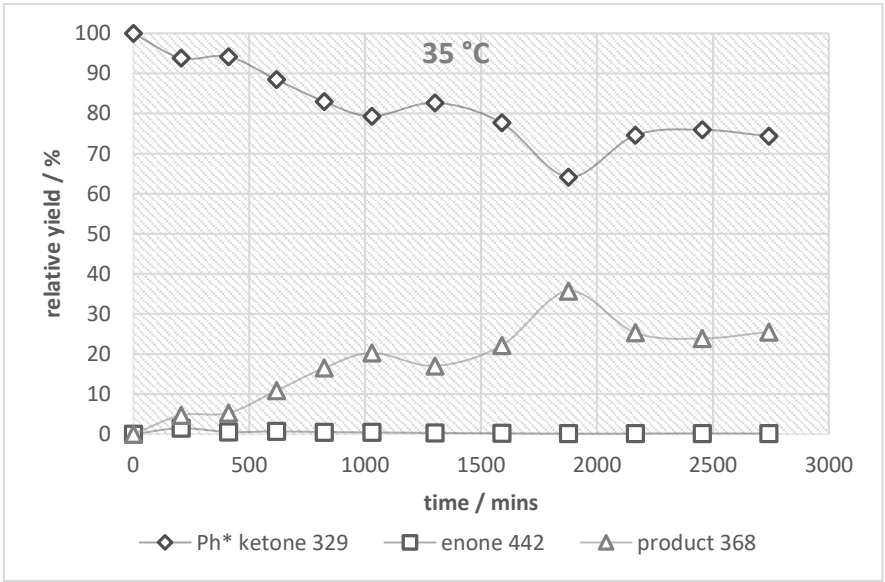


Figure 3.4 Following formation/depletion of compounds in the reaction depicted in **Scheme 3.19** at 35 °C

[*] 5 mol% water was added to the reaction in accordance with studies in **Chapter 3.4.1**, as at the time of investigation, only access to KO*t*Bu (98%) was available

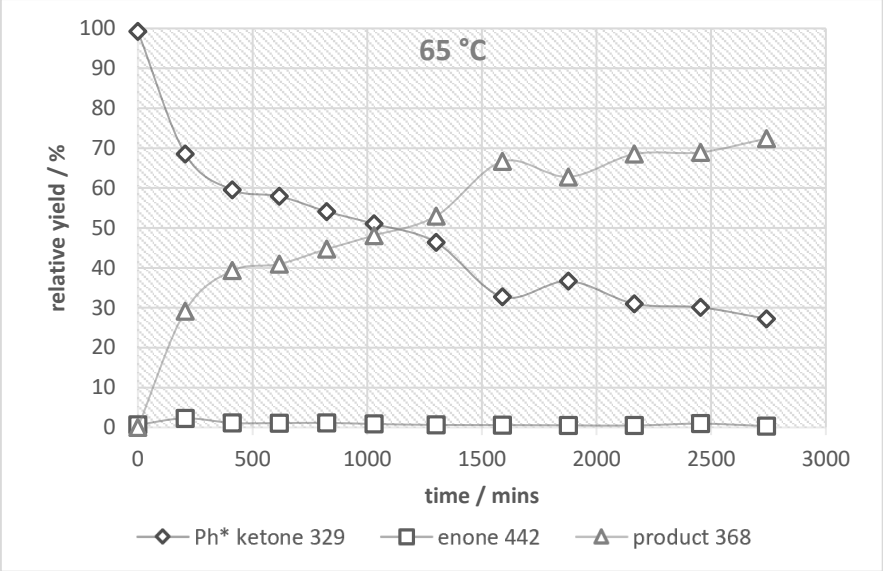


Figure 3.5 Following formation/depletion of compounds in the reaction depicted in **Scheme 3.19** at 65 °C

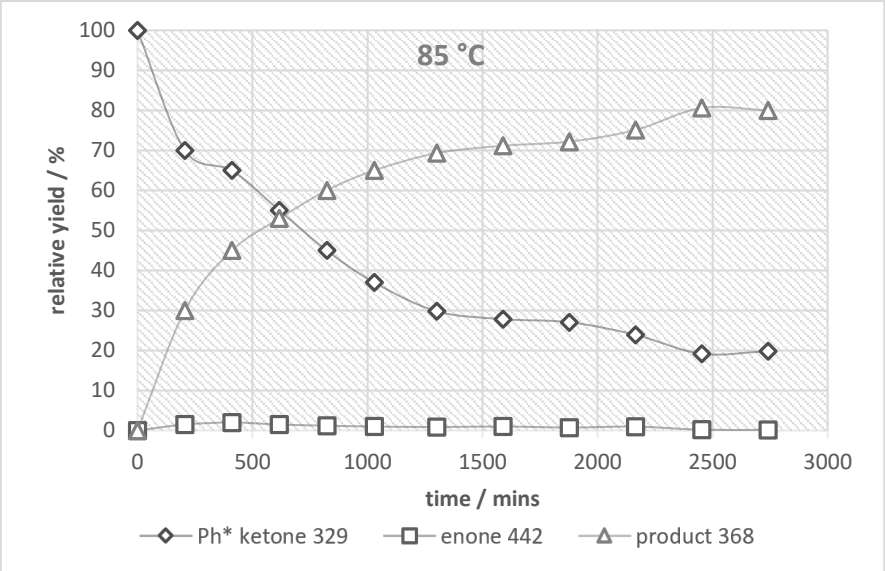
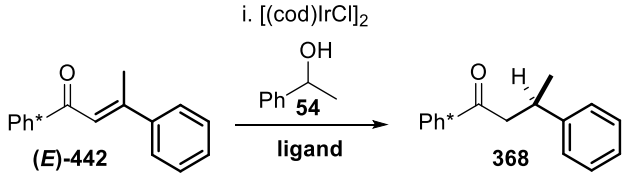


Figure 3.6 Following formation/depletion of compounds in the reaction depicted in **Scheme 3.19** at 85 °C

Surprisingly, the reaction did, in fact, proceed at 35 °C (**Figure 3.4**), but the relative yield of desired ketone **368** plateaued at 25% after 48 h. Running the reaction at 65 °C (**Figure 3.5**) was much more effective in comparison, though 85 °C (**Figure 3.6**) provided the best result, with desired ketone **368** formed in a relative yield of 80% after 48 h. It was interesting to note that in all cases, β-hydroxyketone **441** was not observed in any amounts, whereas enone **442** was observed at a relatively stable, unchanging, low-level amount throughout the reaction.

The decision was therefore made to conduct the preliminary study of the transfer hydrogenation of enone **442** at 85 °C.



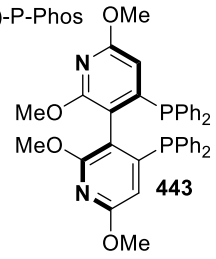
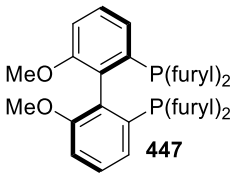
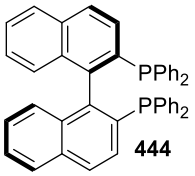
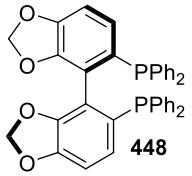
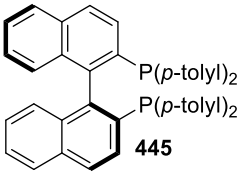
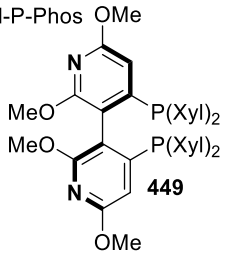
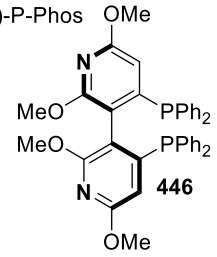
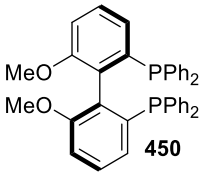
Entry	Ligand	e.r.[a]	Entry	Ligand	e.r.[a]
1	(*R*)-P-Phos  **443**	45:55	**5**	(*R*)-2-furyl-MeOBIPHEP  **447**	43:57
2	(*R*)-BINAP  **444**	45:55	**6**	(*R*)-SEGPHOS  **448**	48:52
3	(*S*)-Tol-BINAP  **445**	53:47	**7**	(*R*)-Xyl-P-Phos  **449**	51:49
4	(*S*)-P-Phos  **446**	53:47	**8**	(*R*)-MeO-BIPHEP  **450**	48:52

Table 3.13 Chiral ligand screen. [a] e.r. measured using chiral HPLC. Reagents and conditions: (i) $[(cod)IrCl]_2$ (2 mol%), ligand (4 mol%), KO*t*Bu (3 equiv), water (5 mol%) 1-phenylethan-1-ol **54** (1.1 equiv), PhMe (4 M), 85 °C, 24 h, N_2

Thus far, we had utilised $[Cp^*IrCl_2]_2$ as the catalyst in our procedure, which required no extra ligand to be added to catalyse the reaction successfully. To provide additional fine-tuning, we decided to switch to $[(cod)IrCl]_2$ which, in our experience[45], had also been capable of catalysing the hydrogen borrowing alkylation reactions of ketones with both primary and secondary

alcohols. To work effectively, it required an additional phosphine ligand to be added, which would allow a possible opportunity for enantiocontrol. With the reaction conditions otherwise unchanged[*], we subjected enone **442** to our protocol, utilising 1-phenylethan-1-ol (**54**) as the source of hydride (**Table 3.13**)[†]. Eight chiral diphosphine ligands were initially chosen to be screened. Pleasingly, clear asymmetric induction was observed in several cases, albeit in low levels. Reactions with (*R*)-P-Phos **443** and (*R*)-BINAP **444** (**Entries 1 and 2**), gave a 10% enantiomeric excess. The opposite enantiomer of ligand **443**, (*S*)-P-Phos **446** (**Entry 4**), afforded a 6% enantiomeric excess, but for the opposite enantiomer of product **368**, as would typically be expected. The ligand which performed the best with respect to asymmetric induction was (*R*)-furylphosphinoBINAP **447** (**Entry 5**), affording product **368** with 14% enantiomeric excess.

Although this was not pursued any further, it continues to be an active area of research within the Donohoe group. It is clear from this preliminary study that asymmetric induction is indeed possible, though requires further optimisation. In screening eight ligands, we have only touched the surface of possible parameters that could be further tuned to improve the enantioselectivity of this procedure.

3.8 Conclusion

We have extended the scope of hydrogen borrowing catalysis by making it possible to utilise a wide range of secondary alcohols to alkylate ketones to form β-branched products.

This was made possible through initial realisation that di-*ortho* phenyl substituted ketones were crucial to the success of this methodology by protecting the carbonyl functionality from attack. The benefits of this were two-fold: (i) undesired 1,2-reduction of the carbonyl group was prevented and (ii) self-condensation of the aryl ketone stating material was also prevented.

[*] 5 mol% water was added to the reaction in accordance with studies in **Chapter 3.4.1**, as at the time of investigation, only access to KO*t*Bu (98%) was available

[†] Analytical amounts of each reaction were purified for chiral HPLC analysis to determine enantiomeric excess. Yields not determined

Pentamethylphenyl (Ph*) methyl ketone was chosen as a model substrate for optimisation of this reaction, along with 3-pentanol. In optimising this reaction, several parameters were investigated, with the key finding that switching from KOH to KO*t*Bu allowed the temperature of the reaction to be reduced to 85 °C. This was presumably due to the increased solubility of the latter in toluene, the reaction solvent. In running control reactions, a reproducibility issue relating to the use of KO*t*Bu was highlighted and investigated thoroughly. The outcome of the investigation led to a more robust protocol which utilised freshly made KO*t*Bu from *t*BuOH and potassium metal, but crucially, without a sublimation step. Alternatively, a second protocol utilising the related base NaO*t*Bu was also established.

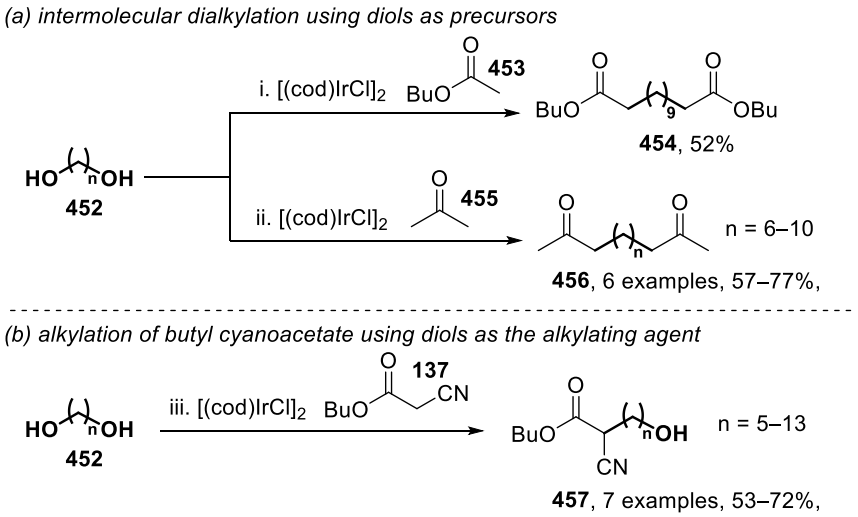
The substrate scope of the aryl group was investigated and although several di-*ortho* substituted aryl ketones afforded corresponding products with 3-pentaol in good yields, Ph* methyl ketone gave the highest yield and held the greater potential of facile derivatisation. Several acyclic and cyclic secondary alcohols were then tested with Ph* methyl ketone, with a wide range of functionalities found to be tolerated within the alcohol. Subsequently, a representative quantity of the β-branched products formed from this reaction were subjected to our previously developed retro-Friedel–Crafts acylation process. This proceeded though bromine-initiated release with the resulting acid bromide, formed *in situ*, trapped with several nucleophiles to form esters and amides.

Finally, to begin development of an enantioselective route towards β-branched ketones *via* hydrogen borrowing catalysis, we conducted some preliminary studies. These studies showed that asymmetric induction was indeed possible, albeit with low enantioselectivity of 14% (best example) and for a simplified model whereby only the crucial enantiodetermining asymmetric transfer hydrogenation step was carried out.

Chapter 4: Results & Discussion – Cyclic Products Using Diols

4.1 Introduction

The use of diols **452** as alkylating agents in C-C bond forming reactions of carbonyl substrates *via* hydrogen borrowing catalysis has been limited. Key contributions to the area have been made by Ishii and co-workers who reported the Ir-catalysed alkylation of butyl acetate **453** using 1,9–nonanediol resulting in the formation of **454** in 52% yield (**Scheme 4.1a**).[104] In a related report, they were also able to apply a similar protocol to acetone (**455**), with a range of diols **452** (n = 6–10) affording products **456** (**Scheme 4.1a**).[52] Conceptually, the formation of these products can be expected to proceed through a standard hydrogen borrowing catalytic cycle, except that each equivalent of diol is able to react with two equivalents of the carbonyl substrate.

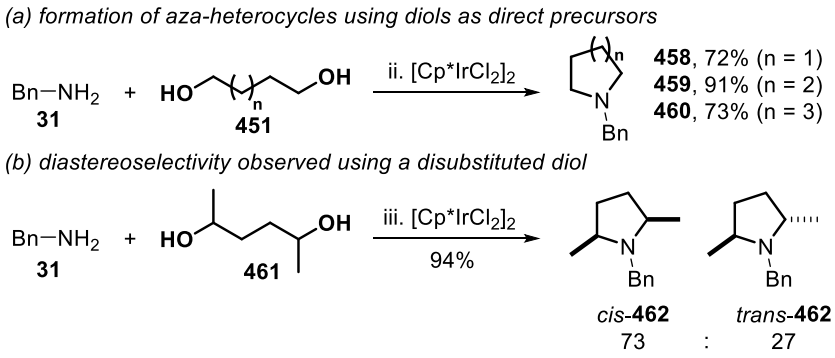


Scheme 4.1 Use of diols as the alkylating agent in C-C bond forming reactions of carbonyl substrates. Reagents and conditions: (i) $[(cod)IrCl]_2$ (10 mol%), PPh_3 (30 mol%), butyl acetate (20 equiv), KO*t*Bu (4 equiv), *t*BuOH (0.5 M), 100 °C, 15 h, (ii) $[(cod)IrCl]_2$ (5 mol%), PPh_3 (15 mol%), acetone (10 equiv), KOH (40 mol%), toluene (2 M), 100 °C, 2 h, (iii) $[(cod)IrCl]_2$ (5 mol%), PPh_3 (20 mol%), diol (3 equiv), dioxane (1 M), 120 °C, 20 h

Interestingly, the use of 1,4-butanediol (n = 4) and 1,5-pentanediol (n = 5) with acetone did not lead to any desired product, though the diols were almost entirely consumed under the reaction conditions. The authors suspected, at least in the case of 1,4-butanediol, this was due to the diol participating in Guerbet-type processes leading to a complex mixture of polymers. In both examples, the diol was used as the limiting reagent, with the carbonyl substrate used in a large

excess. A slightly modified protocol was reported by Ishii and co-workers where the carbonyl substrate, butyl cynanoacetate **137**, was utilised as the limiting reagent with a 3-fold excess of diols **452** (n = 5–13), leading to the formation of α-branched products **457** (**Scheme 4.1b**).[52] In contrast to the previous protocol, the diol only reacts once with butyl cyanoacetate to give a free terminal hydroxy group in the product.

Comparatively, the use of diols as alkylating agents in C-N bond forming reactions *via* hydrogen borrowing catalysis has been much more widespread. Following on from a seminal publication by Grigg and co-workers in 1981 on the C-N annulation of amino alcohols to form pyrrolidines,[12] focus in the area has predominantly been on the utilisation of diols as direct precursors to aza-heterocycles *via* double alkylation of the corresponding amine (**Figure 4.2**). The mechanism for this process is analogous to the transition metal-catalysed alkylation of ketone enolates with alcohols, with the exception that the ketone enolate nucleophile is replaced with an amine and that the second alkylation is intramolecular. Interest in annulation using diols *via* HB catalysis has been high in recent years, perhaps due to the relatively benign nature of the diol starting materials and given that the reaction only generates two equivalents of water as the by-product.[105]

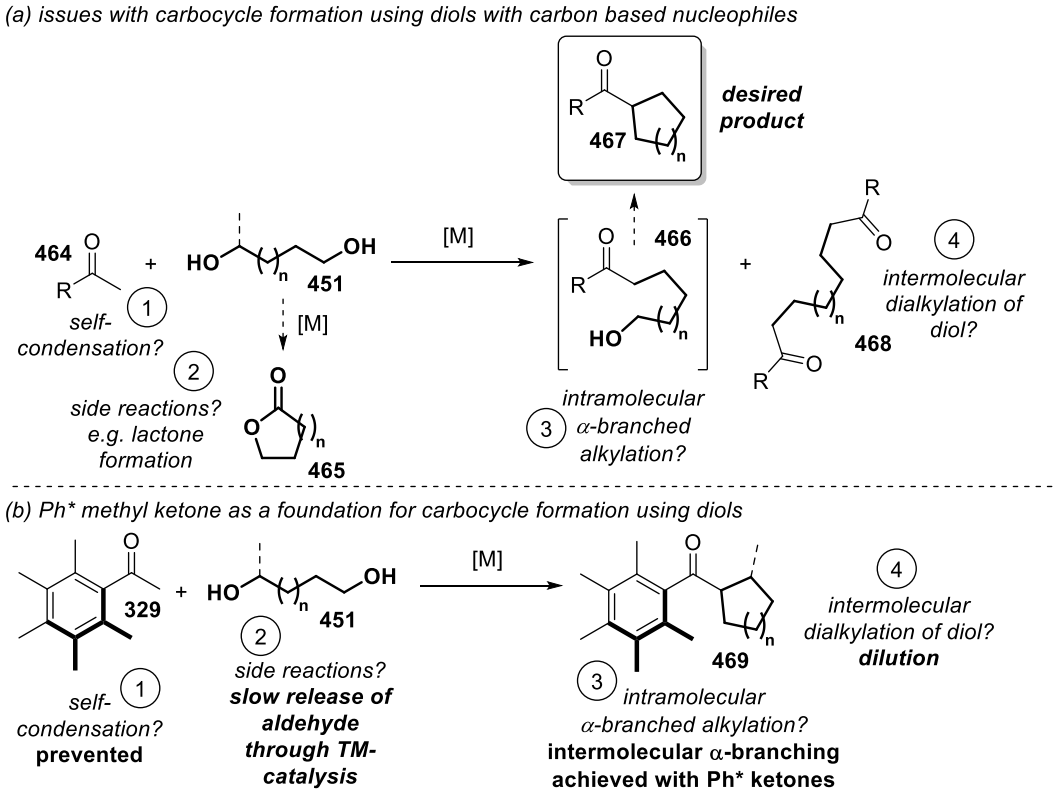


Scheme 4.2 Use of diols in C-N bond formation to generate aza-heterocycles *via* hydrogen borrowing catalysis. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (1-2 mol%), $NaHCO_3$ (1-2 mol%), benzylamine (1.5 equiv), toluene (0.7–2 M), 90–110 °C, 17 h (ii) $[Cp^*IrCl_2]_2$ (1 mol%), Na_2CO_3 (1 mol%), benzylamine (1.5 equiv), toluene (2 M), 110 °C, 17 h

A representative Ir-catalysed protocol for the synthesis of aza-heterocycles from benzylamine (**31**) and diols (**451**) was reported by Fujita, Yamaguchi and co-workers illustrating the generation 5-,

6- and 7-membered rings (**458–460**) using this approach (**Scheme 4.2a**).[68] When disubstituted diol **461** was subjected to the same procedure, the corresponding pyrrolidine **462** was isolated as a mixture of diastereoisomers with a *cis*:*trans* ratio of 73:27 in 94% yield. Interestingly, to the best our knowledge, this is the only diastereoselective example of this type of reaction reported within the literature.

In contrast to C-N annulation, the analogous reaction of a diol with a carbon nucleophile to form a carbocyclic ring is unprecedented using hydrogen borrowing catalysis. Perhaps this is unsurprising, as achieving this transformation is marred by many difficulties (**Scheme 4.3a**). Firstly, there is the issue that the carbon nucleophile, in this case methyl ketone **464**, could self-condense. The mechanism dictates that the nucleophile must be a methyl ketone, as a methylene ketone would be unable to undergo the second intramolecular alkylation step. Secondly, a non-specific issue resulting from the use of diols (**451**) is that any propensity to participate in side reactions must be controlled. As noted earlier, diols, particularly 1,4-butanediol and 1,5-pentanediol have been reported to undergo Guerbet-type processes with strong base at elevated temperatures.[52] Under the reaction conditions, diols may also undergo cyclisation to form the corresponding lactone (**465**)**.** Thirdly, a difficult intramolecular α-branching step must be accomplished (**466**). Finally, reaction of the diol with two equivalents of the carbonyl compound in an intermolecular process leading to products **468** needs to be prevented, while an intramolecular process to form the desired carbocyclic ring **467** must be favoured.



Scheme 4.3 Carbocycle formation using diols with carbon nucleophiles

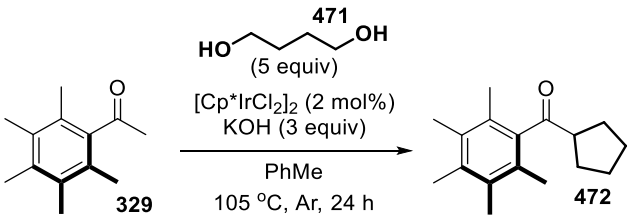
Indeed, we may have already addressed some of these problems (**Scheme 4.3b**) in developing methodology for the alkylation of methylene ketones using primary alcohols to form α-branched products (see **Chapter 2**) and the alkylation of methyl ketones using secondary alcohols to form β-branched products (see **Chapter 3**). We already know that di-*ortho* substituted phenyl methyl ketones are prevented from self-condensing, with Ph* methyl ketone **329** performing particularly well. Though we had not dealt with diols before, we hypothesised that slow release of small amounts of the corresponding aldehyde species *via* a metal-catalysed oxidation in the presence of a large abundance of the ketone enolate would reduce the amount of side reactions. Also, as discussed previously (see **Chapter 2 and 3.2**), α-branching using higher alcohols is difficult, though we discovered that utilising ketones substituted with 'small' groups such as cyclopropanes or di-*ortho* substituted aryl groups were able to carry out facile α-alkylation to form branched products. We envisaged that Ph* methyl ketone **329** may also facilitate the α-branched alkylation step in this process. In addition, this step would be intramolecular and may therefore occur more

readily. Finally, we hoped that reaction of the diol with two equivalents of the carbonyl substrate to form side product **468** could be minimised through careful control of the dilution of the reaction. We also wondered whether any diastereoselectivity could be achieved as seen by Fujita, Yamaguchi & co-workers in their analogous C-N annulation reaction (**Scheme 4.2c**).

Due to the general interest in the formation of carbocyclic motifs[106], particularly six-membered carbocycles[107] we thought a direct route to these structures using diols as precursors would be of great value. We hoped that the basis of our methodology for the alkylation of Ph* methyl ketone (**329**) using secondary alcohols would provide a good foundation upon which to optimise and develop a procedure for the alkylation of ketones using diols to form carbocyclic rings.

4.2 Optimisation

We chose Ph* methyl ketone (**329**) as the substrate on which to optimise our process along with 1,4-butanediol (**471**) as a model diol. The investigation began by subjecting ketone **329** to the protocol we had originally developed for the alkylation of cyclopropyl ketones (see **Chapter 2.3.3**), using a 5-fold excess of diol **471** and no solvent (**Table 4.1, Entry 1**).



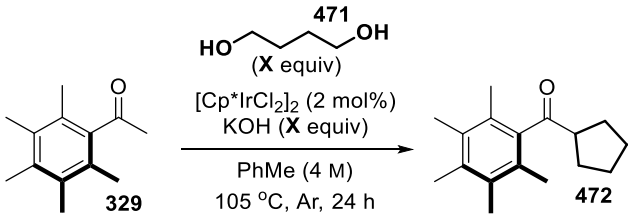
Entry	PhMe (M)	472 (%)	RSM (%)
1	-	11	-
2	8.0	29	-
3	4.0	34	-
4	2.0	14	-
5	0.2	4	84
6	0.02	-	98

Table 4.1 Screen of the concentration of PhMe

We were delighted to find that the desired product **472** containing a 5-membered carbocyclic ring could be isolated cleanly, albeit in a low yield of 11%. We suspected that conducting the reaction

neat resulted in increased side reactions due to observation of large quantities of polymeric insoluble material. It was hoped that diluting with an appropriate solvent would alleviate this issue. We identified toluene as a suitable solvent and began by diluting the reaction to 8.0 M (**Entry 2**). Pleasingly, cyclopentane **472** could be isolated in a higher yield of 29%. Diluting the reaction further to 4.0 M offered a small increase of product to 34% (**Entry 3**). Unfortunately, dilution of the reaction to 2.0 M did not lead to any further beneficial effect, instead product **472** was isolated in a lower yield of 14% (**Entry 4**). When the concentration was increased to 0.2 M, the product was isolated in a heavily diminished yield (**Entry 5**) and increasing the dilution by another factor of 10 led to no isolated product at all, with only starting material recovered (**Entry 6**). The decision was therefore made to move forward by introducing a 4.0 M dilution of toluene to the reaction conditions.

Next, suspecting that the excess of diol may be hindering the reaction by polymerising, the stoichiometry of diol used within the reaction was varied. In addition, we wondered if lowering the amount of KOH may also help deter any side reactions driven by an excess of base.



Entry	Diol (equiv)	KOH (equiv)	472 (%)	RSM (%)
1	1.1	3	65	-
2	2.0	3	59	-
3	5.0	3	34	-
4	10.0	3	25	-
5	1.1	1	53	9
6	1.1	2	55	5
7	1.1	5	60	-

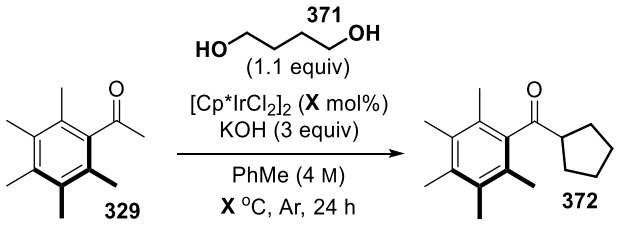
Table 4.2 Screen of the equivalents of diol and KOH

Gratifyingly, reducing the stoichiometry of diol to 2 equivalents afforded product **472** in a yield of 59% (**Table 4.2, Entry 2**) and reducing this further to 1.1 equivalents (**Entry 1**) led to an increased

yield of 65%. Conversely, increasing the loading of diol **471** to 10 equivalents had a detrimental effect on the yield of product **472**, which was isolated in only 25% yield (**Entry 4**).

Next, attention was turned to the loading of KOH used within the reaction. Lowering KOH to 1 or 2 equivalents (**Entries 5 and 6**) provided no beneficial effect and led to slightly lower yields of 53% and 55% respectively. Increasing the amount of KOH to 5 equivalents (**Entry 7**) also did not improve the yield, with desired product **472** isolated in 60% yield. Based on these observations, we decided to proceed using 1.1 equivalents of diol **471** and 3 equivalents of KOH.

In an attempt to increase the yield further, focus was turned to the loading of iridium catalyst used in the reaction, as well as the reaction temperature. Unfortunately, decreasing (**Table 4.3, Entry 1**) or increasing (**Entry 3**) the amount of catalyst appeared to have little to no effect on the yield of carbocyclic product **472**. Lowering the reaction temperature to 85 °C led to a corresponding decrease in yield, with desired product **472** isolated in only 49% yield. Disappointingly, an increase in reaction temperature to 125 °C (**Entry 5**) resulted in no further increase in yield.

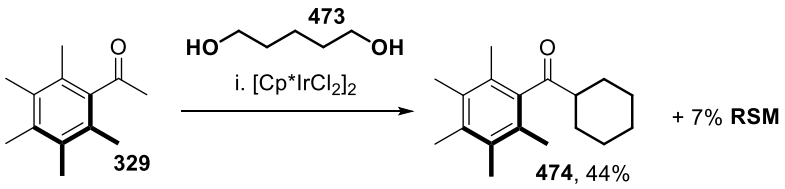


Entry	$[Cp^*IrCl_2]_2$ (mol%)	Temp (°C)	472 (%)	RSM (%)
1	1	105	60	-
2	2	105	65	-
3	4	105	64	-
4	2	85	49	-
5	2	125	63	-

Table 4.3 Screen of loading of $[Cp^*IrCl_2]_2$ and reaction temperature

The catalyst loading was therefore kept at 2 mol% and the reaction temperature maintained at 105 °C. With this preliminary set of conditions in hand, we were curious to know how formation of a six-membered carbocyclic ring would fare. We were disappointed to find that although

subjection of ketone **329** and 1,5-pentanediol **473** to the preliminary reaction conditions gave desired cyclohexane **474**, it was in a relatively modest yield of 44%, along with 7% recovered starting material (**Scheme 4.4**).

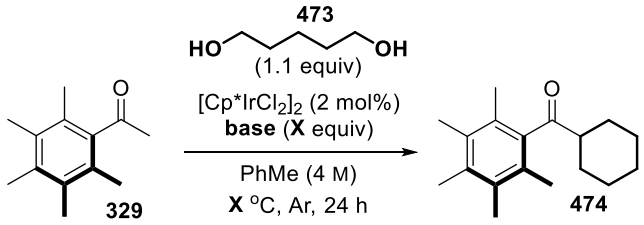


Scheme 4.4 Formation of a cyclohexane under a preliminary set of conditions. Reagents and conditions: (i) [Cp*$IrCl_2$] (2 mol%), KOH (3 equiv), 1,5-pentanediol (1.1 equiv), PhMe (4 M), 105 °C, Ar, 24 h

Changing the approach slightly, focus was turned to the reaction of ketone **329** with 1,5-pentanediol **473** as we were particularly keen to achieve formation of a cyclohexane ring in good yield. Next, several different bases were screened, a parameter which has not yet been explored. In addition, the decision to reinvestigate the loading of base used, as well as reaction temperature was made.

A range of bases were screened, with Cs_2CO_3, $NaHCO_3$ and LiOH (**Table 4.4, Entries 1-3**) resulting in no formation of desired product **474** and returning only unreacted starting material in each case. Using NaOH as the base (**Entry 4**) resulted in a disappointing 15% yield, whereas KO*t*Bu (**Entry 6**) afforded **474** in 44% yield, matching the yield achieved with KOH previously (**Entry 5**). With the use of KO*t*Bu not providing any additional benefits over KOH, we decided to continue to use KOH, particularly as it is considerably cheaper than KO*t*Bu.

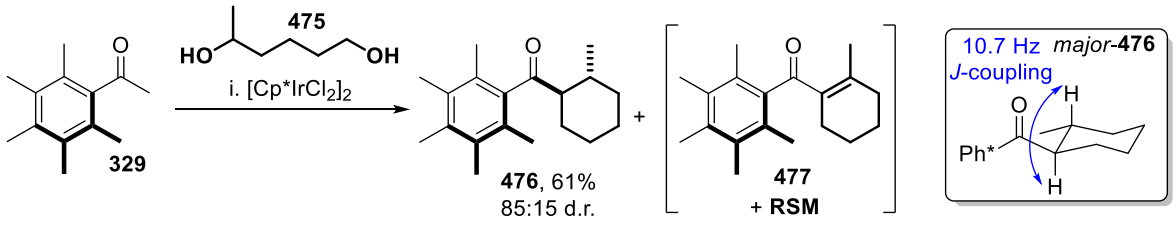
Next, focus was turned to altering the stoichiometry of KOH. Lowering KOH to 2 equivalents had no effect on the reaction (**Entry 7**). Pleasingly, increasing the loading of KOH to 4 equivalents led to an increased yield of 58% (**Entry 8**), though increasing this to 5 equivalents (**Entry 9**) did not have any further benefit. We were delighted to find that increasing the reaction temperature to 115 °C (**Entry 10**) afforded six-membered carbocyclic product **474** in a good yield of 66%.



Entry	Base	Base (equiv)	Temp (°C)	474 (%)	RSM (%)
1	$CsCO_3$	3	105	-	89
2	$NaHCO_3$	3	105	-	94
3	LiOH	3	105	-	91
4	NaOH	3	105	15	12
5	KOH	3	105	44	7
6	KO*t*Bu	3	105	44	trace
7	KOH	2	105	43	-
8	KOH	4	105	58	-
9	KOH	5	105	57	-
10	KOH	4	115	66	-

Table 4.4 Second round of optimisation screening different bases, equivalents of KOH and the reaction temperature, using 1,5-pentanediol

With these conditions in hand, we were curious to test how a more complex diol would behave during cyclisation. The decision was made to subject 1,5-hexanediol (**475**) to the reaction conditions.



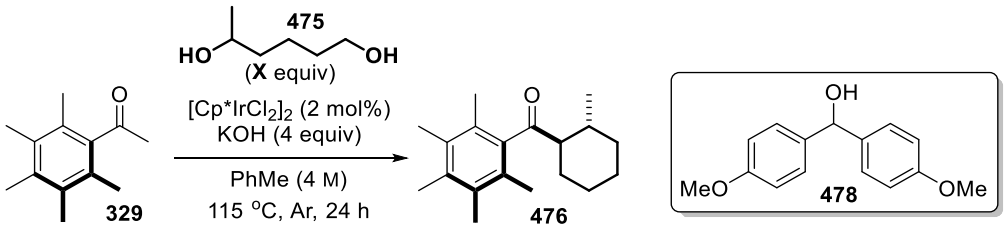
Scheme 4.5 Formation of a 1,2-disubstituted cyclohexane. Reagents and conditions: (i) [Cp*$IrCl_2$] (2 mol%), KOH (4 equiv), 1,5-hexanediol (1.1 equiv), PhMe (4 M), 115 °C, Ar, 24 h

We were delighted to find that disubstituted cyclohexane **476** could be isolated in 61% yield and 85:15 d.r. (**Scheme 4.5**). The structure and relative stereochemistry of the major diastereoisomer could be confirmed by a distinctive 1H triple doublet (*J* = 10.7, 3.3 Hz) at 2.45 ppm in the ^{1}H NMR spectrum corresponding to COC*H*, as well as a peak at 59.4 ppm in the ^{13}C NMR corresponding to CO*C*H (for discussion of stereochemistry, see later). Interestingly, tetrasubstituted enone **477** was

also formed, though it could not be isolated cleanly. Enone **477** was thought to occur as an intermediate, which, on reduction by an iridium hydride species, would lead to saturated product **476**. We theorised that the reason we had not observed this type of compound with unsubstituted diols **471** and **473** was because the intermediate in these cases would have been a trisubstituted enone which could perhaps undergo facile reduction. In contrast, tetrasubstituted enones are known to be challenging substrates for 1,4-reduction.[108]

Therefore, we increased the stoichiometry of the diol to 1.5 equivalents, hoping this would increase the availability of an iridium hydride species to aid the reduction of this difficult intermediate (**Table 4.5, Entry 1**). Pleasingly, this had the desired effect, with product **476** formed in 78% yield, though with traces of starting material and enone **477** still present. Increasing the amount of diol to 2 equivalents (**Entry 2**) led to full conversion to **476**, which was isolated in an excellent yield of 80% and as a single diastereoisomer.

Alternatively, we wondered if a sacrificial source of hydride could be utilised rather than increasing the equivalents of diol. Dibenzylic alcohol **478** was chosen as a suitable hydride source as we hoped it would undergo facile oxidation to provide an abundance of metal hydride species to aid reduction of enone **477**. As a structurally similar secondary alcohol which been explored as part of the substrate scope in developing the protocol for the alkylation of Ph* methyl ketone using secondary alcohols (see **Chapter 3.5.3**), had failed to react, we were confident alcohol **478** would not participate in the reaction as an alkylating agent itself. Pleasingly, keeping the diol stoichiometry at 1.1 equivalents, but adding 2 equivalents of sacrificial alcohol **478**, product **476** could be isolated in an excellent yield of 84% (**Entry 3**). To keep the protocol simple, however, it was decided that the procedure be modified to incorporate the use of 2 equivalents of diol but it was noted that the strategy using sacrificial alcohol **478** could be employed in the case that a valuable diol was being used.

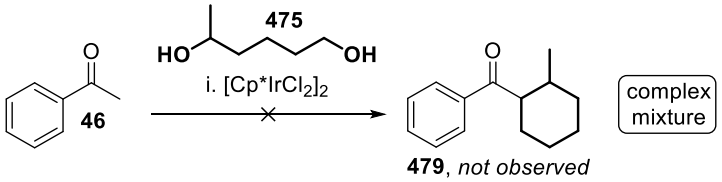


Entry	Diol (equiv)	Alcohol 478 (equiv)	476 (%)
1	1.5	-	78, > 95:5 d.r.
2	2.0	-	80, > 95:5 d.r.
3	1.1	2.0	84, > 95:5 d.r.

Table 4.5 Increasing the equivalents of alcohol

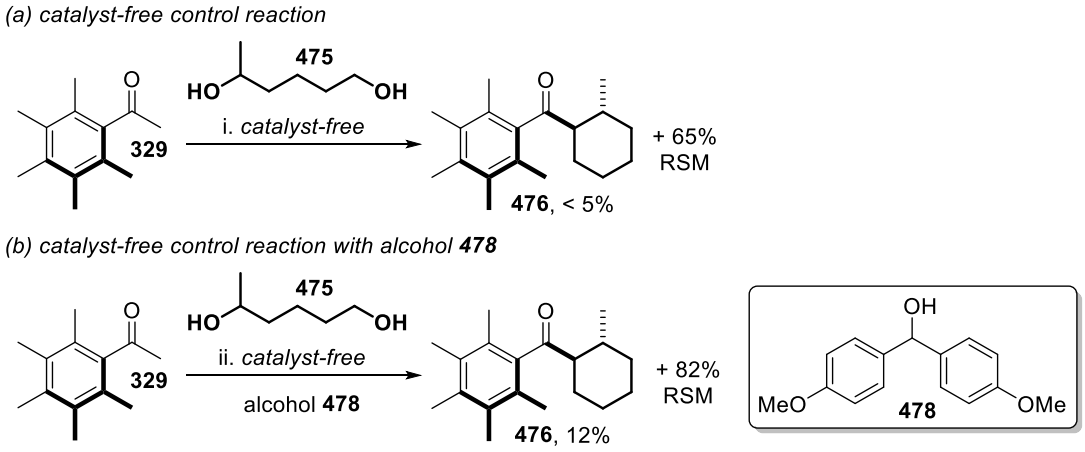
4.3 Control Reactions

Satisfied that we had an optimal procedure for the Ir-catalysed alkylation of **329** with diols, several control experiments were carried out. The decision was made to conduct the control experiments using 1,5-hexanediol (**475**), the example that had been used in our final round of optimisation.



Scheme 4.6 Control experiment: attempted alkylation of acetophenone with diol **475**. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-hexanediol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h

We began by attempting the alkylation of acetophenone (**46**) using diol **475**. When subjected to our optimised procedure, the reaction led to a complex mixture which mostly consisted of an insoluble polymeric black tar (**Scheme 4.6**). This highlights the crucial role of the Ph* group in facilitating the desired reaction by preventing self-condensation of the ketone starting material. As demonstrated by this control reaction, removal of the di-*ortho* methyl substitution pattern on the aryl ring leads to complex polymeric mixtures.



Scheme 4.7 Catalyst-free control reactions. Reagents and conditions: (i) KOH (4 equiv), 1,5-hexanediol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h, (ii) KOH (4 equiv), alcohol **478** (2 equiv), 1,5-hexanediol (1.1 equiv), PhMe (4 M), 115 °C, Ar, 24 h

Next, we omitted the iridium catalyst from our reaction procedure to check if there were any additional background processes which may be of interest. Removal of the catalyst led to a complete shutdown of reactivity, with only traces of product **476** observed and a large amount of unreacted starting material recovered, highlighting the key role of iridium in catalysing the process (**Scheme 4.7a**).

Alcohol **478** was previously identified as a sacrificial hydride source that was effective at driving the alkylation of Ph* methyl ketone with 1,5-hexanediol (**475**) to completion by aiding reduction of a troublesome enone intermediate. We wondered whether due to the propensity of alcohol **478** to undergo facile oxidation, it would enable generation of desired product **476** without the iridium catalyst. Indeed, on conducting this control experiment, a 12% yield of product **476** was observed, which, though higher than the trace amounts of product observed in the catalyst-free control without alcohol **478**, was still substantially lower the yield achieved with iridium present (**Scheme 4.7b**). We hypothesised that increased yield in the presence of alcohol **478** was occurring through a Meerwein-Pondorf-Verley-Oppenauer (MPV-O) type process, as discussed with respect to a similar process previously (see **Chapter 2.3.4**).

4.4 Substrate Scope: Diastereoselectivity, Substitution Pattern and Ring Size

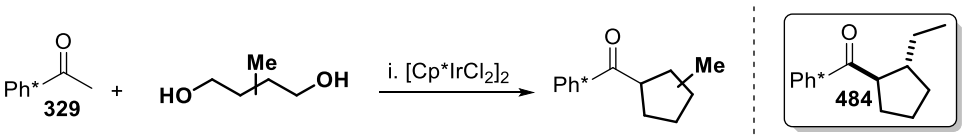
During the optimisation of this reaction we observed that on subjection of **329** and 1,5-hexanediol (**475**), to the optimised reaction conditions, product **476** was isolated as a single diastereoisomer. Spurred on by this result, we were curious to understand the scope and limitations of this diastereoselectivity. As our focus was predominantly on the synthesis of five- and six-membered rings, our strategy would involve the subjection of all possible mono and dimethyl substituted regioisomers of 1,4- and 1,5-diols to the reaction conditions. In addition to diastereoselectivity, we would also be observing the impact of each of these substitution patterns on the reactivity of the diol. Finally, other ring sizes would also be explored.

4.4.1 Five-membered Rings

4.4.1.1 Mono-methyl Substituted 1,4-Diols

The study began by looking at unsubstituted and mono-methyl substituted 1,4 diols, which would react to give the corresponding five-membered rings. Unsubstituted diol **471** had previously been reacted to give product **472** in a moderate 65% yield (**Table 4.6, Entry 1**). We were pleased to find that subjection of methyl-substituted diol **182** the reaction conditions afforded the product as a single diastereoisomer, albeit in a modest yield of 43% (**Entry 2**). The relative stereochemistry of this compound was assigned in analogy to the ethyl analogue **484**[*] (**Table 4.6**), the crystal structure of which depicted a *trans*-1,2 relationship between the substituents on the cyclopentane ring. When the regioisomeric diol **482** was subjected to the reaction conditions, the corresponding cyclopentane containing product **483** was formed in 50% yield, although in this case, no diastereoselectivity was observed (**Entry 3**)[†].

[*] Compound **484** synthesised by and single crystal X-ray diffraction data obtained by Dr James Frost
[†] The relative stereochemistry (*cis* or *trans*) could not be specifically assigned to each diastereoisomer



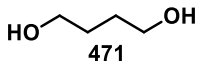
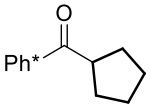
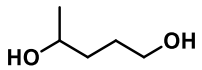
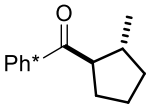
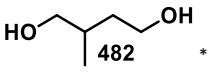
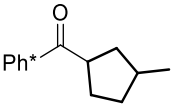
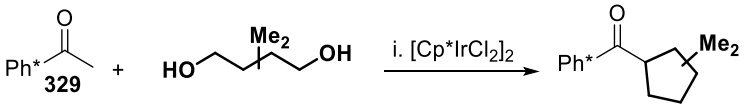
Entry	Diol	Product	Yield (%)
1[a]	 471		65 (**472**)
2[b]	 182		43 (**481**) > 95:5 d.r.
3[b]	 482 *		50 (**483**) 52:48 d.r.

Table 4.6 Substrate scope: mono-methyl substituted 1,4 diols. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,4-diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] KOH (3 equiv), diol (1.1 equiv), 105 °C [b]d.r. determined by ^{1}H NMR analysis of the crude material

4.4.1.2 Dimethyl Substituted 1,4-Diols



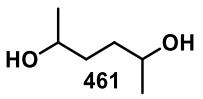
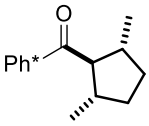
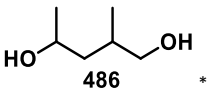
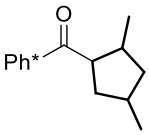
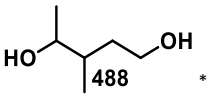
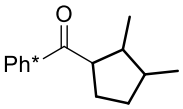
Entry	Diol	Product	Yield (%)
1[a,b]	 461		56 (**485a:485b**) 71:29 d.r.
2[a,c]	 486 *		62 (**487**) 84:16 d.r.
3[a,c]	 488 *		46 (**489**) 77:23 d.r.

Table 4.7 Substrate scope: dimethyl substituted 1,4 diols. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,4-diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material, [b]major diastereoisomer shown, [c] relative stereochemistry of the major and minor diastereoisomer could not be identified

* Diols **482**, **486** and **488** synthesised by Dr James Frost

Next, we turned our focus to dimethyl substituted 1,4-diols. Reacting diol **461** with Ph* methyl ketone **329** afforded the corresponding 1,2,5-substituted cyclopentane ring **485** in 56% yield and a 71:39 d.r. (**Table 4.7, Entry 1**). Although three diastereoisomers could theoretically have been formed, only two were observed in this reaction. The major diastereoisomer **485a** was identified as being a meso compound, exhibiting only a one doublet at 0.96 ppm in the ^{1}H NMR spectrum and a single peak at 21.6 ppm in the ^{13}C NMR spectrum corresponding to the two methyl substituents on the cyclopentane ring. As there were two structural possibilities that would give rise to a meso compound (**Figure 4.1a**), further analysis was required to confirm the structure of major diastereoisomer **485a**. Single crystal X-ray diffraction* of an analytically pure sample of **485a** confirmed that the structure was the *trans-trans* isomer (**Figure 4.1a**). The minor diastereoisomer **485b** was identified as being C2-symmetrical, exhibiting a distinct signal for each proton environment and carbon around the cyclopentane ring (**Figure 4.1b**).

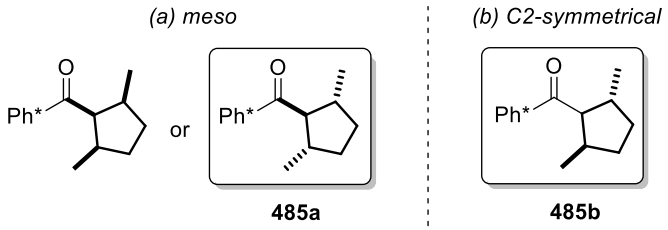


Figure 4.1 Possible meso and C2-symmetrical diastereoisomers resulting from reaction of diol **461**

Next, we subjected dimethyl substituted diol **486** to the reaction conditions which resulted in a good yield of 62% desired product **487** with 84:16 d.r. (**Entry 2**). When the final regioisomeric diol **488** was used, the corresponding product **489** was isolated in a moderate yield of 46% with 77:23 d.r. (**Entry 3**). Although four diastereomers could theoretically have been formed with diols **486** and **488**, only two diastereoisomers were observed in each case.

* Single crystal X-ray diffraction data for **485a** obtained by Dr James Frost

Dimethyl substituted diol **491** (**Figure 4.2**) was the only notable omission from the study of five-membered ring formation and despite our best efforts, could not be synthesised in a high enough quantity to be subjected the reaction conditions.

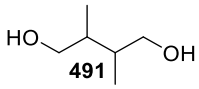


Figure 4.2 The only dimethyl substituted 1,4-diol not explored in our study

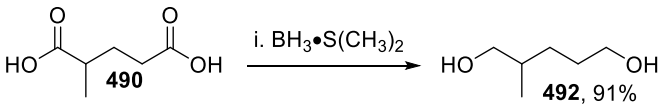
The conformational analysis of substituted cyclopentanes, unlike cyclohexanes, is known to be non-trivial, with the energy difference between axial and equatorial conformations in various envelope and twist conformations generally small.[109] The high conformational flexibility of cyclopentane rings consequently means that $^{3}J_{HH}$ vicinal couplings are variable. Due to this, assignment of relative stereochemistry based on vicinal couplings alone is generally unreliable. In absence of any other detailed conformational analysis for the substituted cyclopentanes we had generated, assignment of the relative stereochemistry was not feasible for the majority of the products.

4.4.2 Six-membered Rings

Having explored the formation of five-membered rings, attention was turned to investigating the formation of substituted cyclohexanes using mono and dimethyl substituted 1,5 diols. We hoped that we could utilise $^{3}J_{HH}$ coupling constants from NMR analyses, which are predictable and diagnostic for cyclohexane rings[110] ($^{3}J_{geminal}$/$^{3}J_{ax\text{-}ax}$ = 9-12 Hz and $^{3}J_{ax\text{-}eq}$/$^{3}J_{eq\text{-}eq}$ = 3-4 Hz) to help assign the relative stereochemical arrangement around the newly formed six-membered rings, complemented by other spectroscopic experiments and methods.

4.4.2.1 Mono-methyl Substituted 1,5 Diols

Exploration of the substrate scope began with the synthesis of diol **492** from 2-methyl glutaric acid **490** *via* a $BH_3{\cdot}S(CH_3)_2$ reduction in 91% yield (**Scheme 4.8**). As the other mono-methyl substituted diols were commercially available, this completed our selection of these diols.



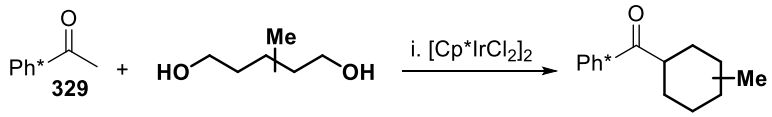
Scheme 4.8 Synthesis of diol **492**. Reagents and conditions: $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h

Subjection of unsubstituted diol **473** to the optimised reaction conditions resulted in isolation of cyclohexane **474** in a good yield of 64% (**Table 4.8, Entry 1**).

As previously discussed, diol **475**, which was used in the final round of optimisation of this reaction, yielded the corresponding product **476** in an excellent yield of 80% as a single diastereoisomer (**Entry 2**). *J*-coupling constant analysis indicated an all equatorial *trans*-1,2 relationship between the substituents as evidenced by the large ^3J-coupling of 10.7 Hz between the corresponding protons. In addition, a crystal structure of compound **476** was obtained which further proved this stereochemical assignment (**Figure 4.3a**).

Next, we subjected diol **492** to the reaction conditions. We were pleased to find that this reacted with ketone **329** to afford product **493** in an excellent 82% yield and 91:9 d.r. (**Entry 3**). The 1,3-relationship between the carbonyl and methyl substituents in the major diastereoisomer was deemed to be the *cis* through *J*-coupling constant analysis, which was further proven by X-ray crystallography (**Figure 4.3b**).

Finally, to complete the set of reactions using mono-methyl substituted 1,5 diols, we subjected diol **494** to the reaction conditions. Gratifyingly, this afforded desired product **495** in 76% yield as a single diastereoisomer (**Entry 4**), which was assigned as the all equatorial 1,4-*trans* product through *J*-coupling constant analysis. Again, we were pleased to find that the crystal structure obtained for this compound confirmed our assignment of the relative stereochemistry (**Figure 4.3c**).



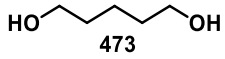
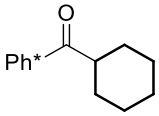
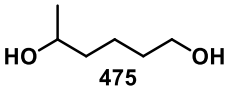
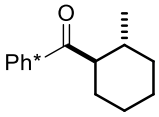
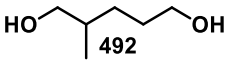
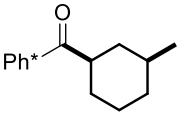
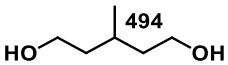
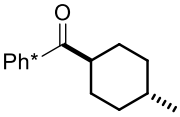
Entry	Diol	Product	Yield (%)
1			64 (**474**)
2[a]			80 (**476**) > 95:5 d.r.
3[a]			82 (**493**) 91:9 d.r.
4[a]			76 (**495**) > 95:5 d.r.

Table 4.8 Substrate scope: mono-methyl substituted 1,5-diols. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material

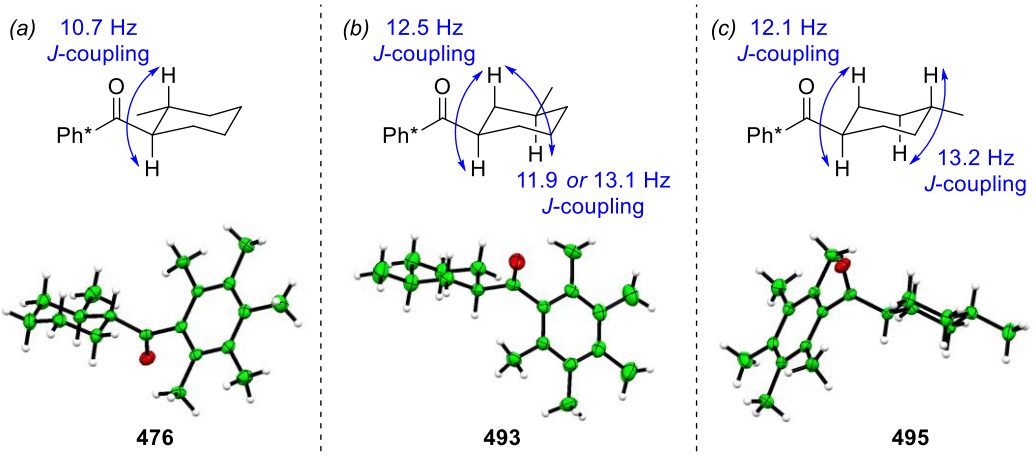


Figure 4.3 *J*-coupling constant analysis, with key stereochemical interactions highlighted, and crystal structures of **476**, **493** and **495**. Key for crystal structures – carbon: green, oxygen: red, hydrogen: white

In rationalising the relative stereochemistry observed for the disubstituted cyclohexane products we had synthesised, we theorised that this stereochemistry had been set under thermodynamic control by base mediated epimerisation at the α-carbonyl centre. This can be exemplified by the formation of product **495**. Epimerisation at the α-centre would drive the reaction to the all

equatorial diastereoisomer, which in the case of this 1,4-substituted cyclohexane would be the all equatorial *trans* product **495** (**Figure 4.4a**). To test this hypothesis, *cis*-**496** was synthesised and re-subjected to the reaction conditions by Dr Roly Armstrong. This led to complete epimerisation to *trans*-**496**, the expected thermodynamic product (**Figure 4.4b**).

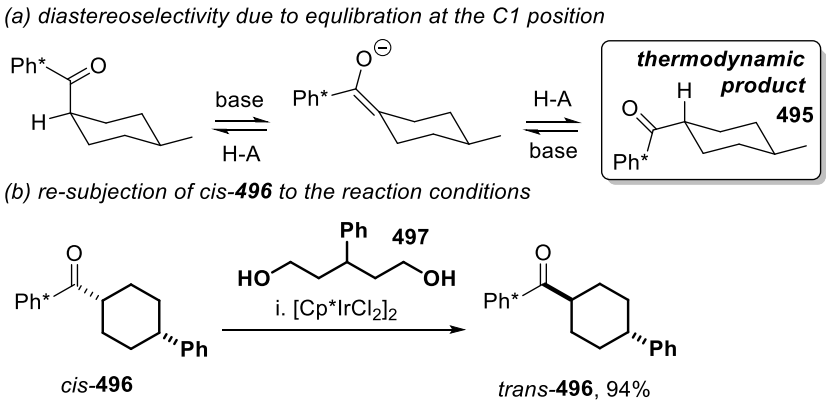
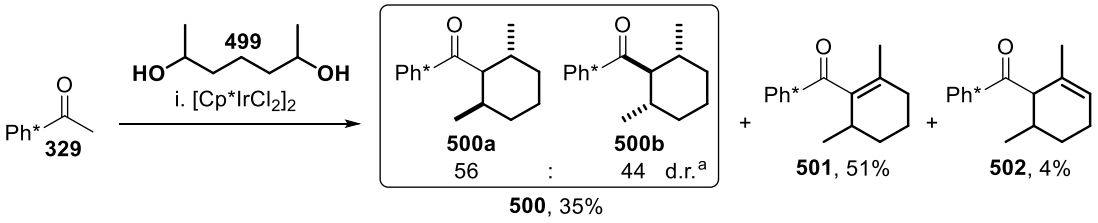


Figure 4.4 Thermodynamic control: base-mediated epimerisation at the α-carbonyl position. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol **497** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. Reaction conducted by Dr Roly Armstrong

4.4.2.2 Dimethyl Substituted 1,5 Diols

Next, we turned our attention towards investigating the use of dimethyl substituted diols under our protocol. We began by subjecting diol **499** to the reaction conditions. Desired cyclic compound **500** was isolated in 35% yield with 56:44 d.r. (**Scheme 4.9**).



Scheme 4.9 Subjection of dimethyl substituted diol **499**[*] to the reaction conditions. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol **499** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **500a** and **500b** isolated as an inseparable mixture

We had anticipated that diol **499** would prove troublesome as the presence of two secondary alcohols likely leads to a very sterically encumbered α-carbonyl centre; therefore, the relatively

[*] Diol **499** synthesised by Dr James Frost

low yield is perhaps not surprising. The reaction of ketone **329** with diol **499** gave rise to a mixture of diastereoisomers, as highlighted by inspection of the signals in the ^{1}H and ^{13}C NMR spectra. To identify the relative stereochemistry of these diastereoisomers, we analysed the *J*-coupling constants between key protons to determine the relationship between the substituents. The major, C2-symmetrical, diastereoisomer **500a** could be assigned as having a *cis-trans* relationship between its substituents, with one of the methyl groups occupying an axial position (**Figure 4.5a**), whereas meso compound **500b** could be assigned as the all equatorial *trans-trans* diastereoisomer (**Figure 4.5b**).

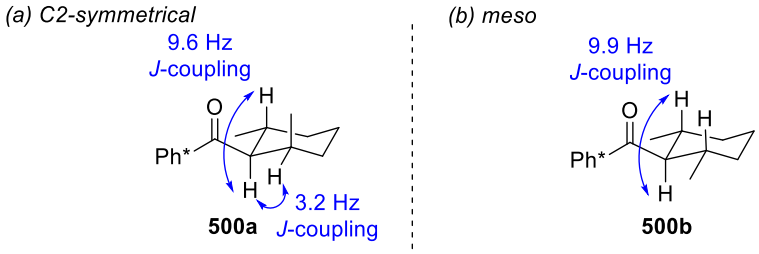
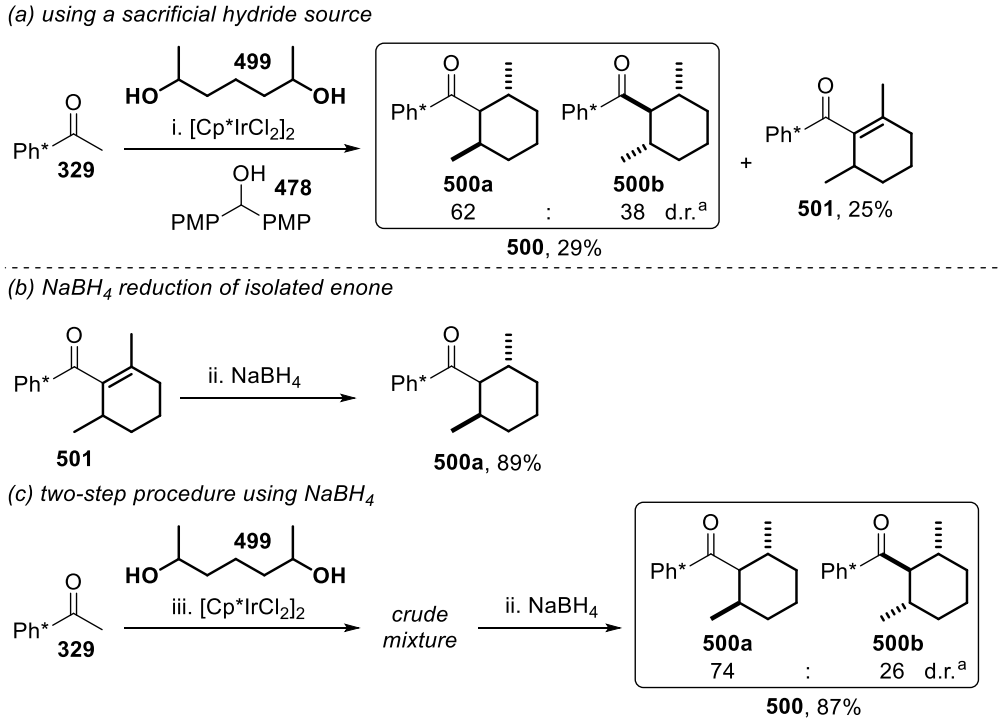


Figure 4.5 *J*-coupling constant analysis with key stereochemical interactions to determine the relative stereochemistry of **500a** and **500b** highlighted

In addition to the desired product **500**, 4% of skipped enone **502** was formed. We were also surprised to isolate tetrasubstituted enone **501** in 51% yield, only a single reduction-step away from desired product **500**. This suggested that perhaps, under the optimised conditions, reduction of tetrasubstituted enone **501** was proving troublesome. As noted during the final round of optimisation for this reaction (see **Chapter 4.2**), we wondered whether isolation of this type of enone suggested that there was a lack of hydride availability. We had previously solved this issue by increasing the equivalents of diol from 1.1 equivalents to 2 equivalents, though clearly this modification was not enough for this particular diol. An alternative strategy we had highlighted was the use of an additive, alcohol **478**, as a sacrificial hydride source, to aid reduction of the enone. We wondered if this approach could solve the problem at hand.

Unfortunately, subjecting diol **499** and ketone **329** to the modified procedure using alcohol **478**, did not result in an improved yield of the desired product, which was isolated in a low yield of 29% (**Scheme 4.10a**). Tetrasubstituted enone **501** was isolated in a lower yield of 25%.



Scheme 4.10 Solving the issue of converting tetrasubstituted enone **501** to product **500.** Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KOH (4 equiv), 1,5-diol **499** (1.1 equiv), alcohol **478** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h, (ii) $NaBH_4$ (10 equiv), THF:MeOH (3:1), 60 °C, 24 h, (iii) $[Cp^*IrCl_2]_2$ (2 mol%), KOH (4 equiv), 1,5-diol **499** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^1H NMR analysis of the crude material. **500a** and **500b** isolated as an inseparable mixture

Changing our approach, we wondered if enone **501** would be susceptible to reduction using $NaBH_4$. To test the feasibility of this, we initially subjected isolated enone **501** to $NaBH_4$ (**Scheme 4.10b**). We were surprised to find that C2-symmetrical compound **500a** was formed as a single diastereoisomer in 89% yield, with no reduction of the ketone observed. Based on this result, we took the crude reaction mixture after an initial hydrogen borrowing alkylation reaction and telescoped it through a $NaBH_4$ reduction step, hoping to drive any unreduced enone to product. We were delighted to find that product **500** could be isolated in an excellent yield of 87% with 74:26 d.r. (**Scheme 4.10c**).

In rationalising the diastereoselectivity observed in the reaction, we suspect that the reduction of enone intermediate **501** is stereodetermining, with the free C6-methyl substituent showing some diastereofacial control. It appears there is a preference for addition of hydride *syn* to the stereocontrolling methyl substituent. It has been suggested in similar systems that the C6-substituent is forced into a pseudo-axial position in a half-chair conformation to minimise $A^{1,2}$ strain between the adjacent substituent (see **503, Figure 4.6**).[111] Preferential axial attack of hydride *via* a chair-like transition state **501** would then lead to C2-symmetrical compound **500a** upon axial protonation of the resulting enolate (**Figure 4.6**). The selectivity of the protonation step is inconsequential however, as the α-carbonyl centre is able to epimerise under the conditions and therefore equilibrate to put the substituent in an equatorial position. In contrast, 'equatorial' attack* *via* twist-boat **504** would lead to meso compound **500b**, which is observed as the minor diastereoisomer (**Figure 4.6**).

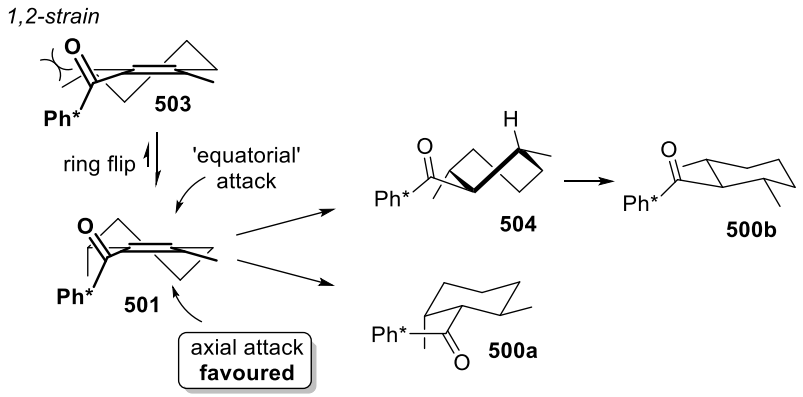


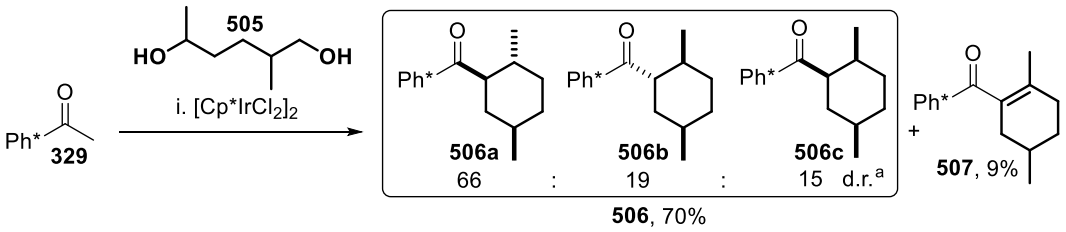
Figure 4.6 Stereocontrolled reduction of enone **501**

We suspect the greater selectivity observed with $NaBH_4$ over the Ir-catalysed process may be partly due to the difference in the reaction temperature for each process, with the $NaBH_4$ reduction conducted at a lower 60 °C than the Ir-catalysed process at 115 °C. Perhaps at this higher temperature, there is smaller difference in axial attack over equatorial attack. In addition, the

* 'equatorial attack' refers to axial attack *via* a boat-like transition state

nature of the source of hydrides is different in each case and may itself be a reason for the difference observed.

Moving forward, we turned our focus to diol **505** with a 1,4-dimethyl substitution pattern. On reacting diol **505** with Ph* ketone **329**, desired product **506** could be isolated in a good yield of 70% with a 66:19:15 d.r. (**Scheme 4.11**). Tetrasubstituted enone **507** was also isolated, albeit in a low yield of 9% in this case.



Scheme 4.11 Subjection of dimethyl substituted diol **505**[*] to the reaction conditions. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol **505** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **506a**, **506b** and **506c** isolated as an inseparable mixture

With the mixture of three diastereoisomers resulting in a complex set of overlapping signals in the NMR spectra, deconvoluting them to extract *J*-coupling constants to aid assignment of the relative stereochemistry was not trivial. Despite the complexity, we were pleased to find that the signals corresponding to COC*H* were non-overlapping for diastereoisomers **506a**, **506b** and **506c** and could be found at 2.54 ppm, 2.80–1.74 ppm and 2.82 ppm respectively in the ^{1}H NMR spectrum. Exploiting the separation of these key signals, we were able to use a 1D TOCSY (Total Correlated Spectroscopy) experiment to generate 'clean' ^{1}H NMR spectra for each diastereoisomer. A 1D TOCSY experiment is able to achieve this by selectively exciting one signal in an NMR spectrum, which is followed by a "spinlock" pulse sequence that allows magnetisation to be transferred from the 'excited' spins to other nuclei in the spin system.

[*] Diol **505** synthesised by Dr James Frost

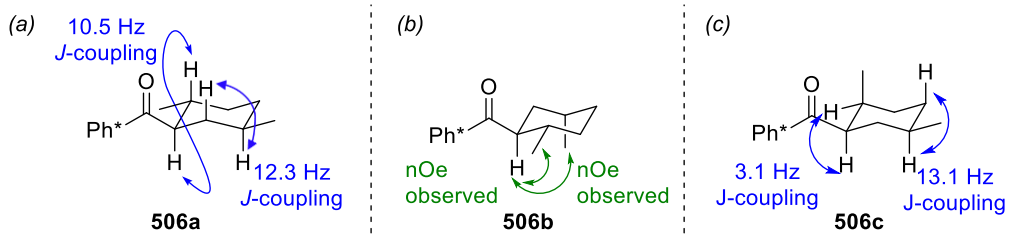


Figure 4.7 *J*-coupling constant analysis and nOe interactions with key stereochemical interactions to determine the relative stereochemistry of **506a**, **506b** and **506c** highlighted

This results in a 1D spectrum in which only the signals that are part of the same spin system that was selectively excited appearing and hence providing a 'clean' ^{1}H NMR spectrum. Using this technique, we were able to extract key $^{3}J_{HH}$ couplings, helping us assign diastereomers **506a** (**Figure 4.7a**) and **506c** (**Figure 4.7c**). To assign the relative stereochemistry of **506b**, we employed a 2D NOESY experiment in which we were able to identify key nOe interactions, leading to its successful assignment (**Figure 4.7b**).

The observed relative stereochemistry in diastereoisomers **506a**, **506b** and **506c** could be rationalised by considering the reduction of enone **507**. With the C5-methyl substituent in a pseudo-equatorial position in the half-chair conformation, preferential axial attack would lead to major diastereoisomer **506a** (**Figure 4.8**). We tentatively propose that as axial attack occurs over the C5-methyl substituent, it is not perfectly controlled, thereby some equatorial attack* also occurs leading to diastereoisomer **506b** possessing both an equatorial and axial methyl substituent, being observed. Epimerisation at the α-carbonyl centre of **506b** leads to diastereoisomer **506c**, which also features both an axial and equatorial methyl substituent, so a thermodynamic mixture of **506b** and **506c** forms under the reaction conditions.

* 'equatorial attack' refers to axial attack *via* a boat-like transition state

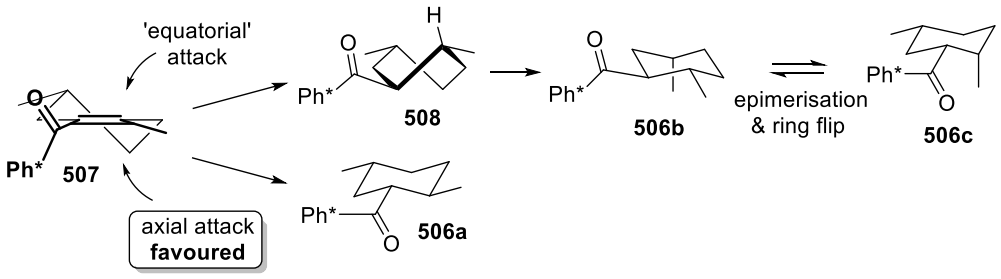
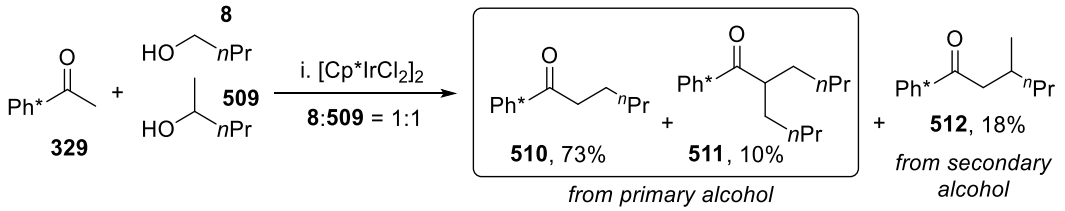


Figure 4.8 Stereocontrolled reduction of enone **507**

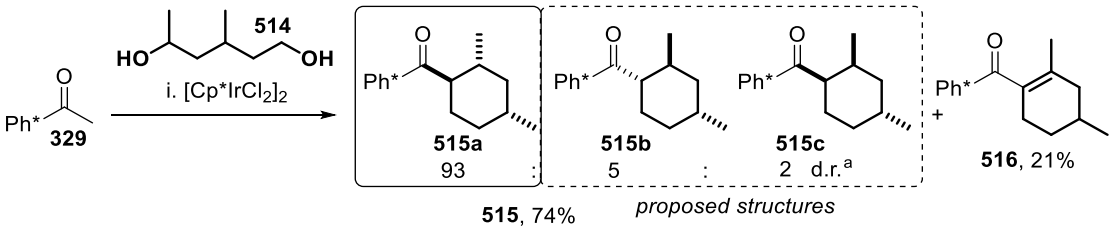
It is also important to note that, in contrast to previous diol **499**, diol **505** is unsymmetrical. For unsymmetrical diols the chemoselectivity of the initial oxidation would dictate the regiochemistry of the resulting enone intermediate and therefore, would also be expected to play an important role in the stereochemical outcome of the reaction. To gain further insight, a control experiment was conducted where ketone **329** was subjected to an alkylation reaction with an equimolar excess of primary alcohol **8** and secondary alcohol **509** under the optimised conditions (**Scheme 4.12**). The major products from this reaction, **510** and **511**, formed in 73% and 10% respectively, both derive from reaction of ketone **329** with primary alcohol **8**. By extension, we therefore propose that alcohols with both primary and secondary alcohols undergo preferential oxidation and C-C bond formation at the primary centre. As a consequence, the secondary centre would react to form an enone intermediate, reduction of which would be stereodetermining.



Scheme 4.12 Primary vs. secondary alcohol. Reagents and conditions: [Cp*$IrCl_2$] (2 mol%), KOH (4 equiv), 1-butanol (2 equiv), 2-pentanol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. **510**, **511**, and **512** isolated as an inseparable mixture. Experiment conducted by Dr Roly Armstrong

Next, we subjected diol **514** to the protocol. We were delighted to find that desired product **515** was formed in a good yield of 74% and an excellent d.r. of 93:5:2 (**Scheme 4.13**). Three diastereoisomers could be identified by characteristic signals in the ^{1}H NMR spectrum appearing

at 2.32 ppm, 2.42 ppm and 2.61 ppm, corresponding to COC*H* for **515a**, **515b** and **515c** respectively. In addition, tetrasubstituted enone **516** was also isolated in 21% yield.



Scheme 4.13 Subjection of dimethyl substituted diol **514**[*] to the reaction conditions. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol **514** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **515a**, **515b** and **515c** isolated as an inseparable mixture

The relative stereochemistry of **515a** could be assigned through analysis of key $^3J_{HH}$ coupling constants (**Figure 4.9a**). We were pleased to find that this assignment was in agreement with a crystal structure obtained for **515a.** As the two minor diastereomers, **515b** and **515c**, were present in very low levels as part of an inseparable mixture, their relative stereochemistry could not be elucidated with certainty. Structures depicting their relative stereochemistry are, however, proposed based on the limited spectroscopic evidence that could be extracted as well as our experience with dealing other similar systems (**Figures 4.9b and 4.9c**).

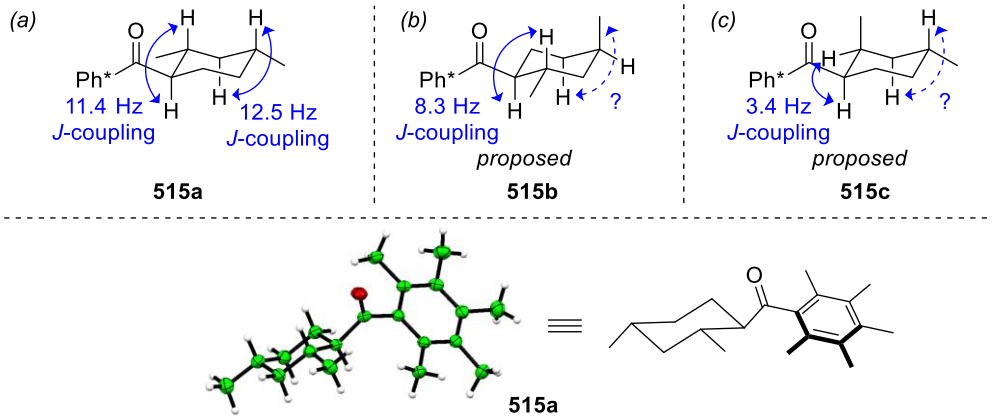


Figure 4.9 *J*-coupling constant analysis with key stereochemical interactions to determine the relative stereochemistry of **515a** highlighted, along with its crystal structure. Limited evidence for **515b** and **515c** also highlighted with proposed structures

[*] Diol **514** synthesised by Dr James Frost

The good diastereoselectivity observed in this reaction can be rationalised by considering hydride attack on the half-chair conformation of tetrasubstituted enone **516** (**Figure 4.10**). In this case, favoured axial attack would occur *anti* to the pseudo-equatorial C4-methyl substituent, in contrast to previous examples, where axial attack was occurring *syn* to the methyl substituent and may therefore have been more hindered. Axial attack leads to major diastereoisomer **515a**. The small amount of equatorial attack[*] would lead to diastereoisomer **515b** which interconverts with epimer **515b**, with both being observed in low levels in the reaction.

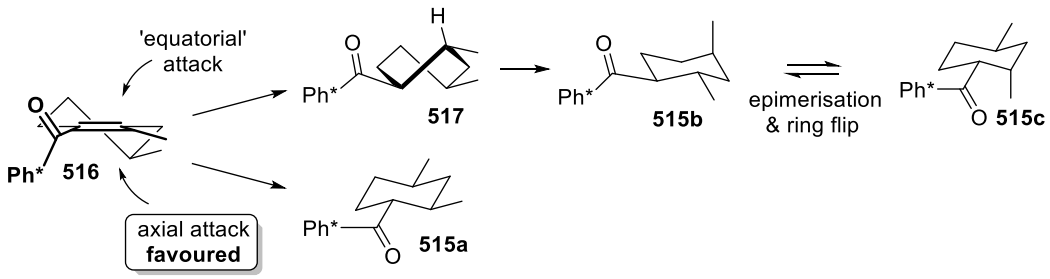
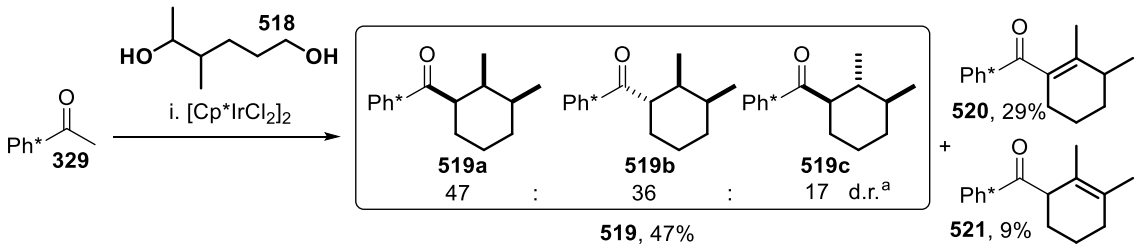


Figure 4.10 Stereocontrolled reduction of enone **516**

We then turned our attention to diol **518**, the last diol in this series to contain a secondary alcohol centre. Subjecting diol **518** to the reaction conditions afforded desired product **519** in a modest yield of 47% with 47:36:17 d.r. (**Scheme 4.14**). In addition, tetrasubstituted enone **520** was isolated in 29%, and skipped enone **521** in 9% yield.



Scheme 4.14 Subjection of dimethyl substituted diol **518**[†] to the reaction conditions. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol **518** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **519a** isolated separately, **519b** and **519c** isolated as an inseparable mixture

[*] 'equatorial attack' refers to axial attack *via* a boat-like transition state
[†] Diol **518** synthesised by Dr James Frost

Using a combination of $^{3}J_{HH}$ coupling constants as well as 2D NOESY experiments, the relative stereochemistry of **519a** (**Figure 4.11a**), **519b** (**Figure 4.11b**) and **519c** (**Figure 4.11c**) could be assigned.

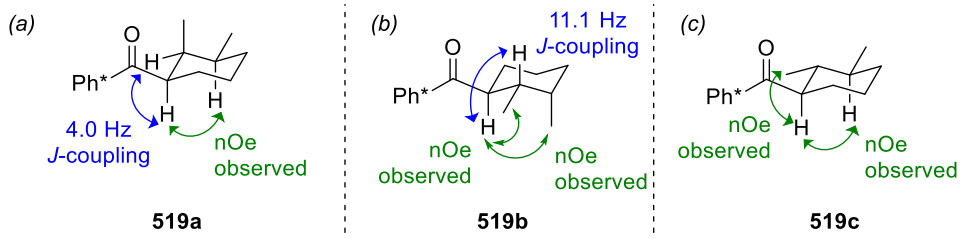
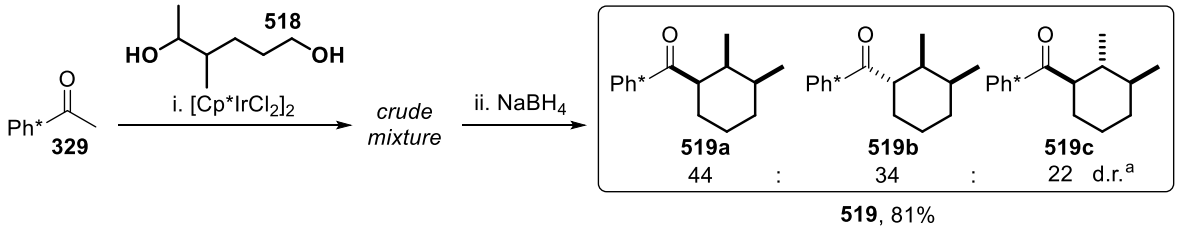


Figure 4.11 *J*-coupling constant analysis and nOe interactions with key stereochemical interactions to determine the relative stereochemistry of **519a**, **519b** and **519c** highlighted

Due to the large quantity of enone isolated from this reaction, we wondered if treating the crude reaction mixture with $NaBH_4$, as had been successful previously in the reaction with diol **499**, would be able to drive this to the desired product. We were delighted to find that telescoping the crude reaction mixture from the reaction of diol **518** and Ph* methyl ketone **329** through a reduction step using $NaBH_4$ resulted in an 81% of desired product with 44:34:22 d.r. (**Scheme 4.15**).



Scheme 4.15 Treatment of the crude reaction mixture with $NaBH_4$. Reagents and conditions: (i) $[Cp^*IrCl_2]_2$ (2 mol%), KOH (4 equiv), 1,5-diol **418*** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h, (ii) $NaBH_4$ (10 equiv), THF:MeOH (3:1), 60 °C, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **519a** isolated separately, **519b** and **519c** isolated as an inseparable mixture

In trying to understand the diastereoselectivity observed in this reaction, it appeared that $A^{1,2}$ strain may force the C3-methyl substituent into a pseudo-axial position in the half-chair conformation of enone **520** preventing a clash between it and the adjacent substituent (see **522**,

* Diol **518** synthesised by Dr James Frost

Figure 4.12). Preferential attack of hydride *anti* to the C3-methyl substituent would then lead to compound **519b**, which on epimerisation can be converted to diastereoisomer **519a** (**Figure 4.12**). Indeed, both are observed as a thermodynamic mixture. The relatively small amount of equatorial attack* therefore leads to the all equatorial compound **519c**.

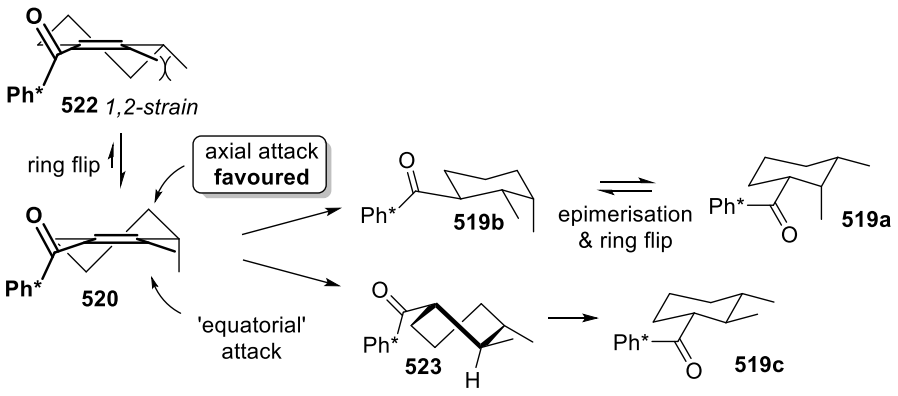
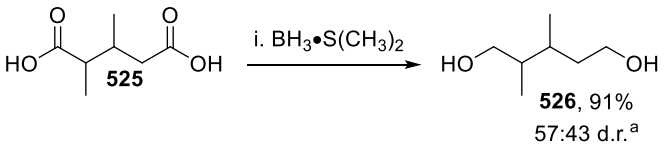


Figure 4.12 Stereocontrolled reduction of enone **520**

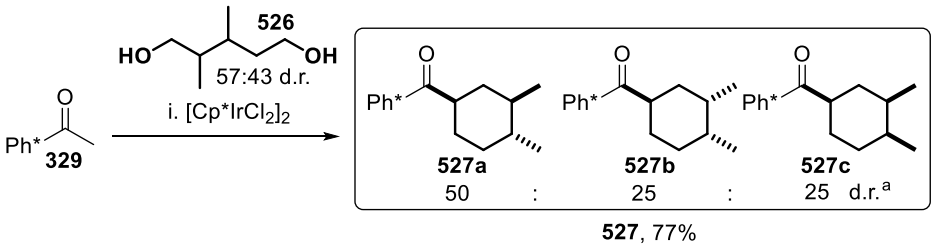
Continuing the investigation, we next synthesised diol **526** from 2,3-dimethylpentanedioic acid (**525**) *via* a $BH_3{\cdot}S(CH_3)_2$ reduction (**Scheme 4.16**), containing two primary alcohol centres.



Scheme 4.16 Synthesis of diol **526**. Reagents and conditions: $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h. [a]d.r. determined by ^{1}H NMR analysis of the crude material. Relative stereochemistry of the diastereoisomers could not be determined

With diol **526** in hand, we subjected it to the Ir-catalysed alkylation conditions. Pleasingly, it underwent facile conversion to the substituted cyclohexane containing product **527** in 77% yield with 50:25:25 d.r. (**Scheme 4.17**).

* 'equatorial attack' refers to axial attack *via* a boat-like transition state



Scheme 4.17 Subjection of dimethyl substituted diol **526** to the reaction conditions. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol **526** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **527a**, **527b** and **527c** isolated as an inseparable mixture

The presence of three diastereoisomers made interpretation of spectroscopic data challenging, as well as difficult to extract the key $^3J_{HH}$ couplings required to assign the relative stereochemistry. As key signals in the ^{1}H NMR spectrum corresponding to COC*H* for **527a**, **527b** and **527c** could be identified at 2.64 ppm, 2.78 ppm and 2.61 ppm respectively, we once again employed a 1D TOCSY experiment (explained previously). This allowed us to deconvolute the complex ^{1}H NMR spectrum into three sets of clean spectra from which valuable *J*-coupling constants could be extracted. The relative stereochemistry of diastereoisomer **527b** could be assigned using *J*-coupling constants alone (**Figure 4.13a**). To fully elucidate the relative stereochemistry of the remaining diastereoisomers, a further 2D NOESY experiment was conducted. The structures of **527a** (**Figure 4.13a**) and **527c** (**Figure 4.13c**) could then be assigned by observation of key nOe interactions alongside previously extracted *J*-coupling constants.

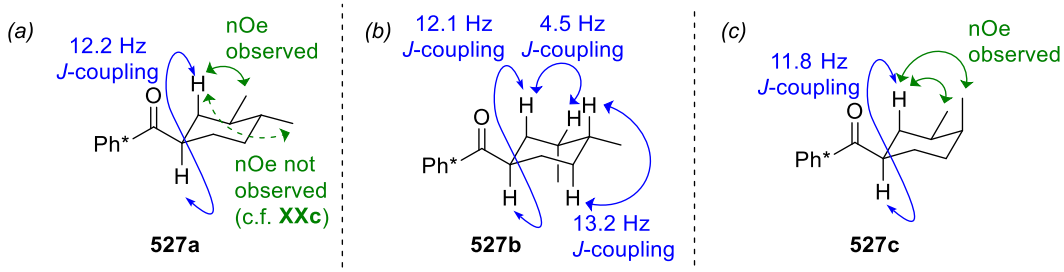
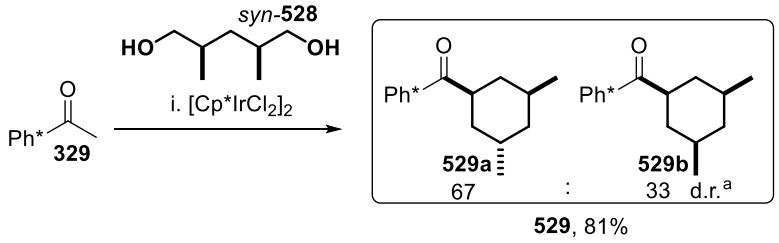


Figure 4.13 *J*-coupling constant analysis and nOe interactions with key stereochemical interactions to determine the relative stereochemistry of **527a**, **527b** and **527c** highlighted

In rationalising the relative stereochemistry of the reaction, it is important to note that with no secondary alcohol centre within diol **526**, the reduction step is expected to be

non-stereodetermining. Therefore, we propose that the diastereoselectivity observed is simply a statistical mixture resulting from the reaction of diastereoisomeric diol **526** with ketone **329**. This gives the product **527** as a 50:50 mixture, in which the two methyl substituents are either *syn* or *anti* with respect to each other. In reality this is observed as a 50:25:25 (**527a**:**527b**:**527c**) mixture as the *syn*-diastereoisomer has *two* similarly stable diastereoisomers, interconvertible *via* epimerisation at the α-carbonyl centre and are both observed in a 1:1 ratio (**527b** and **527c**). In contrast, the *anti*-diastereoisomer **527a** exists only as the all equatorial diastereoisomer as the epimerised diaxial diastereoisomer is presumably energetically disfavoured.

Finally, completing the series of dimethyl substituted diols, we turned our attention to diol **528**. On subjection of the single *syn* diastereoisomer of diol **528** to the reaction conditions, we were delighted to find that product **529** could be obtained in 81% yield with 67:33 d.r. (**Scheme 4.18**).



Scheme 4.18 Subjection of dimethyl substituted diol **528**[*] to the reaction conditions. Reagents and conditions: (i) [Cp*$IrCl_2$] (2 mol%), KOH (4 equiv), 1,5-diol **528** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material. **529a** and **529b** isolated as an inseparable mixture

On analysis of the spectroscopic data, it was evident that of the two diastereoisomers formed, one was meso, whereas the other was C2-symmetrical. To determine the relative stereochemistry, we analysed key $^3J_{HH}$ coupling constants, assigning the structures for both **529a** (**Figure 4.14a**) and **529b** (**Figure 4.14b**).

[*] Diol **528** synthesised by Dr James Frost

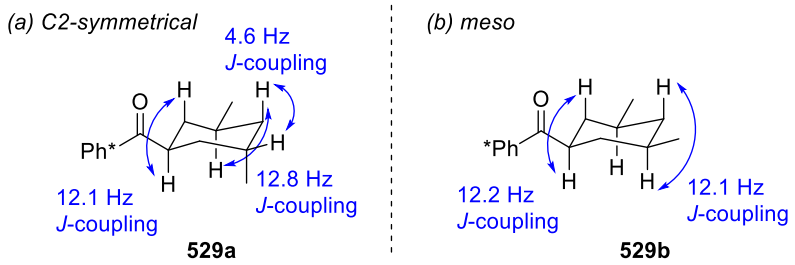


Figure 4.14 *J*-coupling constant analysis with key stereochemical interactions to determine the relative stereochemistry of **529a** and **529b** highlighted

As with diol **526**, diol **528** has no secondary alcohol centres, therefore the final reduction to form the saturated cyclohexane ring is non-stereodetermining. Similarly, we suspect the diastereoselectivity observed predominantly results from a statistical addition of diol **528** to ketone **329**. If this was the only factor responsible, a 50:50 mixture of diastereoisomers would be expected, whereas in reality a slightly perturbed 67:33 (**529a**:**529b**) mixture is observed. One possible explanation may be the relative rates at which the preceding enone leading to diastereoisomers **529a** and **529b** is reduced. It may be reasonable to expect a half chair conformation with the two methyl substituents *anti* with respect to each other (**530**) undergoing attack faster due to the reduced steric interference from the methyl substituent adjacent to the reacting centre (**Figure 4.15a**). In contrast, a *syn* configuration of the methyl substituents (**531**) results in attack occurring on the same face as a methyl group and hence could be slower (**Figure 4.15b**). Assuming the two diastereoisomers could interconvert *via* an extended enolate **532**, this would allow diastereoisomer **529a** to accumulate faster than **529b** and may explain the small imbalance in diastereoselectivity observed. Diastereoselectivity during an intramolecular aldol reaction also cannot be ruled out, or in fact which resulting aldol adduct undergoes preferential E1cB elimination.

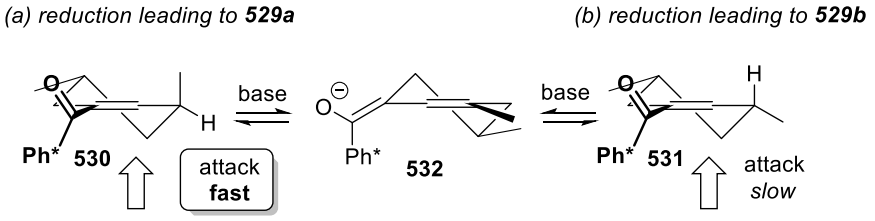
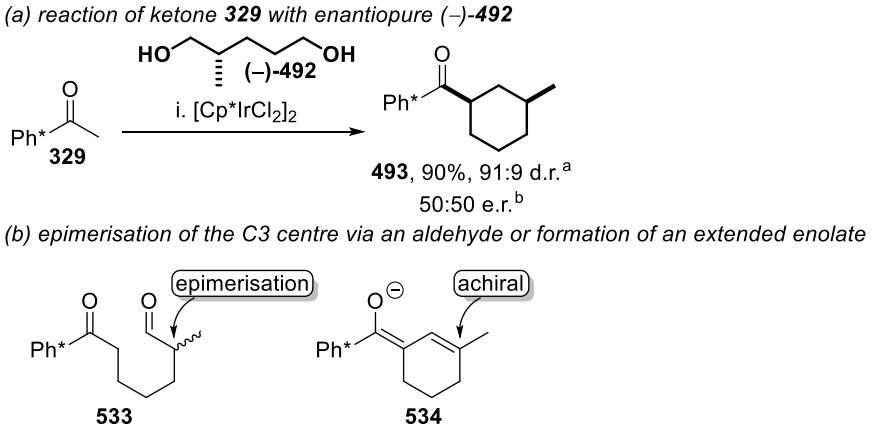


Figure 4.15 Reduction leading to diastereoisomers **529a** and **529b**

It was observed that despite having started with defined diastereomeric ratios of diols **526** and **528**, the relative stereochemistry did not appear to have been translated into the cyclohexane products. Interestingly when enantiopure 2-methyl substituted diol (–)-**492** was subjected to the reaction conditions by Dr Roly Armstrong, the corresponding cyclohexane **493** was formed as a racemate (**Scheme 4.19a**). It was hypothesised that after oxidation to the aldehyde, racemisation could occur at the substituted centre (**533**, **Scheme 4.19b**). Alternatively, epimerisation at the C3 could also occur *via* formation of an extended enolate by deprotonation of an enone intermediate (**534**, **Scheme 4.19b**). This may help to explain the loss of relative stereochemical information in diols **526** and **528** on cyclisation to the products.



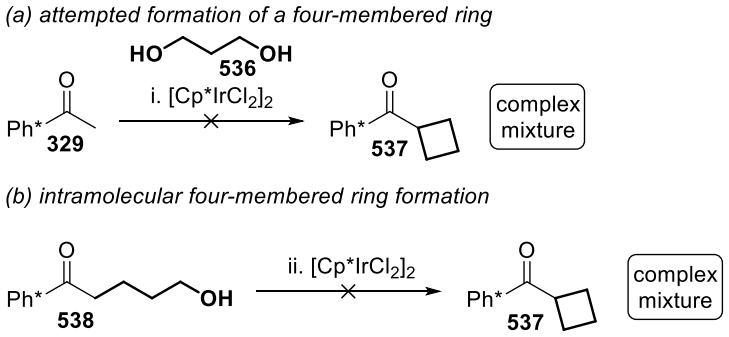
Scheme 4.19 Epimerisation at the C3 position. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,5-diol (–)-**492** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] d.r. determined by ^{1}H NMR analysis of the crude material, [b] e.r. determined by chiral HPLC analysis. Reaction conducted by Dr Roly Armstrong

4.4.3 Other Ring Sizes

Having explored substituted five-membered and six-membered rings, we turned our attention to test the viability of four- and seven-membered ring formation under our developed conditions.

4.4.3.1 Four-membered Rings

We began by attempting to form cyclobutane **537** by reacting 1,3-propanediol (**536**) with Ph* methyl ketone **329** under an optimal set of conditions (**Scheme 4.20a**). Unfortunately, formation of desired product **537** was not detected, with ^{1}H NMR analysis of the crude material showing a complex mixture. We suspected that the cyclisation step concerning intramolecular attack of an enone on the terminal aldehyde may be difficult owing to the shorter carbon chain length. To understand whether this step was indeed troublesome, hydroxyketone **538**[*], expected to be the precursor to the intramolecular cyclisation step, was synthesised.



Scheme 4.20 Attempted formation of four-membered rings using hydrogen borrowing catalysis. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), 1,3-propanediol **536** (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h, (ii) hydroxyketone **538**[*] (1 equiv), [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), PhMe (4 M), 115 °C, Ar, 24 h

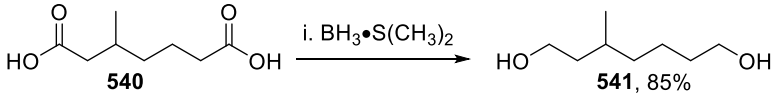
Subjection of hydroxyketone **538** to the reaction conditions, omitting the addition of diol since it had already been incorporated into the starting material, did not result in the formation of any cyclobutane **537**, instead returning a complex mixture (**Scheme 4.20b**). This suggested that the intramolecular step was troublesome as we had anticipated and may be one of the contributing factors towards why generation of four-membered rings had proven difficult.

4.4.3.2 Seven-membered Rings

With 1,6-hexanediol (**539**), required to form an unsubstituted seven-membered ring, already in hand due to its commercial availability, we also sought a methyl-substituted 1,6-diol to allow

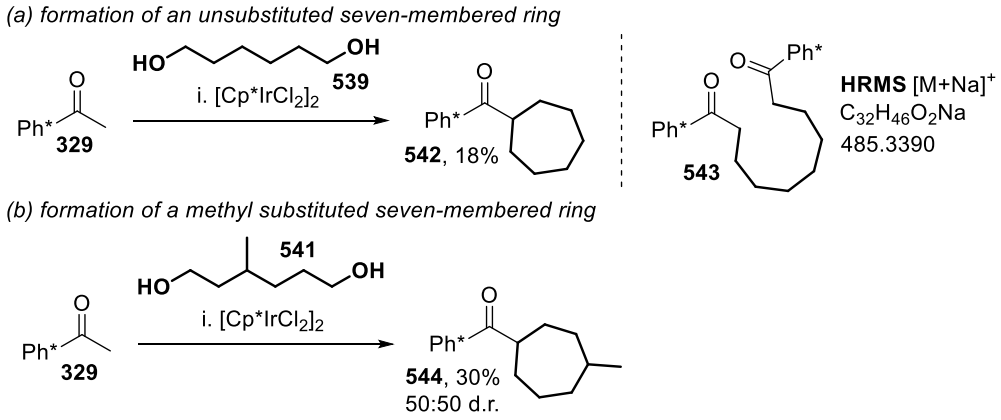
[*] Compound **538** synthesised by Dr James Frost

comparison to 1,6-hexanediol. The reduction of 3-methyladipic acid **540** using $BH_3{\cdot}S(CH_3)_2$ afforded methyl substituted 1,6-diol **541** in 85% yield (**Scheme 4.21**).



Scheme 4.21 Synthesis of diol **541**. Reagents and conditions: $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h

We began by subjecting unsubstituted 1,6-hexanediol **539** to the reaction conditions which afforded desired cycloheptane containing product **542** in 18% yield (**Scheme 4.22a**). We suspect that the majority of the remaining mass balance was accounted for by the formation of side product **543**. In forming the side product, it appeared the diol **539** had undergone intermolecular attack from two equivalents of Ph* methyl ketone **329**. Although side product **543** could not be isolated cleanly for complete characterisation, a characteristic 4H triplet (J = 7.3 Hz) could be observed at 2.68 ppm in the ^{1}H NMR spectrum corresponding to 2 × COC*H*$_2$. In addition, a $[M+Na]^+$ peak corresponding to the expected mass of side product **543** was observed at 485.3390 using HRMS, providing further evidence of its formation.



Scheme 4.22 Attempted formation of seven-membered rings using hydrogen borrowing catalysis. Reagent and conditions: (i) $[Cp^*IrCl_2]$ (2 mol%), KOH (4 equiv), 1,6-diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h

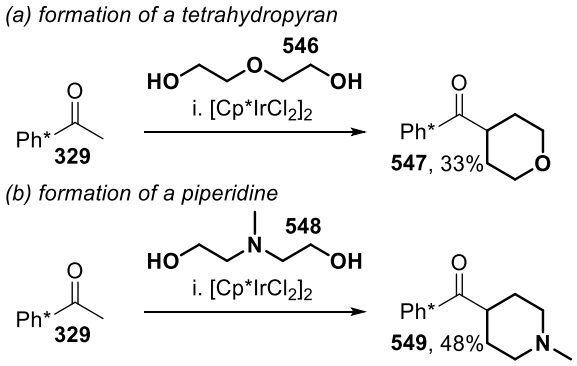
Next, we subjected mono-methyl substituted 1,6-diol **541** to the reaction conditions. This afforded corresponding product **544** in a slightly higher yield of 30%, with no diastereoselectivity observed

(**Scheme 4.22b**). Though a similar side product to **543** was not actively isolated from this reaction, we suspected similar processes may be in effect, leading to the relatively low yield obtained.

4.5 Substrate Scope: General

Having explored a range of diols with various substitution patterns and attempted formation of four-, five-, six- and seven-membered rings, we had amassed valuable insight into the reactivity of diols with Ph* methyl ketone **329**. As the formation of four-membered rings was not possible under our conditions, the formation of seven-membered rings low yielding and formation of five-membered rings resulting in moderate yields at best, we now predominantly turned our focus to the formation of six-membered rings.

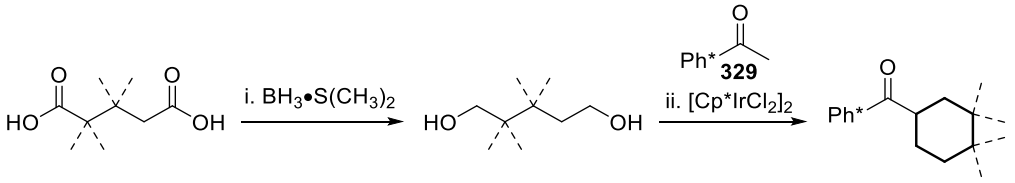
Having only investigated the formation of carbocyclic rings thus far, we wondered if the reaction would still proceed with the introduction of a heteroatom into the diol backbone.



Scheme 4.23 Formation of a tetrahydropyran and a piperidine using hydrogen borrowing catalysis. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h

First, we subjected diethylene glycol (**546**) to the reaction conditions and were pleased to find that tetrahydropyran **547** could be formed successfully, albeit in a low yield of 33% (**Scheme 4.23a**). Next, we attempted to react methyl diethanolamine (**548**) with Ph* methyl ketone **329**. Subjection to the Ir-catalysed conditions afforded the corresponding piperidine **549** in a moderate yield of 48% (**Scheme 4.23b**). We hypothesised that a contributing factor towards the low yields obtained with heteroatom containing diols may be due to the presence of an electronegative atom in a

β-position with respect to the alcohol centres. The electronics may therefore reduce the ease by which the alcohol centres are oxidised and hence retard the reaction to some degree.



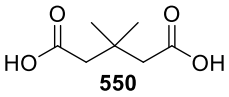
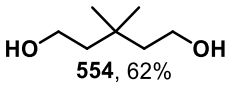
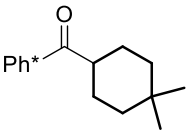
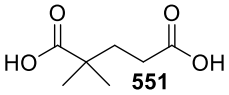
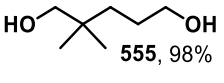
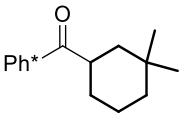
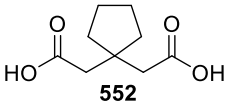
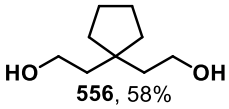
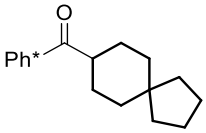
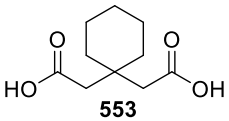
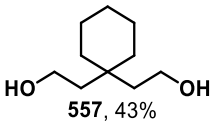
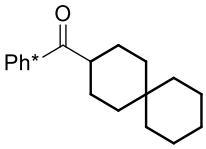
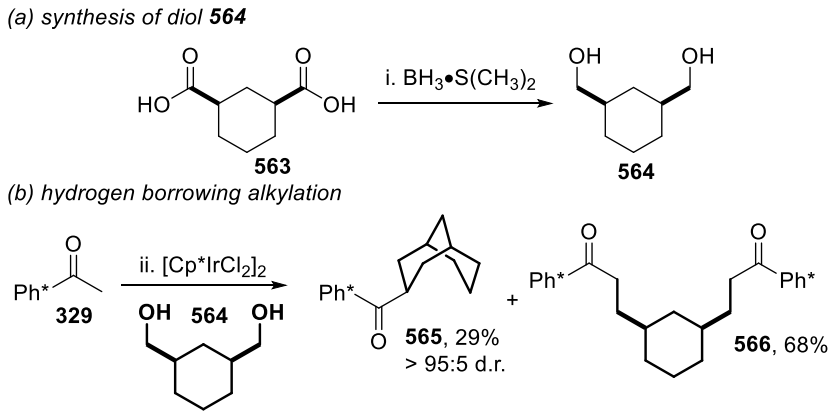
Entry	Acid	Diol (yield %)	Cyclohexane	Yield (%)
1	 **550**	 **554**, 62%		83 (**558**)
2	 **551**	 **555**, 98%		79 (**559**)
3	 **552**	 **556**, 58%		88 (**560**)
4	 **553**	 **557**, 43%		87 (**561**)

Table 4.9 Substrate scope: gem-dimethyl and spirocyclic diols. Reagents and conditions: (i) $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h, (ii) $[Cp^*IrCl_2]$ (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h

We next turned our attention to diols featuring geminal dimethyl groups, as well as those bearing spiro-fused cyclopentane and cyclohexane rings. We began by synthesising these diols from the corresponding dicarboxylic acid using a $BH_3{\cdot}S(CH_3)_2$ reduction (**Table 4.9, Entry 1–4**). With the diols in hand, we subjected them to the Ir-catalysed alkylation conditions. We were pleased to find that diols containing geminal dimethyl groups, **554** and **555**, reacted smoothly to give the corresponding cyclohexane products **558** and **559** in good yields of 83% and 79% respectively (**Entries 1 and 2**). Gratifyingly, when diols **556** and **557** were subjected to the reaction conditions, spirocyclic compounds **560** and **561** could be accessed in excellent yields of 88% and 87% respectively (**Entries 4 and 5**). We suspect that the high yields achieved using geminally

disubstituted diols are likely a consequence of the Thorpe–Ingold effect, which would favour cyclisation to the desired products.[112]



Scheme 4.24 Synthesis of diol **564** followed by hydrogen borrowing alkylation reaction with Ph* methyl ketone **329**. Reagents and conditions: (i) $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h, (ii) $[Cp^*IrCl_2]$ (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h

Next, we synthesised cyclohexane containing diol **564** from dicarboxylic acid **563** *via* a $BH_3{\cdot}S(CH_3)_2$ reduction (**Scheme 4.24a**). Subjection of diol **564** to the hydrogen borrowing alkylation conditions resulted in isolation of bicyclic compound **565** in 29% yield (**Scheme 4.24b**). In addition, side product **566** was isolated in 68% yield, resulting from the reaction of diol **564** with two equivalents of Ph* methyl ketone **329**. It was clear that reaction of diol **564** resulted in competing intermolecular and intramolecular alkylation reactions, with the intermolecular occurring preferentially and thereby lowering the yield of desired product **565** in favour of side product **566**.

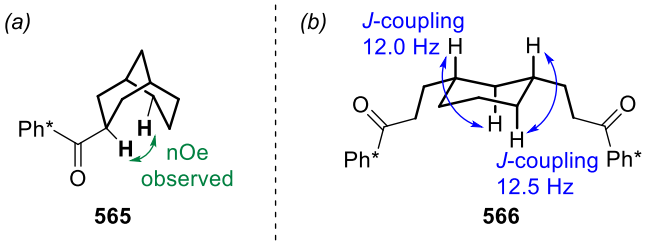
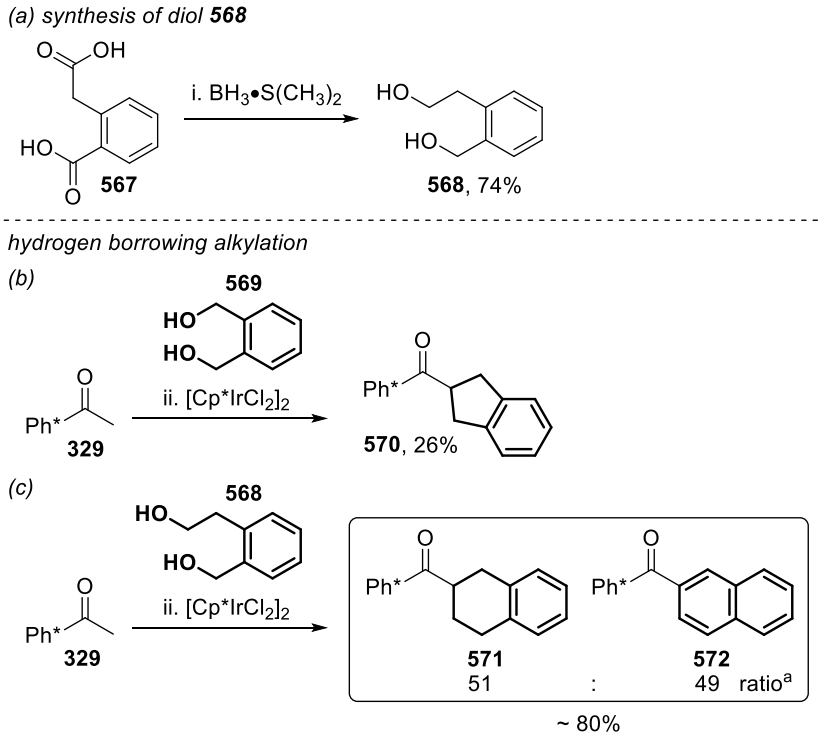


Figure 4.16 *J*-coupling constant analysis and nOe interactions with key stereochemical interactions to determine the relative stereochemistry of **565** and **566** highlighted

The relative stereochemistry of bicyclic compound **565** (**Figure 4.16a**) and side product **566** (**Figure 4.16b**) could be assigned by observation of a key nOe interaction and $^{3}J_{HH}$ coupling constant analysis, respectively.

Our focus then turned to the evaluation of diols bearing phenyl rings. With diol **569** already in hand due to its commercial availability, we synthesised related diol **568** in 74% yield from homophthalic acid (**567**) *via* a $BH_3{\cdot}S(CH_3)_2$ reduction (**Scheme 4.25a**).

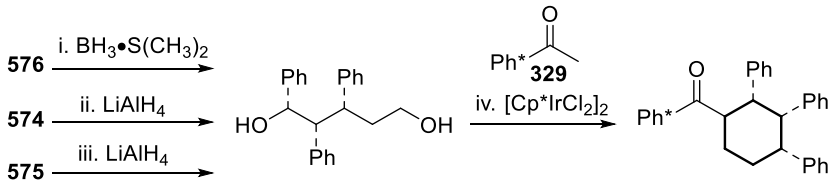


Scheme 4.25 Synthesis of diol **568** and hydrogen borrowing alkylation reactions of diol **569** and diol **568**. Reagents and conditions: (i) $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h, (ii) $[Cp^*IrCl_2]$ (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a] **571** and **572** isolated as an inseparable mixture

Subjection of dibenzylic diol **569** to the Ir-catalsed alkylation conditions afforded desired compound **570** in a low yield of 26% (**Scheme 4.25b**). When related diol **568** was subjected to the reaction conditions the desired product **571** was formed along with aromatised side product **572** in a 51:49 ratio as indicated by ^{1}H NMR analysis (**Scheme 4.25c**). Product **571** showed a characteristic 1H qd (J = 12.0, 5.6 Hz) peak at 1.68 ppm in the ^{1}H NMR spectrum corresponding $COCHCH_{eq}H_{ax}CH_2$, whereas side product **572** showed a characteristic 1H singlet at 8.11 ppm

corresponding to an aromatic C-H. Furthermore, side product **572** could be identified using HRMS analysis, with a peak corresponding to $[M+H]^+$ observed at 303.1743. The yield could not be determined precisely as compounds **571** and **572** were inseparable by column chromatography but could be approximated to ~ 80%. Perhaps unsurprisingly, aromatisation is observed with the reaction of diol **568** as it would be reasonable to assume that the intermediate enone species would be susceptible to oxidation due to a drive towards aromatisation.

Continuing our exploration of aromatic rings, we next turned our attention to phenyl substituted diols. We began by synthesising diol **577** and **578** from **574** and **575** using $LiAlH_4$ which afforded the diols in 97% and 99% yields respectively (**Table 4.10, Entries 1 & 2**). Diol **497** was synthesised from the corresponding dicarboxylic acid *via* a $BH_3{\cdot}S(CH_3)_2$ reduction, affording the desired diol in 92% yield (**Entry 3**). We were pleased to find that subjection of diol **577** to the alkylation conditions resulted in phenyl substituted cyclohexane **579** in 78% yield with > 95:% d.r. (**Entry 1**).



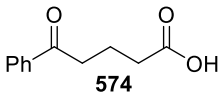
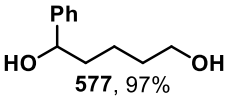
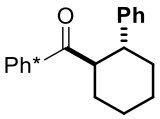
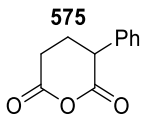
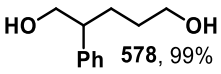
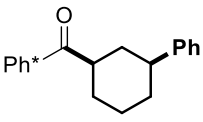
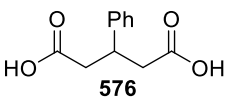
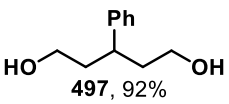
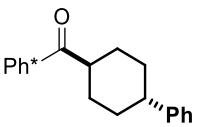
Entry	Starting Material	Diol (yield %)	Cyclohexane	Yield (%)
1[b]	 **574**	 **577**, 97%		78 (**579**) > 95:5 d.r.
2[a,b]		 **578**, 99%		50 (**580**) > 95:5 d.r.
3[b]	 **576**	 **497**, 92%		83 (**496**) > 95:5 d.r.

Table 4.10 Substrate scope: phenyl substituted diols. Reagents and conditions: (i) $BH_3{\cdot}S(CH_3)_2$ (3 equiv), THF, 0 °C to RT, 16 h, (ii) $LiAlH_4$ (4 equiv), THF, 0 °C to RT, 1 h, (iii) $LiAlH_4$ (3 equiv), THF, 0 °C to RT, 4 h, (iv) $[Cp^*IrCl_2]$ (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a]using KOH (2 equiv), [b] d.r. determined by ^1H NMR analysis of the crude material

When phenyl substituted diol **578** was subjected to the reaction conditions, desired product **580** was initially isolated in a relatively low 20% yield. Skipped enone **582** (**Figure 4.17a**) was also observed by ^{1}H NMR spectroscopy though could not be isolated cleanly. We wondered if the increased acidity of the γ-proton in enone **581** (**Figure 4.17a**) increased the propensity for extended enolate formation. In addition, on oxidation of diol **578** to **583** (**Figure 4.17b**), a relatively acidic proton would be found in an α-position to the newly formed aldehyde. The increase in acidity from the presence of a phenyl group as compared to a methyl group is exemplified in related systems **584** and **585 (Figure 4.17b)**, with the acidity of the α-proton increasing by several orders of magnitude when adjacent to a phenyl substituent.[113]

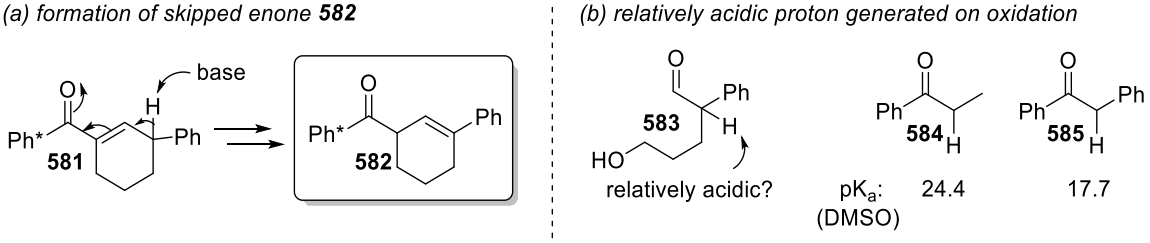


Figure 4.17 Potential problems resulting from the subjection of diol **578** to the reaction conditions

We suspected that these factors combined may be responsible for the low yield. By subjecting diol **578** to a screen of lower equivalents of KOH, we were pleased to find that reducing the amount of KOH to 2 equivalents afforded desired ketone **580** in a better yield of 50% (**Table 4.10, Entry 2**). Further reduction of the equivalents of base led to very poor conversion to product. Finally, subjection of diol **497** to the reaction conditions led to isolation of desired product **496** in an excellent yield of 83% with > 95:5 d.r. (**Entry 3**).

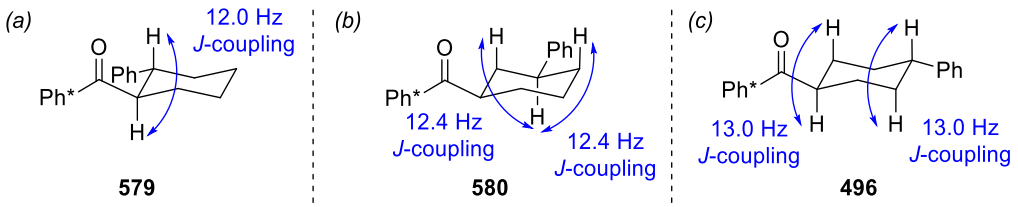
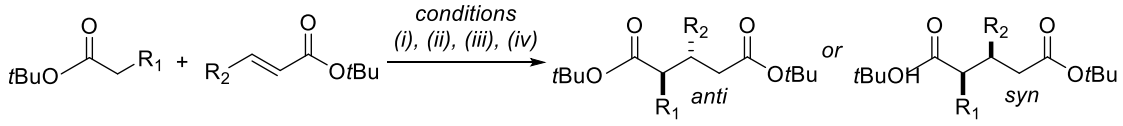


Figure 4.18 *J*-coupling constant analysis with key stereochemical interactions to determine the relative stereochemistry of **579**, **580** and **496** highlighted

The relative stereochemistry of the products **579** (**Figure 4.18a**), **580** (**Figure 4.18b**) and **496** (**Figure 4.18c**) could be assigned by analysis of key $^{3}J_{HH}$ coupling constants.



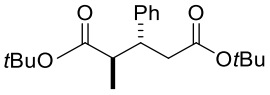
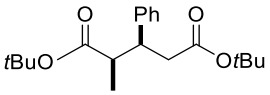
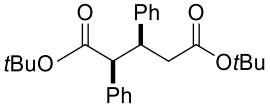
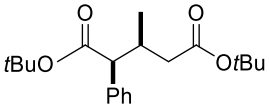
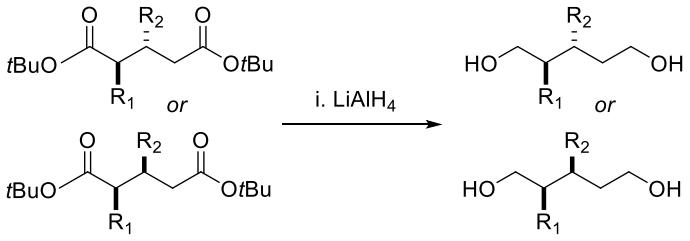
Entry	R_1	R_2	Conditions	Product	Yield (%)
1[a]	Me (**587**)	Ph (**589**)	(i)		68 (**591a**) > 95:5 d.r.
2[a]	Me (**587**)	Ph (**589**)	(ii)		85 (**591b**) > 95:5 d.r.
3[a]	Ph (**588**)	Ph (**589**)	(iii)		75 (**592**) > 95:5 d.r.
4[a]	Ph (**588**)	Me (**590**)	(iv)		98 (**593**) > 95:5 d.r.

Table 4.11 Synthesis of di-*tert*-butyl esters. Reagents and conditions: (i) *n*BuLi (2.1 equiv), diisopropylamine (2.3 equiv), *t*-butyl propionate **587** (2 equiv), $Ti(OiPr)_4$ (2 equiv), *t*-butyl cinnamate **589** (1 equiv), THF, -40 °C, 1 h, (ii) *n*-BuLi (2.1 equiv), diisopropylamine (2.3 equiv), *t*-butyl propionate **587** (2 equiv), *t*-butyl cinnamate **589** (1 equiv), THF, –78 °C, 1.5 h, (iii) LiHMDS (1.2 equiv), *t*-butyl 2-phenyl acetate **588** (1 equiv), *t*-butyl cinnamate **589** (1.2 equiv), THF, –78 °C, 2 h, (iv) LiHMDS (2.3 equiv), *t*-butyl 2-phenyl acetate **588** (2 equiv), *t*-butyl crotonate **590** (1 equiv), THF, –78 °C, 1 h. [a] Data matched that in the literature[114]

Leading on from the investigation of phenyl substituted diols, we looked to build further complexity into the system turning our attention to the evaluation of disubstituted diols featuring both a phenyl and methyl substituent. To access these diols, we began by first synthesising di-*tert*-butyl esters following a protocol by Bernardi and co-workers.[114] This involved the stereoselective Michael addition of lithium ester enolates and ester enolate titanium complexes into α,β-unsaturated esters. The authors noted that use of an enolate Ti complex gave the opposite stereochemical result to the use of the parent lithium enolate without titanium. We were able to exploit this fact to synthesise both *anti*-**591a** (**Table 4.11, Entry 1**) and *syn*-**591b** (**Entry 2**)

diastereoisomers of the desired diester in 68% and 85% yields respectively, achieving > 95:5 d.r. in both cases. To complete the series, we then synthesised diphenyl substituted diester **592** (**Entry 3**) in 75% yield with > 95:5 d.r. and another phenylmethyl ester **593** in 98% yield with > 95:5 d.r., though with the regiochemistry of the two substituents switched as compared to diester **591**.



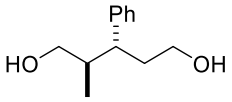
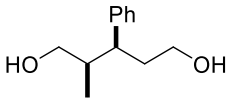
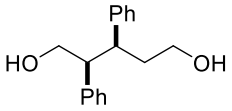
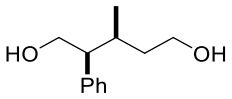
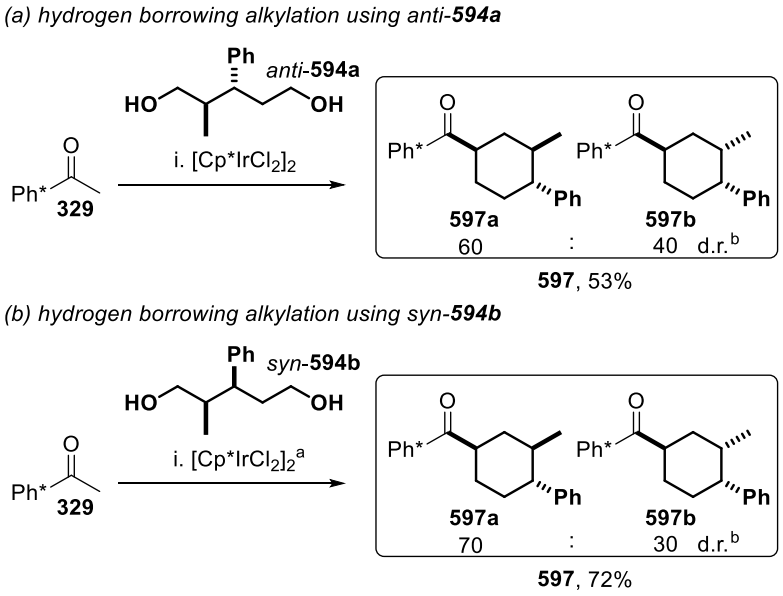
Entry	R_1	R_2	Product	Yield (%)
1[a]	Me	Ph (**591a**)		99 (**594a**) > 95:5 d.r.
2[a,b]	Me	Ph (**591b**)		89 (**594b**) > 95:5 d.r.
3[a]	Ph	Ph (**592**)		92 (**595**) > 95:5 d.r.
4[a]	Ph	Me (**593**)		99 (**596**) > 95:5 d.r.

Table 4.12 Synthesis of diols from diesters. Reagents and conditions: (i) $LiAlH_4$ (4 equiv), THF, 0 °C to RT, 4 h. [a] relative stereochemistry of diastereoisomers assigned in analogy to starting diesters, [b]relative stereochemistry confirmed using X-ray crystallography (see Experimental Section)

The diesters could then converted smoothly to the corresponding diols *via* a $LiAlH_4$ reduction (**Table 4.12, Entries 1-4**). With the diols in hand, we turned our focus to utilising them under our hydrogen borrowing alkylation protocol with Ph* methyl ketone **329**. We began by subjecting *anti*-**594a** (**Scheme 4.26a**) and *syn*-**594b** (**Scheme 4.26b**) to the reaction conditions. Regardless of whether the starting diol was *syn* or *anti*, the same two diastereoisomers of product, **597a** and **597b** were formed in 53% yield albeit with slightly different diastereoselectivities observed in each

case. Noting that *syn*-**594b** had given slightly better diastereoselectivity, we attempted to optimise this by attempting the reaction under a range of lower temperatures and using lower equivalents of KOH.



Scheme 4.26 Hydrogen borrowing alkylation reactions using *anti*-**594a** and *syn*-**594b**. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a]conducted at 105 °C, [b]d.r. determined by ^{1}H NMR analysis of the crude material, **597a** and **597b** isolated as an inseparable mixture

Though the diastereoselectivity did not improve with the use of less KOH and lower temperatures, consistently giving 70:30 d.r., we did find that running the reaction at 105 °C resulted in an improved yield of 72% of product **597**. The relative stereochemistry of products **597a** (**Figure 4.19a**) and **597b** (**Figure 4.19b**) could be determined by identification of key nOe correlations as well as $^3J_{HH}$ coupling constant analysis.

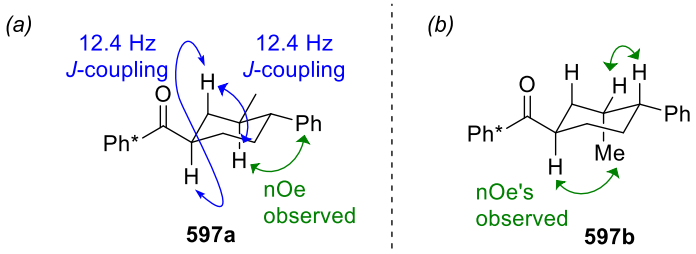
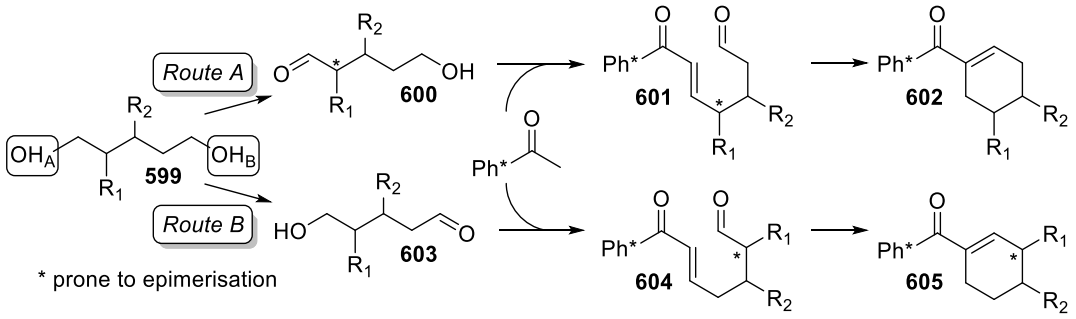


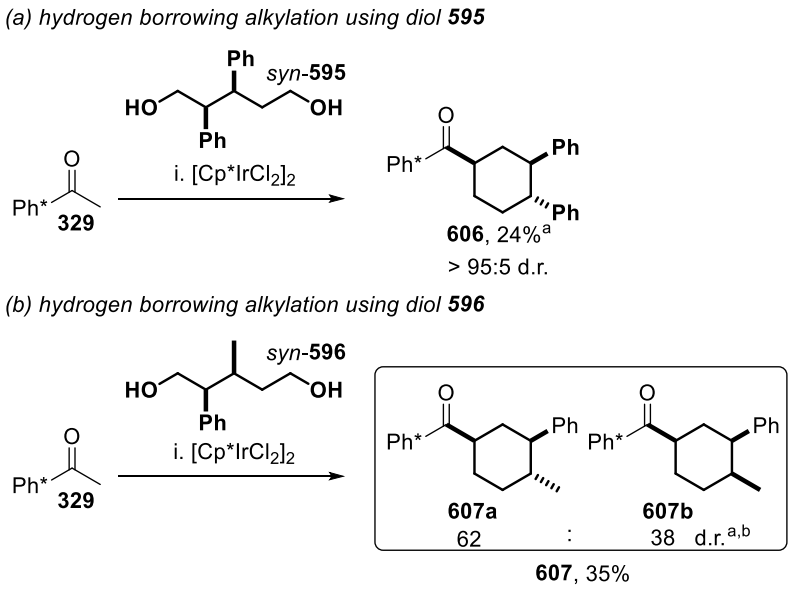
Figure 4.19 *J*-coupling constant analysis and nOe interactions with key stereochemical interactions to determine the relative stereochemistry of **597a** and **597b** highlighted

Unlike with dimethyl substituted diol **526** that featured the same substitution pattern (see **Chapter 4.4.2.2**) and gave three diastereoisomers in a 50:25:25 ratio, we only observe two with the phenylmethyl variant in this case. We suspect this is because the epimer of **597b**, which possesses an axial phenyl group and an equatorial methyl group is most likely less energetically favoured. Therefore, only the diastereoisomer with the phenyl group preferentially occupying an equatorial position is observed.



Scheme 4.27 The order in which the diol reacts may impact diastereoselectivity

A potential explanation for the difference in diastereoselectivity observed when using *anti*-**594a** vs. *syn*-**594b**, may be the ratio of initial oxidation and reaction occurring at centre 'A' compared to centre 'B' within each diol (**599**, **Scheme 4.27**). Conceptually, if centre 'A' is oxidised and reacts first, substituent R_1 may be epimerised in the resulting aldehyde **600**. Following reaction with Ph* methyl ketone, substituent R_1 can equilibrate *via* formation of an extended enolate from enone intermediate **601**. Any diastereoselectivity during the following intramolecular aldol condensation to form **602** would be inconsequential. If centre 'B' reacts first, epimerisation may occur at aldehyde **604**. In this case, any diastereoselectivity during the proceeding intramolecular aldol condensation to form **605** could impact the relative stereochemistry, as well as any equilibration *via* a cyclic extended enolate formed from enone **605**. As each route features different stereodefining steps, a difference in the ratio of diol proceeding through each route may explain the small difference in diastereoselectivity observed.



Scheme 4.28 Hydrogen borrowing alkylation reactions using diols **595** and **596**. Reagents and conditions: (i) [Cp*IrCl$_2$] (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a]relative stereochemistry assigned in analogy to **597a** and **597b** [b] d.r. determined by ^{1}H NMR analysis of the crude material, **607a** and **607b** isolated as an inseparable mixture

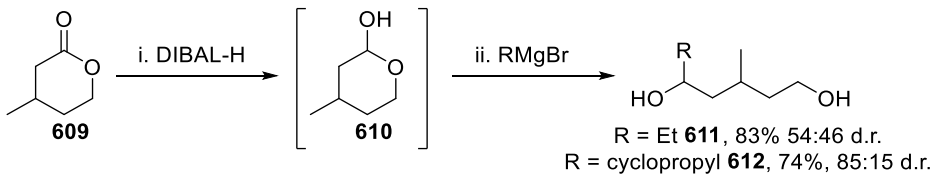
We then turned our attention to diphenyl substituted diol **595**. Interestingly, on subjection to our reaction conditions, cyclohexane **606** was isolated in a relatively low yield of 24%, although what appeared to be a single diastereoisomer[*] (**Scheme 4.28a**). The relative stereochemistry of the compound was tentatively assigned as the all equatorial diastereoisomer in analogy to compound **597a**. Finally, subjection of diol **596** to the reaction conditions resulted in isolation of **607** in 35% yield with 62:38 d.r. (**Scheme 4.28b**). The relative stereochemistry of the diastereoisomers was tentatively assigned in analogy to compounds **597a** and **597b**.

We suspect that the relatively low yields obtained with both diols **595** and **596** in comparison to diol **594** may relate to the position of the phenyl substituent on the diol backbone. As discussed previously in relation to monophenyl substituted diol **578** which also had a phenyl group in the same position, the potential increased propensity for γ-deprotonation of an enone intermediate to occur, as well as increased acidity of the α-proton on oxidation of the diol may result in the diol

[*] A single diastereomer was isolated cleanly after column chromatography, however, due to the complexity of the crude reaction mixture, the formation of additional diastereoisomers cannot be ruled out. Other fractions isolated after column chromatography could not be identified.

participating in other side reactions, leading to lower isolated yields of the product. In the case of diol **578** this was remedied to some degree by lowering the amount of KOH to two equivalents. This modification may also prove beneficial with these examples, though due to time constraints, we were not able to explore this any further.

Owing to the good diastereoselectivity observed with dimethyl substituted 1,5-diol **514**, we decided to explore this substitution pattern further. We began by synthesising diols **611** and **612** from lactone **609**. Reaction of lactone **609**[*] with DIBAL-H led to the formation of diastereomeric lactols **610** which were treated with a Grignard reagent without purification, affording diols **611** and **612** in 83% and 74% yields respectively (**Scheme 4.29**).

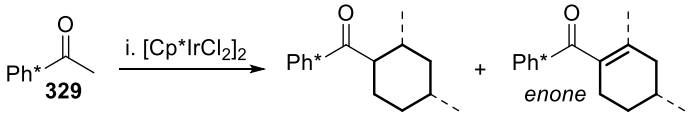


Scheme 4.29 Synthesis of diols **611** and **612**. Reagents and conditions: (i) DIBAL-H (1.8 equiv), CH_2Cl_2, -78 °C, 1 h, (ii) RMgBr (3.5 equiv), THF, 0 °C to RT

With diols **611** and **612** in hand, as well as diol **613**[†], we turned our focus to evaluating their performance under our Ir-catalysed protocol. On subjection of diol **613** to our reaction conditions, corresponding substituted cyclohexane **614** could be isolated in good yield of 67% yield with 91:9 d.r. (**Table 4.13, Entry 1**). Tetrasubsubstituted enone **615** was also isolated in 17% yield. Pleasingly, enantioenriched diol (–)-**613**, featuring a stereogenic centre at the 3-position, cyclised to provide corresponding cyclohexane **614** without any erosion in enantiomeric ratio. This highlighted that chiral information could be translated from the 3-position in the diol to new stereogenic centres on the cyclohexane ring, acting as a reporter site.

[*] Compound **609** synthesised by Dr James Frost
[†] Diol **613** synthesised by Dr James Frost

Next, we subjected ethyl substituted diol **611** to our protocol, affording desired product **616** in 60% yield, with 93:7 d.r. (**Entry 2**), as well as enone **617** in 27% yield. Replacing the ethyl group with a cyclopropyl group in using diol **612** unfortunately led to a relatively low 37% yield of cyclohexane **618** with 91:9 d.r., as well at 20% of enone **619**.



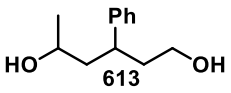
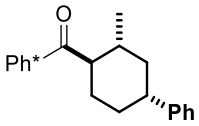
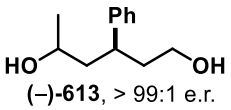
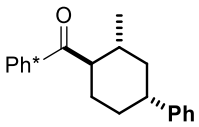
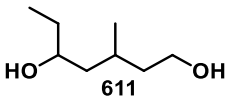
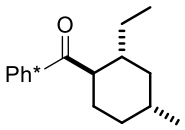
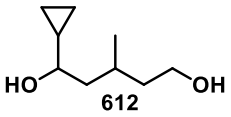
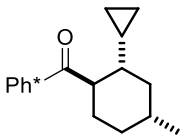
Entry	Diol	Cyclohexane	Yield (%)	Enone (%)
1[a]	 **613**		67 (**614**) 94:6 d.r.	17 (**615**)
2[a,b]	 **(–)-613**, > 99:1 e.r.		76 ((–)-**614**)* 94:6 d.r. > 99:1 e.r.	-[c]
3[a]	 **611**		60 (**616**) 93:7 d.r.	27 (**617**)
4[a]	 **612**		37 (**618**) 91:9 d.r.	20 (**619**)

Table 4.13 Substrate scope: disubstituted diols. Reagents and conditions: (i) [Cp*$IrCl_2$] (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a]d.r. determined by ^{1}H NMR analysis of the crude material, [b]e.r. determined by chiral HPLC, [c]enone not isolated

We suspect the relatively lower yields achieved with these diols may be due to presence of bulkier substituents in the C2 position of the cyclohexane ring, making reduction of the tetrasubstituted enone precursors, which could be isolated in fairly large quantities, much more difficult. The relative stereochemistry of compounds **614** (**Figure 4.20a**), **616** (**Figure 4.20b**) and **618** (**Figure 4.20c**) could be determined by analysis of key $^3J_{HH}$ coupling constants.

* Reaction conducted by Dr Roly Armstrong

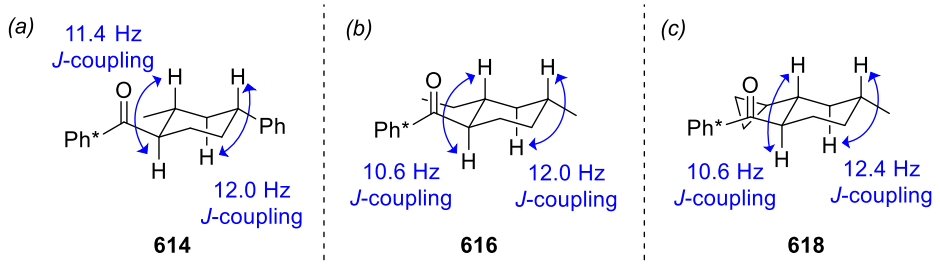


Figure 4.20 *J*-coupling constant analysis with key stereochemical interactions to determine the relative stereochemistry of **614**, **616** and **618** highlighted

Pleasingly, a wide variety of diols with a range of substitution patterns were found to be effective substrates for our Ir-catalysed hydrogen borrowing alkylation protocol. Unfortunately, there were also several diols which did not afford the desired products (**Figure 4.21**).

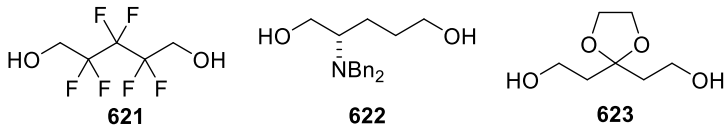
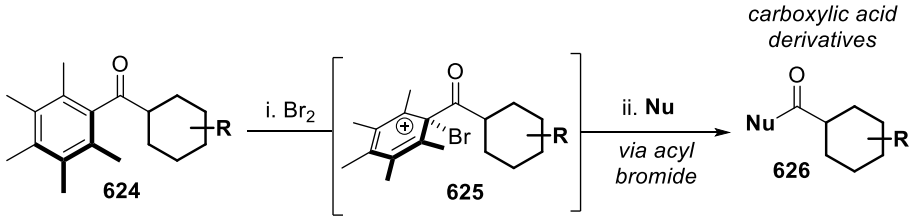


Figure 4.21 Diols that did not lead to formation of product

Hexafluorodiol **621** did not appear to react at all, with ^{1}H NMR analysis of the crude material revealing unreacted Ph* methyl ketone **329** as well as unreacted diol **621**. We suspect the electron-withdrawing nature of the CF_2 groups in the diol backbone electronically disfavour oxidation of the alcohol centres, and therefore results in no observed reaction. Unfortunately, dibenzyl protected amino diol **622**, synthesised from L-glutamic acid, resulted in a complex mixture on subjection to our reaction conditions. Furthermore, whilst the reaction of the carbocyclic analogue of diol **623** had resulted in an excellent yield under our conditions, the acetal-containing diol only resulted in the observation of a complex mixture after ^{1}H NMR analysis of the crude material.

4.6 Derivatisation of Products via Bromine-initiated Ph Release*

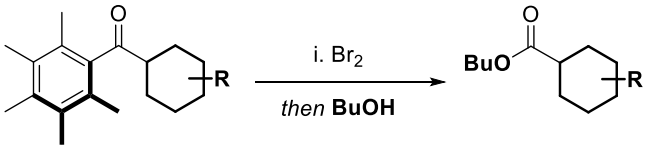
With a range of cyclic products generated using diols under our developed hydrogen borrowing alkylation protocol, we were keen to demonstrate the versatility of the pentamethylphenyl (Ph*) group, as we had done previously (See **Chapter 3.6**). We hoped to achieve this using a method developed within the Donohoe group involving bromine-initiated release of the Ph* group followed by interception of the intermediary acyl bromide with a nucleophile (**Scheme 4.30**).



Scheme 4.30 Derivatisation of cyclic products: concept of bromine-initiated release

Uncertain whether the process would preserve the stereochemical information within the cyclic products, we began by taking several cyclic products generated *via* our Ir-catalysed hydrogen borrowing protocol and attempted to convert them to the corresponding butyl esters.

On subjection of phenyl substituted cyclohexane **579** to the reactions conditions, we were pleased to find that butyl ester **629** could be isolated in an excellent 94% yield as a single diastereomer (**Table 4.14, Entry 1**). Spirocyclic compound **561** could also be converted to corresponding butyl ester **630** in 97% yield (**Entry 2**). Pleasingly, compounds **493** and **627** were converted smoothly to butyl esters **631** and **632** in high yields without any apparent erosion of any stereochemistry (**Entries 3 and 4**). Interestingly, cyclic product **628** had been synthesised from the reaction of a triol with two equivalents of Ph* methyl ketone under the alkylation conditions by Dr Roly Armstrong in the Donohoe group. In this example, one equivalent of Ph* methyl ketone had reacted twice to form a cyclohexane, whereas the other had reacted in an intermolecular fashion resulting in the formation of compound **628**. We were pleased to find that dibutyl ester **633** could be isolated in an excellent yield of 99% with > 95:5 d.r. (**Entry 5**).



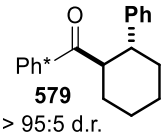
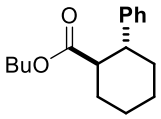
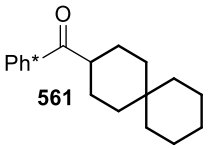
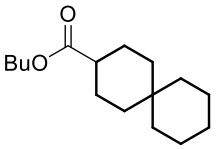
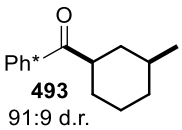
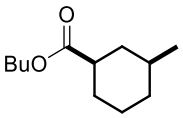
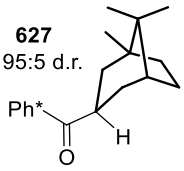
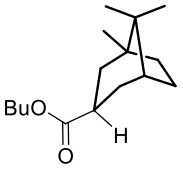
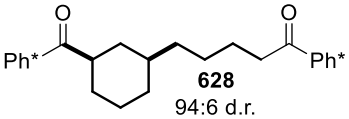
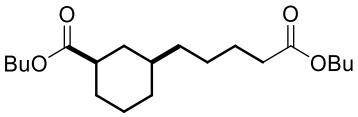
Entry	Ph* ketone	Butyl ester	Yield (%)
1[a]	 **579** > 95:5 d.r.		94 (**629**) > 95:5 d.r.
2[a]	 **561**		97 (**630**)
3[a]	 **493** 91:9 d.r.		96 (**631**) 92:8 d.r.
4[a]	**627** > 95:5 d.r.  *		95 (**632**) > 95:5 d.r.
5[a,b]	 **628** 94:6 d.r. *		99 (**633**) 95:5 d.r

Table 4.14 Derivatisation of cyclic products: formation of butyl esters. Reagents and conditions: Br_2 (2 equiv), CH_2Cl_2, –17 °C, *then* BuOH (3 equiv), –17 °C to RT. [a]d.r. determined by ^1H NMR analysis of the crude material, [b]using Br_2 (4 equiv) and BuOH (6 equiv)

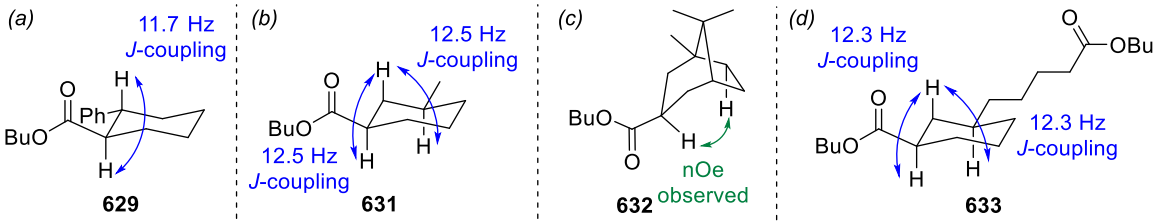
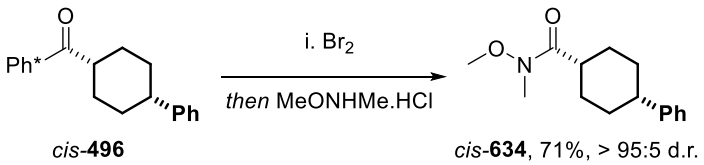


Figure 4.22 *J*-coupling constant analysis and nOe interactions with key stereochemical interactions to determine the relative stereochemistry of **629**, **631**, **632** and **633** highlighted

* Compounds **627** and **628** synthesised by Dr Roly Armstrong

The relative stereochemistry of compounds **629** (**Figure 4.22a**), **631** (**Figure 4.22b**) and **633** (**Figure 4.22d**) could be assigned using key $^{3}J_{HH}$ coupling constants, whereas compound **632** (**Figure 4.22c)** was assigned using the observation of a key nOe interaction.

To further verify that the Br_2-mediated cleavage of Ph* was proceeding stereospecifcally, thermodynamically disfavoured *cis*-**496** was subjected to cleavage to the corresponding Weinreb amide (**Scheme 4.31**). The resulting product, *cis*-**634** was isolated without any stereochemical erosion, verifying that no epimerisation occurs during the cleavage process.



cis-**496** *cis*-**634**, 71%, > 95:5 d.r.

Scheme 4.31 Verifying Br_2-mediated cleavage of Ph* occurs stereospecifically. Reagents and conditions: (i) Br_2 (2 equiv), CH_2Cl_2, –17 °C then MeONHMe.HCl (2 equiv), Et_3N (5 equiv), RT. Experiment conducted by Dr Roly Armstrong

Furthermore, Dr Roly Armstrong from Donohoe group took cyclic product **496** as a model substrate and demonstrated that Ph* could be cleaved to reveal a variety of functionalities (**Figure 4.23**). After cleavage to the acid bromide, treatment with $LiAlH_4$ led to alcohol **636** in 95% yield. The acid bromide could also undergo palladium-catalysed partial reduction to reveal aldehyde **637** in 88% yield. In addition, the acid bromide could be successfully transformed into acid **638**, as well as being successfully trapped with amines to form amides **639** and **640**. Finally, versatile NHP-ester **641** could be isolated in 81% yield on treatment with *N*-hydroxyphthalimide.

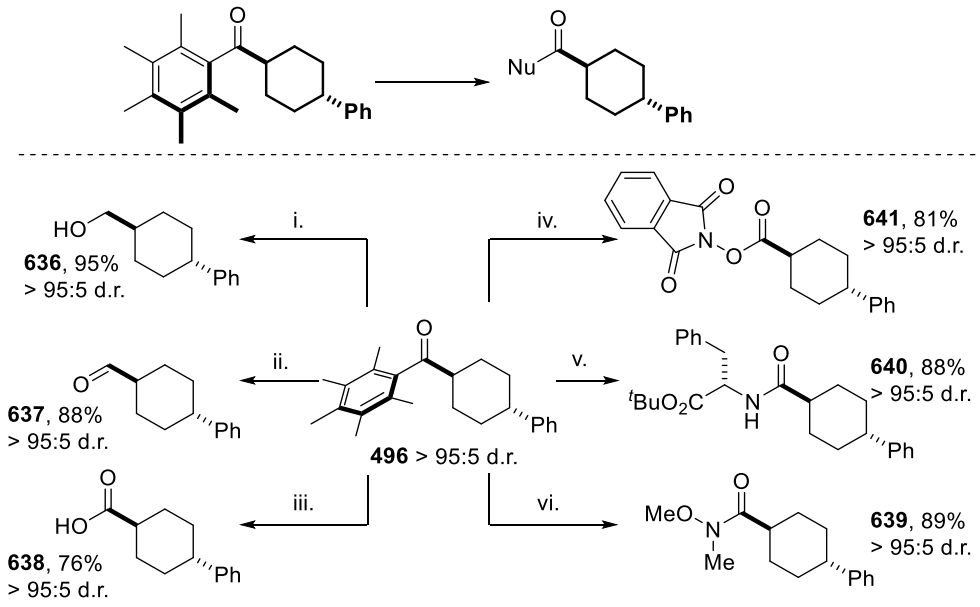


Figure 4.23 Derivatisation of cyclic compound **496** by Dr Roly Armsrong, into a variety of functionalities. Reagents and conditions: (i) Br_2 (2 equiv), CH_2Cl_2, –17 °C then $LiAlH_4$ (5 equiv), THF, RT, (ii) Br_2 (2 equiv), CH_2Cl_2, –17 °C then Bu_3SnH (2 equiv), $Pd(PPh_3)_4$ (5 mol%), C_6H_6, RT, (iii) Br_2 (2 equiv), CH_2Cl_2, –17 °C then $NaHCO_3$, THF/H_2O, RT, (iv) Br_2 (2 equiv), CH_2Cl_2, –17 °C then *N*-hydroxyphthalimide (2 equiv), $^iPrNEt_2$ (4 equiv), RT (v) Br_2 (2 equiv), CH_2Cl_2, –17 °C then H-D-Phe-OtBu.HCl (2 equiv), $^iPrEt_2N$ (4 equiv), RT, (vi) Br_2 (2 equiv), CH_2Cl_2, –17 °C then MeONHMe.HCl (2 equiv), Et_3N (5 equiv), RT

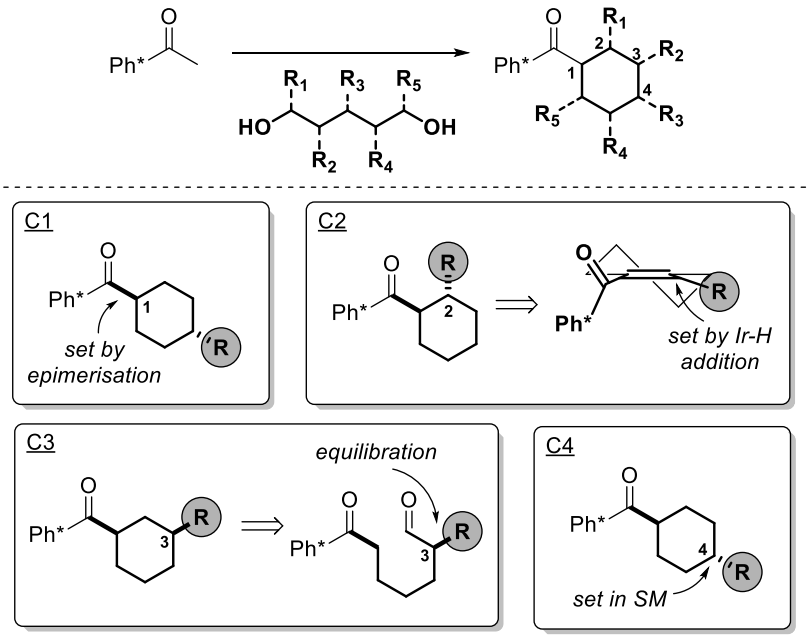
4.7 Conclusion

We have expanded the scope of hydrogen borrowing catalysis to incorporate the use of diols as the alkylating agent with carbon nucleophiles to form cyclic products. A key facilitator towards the successful development of this methodology was the use of pentamethylphenyl (Ph*) methyl ketone as the source for the carbon-based nucleophile. The unique reactivity provided by the di-*ortho* substituted phenyl ring in preventing self-condensation of the ketone enolate is crucial for a successful reaction.

Using Ph* methyl ketone as our carbon-based nucleophile, we initially chose to optimise the reaction using 1,4-butanediol which formed a cyclopentane ring after reaction. In doing so, reaction concentration (dilution with toluene) was found to be one of the key parameters for a successful reaction. The process was optimised further using 1,5-pentanediol which highlighted that elevation of the temperature to 115 °C was important to improve conversion to the desired product. The final round of optimisation was conducted using 1,5-hexanediol which highlighted

the need for two equivalents of diol to maximise conversion and minimise the amount of enone intermediate. The use of 1,5-hexanediol was also intriguing as the cyclohexane product generated from it was isolated as a single diastereoisomer.

Having successfully optimised a protocol, we methodically investigated the formation of different ring sizes, the effect of different substitution patterns, as well as rationalising the diastereoselectivity we had observed. The formation of cyclohexane rings was found to be particularly effective. Factors controlling the stereochemical outcome of the positions around a cyclohexane ring can be summarised: (i) C1 is under thermodynamic control and is set by base-mediated epimerisation, (ii) C2 is set by the facial selectivity of the Ir-H reduction (iii) C3 can epimerise on oxidation to the aldehyde, or *via* the formation of an extended enolate, and (iv) C4 is set in the starting material (**Scheme 4.32**). With the insight gained from this initial substrate scope, a broader substrate scope focusing on the formation of cyclohexane rings was conducted.



Scheme 4.32 Summary of the factors controlling the stereochemical outcome of cyclohexane ring formation

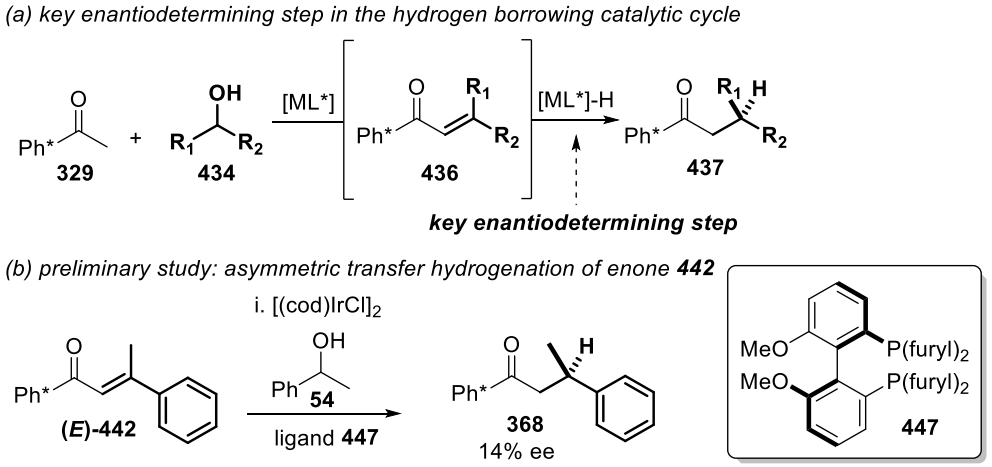
Finally, we were able to take several cyclic products that been generated and derivatise them. This was achieved through bromine-initiated released of the Ph* group, forming the acid bromide in

situ which could subsequently be intercepted with a range of nucleophiles resulting in the formation of many carboxylic acid derivatives and highlighted the versatility of the Ph* group.

4.8 Future Work

There are several areas within the field of hydrogen borrowing catalysis, derived from the investigations that have been conducted during this thesis, which will be explored in greater detail in the future. These predominantly relate to observations made and studies undertaken during **Chapter 3**, the formation of β-branched products using secondary alcohols, as well as **Chapter 4**, the formation of cyclic products using diols.

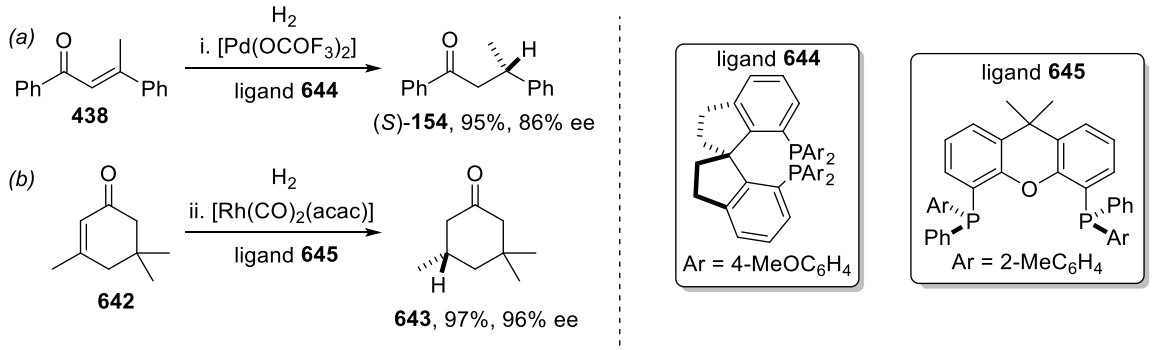
The notion of conducting enantioselective hydrogen borrowing catalysis to form β-chiral products using secondary alcohols (**Scheme 4.33a**) was briefly explored. Preliminary studies, initially only focusing on the key enantiodetermining step, screened $[(cod)IrCl]_2$ along with eight different chiral diphosphine ligands in an attempt at asymmetric transfer hydrogenation of enone **442** (see **Chapter 3.7**). The best result observed showed that a 14% enantiomeric excess could be achieved using (*R*)-2-furyl-MeOBIPHEP (**447**) (**Scheme 4.33b**).



Scheme 4.33 Potential for asymmetric induction with alkylation of ketone **329** with secondary alcohols

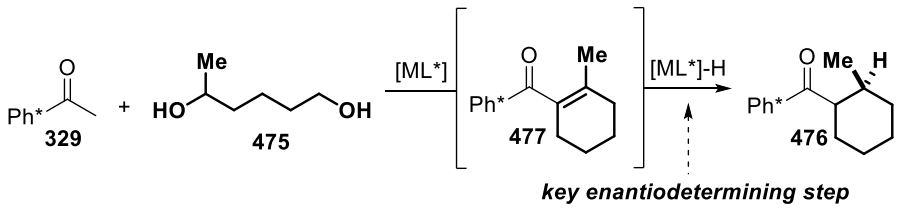
Since the enantiodetermining step in this process shares similarities with that of transition metal catalysed asymmetric hydrogenation, further screening of other catalytic systems capable of

conducting asymmetric hydrogenations will be continued. As well as the example discussed earlier, reported by Pfaltz and co-workers (see **Chapter 3.7, Scheme 3.17**), further examples of the use of chiral ligands with transition metals other than iridium in asymmetric hydrogenations is given. For example, Zhou and co-workers have reported Pd/chiral spiro biphosphine (**644**) system which was able to hydrogenate enone **438** with 86% enantioselectivity (**Scheme 4.34a**).[115] In another example, Börner and co-workers reported a series of P-chirogenic Xantphos ligands, of which ligand **645** was shown to be active with rhodium to hydrogenate isophorone (**642**) with 96% enantioselectivity (**Scheme 4.34b**).[116]



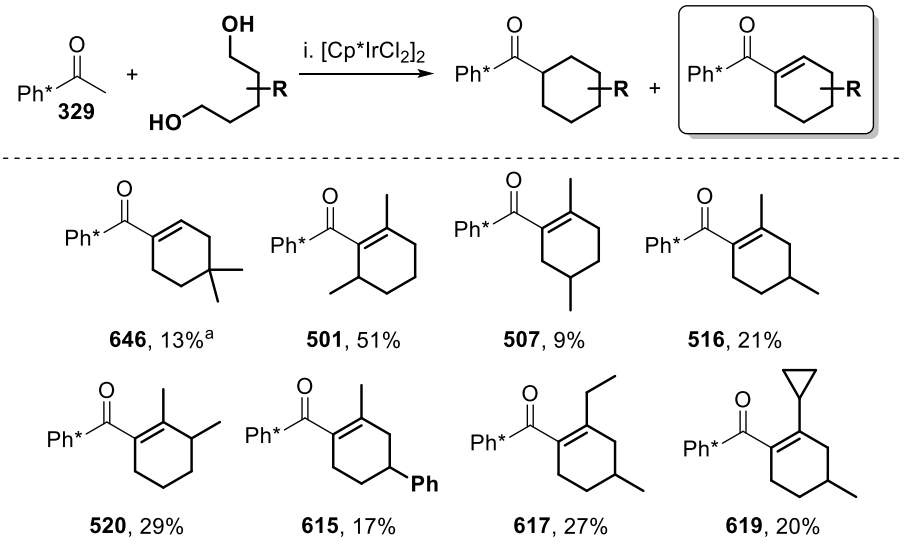
Scheme 4.34 Examples of asymmetric hydrogenation of enones. Reagents and conditions: (i) $[Pd(OCOF_3)_2]$ (2 mol%), ligand **644** (2.5 mol%), H_2 (1 atm), CF_3CH_2OH, RT, 12 h, (ii) $[Rh(CO)_2(acac)]$ (0.5 mol%), ligand **645** (0.6 mol%), H_2 (50 atm), toluene, 40 °C, 4 h

In addition, the screen will be extended to cover the full hydrogen borrowing reaction, not just the key step, to crucially determine if the asymmetric induction persists. Furthermore, considering the development of a protocol for the alkylation of Ph* methyl ketone **329** with diols to form cyclic products, this protocol too, could be investigated with respect to achieving asymmetric induction (**Scheme 4.35**). The geometry of the enone, which could effect the stereoselectivity of the reaction, when cyclic, can be reasonably expected to be fixed. In contrast, the geometry of the enone intermediate on route to β-branched products using secondary alcohols could potentially vary. In this regard, targeting the formation of enantiopure cyclic products may be more straightforward.



Scheme 4.35 Potential for asymmetric induction in the formation of cyclic products using diols

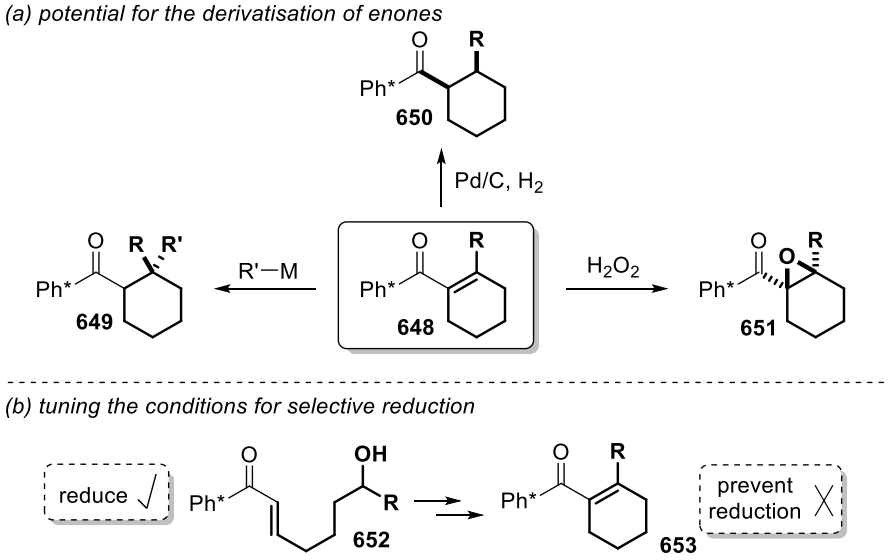
During the investigation of diols that underwent alkylation to form cyclic products (see **Chapter 4**), it was noted that when diols that resulted in sterically encumbered enones (i.e. generally tetrasubstituted) were used, reduction was impeded to some degree (**Scheme 4.36**). Although in most cases strategies were found to push the reactions towards good to excellent yields of the fully saturated ring, we believe that the cyclic enones themselves are interesting targets.



Scheme 4.36 Formation of enones, as observed during the alkylation of ketone **329** using diols. Reagents and conditions: (i) [Cp*$IrCl_2$] (2 mol%), KOH (4 equiv), diol (2 equiv), PhMe (4 M), 115 °C, Ar, 24 h. [a]using diol (1.1 equiv)

With current methods towards the synthesis of substituted endocyclic enones often requiring the multi-step syntheses of prefunctionalised starting materials[117,118], a protocol to form these compounds in one step directly from diols would be of great value. Moreover, the enone adds a further handle for derivatisation and could conceivably undergo several reactions such as epoxidation, asymmetric conjugate addition to form a β-quaternary centre or indeed reduction with Pd/C and H_2 to provide the *cis*–1,2 product, as opposed to the *trans*–1,2 product produced

under the hydrogen borrowing alkylation conditions (**Scheme 4.37a**). After derivatisation, the Ph* group could be removed *via* our bromine-initiated release protocol. As there are thought to be two enone intermediates that occur en-route to the formation of cyclic products from diols, it was envisioned that to form enone **653** as the major product of the reaction, the catalytic system would have to be tuned to allow the reduction of enone **652**, but not enone **653** (**Scheme 4.37b**).



Scheme 4.37 (a) Examples of potential derivatisations of enone substrates (b) selective reduction of enone intermediates, [M] = MgX, Li, CuX

The development of a semi-interrupted procedure could perhaps be approached from several angles: (i) using less equivalents of the diol. It had already been noted that using lower equivalents of diols typically led to increased yields of enone, perhaps due to a lower amount of metal hydride being available, (ii) using an additive that could act as a hydrogen acceptor to regenerate the active catalyst *via* a second pathway thereby impeding reduction of the desired enone. By careful tuning of these parameters, it may indeed be possible to selectively form the enone over the fully reduced carbocyclic ring.

Chapter 5: Experimental Section

5.1 Experimental Techniques

All experiments were performed under an argon atmosphere under anhydrous conditions in flame dried glassware unless otherwise stated.

Solvents and reagents: THF, CH_2Cl_2 and Et_2O were dried by purification through an activated alumina purification column. All other chemical reagents used were commercially available from Alfa Aesar, Fluorochem, Sigma Aldrich, Acros, TCI, ABC and Strem. These were used as supplied or purified by standard laboratory procedures.[119] Commercial *n*-BuLi (in hexanes) and PhLi (in dibutyl ether) were titrated prior to use using 2,6-di-*tert*-butyl-4-methylphenol in Et_2O with 1,10-phenanthroline as an indicator.

KO*t*Bu was prepared according to the following procedure*: To a 2-neck flask fitted with a reflux condenser was added freshly distilled *tert*-butanol (36 mL) and potassium metal (2.60 g, 66.5 mmol) portion-wise. The mixture was heated to 70 °C for 1 h, during which time the potassium metal fully dissolved. The solution was cooled to RT, during which time a white precipitate formed. The *tert*-butanol was carefully decanted using a filter stick and the remaining solid heated under vacuum at 145 °C for 3 h to dry. The solid KO*t*Bu was then used directly as detailed in general procedure **J**.

Chromatography: Thin Layer Chromatography (TLC) was performed on pre-coated aluminium-backed Merck Kieselgel 60 F_{254} plates, visualised using UV irradiation (λ = 254 nm) and/or staining with potassium permanganate or vanillin solutions. Flash column chromatography was performed with Merck Kieselgel 60 (0.040–0.063 mm) according to the method by W. C. Still and co-workers.[120] All solvents used for chromatographic purification were HPLC grade or equivalent and supplied by Sigma Aldrich.

* Prepared by Dr James Frost.

Infrared spectroscopy: Fourier-transform infrared (FT-IR) spectra were recorded from evaporated films on a Bruker Tensor 27 spectrometer equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers ν_{max}/cm^{-1} and for the range 3500–900 cm^{-1}.

NMR spectroscopy: All spectra were recorded on Bruker AVIII HD 400, Bruker AVII 500, Bruker AVIIIHD 600 with Prodigy broadband cryoprobe or Bruker AVIII 700 with $^{1}H/^{13}C/^{15}N$ TCI cryoprobe with the deuterated solvent acting as internal deuterium lock. ^{1}H NMR spectra were recorded at 400 MHz, 500 MHz, 600 MHz or 700 MHz and ^{13}C NMR spectra at 101 MHz, 126 MHz, 151 MHz or 176 MHz with broadband decoupling.

Residual protic solvent signal acted as an internal reference for ^{1}H NMR, and deuterated solvent carbon signal acted as the internal reference for ^{13}C NMR ($CDCl_3$: ^{1}H NMR = 7.26 ppm, ^{13}C NMR = 77.16 ppm; CD_3OD: ^{1}H NMR: 4.87 ppm, ^{13}C NMR: 49.00 ppm).

Chemical shifts δ are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and 0.1 ppm for ^{13}C NMR. The multiplicity of a signal is reported as such: s–singlet, d–doublet, t–triplet, q–quartet, quint.–quintet, sext.–sextet, sept.–septet, m–multiplet, br.–broad, app.–apparent, or combinations thereof. Coupling constants are quoted in Hz to the nearest 0.1 Hz.

Structural assignments were made with the aid of COSY, HSQC, HMBC, NOESY and TOCSY experiments.

High Resolution Mass Spectrometry (HRMS): Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe for ESI^{+} and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most

abundant isotopes, with each value rounded to 4 decimal places and within 5 ppm of the calculated mass.

Electron impact ionisation (EI) HRMS were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass.

Melting points: Melting points (m.p.) were obtained using a Leica VMTG heated-stage microscope equipped with a Testo 720 thermometer and were uncorrected.

Naming and numbering of compounds: Naming of compounds carried out using the computer program ChemDraw. This software generates the systematic name of chemical structures according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). As a result, the numbering system used in these names does not follow that shown in the description. In order to allow for the straightforward comparison of data, the NMR assignments given follow the numbering system which is shown on the chemical structure.

X-ray Crystallography: Single crystal X-ray diffraction was recorded by Kirsten E. Christensen and Wasim M. Akhtar using a Nonius KappaCCD diffractometer or Oxford Diffraction/Agilent Supernovae A. Solutions to the structures and the crystal structure images presented were produced by CRYSTALS[121] for Microsoft Windows.

5.2 General Procedures

General Procedure A: Addition of terminal alkynes to aldehydes[76]

To a solution of the alkyne (1.0 equiv.) in THF (1.4 M) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 1.05 equiv.). The mixture was stirred for 30 mins after which hydrocinnamaldehyde (1.1 equiv.) was added dropwise. The solution was stirred at –78 °C for 30 mins and then warmed to RT and stirred for a further 1 h. The reaction was quenched by the addition of water (0.76 M) and $NaHCO_3$ (0.76 M). The aqueous layer was extracted with Et_2O (× 3), the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography provided the title compound.

General Procedure B: Pyridinium dichromate oxidation of alcohols to ketones[76]

To a solution of the alcohol (1.0 equiv.) in CH_2Cl_2 (0.23 M) at 0 °C was added pyridinium dichromate (1.1 equiv.) portion-wise. Following the addition, the mixture was warmed to RT and stirred for 16 h. The solution was filtered through Celite® eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo* and then purified by flash column chromatography to provide the title compound.

General Procedure C: TEMPO oxidation of alcohols to ketones[85]

To a solution of the alcohol (1.0 equiv.) in CH_2Cl_2 (1.0 M) was added TEMPO (0.10 equiv.) and BAIB (1.1 equiv.) sequentially. The mixture was stirred for 16 h after which it was diluted with CH_2Cl_2 (0.13 M) and washed with $Na_2S_2O_3$ (0.14 M). The aqueous layer was extracted with CH_2Cl_2 (× 4) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo.* Purification by flash column chromatography provided the title compound.

General Procedure D: $[Cp^*IrCl_2]_2$-catalysed alkylation of cyclopropyl ketones

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.), the appropriate alcohol (5.0 equiv.), $[Cp^*IrCl_2]_2$ (2.0 mol%) and KOH (3.0 equiv.) sequentially in the

open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and purged with Ar for 5 mins using a balloon. Following this, the vial (complete with an Ar ballon) was heated to 105 °C in a preheated oil bath for the time stated. The mixture was cooled to RT and filtered through a SiO_2 plug, eluting with Et_2O. The filtrate was concentrated *in vacuo* and then purified by flash column chromatography to provide the title compound.

General Procedure E: Formation of Weinreb amides[91]

To a solution of the carboxylic acid (1.0 equiv.) in CH_2Cl_2 (0.40 M) at 0 °C was added *N*-*O*-dimethylhydroxylamine·HCl (1.4 equiv.), DCC (1.4 eqiuv.), DMAP (0.14 equiv.) and Et_3N (1.4 equiv.) sequentially. The mixture was stirred at 0 °C and allowed to warm to RT over 16 h in the ice bath. The mixture was filtered through Celite®, eluting with CH_2Cl_2. The filtrate was washed with 0.5 *N* HCl and sat. aq. $NaHCO_3$ before being dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography provided the title compound.

General Procedure F: Grignard addition to Weinreb amides

To a solution of the Weinreb amide (1.0 equiv.) in THF (0.50 M) at 0 °C was added cyclopropylmagnesium bromide (1.2 equiv., as a 0.50 M solution in THF) dropwise. The reaction was left to stir and warm to RT ice bath left in place) for 16 h after which it was cooled to 0 °C and sat. aq. NH_4Cl (0.20 M) added. The mixture was extracted with Et_2O ($\times$ 3) and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography provided the title compound.

General Procedure G: Ring-opening of cyclopropyl ketones by cuprate addition[92]

To a suspension of CuCN (3.0 equiv.) in Et_2O (0.16 M) at –30 °C was added the appropriate organolithium (6.0 equiv., *n*-BuLi 2.5 M in hexanes, PhLi 1.9 M in dibutyl ether or vinyl lithium in diethyl ether), dropwise over 15 mins, ensuring that the temperature did not exceed –30 °C. Following this, the mixture was stirred at this temperature for 5 mins, after which it was cooled to

–78 °C. Once this temperature was reached, $BF_3{\cdot}OEt_2$ (3.0 equiv.) was added and the reaction stirred for an additional 2 mins. At this point cyclopropyl ketone **226** (1.0 equiv.) was added as a solution in Et_2O (0.38 M) *via* syringe (+ 2 × 0.60 M Et_2O rinses). The reaction was maintained at –78 °C for 1 h, quenched by the addition of H_2O (0.15 M) and warmed to RT. The mixture was extracted with Et_2O (× 3), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash column chromatography then provided the title compound.

General Procedure H: Hydrogen borrowing of secondary alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.), $[Cp^*IrCl_2]_2$ (0.50 mol%), the appropriate secondary alcohol (1.5 equiv.), PhMe (4.0 M) and NaO*t*Bu (2.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an Ar balloon fitted. The vial was heated to the required temperature (85 °C) in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography provided the β-branched compound.

General Procedure I: Hydrogen borrowing of secondary alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.), $[Cp^*IrCl_2]_2$ (2.0 mol%), the appropriate secondary alcohol (2.0 equiv.), PhMe (4.0 M) and NaO*t*Bu (3.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an Ar balloon fitted. The vial was heated to the required temperature (either 85 °C or 105 °C) in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography provided the β-branched compound.

General Procedure J: Hydrogen borrowing of secondary alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.), $[Cp^*IrCl_2]_2$ (2.0 mol%), the appropriate secondary alcohol (2.0 equiv.), PhMe (4.0 M) and KO*t*Bu (3.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an Ar balloon fitted. The vial was heated to the required temperature (either 85 °C or 105 °C) in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography provided the β-branched compound.

General Procedure K: $BH_3{\cdot}S(CH_3)_2$ reduction of dicarboxylic acids to diols

To a solution of the dicarboxylic acid (1 equiv.) in THF (0.31 M) at 0 °C was added $BH_3{\cdot}S(CH_3)_2$ (3 equiv.) dropwise over 10 mins. The mixture was allowed to warm to RT slowly over 16 h. After this time, the reaction was cooled to 0 °C and quenched with MeOH (1.3 M) and H_2O (0.42 M). The mixture was extracted with EtOAc (× 3) and the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography provided the corresponding diol.

General Procedure L: $LiAlH_4$ reduction of diesters to diols

To a solution of the diester (1 equiv.) in THF (0.17 M) at 0 °C was added $LiAlH_4$ (4 equiv.) portion-wise over 5 mins. The mixture was stirred at 0 °C for 1 h and then stirred at RT for an additional 2 h. After this time, the reaction was cooled to 0 °C and quenched with H_2O (*[grams of $LiAlH_4$]* mL), 15% aq. NaOH (*[grams of $LiAlH_4$]* mL) and H_2O (3 × *[grams of $LiAlH_4$]* mL) added dropwise sequentially. The mixture was warmed to RT and stirred for 30 min, after which $MgSO_4$ was added. The reaction was filtered through Celite® eluting with Et_2O and EtOAc, and then concentrated *in vacuo*. Purification by column chromatography provided the corresponding diol.

General Procedure M: Hydrogen borrowing of diols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.), $[Cp^*IrCl_2]_2$ (2.0 mol%), the appropriate diol (2.0 equiv.), PhMe (4.0 M) and KOH (4.0 equiv.)

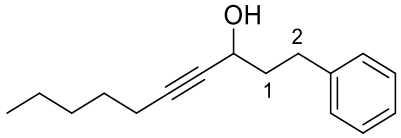
sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an Ar balloon fitted. The vial was heated to the required temperature (either 105 or 115°C) in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O/CH_2Cl_2) and concentrated *in vacuo*. Purification by column chromatography provided the dialkylated product.

General Procedure N: Br_2-mediated cleavage of pentamethylphenyl group

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.) and CH_2Cl_2 (0.2 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and cooled to –17 °C (ice/NaCl bath). Following this, Br_2 (2.0 equiv.) was added dropwise and the mixture stirred until TLC analysis indicated complete consumption of the substrate (typically 15 min). To this, was added *n*-butanol dropwise at –17 °C, and the reaction warmed to RT and stirred for the time stated. The reaction was diluted with Et_2O (0.067 M) and H_2O (0.14 M). The layers were separated, and the aqueous layer extracted with Et_2O (× 3). The combined organics were washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography provided the corresponding *n*-butyl ester.

5.3 Experimental Details

1-Phenyldec-4-yn-3-ol, 210



1-heptyne (1.00 mL, 7.62 mmol), hydrocinnamaldehyde (1.10 mL, 8.38 mmol), THF (6 mL) and *n*-BuLi (3.57 mL, 8.00 mmol) were subjected to **general procedure A** with the following modification: after the addition of *n*-BuLi dropwise, the reaction was stirred for 30 mins at –78 °C, then warmed to –40 °C and stirred at this temperature for a further 30 min before being cooled back to –78 °C

prior to addition of hydrocinnamaldehyde. Purification by flash column chromatography (Pentane:EtOAc, 90:10) provided the title compound (1.66 g, 95%) as a colourless oil.

R_f = 0.36 (Pentane:EtOAc, 90:10), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3027, 2955, 2931, 2861, 2214, 1711, 1674, 1604, 1497, 1454, 1379, 1329, 1286, 1243, 1160, 1106, 1056, 1031, 912.

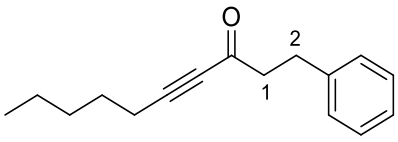
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.25 (2H, m, Ph), 7.24–7.16 (3H, m, Ph), 4.39–4.32 (1H, m, C*H*OH), 2.79 (2H, t, *J* = 7.9 Hz, C2H_2), 2.22 (2H, td, *J* = 7.1, 2.0 Hz, C*H*$_2$CC), 2.06–1.92 (2H, m, C1H_2), 1.74 (1H, d, *J* = 4.6 Hz, OH), 1.57–1.48 (2H, m, C*H*$_2$CH_2CC), 1.42–1.28 (4H, m, CH_3C*H*$_2$ and CH_3CH_2C*H*$_2$), 0.90 (3H, t, *J* = 7.1 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 141.7 (Ar-C), 128.6 (4C, 4 × Ar-CH), 126.1 (Ar-CH), 86.2 (*C*CH(OH)), 81.1 (*C*CCH(OH)), 62.2 (COH), 39.8 (C1H_2), 31.6 (C2H_2), 31.2 (CH_3CH_2*C*H_2), 28.5 (*C*H_2CH_2CC), 22.3 (CH_3*C*H_2), 18.8 (*C*H_2CC), 14.1 (CH_3).

HRMS (EI^+) Found $[M]^+$ = 230.1671; $C_{16}H_{22}O$ requires 230.1671, Δ 3.86 ppm.

All spectroscopic data in agreement with that previously reported.[122]

1-Phenyldec-4-yn-3-one, 211



Alcohol **210** (310 mg, 1.36 mmol), pyridinium dichromate (562 mg, 1.49 mmol) and CH_2Cl_2 (6 mL) were subjected to **general procedure B**. Purification by flash column chromatography (Pentane:EtOAc, 99:1) provided the title compound (198 mg, 64%) as a colourless oil.

R_f = 0.24 (Pentane:EtOAc, 99:1), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3028, 2956, 2930, 2861, 2213, 1673, 1604, 1497, 1454, 1405, 1362, 1286, 1243, 1159, 1076, 1030, 968.

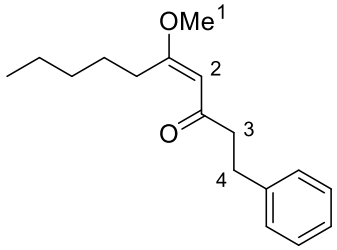
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–7.25 (2H, m, Ph), 7.24–7.16 (3H, m, Ph), 3.02–2.95 (2H, m, C2H_2), 2.91–2.84 (2H, m, C1H_2), 2.36 (2H, t, *J* = 7.1 Hz, C*H*$_2$CC), 1.63–1.54 (2H, m, C*H*$_2$CH$_2$CC), 1.44–

1.29 (4H, m, CH_3CH_2 and $CH_3CH_2CH_2$), 0.91 (3H, t, *J* = 7.1 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 187.3 (C=O), 140.5 (Ar-C), 128.7 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 126.4 (Ar-CH), 95.1 (*C*CO), 81.0 (*C*CCO), 47.1 ($C1H_2$), 31.1 ($CH_3CH_2CH_2$), 30.1 ($C2H_2$), 27.5 (CH_2CH_2CC), 22.2 (CH_3CH_2) 19.1 (CH_2CC), 14.0 (CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 229.1589; $C_{16}H_{21}O$ requires 229.1587, Δ 0.80 ppm.

(*E*)-5-Methoxy-1-phenyldec-4-en-3-one, 213



Isolated as a product following subjection of *ketone* **211** to the following conditions: To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added *ketone* **211** (50 mg, 0.22 mmol), methanol (1.1 mL), $[Ir(cod)Cl]_2$ (1.5 mg, 1.0 mol%), PPh_3 (2.3 mg, 4.0 mol%) and KOH (25 mg, 0.44 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) complete with a balloon of O_2, placed into a preheated oil bath at 65 °C and left to stir for 1 h. The reaction was cooled to RT before being filtered through a plug of silica, eluting with Et_2O. Purification by flash column chromatography (Pentane:EtOAc, 98:2→90:10) provided the title compound (37 mg, 65%) as a colourless oil. The stereochemistry of the double bond was assigned using 1D nOe's.

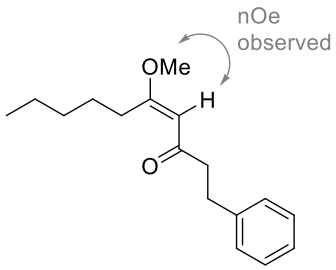
***R*$_f$** = 0.50 (Pentane:EtOAc, 95:5), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3028, 2955, 2928, 2857, 1710, 1604, 1497, 1455, 1363, 1316, 1259, 1213, 1192, 1157, 1122, 1087, 1051, 926.

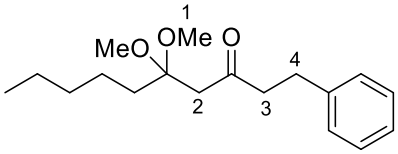
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.24 (2H, m, Ph), 7.23–7.14 (3H, m, Ph), 5.36 (1H, s, C2H), 3.60 (3H, s, $OC1H_3$), 2.97–2.90 (2H, m, $C4H_2$) 2.77–2.70 (4H, m, $C3H_2$ and CH_2COC1H_3), 1.58–1.47 (2H, m, $CH_2CH_2COC1H_3$), 1.34–1.28 (4H, m, CH_3CH_2 and $CH_3CH_2CH_2$), 0.89 (3H, t, *J* = 6.9 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 198.1 (C=O), 177.0 (*C*OC1H_3), 141.8 (Ar-C), 128.5 (4C, 4 × Ar-CH), 126.0 (Ar-CH), 98.5 (C2H), 55.5 (OMe), 46.3 (C3H_2), 32.7 (*C*H_2C(OMe)), 31.8 (*C*$H_2$$CH_2$COC1$H_3$), 30.8 (C4$H_2$), 27.2 ($CH_3CH_2$*C*$H_2$), 22.6 ($CH_3$*C*$H_2$), 14.2 ($CH_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 261.1849; $C_{17}H_{25}O_2$ requires 261.1849, Δ 0.00 ppm.



5,5-Dimethoxy-1-phenyldecan-3-one, 214



Isolated as an undesired product following subjection of *ketone* **211** to the following conditions: To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added *ketone* **211** (50 mg, 0.22 mmol), methanol (1.1 mL), $[Ir(cod)Cl]_2$ (1.5 mg, 1.0 mol%), PPh_3 (2.3 mg, 4.0 mol%) and KOH (25 mg, 0.44 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) complete with a balloon of O_2, placed into a preheated oil bath at 65 °C and left to stir for 1 h. The reaction was cooled to RT before being filtered through a plug of silica, eluting with Et_2O. Purification by flash column chromatography (Pentane:EtOAc, 98:2→9:1) provided the title compound (18 mg, 28%) as a colourless oil. R_f = 0.38 (Pentane:EtOAc, 95:5), [UV, $KMnO_4$].

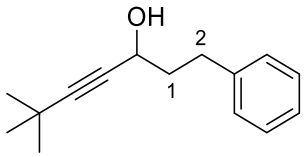
IR (film) ν_{max}/cm^{-1} 2929, 2858, 1680, 1497, 1454, 1428, 1388, 1245, 1173, 1103, 1072, 1029, 937.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.24 (2H, m, Ph), 7.21–7.15 (3H, m, Ph), 3.16 (6H, s, 2 × OC1H_3), 2.92–2.80 (4H, m, C4H_2 and C3H_2), 2.70 (2H, s, C2H_2), 1.64–1.88 (2H, m, C*H*$_2$C(OC1H_3)$_2$), 1.34–1.19 (6H, m, CH_3C*H*$_2$, CH_3CH_2C*H*$_2$ and $CH_3CH_2CH_2$C*H*$_2$), 0.88 (3H, t, *J* = 6.9 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 207.1 (C=O), 141.4 (Ar-C), 128.6 (4C, 4 × Ar-CH), 126.2 (Ar-CH), 102.0 (*C*($OC1H_3$)$_2$), 48.1 (2C, 2 × $OC1H_3$), 46.4 ($C2H_2$), 45.7 ($C3H_2$), 34.2 (*C*H_2C($OC1H_3$)$_2$), 32.1 (CH_2), 29.7 (CH_2 and $C4H_2$), 23.8 (CH_2), 14.2 (CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 315.1932; $C_{18}H_{28}O_3Na$ requires 315.1931, Δ 0.45 ppm.

6,6-Dimethyl-1-phenylhept-4-yn-3-ol, 216



3,3-Dimethylbut-1-yne (0.500 mL, 4.06 mmol), hydrocinnamaldehyde (0.590 mL, 4.47 mmol), THF (3 mL) and *n*-BuLi (1.93 mL, 4.26 mmol) were subjected to **general procedure A**. Workup provided the title compound (774 mg, 88%) as a colourless oil and was used without purification in the next step.

R_f = 0.40 (Pentane:EtOAc, 90:10), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3335, 3027, 2968, 2928, 2865, 1604, 1496, 1476, 1454, 1391, 1362, 1335, 1263, 1204, 1051, 1013, 912.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.26 (2H, m, Ph), 7.24–7.16 (3H, m, Ph), 4.39–4.33 (1H, m, C*H*OH), 2.78 (2H, t, *J* = 7.9 Hz, $C2H_2$), 2.06–1.91 (2H, m, $C1H_2$), 1.23 (9H, s, 3 × CH_3).*

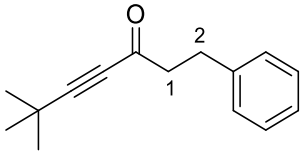
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 141.6 (Ar-C), 128.5 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 125.9 (Ar-CH), 94.3 (*C*CCH(OH)), 79.4 (C*C*CH(OH)), 62.0 (CHOH), 39.8 ($C1H_2$), 31.6 ($C2H_2$), 31.1 (3C, 3 × CH_3), 27.4 (*C*(CH_3)$_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 239.1408; $C_{15}H_{20}ONa$ requires 239.1406, Δ 0.85 ppm.

All spectroscopic data in agreement with that previously reported.[76]

* O*H* not observed.

6,6-Dimethyl-1-phenylhept-4-yn-3-one, 217



Alcohol **216** (650 mg, 3.01 mmol), pyridinium dichromate (1.25 g, 3.31 mmol) and CH_2Cl_2 (14 mL) were subjected to **general procedure B**. Purification by flash column chromatography (Pentane:EtOAc, 98:2) provided the title compound (388 mg, 60%) as a colourless oil.

R_f = 0.60 (Pentane:EtOAc, 90:10), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3029, 2971, 2930, 2869, 2207, 1672, 1604, 1497, 1477, 1454, 1406, 1364, 1262, 1203, 1124, 1075, 1032, 931.

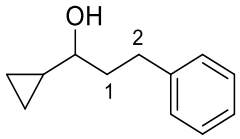
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.26 (2H, m, Ph), 7.23–7.18 (3H, m, Ph), 3.01–2.95 (2H, m, $C2H_2$), 2.90–2.84 (2H, m, $C1H_2$), 1.28 (9H, s, 3 × CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 187.5 (C=O), 140.5 (Ar-C), 128.7 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 126.4 (Ar-CH), 102.2 (*C*CCO), 79.4 (C*C*CO), 47.2 ($C1H_2$), 30.2 (4C, $C2H_2$ and 3 × CH_3), 27.9 ($C(CH_3)_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 215.1432; $C_{15}H_{19}O$ requires 215.1430, Δ 0.68 ppm.

All spectroscopic data in agreement with that previously reported.[76]

1-Cyclopropyl-3-phenylpropan-1-ol, 224



To a solution of hydrocinnamaldehyde (5.55 mL, 42.0 mmol) in THF (34 mL) at –78 °C was added cyclopropylmagnesium bromide (100 mL, 50.0 mmol, 0.50 M in THF) dropwise. Following the addition, the reaction was allowed to warm to RT and stirred for 16 h. The mixture was then cooled to 0 °C and quenched by the dropwise addition of sat. aq. NH_4Cl (140 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 × 150 mL). The combined organic layers

were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (Pentane:EtOAc, 95:5) provided the title compound (3.74 g, 50%) as a colourless oil.

R_f = 0.20 (Pentane:EtOAc, 90:10), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3376, 3082, 3063, 3026, 3003, 2921, 2861, 1711, 1603, 1496, 1454, 1431, 1413, 1292, 1271, 1073, 1031, 999.

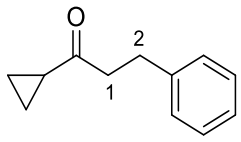
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.19 (5H, m, Ph), 2.97–2.90 (1H, m, C*H*OH), 2.90–2.83 (1H, m, C2H_AH$_B$), 2.82–2.73 (1H, m, C2H$_A$$H_B$), 2.01–1.94 (2H, m, C1H$_AH_B$), 1.04–0.94 (1H, m, CH cyclopropyl), 0.62–0.50 (2H, m, 2 × CH_AH$_B$ cyclopropyl), 0.35–0.28 (1H, m, CH$_A$$H_B$ cyclopropyl), 0.28–0.21 (1H, m, CH$_A$$H_B$ cyclopropyl). *

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 142.3 (Ar-C), 128.4 (4C, 4 × Ar-CH), 125.8 (Ar-CH), 76.2 (CH-OH), 38.7 (C1H$_2$), 32.1 (C2H$_2$), 18.1 (CH cyclopropyl), 2.8 (C$_A$H$_2$ cyclopropyl), 2.6 (C$_B$H$_2$ cyclopropyl).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 199.1096; $C_{12}H_{16}ONa$ requires 199.1093, Δ 1.50 ppm.

All spectroscopic data in agreement with that previously reported.[44]

1-Cyclopropyl-3-phenylpropan-1-one, 90



Alcohol **224** (2.39 g, 13.6 mmol), CH_2Cl_2 (14 mL), TEMPO (213 mg, 1.36 mmol) and BAIB (4.81 g, 14.9 mmol) were subjected to **general procedure C** for 36 h. Purification by flash column chromatography (Pentane:EtOAc, 98:2) provided the title compound (2.20 g, 93%) as a colourless oil.

R_f = 0.57 (Pentane:EtOAc, 90:10), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3086, 3063, 3027, 3008, 2928, 1969, 1696, 1604, 1584, 1497, 1453, 1387, 1267,

* O*H* not observed.

1195, 1100, 1085, 1072, 1032, 1011, 1001, 968.

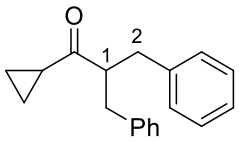
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35–7.28 (2H, m, Ph), 7.26–7.20 (3H, m, Ph), 2.99–2.88 (4H, m, $C1H_2$ and $C2H_2$), 1.98–1.91 (1H, m, CH cyclopropyl), 1.08–1.02 (2H, m, 2 × CH_AH_B cyclopropyl), 0.92–0.86 (2H, m, 2 × CH_AH_B cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.0 (C=O), 141.2 (Ar-C), 128.5 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.1 (Ar-CH), 45.0 ($C1H_2$), 30.0 ($C2H_2$), 20.6 (CH cyclopropyl), 10.8 (2C, 2 × CH_2 cyclopropyl)

HRMS (ESI^+) Found $[M+Na]^+$ = 197.0938; $C_{12}H_{14}ONa$ requires 197.0937, Δ 0.71 ppm.

All spectroscopic data in agreement with that previously reported.[44]

2-Benzyl-1-cyclopropyl-3-phenylpropan-1-one, 222



Ketone **90** (52 mg, 0.30 mmol), benzyl alcohol (0.16 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:EtOAc, 99:1) provided the title compound (58 mg, 73%) as a colourless oil.

***R*$_f$** = 0.64 (Pentane:EtOAc, 90:10), [UV, vanillin].

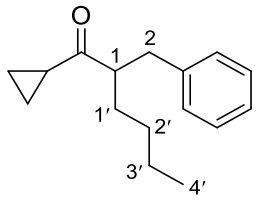
IR (film) ν_{max}/cm^{-1} 3086, 3062, 3027, 2922, 2855, 1693, 1603, 1584, 1496, 1454, 1444, 1417, 1386, 1271, 1195, 1105, 1088, 1071, 1030, 1001, 971.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.00 (10H, m, 2 × Ph), 3.23–3.12 (1H, m, C1H), 2.90 (2H, dd, *J* = 13.6, 8.6 Hz, 2 × $C2H_AH_B$), 2.64 (2H, dd, *J* = 13.7, 6.1 Hz, 2 × $C2H_AH_B$), 1.58–1.49 (1H, m, CH cyclopropyl), 0.73–0.67 (2H, m, 2 × CH_AH_B cyclopropyl), 0.56–0.50 (2H, m, 2 × CH_AH_B cyclopropyl)

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.4 (C=O), 139.7 (2C, 2 × Ar-C), 129.1 (4C, 4 × Ar-CH), 128.5 (4C, 4 × Ar-CH), 126.4 (2C, 2 × Ar-CH), 56.8 (C1H), 38.0 (2C, 2 × $C2H_2$), 21.7 (CH cyclopropyl), 11.1 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 287.1406; $C_{19}H_{20}ONa$ requires 287.1406, Δ 0.15 ppm.

2-Benzyl-1-cyclopropylhexan-1-one, 226



Ketone **90** (52 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:EtOAc, 99:1) provided the title compound (60 mg, 86%) as a pale yellow oil.

R_f = 0.55 (Pentane:EtOAc, 90:10), [UV, vanillin].

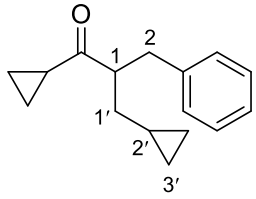
IR (film) ν_{max}/cm^{-1} 3063, 3028, 3008, 2956, 2930, 2859, 1693, 1604, 1496, 1467, 1454, 1444, 1417, 1385, 1195, 1156, 1121, 1067, 1030, 1001, 938.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23–7.14 (2H, m, Ph), 7.13–7.03 (3H, m, Ph), 2.91–2.80 (2H, m, C2H_AH$_B$ and C1H), 2.67–2.57 (1H, m, C2H$_A$$H_B$), 1.81–1.72 (1H, m, CH cyclopropyl), 1.66–1.56 (1H, m, C1′H_AH$_B$), 1.46–1.36 (1H, m, C1′H$_A$$H_B$), 1.27–1.11 (4H, m, C2′H$_2$ and C3′H$_2$), 0.79 (3H, t, *J* = 6.0 Hz, C4′H$_3$), 0.89-0.76 (2H, m, 2 × CH_AH$_B$ cyclopropyl), 0.76–0.69 (1H, m, CH$_A$$H_B$ cyclopropyl), 0.68–0.60 (1H, m, CH$_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.0 (C=O), 140.1 (Ar-C), 129.1 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 55.1 (C1H), 38.0 (C2H$_2$), 31.4 (C1′H$_2$), 29.9 (C2′H$_2$), 22.9 (C3′H$_2$), 20.6 (CH cyclopropyl), 14.0 (C4′H$_3$), 11.0 (2C, 2 × CH$_2$ cyclopropyl).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 253.1563; $C_{16}H_{22}ONa$ requires 253.1563, Δ 0.16 ppm.

2-Benzyl-1,3-dicyclopropylpropan-1-one, 227



Ketone **90** (52 mg, 0.30 mmol), cyclopropyl carbinol (0.12 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg,

2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:EtOAc, 99:1) provided the title compound (59 mg, 86%) as a colourless oil.

R_f = 0.63 (Pentane:EtOAc, 90:10), [UV, vanillin].

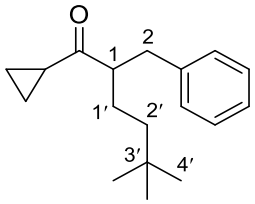
IR (film) ν_{max}/cm^{-1} 3077, 3027, 3004, 2919, 2852, 1693, 1604, 1496, 1455, 1443, 1417, 1382, 1237, 1194, 1156, 1085, 1072, 1046, 1030, 1016, 971.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.25 (2H, m, Ph), 7.22–7.15 (3H, m, Ph), 3.13–3.03 (1H, m, C1H), 2.98 (1H, dd, *J* = 14.0, 8.0 Hz, C2H_AH_B), 2.75 (1H, dd, *J* = 13.7, 6.4 Hz, C2H_AH_B), 1.93–1.85 (1H, m, CH cyclopropyl), 1.69–1.60 (1H, m, C1′H_AH_B), 1.42–1.33 (1H, m, C1′H_AH_B), 1.00–0.87 (2H, m, 2 × CH_AH_B cyclopropyl), 0.86–0.78 (1H, m, CH_AH_B cyclopropyl), 0.77–0.71 (1H, m, CH_AH_B cyclopropyl), 0.72–0.64 (1H, m, C2′H), 0.49–0.38 (2H, m, 2 × C3′H_AH_B), 0.08– −0.02 (2H, m, 2 × C3′H_AH_B).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.2 (C=O), 140.1 (Ar-C), 129.1 (2C, 2 × Ar- CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 55.4 (C1H), 38.0 (C2H_2), 37.0 (C1′H_2), 21.1 (CH cyclopropyl), 11.2 (2C, 2 × CH_2 cyclopropyl), 9.3 (C2′H), 5.2 (C3′$_AH_2$), 4.8 (C3′$_BH_2$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 251.1407; $C_{16}H_{20}ONa$ requires 251.1406, Δ 0.08 ppm.

2-Benzyl-1-cyclopropyl-5,5-dimethylhexan-1-one, 228



Ketone **90** (52 mg, 0.30 mmol), 3,3-dimethylbutan-1-ol (0.19 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 98:2) provided the title compound (53.0 mg, 68%) as a colourless oil.

R_f = 0.41 (Pentane:Et_2O, 90:10), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3028, 2952, 2865, 1694, 1604, 1496, 1475, 1454, 1388, 1364, 1248, 1195, 1089,

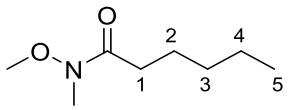
1053, 1031, 1002, 954.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.21–7.14 (2H, m, Ph), 7.13–7.05 (3H, m, Ph), 2.88 (1H, dd, *J* = 13.1, 8.2 Hz, C2$H_A$$H_B$), 2.83–2.75 (1H, m, C1H), 2.65 (1H, dd, *J* = 13.1, 6.0 Hz, C2$H_A$$H_B$), 1.80–1.72 (1H, m, CH cyclopropyl), 1.64–1.53 (1H, m, C1′$H_A$$H_B$), 1.49–1.38 (1H, m, C1′$H_A$$H_B$), 1.15–1.01 (2H, m, C2′$H_2$), 0.89–0.80 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.78 (9H, s, 3 × C4′H_3), 0.76–0.68 (1H, m, $CH_A$$H_B$ cyclopropyl), 0.67–0.60 (1H, m, $CH_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.9 (C=O), 140.1 (Ar-C), 129.1 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 55.7 (C1H), 41.3 (C2′H_2), 37.8 (C2H_2), 30.4 (C3′), 29.4 (3C, 3 × C4′H_3), 26.7 (C1′H_2), 20.5 (CH cyclopropyl), 10.9 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+H]^+$ = 259.2066; $C_{18}H_{27}O$ requires 259.2056, Δ 3.59 ppm.

_N_-Methoxy-_N_-methylhexanamide, 231



Hexanoic acid (1.25 mL, 10.0 mmol), CH_2Cl_2 (25 mL), *N*,*O*-dimethylhydroxyamine·HCl (1.37 g, 14.0 mmol), DCC (2.89 g, 14.0 mmol), Et_3N (1.95 mL, 14.0 mmol) and DMAP (171 mg, 1.40 mmol) were subjected to **general procedure E** for 16 h. Purification by flash column chromatography (Pentane:EtOAc 75:25) provided the title compound (1.49 g, 94%) as a colourless oil.

***R*$_f$** = 0.30 (Pentane:EtOAc, 70:30), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2957, 2934, 2873, 1662, 1463, 1414, 1383, 1343, 1319, 1177, 1152, 1123, 1085, 1004.

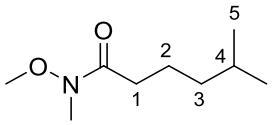
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.49 (3H, s, $NOCH_3$), 2.97 (3H, s, NCH_3), 2.20 (2H, t, *J* = 7.2 Hz, C1H_2), 1.48–1.37 (2H, m, C2H_2), 1.19–1.07 (4H, m, C3H_2 and C4H_2), 0.70 (3H, t, *J* = 6.3 Hz, C5H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.4 (C=O), 60.9 ($NOCH_3$), 31.5 (NCH_3), 31.3 (C1H_2 and C3H_2), 24.0 (C2H_2), 22.2 (C4H_2), 13.6 (C5H_3).

HRMS (ESI+) Found $[M+Na]^+$ = 182.1153; $C_8H_{17}NO_2Na$ requires 182.1152, Δ 0.68 ppm.

All spectroscopic data in agreement with that previously reported.[123]

_N_-Methoxy-_N_,5-dimethylhexanamide, 232



5-Methylhexanoic acid (1.43 mL, 10.0 mmol), CH_2Cl_2 (25 mL), *N*,*O*-dimethylhydroxyamine·HCl (1.37 g, 14.0 mmol), DCC (2.89 g, 14.0 mmol), Et_3N (1.95 mL, 14.0 mmol) and DMAP (171 mg, 1.40 mmol) were subjected to **general procedure E** for 16 h. Purification by flash column chromatography (Pentane:EtOAc, 75:25) provided the title compound (1.59 g, 92%) as a colourless oil.

R_f = 0.52 (Pentane:EtOAc, 70:30), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2954, 2871, 1664, 1463, 1414, 1384, 1366, 1331, 1176, 1117, 1089, 992;

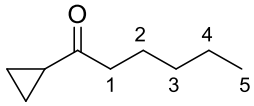
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.68 (3H, s, $NOCH_3$), 3.18 (3H, s, NCH_3), 2.39 (2H, t, *J* = 7.6 Hz, C1H_2), 1.70–1.53 (3H, m, C2H_2 and C4H), 1.28–1.20 (2H, m, C3H_2), 0.89 (6H, d, *J* = 6.6 Hz, 2 × C5H_3);

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.6 (C=O), 61.1 ($NOCH_3$), 38.6 (C3H_2), 32.0 (NCH_3 and C1H_2), 27.8 (C4H), 22.4 (C2H_2 and 2 × C5H_3);

HRMS (ESI+) Found $[M+Na]^+$ = 196.1309; $C_9H_{19}O_2NNa$ requires 196.1308, Δ 0.27 ppm.

All spectroscopic data in agreement with that previously reported.[91]

1-Cyclopropylhexan-1-one, 233



Weinreb amide **231** (500 mg, 3.14 mmol), cyclopropylmagnesium bromide (7.60 mL, 3.77 mmol, 0.50 M in THF) and THF (6 mL) were subjected to **general procedure F**. Purification by flash column chromatography (Pentane:Et_2O, 90:10) provided the title compound (313 mg, 71%) as a colourless oil.

R_f = 0.59 (Pentane:EtOAc, 95:5), [$KMnO_4$].

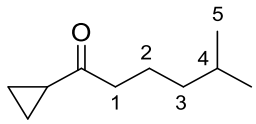
IR (film) ν_{max}/cm^{-1} 3010, 2957, 2931, 2861, 1697, 1449, 1385, 1196, 1130, 1069, 1019, 969.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.53 (2H, t, *J* = 7.6 Hz, C1H_2), 1.95–1.88 (1H, m, CH cyclopropyl), 1.66–1.56 (2H, m, C2H_2), 1.36–1.22 (4H, m, C3H_2 and C4H_2), 1.02–0.97 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.89 (3H, t, *J* = 7.0 Hz, C5H_3), 0.87–0.81 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.5 (C=O), 43.7 (C1H_2), 31.6 (C3H_2), 23.9 (C2H_2), 22.6 (C4H_2), 20.4 (CH cyclopropyl), 14.1 (C5H_3), 10.7 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI+) Found $[M+H]^+$ = 141.1274; $C_9H_{17}O$ requires 141.1274, Δ 0.30 ppm.

1-Cyclopropyl-5-methylhexan-1-one, 234



Weinreb amide **232** (1.20 g, 6.93 mmol), cyclopropylmagnesium bromide (16.6 mL, 8.31 mmol, 0.50 M in THF) and THF (14 mL) were subjected to **general procedure F**. Purification by flash column chromatography (Pentane:Et_2O, 95:5) provided the title compound (811 mg, 76%) as a colourless oil.

R_f = 0.59 (Pentane:EtOAc, 95:5), [$KMnO_4$].

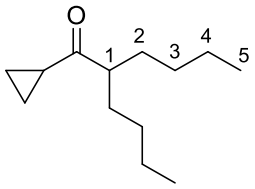
IR (film) ν_{max}/cm^{-1} 3010, 2954, 2871, 1698, 1468, 1385, 1367, 1195, 1169, 1137, 1079, 1023, 1009, 901.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.50 (2H, t, *J* = 7.4, C1H_2), 1.94–1.87 (1H, m, CH cyclopropyl), 1.63–1.47 (3H, m, C2H_2 and C4H), 1.20–1.12 (2H, m, C3H_2), 1.01–0.96 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.86 (6H, d, *J* = 6.6 Hz, 2 × C5H_3), 0.85–0.80 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.4 (C=O), 43.9 (C1H_2), 38.6 (C3H_2), 28.0 (C4H), 22.6 (2C, 2 × C5H_3), 22.0 (C2H_2), 20.4 (CH cyclopropyl), 10.6 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+H]^+$ = 155.1430; $C_{10}H_{19}O$ requires 155.1430, Δ 0.23 ppm.

2-Butyl-1-cyclopropylhexan-1-one, 242



Ketone **233** (42 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (38 mg, 65%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.56 (Pentane:Et_2O, 90:10), [UV, vanillin].

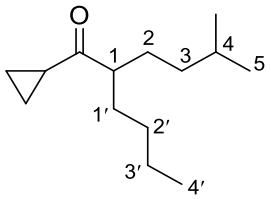
IR (film) ν_{max}/cm^{-1} 3009, 2957, 2930, 2873, 2859, 1695, 1467, 1458, 1417, 1382, 1196, 1159, 1063, 1022, 997.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.59–2.50 (1H, m, C1H), 1.99–1.92 (1H, m, CH cyclopropyl), 1.70–1.59 (2H, m, 2 × C2$H_A$$H_B$), 1.49–1.39 (2H, m, 2 × C2$H_A$$H_B$), 1.35–1.17 (8H, m, 2 × $C3H_2$ and 2 × $C4H_2$), 1.02–0.97 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.88 (6H, t, *J* = 7.1 Hz, 2 × $C5H_3$), 0.86–0.81 (2H, m, 2 × CH_AH_B cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.0 (C=O), 53.6 (C1H), 31.7 (2C, 2 × $C2H_2$), 29.9 (2C, 2 × $C3H_2$), 23.0 (2C, 2 × $C4H_2$), 19.5 (CH cyclopropyl), 14.1 (2C, 2 × $C5H_3$), 10.8 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+H]^+$ = 197.1901; $C_{13}H_{25}O$ requires 197.1900, Δ 0.75 ppm.

2-Butyl-1-cyclopropyl-5-methylhexan-1-one, 243



Ketone **234** (47 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:EtOAc, 99:1) provided the title compound (45 mg, 71%) as a pale yellow

oil.

R_f = 0.73 (Pentane:Et_2O, 90:10), [vanillin]

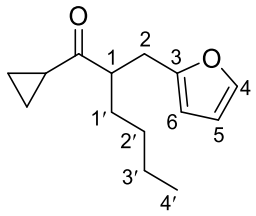
IR (film) ν_{max}/cm^{-1} 3009, 2955, 2930, 2871, 1695, 1467, 1417, 1384, 1367, 1196, 1170, 1067, 1023, 1004, 934.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.55–2.47 (1H, m, C1H), 1.98–1.91 (1H, m, CH cyclopropyl), 1.71–1.57 (2H, m, C2$H_A$$H_B$ and C1′$H_A$$H_B$), 1.56–1.38 (3H, m, C4H, C2$H_A$$H_B$ and C1′$H_A$$H_B$), 1.35–1.16 (4H, m, C3′$H_2$ and C2′H_2), 1.15–1.07 (2H, m, C3H_2), 1.01–0.96 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.87 (3H, t, *J* = 7.1 Hz, C4′H_3), 0.86 (6H, d, *J* = 6.6 Hz, C5$_A$$H_3$ and C5$_B$$H_3$), 0.84–0.80 (2H, m, 2 × CH$_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.9 (C=O), 53.8 (C1H), 36.8 (C3H_2), 31.6 (C1′H_2), 29.7 (C2H_2 and C2′H_2), 28.3 (C4H), 23.0 (C5$_A$$H_3$ and C5$_B$$H_3$), 22.7 (C3′$H_2$), 19.5 (CH cyclopropyl), 14.1 (C4′H_3), 10.8 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI$^+$) Found $[M+H]^+$ = 211.2057; $C_{14}H_{27}O$ requires 211.2056, Δ 0.44 ppm.

1-Cyclopropyl-2-(furan-2-ylmethyl)hexan-1-one, 245



1-cyclopropyl-3-(furan-2-yl)propan-1-one* (49 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), [Cp*$IrCl_2$]$_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 98:2) provided the title compound (18 mg, 22%) as a colourless oil.

R_f = 0.36 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2958, 2931, 2861, 2360, 2342, 1697, 1541, 1507, 1458, 1387, 1147, 1071, 1011,

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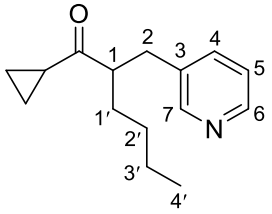
939.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29 (1H, d, *J* = 1.8 Hz, C4H), 6.25 (1H, t, *J* = 2.4 Hz, C5H), 5.98 (1H, d, *J* = 3.1 Hz, C6H), 3.07–2.92 (2H, m, C1H and C2$H_A$$H_B$), 2.73 (1H, dd, *J* = 14.4, 5.7 Hz, C2$H_A$$H_B$), 1.91 (1H, tt, *J* = 8.1, 4.5 Hz, CH cyclopropyl), 1.74–1.63 (1H, m, C1'$H_A$$H_B$), 1.55–1.45 (1H, m, C1'$H_A$$H_B$), 1.35–1.18 (4H, m, C2'$H_2$ and C3'H_2), 1.02–0.93 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.87 (3H, t, *J* = 6.9 Hz, C4'H_3), 0.85–0.77 (2H, m, 2 × $CH_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.6 (C=O), 153.9 (C3), 141.2 (C4H), 110.3 (C5H), 106.3 (C6H), 51.9 (C1H), 31.3 (C1'H_2), 30.0 (C2H_2), 29.4 (C2'H_2), 22.9 (C3'H_2), 20.4 (CH cyclopropyl), 14.0 (C4'H_3), 11.1 (CH_2 cyclopropyl), 11.0 (CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 243.1355; $C_{14}H_{20}O_2Na$ requires 243.1356, Δ –0.03 ppm.

1-Cyclopropyl-2-(pyridin-3-ylmethyl)hexan-1-one, 246



1-cyclopropyl-3-(pyridin-3-yl)propan-1-one* (53 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 90:10) provided the title compound (31 mg, 45%) as a colourless oil.

R_f = 0.33 (Et_2O), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2957, 2930. 2859, 2360, 2342, 1693, 1653, 1575, 1541, 1478, 1444, 1422, 1388, 1195, 1071, 1027, 1004, 871.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.43 (2H, m, C6H and C7H), 7.46 (1H, br d, *J* = 7.8 Hz, C4H), 7.18 (1H, dd, *J* = 7.8, 4.8 Hz, C5H), 2.99–2.88 (2H, m, C1H and C2$H_A$$H_B$), 2.75–2.65 (1H, m, C2$H_A$$H_B$), 1.84 (1H,

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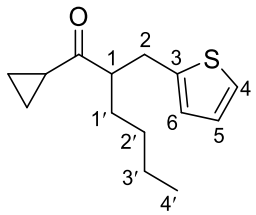
ddd, *J* = 12.4, 7.9, 4.6 Hz, CH cyclopropyl), 1.76–1.63 (1H, m, C1'$H_A$$H_B$), 1.57–1.45 (1H, m, C1'$H_A$$H_B$), 1.35–1.22 (4H, m, C3'$H_2$ and C2'H_2), 0.98–0.90 (1H, m, C$H_A$$H_B$ cyclopropyl), 0.91–0.85 (1H, m, C$H_A$$H_B$ cyclopropyl) 0.87 (3H, t, *J* = 6.8 Hz, C4'H_3), 0.84–0.78 (1H, m, $CH_A$$H_B$ cyclopropyl), 0.78–0.69 (1H, m, $CH_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.4 (C=O), 150.4 (C7H), 147.8 (C6H), 136.6 (C4H), 135.5 (C3), 123.4 (C5H), 54.8 (C1H), 34.7 (C2H_2), 31.6 (C1'H_2), 29.5 (C2'H_2), 22.9 (C3'H_2), 20.7 (CH cyclopropyl), 14.0 (C4'H_3), 11.3 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI$^+$) Found $[M+H]^+$ = 232.1696; $C_{15}H_{22}ON$ requires 232.1696, Δ 0.18 ppm.

1-Cyclopropyl-2-(thiophen-2-ylmethyl)hexan-1-one, 247



1-cyclopropyl-3-(thiophen-2-yl)propan-1-one * (54 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 98:2) provided the title compound (32 mg, 45%) as a colourless oil.

***R*$_f$** = 0.45 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2957, 2930, 2859, 2360, 2342, 1694, 1440, 1387, 1196, 1071, 1002, 851.

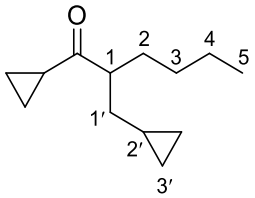
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.11 (1H, d, *J* = 5.1 Hz, C4H), 6.89 (1H, dd, *J* = 5.1, 3.4 Hz, C5H), 6.76 (1H, d, *J* = 3.4 Hz, C6H), 3.19 (1H, dd, *J* = 13.9, 7.3 Hz, C2$H_A$$H_B$), 3.01–2.87 (2H, m, C1H and C2$H_A$$H_B$), 1.92 (1H, tt, *J* = 8.1, 4.5 Hz, CH cyclopropyl), 1.75–1.65 (1H, m, C1'$H_A$$H_B$), 1.60–1.48 (1H, m, C1'$H_A$$H_B$), 1.36–1.22 (4H, m, C3$H_2$ and C2H_2), 1.03–0.92 (2H, 2 × C$H_A$$H_B$ cyclopropyl), 0.88 (3H, t, *J* = 6.7 Hz, C4'H_3), 0.85–0.76 (2H, m, 2 × $CH_A$$H_B$ cyclopropyl).

* Synthesised by Dr James Frost.

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.5 (C=O), 142.6 (C3), 126.8 (C5H), 125.5 (C6H), 123.6 (C4H), 55.3 (C1H), 31.6 ($C2H_2$), 31.4 ($C1'H_2$), 29.4 ($C2'H_2$), 22.9 ($C3'H_2$), 20.7 (CH cyclopropyl), 14.0 ($C4'H_3$), 11.2 (CH_2 cyclopropyl), 11.1 (CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 259.1128; $C_{14}H_{20}OSNa$ requires 259.1127, Δ 0.21 ppm.

1-Cyclopropyl-2-(cyclopropylmethyl)hexan-1-one, 251



Ketone **233** (42 mg, 0.30 mmol), cyclopropyl carbinol (0.12 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (40 mg, 68%) as a colourless oil.

R_f = 0.65 (Pentane:Et_2O, 90:10), [UV, vanillin].

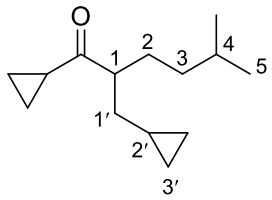
IR (film) ν_{max}/cm^{-1} 3078, 3005, 2957, 2929, 2859, 1694, 1459, 1443, 1417, 1381, 1196, 1155, 1066, 1015, 936.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.74–2.65 (1H, m, C1H), 2.02–1.94 (1H, m, CH cyclopropyl), 1.71–1.53 (2H, m, $C2H_AH_B$ and $C1'H_AH_B$), 1.51–1.43 (1H, m, $C2H_AH_B$), 1.36–1.17 (5H, m, $C1'H_AH_B$, $C3H_2$ and $C4H_2$), 1.03–0.97 (2H, m, 2 × CH_AH_B cyclopropyl), 0.87 (3H, t, J = 6.8 Hz, $C5H_3$) 0.90–0.81 (2H, m, 2 × CH_AH_B cyclopropyl), 0.69–0.59 (1H, m, C2′H), 0.44–0.38 (2H, m, 2 × $C3'H_AH_B$), 0.04– −0.01 (2H, m, 2 × $C3'H_AH_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.0 (C=O), 53.9 (C1H), 37.2 ($C1'H_2$), 31.6 ($C2H_2$), 29.9 ($C3H_2$), 23.0 ($C4H_2$), 20.0 (CH cyclopropyl), 14.1 ($C5H_3$), 11.0 (2C, 2 × CH_2 cyclopropyl), 9.4 (C2′H), 5.1 ($C3'_AH_2$), 4.8 ($C3'_BH_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 195.1745; $C_{13}H_{23}O$ requires 195.1743, Δ 0.13 ppm.

1-Cyclopropyl-2-(cyclopropylmethyl)-5-methylhexan-1-one, 252



Ketone **234** (47 mg, 0.30 mmol), cyclopropyl carbinol (0.12 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (43 mg, 69%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.61 (Pentane:Et_2O, 90:10), [UV, vanillin]

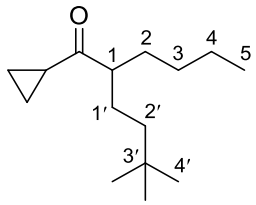
IR (film) ν_{max}/cm^{-1} 3078, 3006, 2955, 2930, 2870, 1694, 1468, 1443, 1417, 1384, 1367, 1196, 1170, 1075, 1061, 1016, 970.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.71–2.62 (1H, m, C1H), 2.02–1.94 (1H, m, CH cyclopropyl), 1.71–1.41 (4H, m, C2H_AH$_B$, C1′H_AH$_B$, C4H and C2H$_A$$H_B$), 1.37–1.28 (1H, m, C1′H$_A$$H_B$), 1.15–1.07 (2H, m, C3$H_2$), 1.04–0.97 (2H, m, 2 × CH_AH$_B$ cyclopropyl), 0.86 (6H, d, *J* = 6.6 Hz, C5$_A$H$_3$ and C5$_B$H$_3$), 0.88–0.81 (2H, m, 2 × CH$_A$$H_B$ cyclopropyl), 0.69–0.58 (1H, m, C2′H), 0.44–0.38 (2H, m, 2 × C3′H_AH$_B$), 0.05–0.00 (2H, m, 2 × C3′H$_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.9 (C=O), 54.1 (C1H), 37.2 (C1′H_2), 36.8 (C3H_2), 29.7 (C2H_2), 28.3 (C4H), 22.7 (C5$_A$H$_3$), 22.6 (C5$_B$H$_3$), 19.9 (CH cyclopropyl), 11.0 (2C, 2 × CH_2 cyclopropyl), 9.4 (C2′H), 5.1 (C3′$_A$H$_2$), 4.8 (C3′$_B$H$_2$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 209.1901; $C_{14}H_{25}O$ requires 209.1900, Δ 0.56 ppm.

2-Butyl-1-cyclopropyl-5,5-dimethylhexan-1-one, 254



Ketone **233** (42 mg, 0.30 mmol), 3,3-dimethylbutan-1-ol (0.19 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg,

2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (55 mg, 82%) as a colourless oil.

R_f = 0.71 (Pentane:Et_2O, 90:10), [vanillin].

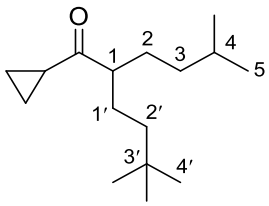
IR (film) ν_{max}/cm^{-1} 3009, 2954, 2935, 2864, 1695, 1467, 1417, 1388, 1364, 1248, 1169, 1060, 1019, 999.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.51–2.42 (1H, m, C1H), 1.98–1.91 (1H, m, CH cyclopropyl), 1.68–1.56 (2H, m, C2$H_A$$H_B$ and C1′$H_A$$H_B$), 1.50–1.37 (2H, m, C2$H_A$$H_B$ and C1′$H_A$$H_B$), 1.33–1.18 (4H, m, $C3H_2$ and $C4H_2$), 1.14–1.02 (2H, m, $C2'H_2$), 1.01–0.94 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.92–0.79 (14H, m, $C5H_3$, 3 × $C4'H_3$ and 2 × CH_AH_B cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.8 (C=O), 54.2 (C1H), 41.7 ($C2'H_2$), 31.6 ($C2H_2$), 30.4 (C3′), 29.9 ($C3H_2$), 29.4 (3C, 3 × $C4'H_3$), 26.8 ($C1'H_2$), 23.0 ($C4H_2$), 19.3 (CH cyclopropyl), 14.1 ($C5H_3$), 10.8 (C_AH_2 cyclopropyl), 10.7 (C_BH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+H]^+$ = 225.2215; $C_{15}H_{29}O$ requires 225.2213, Δ 0.70 ppm.

1-Cyclopropyl-2-isopentyl-5,5-dimethylhexan-1-one, 255



Ketone **234** (47 mg, 0.30 mmol), 3,3-dimethylbutan-1-ol (0.19 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D.** Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (63 mg, 88%) as a colourless oil.

R_f = 0.63 (Pentane:Et_2O, 90:10), [vanillin].

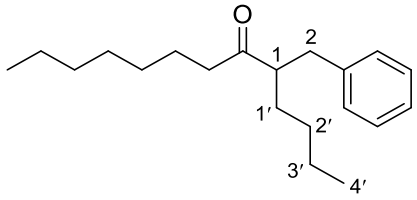
IR (film) ν_{max}/cm^{-1} 2953, 2868, 1695, 1657, 1468, 1417, 1385, 1365, 1248, 1196, 1053, 1020, 1005, 985.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.48–2.39 (1H, m, C1H), 1.98–1.90 (1H, m, CH cyclopropyl), 1.70–1.54 (2H, m, C2$H_A$$H_B$ and C1′$H_A$$H_B$), 1.53–1.38 (3H, m, C2$H_A$$H_B$, C1′$H_A$$H_B$ and C4H), 1.17–1.05 (4H, m, C3H_2 and C2′H_2), 1.00–0.95 (2H, m, 2 × C$H_A$$H_B$ cyclopropyl), 0.89–0.79 (17H, m, C5$_A$$H_3$, C5$_B$$H_3$, 3 × C4′$H_3$ and 2 × C$H_A$$H_B$ cyclopropyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.8 (C=O), 54.4 (C1H), 41.7 (C2′H_2), 36.8 (C3H_2), 30.4 (C3′), 29.6 (C2H_2), 29.4 (3C, 3 × C4′H_3), 28.3 (C4H), 26.8 (C1′H_2), 22.7 (C5$_A$$H_3$), 22.6 (C5$_B$$H_3$), 19.3 (CH cyclopropyl), 10.7 (2C, 2 × CH_2 cyclopropyl).

HRMS (ESI^+) Found $[M+H]^+$ = 239.2370; $C_{16}H_{31}O$ requires 239.2369, Δ 0.34 ppm.

5-Benzyltridecan-6-one, 260



Cyclopropyl ketone **226** (69 mg, 0.30 mmol), CuCN (80 mg, 0.90 mmol), Et_2O (1.8 mL), BF_3·Et_2O (0.12 mL, 0.90 mmol) and *n*-BuLi (0.83 mL, 1.8 mmol, 2.2 M in hexanes) were subjected to **general procedure G**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (55 mg, 63%) as a colourless oil.

R_f = 0.26 (Pentane:Et_2O, 99:1), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3028, 2956, 2927, 2856, 1711, 1604, 1496, 1455, 1405, 1377, 1261, 1215, 1127, 1071, 1030.

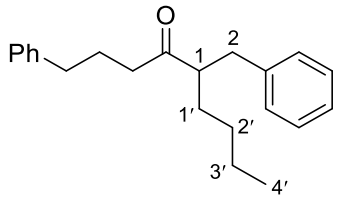
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.23 (2H, m, Ph), 7.20–7.15 (1H, m, Ph), 7.14–7.10 (2H, m, Ph), 2.89–2.74 (2H, m, C2$H_A$$H_B$ and C1H), 2.65 (1H, dd, *J* = 12.5, 5.4 Hz, C2$H_A$$H_B$), 2.32–2.22 (1H, m, C$H_A$$H_B$CO), 2.15–2.05 (1H, m, CH_ACH_BCO), 1.68–1.58 (1H, m, C1′$H_A$$H_B$), 1.47–1.36 (3H, m, C1′$H_A$$H_B$ and C$H_2$$CH_2$CO), 1.32–1.08 (12H, m, CH_3CH_2CH_2CH_2CH_2, C2′H_2 and C3′H_2), 0.90–0.83 (6H, m, C4′H_3 and C$H_3$$CH_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.8 (C=O), 140.0 (Ar-C), 129.0 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-

CH), 126.3 (Ar-CH), 54.2 (C1H), 43.9 ($CH_2C\mathit{H}_2CO$), 38.3 ($C2H_2$), 31.8 ($C1'H_2$ and CH_2), 29.7 ($C2'H_2$), 29.2 (2C, 2 × CH_2), 23.3 ($C\mathit{H}_2CH_2CO$), 22.9 ($C3'H_2$), 22.7 (CH_2), 14.2 (CH_3), 14.0 (CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 289.2527; $C_{20}H_{33}O$ requires 289.2526, Δ 0.43 ppm.

5-Benzyl-1-phenylnonan-4-one, 261



Cyclopropyl ketone **226** (69 mg, 0.30 mmol), CuCN (80 mg, 0.90 mmol), Et_2O (1.8 mL), $BF_3{\cdot}Et_2O$ (0.12 mL, 0.90 mmol) and PhLi (1.1 mL, 1.8 mmol, 1.6 M in dibutyl ether) were subjected to **general procedure G**. Purification by flash column chromatography (Pentane:Et_2O, 99:1→98:2) provided the title compound (65 mg, 70%) as a pale yellow oil.

$\boldsymbol{R}_f$ = 0.22 (Pentane:Et_2O, 98:2), [UV, vanillin].

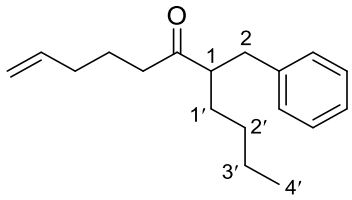
IR (film) ν_{max}/cm^{-1} 3062, 3027, 2930, 2858, 1709, 1603, 1496, 1454, 1376, 1179, 1071, 1030, 910.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.22 (4H, m, Ph), 7.21–7.14 (2H, m, Ph), 7.13–7.06 (4H, m, Ph), 2.85 (1H, dd, *J* = 12.6, 8.6 Hz, $C2\mathit{H}_A H_B$), 2.81–2.72 (1H, m, C1H), 2.66 (1H, dd, *J* = 12.6, 5.5 Hz, $C2H_A\mathit{H}_B$), 2.54–2.40 (2H, m, $CH_2C\mathit{H}_2Ph$), 2.30 (1H, dt, *J* = 17.6, 7.1 Hz, $C\mathit{H}_A H_B CO$), 2.11 (1H, dt, *J* = 17.6, 7.1 Hz, $CH_A\mathit{H}_B CO$), 1.80–1.71 (2H, m, $C\mathit{H}_2CH_2CO$), 1.68–1.57 (1H, m, $C1'\mathit{H}_A H_B$), 1.46–1.36 (1H, m, $C1'H_A\mathit{H}_B$), 1.33–1.15 (4H, m, $C2'H_2$ and $C3'H_2$), 0.86 (3H, t, *J* = 7.1 Hz, $C4'H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.3 (C=O), 141.9 (Ar-C), 140.0 (Ar-C), 129.0, (2C, 2 × Ar-CH), 128.5 (4C, 4 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.3 (Ar-CH), 126.0 (Ar-CH), 54.2 (C1H), 43.0 ($C\mathit{H}_2CO$), 38.3 ($C2H_2$), 35.1 ($\mathit{C}H_2Ph$), 31.8 ($C1'H_2$), 29.7 ($C2'H_2$), 24.7 ($C\mathit{H}_2CH_2CO$), 22.9 ($C3'H_2$), 14.0 ($C4'H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 309.2213; $C_{22}H_{29}O$ requires 309.2213, Δ 0.17 ppm.

7-Benzylundec-1-en-6-one, 262



To a solution of tetravinyl tin (0.15 mL, 0.80 mmol) in Et_2O (1.1 mL) at 0 °C was added *n*-BuLi (1.40 mL, 3.05 mmol, 2.18 M) dropwise over 10 mins. *Cyclopropyl ketone* **226** (115 mg, 0.50 mmol), CuCN (134 mg, 1.50 mmol), Et_2O (3.0 mL), $BF_3{\cdot}Et_2O$ (0.19 mL, 1.5 mmol) and the prepared vinyl lithium (2.5 mL, 3.0 mmol) were then subjected to **general procedure G**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (60 mg, 46%) as a pale yellow oil.

$\boldsymbol{R_f}$ = 0.20 (Pentane:Et_2O, 99:1), [UV, vanillin].

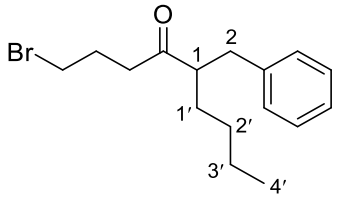
IR (film) ν_{max}/cm^{-1} 2956, 2929, 2858, 1710, 1496, 1455, 1404, 1376, 1121, 1072, 1030, 994.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23–7.03 (5H, m, Ph), 5.61 (1H, ddt, *J* = 17.2, 10.5, 6.7 Hz, *H*C=CH_2), 4.89–4.83 (2H, m, HC=C*H*$_2$), 2.82–2.67 (2H, m, C2*H*$_A$H$_B$ and C1H), 2.58 (1H, dd, *J* = 12.5, 5.4 Hz, C2H$_A$*H*$_B$), 2.29–2.15 (1H, m, COC*H*$_A$H$_B$), 2.08–1.97 (1H, m, COCH$_A$*H*$_B$), 1.89–1.81 (2H, m, HC=CH$_2$C*H*$_2$), 1.62–1.51 (1H, m, C1'*H*$_A$H$_B$), 1.50–1.41 (2H, m, COCH$_2$C*H*$_2$), 1.40–1.30 (1H, m, C1'H$_A$*H*$_B$), 1.26–1.10 (4H, m, C3'H$_2$ and C2'H$_2$), 0.79 (3H, t, *J* = 7.1 Hz, C4'H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.4 (C=O), 140.0 (Ar-C), 138.2 (H*C*=CH_2), 129.0 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 126.3 (Ar-CH), 115.1 (HC=*C*H$_2$), 54.2 (C1H), 43.0 (CO*C*H$_2$), 38.3 (C2H$_2$), 33.1 (HC=CH$_2$*C*H$_2$), 31.8 (C1'H$_2$), 29.7 (C2'H$_2$), 22.9 (C3'H$_2$), 22.3 (COCH$_2$*C*H$_2$), 14.0 (C4'H$_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 259.2057; $C_{18}H_{27}O$ requires 259.2056, Δ 0.06 ppm.

5-Benzyl-1-bromononan-4-one, 263



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added *cyclopropyl ketone* **226** (69 mg, 0.30 mmol) and $HBr_{(aq)}$ (48%, 0.20 mL) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), placed into a preheated oil bath at 40 °C and left to stir for 16 h. The reaction was quenched with $NaHCO_3$ (10 mL) and the aqueous layer extracted with Et_2O (2 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (Pentane:CH_2Cl_2, 80:20) provided the title compound (85 mg, 91%) as a pale yellow oil.

R_f = 0.76 (Pentane:CH_2Cl_2, 50:50), [UV, vanillin].

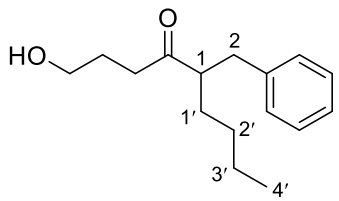
IR (film) ν_{max}/cm^{-1} 3027, 2956, 2930, 2858, 1710, 1603, 1496, 1455, 1404, 1376, 1277, 1245, 1212, 1190, 1073, 1030, 989.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.24 (2H, m, Ph), 7.22–7.16 (1H, m, Ph), 7.15–7.10 (2H, m, Ph), 3.37–3.23 (2H, m, CH_2Br), 2.89–2.77 (2H, m, C2$H_A$$H_B$ and C1H), 2.75–2.64 (1H, m, C2$H_A$$H_B$), 2.51 (1H, dt, *J* = 18.3, 6.8 Hz, C$H_A$$H_B$CO), 2.24 (1H, dt, *J* = 18.3, 6.8 Hz, CH_AH_BCO), 2.06–1.89 (2H, m, C$H_2$$CH_2$CO), 1.72–1.61 (1H, m, C1′$H_A$$H_B$), 1.51–1.41 (1H, m, C1′$H_A$$H_B$), 1.35–1.18 (4H, m, C2′$H_2$ and C3′H_2), 0.88 (3H, t, *J* = 7.1 Hz, C4′H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.3 (C=O), 139.7 (Ar-C), 128.9 (2C, 2 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 126.4 (Ar-CH), 54.4 (C1H), 41.7 (CH_2CO), 38.4 (C2H_2), 33.4 (CH_2Br), 31.9 (C1′H_2), 29.7 (C2′H_2), 26.2 (C$H_2$$CH_2$CO), 22.9 (C3′$H_2$), 14.0 (C4′$H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 311.1006; $C_{16}H_{24}O^{79}Br$ requires 311.1005, Δ 0.36 ppm.

5-Benzyl-1-hydroxynonan-4-one, 265[95]



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added *cyclopropyl ketone* **226** (69 mg, 0.30 mmol) and $H_2SO_{4(aq)}$ (95%, 0.60 mL) sequentially in the open atmosphere. The

reaction vessel was sealed with a microwave vial cap (containing a Reseal^{TM} septum), placed into a preheated oil bath at 80 °C and left to stir for 1 h. After this time, the reaction was cooled to RT and diluted with ice water. The reaction mixture was then washed with sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (Pentane:EtOAc, 80:20) provided the title compound (62 mg, 83%) as a colourless oil.

R_f = 0.21 (Pentane:EtOAc, 80:20), [UV, vanillin].

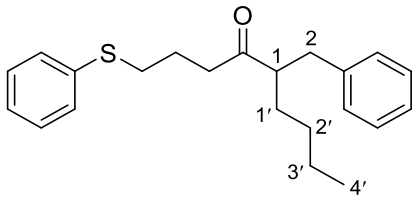
IR (film) ν_{max}/cm^{-1} 3411, 3062, 3028, 2956, 2930, 2859, 2361, 2340, 1708, 1603, 1496, 1454, 1378, 1059, 1030, 913.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26–6.98 (5H, m, Ph), 3.47–3.36 (2H, m, CH_2OH), 2.81–2.71 (2H, m, C2H_AH$_B$ and C1H), 2.67–2.58 (1H, m, C2H$_A$$H_B$), 2.37 (1H, dt, *J* = 18.1, 6.7 Hz, CH_AH$_B$CO), 2.14 (1H, dt, *J* = 18.1, 6.8 Hz, CH$_A$$H_B$CO), 1.64–1.54 (3H, m, C$H_2CH_2$CO and C1'$H_AH_B$), 1.44–1.32 (1H, m, C1'H$_A$$H_B$), 1.27–1.11 (4H, m, C3'H$_2$ and C2'H$_2$), 0.80 (3H, t, *J* = 7.1 Hz, C4'H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.2 (C=O), 139.8 (Ar-C), 129.0 (2C, 2 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 126.4 (Ar-CH), 62.3 (CH_2OH), 54.3 (C1H), 40.8 (CO*C*H$_2$), 38.5 (C2H$_2$), 31.9 (C1'H$_2$), 29.7 (C2'H$_2$), 26.1 (COCH$_2$*C*H$_2$), 22.9 (C3'H$_2$), 14.0 (C4'H$_3$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 271.1667; $C_{16}H_{24}O_2Na$ requires 271.1669, Δ –0.41 ppm.

5-benzyl-1-(phenylthio)nonan-4-one, 266



To an oven dried flask under Ar was added *cyclopropyl ketone* **226** (69 mg, 0.30 mmol)**,** CH_2Cl_2 (3.2 mL) and thiophenol (62 µL, 0.60 mmol). The solution was cooled to 0 °C and $BF_3{\cdot}Et_2O$ (0.12 mL, 0.90 mmol) added dropwise. The mixture was warmed to RT over 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and the layers separated. The aqueous layer was extracted

with CH_2Cl_2 (3 ×10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (Pentane:Et_2O, 98:2) provided the title compound (82 mg, 80%) as a colourless oil.

R_f = 0.23 (Pentane:Et_2O, 98:2), [UV, vanillin].

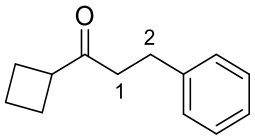
IR (film) ν_{max}/cm^{-1} 3061, 3027, 2954, 2928, 2857, 1709, 1603, 1584, 1495, 1481, 1454, 1439, 1403, 1375, 1303, 1215, 1156, 1086, 1026, 989.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.22 (6H, m, Ph), 7.20–7.14 (2H, m, Ph), 7.13–7.09 (2H, m, Ph), 2.87–2.65 (5H, m, C2$H_A$$H_B$, C1H, C$H_2$SPh and C2$H_A$$H_B$), 2.48 (1H, app. dt, *J* = 18.0, 6.9 Hz, C$H_A$$H_B$CO), 2.23 (1H, app. dt, *J* = 18.0, 7.0 Hz, C$H_A$$H_B$CO), 1.80–1.71 (2H, m, C$H_2$$CH_2$SPh), 1.69–1.58 (1H, m, C1′$H_A$$H_B$), 1.48–1.38 (1H, m, C1′$H_A$$H_B$), 1.34–1.16 (4H, m, C2′$H_2$ and C3′H_2), 0.87 (3H, t, *J* = 7.1 Hz, C4′H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.8 (C=O), 139.8 (Ar-C), 136.3 (Ar-C), 129.3 (2C, 2 × Ar-CH), 128.98 (4C, 4 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 126.4 (Ar-CH), 126.0 (Ar-CH), 54.3 (C1H), 42.2 (*C*H_2CO), 38.4 (C2H_2), 32.9 (CH_2SPh), 31.9 (C1′H_2), 29.7 (C2′H_2), 22.9 (C3′H_2), 22.6 (*C*$H_2$$CH_2$SPh), 14.0 (C4′$H_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 341.1945; $C_{22}H_{29}OS$ requires 341.1935, Δ 2.96 ppm.

1-Cyclobutyl-3-phenylpropan-1-one, 273



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added cyclobutylmethyl ketone (589 mg, 6.00 mmol), $[(cod)IrCl]_2$ (40 mg, 1.0 mol%), PPh_3 (63 mg, 0.24 mmol), KOH (34 mg, 0.60 mmol), and benzyl alcohol (0.75 mL, 7.2 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and purged with Ar for 5 mins using a balloon. Following this, the vial (complete with an Ar balloon) was heated to 100 °C in a preheated oil bath for 24 h, and then cooled to RT. Purification by column chromatography (SiO_2, eluent load, Pentane:Et_2O, 99:1) provided the title compound (728 mg,

64%) as a colourless oil.

R_f = 0.36 (Pentane:Et_2O, 95:5), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 2943, 1705, 1604, 1496, 1453, 1408, 1367, 1245, 1367, 1245, 1200, 1122, 1030, 979.

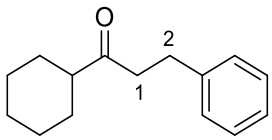
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.20 (5H, m, Ph), 3.29 (1H, quint., *J* = 8.5 Hz, CH cyclobutyl), 2.97 (2H, t, *J* = 7.7 Hz, $C2H_2$), 2.74 (2H, t, *J* = 7.7 Hz, $C1H_2$), 2.34–2.12 (4H, m, 2 × $CHCH_2$ cyclobutyl), 2.11–1.94 (1H, m, $CHCH_2CH_AH_B$ cyclobutyl), 1.92–1.77 (1H, m, $CHCH_2CH_AH_B$, cyclobutyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.1 (C=O), 141.4 (Ar-C), 128.5 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.1 (Ar-CH), 45.6 (CH cyclobutyl), 41.6 ($C1H_2$), 29.8 ($C2H_2$), 24.3 (2C, 2 × $CHCH_2$ cyclobutyl), 17.8 ($CHCH_2CH_2$ cyclobutyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 211.1094; $C_{13}H_{16}ONa$ requires 211.1093, Δ 0.18 ppm.

All spectroscopic data in agreement with that previously reported.[124]

1-Cyclohexyl-3-phenylpropan-1-one, 275



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added cyclohexylmethyl ketone (757 mg, 6.00 mmol), $[(cod)IrCl]_2$ (40 mg, 1.0 mol%), PPh_3 (63 mg, 0.24 mmol), KOH (34 mg, 0.60 mmol), and benzyl alcohol (0.75 mL, 7.2 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and purged with Ar for 5 mins using a balloon. Following this, the vial (complete with an Ar balloon) was heated to 100 °C in a preheated oil bath for 24 h, and then cooled to RT. Purification by column chromatography (SiO_2, eluent load, Pentane:Et_2O, 98:2) provided the title compound (995 mg, 77%) as a colourless oil.

R_f = 0.32 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2928, 2854, 2360, 1705, 1496, 1450, 1407, 1373, 1143, 1087, 1030, 991.

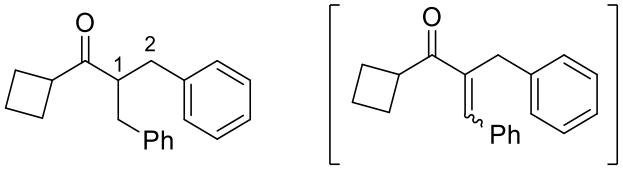
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.05 (5H, m, Ph), 2.80 (2H, t, *J* = 7.6 Hz, C2H_2), 2.67 (2H, t, *J* = 7.6 Hz, C1H_2), 2.23 (1H, tt, *J* = 11.2, 3.5 Hz, CH cyclohexyl), 1.78–1.64 (4H, m, 2 × CHC$H_A$$H_B$ cyclohexyl and 2 × $CHCH_2C$$H_A$$H_B$ cyclohexyl), 1.65–1.53 (1H, $CHCH_2CH_2C$$H_A$$H_B$ cyclohexyl), 1.31–1.04 (5H, m, 2 × $CHCH_A$$H_B$ cyclohexyl, 2 × $CHCH_2CH_AC$$H_B$ cyclohexyl and $CHCH_2CH_2CH_A$$H_B$ cyclohexyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.3 (C=O), 141.5 (Ar-C), 128.5 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.1 (Ar-CH), 51.1 (CH cyclohexyl), 42.3 (C1H_2), 29.8 (C2H_2), 28.5 (2C, 2 × CHCH_2 cyclohexyl), 25.9 ($CHCH_2CH_2CH_2$ cyclohexyl), 25.7 (2C, 2 × $CHCH_2CH_2$ cyclohexyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 239.1407; $C_{15}H_{20}ONa$ requires 239.1406, Δ 0.08 ppm.

All spectroscopic data in agreement with that previously reported.[124]

2-Benzyl-1-cyclobutyl-3-phenylpropan-1-one, 276



276 **S1**

Ketone **273** (57 mg, 0.30 mmol), benzyl alcohol (0.16 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (11 mg, 13%), and **S1**[*] (3 mg, 3%) as an inseparable mixture in a 79:21 ratio.

R_f = 0.35 (Pentane:Et_2O, 95:5), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3027, 2944, 2360, 1704, 1603, 1496, 1455, 1371, 1244, 1205, 1121, 1079, 1028, 972.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–6.98 (10H, m, 2 × Ph), 3.03–2.93 (1H, m, C1H), 2.83 (2H, dd, *J* = 13.2, 9.0 Hz, 2 × C2$H_A$$H_B$), 2.62 (2H, dd, *J* = 13.4, 5.8 Hz, 2 × C2$H_A$$H_B$), 2.60–2.54 (1H, m, CH

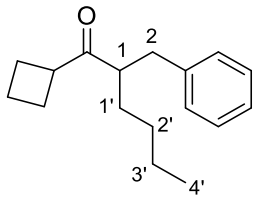
[*] Not all peaks belonging to **S1** could be distinguished clearly.

cyclobutyl), 1.66–1.54 (5H, m, 2 × CHCH_2 cyclobutyl and $CHCH_2CH_AH_B$ cyclobutyl), 1.45–1.39 (1H, m, $CHCH_2CH_AH_B$ cyclobutyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.4 (C=O), 139.7 (2C, 2 × Ar-C), 129.1 (4C, 4 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 126.5 (2C, 2 × Ar-CH), 54.6 (C1H), 46.6 (CH cyclobutyl), 38.7 ($C2H_2$), 23.3 (2C, 2 × CH_2 cyclobutyl), 17.4 ($CHCH_2CH_2$ cyclobutyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 301.1562; $C_{20}H_{22}ONa$ requires 301.1563, Δ –0.22 ppm.

2-Benzyl-1-cyclobutylhexan-1-one, 277



Ketone **273** (57 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (20 mg, 27%) as a colourless oil.

***R*$_f$** = 0.32 (Pentane:Et_2O, 95:5), [UV, vanillin].

IR (film) ν_{max}/cm^{-1} 3028, 2931, 2859, 2360, 2342, 1703, 1604, 1496, 1455, 1375, 1244, 1214, 1118, 1030, 971.

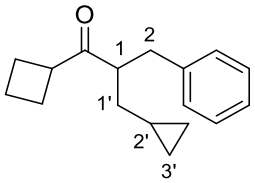
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23–7.01 (5H, m, Ph), 3.00 (1H, quint., *J* = 8.4 Hz, CH cyclobutyl), 2.79 (1H, dd, *J* = 12.9, 8.5 Hz, C2H_AH_B), 2.68 (1H, quint., *J* = 6.9 Hz, C1H), 2.56 (1H, dd, *J* = 13.0, 5.8 Hz, $C2H_AH_B$), 2.14–2.01 (1H, m, $CHCH_AH_B$ cyclobutyl), 1.95–1.85 (1H, m, $CHCH_{A'}H_{B'}$ cyclobutyl), 1.81–1.67 (3H, m, $CHCH_AH_B$ cyclobutyl, $CHCH_{A'}H_{B'}$ cyclobutyl, and $CHCH_2CH_AH_B$ cyclobutyl), 1.64–1.48 (2H, m, $CHCH_2CH_AH_B$ cyclobutyl and C1'H_AH_B), 1.38–1.27 (1H, m, C1'H_AH_B), 1.26–1.09 (4H, m, C3'H_2 and C2'H_2), 0.79 (3H, t, *J* = 7.0 Hz, C4'H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.0 (C=O), 140.2 (Ar-C), 129.1 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 126.3 (Ar-CH), 52.4 (C1H), 45.8 (CH cyclobutyl), 38.2 ($C2H_2$), 31.8 (C1'H_2), 29.8 (C2'H_2), 24.0

(CHC_AH$_2$ cyclobutyl), 23.9 (CHC_BH$_2$ cyclobutyl), 22.9 (C3'H$_2$), 17.6 (CHCH$_2$$CH_2$ cyclobutyl), 14.1 (C4'H$_2$).

HRMS (ESI$^+$) Found [M+Na]$^+$ = 267.1718; $C_{17}H_{24}ONa$ requires 267.1719, Δ –0.34 ppm.

2-Benzyl-1-cyclobutyl-3-cyclopropylpropan-1-one, 278



Ketone **273** (57 mg, 0.30 mmol), cyclopropyl carbinol (0.12 mL, 1.5 mmol), [Cp*IrCl$_2$]$_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et$_2$O, 99:1) provided the title compound (25 mg, 34%) as a colourless oil.

***R*$_f$** = 0.42 (Pentane:Et$_2$O, 95:5), [UV, vanillin].

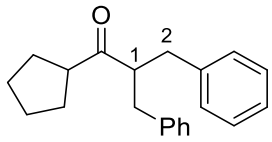
IR (film) ν_{max}/cm^{-1} 2942, 2360, 1703, 1604, 1496, 1455, 1369, 1244, 1120, 1018, 974.

^{1}H NMR (CDCl$_3$, 400 MHz) δ = 7.29–7.09 (5H, m, Ph), 3.11 (1H, quint., *J* = 8.2 Hz, CH cyclobutyl), 2.95–2.82 (2H, m, C1H and C2H_AH$_B$), 2.72–2.63 (1H, m, C2H$_A$$H_B$), 2.20 (1H, m, CHC$H_AH_B$ cyclobutyl), 2.02–1.92 (1H, m, CHC$H_{A'}$H$_{B'}$ cyclobutyl), 1.89–1.80 (2H, m, CHCH$_A$$H_B$ cyclobutyl and CHCH$_2$CH_AH$_B$ cyclobutyl), 1.80–1.70 (1H, m, CHCH$_{A'}$$H_{B'}$ cyclobutyl), 1.70–1.60 (1H, m, CHCH$_2$CH$_A$$H_B$ cyclobutyl), 1.52 (1H, dt, *J* = 14.8, 7.6 Hz, C1'H_AH$_B$), 1.34 (1H, dt, *J* = 13.9, 5.6 Hz, C1'H$_A$$H_B$), 0.67–0.55 (1H, m, C2'H), 0.45–0.37 (2H, m, 2 × C3'H_AH$_B$), 0.03– –0.03 (2H, m, 2 × C3'H$_A$$H_B$).

^{13}C NMR (CDCl$_3$, 101 MHz) δ = 215.2 (C=O), 140.2 (Ar-C), 129.1 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 126.3 (Ar-CH), 52.7 (C1H), 46.4 (CH cyclobutyl), 38.5 (C2H$_2$), 37.5 (C1'H$_2$), 23.9 (CHC_AH$_2$ cyclobutyl), 23.7 (CHC_BH$_2$ cyclobutyl), 17.6 (CHCH$_2$$CH_2$ cyclobutyl), 9.5 (C2'H), 5.2 (C3'$_A$H$_2$), 4.7 (C3'$_B$H$_2$).

HRMS (ESI$^+$) Found [M+Na]$^+$ = 265.1563; $C_{17}H_{22}ONa$ requires 265.1563, Δ –0.02 ppm.

2-Benzyl-1-cyclopentyl-3-phenylpropan-1-one, 279



1-cyclopentyl-3-phenylpropan-1-one* (61 mg, 0.30 mmol), benzyl alcohol (0.16 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (16 mg, 18%) as a colourless oil.

R_f = 0.39 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

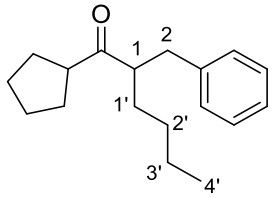
IR (film) ν_{max}/cm^{-1} 3028, 2950, 2868, 2360, 2342, 1705, 1603, 1496, 1454, 1372, 1109, 1081, 1028, 912.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.22–7.03 (10H, m, 2 × Ph), 3.11 (1H, tt, *J* = 8.9, 5.8 Hz, C1H), 2.85 (2H, dd, *J* = 13.3, 8.9 Hz, 2 × C2H_AH_B), 2.62 (2H, dd, *J* = 13.3, 5.8 Hz, 2 × C2H_AH_B), 2.23 (1H, quint., *J* = 7.7 Hz, CH cyclopentyl), 1.35–1.10 (8H, m, 2 × CHCH_2 cyclopentyl and 2 × $CHCH_2CH_2$ cyclopentyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.9 (C=O), 139.7 (2C, 2 × Ar-C), 129.2 (4C, 4 × Ar-CH), 128.5 (4C, 4 × Ar-CH), 126.4 (2C, Ar-CH), 56.2 (C1H), 52.8 (CH cyclopentyl), 38.8 (2C, 2 × $C2H_2$), 27.8 (2C, 2 × $CHCH_2$ cyclopentyl), 25.8 (2C, 2 × $CHCH_2CH_2$ cyclopentyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 315.1718; $C_{21}H_{24}ONa$ requires 315.1719, Δ –0.39 ppm.

2-benzyl-1-cyclopentylhexan-1-one, 280



1-cyclopentyl-3-phenylpropan-1-one* (61 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol),

* Synthesised by Dr James Frost

$[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (31 mg, 40%) as a colourless oil.

R_f = 0.51 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

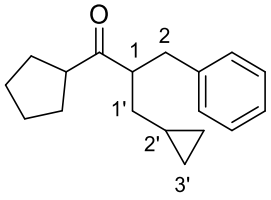
IR (film) ν_{max}/cm^{-1} 2955, 2869, 2361, 2342, 1705, 1496, 1454, 1376, 1097, 1030, 747.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.21–7.02 (5H, m, Ph), 2.85–2.75 (2H, m, C1H and C2$H_A$$H_B$), 2.68–2.51 (2H, m, CH cyclopentyl and C2$H_A$$H_B$), 1.62–1.48 (4H, m, CHC$H_A$$H_B$ cyclopentyl, CHC$H_{A'}$$H_{B'}$ cyclopentyl, C1'$H_A$$H_B$ and $CHCH_2C$$H_A$$H_B$ cyclopentyl), 1.47–1.30 (5H, m, $CHCH_2C$$H_{A'}$$H_{B'}$ cyclopentyl, $CHCH_2CH_A$$H_B$ cyclopentyl, $CHCH_2CH_{A'}$$H_{B'}$ cyclopentyl, $CHCH_A$$H_B$ cyclopentyl and C1'$H_A$$H_B$), 1.29–1.11 (5H, m, $CHCH_{A'}$$H_{B'}$ cyclopentyl, C3'H_2 and C2'H_2), 0.80 (3H, t, *J* = 7.0 Hz, C4'H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.7 (C=O), 140.3 (Ar-C), 129.2 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 53.9 (C1H), 51.9 (CH cyclopentyl), 38.3 ($C2H_2$), 31.9 (C1'H_2), 29.8 (C2'H_2), 28.6 (2 × $CHCH_2$ cyclopentyl), 26.0 ($CHCH_2C_AH_2$ cyclopentyl), 25.9 ($CHCH_2C_BH_2$ cyclopentyl), 23.0 (C3'H_2), 14.1 (C4'H_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 281.1875; $C_{18}H_{26}ONa$ requires 281.1876, Δ –0.20 ppm.

2-Benzyl-1-cyclopentyl-3-cyclopropylpropan-1-one, 281



1-cyclopentyl-3-phenylpropan-1-one* (61 mg, 0.30 mmol), cyclopropyl carbinol (0.12 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (46 mg, 60%) as a colourless oil.

R_f = 0.43 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

* Synthesised by Dr James Frost.

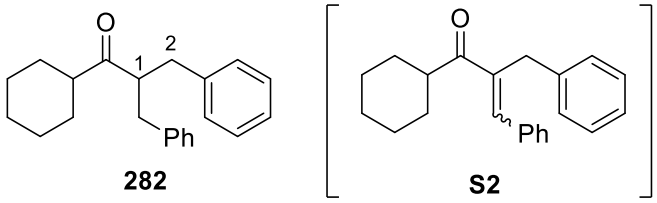
IR (film) ν_{max}/cm^{-1} 2952, 2868, 2361, 2342, 1705, 1496, 1454, 1371, 1108, 1046, 1017, 947.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.30–7.09 (5H, m, Ph), 3.03 (1H, tt, *J* = 8.6, 5.7 Hz, C1H), 2.88 (1H, dd, *J* = 13.3, 8.7 Hz, C2H_AH$_B$), 2.74 (1H, quint., *J* = 7.8 Hz, CH cyclopentyl), 2.67 (1H, dd, *J* = 13.3, 6.1 Hz, C2H$_A$$H_B$), 1.80–1.69 (1H, m, CHC$H_AH_B$ cyclopentyl), 1.69–1.63 (1H, m, CHC$H_{A'}$H$_{B'}$ cyclopentyl), 1.62–1.50 (2H, m, CHCH$_2$CH_AH$_B$ cyclopentyl and C1'H_AH$_B$), 1.49–1.39 (4H, m, CHCH$_A$$H_B$ cyclopentyl, CHCH$_2$CH$_A$$H_B$ cyclopentyl, CHCH$_2$C$H_{A'}$$H_{B'}$ cyclopentyl), 1.38–1.24 (2H, m, C1'H$_A$$H_B$ and CHCH$_{A'}$$H_{B'}$ cyclopentyl), 0.68–0.57 (1H, m, C2'H), 0.45–0.38 (2H, m, 2 × C3'H_AH$_B$), 0.03– –0.03 (2H, m, 2 × C3'H$_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.6 (C=O), 140.2 (Ar-C), 129.2 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 54.2 (C1H), 52.6 (CH cyclopentyl), 38.6 (C2H$_2$), 37.6 (C1'H$_2$), 28.3 (2C, 2 × CH*C*H$_2$ cyclopentyl), 26.0 (CHCH$_2$$C_AH_2$ cyclopentyl), 25.9 (CHCH$_2$$C_BH_2$ cyclopentyl), 9.5 (C2'H), 5.3 (C3$_A$'H$_2$), 4.8 (C3$_B$'H$_2$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 279.1719; $C_{18}H_{24}ONa$ requires 279.1719, Δ –0.31 ppm.

2-Benzyl-1-cyclohexyl-3-phenylpropan-1-one, 282



282 **S2**

Ketone **275** (65 mg, 0.30 mmol), benzyl alcohol (0.16 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (10 mg, 11%) and **S2**[*] (3 mg, 3%), as an inseparable mixture in a 77:23 ratio.

R_f = 0.48 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3028, 2928, 2854, 2361, 2342, 1705, 1604, 1496, 1452, 1376, 1206, 1142, 1069,

[*] Not all peaks belonging to **S2** could be distinguished clearly.

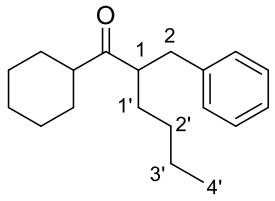
1027, 980.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.22–7.02 (10H, m, Ph), 3.14 (1H, tt, *J* = 8.8, 6.0 Hz, C1H), 2.82 (2H, dd, *J* = 13.3, 8.8 Hz, 2 × C2$H_A$$H_B$), 2.60 (2H, dd, *J* = 13.3, 6.0 Hz, 2 × C2$H_A$$H_B$), 1.64 (1H, tt, *J* = 10.9, 3.4 Hz, CH cyclohexyl), 1.51–1.43 (2H, m, 2 × $CHCH_2CH_AH_B$ cyclohexyl), 1.44–1.38 (1H, m, $CHCH_2CH_2CH_AH_B$ cyclohexyl) 1.26–1.17 (2H, m, 2 × $CHCH_AH_B$ cyclohexyl), 1.00–0.73 (5H, m, 2 × $CHCH_2CH_AH_B$ cyclohexyl, $CHCH_2CH_2CH_AH_B$ cyclohexyl and 2 × $CHCH_AH_B$ cyclohexyl).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 216.7 (C=O), 139.8 (2C, 2 × Ar-C), 129.2 (4C, 4 × Ar-CH), 128.5 (4C, 4 × Ar-CH), 126.4 (Ar-CH), 55.1 (C1H), 52.2 (CH cyclohexyl), 38.7 (2C, 2 × $C2H_2$), 27.3 (2C, 2 × $CHCH_2$ cyclohexyl), 25.8 ($CHCH_2CH_2CH_2$ cyclohexyl), 25.6 (2C, 2 × $CHCH_2CH_2$ cyclohexyl).

HRMS (ESI^+) Found $[M+Na]^+$ = 329.1875; $C_{22}H_{26}ONa$ requires 329.1976, Δ –0.26 ppm.

2-Benzyl-1-cyclohexylhexan-1-one, 283



Ketone **275** (65 mg, 0.30 mmol), *n*-butanol (0.14 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (37 mg, 45%) as a colourless oil.

***R*$_f$** = 0.51 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2928, 2855, 2361, 2342, 1705, 1496, 1450, 1377, 1236, 1143, 1066, 1029, 981.

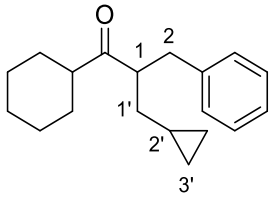
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.22–7.02 (5H, m, Ph), 2.88–2.73 (2H, m, C1H and C2$H_A$$H_B$), 2.54 (1H, dd, *J* = 12.7, 5.5 Hz, C2$H_A$$H_B$), 2.03 (1H, tt, *J* = 11.1, 3.3 Hz, CH cyclohexyl), 1.67–1.60 (2H, m, $CHCH_2CH_2CH_AH_B$ cyclohexyl and $CHCH_AH_B$ cyclohexyl), 1.59–1.49 (3H, m, $CHCH_2CH_AH_B$ cyclohexyl, $CHCH_2CH_{A'}H_{B'}$ cyclohexyl and C1'$H_A$$H_B$), 1.39–1.26 (2H, m, $CHCH_{A'}H_{B'}$ cyclohexyl and C1'$H_A$$H_B$), 1.25–1.08 (6H, m, C3'$H_2$, C2'$H_2$, $CHCH_AH_B$ cyclohexyl and $CHCH_2CH_2CH_AH_B$ cyclohexyl), 1.07–0.86 (3H, m,

$CHCH_2CH_AH_B$ cyclohexyl, $CHCH_2CH_{A'}H_{B'}$ cyclohexyl and $CHCH_{A'}H_{B'}$), 0.79 (3H, t, *J* = 7.0 Hz, $C4H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 217.3 (C=O), 140.3 (Ar-C), 129.1 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 52.8 (C1H), 51.5 (CH cyclohexyl), 38.3 ($C2H_2$), 31.9 ($C1'H_2$), 29.8 ($C2'H_2$), 28.0 (CHC_AH_2 cyclohexyl), 27.8 (CHC_BH_2 cyclohexyl), 25.9 ($CHCH_2CH_2CH_2$ cyclohexyl), 25.8 (2C, $CHCH_2C_AH_2$ cyclohexyl and $CHCH_2C_BH_2$ cyclohexyl), 23.0 ($C3'H_2$), 14.1 ($C4'H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 295.2032; $C_{19}H_{28}ONa$ requires 295.2032, Δ –0.28 ppm.

2-Benzyl-1-cyclohexyl-3-cyclopropylpropan-1-one, 284



Ketone **275** (65 mg, 0.30 mmol), cyclopropyl carbinol (0.12 mL, 1.5 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (50 mg, 0.90 mmol) were subjected to **general procedure D**. Purification by flash column chromatography (Pentane:Et_2O, 99:1) provided the title compound (50 mg, 62%) as a colourless oil.

***R*$_f$** = 0.43 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

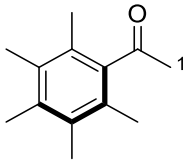
IR (film) ν_{max}/cm^{-1} 3001, 2928, 2853, 2360, 2342, 1705, 1496, 1449, 1375, 1288, 1241, 1142, 1069, 1017, 984.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.10 (5H, m, Ph), 3.12–3.02 (1H, m, C1H), 2.85 (1H, dd, *J* = 13.3, 8.5 Hz, $C2H_AH_B$), 2.66 (1H, dd, *J* = 13.3, 6.2 Hz, $C2H_AH_B$), 2.15 (1H, tt, *J* = 11.3, 3.5 Hz, CH cyclohexyl), 1.80–1.70 (2H, m, $CHCH_AH_B$ cyclohexyl and $CHCH_2CH_2CH_AH_B$ cyclohexyl), 1.68–1.57 (2H, m, $CHCH_2CH_AH_B$ cyclohexyl and $CHCH_2CH_{A'}H_{B'}$ cyclohexyl), 1.56–1.49 (1H, m, $C1'H_AH_B$), 1.48–1.41 (1H, m, $CHCH_{A'}H_{B'}$ cyclohexyl), 1.35–1.28 (1H, m, $C1'H_AH_B$), 1.28–1.04 (4H, m, $CHCH_AH_B$ cyclohexyl, $CHCH_2CH_2CH_AH_B$ cyclohexyl, $CHCH_2CH_AH_B$ cyclohexyl and $CHCH_2CH_{A'}H_{B'}$ cyclohexyl), 1.04–0.91 (1H, m, $CHCH_{A'}H_{B'}$ cyclohexyl), 0.68–0.53 (1H, m, C2'H), 0.45–0.37 (2H, m, 2 × $C3'H_AH_B$), 0.04– –0.05 (2H, m, 2 × $C3'H_AH_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 217.4 (C=O), 140.2 (Ar-C), 129.2 (2C, 2 × Ar-CH), 128.4 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 53.1 (C1H), 52.1 (CH cyclohexyl), 38.7 ($C2H_2$), 37.6 ($C1'H_2$), 27.9 (CHC_AH_2 cyclohexyl), 27.6 (CHC_BH_2 cyclohexyl), 25.9 ($CHCH_2CH_2CH_2$ cyclohexyl), 25.8 (2C, $CHCH_2C_AH_2$ cyclohexyl and $CHCH_2C_BH_2$ cyclohexyl), 9.5 (C2'H), 5.3 ($C3'H_2$), 4.8 ($C3'H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 293.1875; $C_{19}H_{26}ONa$ requires 293.1876, Δ –0.19 ppm.

1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 329



A solution of pentamethylbenzene (10.0 g, 67.4 mmol) and acetyl chloride (5.27 mL, 74.2 mmol) in CH_2Cl_2 (400 mL) was cooled in an ice bath. Then aluminium chloride (11.2 g, 84.3 mmol) was added portionwise over 10 mins. The resulting mixture was warmed to RT and stirred for 4 h and then poured onto crushed ice (c.a. 500 g). After the ice had melted, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5) provided the title compound (12.0 g, 93%) as a white solid.

***R*$_f$ =** 0.21 (Pentane:Et2O, 95:5), [UV, $KMnO_4$].

m.p. = 83–84 °C.

IR (film) ν_{max}/cm^{-1} 2925, 1697, 1416, 1385, 1350, 1305, 1267, 1168, 1070, 998.

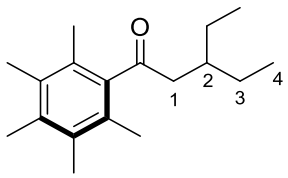
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.46 (3H, s, $C1H_3$), 2.23 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 x Ar-CH_3), 2.13 (6H, s, 2 x Ar-CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.3 (C=O), 141.0 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 x Ar-C), 127.1 (2C, 2 x Ar-C), 33.3 ($C1H_3$), 17.2 (2C, 2 x Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 x Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 191.1433; $C_{13}H_{19}O$ requires 191.1430, Δ 1.10 ppm.

All spectroscopic data in agreement with that previously reported.[125]

3-Ethyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 333



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 3-pentanol (79 mg, 0.90 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (152 mg, 97%) as a white solid.

R_f = 0.40 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 46–47 °C**.**

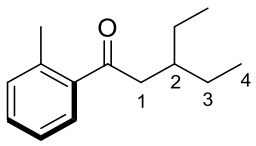
IR (film) ν_{max}/cm^{-1} 2959, 2922, 2875, 1700, 1459, 1402, 1380, 1335, 1305, 1098, 1002, 925.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.64 (2H, d, J = 6.2 Hz, C1H_2), 2.24 (3H, s, Ar-CH_3), 2.20 (6H, s, 2 × Ar-CH_3), 2.13 (6H, s, 2 × Ar-CH_3), 2.08–1.98 (1H, m, C2H), 1.53–1.35 (4H, m, 2 × C3H_2), 0.91 (6H, t, J = 7.4 Hz, 2 × C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.6 (C=O), 140.9 (Ar-C), 135.2 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.3 (2C, 2 × Ar-C), 49.6 (C1H_2), 35.1 (C2H), 25.5 (2C, 2 × C3H_2), 17.1 (2C, 2 × Ar-CH_3), 16.7 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3), 10.8 (2C, 2 × C4H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 261.2213; $C_{18}H_{29}O$ requires 261.2213, Δ –0.08 ppm.

3-Ethyl-1-(o-tolyl)pentan-1-one, 339



1-(o-tolyl)ethan-1-one (81 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 3-pentanol (79 mg, 0.90 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 99:1→97:3) provided the title compound (19 mg, 15%) as a colourless oil.

R_f = 0.50 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

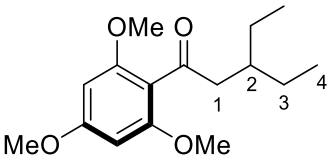
IR (film) ν_{max}/cm^{-1} 2961, 2931, 2876, 2858, 1682, 1601, 1572, 1486, 1458, 1381, 1363, 1337, 1296, 1262, 1216, 1193, 1036, 1007, 959.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.57–7.51 (1H, m, Ph), 7.33–7.26 (1H, m, Ph), 7.22–7.16 (2H, m, Ph), 2.75 (2H, d, *J* = 6.8 Hz, C1H_2), 2.43 (3H, s, Ar-CH_3), 1.89 (1H, sept., *J* = 6.4 Hz, C2H), 1.39–1.22 (4H, m, 2 × C3H_2), 0.83 (6H, t, *J* = 7.4 Hz, 2 × C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 205.4 (C=O), 139.0 (Ar-C), 137.8 (Ar-C), 132.0 (Ar-CH), 131.0 (Ar-CH), 128.3 (Ar-CH), 125.7 (Ar-CH), 46.0 (C1H_2), 37.3 (C2H), 26.1 (2C, 2 × C3H_2), 21.2 (Ar-CH_3), 11.1 (2C, 2 × C4H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 205.1589; $C_{14}H_{21}O$ requires 205.1587, Δ 1.19 ppm.

3-Ethyl-1-(2,4,6-trimethoxyphenyl)pentan-1-one, 342



1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (126 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 3-pentanol (79 mg, 0.90 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 70:30) provided the title compound (53 mg, 32%) as a white solid.

R_f = 0.23 (Pentane:Et_2O, 70:30), [UV, $KMnO_4$].

m.p. = 48–50 °C**.**

IR (film) ν_{max}/cm^{-1} 2961, 2876, 2840, 1702, 1607, 1586, 1494, 1468, 1456, 1414, 1336, 1228, 1206, 1156, 1129, 1060, 1037, 1010, 947.

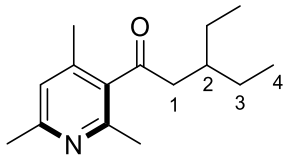
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.09 (2H, s, 2 × Ar-CH), 3.81 (3H, s, OMe), 3.76 (6H, s, 2 × OMe), 2.66 (2H, d, *J* = 6.7 Hz, C1H_2), 1.85 (1H, sept., *J* = 6.4 Hz, C2H), 1.39–1.29 (4H, m, 2 × C3H_2), 0.84 (6H, t, *J* = 7.4 Hz, 2 × C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 205.0 (C=O), 162.1 (*C*-OMe), 158.1 (2C, 2 × C-OMe), 114.1 (Ar-C),

90.6 (2C, 2 × Ar-CH), 55.8 (2C, 2 × OMe), 55.5 (OMe), 49.2 ($C1H_2$), 36.7 (C2H), 25.8 (2C, 2 × $C3H_2$), 10.9 (2C, 2 × $C4H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 281.1747; $C_{16}H_{24}O_4$ requires 281.1747, Δ –0.30 ppm.

3-Ethyl-1-(2,4,6-trimethylpyridin-3-yl)pentan-1-one, 344



1-(2,4,6-trimethylpyridin-3-yl)ethan-1-one (98 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 3-pentanol (79 mg, 0.90 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 60:40) provided the title compound (109 mg, 78%) as a colourless oil.

R_f = 0.18 (Pentane:Et_2O, 70:30), [UV, $KMnO_4$].

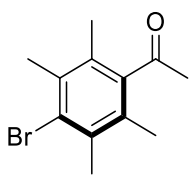
IR (film) ν_{max}/cm^{-1} 2961, 2922, 2877, 1701, 1591, 1557, 1461, 1444, 1401, 1378, 1336, 1314, 1266, 1247, 1169, 1031, 1002, 961.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.80 (1H, s, CH pyridine), 2.63 (2H, d, J = 6.4 Hz, $C1H_2$), 2.45 (3H, s, CH_3 pyridine), 2.39 (3H, s, CH_3 pyridine), 2.16 (3H, s, CH_3 pyridine), 1.94 (1H, sept., J = 6.2 Hz, C2H), 1.37 (4H, qd, J = 7.5, 6.2 Hz, 2 × $C3H_2$), 0.86 (6H, t, J = 7.4 Hz, 2 × $C4H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 208.7 (C=O), 157.6 (C*C*(CH_3)N), 151.9 (CH*C*(CH_3)N), 142.8 (CH*C*(CH_3)C), 135.2 (*C*CO), 122.4 (CH pyridine), 49.0 ($C1H_2$), 35.7 (C2H), 25.7 (2C, 2 × $C3H_2$), 24.3 (CH_3 pyridine), 22.6 (CH_3 pyridine), 18.9 (CH_3 pyridine), 10.9 (2C, 2 × $C4H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 234.1849; $C_{15}H_{24}ON$ requires 234.1852, Δ –1.50 ppm.

1-(4-Bromo-2,3,5,6-tetramethylphenyl)ethan-1-one, 347



To a solution of 3-bromo-1,2,4,5-tetramethylbenzene (2.00 g, 9.38 mmol) and acetyl bromide (0.760 mL, 10.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added $AlCl_3$ (1.56 g, 11.7 mmol) portionwise over 5 mins. Following the addition, the mixture stirred for 1 h. The mixture was carefully poured into ice cold H_2O (100 mL). The layers were separated and the organic layer washed with sat. aq. $NaHCO_3$ (50 mL). The aqueous layers were extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 85:15) provided the title compound (2.2 g, 90%) as a white crystalline solid.

R_f = 0.14 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 99–101 °C.

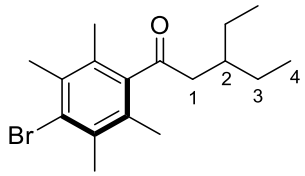
IR (film) ν_{max}/cm^{-1} 2984, 1698, 1550, 1451, 1413, 1381, 1349, 1303, 1229, 1154, 1021, 995.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.44 (3H, s, CH_3CO), 2.38 (6H, s, 2 × Ar-CH_3), 2.17 (6H, s, 2 × Ar-CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 209.0 (C=O), 142.1 (Ar-C), 134.9 (2C, 2 × Ar-C), 129.4 (C-Br), 128.9 (2C, 2 × Ar-C), 33.0 (*C*H_3CO), 20.6 (2C, 2 × Ar-CH_3), 17.8 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 255.0380; $C_{12}H_{16}O^{79}Br$ requires 255.0379, Δ 0.17 ppm.

1-(4-Bromo-2,3,5,6-tetramethylphenyl)-3-ethylpentan-1-one, 348



Ketone **347** (153 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 3-pentanol (79 mg, 0.90 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 99:1) provided the title compound (136 mg, 70%) as a white solid.

R_f = 0.33 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 52–53 °C**.**

IR (film) ν_{max}/cm^{-1} 2964, 2922, 2873, 1698, 1553, 1467, 1441, 1417, 1401, 1379, 1357, 1338, 1322,

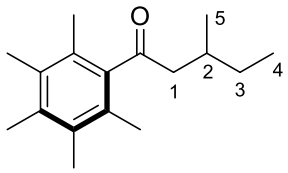
1301, 1249, 1125, 1113, 1088, 997.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.60 (2H, d, J = 6.2 Hz, C1H_2), 2.38 (6H, s, 2 × Ar-CH_3), 2.15 (6H, s, 2 × Ar-CH_3), 2.00 (1H, sept., J = 6.2 Hz, C2H), 1.53–1.33 (4H, m, 2 × C3H_2), 0.89 (6H, t, J = 7.4 Hz, 2 × C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.6 (C=O), 142.2 (Ar-C), 134.9 (2C, 2 × Ar-C), 129.3 (C-Br), 129.2 (2C, 2 × Ar-C), 49.5 (C1H_2), 35.1 (C2H), 25.6 (2C, 2 × C3H_2), 20.6 (2C, 2 × Ar-CH_3), 17.8 (2C, 2 × Ar-CH_3), 10.9 (2C, 2 × C4H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 325.1162; $C_{17}H_{26}O^{79}Br$ requires 325.1162, Δ 0.27 ppm.

3-Methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 355



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 2-butanol (67 mg, 0.90 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (124 mg, 84%) as a white solid.

R_f = 0.30 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]

m.p. = 40–41 °C**.**

IR (film) ν_{max}/cm^{-1} 2958, 2924, 2874, 1699, 1459, 1401, 1378, 1360, 1303, 1144, 1096, 999.

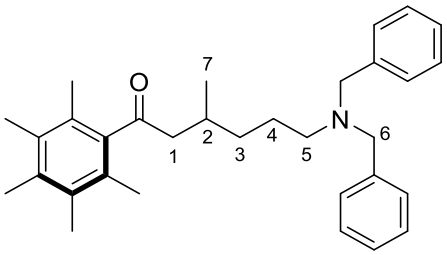
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.70 (1H, dd, J = 18.9, 5.0 Hz, C1$H_A$$H_B$), 2.53 (1H, dd, J = 18.8, 7.8 Hz, C1$H_A$$H_B$), 2.24 (3H, s, Ar-$CH_3$), 2.20 (6H, s, 2 × Ar-$CH_3$), 2.15–2.11 (1H, m, C2H), 2.12 (6H, s, 2 × Ar-CH_3), 1.58–1.39 (1H, m, C3$H_A$$H_B$), 1.33–1.39 (1H, m, C3$H_A$$H_B$), 1.04 (3H, d, J = 6.7 Hz, C5H_3), 0.93 (3H, t, J = 7.4 Hz, C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.5 (C=O), 140.9 (Ar-C), 135.3 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.4 (2C, 2 × Ar-C), 52.7 (C1H_2), 29.5 (2C, C2H and C3H_2), 19.6 (C5H_3), 17.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-

CH_3), 16.1 (2C, 2 × Ar-CH_3), 11.4 (C4H_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 247.2057; $C_{17}H_{27}O$ requires 247.2056, Δ –0.19 ppm.

6-(Dibenzylamino)-3-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one, 363



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 5-(dibenzylamino)pentan-2-ol* (255 mg, 0.900 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 95:5) provided the title compound (214 mg, 78%) as a colourless oil.

R_f = 0.25 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]

IR (film) ν_{max}/cm^{-1} 2927, 2793, 1699, 1559, 1541, 1494, 1453, 1398, 1310, 1125, 1068, 1028, 978.

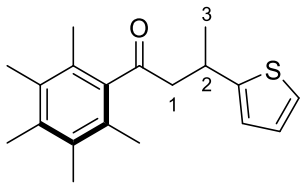
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.11 (10H, m, 2 × Ph), 3.47 (4H, s, 2 × C6H_2), 2.55 (1H, dd, *J* = 18.8, 5.0 Hz, C1H_AH$_B$), 2.41 (1H, dd, *J* = 18.8, 7.7 Hz, C1H$_A$$H_B$), 2.33 (2H, t, *J* = 7.2 Hz, C5H_2), 2.15 (3H, s, Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 2.08–2.03 (1H, m, C2H), 2.00 (6H, s, 2 × Ar-CH_3), 1.52–1.38 (2H, m, C4H_2), 1.36–1.25 (1H, m, C3H_AH$_B$), 1.14–1.03 (1H, m, C3H$_A$$H_B$), 0.92 (3H, d, *J* = 6.6 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.3 (C=O), 140.9 (Ar-C), 140.1 (2C, 2 × Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.9 (4C, 4 × Ar-CH), 128.3 (4C, 4 × Ar-CH), 127.4 (2C, 2 × Ar-C), 126.8 (2C, 2 × Ar-CH), 58.5 (2C, 2 × C6H_2), 53.9 (C5H_2), 53.1 (C1H_2), 34.6 (C3H_2), 28.0 (C2H), 24.6 (C4H_2), 20.1 (C7H_3), 17.2 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 456.3254; $C_{32}H_{42}ON$ requires 456.3261, Δ –1.50 ppm.

* Synthesised by Dr James Frost.

1-(2,3,4,5,6-Pentamethylphenyl)-3-(thiophen-2-yl)butan-1-one, 366



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), 1-(thiophen-2-yl)ethan-1-ol (154 mg, 1.20 mmol), PhMe (0.15 mL) and NaO*t*Bu (173 mg, 1.80 mmol) were subjected to **general procedure I** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (148 mg, 82%) as a white solid.

R_f = 0.40 (Pentane:Et_2O, 96:4), [UV, $KMnO_4$].

m.p. = 77–78°C.

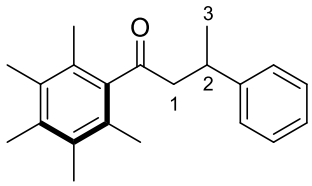
IR (film) ν_{max}/cm^{-1} 2926, 1701, 1653, 1559, 1541, 1521, 1507, 1457, 1399, 1343, 1304, 1276, 1119, 940.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.16 (1H, dd, *J* = 5.0, 1.2 Hz, SCH), 6.99–6.92 (2H, m, SCHC*H* and SCCH), 3.99–3.88 (1H, m, C2H), 3.14 (1H, dd, *J* = 19.0, 5.5 Hz, C1$H_A$$H_B$), 3.01 (1H, dd, *J* = 19.0, 7.7 Hz, C1$H_A$$H_B$), 2.27 (3H, s, Ar-$CH_3$), 2.22 (6H, s, 2 × Ar-$CH_3$), 2.09 (6H, br s, 2 × Ar-CH_3), 1.53 (3H, d, *J* = 6.9 Hz, C3H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 209.6 (C=O), 150.7 (S-C), 140.2 (Ar-C), 135.5 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.4 (2C, 2 × Ar-C), 126.6 (thiophene SCH*C*H), 123.2 (SC*C*H), 122.8 (SCH), 54.7 (C1H_2), 29.9 (C2H), 23.2 (C3H_3), 16.9 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 323.1440; $C_{19}H_{24}ONaS$ requires 323.1440, Δ –0.08 ppm.

1-(2,3,4,5,6-Pentamethylphenyl)-3-phenylbutan-1-one, 368



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), sec-phenethyl alcohol (110 mg,

0.900 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Following completion of the reaction, the mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. The residue was dissolved in THF (2.3 mL), MeOH (0.75 mL) and $NaBH_4$ (45 mg, 1.2 mmol) added portion-wise over 5 min. The reaction mixture was stirred for 20 h, after which it was poured into a separating funnel consisting of sat. aq. NH_4Cl (5 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer further extracted with Et_2O (2 × 10 mL). The combined organics were washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (163 mg, 92% over 2 steps) as a white solid. [Note: small quantities of 1,3-diphenylbutan-1-one were observed during the reaction. This was found to co-run with the desired product, and so the crude mixture was treated with sodium borohydride to facilitate straightforward purification.]

R_f = 0.30 (Pentane:Et2O, 95:5), [UV, KMnO4].

m.p. = 70–71 °C.

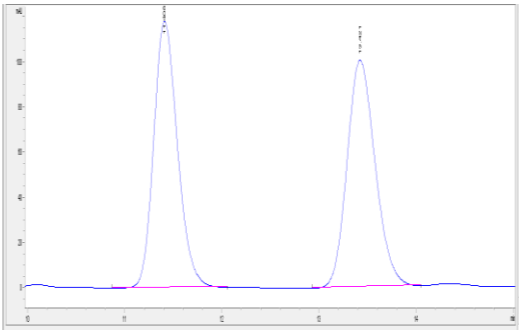
IR (film) ν_{max}/cm^{-1} 3062, 3027, 3004, 2985, 2963, 2924, 2879, 1692, 1604, 1582, 1576, 1496, 1451, 1403, 1391, 1379, 1363, 1339, 1316, 1272, 1229, 1119, 1082, 1065, 1017, 994.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.14 (4H, m, Ph), 7.13–7.08 (1H, m, Ph), 3.52–3.42 (1H, m, C2H), 2.94 (1H, dd, *J* = 18.9, 5.8 Hz, C1H_AH$_B$), 2.86 (1H, dd, *J* = 18.9, 7.7 Hz, C1H$_A$$H_B$), 2.13 (3H, s, Ar-$CH_3$), 2.07 (6H, s, 2 × Ar-$CH_3$), 2.01–1.78 (6H, br. s, 2 × Ar-CH_3), 1.30 (3H, d, *J* = 6.9 Hz, C3H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.3 (C=O), 146.8 (Ar-C), 140.5 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.6 (2C, 2 × Ar-CH), 127.4 (2C, 2 × Ar-C), 127.2 (2C, 2 × Ar-CH), 126.3 (Ar-CH), 53.9 (C1H_2), 34.3 (C2H), 22.5 (C3H_3), 17.0 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

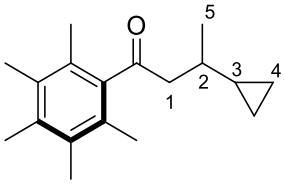
HRMS (ESI^+) Found $[M+H]^+$ = 295.2056; $C_{21}H_{27}O$ requires 295.2056, Δ –0.26 ppm.

Chiral HPLC (Chiralpak IC with guard, 1% IPA, 99% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection):



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.408	BB	2017	118.3	0.2629	49.852	0.8
2	13.421	BB	2029	100.6	0.3112	50.148	0.823

3-Cyclopropyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 372



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), 1-cyclopropylethan-1-ol (103 mg, 1.20 mmol), PhMe (0.15 mL) and NaO*t*Bu (173 mg, 1.80 mmol) were subjected to **general procedure I** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (149 mg, 96%) as a white solid.

R_f = 0.33 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 46–47 °C**.**

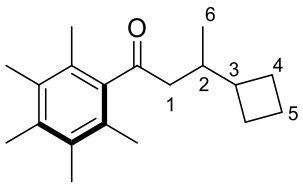
IR (film) ν_{max}/cm^{-1} 2954, 1700, 1457, 1401, 1351, 1313, 1270, 1129, 1016, 934.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.88 (1H, dd, *J* = 19.1, 4.2 Hz, C1H_AH$_B$), 2.65 (1H, dd, J = 19.1, 8.3 Hz, C1H$_A$$H_B$), 2.23 (3H, Ar-$CH_3$), 2.19 (6H, s, 2 × Ar-$CH_3$), 2.12 (6H, s, 2 × Ar-$CH_3$), 1.53–1.43 (1H, m, C2H), 1.13 (3H, d, *J* = 6.7 Hz, C5H_3), 0.68–0.58 (1H, m, C3H), 0.50–0.37 (2H, m, 2 × C4H_AH$_B$), 0.23–0.12 (2H, m, 2 × C4H$_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.3 (C=O), 140.9 (Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.4 (2C, 2 × Ar-C), 53.0 (C1H_2), 33.5 (C2H), 20.1 (C5H_3), 18.2 (C3H), 17.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3), 4.3 (C4$_A$$H_2$), 4.1 (C4$_B$$H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 281.1875; $C_{18}H_{26}ONa$ requires 281.1876, Δ –0.20 ppm.

3-Cyclobutyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 374



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), 1-cyclobutylethan-1-ol (120 mg, 1.20 mmol), PhMe (0.15 mL) and NaO*t*Bu (173 mg, 1.80 mmol) were subjected to **general procedure I** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (145 mg, 89%) as a white solid.

R_f = 0.20 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 65–66 °C

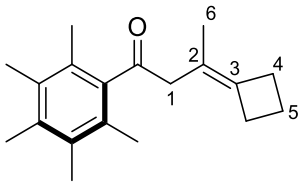
IR (film) ν_{max}/cm^{-1} 2953, 1700, 1457, 1400, 1380, 1351, 1317, 1273, 1129, 1097, 998.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.67 (1H, dd, *J* = 18.9, 2.3 Hz, C1$H_A$$H_B$), 2.36 (1H, dd, *J* = 19.0, 9.3 Hz, C1$H_A$$H_B$), 2.24 (3H, Ar-$CH_3$), 2.20 (6H, s, 2 × Ar-$CH_3$), 2.15–2.11 (2H, m, C2H and C3H), 2.12 (6H, m, 2 × Ar-CH_3), 2.11–1.93 (3H, m, C5$H_A$$H_B$ and 2 × C4$H_A$$H_B$), 1.89–1.60 (3H, m, C5$H_A$$H_B$ and 2 × C4$H_A$$H_B$), 0.99 (3H, d, *J* = 6.1 Hz, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.7 (C=O), 140.9 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.3 (2C, 2 × Ar-C), 49.8 (C1H_2), 41.7 (C3H), 34.7 (C2H), 26.8 (C4$_A$$H_2$), 26.7 (C4$_B$$H_2$), 17.4 (C6$H_3$), 17.1 (3C, 2 × Ar-$CH_3$ and C5H_2) , 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 295.2032; $C_{19}H_{28}ONa$ requires 295.2032, Δ –0.07 ppm.

3-Cyclobutylidene-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 375



In the preparation of *ketone* **374** under **general procedure I**, the title compound (13 mg, 8%) was isolated as a white solid.

R_f = 0.15 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 77–79 °C.

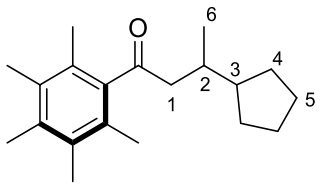
IR (film) ν_{max}/cm^{-1} 2915, 1703, 1444, 1402, 1323, 1264, 1111, 1067, 1021, 995.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.26 (2H, br s, C1H_2), 2.69 (2H, br s, 2 × C4$H_A$$H_B$), 2.51 (2H, br s, 2 × C4$H_A$$H_B$), 2.23 (3H, s, Ar-$CH_3$), 2.18 (6H, s, 2 × Ar-$CH_3$), 2.12 (6H, s, 2 × Ar-$CH_3$), 1.89 (2H, quint., *J* = 7.9 Hz, C5H_2), 1.64 (3H, quint., *J* = 1.8 Hz, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 209.6 (C=O), 140.8 (Ar-C), 138.2 (C3), 135.4 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.5 (2C, 2 × Ar-C), 118.9 (C2), 49.3 (C1H_2), 29.4 (C4$_A$$H_2$), 29.2 (C4$_B$$H_2$), 17.3 (2C, 2 × Ar-$CH_3$), 17.1 (C6$H_3$), 16.8 (Ar-$CH_3$), 16.1 (2C, 2 × Ar-$CH_3$), 15.8 (C5$H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 293.1876; $C_{19}H_{26}ONa$ requires 293.1876, Δ 0.12 ppm.

3-Cyclopentyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 377



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), 1-cyclopentylethan-1-ol (137 mg, 1.20 mmol), PhMe (0.15 mL) and NaO*t*Bu (173 mg, 1.80 mmol) were subjected to **general procedure I** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 99:1) provided the title compound (116 mg, 67%) as a white solid.

R_f = 0.29 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 59–60 °C.

IR (film) ν_{max}/cm^{-1} 2947, 2868, 2360, 1702, 1451, 1402, 1373, 1351, 1308, 1100, 999.

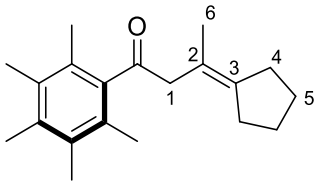
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.82 (1H, dd, *J* = 19.1, 2.8 Hz, C1$H_A$$H_B$), 2.53 (1H, dd, *J* = 19.1, 9.6 Hz, C1$H_A$$H_B$), 2.25 (3H, s, Ar-$CH_3$), 2.20 (6H, s, 2 × Ar-$CH_3$), 2.13 (6H, s, 2 × Ar-$CH_3$), 2.11–2.07 (1H, m, C2H), 1.80–1.65 (3H, m, C4$H_A$$H_B$, C4$H_{A'}$$H_{B'}$ and C3H), 1.65–1.56 (2H, m, C5$H_A$$H_B$ and C5$H_{A'}$$H_{B'}$), 1.56–1.49 (2H, m, C5$H_A$$H_B$ and C5$H_{A'}$$H_{B'}$), 1.24–1.11 (2H, m, C4$H_A$$H_B$ and C4$H_{A'}$$H_{B'}$), 1.08 (3H, d, *J* = 6.6 Hz,

$C6H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.6 (C=O), 141.0 (Ar-C), 135.3 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.3 (2C, 2 × Ar-C), 51.8 ($C1H_2$), 45.8 (C3H), 33.0 (C2H), 30.6 ($C4_AH_2$), 30.2 ($C4_BH_2$), 25.7 ($C5_AH_2$), 25.6 ($C5_BH_2$), 18.9 ($C6H_3$), 17.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 287.2369; $C_{20}H_{31}O$ requires 287.2369, Δ –0.12 ppm.

3-Cyclopentylidene-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 378



In the preparation of *ketone* **377** under **general procedure I**, the title compound (22 mg, 13%) was isolated as a white solid.

***R*$_f$** = 0.22 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 70–71 °C.

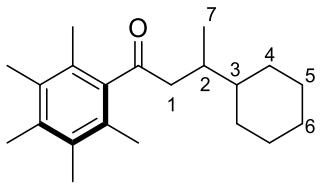
IR (film) ν_{max}/cm^{-1} 2955, 2360, 2341, 1702, 1449, 1322, 1259, 1015, 912.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.42 (2H, br s, $C1H_2$), 2.30–2.24 (2H, m, $C4H_AH_B$ and $C4H_{A'}H_{B'}$), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, m, 2 × Ar-CH_3), 2.14–2.08 (2H, m, $C4H_AH_B$ and $C4H_{A'}H_{B'}$), 2.12 (6H, s, 2 × Ar-CH_3) 1.74 (3H, quint., *J* = 1.7 Hz, $C6H_3$), 1.71–1.56 (4H, m, $C5H_AH_B$ and $C5H_{A'}H_{B'}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 209.4 (C=O), 142.0 (C3), 140.8 (Ar-C), 135.4 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.5 (2C, 2 × Ar-C), 117.8 (C2), 52.6 ($C1H_2$), 31.1 ($C4_AH_2$), 30.9 ($C4_BH_2$), 27.0 ($C5_AH_2$), 26.9 ($C5_BH_2$), 20.2 ($C6H_3$), 17.3 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 307.2033; $C_{20}H_{28}ONa$ requires 307.2032, Δ 0.13 ppm.

3-Cyclohexyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 380



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), 1-cyclohexylethan-1-ol (154 mg, 1.20 mmol), PhMe (0.15 mL) and NaO*t*Bu (173 mg, 1.8 mmol) were subjected to **general procedure I** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 99:1→95:5) provided the title compound (151 mg, 84%) as a white solid.

R_f = 0.26 (Pentane:Et_2O, 98:2), [UV, $KMnO_4$].

m.p. = 71–72 °C.

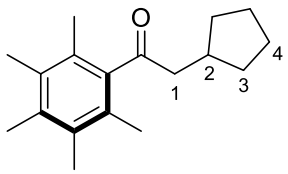
IR (film) ν_{max}/cm^{-1} 2922, 2851, 1702, 1448, 1402, 1379, 1352, 1311, 1276, 1111, 1070, 994.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.77 (1H, dd, *J* = 19.0, 3.5 Hz, C1H_AH$_B$), 2.50 (1H, dd, *J* = 19.0, 9.2 Hz, C1H$_A$$H_B$), 2.25 (3H, s, Ar-$CH_3$), 2.20 (6H, 2 × Ar-$CH_3$), 2.18–2.14 (1H, m, C2H), 2.12 (6H, 2 × Ar-CH_3), 1.80–1.57 (5H, m, C5H_AH$_B$, C5$H_{A'}$H$_{B'}$, C6H_AH$_B$, C4H_AH$_B$ and C4$H_{A'}$H$_{B'}$), 1.35–1.09 (4H, m, C3H, C5H$_A$$H_B$, C5H$_{A'}$$H_{B'}$ and C6H$_A$$H_B$), 1.08–0.93 (2H, m, C4H$_A$$H_B$ and C4H$_{A'}$$H_{B'}$), 1.02 (3H, d, *J* = 6.8 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.7 (C=O), 141.0 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.3 (2C, 2 × Ar-C), 50.3 (C1H_2), 42.8 (C3H), 32.7 (C2H), 30.3 (C4$_A$$H_2$), 29.1 (C4$_B$$H_2$), 26.9 (C5$_A$$H_2$), 26.8 (C5$_B$$H_2$), 26.7 (C6$H_2$), 17.1 (2C, 2 × Ar-$CH_3$), 16.9 (Ar-$CH_3$), 16.8 (C7$H_3$), 16.0 (2C, 2 × Ar-$CH_3$).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 323.2344; $C_{21}H_{32}ONa$ requires 323.2345, Δ –0.31 ppm.

2-Cyclopentyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 385



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), cyclopentanol (103 mg, 1.20 mmol), PhMe (0.15 mL) and KO*t*Bu (202 mg, 1.80 mmol) were subjected to **general**

procedure J at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (127 mg, 82%) as a white solid.

R_f = 0.55 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]

m.p. = 51–52 °C.

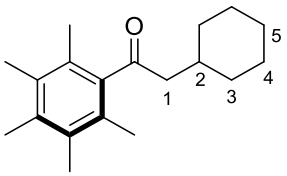
IR (film) ν_{max}/cm^{-1} 2947, 2868, 1732, 1701, 1451, 1400, 1333, 1303, 1112, 931.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.73 (2H, d, J = 6.8 Hz, C1H_2), 2.54–2.31 (1H, m, C2H), 2.23 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 1.99–1.91 (2H, m, 2 × C3$H_A$$H_B$), 1.70–1.54 (4H, m, 2 × C4$H_A$$H_B$), 1.24–1.09 (2H, m, 2 × C3$H_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.9 (C=O), 140.9 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.4 (2C, 2 × Ar-C), 52.1 (C1H_2), 34.7 (C2H), 32.9 (2C, 2 × C3H_2), 25.1 (2C, 2 × C4H_2), 17.2 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 259.2063; $C_{18}H_{27}O$ requires 259.2056, Δ –2.53 ppm.

2-Cyclohexyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 387



Ketone **329** (114 mg, 0.600 mmol), [Cp*$IrCl_2$]$_2$ (9.6 mg, 2.0 mol%), cyclohexanol (120 mg, 1.20 mmol), PhMe (0.15 mL) and KO*t*Bu (202 mg, 1.80 mmol) were subjected to **general procedure J** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (141 mg, 86%) as a white solid.

R_f = 0.40 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]

m.p. = 109–111 °C.

IR (film) ν_{max}/cm^{-1} 2918, 2848, 1696, 1447, 1401, 1378, 1354, 1303, 1284, 1133, 1111, 1089, 1002, 929.

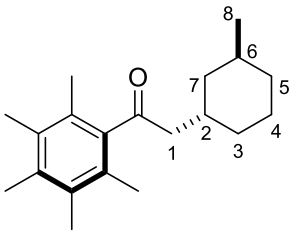
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.59 (2H, d, J = 4.0 Hz, C1H_2), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, 2 × Ar-

CH_3), 2.12 (6H, 2 × Ar-CH_3), 2.10–2.01 (1H, m, C2H), 1.92–1.84 (2H, m, 2 × C3H_AH_B), 1.77–1.65 (3H, m, 2 x C4H_AH_B and C5H_AH_B), 1.43–1.31 (2H, m, 2 × C4H_AH_B), 1.25–1.12 (1H, m, C5H_AH_B), 1.00 (2H, dq, *J* = 12.0, 4.0 Hz, 2 × C3H_AH_B).

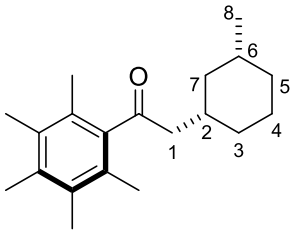
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.2 (C=O), 140.9 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.4 (2C, 2 × Ar-C), 53.3 (C1H_2), 33.4 (2C, 2 × C3H_2), 32.4 (C2H), 26.5 (C5H_2), 26.2 (2C, 2 × C4H_2), 17.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 273.2213; $C_{19}H_{29}O$ requires 273.2213, Δ –0.15 ppm.

***rac*-2-((1*S*,3*S*)-3-Methylcyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 391a and *rac*-2-((1*S*,3*R*)-3-Methylcyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 391b**



391a (major)



391b (minor)

Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), *cis*-3-methylhexan-1-ol (137 mg, 1.20 mmol), PhMe (0.15 mL) and KO*t*Bu (202 mg, 1.80 mmol) were subjected to **general procedure J** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 96:4) provided the diastereoisomeric ketones **391a** and **391b** (150 mg, 87%, 90:10 d.r.) as an inseparable mixture of white solids. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 2.70 (2H, ddd, *J* = 6.3, 1.9, 1.2 Hz, C1H_2, **391a**), 2.60 (2H, dt, *J* = 6.4, 1.3 Hz, C1H_2, **391b**). The relative stereochemistry was assigned using a 2D-NOESY experiment.

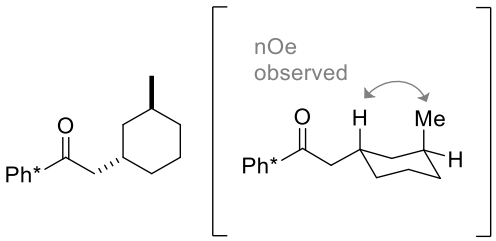
Data for **391a**/**391b** (90:10 d.r.):

R_f = 0.40 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2919, 1700, 1456, 1399, 1307, 1261, 1108, 1023, 927.

HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2369; $C_{20}H_{31}O$ requires 287.2369, Δ –0.12 ppm.

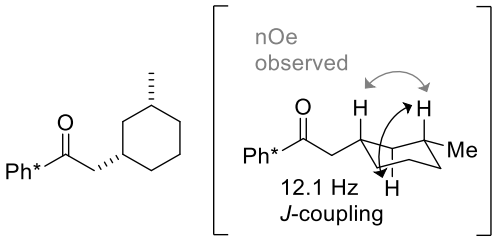
NMR data for **391a:**



^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.70 (2H, ddd, J = 6.3, 1.9, 1.2 Hz, C1H_2), 2.55–2.47 (1H, m, C2H), 2.26 (3H, s, Ar-CH_3), 2.21 (6H, s, 2 × Ar-CH_3), 2.14 (6H, s, 2 × Ar-CH_3), 1.77–1.66 (2H, m, C6H and C3H_AH$_B$), 1.64-1.55 (2H, m, C5H_AH$_B$ and C4H_AH$_B$), 1.53–1.32 (4H, m, C7H$_A$H$_B$, C4H$_A$$H_B$ and C3H$_A$$H_B$), 1.15 (1H, q, J = 8.6 Hz, C5H$_A$$H_B$), 0.97 (3H, d, J = 6.8 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 126 MHz) δ = 211.2 (C=O), 141.0 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.3 (2C, 2 × Ar-C), 50.6 (C1H_2), 39.3 (C7H_2), 33.9 (C5H_2), 31.7 (C3H_2), 27.6 (C6H), 27.4 (C2H), 21.1 (C4H_2), 21.0 (C8H_3), 17.1 (2C, 2 × Ar-CH_3), 16.7 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

NMR data for **391b**:

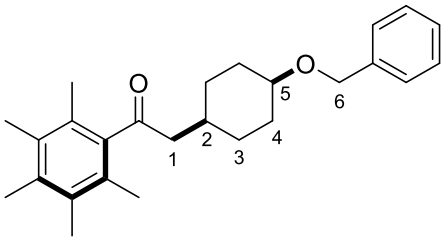


^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.60 (2H, dt, J = 6.4, 1.3 Hz, C1H_2), 2.26 (3H, s, Ar-CH_3), 2.21 (6H, s, 2 × Ar-CH_3), 2.14 (6H, s, 2 × Ar-CH_3), 2.13–2.07 (1H, m, C2H), 1.93–1.85 (2H, m, C3H_AH$_B$ and C7H_AH$_B$), 1.80–1.76 (1H, m, C4H_AH$_B$), 1.77–1.66 (1H, m, C5H_AH$_B$) 1.53–1.46 (1H, m, C6H), 1.45–1.33 (1H, m, C4H$_A$$H_B$), 0.92 (3H, d, J = 6.8 Hz, C8H_3), 0.91–0.88 (1H, m, C3H$_A$$H_B$), 0.87–0.83 (1H, m, C5H$_A$$H_B$), 0.66 (1H, q, J = 12.1 Hz, C7H$_A$$H_B$).

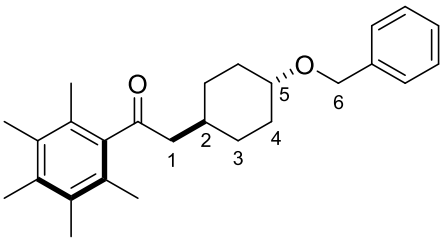
^{13}C NMR ($CDCl_3$, 126 MHz) δ = 211.1 (C=O), 140.9 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.3

(2C, 2 × Ar-C), 53.4 ($C1H_2$), 42.2 ($C7H_2$), 35.1 ($C5H_2$), 33.1 ($C3H_2$), 32.7 (C6H), 32.6 (C2H), 23.0 ($C8H_3$), 26.2 ($C4H_2$), 17.1 (2C, 2 × Ar-CH_3), 16.7 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

***rac*-2-((1*s*,4*s*)-4-(Benzyloxy)cyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 399a and *rac*-2-((1*s*,4*s*)-4-(Benzyloxy)cyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one, 399b**



399a (major)



399b (minor)

Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 0.0012 mmol), 4-(benzyloxy)cyclohexan-1-ol* (248 mg, 1.20 mmol), PhMe (0.15 mL) and KO*t*Bu (202 mg, 1.80 mmol) were subjected to **general procedure J** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 95:5→90:10) provided the separable diastereoisomeric ketones **399a** (117 mg, 52%) and **399b** (66 mg 29%) as colourless solids with d.r. 70:30. The d.r. was determined by ^1H NMR analysis of the crude mixture by comparison of the following signals: δ 4.41 (2H, s, $C6H_2$, **399a**) and 4.48 (2H, s, $C6H_2$, **399b**). The structure and relative stereochemistry of **399a** were confirmed by X-ray crystallographic analysis after crystallization from HPLC grade Et_2O.

Data for **399a**:

R_f = 0.25 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]

m.p. = 86–87 °C.

IR (film) ν_{max}/cm^{-1} 2924, 2858, 1700, 1496, 1454, 1398, 1330, 1303, 1281, 1123, 1091, 1066, 1028, 957.

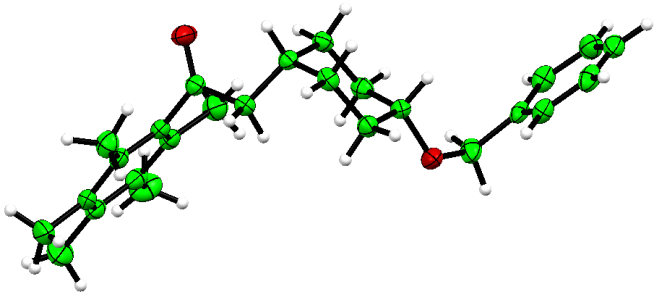
^1H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.13 (5H, m, Ph), 4.41 (2H, s, $C6H_2$), 3.57–3.51 (1H, m, C5H),

*Synthesised by Dr James Frost.

2.54 (2H, d, *J* = 6.5 Hz, C1H$_2$), 2.13 (3H, s, Ar-CH$_3$), 2.12 (6H, s, 2 × Ar-CH$_3$) 2.11–2.05 (1H, m, C2H), 2.01 (6H, s, 2 × Ar-CH$_3$), 1.86–1.77 (2H, m, 2 × C4H_AH$_B$), 1.61–1.53 (2H, m, 2 × C3H_AH$_B$), 1.53–1.44 (2H, m, 2 × C4H$_A$$H_B$), 1.43–1.35 (2H, m, 2 × C3H$_A$$H_B$).

^{13}C NMR (CDCl$_3$, 101 MHz) δ = 211.1 (C=O), 140.8 (Ar-C), 139.3 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.4 (2C, 2 × Ar-C), 128.4 (2C, 2 × Ar-CH), 127.4 (2C, 2 × Ar-CH), 127.3 (Ar-CH), 73.3 (C5H), 69.7 (C6H$_2$), 52.3 (C1H$_2$), 31.3 (C2H), 29.4 (2C, 2 × C4H$_2$), 27.5 (2C, 2 × C3H$_2$), 17.1 (2C, 2 × Ar-CH$_3$), 16.7 (Ar-CH$_3$), 16.0 (2C, 2 × Ar-CH$_3$).

HRMS (ESI$^+$) Found [M+Na]$^+$ = 401.2451; C$_{26}$H$_{34}$O$_2$Na requires 401.2451, Δ –0.11 ppm.



Cambridge Crystallography Data Centre (CCDC) Identifier: 1521310

Data for **399b**:

***R*$_f$** = 0.14 (Pentane:Et$_2$O, 95:5), [UV, KMnO$_4$].

m.p. = 116–117 °C.

IR (film) ν_{max}/cm^{-1} 2927, 2858, 1698, 1653, 1559, 1541, 1521, 1507, 1497, 1455, 1398, 1102, 1071, 1029, 957.

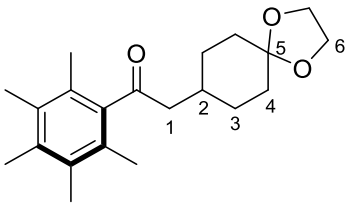
^{1}H NMR (CDCl$_3$, 400 MHz) δ = 7.29–7.14 (5H, m, Ph), 4.48 (2H, s, C6H$_2$), 3.26–3.17 (1H, m, C5H), 2.47 (2H, d, *J* = 6.2 Hz, C1H$_2$), 2.13 (3H, s, Ar-CH$_3$), 2.08 (6H, m, 2 × Ar-CH$_3$), 2.07–1.98 (2H, m, 2 × C4H_AH$_B$), 2.05 (6H, s, 2 × Ar-CH$_3$), 1.97–1.92 (1H, m, C2H), 1.91–1.83 (2H, m, 2 × C3H_AH$_B$), 1.39–1.26 (2H, m, 2 × C4H$_A$$H_B$), 0.99–0.86 (2H, m, 2 × C3H$_A$$H_B$).

^{13}C NMR (CDCl$_3$, 101 MHz) δ = 211.0 (C=O), 140.7 (Ar-C), 139.2 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 ×

Ar-C), 128.5 (2C, 2 × Ar-C), 127.7 (2C, 2 × Ar-CH), 127.5 (2C, 2 × Ar-CH), 127.4 (Ar-CH), 77.4 (C5H), 70.0 ($C6H_2$), 52.5 ($C1H_2$), 32.2 (2C, 2 × $C4H_2$), 32.0 (C2H), 31.4 (2C, 2 × $C3H_2$), 17.2 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 401.2449; $C_{26}H_{34}O_2Na$ requires 401.2451, Δ –0.49 ppm.

1-(2,3,4,5,6-Pentamethylphenyl)-2-(1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-one, 405



Ketone **329** (114 mg, 0.600 mmol), $[Cp^*IrCl_2]_2$ (2.4 mg, 0.50 mol%), 1,4-dioxaspiro[4.5]decan-8-ol (142 mg, 0.900 mmol), PhMe (0.15 mL) and NaO*t*Bu (115 mg, 1.20 mmol) were subjected to **general procedure H** at 85 °C. Purification by column chromatography (Pentane:Et_2O, 70:30) provided the title compound (196 mg, 99%) as a white solid.

R_f = 0.30 (Pentane:Et_2O, 70:30), [UV, $KMnO_4$]

m.p. = 145–146 °C.

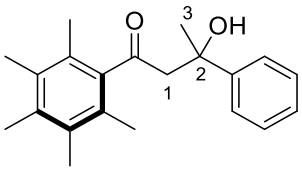
IR (film) ν_{max}/cm^{-1} 2942, 2873, 1696, 1444, 1402, 1378, 1336, 1310, 1285, 1194, 1172, 1141, 1104, 1078, 1030, 1005, 974.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.04–3.85 (4H, m, 2 × $C6H_2$), 2.62 (2H, d, J = 6.5 Hz, $C1H_2$), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.16–2.10 (1H, m, C2H), 2.09 (6H, s, 2 × Ar-CH_3), 1.96–1.85 (2H, m, 2 × C3$H_A$$H_B$), 1.80–1.73 (2H, m, 2 × C4$H_A$$H_B$), 1.65 (2H, td, J = 13.2, 4.2 Hz, 2 × C4$H_A$$H_B$), 1.32 (2H, qd, J = 11.5, 3.9 Hz, 2 × C3$H_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 210.9 (C=O), 140.6 (Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.3 (2C, 2 × Ar-C), 108.9 (C5), 64.3 (2C, 2 × $C6H_2$), 52.0 ($C1H_2$), 34.5 (2C, 2 × $C4H_2$), 31.1 (C2H), 30.2 (2C, 2 × $C3H_2$), 17.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 331.2265; $C_{21}H_{31}O_3$ requires 331.2268, Δ –0.91 ppm.

3-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)-3-phenylbutan-1-one, 441[103]



To a stirred solution of EtMgBr (10.5 mL, 31.6 mmol, 3.00 M in Et_2O) in a 2-neck round bottom flask fitted with a reflux condenser was added a solution of *ketone* **329** (5.00 g, 26.3 mmol) in Et_2O (25 mL) dropwise over 90 mins. The mixture was heated to 40 °C for 30 mins, after which a solution of acetophenone (3.5 mL, 30.0 mmol) in Et_2O (5 mL) was added dropwise. The resulting mixture was maintained at 40 °C for 16 h. The reaction was cooled to RT, diluted with Et_2O (50 mL) and poured onto an ice/12 M HCl mixture (10 mL). The layers were separated, and the aqueous layer extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography provided the title compound (6.59 g, 81%) as a white solid.

R_f = 0.36 (Pentane:Et_2O, 80:20), [UV, $KMnO_4$].

m.p. = 94–96 °C**.**

IR (film) ν_{max}/cm^{-1} 3495, 3058, 2978, 2930, 2361, 2341, 1688, 1602, 1576, 1494, 1447, 1385, 1330, 1294, 1261, 1183, 1113, 1069, 1028, 1000, 951.

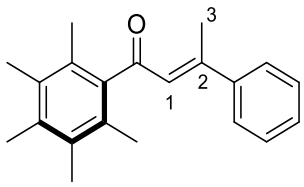
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.51–7.46 (2H, m, Ph), 7.36–7.30 (2H, m, Ph), 7.25–7.19 (1H, m, Ph), 3.34 (1H, d, *J* = 18.9 Hz, C1H_AH$_B$), 3.17 (1H, d, *J* = 18.9 Hz, C1H$_A$$H_B$), 2.20 (3H, s, Ar-$CH_3$), 2.13 (6H, s, 2 × Ar-$CH_3$), 1.96 (6H, br s, 2 × Ar-CH_3), 1.62 (3H, s, C3H_3).*

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.5 (C=O), 147.4 (Ar-C), 139.5 (Ar-C), 136.0 (Ar-C), 133.3 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-CH), 127.4 (2C, 2 × Ar-C), 126.8 (Ar-CH), 124.6 (2C, 2 × Ar-CH), 73.4 (C2), 56.4 (C1H_2), 30.7 (C3H_3), 16.9 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 333.1824; $C_{21}H_{26}O_2Na$ requires 333.1825, Δ –0.26 ppm.

* O*H* not observed

(*E*)-1-(2,3,4,5,6-Pentamethylphenyl)-3-phenylbut-2-en-1-one, 442



To a solution of *ketone* **441** (6.59 g, 21.2 mmol) in Et_2O (30 mL) was added conc. HCl (37%, 20 mL). The resulting solution was heated to 40 °C and stirred for 24 h. After this time, the reaction mixture was cooled to RT and the layers separated. The aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide the title compound (5.78 g, 93%) as a yellow solid. [The double bond geometry was assigned using a 2D-NOESY experiment. Key nOe correlations are depicted below]

R_f = 0.16 (Heptane:EtOAc, 98:2), [UV, $KMnO_4$].

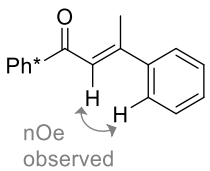
m.p. = 87–89 °C.

IR (film) ν_{max}/cm^{-1} 2921, 2361, 1664, 1631, 1590, 1572, 1493, 1445, 1377, 1348, 1303, 1272, 1189, 1127, 1072, 1026, 926.

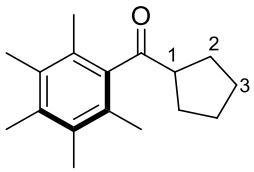
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.58–7.52 (2H, m, Ph), 7.42–7.36 (3H, m, Ph), 6.75 (1H, s, C1H), 2.65 (3H, s, $C3H_3$), 2.29 (3H, s, Ar-CH_3), 2.24 (6H, s, 2 × Ar-CH_3), 2.22 (6H, s, 2 × Ar-CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.7 (C=O), 154.3 (C2), 142.4 (Ar-C), 141.7 (Ar-C), 135.4 (Ar-C), 133.1 (2C, 2 × Ar-C), 129.4 (Ar-CH), 128.6 (2C, 2 × Ar-CH), 128.1 (2C, 2 × Ar-C), 126.7 (2C, 2 × Ar-CH), 126.6 (C1H), 18.3 ($C3H_3$), 17.2 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 315.1718; $C_{21}H_{24}ONa$ requires 315.1719, Δ –0.54 ppm.



Cyclopentyl(2,3,4,5,6-pentamethylphenyl)methanone, 472



Ketone **329** (114 mg, 0.600 mmol), 1,4-butanediol (60 mg, 0.66 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (101 mg, 1.80 mmol) were subjected to a modified **general procedure M** at 105 °C**.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (75 mg, 65%) as a white solid.

R_f = 0.24 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 73–74 °C

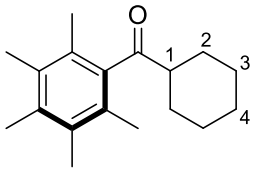
IR (film) ν_{max}/cm^{-1} 2960, 2870, 1688, 1448, 1354, 1308, 1264, 1121, 1067, 1019, 738.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.19 (1H, quint., *J* = 8.1 Hz, C1H), 2.25 (3H, s, Ar-CH_3), 2.20 (6H, 2 × Ar-CH_3), 2.13 (6H, 2 × Ar-CH_3), 1.98–1.83 (4H, m, 2 × C2H_AH_B), 1.83–1.71 (2H, m, 2 × C3$H_A$$H_B$), 1.68–1.55 (2H, m, 2 × C3$H_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.2 (C=O), 141.3 (Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 54.5 (C1H), 29.8 (2C, 2 × $C2H_2$), 26.0 (2C, 2 × $C3H_2$), 17.9 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 245.1900; $C_{17}H_{25}O$ requires 245.1900, Δ –0.12 ppm.

Cyclohexyl(2,3,4,5,6-pentamethylphenyl)methanone, 474



Ketone **329** (114 mg, 0.600 mmol), 1,5-pentanediol (125 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (100 mg, 64%) as a white solid.

***R*$_f$** = 0.26 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 113–114 °C

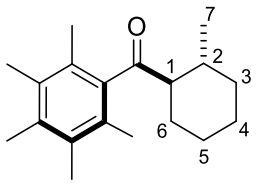
IR (film) ν_{max}/cm^{-1} 2928, 2851, 2360, 1685, 1447, 1383, 1315, 1262, 1181, 1147, 1111, 1019, 990.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.62 (1H, tt, *J* = 11.9, 3.4 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.98–1.90 (2H, m, 2 × C2$H_A$$H_B$), 1.87–1.77 (2H, m, 2 × C3$H_A$$H_B$), 1.72–1.65 (1H, m, C4$H_A$$H_B$), 1.50–1.34 (2H, m, 2 × C2$H_A$$H_B$), 1.30–1.17 (3H, m, 2 × C3$H_A$$H_B$ and C4$H_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.2 (C=O), 140.3 (Ar-C), 135.5 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 53.3 (C1H), 28.4 (2C, 2 × C2H_2), 26.1 (3C, 2 × C3H_2 and C4H_2), 18.0 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 259.2055; $C_{18}H_{27}O$ requires 259.2056, Δ –0.52 ppm.

***rac*-(1*R*,2*R*)-2-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 476**



Ketone **329** (114 mg, 0.600 mmol), hexane-1,5-diol (142 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (130 mg, 80%, > 95:5 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.45 (1H, td, *J* = 10.7, 3.3 Hz, C1H, major diastereoisomer), 2.77 (1H, dt, *J* = 12.9, 3.6 Hz, C1H, minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from HPLC grade MeOH.

***R*$_f$** = 0.20 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

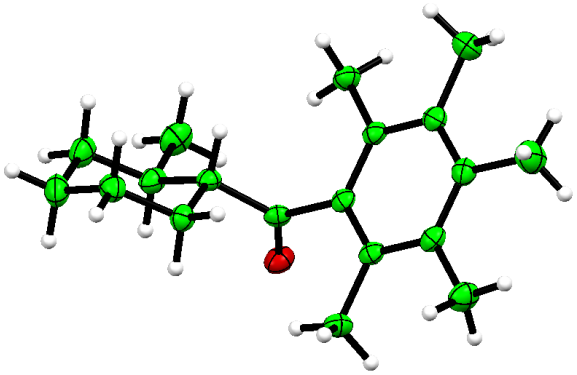
m.p. = 129–130 °C

IR (film) ν_{max}/cm^{-1} 2956, 2927, 2877, 2849, 1681, 1569, 1449, 1375, 1363, 1313, 1281, 1262, 1162, 1141, 1109, 1019, 1003, 920.

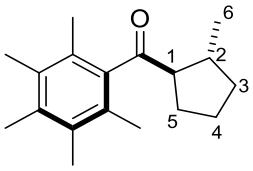
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.45 (1H, td, *J* = 10.7, 3.3 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.13 (6H, s, 2 × Ar-CH_3), 2.02–1.90 (1H, m, C2H), 1.89–1.64 (4H, m, C6$H_{eq}$$H_{ax}$, C3$H_{eq}$$H_{ax}$, C5$H_{eq}$$H_{ax}$ and C4$H_{eq}$$H_{ax}$), 1.33–1.13 (3H, m, C4$H_{eq}$$H_{ax}$, C6$H_{eq}$$H_{ax}$ and C5$H_{eq}$$H_{ax}$), 1.09 (3H, d, *J* = 6.9 Hz, C7H_3), 1.03 (1H, qd, *J* = 12.6, 3.6 Hz, C3$H_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.2 (C=O), 140.9 (Ar-C), 139.8 (Ar-C), 135.6 (2C, 2 × Ar-C), 133.2 (2C, 2 × Ar-C), 59.4 (C1H), 34.8 (C3H_2), 32.6 (C2H), 29.7 (C6H_2), 26.7 (C5H_2), 26.0 (C4H_2), 21.1 (C7H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 273.2213; $C_{19}H_{29}O$ requires 273.2213, Δ 0.17 ppm.



***rac*-((1*R*,2*R*)-2-Methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, 481**



Ketone **329** (114 mg, 0.600 mmol), 3-methylpentane-1,5-diol (125 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (66 mg, 43%, > 95:5 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 1.01 (3H, d, *J* = 6.6 Hz, C6H_3, major diastereoisomer),

1.09 (3H, d, *J* = 6.9 Hz, C6H_3, minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was confirmed in analogy to X-ray crystallographic analysis of (2-ethylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, which was shown to be *trans* by Dr. James Frost.

***R*$_f$** = 0.35 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 55–56 °C**.**

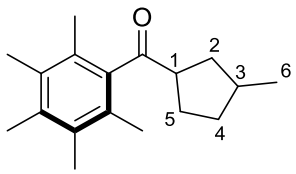
IR (film) ν_{max}/cm^{-1} 2952, 2869, 1689, 1453, 1381, 1306, 1265, 1118, 1000, 835.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.78 (1H, q, *J* = 8.1 Hz, C1H), 2.37 (1H, sept., *J* = 7.5 Hz, C2H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.00–1.82 (3H, m, C3$H_A$$H_B$ and C5$H_A$$H_B$), 1.74–1.58 (2H, m, C4$H_A$$H_B$), 1.32–1.20 (1H, m, C3$H_A$$H_B$), 1.01 (3H, d, *J* = 6.6 Hz, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.6 (C=O), 141.1 (Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 61.8 (C1H), 37.2 (C2H), 35.3 (C3H_2), 30.2 (C5H_2), 24.9 (C4H_2), 20.8 (C6H_3), 18.0 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 259.2056; $C_{18}H_{27}O$ requires 259.2056, Δ –0.08 ppm.

(3-Methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, 483



Ketone **329** (114 mg, 0.600 mmol), 2-methylbutane-1,4-diol* (125 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (77 mg, 50%, 52:48 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 0.98 (3H, d, *J* = 5.6 Hz, C6H_3, diastereoisomer A), 1.06

* Synthesised by Dr James Frost

(3H, d, *J* = 5.5 Hz, C6H_3, diastereoisomer B). The relative stereochemistry of the diastereoisomers could not be distinguished.

Data for diastereoisomer A/B (52:48 d.r.):

R_f = 0.45 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2952, 2868, 1687, 1573, 1448, 1378, 1348, 1300, 1259, 1120, 1067, 1005, 921.

HRMS (ESI^+) Found $[M+H]^+$ = 259.2056; $C_{18}H_{27}O$ requires 259.2056, Δ –0.32 ppm.

NMR data for diastereoisomer A

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.36–3.28 (1H, m, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.18–2.13 (2H, m, C3H and C2$H_A$$H_B$), 2.11 (6H, s, 2 × Ar-$CH_3$), 1.89–1.81 (3H, m, C5$H_A$$H_B$ and C4$H_A$$H_B$), 1.37–1.29 (1H, m, C2$H_A$$H_B$), 1.15–1.04 (1H, m, C4$H_A$$H_B$), 0.98 (3H, d, *J* = 5.6 Hz, C6H_3).

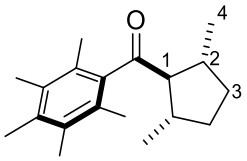
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.0 (C=O), 141.1 (Ar-C), 135.1 (Ar-C), 132.9 (2C, 2 × Ar-C), 127.6 (2C, 2 × Ar-C), 53.1 (C1H), 37.2 (C2H_2), 34.9 (C4H_2), 33.9 (C3H), 29.4 (C5H_2), 20.5 (C6H_3), 17.6 (2C, 2 × Ar-CH_3), 16.5 (Ar-CH_3), 15.8 (2C, 2 × Ar-CH_3).

NMR data for diastereoisomer B

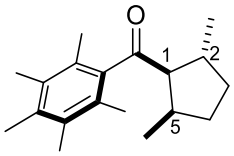
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.27–3.19 (1H, m, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.08–1.96 (3H, m, C5$H_A$$H_B$, C2$H_A$$H_B$ and C3H), 1.89–1.76 (2H, m, C5$H_A$$H_B$ and C4$H_A$$H_B$), 1.51–1.43 (1H, m, C2$H_A$$H_B$), 1.35–1.25 (1H, m, C4$H_A$$H_B$), 1.06 (3H, d, *J* = 5.5 Hz, C6H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.8 (C=O), 140.9 (Ar-C), 135.1 (Ar-C), 132.9 (2C, 2 × Ar-C), 127.5 (2C, 2 × Ar-C), 54.5 (C1H), 38.7 (C2H_2), 35.2 (C3H), 33.8 (C4H_2), 28.4 (C5H_2), 19.9 (C6H_3), 17.6 (2C, 2 × Ar-CH_3), 16.5 (Ar-CH_3), 15.8 (2C, 2 × Ar-CH_3).

***rac*-((1*r*,2*R*,5*S*)-2,5-Dimethylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, 485a and rac-((2*R*,5*R*)-2,5-Dimethylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, 485b**



485a (major)



485b (minor)

Ketone **329** (114 mg, 0.600 mmol), hexane-2,5-diol (142 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compounds (92 mg, 56%, 71:29 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 1.38–1.28 (2H, m, 2 × C3H$_A$*H$_B$*, **485a**), 1.28–1.18 (1H, m, C'H$_A$*H$_B$*, **485b**). A small amount of the **485a** was isolated cleanly by Dr. James Frost to aid characterisation. The relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization of cleanly isolated **485a** from HPLC grade MeOH by Dr. James Frost.

Data for **485a**/**485b** (71:29 d.r.):

***R*$_f$** = 0.51 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2950, 2868, 1686, 1573, 1458, 1379, 1305, 1093, 1000, 828.

HRMS (ESI$^+$) Found $[M+H]^+$ = 273.2212; $C_{19}H_{29}O$ requires 273.2213, Δ –0.49 ppm.

NMR data for **485a**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.49–2.31 (3H, m, C1H and 2 × C2H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 1.90–1.76 (2H, m, 2 × C3*H$_A$*H$_B$), 1.38–1.28 (2H, m, 2 × C3H$_A$*H$_B$*), 0.96 (6H, d, *J* = 5.8 Hz, 2 × C4H$_3$).

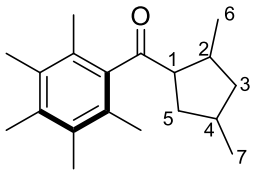
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.0 (C=O), 141.2 (Ar-C), 135.4 (Ar-C), 133.1 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 69.5 (C1H), 37.9 (2C, 2 × C2H) , 34.0 (2C, 2 × C3H_2), 21.6 (2C, 2 × C4H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

NMR data for **485b**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.85 (1H, t, *J* = 7.2 Hz, C1H), 2.49–2.40 (2H, m, C2H and C5H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.09–2.02 (1H, m, CH_AH$_B$), 1.82–1.72 (1H, m, C'H_AH$_B$), 1.57–1.46 (1H, m, CH$_A$$H_B$), 1.28–1.18 (1H, m, C'H$_A$$H_B$), 1.12 (3H, d, *J* = 7.0 Hz, CH_3), 0.96–0.91 (3H, m, C'H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.5 (C=O), 141.4 (Ar-C), 135.6 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.5 (2C, 2 × Ar-C), 65.0 (C1H), 37.7 (C2H *or* C5H), 35.8 (C2H *or* C5H), 33.8 (CH_2), 32.4 (CH_2), 18.1 (2C, 2 × Ar-CH_3), 17.3 (CH_3), 16.9 (Ar-CH_3), 16.5 (CH_3), 16.3 (2C, 2 × Ar-CH_3).

(2,4-Dimethylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, 487



Ketone **329** (114 mg, 0.600 mmol), 2-methylpentane-1,4-diol* (142 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2→95:5) provided the title compound (102 mg, 62%, 84:16 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.44–2.32 (1H, m, C2H, major diastereoisomer), 2.60–2.46 (1H, m, C2H, minor diastereoisomer). The relative stereochemistry of the diastereoisomers could not be determined.

Data for major/minor diastereoisomer (84:16 d.r.):

***R*$_f$** = 0.46 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2951, 2868, 1689, 1574, 1457, 1379, 1341, 1304, 1119, 1000, 934.

HRMS (ESI$^+$) Found $[M+H]^+$ = 273.2213; $C_{19}H_{29}O$ requires 273.2213, Δ 0.16 ppm.

* Synthesised by Dr James Frost

NMR data for major diastereoisomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.93–2.84 (1H, m, C1H), 2.44–2.32 (1H, m, C2H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, m, 2 × Ar-CH_3), 2.16–1.99 (9H, m, 2 × Ar-CH_3, C5H_AH$_B$, C4H and C3H_AH$_B$), 1.49–1.40 (1H, m, C5H$_A$$H_B$), 1.00 (3H, d, *J* = 6.6 Hz, C6H_3), 0.98 (3H, d, *J* = 5.4 Hz, C7H_3), 0.92–0.80 (1H, m, C3H$_A$$H_B$).

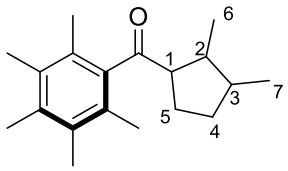
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.6 (C=O), 141.0 (Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 61.0 (C1H), 45.2 (C3H_2), 38.0 (C2H), 37.8 (C5H_2), 33.9 (C4H), 20.8 (C7H_3), 20.7 (C6H_3), 18.0 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

NMR data for minor diastereoisomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.86–2.78 (1H, m, C1H), 2.60–2.46 (1H, m, C2H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, m, 2 × Ar-CH_3), 2.16–1.99 (9H, m, 2 × Ar-CH_3, C5H_AH$_B$, C4H and C3H_AH$_B$), 1.61–1.49 (1H, m, C3H$_A$$H_B$), 1.40–1.31 (1H, m, C5H$_A$$H_B$), 0.96–0.85 (6H, m, C6$H_3$ and C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.6 (C=O), 141.0 (Ar-C), 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 62.9 (C1H), 42.9 (C3H_2), 39.8 (C5H_2), 35.7 (C2H), 33.3 (C4H), 21.6 (C7H_3), 20.5 (C6H_3), 18.0 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

(2,3-Dimethylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone, 489



Ketone **329** (114 mg, 0.600 mmol), 3-methylpentane-1,4-diol* (142 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2→95:5) provided the title compound (76 mg, 46%, 77:23 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 0.91–0.84 (6H, m, C6H_3 and C7H_3, major

* Synthesised by Dr James Frost

diastereoisomer), 1.01 (3H, d, *J* = 7.0 Hz, C7H$_3$, minor diastereoisomer). The relative stereochemistry of the diastereoisomers could not be determined.

Data for major/minor diastereoisomer (77:23 d.r.):

***R*$_f$** = 0.44 (Pentane:Et$_2$O, 95:5), [UV, KMnO$_4$].

IR (film) ν_{max}/cm^{-1} 2957, 2871, 1686, 1456, 1379, 1124, 1067, 1021.

HRMS (ESI$^+$) Found [M+H]$^+$ = 273.2212; C$_{19}$H$_{29}$O requires 273.2213, Δ –0.39 ppm.

NMR data for major diastereoisomer:

^{1}H NMR (CDCl$_3$, 400 MHz) δ = 2.95–2.86 (1H, m, C1H), 2.42–2.31 (1H, m, C2H), 2.24 (3H, s, Ar-CH$_3$), 2.18 (6H, s, 2 × Ar-CH$_3$), 2.16–2.09 (1H, m, C3H), 2.12 (6H, s, 2 × Ar-CH$_3$), 1.97–1.77 (3H, m, C5H$_A$H$_B$ and C4*H$_A$*H$_B$), 1.38–1.25 (1H, m, C4H$_A$*H$_B$*), 0.91–0.84 (6H, m, C6H$_3$ and C7H$_3$).

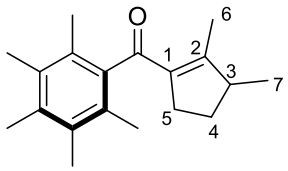
^{13}C NMR (CDCl$_3$, 101 MHz) δ = 214.9 (C=O), 141.2 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 60.7 (C1H), 39.8 (C2H), 37.7 (C3H), 33.1 (C4H$_2$), 27.9 (C5H$_2$), 18.1 (2C, 2 × Ar-CH$_3$), 16.9 (Ar-CH$_3$), 16.2 (2C, 2 × Ar-CH$_3$), 15.9 (CH$_3$), 15.3 (CH$_3$).

NMR data for minor diastereoisomer:

^{1}H NMR (CDCl$_3$, 400 MHz) δ = 2.89–2.82 (1H, m, C1H), 2.24 (3H, s, Ar-CH$_3$), 2.18 (6H, s, 2 × Ar-CH$_3$), 2.12 (6H, s, 2 × Ar-CH$_3$), 2.05–1.96 (1H, m, C5*H$_A$*H$_B$), 1.83–1.72 (3H, m, C4*H$_A$*H$_B$, C5H$_A$*H$_B$* and C2H), 1.54–1.41 (1H, m, C3H), 1.38–1.25 (1H, m, C4H$_A$*H$_B$*), 1.01 (3H, d, *J* = 7.0 Hz, C7H$_3$), 0.98 (3H, d, *J* = 6.3 Hz, C6H$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz) δ = 214.5 (C=O), 141.2 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 61.9 (C1H), 45.1 (C2H), 43.4 (C3H), 33.9 (C4H$_2$), 27.8 (C5H$_2$), 18.4 (2C, C6H$_3$ and C7H$_3$), 8.1 (2C, 2 × Ar-CH$_3$), 16.9 (Ar-CH$_3$), 16.2 (2C, 2 × Ar-CH$_3$).

(2,3-Dimethylcyclopent-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, S3



In the preparation of *ketone* **489** under **general procedure M**, the title compound (6 mg, 4%) was obtained as a white solid.

R_f = 0.24 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 98–99 °C.

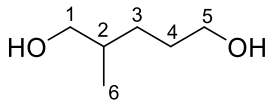
IR (film) ν_{max}/cm^{-1} 2957, 2871, 1686, 1456, 1379, 1124, 1067, 1021.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.78–2.68 (1H, m, C3H), 2.68–2.59 (1H, m, C5H_AH_B), 2.58–2.49 (1H, m, C5H_AH_B), 2.22 (3H, s, Ar-CH_3), 2.17 (6H, s, 2 × Ar-CH_3), 2.10–2.00 (1H, m, C4H_AH_B), 2.09 (6H, m, 2 × Ar-CH_3), 1.55 (3H, s, C6H_3), 1.45–1.34 (1H, m, C4H_AH_B), 1.07 (3H, d, *J* = 7.0 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 201.3 (C=O), 160.3 (C2), 140.9 (Ar-C), 137.0 (C1), 135.0 (Ar-C), 133.0 (2C, 2 × Ar-C), 128.0 (2C, 2 × Ar-C), 47.3 (C3H), 31.5 (C5H_2), 30.3 (C4H_2), 18.6 (C7H_3), 17.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3), 14.2 (C6H_3).

HRMS (ESI^+) Found $[M+H]^+$ = 271.2055; $C_{19}H_{27}O$ requires 271.2056, Δ –0.73 ppm.

2-methylpentane-1,5-diol, 492



2-methylgluaric acid (1.00 g, 6.84 mmol), $BH_3{\cdot}S(CH_3)_2$ (1.95 mL, 20.5 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound as a colourless oil (738 mg, 91%).

R_f = 0.12 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3312, 2932, 2873, 1419, 1338, 1105, 1039, 941.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.65–3.56 (2H, m, C5H_2), 3.49–3.37 (2H, m, C1H_2), 3.03–2.47 (2H, br s, 2 × OH), 1.68–1.56 (2H, m, C2H and C4H_AH_B), 1.56–1.46 (2H, m, C4H_AH_B and C3H_AH_B), 1.21–1.10

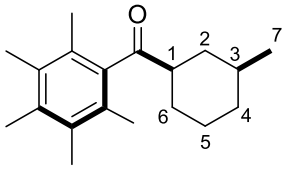
(1H, m, C3H$_A$*H$_B$*), 0.89 (3H, d, *J* = 6.7 Hz, C6H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 67.9 (C1H$_2$), 62.9 (C5H$_2$), 35.4 (C2H), 29.9 (C4H$_2$), 29.2 (C3H$_2$), 16.7 (C6H$_3$).

HRMS (ESI$^+$) Found $[M+H]^+$ = 141.0885; $C_6H_{15}O_2$ requires 141.0886, Δ –1.01 ppm.

All spectroscopic data in agreement with that previously reported.[126]

***rac*-((1*R*,3*S*)-3-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 493**



Ketone **329** (114 mg, 0.600 mmol), 2-methylpentane-1,5-diol (142 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (134 mg, 82%, 91:9 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.67 (1H, tt, *J* = 12.0, 3.2 Hz, C1H, major diastereoisomer), 2.85 (1H, tt, *J* = 8.6, 4.3 Hz, C1H, minor diastereoisomer). The peaks for the minor diastereoisomer could not be fully distinguished, so only the data for the major diastereoisomer is reported. The relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from HPLC grade MeOH.

***R*$_f$** = 0.20 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

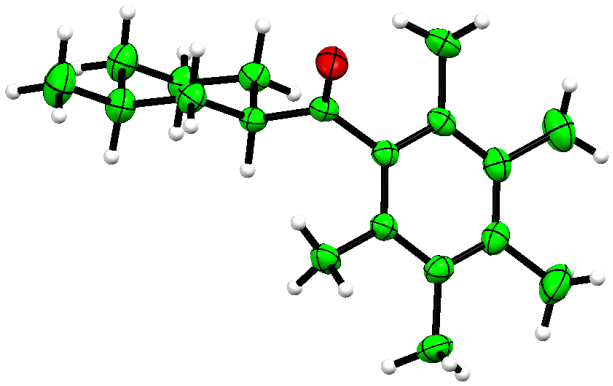
m.p. = 88–89 °C.

IR (film) ν_{max}/cm^{-1} 2924, 2855, 1691, 1456, 1381, 1306, 1265, 1143, 1110, 1002, 926.

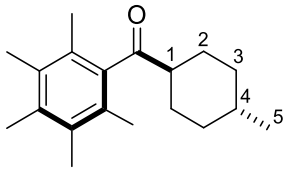
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.67 (1H, tt, *J* = 12.0, 3.2 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.96–1.87 (2H, m, C6*H$_{eq}$*H$_{ax}$ and C2*H$_{eq}$*H$_{ax}$), 1.86–1.79 (1H, m, C5*H$_{eq}$*H$_{ax}$), 1.74–1.64 (1H, m, C4*H$_{eq}$*H$_{ax}$), 1.43–1.29 (2H, m, C3H and C6H$_{eq}$*H$_{ax}$*), 1.25 (1H, qt, *J* = 13.2, 3.7 Hz, C5H$_{eq}$*H$_{ax}$*), 1.10 (1H, dt, *J* = 13.1, 11.9 Hz, C2H$_{eq}$*H$_{ax}$*), 0.92 (3H, d, *J* = 6.5 Hz, C7H$_3$), 0.89 (1H, qd, *J* = 12.5, 3.3 Hz, C4H$_{eq}$*H$_{ax}$*).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.0 (C=O), 140.4 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 53.4 (C1H), 36.6 ($C2H_2$), 34.8 ($C4H_2$), 32.6 (C3H), 28.0 ($C6H_2$), 26.0 ($C5H_2$), 22.8 ($C7H_3$), 18.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 273.2213; $C_{19}H_{29}O$ requires 273.2213, Δ 0.14 ppm.



***rac*-((1*r*,4*r*)-4-Methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 495**



Ketone **329** (114 mg, 0.600 mmol), 3-methylpentane-1,5-diol (142 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (125 mg, 76%, > 95:5 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.56 (1H, tt, *J* = 12.1, 3.3 Hz, C1H, major diastereoisomer), 2.70 (1H, tt, *J* = 9.1, 4.2 Hz, C1H, minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from HPLC grade MeOH

R_f = 0.19 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

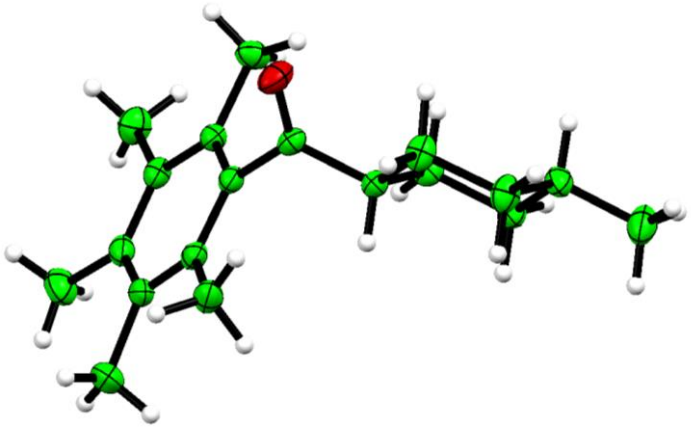
m.p. = 124–125 °C.

IR (film) ν_{max}/cm^{-1} 2926, 2853, 1690, 1447, 1315, 1262, 1171, 1146, 1113, 1019, 931.

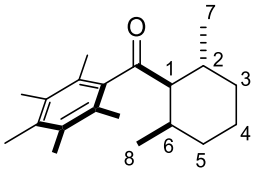
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.56 (1H, tt, *J* = 12.1, 3.3 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.98–1.88 (2H, m, 2 × C2$H_{eq}$$H_{ax}$), 1.81–1.73 (2H, m, 2 × C3$H_{eq}$$H_{ax}$), 1.47 (2H, qd, *J* = 13.2, 3.6 Hz, 2 × C2$H_{eq}$$H_{ax}$), 1.41–1.30 (1H, m, C4H), 0.90 (2H, qd, *J* = 13.2, 3.3 Hz, 2 × C3$H_{eq}$$H_{ax}$), 0.88 (3H, d, *J* = 6.6 Hz, C5H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.3 (C=O), 140.4 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 53.0 (C1H), 34.7 (2C, 2 × C3H_2), 32.4 (C4H), 28.3 (2C, 2 × C2H_2), 22.6 (C5H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

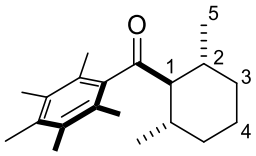
HRMS (ESI^+) Found $[M+H]^+$ = 273.2211; $C_{19}H_{29}O$ requires 273.2213, Δ –0.69 ppm.



***rac*-((2*R*,6*R*)-2,6-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 500a and *rac*-((1*r*,2*R*,6*S*)-2,6-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 500b**



500a (major)



500b (minor)

Procedure 1: without $NaBH_4$ reduction

Ketone **329** (114 mg, 0.600 mmol), heptane-2,6-diol* (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg,

* Synthesised by Dr James Frost.

2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2→9:1) provided the title compound (60 mg, 35%, 56:44 d.r.) as an inseparable mixture of diastereoisomers, as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.69 (1H, dd, *J* = 9.6, 3.2 Hz, C1H, **500a**), 2.47 (1H, t, *J* = 9.9 Hz, C1H, **500b**). The relative stereochemistry was determined by *J*-coupling constant analysis.

Procedure 2: with $NaBH_4$ reduction

Ketone **329** (114 mg, 0.600 mmol), heptane-2,6-diol (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. The residue was dissolved in a mixture of THF (3 mL) and MeOH (1 mL) and $NaBH_4$ (227 mg, 6.00 mmol) was added in portionwise. The resulting solution was stirred at 60 °C for 24 h and then after cooling to RT, was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5) provided the title compound (150 mg, 87%, 74:26 d.r.) as an inseparable mixture of diastereoisomers, as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.69 (1H, dd, *J* = 9.6, 3.2 Hz, C1H, **500a**), 2.47 (1H, t, *J* = 9.9 Hz, C1H, **500b**). The relative stereochemistry was determined by *J*-couping constant analysis.

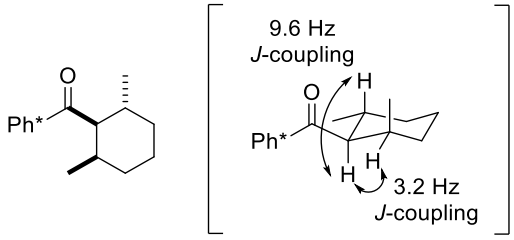
Data for **500a**/**500b** (56:44 d.r.):

R_f = 0.51 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2980, 2923, 1687, 1570, 1459, 1383, 1306, 1261, 1148, 1106, 1001, 942.

HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2368; $C_{20}H_{31}O$ requires 287.2369, Δ –0.54 ppm.

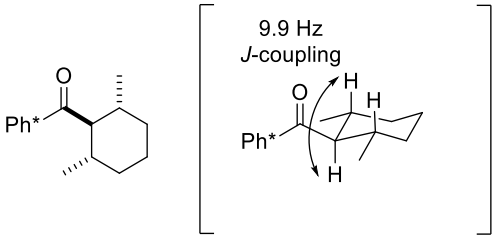
NMR data for **500a**:



^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.69 (1H, dd, *J* = 9.6, 3.2 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.18 (12H, s, 4 × Ar-CH_3), 2.16–2.09 (1H, m, C2H), 2.08–2.01 (1H, m, C6H), 1.79–1.70 (1H, m, C3$H_{eq}H_{ax}$), 1.68–1.55 (2H, m, C4$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.50–1.37 (2H, m, C4$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.11–1.03 (1H, m, C3$H_{eq}H_{ax}$), 1.06 (3H, d, *J* = 6.5 Hz, C7H_3), 1.01 (3H, d, *J* = 6.9 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.8 (C=O), 140.1 (Ar-C), 135.7 (Ar-C), 133.2 (2C, 2 × Ar-C), 129.5 (2C, 2 × Ar-C), 62.4 (C1H), 34.3 (C3H_2), 32.9 (C5H_2), 29.3 (C6H), 27.4 (C2H), 20.8 (C7H_3), 20.1 (C4H_2), 18.1 (2C, 2 × Ar-CH_3), 17.0 (Ar-CH_3), 16.3 (2C, 2 × Ar-CH_3), 14.7 (C8H_3).

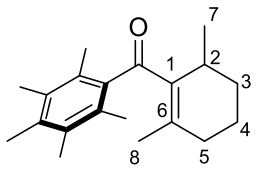
NMR data for **500b**:



^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.47 (1H, t, *J* = 9.9 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.18 (12H, s, 4 × Ar-CH_3), 1.88–1.78 (2H, m, 2 × C2H), 1.78–1.69 (2H, m, 2 × C3$H_{eq}H_{ax}$), 1.68–1.64 (1H, m, C4$H_{eq}H_{ax}$), 1.37–1.26 (1H, m, C4$H_{eq}H_{ax}$), 1.11–1.02 (2H, m, 2 × C3$H_{eq}H_{ax}$), 0.86 (6H, d, *J* = 6.4 Hz, 2 × C5H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.1 (C=O), 142.3 (Ar-C), 136.0 (Ar-C), 133.4 (2C, 2 × Ar-C), 129.6 (2C, 2 × Ar-C), 64.4 (C1H), 35.8 (2C, 2 × C3H_2), 34.0 (2C, 2 × C2H), 25.2 (C4H_2), 22.1 (2C, 2 × C5H_3), 18.5 (2C, 2 × Ar-CH_3), 17.1 (Ar-CH_3), 16.4 (2C, 2 × Ar-CH_3).

(2,6-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 501



In the preparation of *ketone* **500** under **general procedure M**, the title compound (87 mg, 51%) was obtained as a white solid.

R_f = 0.17 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 136–137 °C.

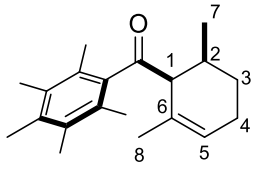
IR (film) ν_{max}/cm^{-1} 2930, 2870, 1726, 1660, 1634, 1613, 1450, 1419, 1380, 1306, 1270, 1219, 1168, 1086, 1068, 1020, 981.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.83 (1H, s, C2H), 2.23 (3H, s, Ar-CH_3), 2.19–2.11 (2H, m, C5$H_{eq}H_{ax}$), 2.17 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.78–1.52 (7H, m, C4$H_{eq}H_{ax}$, C8H_3 and C3$H_{eq}H_{ax}$), 1.01 (3H, d, *J* = 6.9 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 203.1 (C=O), 149.2 (C6), 141.5 (C1), 139.4 (Ar-C), 135.1 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.8 (2C, 2 × Ar-C), 35.3 (C5H_2), 30.2 (C3H_2), 29.0 (C2H), 22.2 (C8H_3), 20.7 (C7H_3), 17.7 (C4H_2), 17.3 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 285.2212; $C_{20}H_{29}O$ requires 285.2213, Δ –0.30 ppm.

(2,6-Dimethylcyclohex-2-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 502



In the preparation of *ketone* **500** under **general procedure M**, the title compound (7 mg, 4%) was obtained as a white solid.

R_f = 0.39 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

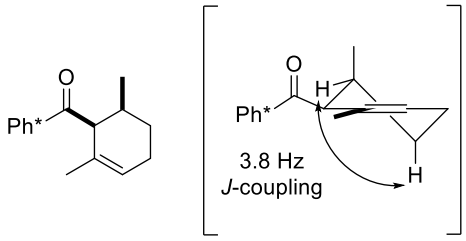
m.p. = 109–110 °C

IR (film) ν_{max}/cm^{-1} 2927, 1689, 1455, 1381, 1304, 1264, 1150, 1109, 944.

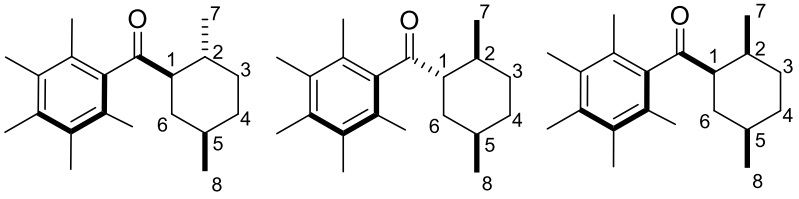
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.60 (1H, br s, C5H), 2.99 (1H, s, C1H), 2.25–2.18 (1H, m, C2H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.07 (6H, s, 2 × Ar-CH_3), 1.99–1.92 (2H, m, C4$H_{ax}H_{eq}$), 1.74–1.64 (1H, m, C3$H_{eq}H_{ax}$), 1.62 (3H, br s, C8H_3), 1.31 (1H, dq, *J* = 13.3, 3.8 Hz, C3$H_{eq}H_{ax}$), 0.86 (3H, d, *J* = 7.0 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.4 (C=O), 140.1 (Ar-C), 135.6 (2C, Ar-C and C6), 133.1 (2C, 2 × Ar-C), 128.7 (2C, 2 × Ar-C), 125.4 (C5H), 61.2 (C1H), 27.2 (C2H), 24.4 (C8H_3), 24.2 (C3H_2), 21.0 (C4H_2), 19.1 (C7H_3), 18.0 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 307.2034; $C_{20}H_{28}ONa$ requires 307.2032, Δ 0.39 ppm.



***rac*-((1*R*,2*R*,5*R*)-2,5-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 506a, *rac*-((1*S*,2*S*,5*R*)-2,5-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 506b and *rac*-((1*R*,2*S*,5*R*)-2,5-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 506c**



506a **506b** **506c**

Ketone **329** (114 mg, 0.600 mmol), 2-methylhexane-1,5-diol* (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (120 mg, 70%, 66:19:15 d.r.) as an inseparable mixture of diastereoisomers, as a white solid. The

* Synthesised by Dr James Frost.

d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 2.54 (1H, ddd, *J* = 12.3, 10.5, 3.3 Hz, C1H, **506a**), 2.80–1.74 (1H, m, C1H, **506b**), 2.82 (1H, dt, *J* = 12.5, 3.1 Hz, C1H, **506c**). The mixture of diastereoisomers were analysed by 1D TOCSY to obtain clean ^{1}H NMR spectra for each diastereoisomer. Key nOe correlations from 2D NOESY data and *J*-coupling constant analysis were then used to determine the relative stereochemistry of each diastereoisomer.

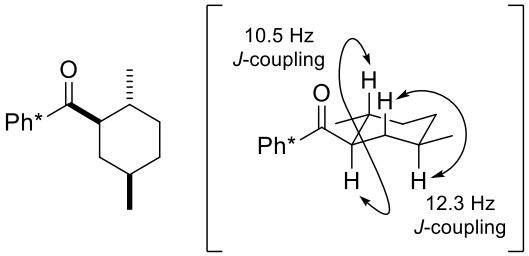
Data for **506a**/**506b**/**506c** (66:19:15 d.r.):

R_f = 0.42 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2948, 2921, 1690, 1456, 1380, 1303, 1268, 1222, 1165, 1110, 1086, 1040, 1004, 909.

HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2367; $C_{20}H_{31}O$ requires 287.2369, Δ –1.02 ppm.

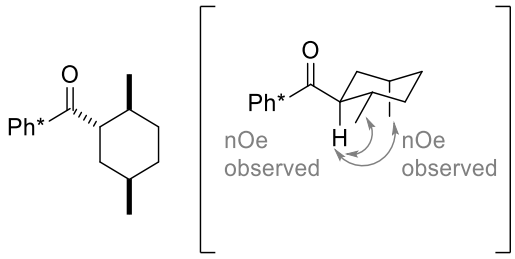
NMR data for **506a**



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.54 (1H, ddd, *J* = 12.3, 10.5, 3.3 Hz, C1H), 2.17 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.06 (6H, s, 2 × Ar-CH_3), 1.97–1.89 (1H, m, C2H), 1.83–1.77 (1H, m, C6H_{eq}H$_{ax}$ and C3H_{eq}H$_{ax}$), 1.70–1.65 (1H, m, C4H_{eq}H$_{ax}$), 1.37–1.28 (1H, m, C5H), 1.12 (3H, d, *J* = 6.4 Hz, C7H$_3$), 1.11 (1H, qd, *J* = 13.3, 3.5 Hz, C4H$_{eq}$$H_{ax}$), 0.98 (1H, qd, *J* = 13.0, 3.5 Hz, C3H$_{eq}$$H_{ax}$), 0.89 (1H, q, *J* = 12.3 Hz, C6H$_{eq}$$H_{ax}$), 0.87 (3H, d, *J* = 6.6 Hz, C8H$_3$)

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.0 (C=O), 139.8 (Ar-C), 135.6 (Ar-C), 133.2 (2 × Ar-C), 133.1 (2 × Ar-C), 59.5 (C1H), 37.8 (C6H$_2$), 34.8 (C3H$_2$ and C4H$_2$), 33.2 (C5H), 32.3 (C2H), 22.5 (C8H$_3$), 20.8 (C7H$_3$), 18.1 (2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2 × Ar-CH_3).

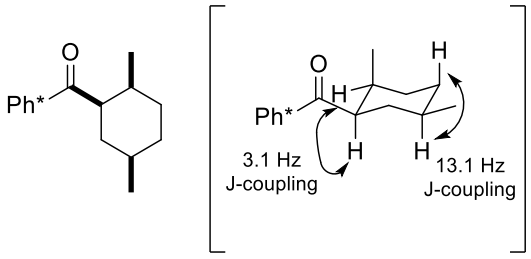
NMR data for **506b**:



^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.80–2.73 (1H, m, C1H), 2.12–2.06 (1H, m, C2H), 2.17 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.06 (6H, s, 2 × Ar-CH_3), 2.00–1.93 (1H, m, C5H), 1.80–1.74 (1H, m, C3$H_A$$H_B$), 1.65–1.58 (2H, m, C6$H_A$$H_B$ and C4$H_A$$H_B$), 1.58–1.52 (1H, m, C4$H_A$$H_B$), 1.51–1.45 (1H, m, C6$H_A$$H_B$), 1.39–1.30 (1H, m, C3$H_A$$H_B$), 1.09 (3H, d, *J* = 6.8 Hz, C7H_3), 0.90 (3H, d, *J* = 6.9 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.5 (C=O), 140.1 (Ar-C), 135.4 (Ar-C), 133.2 (2 × Ar-C), 133.1 (2 × Ar-C), 54.0 (C1H), 33.4 (C6H_2), 30.7 (C2H), 30.5 (C4H_2), 28.8 (C3H_2), 28.0 (C5H), 20.5 (C7H_3), 19.6 (C8H_3), 18.0 (2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2 × Ar-CH_3).

NMR data for **506c**:

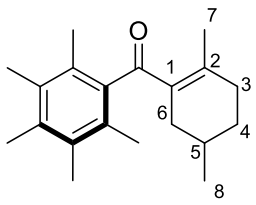


^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.82 (1H, dt, *J* = 12.5, 3.1 Hz, C1H), 2.40–2.35 (1H, m, C2H), 2.17 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.06 (6H, s, 2 × Ar-CH_3), 1.63 (1H, br d, *J* = 13.2 Hz, C6$H_{eq}$$H_{ax}$), 1.61–1.59 (1H, m, C3$H_{eq}$$H_{ax}$), 1.52 (1H, tt, *J* = 13.5, 4.0 Hz, C3$H_{eq}$$H_{ax}$), 1.49–1.44 (1H, m, C4$H_{eq}$$H_{ax}$), 1.46 (1H, q, *J* = 12.3 Hz, C6$H_{eq}$$H_{ax}$), 1.43–1.35 (1H, m, C5H), 1.21 (1H, qd, *J* = 13.1, 3.9 Hz, C4$H_{eq}$$H_{ax}$), 1.07 (3H, d, *J* = 7.0 Hz, C7H_3), 0.95 (3H, d, *J* = 6.2 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.7 (C=O), 140.7 (Ar-C), 135.3 (Ar-C), 133.2 (2 × Ar-C), 133.1 (2 ×

Ar-C), 56.7 (C1H), 33.3 (C5H and C3H_2), 30.5 (C6H_2), 28.8 (C4H_2), 27.9 (C2H), 22.8 (C8H_3), 18.0 (2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2 × Ar-CH_3), 13.3 (C7H_3).

(2,5-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 507



In the preparation of *ketone* **329** under **general procedure M**, the title compound (15 mg, 9%) was obtained as a white solid.

***R*$_f$** = 0.24 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 105–106 °C.

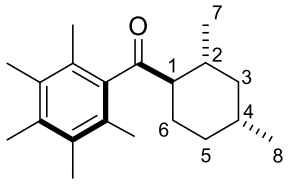
IR (film) ν_{max}/cm^{-1} 2949, 2922, 1668, 1622, 1455, 1380, 1307, 1266, 1217, 1176, 1156, 1111, 1070, 953.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.41–2.30 (1H, m, C6H_{eq}H$_{ax}$), 2.28–2.21 (1H, m, C4H_{eq}H$_{ax}$), 2.23 (3H, s, Ar-CH_3), 2.20–2.11 (1H, m, C4H$_{ax}$$H_{eq}$), 2.17 (6H, s, 2 × Ar-C$H_3$), 2.05 (6H, s, 2 × Ar-C$H_3$), 1.82 (3H, s, C7$H_3$), 1.76–1.56 (3H, m, C6H$_{eq}$$H_{ax}$, C3$H_{eq}H_{ax}$ and C5H), 1.26–1.11 (1H, m, C3H$_{eq}$$H_{ax}$), 0.94 (3H, d, *J* = 5.9 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.1 (C=O), 148.7 (C2), 141.4 (Ar-C) 135.0 (Ar-C), 133.0 (3C, C1 and 2 × Ar-C), 128.2 (2C, 2 × Ar-C), 35.2 (C4H_2), 34.7 (C6H_2), 30.6 (C3H_2), 28.7 (C5H), 21.9 (C7H_3), 21.6 (C8H_3), 17.2 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 285.2211; $C_{20}H_{29}O$ requires 285.2213, Δ –0.56 ppm.

***rac*-((1*R*,2*R*,4*R*)-2,4-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 515**



Ketone **329** (114 mg, 0.600 mmol), 3-methylhexane-1,5-diol* (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (128 mg, 74%, 93:5:2 d.r.) as a white solid. The d.r. was determined by ^1H NMR analysis of the crude mixture by comparison of the following signals: 2.32 (1H, td, *J* = 11.4, 3.2 Hz, C1H, **515a**), 2.42 (1H, td, *J* = 8.3, 4.5 Hz, C1H, **5% (515b)**), 2.61 (1H, dt, *J* = 12.6, 3.4 Hz, C1H, **2% (515c)**). The peaks for the minor diastereoisomers could not be fully distinguished, so only the data for the major diastereoisomer is reported. The relative stereochemistry was confirmed by X-ray crystallographic analysis after crystallization from HPLC grade MeOH, as well as *J*-coupling constant analysis.

R_f = 0.32 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 118–119 °C.

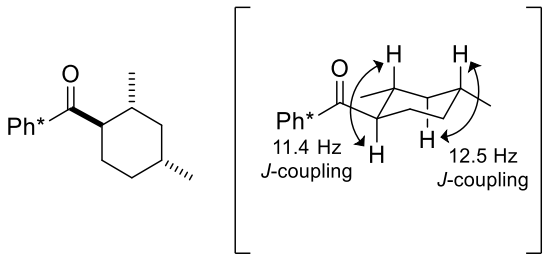
IR (film) ν_{max}/cm^{-1} 2954, 2926, 1681, 1569, 1453, 1372, 1311, 1262, 1180, 1145, 1110, 1001, 947.

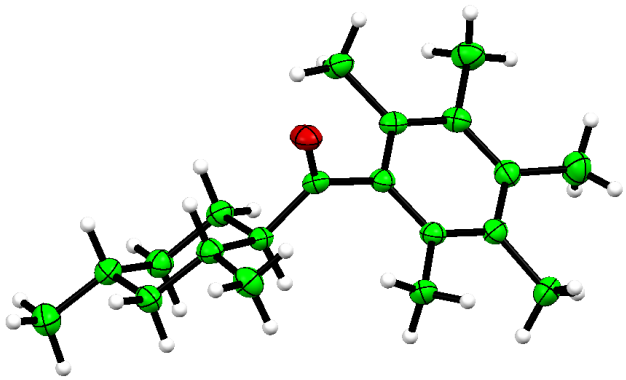
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.32 (1H, td, *J* = 11.4, 3.2 Hz, C1H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.05 (6H, s, 2 × Ar-CH_3), 1.97–1.85 (1H, m, C2H), 1.76 (1H, dq, *J* = 12.8, 3.4 Hz, C6$H_{eq}H_{ax}$), 1.70–1.58 (2H, m, C3$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.39–1.28 (1H, m, C4H), 1.16 (1H, qd, *J* = 12.7, 3.4 Hz, C6$H_{eq}H_{ax}$), 1.01 (3H, d, *J* = 6.4 Hz, C7H_3), 0.79 (3H, d, *J* = 6.6 Hz, C8H_3), 0.77–0.69 (1H, m, C5$H_{eq}H_{ax}$), 0.65 (1H, q, *J* = 12.5 Hz, C3$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.4 (C=O), 139.9 (Ar-C), 135.6 (Ar-C), 133.2 (4C, 4 × Ar-C), 59.2 (C1H), 43.7 (C3H_2), 35.2 (C5H_2), 32.6 (C2H), 32.2 (C4H), 29.8 (C6H_2), 22.6 (C8H_3), 21.0 (C7H_3), 18.0 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

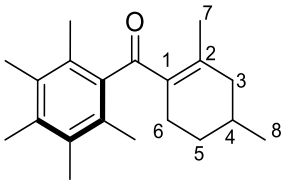
HRMS (ESI^+) Found $[M+H]^+$ = 287.2368; $C_{20}H_{31}O$ requires 287.2369, Δ –0.50 ppm.

* Synthesised by Dr James Frost.





(2,4-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 516



In the preparation of *ketone* **515** under **general procedure M**, the title compound (36 mg, 21%) was obtained as a white solid.

***R*$_f$** = 0.16 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 110–111 °C.

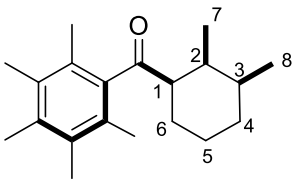
IR (film) ν_{max}/cm^{-1} 2949, 2913, 1668, 1619, 1456, 1378, 1305, 1265, 1212, 1173, 1116, 1069, 1018, 896.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.35–2.24 (2H, m, C6H_{eq}H$_{ax}$ and C3H_{eq}H$_{ax}$), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.15–2.07 (1H, m, C6H$_{eq}$$H_{ax}$), 2.05 (6H, s, 2 × Ar-$CH_3$), 1.92–1.82 (4H, m, C7$H_3$ and C3H$_{eq}$$H_{ax}$), 1.75–1.61 (2H, m, C5$H_{eq}H_{ax}$ and C4H), 1.15 (1H, qd, *J* = 11.4, 4.9 Hz, C5H$_{eq}$$H_{ax}$), 0.96 (3H, d, *J* = 6.2 Hz, C8H_3).

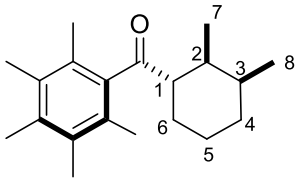
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.0 (C=O), 148.6 (C2), 141.3 (Ar-C), 134.9 (Ar-C), 133.0 (2C, 2 × Ar-C), 132.9 (C1), 128.2 (2C, 2 × Ar-C), 43.7 ($C3H_2$), 30.9 ($C5H_2$), 28.3 (C4H), 26.7 ($C6H_2$), 22.1 ($C7H_3$), 21.5 ($C8H_3$), 17.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 285.2215; $C_{20}H_{29}O$ requires 285.2213, Δ 0.62 ppm.

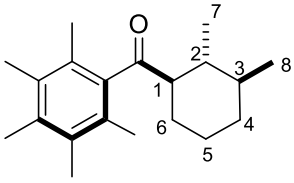
***rac*-((1*R*,2*S*,3*S*)-2,3-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 519a, *rac*-((1*R*,2*R*,3*R*)-2,3-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 519b and *rac*-((1*R*,2R,3*S*)-2,3-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 519c**



519a



519b



519c

Procedure 1: without $NaBH_4$ reduction

Ketone **329** (75 mg, 0.39 mmol), 4-methylhexane-1,5-diol* (104 mg, 0.790 mmol), $[Cp^*IrCl_2]_2$ (6.3 mg, 2.0 mol%) and KOH (88 mg, 1.57 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2→95:5) provided **519a** (25 mg, 22%) cleanly and **519b** and **519c** (28 mg, 25%, 69:31 d.r.) as an inseparable mixture of diastereoisomers, as white solids. The overall d.r. was determined to be 47:36:17. The d.r. was determined by ^{1}H NMR analysis of the isolated mixture of **519b** and **519c** by comparison of the following signals: *δ* 2.77 (1H, td, *J* = 8.5, 4.3, C1H, **519b**), 2.55 (1H, td, *J* = 11.1, 3.1 Hz, C1H, **519c**). This was compared to the isolated mass of **519a**. Key nOe correlations from 2D NOESY data and *J*-coupling constant analysis were used to determine the relative stereochemistry of each diastereoisomer.

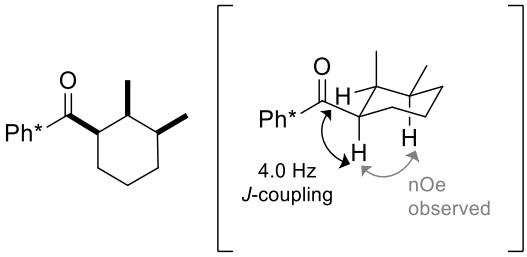
Procedure 2: with $NaBH_4$ reduction

Ketone **329** (114 mg, 0.600 mmol), 4-methylhexane-1,5-diol (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$

* Synthesised by Dr James Frost and Dr Roly Armstrong.

(9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M**. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. The residue was dissolved in a mixture of THF (3 mL) and MeOH (1 mL) and $NaBH_4$ (227 mg, 6.00 mmol) was added in several portions. The resulting solution was stirred at 60 °C for 24 h and then after cooling to RT, was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2) provided **519a** (61 mg, 35%) cleanly and **519b** and **519c** (79 mg, 46%, 61:39 d.r.) as an inseparable mixture of diastereoisomers, as white solids. The overall d.r. was determined to be 44:34:22. The d.r. was determined by ^{1}H NMR analysis of the isolated mixture of **519b** and **519c** by comparison of the following signals: δ 2.77 (1H, td, J = 8.5, 4.3, C1H, **519b**), 2.55 (1H, td, J = 11.1, 3.1 Hz, C1H, **519c**). This was compared to the isolated mass of **519a**. Key nOe correlations from 2D NOESY data and J-coupling constant analysis were used to determine the relative stereochemistry of each diastereoisomer.

Data for **519a**



R_f = 0.30 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 90–91 °C.

IR (film) ν_{max}/cm^{-1} 2925, 2870, 1689, 1451, 1382, 1306, 1270, 1146, 1106, 1000, 892.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.74 (1H, dt, J = 12.3, 4.0 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.16–2.13 (1H, m, C2H), 2.12 (6H, s, 2 × Ar-CH_3), 1.82–1.74 (1H, m, C5H_{eq}H$_{ax}$), 1.73–1.51 (3H, m, C6H$_{eq}$H$_{ax}$ and C3H), 1.40–1.29 (1H, m, C4H_{eq}H$_{ax}$), 1.29–1.18 (2H, m, C5H$_{eq}$$H_{ax}$ and

C4H$_{eq}$*H$_{ax}$*), 0.91 (3H, d, *J* = 7.0 Hz, C7H$_3$), 0.86 (3H, d, *J* = 6.6 Hz, C8H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.6 (C=O), 140.7 (Ar-C), 135.3 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.4 (2C, 2 × Ar-C), 58.5 (C1H), 36.8 (C3H), 33.7 (C2H), 27.9 (C4H$_2$), 26.2 (C5H$_2$), 21.5 (C6H$_2$), 20.0 (C8H$_3$), 18.0 (2C, 2 × Ar-CH$_3$), 16.9 (Ar-CH$_3$), 16.2 (2C, 2 × Ar-CH$_3$), 7.5 (C7H$_3$).

HRMS (ESI$^+$) Found [M+H]$^+$ = 287.2369; $C_{20}H_{31}O$ requires 287.2369, Δ –0.28 ppm.

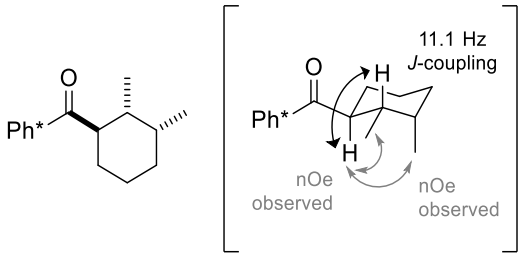
Data for **519b**/**519c** (69:31 d.r.):

***R*$_f$** = 0.35 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2937, 1691, 1460, 1381, 1300, 1270, 1149, 1103, 996.

HRMS (ESI$^+$) Found [M+H]$^+$ = 287.2367; $C_{20}H_{31}O$ requires 287.2369, Δ –0.28 ppm.

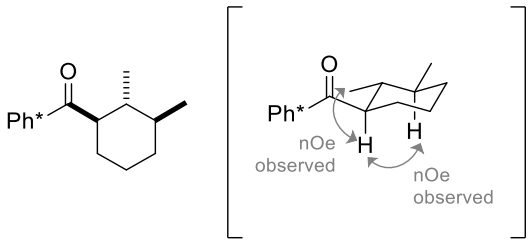
NMR data for **519b**:



^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.77 (1H, td, *J* = 8.5, 4.3 Hz, C1H), 2.24 (3H, s, Ar-CH$_3$), 2.19 (6H, s, 2 × Ar-CH$_3$), 2.17–2.08 (1H, m, C2H), 2.11 (6H, s, 2 × Ar-CH$_3$), 2.02–1.92 (1H, m, C3H), 1.79–1.68 (1H, m, C6*H$_{eq}$*H$_{ax}$), 1.60–1.51 (1H, m, C5*H$_{eq}$*H$_{ax}$), 1.50–1.40 (3H, m, C4H$_{eq}$H$_{ax}$ and C5H$_{eq}$*H$_{ax}$*), 1.39–1.31 (1H, m, C6H$_{eq}$*H$_{ax}$*), 1.03 (3H, d, *J* = 7.0 Hz, C7H$_3$), 0.87 (3H, d, *J* = 7.1 Hz, C8H$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.8 (C=O), 140.1 (Ar-C), 135.4 (Ar-C), 133.1 (4C, 4 × Ar-C), 53.7 (C1H), 34.5 (C2H), 32.6 (C3H), 31.5 (C4H$_2$), 27.4 (C6H$_2$), 21.2 (C5H$_2$), 17.9 (2C, 2 × Ar-CH$_3$), 16.8 (Ar-CH$_3$), 16.5 (C7H$_3$), 16.1 (2C, 2 × Ar-CH$_3$), 15.1 (C8H$_3$).

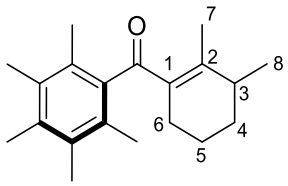
NMR data for **519c**:



^{1}H NMR (CD_2Cl_2, 400 MHz) δ = 2.55 (1H, td, *J* = 11.1, 3.1 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.13 (6H, s, 2 × Ar-CH_3), 1.85–1.78 (1H, m, C6$H_{eq}H_{ax}$), 1.71–1.62 (1H, m, C5$H_{eq}H_{ax}$), 1.68–1.60 (2H, m, C4$H_{eq}H_{ax}$ and C2H), 1.25–1.14 (2H, m, C5$H_{eq}H_{ax}$ and C6$H_{eq}H_{ax}$), 1.15–1.09 (1H, m, C3H), 1.12 (3H, d, *J* = 6.4 Hz, C7H_3), 1.04–1.00 (1H, m, C4$H_{eq}H_{ax}$), 0.99 (3H, d, *J* = 6.3 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.0 (C=O), 139.7 (Ar-C), 135.5 (Ar-C), 133.1 (4C, 4 × Ar-C), 59.1 (C1H), 38.8 (C2H), 38.1 (C3H), 35.3 (C4H_2), 30.1 (C6H_2), 26.5 (C5H_2), 20.4 (C8H_3), 17.9 (3C, 2 × Ar-CH_3 and C7H_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

(2,3-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 520



In the preparation of *ketone* **519** under **general procedure M**, the title compound (32 mg, 29%) was obtained as a white solid.

***R*$_f$** = 0.23 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 85–86 °C.

IR (film) ν_{max}/cm^{-1} 2930, 2870, 1666, 1637, 1609, 1456, 1380, 1305, 1264, 1222, 1179, 1101, 1068, 969.

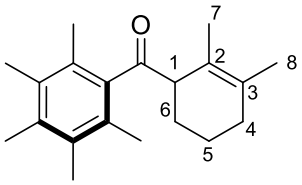
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.30–2.24 (1H, m, C3H), 2.22 (3H, s, Ar-CH_3), 2.17 (6H, s, 2 × Ar-CH_3), 2.16–2.08 (2H, m, C6H_2), 2.06 (6H, s, 2 × Ar-CH_3), 1.92 (3H, s, C7H_3), 1.74–1.65 (1H, m, C4H_AH_B), 1.65–1.58 (1H, m, C5H_AH_B), 1.57–1.48 (1H, m, C5H_AH_B), 1.46–1.36 (1H, m, C4H_AH_B), 1.12 (3H, d,

J = 7.1 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.8 (C=O), 152.2 (C2), 141.2 (Ar-C), 135.0 (Ar-C), 133.2 (C1), 132.9 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 37.5 (C3H), 30.5 (C4H_2), 27.3 (C6H_2), 20.9 (C8H_3), 19.7 (C7H_3), 19.4 (C5H_2), 17.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 285.2210; $C_{20}H_{29}O$ requires 285.2213, Δ –1.10 ppm.

(2,3-Dimethylcyclohex-2-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 521



In the preparation of *ketone* **519** under **general procedure M**, the title compound (10 mg, 9%) was obtained as a white solid.

***R*$_f$** = 0.28 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 82–83 °C

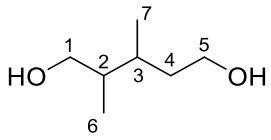
IR (film) ν_{max}/cm^{-1} 2929, 1691, 1448, 1383, 1300, 1259, 1106, 997.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.37 (1H, br s, C1H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.15 (6H, s, 2 × Ar-CH_3), 2.04–1.90 (3H, m, C4$H_{eq}H_{ax}$ and C6$H_{eq}H_{ax}$), 1.69 (3H, s, C7H_3), 1.66 (3H, s, C8H_3), 1.65–1.56 (3H, m, C6$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.5 (C=O), 140.1 (Ar-C), 135.5 (Ar-C), 133.1 (3C, 2 × Ar-C and C2), 131.3 (2C, 2 × Ar-C), 122.9 (C3), 55.8 (C1H), 32.0 (C4H_2), 25.2 (C6H_2), 20.6 (C5H_2), 19.8 (C7H_3), 19.0 (C8H_3), 17.9 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 307.2031; $C_{20}H_{28}ONa$ requires 307.2032, Δ –0.57 ppm.

2,3-Dimethylpentane-1,5-diol, 526



2,3-Dimethylpentanedioic acid (600 mg, 3.75 mmol), $BH_3{\cdot}S(CH_3)_2$ (1.07 mL, 11.3 mmol) and THF (10 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (372 mg, 75%, 57:43 d.r.) as a colourless oil. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 1.50–1.38 (1H, m, C4H$_A$*H$_B$*, major diastereoisomer), 1.35–1.18 (1H, m, C4H$_A$*H$_B$*, minor diastereoisomer). The relative stereochemistry of the diastereoisomers could not be distinguished.

Data for major/minor diastereoisomer (57:43 d.r.):

***R*$_f$** = 0.17 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3312, 2958, 2926, 2877, 1456, 1417, 1380, 1362, 1340, 1120, 1049, 667.

HRMS (ESI$^+$) Found [M+Na]$^+$ = 155.1040; $C_7H_{16}O_2Na$ requires 155.1043, Δ –1.64 ppm.

NMR data for major diastereoisomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.77–3.59 (2H, m, C5H$_2$), 3.58–3.41 (2H, m, C1H$_2$), 1.89–1.73 (1H, m, C2H), 1.71–1.55 (2H, m, C3H and C4*H$_A$*H$_B$), 1.50–1.38 (1H, m, C4H$_A$*H$_B$*), 0.87–0.74 (6H, m, C6H$_3$ and C7H$_3$).*

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 66.4 (C1H$_2$), 61.1 (C5H$_2$), 40.4 (C3H), 37.7 (C4H$_2$), 29.4 (C2H), 14.4 (CH$_3$), 11.5 (CH$_3$).

Data for minor diastereoisomer

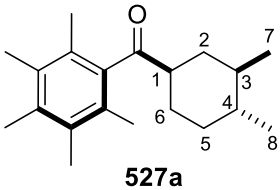
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.77–3.59 (2H, m, C5H$_2$), 3.58–3.41 (2H, m, C1H$_2$), 1.89–1.73 (1H, m, C2H), 1.71–1.55 (2H, m, C3H and C4*H$_A$*H$_B$), 1.35–1.18 (1H, m, C4H$_A$*H$_B$*), 0.92 (3H, d, *J* = 7.1 Hz, CH$_3$)

* 2 × O*H* not observed

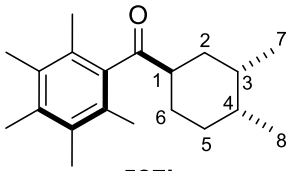
0.87–0.74 (3H, m, CH_3).*

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 65.7 ($C1H_2$), 61.4 ($C5H_2$), 39.4 (C3H), 34.5 ($C4H_2$), 29.9 (C2H), 17.5 (CH_3), 14.4 (CH_3).

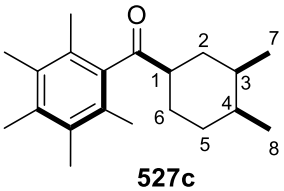
***rac*-((1*R*,3*R*,4*R*)-3,4-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 527a, *rac*-((1*R*,3*S*,4*R*)-3,4-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 527b and *rac*-((1*R*,3*R*,4*S*)-3,4-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 527c**



527a



527b



527c

Ketone **329** (114 mg, 0.600 mmol), 2,3-dimethylpentane-1,5-diol **526** (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (133 mg, 77%, 50:25:25 d.r.) as an inseparable mixture of diastereoisomers, as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.64 (1H, tt, *J* = 12.2, 3.3 Hz, C1H, **527a**), 2.78 (1H, tt, *J* = 12.1, 3.5 Hz, C1H, **527b**), 2.61 (1H, tt, *J* = 11.8, 3.8 Hz, C1H, **527c**). The mixture of diastereoisomers were analysed by 1D TOCSY to obtain clean ^{1}H NMR spectra for each diastereoisomer. Key nOe correlations from 2D NOESY data and *J*-coupling constant analysis were then used to determine the relative stereochemistry of each diastereoisomer.

Data for **527a**/**527b**/**527c** (50:25:25 d.r.):

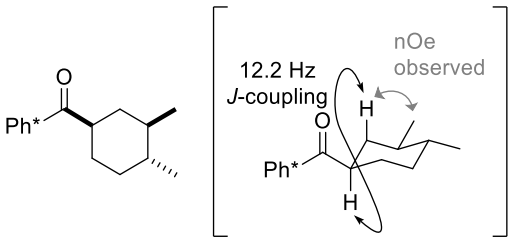
***R*$_f$** = 0.33 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2924, 2871, 1692, 1453, 1381, 1308, 1262, 1152, 1090, 1000, 950.

HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2370; $C_{20}H_{31}O$ requires 287.2369, Δ 0.27 ppm.

* 2 × O*H* not observed

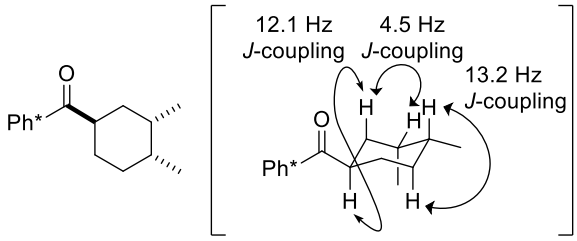
NMR data for **527a**:



^{1}H NMR (CD_2Cl_2, 700 MHz) δ = 2.64 (1H, tt, *J* = 12.2, 3.3 Hz, C1H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s. 2 × Ar-CH_3), 2.02 (6H, s, 2 × Ar-CH_3), 1.87 (1H, d. of quint., *J* = 11.3, 3.1 Hz, C6$H_{eq}H_{ax}$), 1.82 (1H, dq, *J* = 13.2, 3.0 Hz, C2$H_{eq}H_{ax}$), 1.76–1.72 (1H, m, C5$H_{eq}H_{ax}$), 1.41 (1H, qd, *J* = 12.9, 3.8 Hz, C6$H_{eq}H_{ax}$), 1.15 (1H, q, *J* = 12.4 Hz, C2$H_{eq}H_{ax}$), 1.03–0.95 (3H, m, C3H, C4H and C5$H_{eq}H_{ax}$), 0.92 (3H, d, *J* = 5.8 Hz, C7H_3), 0.89 (3H, d, *J* = 5.3 Hz, C8H_3).

^{13}C NMR (CD_2Cl_2, 176 MHz) δ = 214.3 (C=O), 140.2 (Ar-C), 135.2 (Ar-C), 132.9 (2C, 2 × Ar-C), 128.0 (2C, 2 × Ar-C), 53.3 (C1H), 38.7 (C3H *or* C4H), 38.6 (C3H *or* C4H), 36.8 (C2H_2), 35.0 (C5H_2), 28.3 (C6H_2), 19.8 (C7H_3), 19.6 (C8H_3), 17.7 (2C, 2 × Ar-CH_3), 16.4 (Ar-CH_3), 15.7 (2C, 2 × Ar-CH_3).

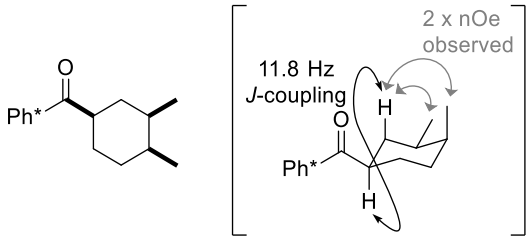
NMR data for **527b**:



^{1}H NMR (CD_2Cl_2, 700 MHz) δ = 2.78 (1H, tt, *J* = 12.1, 3.5 Hz, C1H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.02 (6H, s, 2 × Ar-CH_3), 1.93–1.90 (1H, m, C3H), 1.86 (1H, d. of quint., *J* = 12.9, 3.4 Hz, C6$H_{eq}H_{ax}$), 1.75 (1H, dq, *J* = 13.3, 3.0 Hz, C2$H_{eq}H_{ax}$), 1.68 (1H, td, *J* = 12.7, 4.5 Hz, C2$H_{eq}H_{ax}$), 1.64–1.60 (1H, m, C4H), 1.46 (1H, dq, *J* = 13.2, 3.6 Hz, C5$H_{eq}H_{ax}$), 1.40 (1H, qd, *J* = 12.7, 4.1 Hz, C6$H_{eq}H_{ax}$), 1.21 (1H, qd, *J* = 12.9, 3.8 Hz, C5$H_{eq}H_{ax}$), 0.86 (3H, d, *J* = 7.0 Hz, C8H_3), 0.81 (3H, d, *J* = 7.2 Hz, C7H_3).

^{13}C NMR (CD_2Cl_2, 176 MHz) δ = 215.1 (C=O), 140.3 (Ar-C), 135.1 (Ar-C), 132.9 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 46.6 (C1H), 35.2 ($C2H_2$), 34.5 (C3H), 32.8 (C4H), 28.5 ($C6H_2$), 27.9 ($C5H_2$), 19.4 ($C8H_3$), 17.7 (2C, 2 × Ar-CH_3), 16.4 (Ar-CH_3), 15.7 (2C, 2 × Ar-CH_3), 11.1 ($C7H_3$).

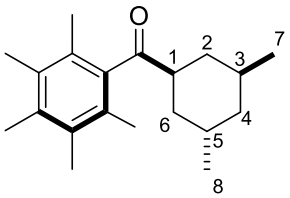
NMR data for **527c**:



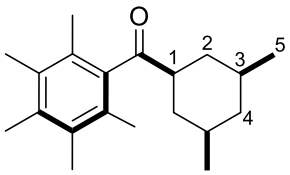
^{1}H NMR (CD_2Cl_2, 700 MHz) δ = 2.61 (1H, tt, *J* = 11.8, 3.8 Hz, C1H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s. 2 × Ar-CH_3), 2.02 (6H, s, 2 × Ar-CH_3), 1.79–1.75 (1H, m, C4H), 1.67–1.49 (6H, m, C2$H_{eq}$$H_{ax}$, C3H, C5$H_{eq}$$H_{ax}$ and C6$H_{eq}$$H_{ax}$), 1.33 (1H, q, *J* = 12.6 Hz, C2$H_{eq}$$H_{ax}$), 0.87 (3H, d, *J* = 6.9 Hz, $C7H_3$), 0.84 (3H, d, *J* = 7.2 Hz, $C8H_3$).

^{13}C NMR (CD_2Cl_2, 176 MHz) δ = 214.4 (C=O), 140.2 (Ar-C), 135.2 (Ar-C), 132.9 (2C, 2 × Ar-C), 128.0 (2C, 2 × Ar-C), 53.8 (C1H), 34.8 (C3H), 33.0 ($C5H_2$), 32.4 (C4H), 29.8 ($C2H_2$), 21.8 ($C6H_2$), 19.8 ($C8H_3$), 17.7 (2C, 2 × Ar-CH_3), 16.4 (Ar-CH_3), 15.7 (2C, 2 × Ar-CH_3), 11.1 ($C7H_3$).

***rac*-((3*S*,5*S*)-3,5-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 529a and *rac*-((1*s*,3*R*,5*S*)-3,5-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 529b**



529a (major)



529b (minor)

Ketone **329** (114 mg, 0.600 mmol), *syn*-2,4-dimethylpentane-1,5-diol[*] (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure**

[*] Synthesised by Dr James Frost.

M. Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (140 mg, 81%, 67:33 d.r.) as an inseparable mixture of diastereoisomers, as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 2.92 (1H, tt, *J* = 12.1, 3.7 Hz, C1H, **529a**), 2.72 (1H, tt, *J* = 12.3, 3.3 Hz, C1H, **529b**). A small amount of **529b** was isolated cleanly to aid characterisation. The relative stereochemistry was determined by *J*-coupling constant analysis.

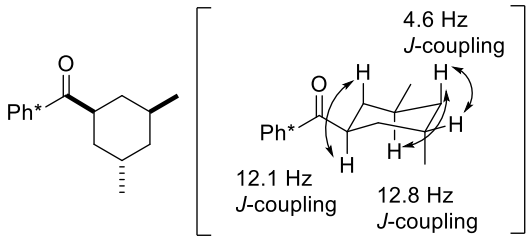
Data for **529a**/**529b** (67:33 d.r.):

R_f = 0.50 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2950, 2916, 1686, 1456, 1381, 1303, 1267, 1166, 1118, 1090, 1001, 938.

HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2371; $C_{20}H_{31}O$ requires 287.2369, Δ 0.54 ppm.

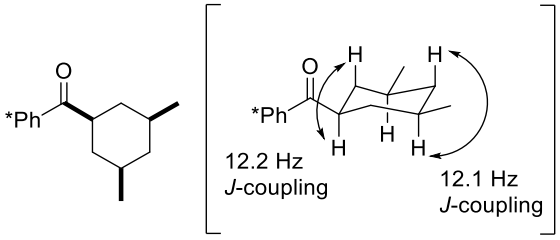
NMR data for **529a**:



^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.92 (1H, tt, *J* = 12.1, 3.7 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.17–2.12 (1H, m, C5H), 2.10 (6H, s, 2 × Ar-CH_3), 1.92–1.84 (1H, m, C2$H_{eq}$$H_{ax}$), 1.74–1.58 (3H, m, C6$H_{eq}H_{ax}$ and C3H), 1.51–1.40 (1H, m, C4$H_{eq}$$H_{ax}$), 1.13 (1H, td, *J* = 12.8, 4.6 Hz, C4$H_{eq}$$H_{ax}$), 1.07–0.98 (1H, m, C2$H_{eq}$$H_{ax}$), 0.96 (3H, d, *J* = 7.2 Hz, C8H_3), 0.88 (3H, d, *J* = 6.5 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.5 (C=O), 140.5 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 47.6 (C1H), 40.3 (C4H_2), 37.1 (C2H_2), 33.2 (C6H_2), 27.8 (C5H), 26.2 (C3H), 22.9 (C7H_3), 18.5 (C8H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

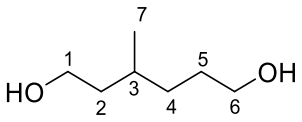
NMR data for **529b**:



^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.72 (1H, tt, *J* = 12.3, 3.3 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.86 (2H, br. d, *J* = 12.2 Hz, 2 × C2$H_{eq}$$H_{ax}$), 1.65 (1H, br d, *J* = 13.0 Hz, C4$H_{eq}$$H_{ax}$), 1.47–1.35 (2H, m, 2 × C3H), 1.04 (2H, q, *J* = 12.4 Hz, 2 × C2$H_{eq}$$H_{ax}$), 0.91 (6H, d, *J* = 6.5 Hz, 2 × C5H_3), 0.59 (1H, q, *J* = 12.1 Hz, C4$H_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.9 (C=O), 140.4 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 53.3 (C1H), 43.7 (C4H_2), 36.2 (2C, 2 × C2H_2), 32.3 (2C, 2 × C3H), 22.6 (2C, 2 × C5H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

3-Methylhexane-1,6-diol, 541



3-Methyladipic acid (1.28 g, 8.00 mmol), BH_3·$S(CH_3)_2$ (2.28 mL, 24.0 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (900 mg, 85%) as a colourless oil.

***R*$_f$** = 0.25 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3314, 2930, 2870, 1420, 1336, 1055, 1011, 899.

^{1}H NMR (CD_3OD, 400 MHz) δ = 3.62–3.53 (2H, m, C1H_2), 3.51 (2H, t, *J* = 6.7 Hz, C6H_2), 1.62–1.43 (4H, m, C2$H_A$$H_B$, C5$H_A$$H_B$ and C3H), 1.42–1.28 (2H, m, C4$H_A$$H_B$ and C2$H_A$$H_B$), 1.24–1.10 (1H, m, C4$H_A$$H_B$), 0.89 (3H, d, *J* = 6.5 Hz, C7H_3).*

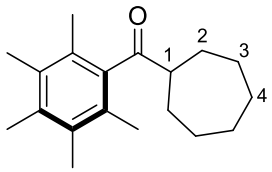
^{13}C NMR (CD_3OD, 101 MHz) δ = 63.2 (C6H_2), 61.0 (C1H_2), 40.7 (C2H_2), 34.3 (C4H_2), 31.0 (C5H_2), 30.5

* 2 × O*H* not observed

(C3H), 20.0 ($C7H_3$).

HRMS (ESI^+) Found $[M+H]^+$ = 133.1222; $C_7H_{17}O_2$ requires 133.1223, Δ –0.75 ppm.

3-Cyclopentyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 542



Ketone **329** (57 mg, 0.30 mmol), 1,6-hexanediol (71 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (67 mg, 1.2 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 95:5) provided the title compound (15 mg, 18%) as a white solid.

R_f = 0.36 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 55–57 °C.

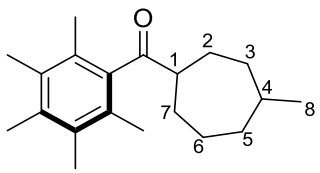
IR (film) ν_{max}/cm^{-1} 2936, 2857, 2361, 2341, 1692, 1495, 1450, 1381, 1354, 1309, 1265, 1101, 1022, 909.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.83 (1H, tt, *J* = 9.7, 4.3 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 2.03–1.94 (2H, m, 2 × C2$H_A$$H_B$), 1.80–1.70 (2H, m, 2 × C3$H_A$$H_B$), 1.70–1.61 (2H, m, 2 × C2$H_A$$H_B$), 1.61–1.50 (4H, m, 2 × C4$H_A$$H_B$), 1.49–1.38 (2H, m, 2 × C3$H_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.3 (C=O), 140.4 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.5 (2C, 2 × Ar-C), 54.9 (C1H), 29.6 (2C, 2 × $C2H_2$), 28.6 (2C, 2 × $C4H_2$), 26.6 (2C, 2 × $C3H_2$), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 295.2031; $C_{19}H_{28}ONa$ requires 295.2032, Δ –0.38 ppm.

(4-Methylcycloheptyl)(2,3,4,5,6-pentamethylphenyl)methanone, 544



Ketone **329** (114 mg, 0.600 mmol), *diol* **541** (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 95:5) provided the title compound (51 mg, 30%, 50:50 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 0.91 (3H, d, J = 5.6 Hz, C8H_3), 0.89 (3H, d, J = 6.0 Hz, C8H_3). NMR data for both diastereoisomers is presented together as it was not possible to differentiate the two sets of signals sufficiently for complete characterisation.

Data for diastereoisomer A/B (50:50 d.r.):

$\boldsymbol{R_f}$ = 0.17 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2924, 2866, 1685, 1453, 1378, 1304, 1110, 1067, 1020, 902.

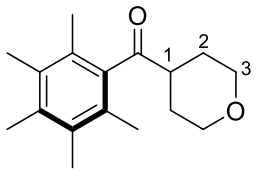
HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2367; $C_{20}H_{31}O$ requires 287.2369, Δ –0.76 ppm.

NMR data for both diastereoisomers combined:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.92–2.79 (2H, m, 2 × C1H), 2.23 (6H, s, 2 × Ar-CH_3), 2.16 (12H, s, 4 × Ar-CH_3), 1.97 (12H, s, 4 × Ar-CH_3), 2.06–1.93 (2H, m, 2 × C$H_A$$H_B$), 1.92–1.69 (8H, m, 2 × CH_AH_B, 4 × C$H_A$$H_B$), 1.66–1.53 (7H, m, CH_AH_B, C$H_A$$H_B$, 2 × CH_AH_B and 2 × C4H), 1.50–1.38 (1H, m, CH_AH_B), 1.37–1.22 (1H, m, CH_AH_B), 1.21–1.02 (3H, m, 3 × CH_AH_B), 0.91 (3H, d, J = 5.6 Hz, C8H_3), 0.89 (3H, d, J = 6.0 Hz, C8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.3 (C=O), 215.2 (C=O), 140.4 (2C, 2 × Ar-C), 135.5 (2C, 2 × Ar-C), 133.2 (4C, 4 × Ar-C), 128.5 (2C, 2 × Ar-C), 128.4 (2C, 2 × Ar-C), 55.1 (C1H), 54.3 (C1H), 38.3 (CH_2), 36.6 (CH_2), 36.1 (CH_2), 33.3 (CH_2), 30.2 (CH_2), 29.1 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 23.7 (CH_2), 18.1 (4C, 4 × Ar-CH_3), 16.9 (2C, 2 × Ar-CH_3), 16.2 (4C, 4 × Ar-CH_3).

(2,3,4,5,6-Pentamethylphenyl)(tetrahydro-2H-pyran-4-yl)methanone, 547



Ketone **329** (57 mg, 0.30 mmol), diethylene glycol (64 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (67 mg, 1.2 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 95:5→85:15) provided the title compound (26 mg, 33%) as a white solid.

R_f = 0.34 (Pentane:Et_2O, 85:15), [UV, vanillin].

m.p. = 141–142 °C.

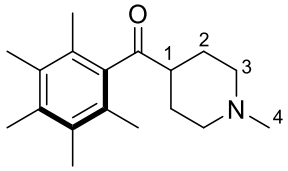
IR (film) ν_{max}/cm^{-1} 2933, 2838, 1688, 1441, 1384, 1318, 1299, 1274, 1237, 1150, 1114, 1088, 1014, 984.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.03 (2H, dt, *J* = 11.5, 3.5 Hz, 2 × C3$H_{eq}H_{ax}$), 3.42–3.33 (2H, m, 2 × C3$H_{eq}H_{ax}$), 2.89–2.76 (1H, m, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.87–1.75 (4H, m, 2 × C2$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.1 (C=O), 139.5 (Ar-C), 135.8 (Ar-C), 133.3 (2C, 2 × Ar-C), 128.1 (2C, 2 × Ar-C), 67.6 (2C, 2 × $C3H_2$), 50.0 (C1H), 28.2 (2C, 2 × $C2H_2$), 18.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 261.1849; $C_{17}H_{25}O_2$ requires 261.1849, Δ –0.13 ppm.

(1-Methylpiperidin-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 549



Ketone **329** (114 mg, 0.600 mmol), methyl diethanolamine (143 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.**

Purification by column chromatography (CH_2Cl_2:MeOH, 96:4, 1% Et_3N) provided the title compound (78 mg, 48%) as an off-white solid.

R_f = 0.15 (Pentane:Et_2O, 30:70, 1% Et_3N), [UV, $KMnO_4$].

m.p. = 110–111 °C.

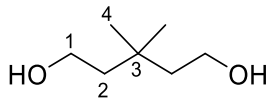
IR (film) ν_{max}/cm^{-1} 3368, 2937, 2781, 1692, 1447, 1380, 1313, 1277, 1148, 1120, 1068, 986.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.91 (2H, dt, *J* = 11.9, 3.3 Hz, 2 × C3$H_{eq}H_{ax}$), 2.60 (1H, tt, *J* = 11.9, 3.8 Hz, C1H), 2.24 (3H, s, C4H_3), 2.20 (3H, s, Ar-CH_3), 2.15 (6H, s, 2 × Ar-CH_3), 2.07–1.94 (8H, m, 2 × Ar-CH_3 and 2 × C3$H_{eq}H_{ax}$), 1.83 (2H, d, *J* = 13.4 Hz, 2 × C2$H_{eq}H_{ax}$), 1.67 (2H, qd, *J* = 12.5, 3.9 Hz, 2 × C2$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.9 (C=O), 140.5 (Ar-C), 136.7 (Ar-C), 134.2 (2C, 2 × Ar-C), 128.9 (2C, 2 × Ar-C), 56.1 (2C, 2 × C3H_2), 51.2 (C1H), 46.1 (C4H_3), 28.3 (2C, 2 × C2H_2), 18.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 274.2166; $C_{18}H_{28}NO$ requires 274.2165, Δ 0.23 ppm.

3,3-Dimethylpentane-1,5-diol, 554



3,3-dimethylpentanedioic acid (1.00 g, 6.24 mmol), $BH_3{\cdot}S(CH_3)_2$ (1.77 mL, 18.7 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (510 mg, 62%) as a colourless oil.

R_f = 0.12 (Pentane:EtOAc, 50:50), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3310, 2955, 1470, 1366, 1153, 1032, 1008.

^{1}H NMR (CD_3OD), 400 MHz) δ = 3.62 (4H, t, *J* = 7.7 Hz, 2 × C1H_2), 1.51 (4H, t, *J* = 7.3 Hz, 2 × C2H_2), 0.94 (6H, s, 2 × C4H_3).*

^{13}C NMR (CD_3OD), 101 MHz) δ = 59.6 (2C, 2 × C1H_2), 45.3 (2C, 2 × C2H_2), 32.3 (C3), 28.3 (2C,

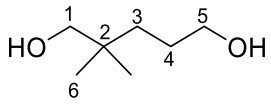
* 2 × O*H* not observed

2 × C4H$_3$).

HRMS (ESI$^+$) Found [M+H]$^+$ = 133.1221; $C_7H_{17}O_2$ requires 133.1223, Δ –1.35 ppm.

All spectroscopic data in agreement with that previously reported.[127]

2,2-Dimethylpentane-1,5-diol, 555



2,2-Dimethylglutaric acid (1.28 g, 8.00 mmol), $BH_3{\cdot}S(CH_3)_2$ (2.28 mL, 24.0 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (1.04 g, 98%) as a colourless oil.

***R*$_f$** = 0.15 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3324, 2948, 2871, 1473, 1416, 1383, 1340, 1033.

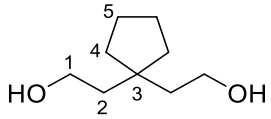
^{1}H NMR (CD_3OD, 400 MHz) δ = 3.46 (2H, t, *J* = 6.7 Hz, C5H$_2$), 3.18 (2H, s, C1H$_2$), 1.50–1.37 (2H, m, C4H$_2$), 1.25–1.16 (2H, m, C3H$_2$), 0.80 (6H, s, 2 × C6H$_3$).

^{13}C NMR (CD_3OD, 101 MHz) δ = 71.8 (C1H$_2$), 63.9 (C5H$_2$), 35.7 (2C, C3H$_2$ and C2), 28.1 (C4H$_2$), 24.4 (2C, 2 × C6H$_3$).

HRMS (ESI$^+$) Found [M+H]$^+$ = 133.1222; $C_7H_{17}O_2$ requires 133.1223, Δ –0.90 ppm.

All spectroscopic data in agreement with that previously reported.[128]

2,2'-(Cyclopentane-1,1-diyl)bis(ethan-1-ol), 556



3,3-Tetramethyleneglutaric acid (1.12 g, 6.00 mmol), $BH_3{\cdot}S(CH_3)_2$ (1.71 mL, 18.0 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (554 mg, 58%) as a colourless oil.

***R*$_f$** = 0.12 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

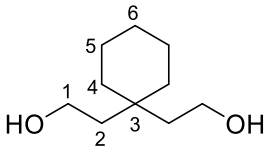
IR (film) ν_{max}/cm^{-1} 3318, 2942, 2864, 1602, 1420, 1344, 1172, 1041, 1008.

^{1}H NMR (CD_3OD, 400 MHz) δ = 3.66–3.55 (4H, m, 2 × C1H_2), 1.65–1.60 (4H, m, 2 × C5H_AH_B), 1.59–1.52 (4H, m, 2 × C2H_2), 1.47–1.40 (4H, m, 2 × C4H_AH_B).

^{13}C NMR (CD_3OD, 101 MHz) δ = 60.2 (2C, 2 × C1H_2), 43.8 (C3), 42.0 (2C, 2 × C2H_2), 39.4 (2C, 2 × C4H_2), 25.3 (2C, 2 × C5H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 159.1379; $C_9H_{19}O_2$ requires 159.1380, Δ –0.24 ppm.

2,2'-(Cyclohexane-1,1-diyl)bis(ethan-1-ol), 557



1,1-Cyclohexanediacetic acid (1.20 g, 6.00 mmol), $BH_3{\cdot}S(CH_3)_2$ (1.71 mL, 18.0 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (440 mg, 43%) as a colourless oil.

R_f = 0.14 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

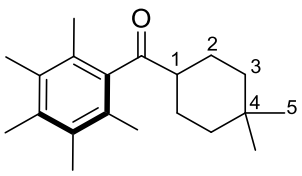
IR (film) ν_{max}/cm^{-1} 3314, 2922, 2853, 1456, 1420, 1344, 1042, 1009.

^{1}H NMR (CD_3OD, 400 MHz) δ = 3.63–3.54 (4H, m, 2 × C1H_2), 1.59–1.53 (4H, m, 2 × C2H_2), 1.51–1.37 (6H, m, 2 × C5$H_{eq}H_{ax}$ and C6$H_{eq}H_{ax}$), 1.35–1.27 (4H, m, 2 × C4$H_{eq}H_{ax}$).

^{13}C NMR (CD_3OD, 101 MHz) δ = 58.9 (2C, 2 × C1H_2), 40.8 (2C, 2 × C2H_2), 37.6 (2C, 2 × C4H_2), 34.8 (C3), 27.5 (C6H_2), 22.6 (2C, 2 × C5H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 173.1530; $C_{10}H_{21}O_2$ requires 173.1536, Δ –3.59 ppm.

(4,4-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 558



Ketone **329** (114 mg, 0.600 mmol), *diol* **554** (125 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%)

and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (143 mg, 83%) as a white solid.

R_f = 0.35 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 109–110 °C.

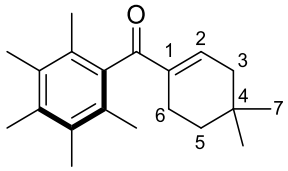
IR (film) ν_{max}/cm^{-1} 2902, 2844, 2360, 1688, 1455, 1385, 1363, 1317, 1270, 1162, 1109, 931.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.55 (1H, tt, *J* = 12.0, 3.8 Hz, C1H), 2.25 (3H, s, Ar-CH_3), 2.20 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 1.81–1.72 (2H, m, 2 × C2$H_{eq}H_{ax}$), 1.66 (2H, qd, *J* = 13.4, 3.5 Hz, 2 × C2$H_{eq}H_{ax}$), 1.51–1.43 (2H, m, 2 × C3$H_{eq}H_{aq}$), 1.17 (2H, td, *J* = 13.3, 4.1 Hz, 2 × C3$H_{eq}H_{aq}$), 0.94 (3H, s, C5H_3), 0.91 (3H, s, C5'H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.3 (C=O), 140.3 (Ar-C), 135.4 (Ar-C), 133.1 (2 × Ar-C), 128.1 (2 × Ar-C), 53.2 (C1H), 38.7 (2 × C3H_2), 32.9 (C5'H_3), 29.9 (C4), 24.2 (2 × C2H_2), 24.1 (C5H_3), 18.0 (2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 287.2366; $C_{20}H_{31}O$ requires 287.2369, Δ –1.25 ppm.

(4,4-Dimethylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 646



The title compound was isolated (22 mg, 13%) as a side product from the preparation of *ketone* **329** under a modified **general procedure M** using 1.1 equiv. of diol **554**.

R_f = 0.26 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 122–123 °C

IR (film) ν_{max}/cm^{-1} 2922, 2866, 2360, 2341, 1687, 1651, 1636, 1458, 1378, 1302, 1269, 1207, 1170, 1128, 1066, 1026, 856.

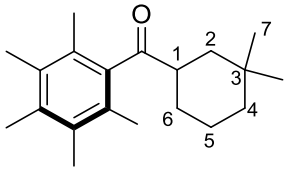
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.44 (1H, tt, *J* = 4.0, 1.7 Hz, C2H), 2.49–2.43 (2H, m, C6H_AH_B), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.02 (6H, s, 2 × Ar-CH_3), 1.94 (2H, dt, *J* = 4.5, 2.4 Hz, C3H_AH_B),

1.48 (2H, t, *J* = 6.5 Hz, C5H_AH_B), 0.93 (6H, s, 2 × C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 203.5 (C=O), 144.9 (C2H), 139.6 (C1), 138.4 (Ar-C), 135.1 (Ar-C), 132.7 (2C, 2 × Ar-C), 129.2 (2C, 2 × Ar-C), 40.3 (C3H_2), 35.0 (C5H_2), 28.9 (C4), 28.2 (2C, 2 × C7H_3), 20.4 (C6H_2), 17.6 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 285.2212; $C_{20}H_{29}O$ requires 285.2213, Δ –0.50 ppm.

(3,3-Dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 559



Ketone **329** (114 mg, 0.600 mmol), 2,2-dimethylpentane-1,5-diol **555** (159 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (136 mg, 79%) as a white solid.

***R*$_f$** = 0.39 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 124–125 °C.

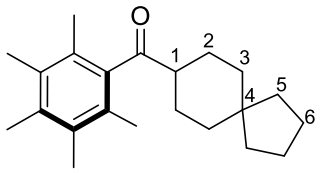
IR (film) ν_{max}/cm^{-1} 2928, 2863, 1692, 1457, 1384, 1365, 1305, 1275, 1185, 1122. 1000, 968.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.83 (1H, tt, *J* = 12.4, 3.4 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.96–1.87 (1H, m, C6$H_{eq}H_{ax}$), 1.66–1.57 (2H, m, C2$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.48–1.33 (3H, m, C5$H_{eq}H_{ax}$, C2$H_{eq}H_{ax}$ and C4$H_{eq}H_{ax}$), 1.25 (1H, qd, *J* = 12.7, 3.9 Hz, C6$H_{eq}H_{ax}$), 1.14 (1H, td, *J* = 13.3, 4.3 Hz, C4$H_{eq}H_{ax}$), 0.96 (3H, s, C7H_3), 0.87 (3H, s, C7'H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.4 (C=O), 140.5 (Ar-C), 135.5 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.2 (2C, 2 × Ar-C), 49.3 (C1H), 40.6 (C2H_2), 38.8 (C4H_2), 33.4 (C7$_A$H$_3$), 30.7 (C3), 28.6 (C6H_2), 24.4 (C7$_B$H$_3$), 22.1 (C5H_2), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 287.2369; $C_{20}H_{31}O$ requires 287.2369, Δ –0.26 ppm.

(2,3,4,5,6-Pentamethylphenyl)(spiro[4.5]decan-8-yl)methanone, 560



Ketone **329** (114 mg, 0.600 mmol), *diol* **556** (190 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (165 mg, 88%) as a white solid.

$\boldsymbol{R_f}$ = 0.50 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 114–115 °C.

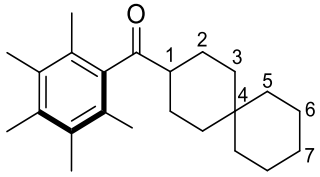
IR (film) ν_{max}/cm^{-1} 2934, 2861, 1692, 1447, 1383, 1313, 1264, 1157, 1109, 985.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.50 (1H, tt, *J* = 12.3, 3.6 Hz, C1H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.02 (6H, s, 2 × Ar-CH_3), 1.78–1.68 (2H, m, 2 × C2$H_{eq}$$H_{ax}$), 1.58–1.42 (8H, m, 2 × C2$H_{eq}$$H_{ax}$, 2 × C3$H_{eq}$$H_{ax}$, C6$H_AH_B$ and C6'H_AH_B), 1.37 (2H, t, *J* = 6.9 Hz, C5H_AH_B), 1.25 (2H, t, *J* = 6.9 Hz, C5'H_AH_B), 1.16 (2H, td, *J* = 13.8, 3.8 Hz, 2 × C3$H_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.4 (C=O), 140.4 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.2 (2C, 2 × Ar-C), 53.2 (C1H), 42.3 (C4), 42.1 ($C5_BH_2$), 37.6 (2C, 2 × $C3H_2$), 34.6 ($C5_AH_2$), 25.6 (2C, 2 × $C2H_2$), 25.1 ($C6_AH_2$), 24.2 ($C6_BH_2$), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 313.2526; $C_{22}H_{33}O$ requires 313.2526, Δ –0.01 ppm.

(2,3,4,5,6-Pentamethylphenyl)(spiro[5.5]undecan-3-yl)methanone, 561



Ketone **329** (114 mg, 0.600 mmol), *diol* **557** (207 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (170 mg, 87%) as a white solid.

R_f = 0.35 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 120–121 °C.

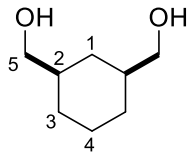
IR (film) ν_{max}/cm^{-1} 2924, 2859, 1691, 1448, 1382, 1314, 1265, 1187, 1136, 1109, 998.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.57 (1H, tt, *J* = 11.7, 3.9 Hz, C1H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.78–1.66 (4H, m, 2 × C3$H_{eq}H_{ax}$, 2 × C2$H_{eq}H_{ax}$), 1.66–1.53 (2H, m, 2 × C2$H_{eq}H_{ax}$), 1.42 (8H, br. s, C5$H_{eq}H_{ax}$, C7$H_{eq}H_{ax}$, C6$H_{eq}H_{ax}$ and C6'$H_{eq}H_{ax}$), 1.22–1.15 (2H, m, C5'$H_{eq}H_{ax}$), 1.00 (2H, td, *J* = 13.2, 4.4 Hz, 2 × C3$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.4 (C=O), 140.4 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.2 (2C, 2 × Ar-C), 53.8 (C1H), 41.7 ($C5_BH_2$), 36.3 (2C, 2 × $C3H_2$), 32.2 (C4), 31.9 ($C5_AH_2$), 27.0 ($C7H_2$), 23.4 (2C, 2 × $C2H_2$), 21.8 ($C6_AH_2$), 21.7 ($C6_BH_2$), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 327.2678; $C_{23}H_{35}O$ requires 327.2682, Δ –1.37 ppm.

***rac*-((1*R*,3*S*)-Cyclohexane-1,3-diyl)dimethanol, 564**



cis-1,3-Cyclohexanedicarboxylic acid (1.38 g, 8.00 mmol), $BH_3{\cdot}S(CH_3)_2$ (2.28 mL, 24.0 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (1.15 g, 99%) as a colourless oil.

R_f = 0.18 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

m.p. = 55–56 °C.

IR (film) ν_{max}/cm^{-1} 3324, 2917, 2853, 1448, 1416, 1332, 1269, 1064, 1030.

^{1}H NMR (CD_3OD, 400 MHz) δ = 3.31 (4H, d, *J* = 6.4 Hz, 2 × $C5H_2$), 1.85–1.70 (4H, m, C1$H_{eq}H_{ax}$, C4$H_{eq}H_{ax}$ and 2 × C3$H_{eq}H_{ax}$), 1.49–1.37 (2H, m, 2 × C2H), 1.26 (1H, qt, *J* = 13.1, 3.5 Hz, C4$H_{eq}H_{ax}$), 0.81 (1H, qd, *J* = 12.8, 4.0 Hz, 2 × C3$H_{eq}H_{ax}$), 0.53 (1H, q, *J* = 12.1 Hz, C1$H_{eq}H_{ax}$).

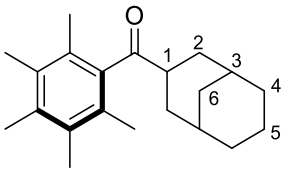
^{13}C NMR (CD_3OD, 101 MHz) δ = 68.9 (2C, 2 × $C5H_2$), 41.4 (2C, 2 × C2H), 33.9 ($C1H_2$), 30.8 (2C,

2 × $C3H_2$), 26.5 ($C4H_2$).

HRMS (ESI^+) Found $[M+H]^+$ = 145.1223; $C_8H_{17}O_2$ requires 145.1223, Δ –0.07 ppm.

All spectroscopic data in agreement with that previously reported.[129]

Bicyclo[3.3.1]nonan-3-yl(2,3,4,5,6-pentamethylphenyl)methanone, 565



Ketone **329** (114 mg, 0.600 mmol), *cis-diol* **564** (173 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (52 mg, 29%) as a white solid. A key nOe correlation from 2D NOESY data was used to determine the relative stereochemistry.

$\boldsymbol{R_f}$ = 0.32 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

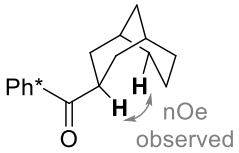
m.p. = 113–114 °C.

IR (film) ν_{max}/cm^{-1} 2916, 2850, 1694, 1445, 1383, 1304, 1262, 1129, 1007, 944.

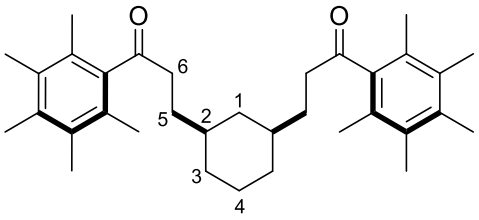
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.50–3.37 (1H, m, C1H), 2.17 (3H, s, Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.03 (6H, s, 2 × Ar-CH_3), 1.96–1.88 (2H, m, 2 × C3H), 1.82–1.74 (4H, m, 2 × $C2H_AH_B$), 1.68–1.54 (5H, m, 2 × $C4H_AH_B$ and $C5H_AH_B$), 1.51–1.42 (3H, m, $C6H_AH_B$ and $C5H_AH_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.4 (C=O), 140.8 (Ar-C), 135.5 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.2 (2C, 2 × Ar-C), 48.8 (C1H), 34.4 ($C6H_2$), 33.3 (2C, 2 × $C2H_2$), 31.0 (2C, 2 × $C4H_2$), 27.8 (2C, 2 × C3H), 22.3 ($C5H_2$), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 299.2369; $C_{21}H_{31}O$ requires 299.2369, Δ –0.15 ppm.



***rac*-3,3'-((1*R*,3*S*)-Cyclohexane-1,3-diyl)bis(1-(2,3,4,5,6-pentamethylphenyl)propan-1-one), 566**



In the preparation of *ketone* **565** under **general procedure M**, the title compound (100 mg, 68%) was obtained as a white solid. The relative stereochemistry was determined by *J*-coupling constant analysis.

R_f = 0.05 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

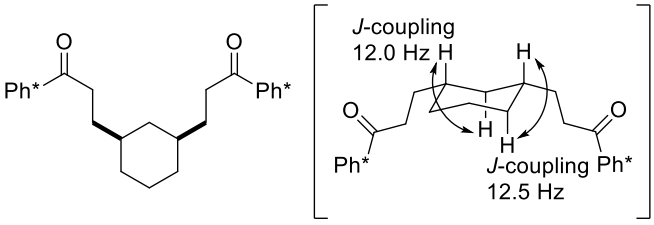
m.p. = 86–86 °C.

IR (film) ν_{max}/cm^{-1} 2919, 2853, 1700, 1448, 1406, 1382, 1319, 1269, 1114, 933.

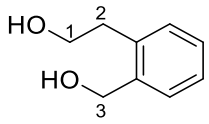
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.71 (4H, t, *J* = 7.6 Hz, 2 × C6H_2), 2.26 (6H, s, 2 × Ar-CH_3), 2.21 (12H, s, 4 × Ar-CH_3), 2.12 (12H, s, 4 × Ar-CH_3), 1.83–1.71 (4H, m, 2 × C3$H_{eq}$$H_{ax}$, C1$H_{eq}$$H_{ax}$ and C4$H_{eq}$$H_{ax}$), 1.64 (q, *J* = 7.4 Hz, 2 × C5H_2), 1.39–1.18 (3H, m, 2 × C2H and C4$H_{eq}$$H_{ax}$), 0.86 (2H, qd, *J* = 12.5, 3.7 Hz, C3$H_{eq}$$H_{ax}$), 0.64 (1H, q, *J* = 12.0 Hz, C1$H_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.6 (2C, 2 × C=O), 141.0 (2C, 2 × Ar-C), 135.4 (2C, 2 × Ar-C), 133.2 (4C, 4 × Ar-C), 127.4 (4C, 4 × Ar-C), 43.2 (2C, 2 × C6H_2), 40.0 (C1H_2), 37.3 (2C, 2 × C2H), 33.1 (2C, 2 × C3H_2), 30.8 (2C, 2 × C5H_2), 26.2 (C4H_2), 17.4 (4C, 4 × Ar-CH_3), 16.8 (2C, 2 × Ar-CH_3), 16.1 (4C, 4 × Ar-CH_3).

HRMS (ESI^+) Found $[M+Na]^+$ = 511.3545; $C_{34}H_{48}O_2Na$ requires 511.3547, Δ –0.38 ppm.



2-(2-(Hydroxymethyl)phenyl)ethan-1-ol, 568



Homophthalic acid (1.44 g, 8.00 mmol), $BH_3{\cdot}S(CH_3)_2$ (2.28 mL, 24.0 mmol) and THF (20 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (900 mg, 74%) as a pale yellow oil.

R_f = 0.17 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3290, 2878, 1702, 1452, 1335, 1296, 1247, 1212, 1124, 1039, 1006, 878.

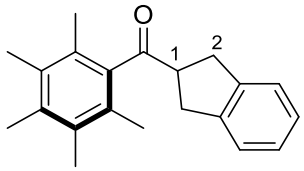
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.32 (1H, m, Ph), 7.21–7.11 (3H, m, Ph), 4.62 (2H, s, $C3H_2$), 3.71 (2H, t, *J* = 7.1 Hz, $C1H_2$), 2.88 (2H, t, *J* = 7.1 Hz, $C2H_2$).

^{13}C NMR (CD_3OD, 101 MHz) δ = 140.4 (Ar-C), 138.5 (Ar-C), 131.0 (Ar-CH), 129.7 (Ar-CH), 128.8 (Ar-CH), 127.4 (Ar-CH), 63.9 ($C1H_2$), 63.1 ($C3H_2$), 36.4 ($C2H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 175.0729; $C_9H_{12}O_2Na$ requires 175.0730, Δ –0.20 ppm.

All spectroscopic data in agreement with that previously reported.[130]

(2,3-Dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 570



Ketone **329** (57 mg, 0.30 mmol), 1,2-phenylenedimethanol (83 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2.0 mol%) and KOH (68 mg, 1.2 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 97:3) provided the title compound (23 mg, 26%) as a white solid.

R_f = 0.22 (Pentane:Et_2O, 95:5), [UV, vanillin].

m.p. = 113–114 °C

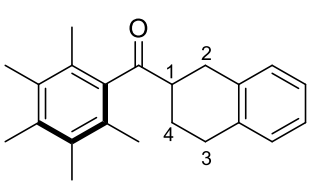
IR (film) ν_{max}/cm^{-1} 2922, 1686, 1459, 1262, 1114, 753.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23–7.15 (4H, m, Ph), 3.77 (1H, quint., *J* = 8.4 Hz, C1H), 3.36 (2H, dd, *J* = 15.6, 8.2 Hz, 2 × C2H_AH$_B$), 3.14 (2H, dd, *J* = 15.6, 8.7 Hz, 2 × C2H$_A$$H_B$), 2.27 (3H, s, Ar-$CH_3$), 2.22 (6H, s, 2 × Ar-$CH_3$), 2.13 (6H, s, 2 × Ar-$CH_3$).

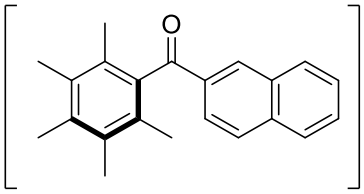
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.4 (C=O), 141.8 (2C, 2 × Ar-C), 140.2 (Ar-C), 135.7 (Ar-C), 133.3 (2C, 2 × Ar-C), 127.9 (2C, 2 × Ar-C), 126.7 (2C, 2 × Ar-CH), 124.5 (2C, 2 × Ar-CH), 54.0 (C1H), 35.6 (2C, 2 × $C2H_2$), 18.0 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI$^+$) Found $[M+H]^+$ = 293.1899; $C_{21}H_{25}O$ requires 293.1900, Δ –0.39 ppm.

(2,3,4,5,6-Pentamethylphenyl)(1,2,3,4-tetrahydronaphthalen-2-yl)methanone, 571 and Naphthalen-2-yl(2,3,4,5,6-pentamethylphenyl)methanone, 572



571



572

Ketone **329** (114 mg, 0.600 mmol), *diol* **568** (183 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compounds **571** and **572** as a white solid and as an inseparable mixture (163 mg, **571**:**572**, 51:49). The ratio was determined by ^{1}H NMR analysis of the mixture by comparison of the following signals: *δ* 1.68 (1H, qd, *J* = 12.0, 5.6 Hz, C4H$_{eq}$$H_{ax}$, **571**), 8.11 (1H, s, Ar-CH, **572**).

Data for **571**/**572** (51:49 ratio):

***R*$_f$** = 0.27 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2928, 1663, 1626, 1595, 1462, 1384, 1351, 1310, 1278, 1211, 1178, 1125, 1068, 1020, 913.

NMR and HRMS data for **571**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.13–6.97 (4H, m, Ph), 3.12–2.95 (2H, m, C2$H_{eq}$$H_{ax}$ and C1H), 2.93–2.68 (3H, m, C2$H_{eq}$$H_{ax}$, C3$H_{eq}$$H_{ax}$), 2.23 (3H, s, Ar-$CH_3$), 2.20–2.13 (1H, m, C4$H_{eq}$$H_{ax}$) 2.12 (6H, s, 2 × Ar-$CH_3$), 2.05 (6H, s, 2 × Ar-$CH_3$), 1.68 (1H, qd, *J* = 12.0, 5.6 Hz, C4$H_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.9 (C=O), 139.8 (Ar-C), 135.8 (Ar-C), 135.7 (Ar-C) 135.4 (Ar-C), 133.2 (2C, 2 × Ar-C), 129.3 (2C, 2 × Ar-CH), 128.8 (2C, 2 × Ar-C), 125.9 (Ar-CH), 125.8 (Ar-CH), 49.7 (C1H), 30.7 (C2H_2), 29.4 (C3H_2), 25.5 (C4H_2), 18.0 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 307.2056; $C_{22}H_{27}O$ requires 307.2056, Δ –0.27 ppm.

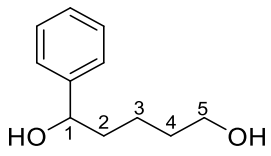
NMR and HRMS data for **572**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.11 (1H, s, Ar-CH), 7.98 (1H, d, *J* = 8.6 Hz, Ar-CH), 7.85–7.76 (3H, m, 3 × Ar-CH), 7.51 (1H, t, *J* = 7.5 Hz, Ar-CH), 7.42 (1H, t, *J* = 7.2 Hz, Ar-CH), 2.23 (3H, s, Ar-CH_3), 2.16 (6H, s, 2 × Ar-CH_3), 1.97 (6H, s, 2 × Ar-CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 202.0 (C=O), 137.8 (Ar-C), 135.9 (Ar-C), 135.1 (Ar-C), 133.0 (2C, 2 × Ar-C), 132.7 (Ar-C), 132.2 (Ar-CH), 129.8 (Ar-CH), 129.2 (2C, 2 × Ar-C), 128.7 (Ar-CH), 128.7 (Ar-CH), 127.8 (Ar-CH), 126.7 (Ar-CH), 124.4 (Ar-CH), 17.7 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 303.1743; $C_{22}H_{23}O$ requires 303.1743, Δ –0.26 ppm.

1-Phenylpentane-1,5-diol, 577



To a solution of 5-oxo-5-phenylpentanoic acid (2.00 g, 10.4 mmol) in THF (60 mL) at 0 °C was added $LiAlH_4$ (1.58 g, 41.6 mmol) portionwise. The reaction was slowly warmed to RT over 1 h. After this time, the reaction was quenched by careful dropwise addition of water (1.6 mL), $NaOH_{(aq)}$

(15% w/v, 1.6 mL) and water (4.7 mL). The reaction mixture was diluted with Et_2O (20 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (1.82 g, 97%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.14 (CH_2Cl_2:MeOH, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3319, 2936, 2863, 1493, 1453, 1202, 1054, 1026, 915.

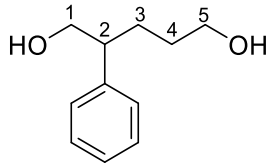
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.37–7.20 (5H, m, Ph), 4.60 (1H, dd, *J* = 7.4, 6.0 Hz, C1H), 3.52 (2H, t, *J* = 6.5 Hz, C5H_2), 1.87–1.65 (2H, m, C2H_AH_B), 1.61–1.50 (2H, m, C4H_2), 1.49–1.40 (1H, m, C3H_AH_B), 1.38–1.26 (1H, m, C3H_AH_B).

^{13}C NMR (CD_3OD, 101 MHz) δ = 146.5 (Ar-C), 129.2 (2C, 2 × Ar-CH), 128.2 (Ar-CH), 127.1 (2C, 2 × Ar-CH), 75.1 (C1H), 62.9 (C5H_2), 40.1 (C2H_2), 33.5 (C4H_2), 23.3 (C3H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 203.1043; $C_{11}H_{16}O_2Na$ requires 203.1043, Δ 0.09 ppm.

All spectroscopic data in agreement with that previously reported.[131]

2-Phenylpentane-1,5-diol, 578[132]



To a solution of 2-phenyl glutaric anhydride (761 mg, 4.00 mmol) in THF (15 mL) at 0 °C was added $LiAlH_4$ (455 mg, 12.0 mmol) portionwise. The reaction was slowly warmed to RT over 4 h. After this time, the reaction was quenched by careful dropwise addition of water (0.46 mL), $NaOH_{(aq)}$ (15% w/v, 0.46 mL) and water (1.4 mL). The reaction mixture was diluted with Et_2O (20 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (735 mg, 99%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.18 (CH_2Cl_2:MeOH, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3315, 2935, 2868, 1602, 1494, 1452, 1036, 903.

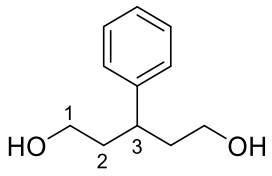
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.33–7.27 (2H, m, Ph), 7.25–7.17 (3H, m, Ph), 3.68 (2H, dd, *J* = 6.8, 1.1 Hz, C1H_2), 3.51 (2H, td, *J* = 6.7, 1.4 Hz, C5H_2), 2.73 (1H, dtd, *J* = 10.2, 6.8, 4.6 Hz, C2H), 1.95–1.84 (1H m, C3H_AH$_B$), 1.68–1.55 (1H, m, C3H$_A$$H_B$), 1.48–1.36 (2H, m, C4$H_2$).

^{13}C NMR (CD_3OD, 101 MHz) δ = 144.2 (Ar-C), 129.4 (2C, 2 × Ar-CH), 129.1 (2C, 2 × Ar-CH), 127.4 (Ar-CH), 68.1 (C1H_2), 63.0 (C5H_2), 49.8 (C2H), 31.5 (C4H_2), 29.5 (C3H_2).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 203.1043; $C_{11}H_{16}O_2Na$ requires 203.1043, Δ 0.42 ppm.

All spectroscopic data in agreement with that previously reported.[132]

3-Phenylpentane-1,5-diol, 497



3-phenylpentanedioic acid (1.00 g, 4.80 mmol), $BH_3{\cdot}S(CH_3)_2$ (1.37 mL, 14.4 mmol) and THF (15 mL) were subjected to **general procedure K**. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (795 mg, 92%) as a colourless oil.

***R*$_f$** = 0.13 (CH_2Cl_2:MeOH, 95:5), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3313, 3027, 2933, 1602, 1493, 1452, 1420, 1335, 1040, 889.

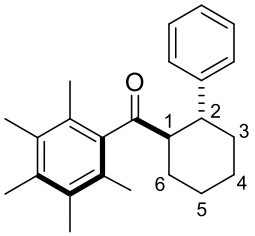
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.33–7.13 (5H, m, Ph), 3.44–3.32 (4H, m, 2 × C1H_2), 2.86 (1H, tt, *J* = 10.0, 5.1 Hz, C3H), 1.96–1.74 (4H, m, 2 × C2H_2).

^{13}C NMR (CD_3OD, 101 MHz) δ = 146.0 (Ar-C), 129.5 (2C, 2 × Ar-CH), 128.7 (2C, 2 × Ar-CH), 127.3 (Ar-CH), 60.9 (2C, 2 × C1H_2), 40.6 (2C, 2 × C2H_2), 39.7 (C3H).

HRMS (ESI$^+$) Found $[M+H]^+$ = 181.1223; $C_{11}H_{17}O_2$ requires 181.1223, Δ –0.21 ppm.

All spectroscopic data in agreement with that previously reported.[133]

***rac*-(2,3,4,5,6-Pentamethylphenyl)((1*R*,2*R*)-2-phenylcyclohexyl)methanone, 579**



Ketone **329** (114 mg, 0.600 mmol), *diol* **577** (216 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 97:3) provided the title compound (156 mg, 78%, > 95:5 d.r.) as a white solid. The relative stereochemistry was determined by *J*-coupling constant analysis.

$\boldsymbol{R_f}$ = 0.38 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

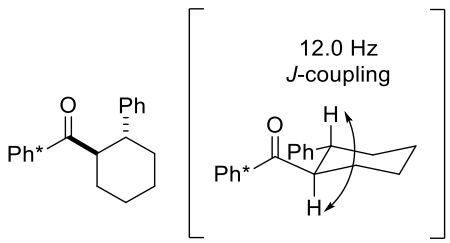
m.p. = 170–171 °C

IR (film) ν_{max}/cm^{-1} 2926, 2851, 1686, 1494, 1445, 1302, 1262, 1232, 1135, 1103, 1068, 1019, 935.

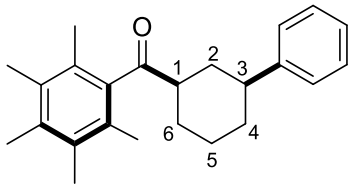
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.31–7.23 (2H, m, Ph), 7.19–7.11 (2H, m, Ph), 7.10–7.02 (1H, m, Ph), 3.04 (1H, td, *J* = 12.0, 3.8 Hz, C2H), 2.92 (1H, td, *J* = 11.2, 3.4 Hz, C1H), 2.10 (3H, s, Ar-CH_3), 2.02 (6H, s, 2 × Ar-CH_3), 1.95–1.89 (1H, m, C6$H_{eq}H_{ax}$), 1.88–1.81 (1H, m, C3$H_{eq}H_{ax}$) 1.93–1.19 (6H, br. s, 2 × Ar-CH_3), 1.80–1.71 (2H, m, C4$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.54 (1H, qd, *J* = 12.5, 3.1 Hz, C3$H_{eq}H_{ax}$), 1.36–1.17 (3H, m, C6$H_{eq}H_{ax}$, C4$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.8 (C=O), 145.2 (Ar-C), 139.4 (Ar-C), 135.5 (Ar-C), 132.9 (2C, 2 × Ar-C), 128.9 (4C, 2 × Ar-C and 2 × Ar-CH), 127.9 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 58.6 (C1H), 44.3 (C2H), 34.0 ($C3H_2$), 30.0 ($C6H_2$), 26.4 ($C5H_2$), 26.3 ($C4H_2$), 17.9 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 335.2367; $C_{24}H_{31}O$ requires 335.2369, Δ –0.67 ppm.



***rac*-(2,3,4,5,6-Pentamethylphenyl)((1*R*,3*S*)-3-phenylcyclohexyl)methanone, 580**



Ketone **329** (114 mg, 0.600 mmol), *diol* **578** (216 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (67 mg, 1.20 mmol) were subjected to a modified **general procedure M**, using 2 equiv. of KOH**.** Purification by column chromatography (Pentane:Et_2O, 95:5) provided the title compound (100 mg, 50%, > 95:5 d.r.) as a white solid. The relative stereochemistry was determined by *J*-coupling constant analysis.

***R*$_f$** = 0.29 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

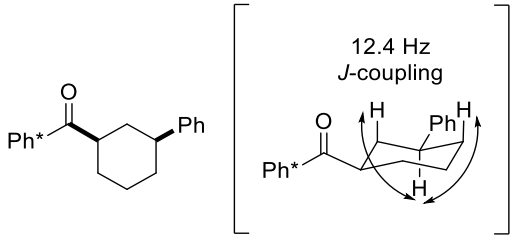
m.p. = 149–150 °C.

IR (film) ν_{max}/cm^{-1} 2929, 2856, 1691, 1601, 1494, 1447, 1382, 1312, 1263, 1192, 1141, 1092, 1070, 1009, 933.

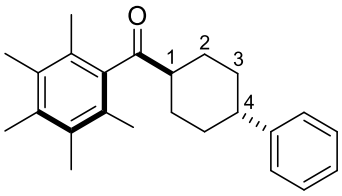
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.08 (5H, m, Ph), 2.75 (1H, tt, *J* = 11.9, 3.2 Hz, C1H), 2.46 (1H, tt, *J* = 11.9, 3.4 Hz, C3H), 2.15 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.08–1.99 (1H, m, C2$H_{eq}H_{ax}$), 2.03 (6H, m, 2 × Ar-CH_3), 1.98–1.85 (2H, m, C6$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.85–1.78 (1H, m, C4$H_{eq}H_{ax}$), 1.59 (1H, q, *J* = 12.4 Hz, C2$H_{eq}H_{ax}$), 1.46–1.31 (3H, m, C6$H_{eq}H_{ax}$, C4$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.5 (C=O), 146.9 (Ar-C), 140.2 (Ar-C), 135.6 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.5 (2C, 2 × Ar-CH), 128.3 (2C, 2 × Ar-C), 127.0 (2C, 2 × Ar-CH), 126.3 (Ar-CH), 53.5 (C1H), 44.2 (C3H), 35.4 ($C2H_2$), 34.1 ($C4H_2$), 28.0 ($C6H_2$), 26.3 ($C5H_2$), 18.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 335.2367; $C_{24}H_{31}O$ requires 335.2369, Δ –0.60 ppm.



rac-(2,3,4,5,6-Pentamethylphenyl)((1*r*,4*r*)-4-phenylcyclohexyl)methanone, 496



Ketone **329** (114 mg, 0.600 mmol), *diol* **497** (216 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 96:4) provided the title compound (167 mg, 83%, > 95:5 d.r.) as a white solid. The relative stereochemistry was determined by *J*-coupling constant analysis.

$\boldsymbol{R_f}$ = 0.15 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

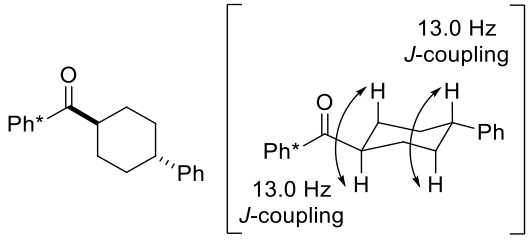
m.p. = 153–154 °C.

IR (film) ν_{max}/cm^{-1} 2918, 2850, 1688, 1599, 1491, 1446, 1265, 1314, 1262, 1143, 1112, 1020, 988.

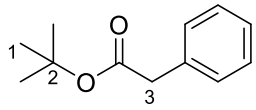
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.24–7.08 (5H, m, Ph), 2.63 (1H, tt, *J* = 12.0, 3.3 Hz, C1H), 2.46 (1H, tt, *J* = 12.0, 3.4 Hz, C4H), 2.17 (3H, s, Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.05 (6H, s, 2 × Ar-CH_3), 2.04–1.99 (2H, m, 2 × C2$H_{eq}H_{ax}$), 1.97–1.88 (2H, m, 2 × C3$H_{eq}H_{ax}$), 1.56 (2H, qd, *J* = 13.0, 3.2 Hz, 2 × C2$H_{eq}H_{ax}$), 1.39 (2H, qd, *J* = 13.0, 3.2 Hz, 2 × C3$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.8 (C=O), 147.0 (Ar-C), 140.2 (Ar-C), 135.6 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.5 (2C, 2 × Ar-CH), 128.2 (2C, 2 × Ar-C), 126.9 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 52.8 (C1H), 43.9 (C4H), 33.7 (2C, 2 × $C3H_2$), 28.6 (2C, 2 × $C2H_2$), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 335.2369; $C_{24}H_{31}O$ requires 335.2369, Δ –0.29 ppm.



tert-Butyl 2-phenylacetate, 588



To a solution of DCC (8.30 g, 40.3 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added DMAP (3.60 g, 29.4 mmol) and phenylacetic acid (5.00 g, 36.7 mmol). To the resulting suspension was then added *tert*-butyl alcohol (10.6 mL, 110 mmol). The reaction mixture was stirred whilst slowly warming to RT over 15 h. After this time, the reaction mixture was concentrated *in vacuo*, diluted with Et_2O (150 mL), filtered through Celite® and rinsed with Et_2O. The filtrate was washed sequentially with 1N NaOH (100 mL), 1N HCl (100 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The resulting mixture was distilled under vacuum (145 °C, 5 mbar) to provide the title compound (4.21 g, 60%) as a colourless oil.

b.p. = 98 °C (5 mbar).

IR (film) ν_{max}/cm^{-1} 2979, 1730, 1604, 1497, 1455, 1392, 1368, 1255, 1138, 1075, 1031, 954.

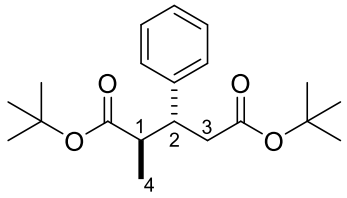
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.25 (5H, m, Ph), 3.56 (2H, s, $C3H_2$), 1.47 (9H, s, *t*Bu).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.4 (C=O), 135.1 (Ar-C), 129.6 (2C, 2 × Ar-CH), 128.9 (2C, 2 × Ar-CH), 127.3 (Ar-CH), 81.2 (C2), 43.1 ($C3H_2$), 28.5 (3C, $(C1H_3)_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 215.1043; $C_{12}H_{16}O_2Na$ requires 215.1043, Δ 0.24 ppm.

All spectroscopic data in agreement with that previously reported.[134]

***rac*-Di-*tert*-butyl (2*R*,3*R*)-2-methyl-3-phenylpentanedioate, 591a**[114]



To a solution of diisopropylamine (1.58 mL, 11.3 mmol) in THF (60 mL) at –78 °C was added *n*-BuLi (4.47 mL, 10.3 mmol, 2.30 M in hexanes) dropwise and stirred for 1 min. *tert*-Butyl propionate (1.47 mL, 9.79 mmol) was added dropwise and the solution stirred for 20 mins. Titanium isopropoxide (2.90 mL, 9.79 mmol) was added dropwise over 15 mins, and the reaction warmed to –40 °C. The reaction was maintained at this temperature for 30 mins. A solution of *tert*-butyl cinnamate (1.00 g, 4.90 mmol) in THF (20 mL) was then added dropwise over 25 mins. The mixture was stirred for a further 30 mins at –40 °C. After this time, the reaction was quenched with sat. aq. NH_4Cl (10 mL) and water (10 mL) and then warmed to RT. The mixture was concentrated *in vacuo* to remove THF and the remaining aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5→90:10) provided the title compound (1.11 g, 68%, > 95:5 d.r.) as a white solid.

$\boldsymbol{R_f}$ = 0.13 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 46–47 °C**.**

IR (film) ν_{max}/cm^{-1} 2977, 2934, 2360, 1456, 1392, 1367, 1256, 1147, 951.

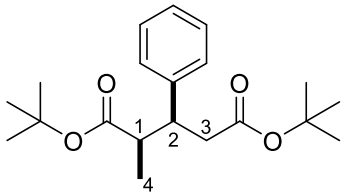
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.22–7.06 (5H, m, Ph), 3.19 (1H, ddd, *J* = 10.7, 9.2, 5.0 Hz, C2H), 2.64 (1H, dd, *J* = 14.7, 5.0 Hz, C3$H_A$$H_B$), 2.54 (1H, dq, *J* = 9.2, 6.9 Hz, C1H), 2.39 (1H, dd, *J* = 14.8, 10.7 Hz, C3$H_A$$H_B$), 1.15 (9H, s, *t*Bu), 1.12 (9H, s, *t*Bu), 1.11 (3H, d, *J* = 7.1 Hz, C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 174.4 (C=O), 171.5 (C=O), 141.8 (Ar-C), 128.6 (2C, 2 × Ar-CH), 128.1 (2C, 2 × Ar-CH), 126.8 (Ar-CH), 80.5 ($C(CH_3)_3$), 80.2 ($C(CH_3)_3$), 46.5 (C1H), 45.6 (C2H), 39.4 (C3H_2), 27.9 (3C, C(CH_3)$_3$), 27.8 (3C, C(CH_3)$_3$), 15.4 (C4H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 357.2034; $C_{20}H_{30}O_4Na$ requires 357.2036, Δ –0.62 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-Di-*tert*-butyl (2*R*,3*S*)-2-methyl-3-phenylpentanedioate, 591b**[114]



To a solution of diisopropylamine (1.58 mL, 11.3 mmol) in THF (60 mL) at –78 °C was added *n*-BuLi (4.47 mL, 10.3 mmol, 2.30 M in hexanes) dropwise and stirred for 1 min. *tert*-Butyl propionate (1.47 mL, 9.79 mmol) was added dropwise and the solution stirred for 20 mins. A solution of *tert*-butyl cinnamate (1.00 g, 4.90 mmol) in THF (20 mL) was then added dropwise over 25 mins. The mixture was stirred for a further 1 h at –78 °C. After this time, the reaction was quenched with sat. aq. NH_4Cl (10 mL), and water (10 mL) and then warmed to RT. The mixture was concentrated *in vacuo* to remove THF and the remaining aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5→90:10) provided the title compound (1.39 g, 85%, > 95:5 d.r.) as a white solid.

R_f = 0.20 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 59–61 °C.

IR (film) ν_{max}/cm^{-1} 2969, 2931, 2364, 1449, 1383, 1370, 1256, 1147, 1111, 949.

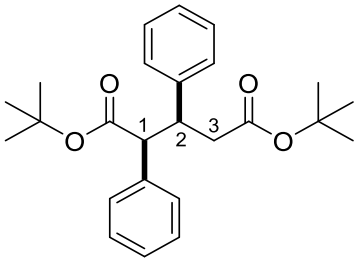
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.03 (5H, m, Ph), 3.15 (1H, td, *J* = 10.6, 4.6 Hz, C2H), 2.61–2.53 (1H, m, C3H_AH$_B$), 2.51–2.37 (2H, m, C3H$_A$$H_B$ and C1H), 1.40 (9H, s, *t*Bu), 1.11 (9H, s, *t*Bu), 0.83 (3H, d, *J* = 7.0 Hz, C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 175.1 (C=O), 171.0 (C=O), 141.1 (Ar-C), 128.5 (2C, 2 × Ar-CH), 128.3 (2C, 2 × Ar-CH), 126.8 (Ar-CH), 80.6 (*C*(CH_3)$_3$), 80.2 (*C*(CH_3)$_3$), 46.4 (C1H), 45.7 (C2H), 40.7 (C3H_2), 28.2 (3C, C(*C*H_3)$_3$), 27.8 (3C, C(*C*H_3)$_3$), 16.1 (C4H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 357.2034; $C_{20}H_{30}O_4Na$ requires 357.2036, Δ –0.65 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-Di-*tert*-butyl (2*S*,3*S*)-2,3-diphenylpentanedioate, 592**[114]



To a solution of LiHMDS (31 mL, 4.6 mmol, 0.15 M in THF) at –78 °C, was added *tert*-butyl 2-phenylacetate, **588** (0.78 mL, 4.0 mmol) dropwise over 5 mins and the resulting solution stirred for 1 h. To this was added *tert*-butyl cinnamate (1.00 g, 4.90 mmol) in THF (20 mL) dropwise over 15 mins. The mixture was maintained at –78 °C for 1 h, after which sat. aq. NH_4Cl (5 mL) and water (5 mL) were added sequentially. The reaction was warmed to RT and then concentrated *in vacuo* to remove THF. The remaining aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2→95:5) provided the title compound (591 mg, 75%, > 95:5 d.r.) as a white solid.

R_f = 0.26 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 64–65 °C.

IR (film) ν_{max}/cm^{-1} 2978, 1723, 1495, 1455, 1392, 1367, 1256, 1140, 1076, 953.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.07–6.89 (10H, m, Ph), 3.63 (1H, td, *J* = 10.8, 4.2 Hz, C2H), 3.56 (1H, d, *J* = 10.9 Hz, C1H), 2.75 (1H, dd, *J* = 14.7, 4.2 Hz, C3H_AH$_B$), 2.60 (1H, dd, *J* = 14.6, 10.8 Hz, C3H$_A$$H_B$), 1.35 (9H, s, *t*Bu), 1.10 (9H, s, *t*Bu).

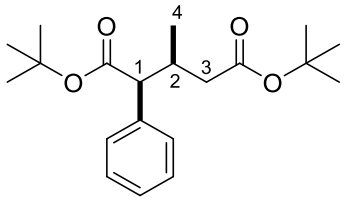
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.2 (C=O), 170.9 (C=O), 140.5 (Ar-C), 137.3 (Ar-C), 128.6 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 128.2 (2C, 2 × Ar-CH), 127.9 (2C, 2 × Ar-CH), 127.0 (Ar-CH), 126.5 (Ar-CH), 81.4 (*C*$(CH_3)_3$), 80.4 (*C*$(CH_3)_3$), 58.9 (C1H), 46.2 (C2H), 40.6 (C3H_2), 28.1 (3C, C(*C*$H_3)_3$), 27.9

(3C, C(CH_3)$_3$).

HRMS (ESI$^+$) Found [M+Na]$^+$ = 419.2189; $C_{25}H_{32}O_4Na$ requires 419.2193, Δ –0.97 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-Di-*tert*-butyl (2*S*,3*S*)-3-methyl-2-phenylpentanedioate, 593**[114]



To a solution of LiHMDS (61 mL, 9.2 mmol, 0.15 M) at –78 °C, was added *tert*-butyl 2-phenylacetate, **588** (1.57 mL, 8.00 mmol) dropwise over 5 mins and the resulting solution stirred for 1 h. To this was added a solution of *tert*-butyl crotonate (0.64 mL, 4.0 mmol) in THF (20 mL) dropwise over 15 mins. The mixture was maintained at –78 °C for 1 h, after which sat. aq. NH_4Cl (5 mL) and water (5 mL) were added sequentially. The reaction was then warmed to RT and then concentrated *in vacuo* to remove THF. The resulting aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O 98:2→95:5) provided the title compound (1.32 g, 98%, > 95:5 d.r.) as a colourless oil.

R_f = 0.25 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2977, 1725, 1455, 1392, 1367, 1279, 1250, 1213, 1144, 1083, 957.

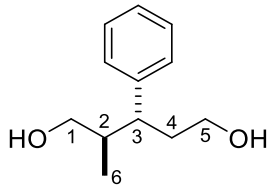
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.25 (5H, m, Ph), 3.29 (1H, d, *J* = 10.0 Hz, C1H), 2.69–2.57 (1H, m, C2H), 2.46 (1H, dd, *J* = 14.8, 2.3 Hz, C3H_AH$_B$), 2.13 (1H, dd, *J* = 14.4, 9.4 Hz, C3H$_A$$H_B$), 1.48 (9H, s, *t*Bu, 1.41 (9H, s, *t*Bu), 0.78 (3H, d, *J* = 6.8 Hz, C4H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.6 (C=O), 172.0 (C=O), 138.0 (Ar-C), 128.7 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 127.3 (Ar-CH), 80.9 (C(CH$_3$)$_3$), 80.4 (C(CH$_3$)$_3$), 58.5 (C1H), 41.0 (C3H_2), 33.8 (C2H), 28.3 (3C, C(CH$_3$)$_3$), 28.1 (3C, C(CH$_3$)$_3$), 17.2 (C4H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 357.2037; $C_{20}H_{30}O_4Na$ requires 357.2036, Δ 0.06 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-(2*R*,3*R*)-2-Methyl-3-phenylpentane-1,5-diol, 594a**



To a solution of **591a** (1.05 g, 3.14 mmol) in THF (19 mL) at 0 °C was added $LiAlH_4$ (477 mg, 12.6 mmol) portionwise. The reaction was slowly warmed to RT over 4 h. After this time, the reaction was quenched by careful dropwise addition of water (0.48 mL), $NaOH_{(aq)}$ (15% w/v, 0.48 mL) and water (1.4 mL). The reaction mixture was diluted with Et_2O (20 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (603 mg, 99%, > 95:5 d.r.) as a viscous colourless oil.

R_f = 0.11 (Pentane:Et_2O, 50:50), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3312, 2878, 1601, 1493, 1452, 1380, 1027, 909.

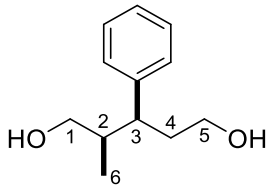
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.27–7.20 (2H, m, Ph), 7.16–7.10 (3H, m, Ph), 3.35–3.24 (2H, m, C1H_AH$_B$ and C5H_AH$_B$), 3.24–3.15 (1H, m, C5H$_A$$H_B$), 3.05 (1H, dd, *J* = 10.7, 7.5 Hz, C1H$_A$$H_B$), 2.58 (1H, ddd, *J* = 11.7, 8.1, 3.5 Hz, C3H), 2.04–1.94 (1H, m, C4H_AH$_B$), 1.84–1.70 (2H, m, C2H and C4H$_A$$H_B$), 0.98 (3H, d, *J* = 6.7 Hz, C6H_3).

^{13}C NMR (CD_3OD, 101 MHz) δ = 145.0 (Ar-C), 129.3 (4C, 4 × Ar-CH), 127.2 (Ar-CH), 66.5 (C1H_2), 61.4 (C5H_2), 45.6 (C3H), 42.6 (C2H), 35.8 (C4H_2), 15.2 (C6H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 217.1200; $C_{12}H_{18}O_2Na$ requires 217.1199, Δ 0.27 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-(2*R*,3*S*)-2-Methyl-3-phenylpentane-1,5-diol, 594b**



To a solution of **591b** (1.26 g, 3.77 mmol) in THF (23 mL) at 0 °C was added $LiAlH_4$ (572 mg, 15.1 mmol) portionwise. The reaction was slowly warmed to RT over 4 h. After this time, the reaction was quenched by careful dropwise addition of water (0.58 mL), $NaOH_{(aq)}$ (15% w/v, 0.58 mL) and water (1.7 mL). The reaction mixture was diluted with Et_2O (20 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (653 mg, 89%, > 95:5 d.r.) as a white solid. The relative stereochemistry was confirmed by X-ray crystallographic analysis after recrystallisation from HLPC grade Et_2O.

R_f = 0.15 (CH_2Cl_2:MeOH, 95:5), [UV, $KMnO_4$].

m.p. = 117–118 °C.

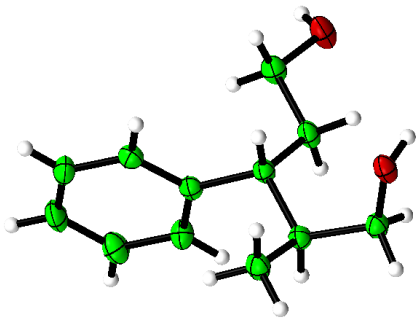
IR (film) ν_{max}/cm^{-1} 3311, 3027, 2969, 2882, 1602, 1494, 1453, 1382, 1252, 1153, 1044, 969.

^{1}H NMR (CD_3OD, 400 MHz) δ = 7.27–7.20 (2H, m, Ph), 7.16–7.10 (3H, m, Ph), 3.46 (1H, dd, *J* = 10.7, 5.6 Hz, C1H_AH$_B$), 2.58 (3H, m, C1H$_A$$H_B$ and C5H_2), 2.77 (1H, ddd, *J* = 11.1, 7.0, 4.4 Hz, C3H), 2.03–1.92 (1H, m, C4H_AH$_B$), 1.91–1.85 (1H, m, C4H$_A$$H_B$), 1.84–1.75 (1H, m, C2H), 0.70 (3H, d, *J* = 6.9 Hz, C6H_3).

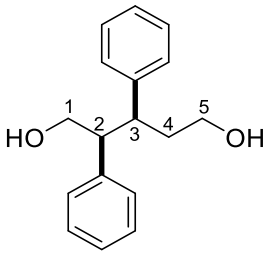
^{13}C NMR (CD_3OD, 101 MHz) δ = 143.7 (Ar-C), 129.9 (2C, 2 × Ar-CH), 129.1 (2C, 2 × Ar-CH), 127.2 (Ar-CH), 66.3 (C1H_2), 61.4 (C5H_2), 44.6 (C3H), 41.8 (C2H), 37.0 (C4H_2), 14.6 (C6H_3).

HRMS (ESI$^+$) Found $[M+Na]^+$ = 217.1200; $C_{12}H_{18}O_2Na$ requires 217.1199, Δ 0.30 ppm.

All spectroscopic data in agreement with that previously reported.[114]



***rac*-(2*S*,3*S*)-2,3-Diphenylpentane-1,5-diol, 595**



To a solution of **592** (570 mg, 1.44 mmol) in THF (9 mL) at 0 °C was added $LiAlH_4$ (218 mg, 5.75 mmol) portionwise. The reaction was slowly warmed to RT over 4 h. After this time, the reaction was quenched by careful dropwise addition of water (0.22 mL), $NaOH_{(aq)}$ (15% w/v, 0.22 mL) and water (0.66 mL). The reaction mixture was diluted with Et_2O (10 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (340 mg, 92%, > 95:5 d.r.) as a white solid.

R_f = 0.18 (CH_2Cl_2:MeOH, 95:5), [UV, $KMnO_4$].

m.p. = 89–90 °C.

IR (film) ν_{max}/cm^{-1} 3333, 3028, 2935. 1602, 1494, 1452, 1028, 760.

^{1}H NMR (CD_3OD, 400 MHz) δ = 7.11–6.81 (10H, m, 2 × Ph), 3.86 (1H, dd, *J* = 10.9, 6.2 Hz, C1H_AH_B), 3.77 (1H, dd, *J* = 10.9, 6.9 Hz, C1H_AH_B), 3.39–3.26 (2H, m, C5H_2), 3.25–3.17 (1H, m, C3H), 3.02 (1H, q, *J* = 6.8 Hz, C2H), 2.16–2.04 (1H, m, C4H_AH_B), 1.89–1.76 (1H, m, C4H_AH_B).

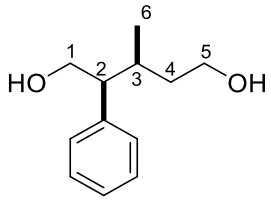
^{13}C NMR (CD_3OD, 101 MHz) δ = 143.0 (Ar-C), 142.3 (Ar-C), 130.4 (2C, 2 × Ar-CH), 130.2 (2C, 2 × Ar-CH), 128.7 (2C, 2 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 65.0 (C1H_2), 61.2

($C5H_2$), 54.7 (C2H), 44.8 (C3H), 37.5 ($C4H_2$).

HRMS (ESI^+) Found $[M+Na]^+$ = 279.1354; $C_{17}H_{20}O_2Na$ requires 279.1356, Δ –0.46 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-(2*S*,3*S*)-3-Methyl-2-phenylpentane-1,5-diol, 596**



To a solution of **593** (1.17 g, 3.50 mmol) in THF (21 mL) at 0 °C was added $LiAlH_4$ (531 mg, 14.0 mmol) portionwise. The reaction was slowly warmed to RT over 4 h. After this time, the reaction was quenched by careful dropwise addition of water (0.53 mL), $NaOH_{(aq)}$ (15% w/v, 0.53 mL) and water (1.6 mL). The reaction mixture was diluted with Et_2O (20 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (675 mg, 99%, > 95:5 d.r.) as a white solid.

R_f = 0.18 (CH_2Cl_2:MeOH, 95:5), [UV, $KMnO_4$].

m.p. = 37–39 °C.

IR (film) ν_{max}/cm^{-1} 3316, 3028, 2930, 2879, 1494, 1453, 1380, 1053, 1010, 854.

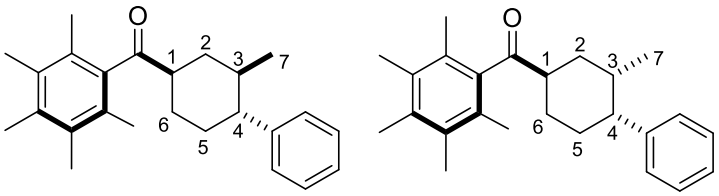
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.37–7.17 (5H, m, Ph), 3.93 (1H, dd, *J* = 10.9, 6.2 Hz, C1H_AH_B), 3.85 (1H, dd, *J* = 10.9, 7.5 Hz, C1H_AH_B), 3.73–3.58 (2H, m, $C5H_2$), 2.70 (1H, q, *J* = 6.7 Hz, C2H), 2.12–2.01 (1H, m, C3H), 1.83–1.71 (1H, m, C4H_AH_B), 1.35–1.23 (1H, m, C4H_AH_B), 0.78 (3H, d, *J* = 6.8 Hz, $C6H_3$).

^{13}C NMR (CD_3OD, 101 MHz) δ = 142.7 (Ar-C), 130.0 (2C, 2 × Ar-CH), 129.0 (2C, 2 × Ar-CH), 127.3 (Ar-CH), 64.9 ($C1H_2$), 61.0 ($C5H_2$), 54.5 (C2H), 38.7 ($C4H_2$), 32.2 (C3H), 16.7 ($C6H_3$).

HRMS (ESI^+) Found $[M+Na]^+$ = 217.1200; $C_{12}H_{18}O_2Na$ requires 217.1199, Δ 0.36 ppm.

All spectroscopic data in agreement with that previously reported.[114]

***rac*-((1*R*,3*R*,4*R*)-3-Methyl-4-phenylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 597a and *rac*-((1*R*,3*S*,4*R*)-3-Methyl-4-phenylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 597b**



597a (major) **597b** (minor)

Procedure 1: using *anti*-diol **594a**:

Ketone **329** (114 mg, 0.600 mmol), *diol* **594a** (233 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (110 mg, 53%, 60:40 d.r.) as a white solid and as an inseparable mixture of diastereoisomers. The d.r. was determined by ^1H NMR analysis of the crude mixture by comparison of the following signals: δ 0.63 (3H, d, J = 6.5 Hz, $C7H_3$, **597a**), 0.57 (3H, d, J = 7.1 Hz, $C7H_3$, **597b**). The relative stereochemistry was determined by *J*-coupling constant analysis and using key nOe correlations from 2D NOESY data.

Procedure 2: using *syn*-diol **594b**:

Ketone **329** (114 mg, 0.600 mmol), *diol* **594b** (233 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to a modified **general procedure M**, heating to 105 °C**.** Purification by column chromatography (Pentane:Et_2O, 98:2) provided the title compound (150 mg, 72%, 70:30 d.r.) as a white solid and as an inseparable mixture of diastereoisomers. The d.r. was determined by ^1H NMR analysis of the crude mixture by comparison of the following signals: δ 0.63 (3H, d, J = 6.5 Hz, $C7H_3$, **597a**), 0.57 (3H, d, J = 7.1 Hz, $C7H_3$, **597b**). The relative stereochemistry was determined by *J*-coupling constant analysis and using key nOe correlations from 2D NOESY data.

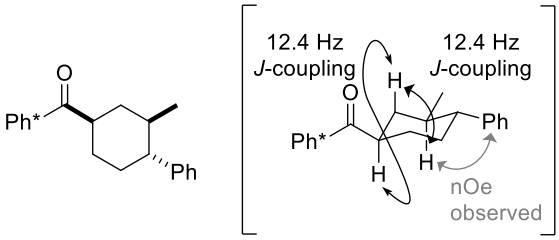
Data for **597a**/**597b** (70:30 d.r.):

R_f = 0.25 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2926, 2360, 1691, 1602, 1493, 1451, 1380, 1305, 1267, 1119, 1000, 931.

HRMS (ESI^+) Found $[M+H]^+$ = 349.2526; $C_{25}H_{33}O$ requires 349.2526, Δ –0.09 ppm.

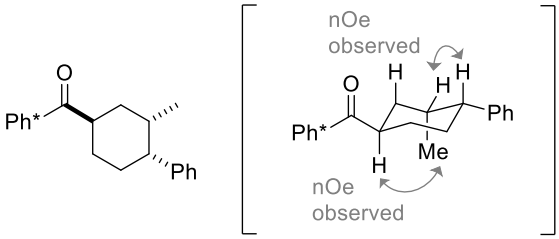
NMR data for **597a**:



^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–6.99 (5H, m, Ph), 2.76 (1H, tt, *J* = 12.1, 3.4 Hz, C1H), 2.17 (3H, s, Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.05 (6H, s, 2 × Ar-CH_3), 2.04–1.92 (3H, m, C4H, C2$H_{eq}H_{ax}$ and C6$H_{eq}H_{ax}$), 1.88–1.80 (1H, m, C5$H_{eq}H_{ax}$), 1.63–1.53 (1H, m, C3H), 1.53–1.38 (2H, m, C6$H_{eq}H_{ax}$ and C5$H_{eq}H_{ax}$), 1.28 (1H, q, *J* = 12.4 Hz, C2$H_{eq}H_{ax}$), 0.63 (3H, d, *J* = 6.5 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.6 (C=O), 145.9 (Ar-C), 140.2 (Ar-C), 135.5 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.4 (2C, 2 × Ar-C), 128.2 (2C, 2 × Ar-CH), 127.6 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 53.2 (C1H), 51.8 (C4H), 37.2 (C3H), 36.8 (C2H_2), 34.9 (C5H_2), 28.6 (C6H_2), 20.6 (C7H_3), 18.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3).

NMR data for **597b**:

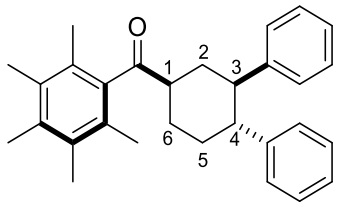


^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–6.99 (5H, m, Ph), 2.85 (1H, tt, *J* = 12.1, 3.8 Hz, C1H), 2.81–2.72 (1H, m, C4H), 2.23–2.18 (1H, m, C3H), 2.17 (3H, s, Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.04 (6H, s, 2 ×

Ar-CH_3), 2.04–2.01 (1H, m, C6$H_{eq}$$H_{ax}$), 1.93–1.88 (1H, m, C2$H_{eq}$$H_{ax}$), 1.81–1.77 (1H, m, C5$H_{eq}$$H_{ax}$), 1.73–1.65 (1H, m, C5$H_{eq}$$H_{ax}$), 1.54–1.44 (1H, m, C6$H_{eq}$$H_{ax}$), 1.43–1.37 (1H, m, C2$H_{eq}$$H_{ax}$), 0.57 (3H, d, *J* = 7.1 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.3 (C=O), 145.3 (Ar-C), 140.3 (Ar-C), 135.6 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.5 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-CH), 127.5 (2C, 2 × Ar-CH), 125.9 (Ar-CH), 46.7 (C1H), 45.8 (C4H), 35.3 (C2H_2), 34.3 (C3H), 29.0 (C6H_2), 23.8 (C5H_2), 18.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3), 12.5 (C7H_3).

***rac*-((1*R*,3*R*,4*R*)-3,4-Diphenylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 606**



Ketone **329** (114 mg, 0.600 mmol), *diol* **595** (308 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 95:5→90:10) provided the title compound (58 mg, 24%, > 95:5 d.r.) as a white solid. The relative stereochemistry was assigned by analogy to compound **597a**.

***R*$_f$** = 0.40 (Pentane:Et_2O, 90:10), [UV, $KMnO_4$].

m.p. = 166–168 °C.

IR (film) ν_{max}/cm^{-1} 3027, 2930, 1692, 1602, 1493, 1452. 1312. 1265, 1029, 934.

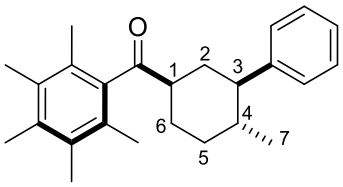
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.08–6.87 (10H, m, 2 × Ph), 2.90 (1H, tt, *J* = 12.1, 3.3 Hz, C1H), 2.75–2.64 (2H, m, C3H and C4H), 2.19–1.98 (18H, m, 5 × Ar-CH_3, C2$H_{eq}$$H_{ax}$, C6$H_{eq}$$H_{ax}$ and C5$H_{eq}$$H_{ax}$), 1.89–1.79 (1H, m, C2$H_{eq}$$H_{ax}$), 1.77–1.55 (2H, m, C6$H_{eq}$$H_{ax}$ and C5$H_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.2 (C=O), 144.7 (Ar-C), 144.5 (Ar-C), 140.1 (Ar-C), 135.7 (Ar-C), 133.3 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-C), 128.1 (4C, 4 × Ar-CH), 127.7 (2C, 2 × Ar-CH), 127.6 (2C, 2 × Ar-CH), 126.1 (Ar-CH), 126.0 (Ar-CH), 53.4 (C1H), 50.3 (C4H), 50.0 (C3H), 36.5 (C2H_2), 34.9 (C5H_2),

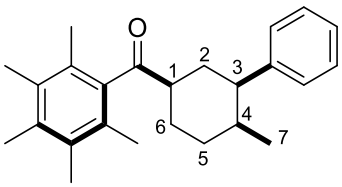
28.6 ($C6H_2$), 18.2 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI^+) Found $[M+H]^+$ = 411.2681; $C_{30}H_{35}O$ requires 411.2682, Δ –0.33 ppm.

***rac*-((1*R*,3*R*,4*R*)-4-Methyl-3-phenylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 607a and *rac*-((1*R*,3*R*,4*S*)-4-Methyl-3-phenylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 607b**



607a (major)



607b (minor)

Ketone **329** (114 mg, 0.600 mmol), *diol* **596** (233 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 97:3) provided the title compound (73 mg, 35%, 62:38 d.r.) a white solid and as an inseparable mixture of diastereoisomers. The d.r. was determined by ^1H NMR analysis of the crude mixture by comparison of the following signals: δ 0.59 (3H, d, J = 6.5 Hz, $C7H_3$, **607a**), 0.63 (3H, d, J = 7.2 Hz, $C7H_3$, **607b**). The relative stereochemistry was assigned in analogy to compounds **597a and 597b**.

Data for **607a**/**607b** (62:38 d.r.):

R_f = 0.29 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2928, 1692, 1493, 1453, 1381, 1310, 1262, 1140, 1100, 1002, 933.

HRMS (ESI^+) Found $[M+H]^+$ = 349.2525; $C_{25}H_{33}O$ requires 349.2526, Δ –0.35 ppm.

NMR data for **607a**:

^1H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.03 (5H, m, Ph), 2.78–2.68 (2H, m, C1H and C3H), 2.20–1.91 (17H, m, 5 × Ar-CH_3, C6$H_{eq}H_{ax}$ and C2$H_{eq}H_{ax}$), 1.90–1.80 (1H, m, C5$H_{eq}H_{ax}$), 1.73–1.47 (3H, m, C2$H_{eq}H_{ax}$ and C6$H_{eq}H_{ax}$ and C4H), 1.06 (1H, qd, J = 13.4, 3.6 Hz, C5$H_{eq}H_{ax}$), 0.59 (3H, d, J = 6.5 Hz,

$C7H_3$).

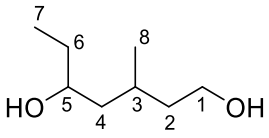
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.3 (C=O), 145.5 (Ar-C), 140.1 (Ar-C), 135.5 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.3 (2C, 2 × Ar-CH), 127.6 (2C, 2 × Ar-CH), 127.4 (2C, 2 × Ar-C), 126.2 (Ar-CH), 53.9 (C1H), 53.5 (C3H), 37.4 (C4H), 36.3 ($C2H_2$), 35.0 ($C5H_2$), 28.3 ($C6H_2$), 20.3 ($C7H_3$), 18.0 (2C, 2 × Ar-CH_3), 16.7 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3).

NMR data for **607b**:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.25–7.03 (5H, m, Ph), 2.82–2.72 (1H, m, C1H), 2.20–1.91 (18H, m, 5 × Ar-CH_3, C3H, C4H and C2$H_{eq}$$H_{ax}$), 1.90–1.80 (1H, m, C2$H_{eq}$$H_{ax}$), 1.74–1.61 (4H, m, C6$H_{eq}$$H_{ax}$ and C5$H_{eq}$$H_{ax}$), 0.63 (3H, d, *J* = 7.2 Hz, $C7H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 214.9 (C=O), 145.1 (Ar-C), 140.1 (Ar-C), 135.5 (Ar-C), 133.1 (2C, 2 × Ar-C), 128.2 (2C, 2 × Ar-CH), 128.1 (2C, 2 × Ar-CH), 127.4 (2C, 2 × Ar-C), 125.9 (Ar-CH), 51.7 (C3H), 45.9 (C1H), 34.0 (C4H), 33.0 ($C6H_2$), 25.7 ($C2H_2$), 22.2 ($C5H_2$), 18.0 (2C, 2 × Ar-CH_3), 16.7 (Ar-CH_3), 16.0 (2C, 2 × Ar-CH_3), 12.0 ($C7H_3$).

3-Methylheptane-1,5-diol, 611



To a solution of 4-methyltetrahydro-2*H*-pyran-2-one* (944 mg, 6.55 mmol) in CH_2Cl_2 (14 mL) at –78 °C was added DIBAL-H (11.7 mL, 11.7 mmol, 1.00 M in hexanes) dropwise over 10 mins. The solution was stirred at –78 °C for 1 h, after which TLC analysis indicated complete conversion to the corresponding diastereomeric lactols. Rochelle's salt (20 mL) was added and the mixture allowed to warm to RT over 16 h with vigorous stirring. The layers were separated and the aqueous layer extracted with Et_2O (3 × 50 mL) and CH_2Cl_2 (50 mL). The combined organics were dried

* Synthesised by Dr James Frost.

($MgSO_4$) and concentrated *in vacuo*. The crude lactols were carried through to the next step in the synthesis without further purification.

To a solution of EtMgBr (7.60 mL, 22.9 mmol, 3.00 M in Et_2O) at 0 °C was added a solution of the crude lactols (assumed quant., 6.55 mmol) in THF (3 mL + 1 mL rinse) dropwise over 10 mins. Following the addition the ice/water bath was removed and the mixture stirred at RT for 2 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (15 mL) and the layers separated. The aqueous layer was extracted with Et_2O (2 × 30 mL), EtOAc (30 mL) and the combined organics dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (Et_2O) provided the title compound (792 mg, 83%, 54:46 d.r.) as a diastereomeric mixture, as a colourless oil. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 1.89–1.73 (1H, m, C3H, major diastereoisomer), 1.72–1.63 (1H, m, C3H, minor diastereoisomer). The relative stereochemistry of the diastereoisomers could not be distinguished.

Data for major/minor diastereoisomer (54:46 d.r.):

R_f = 0.17 (Et_2O), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3317, 2959, 2926, 2876, 1459, 1377, 1117, 1057, 1013, 962.

HRMS (ESI+) Found $[M+H]^+$ = 169.1199; $C_8H_{18}O_2Na$ requires 169.1199, Δ – 0.18 ppm.

NMR data for major diastereoisomer

^{1}H NMR (MeOD, 400 MHz) δ = 3.69–3.52 (3H, m, C1H_2 and C5H), 1.89–1.73 (1H, m, C3H), 1.60–1.25 (6H, m, C2H_AH_B, C4H_AH_B and C6H_AH_B), 0.99–0.91 (6H, m, C7H_3 and C8H_3).

^{13}C NMR (MeOD, 101 MHz) δ = 70.3 (C5H), 59.6 (C1H_2), 44.4 (C2H_2), 38.9 (C4H_2), 29.9 (C6H_2), 26.2 (C3H), 19.5 (C8H_3), 8.9 (C7H_3).

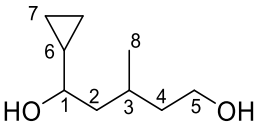
NMR data for minor diastereoisomer

^{1}H NMR (MeOD, 400 MHz) δ = 3.69–3.52 (3H, m, C1H_2 and C5H), 1.72–1.63 (1H, m, C3H), 1.60–

1.25 (6H, m, $C2H_AH_B$, $C4H_AH_B$ and $C6H_AH_B$), 0.99–0.91 (6H, m, $C7H_3$ and $C8H_3$).

^{13}C NMR (MeOD, 101 MHz) δ = 70.0 (C5H), 59.6 ($C1H_2$), 44.1 ($C2H_2$), 40.3 ($C4H_2$), 30.6 ($C6H_2$), 25.8 (C3H), 18.3 ($C8H_3$), 9.0 ($C7H_3$).

1-Cyclopropyl-3-methylpentane-1,5-diol, 612



To a solution of 4-methyltetrahydro-2*H*-pyran-2-one* (944 mg, 6.55 mmol) in CH_2Cl_2 (14 mL) at –78 °C was added DIBAL-H (11.7 mL, 11.7 mmol, 1.00 M in hexanes) dropwise over 10 mins. The solution was stirred at –78 °C for 1 h, after which TLC analysis indicated complete conversion to the corresponding diastereomeric lactols. Rochelle's salt (20 mL) was added and the mixture allowed to warm to RT over 16 h with vigorous stirring. The layers were separated and the aqueous layer extracted with Et_2O (3 × 50 mL) and CH_2Cl_2 (50 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude lactols were carried through to the next step in the synthesis without further purification.

To a solution of cyclopropylmagnesium bromide (46.0 mL, 22.9 mmol, 0.5 M in THF) at 0 °C was added a solution of the crude lactols (assumed quant., 6.55 mmol) in THF (3 mL + 1 mL rinse) dropwise over 10 mins. Following the addition the ice/water bath was removed and the mixture stirred at RT for 2 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (15 mL) and the layers separated. The aqueous layer was extracted with Et_2O (2 × 30 mL), EtOAc (30 mL) and the combined organics dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (Et_2O) provided the title compound (771 mg, 74%, 85:15 d.r.) as a diastereomeric mixture, as a colourless oil. The d.r. was determined by ^{1}H NMR analysis of the following signals: 0.96 (3H, d, *J* = 6.7 Hz, $C8H_3$, major diastereoisomer), 0.92 (3H, d, *J* = 6.7 Hz, $C8H_3$, minor

* Synthesised by Dr James Frost.

diastereoisomer). Not all peaks belonging to the minor diasteroisomer could be distinguished in NMR analysis, and so only the data for the major diastereoisomer is reported. The relative stereochemistry of the diastereoisomers could not be determined.

Data for major/minor diastereoisomer (85:15 d.r.)

R_f = 0.15 (Et_2O), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3314, 3080, 3003, 2925, 1458, 1439, 1377, 1101, 1057, 1020, 964.

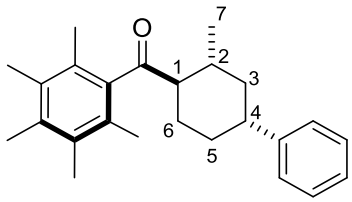
HRMS (ESI+) Found $[M+Na]^+$ = 181.1198; $C_9H_{18}O_2Na$ requires 181.1199, Δ –0.56 ppm.

NMR data for major diastereomer

^{1}H NMR (CD_3OD, 400 MHz) δ = 3.70–3.53 (2H, m, $C5H_2$), 2.98 (1H, td, *J* = 8.0, 5.2 Hz, C1H), 1.92–1.80 (1H, m, C3H), 1.71–1.61 (1H, m, $C4H_AH_B$), 1.60–1.43 (2H, m, $C2H_AH_B$), 1.40–1.27 (1H, m, $C4H_AH_B$), 0.96 (3H, d, *J* = 6.7 Hz, $C8H_3$), 0.89–0.78 (1H, m, C6H), 0.56–0.43 (2H, m, $C7H_AH_B$ and $C7'H_AH_B$), 0.36–0.28 (1H, m, $C7H_AH_B$), 0.25–0.17 (1H, m, $C7'H_AH_B$).

^{13}C NMR (CD_3OD, 101 MHz) δ = 74.9 (C1H), 61.0 ($C5H_2$), 46.3 ($C2H_2$), 40.3 ($C4H_2$), 27.5 (C3H), 20.9 ($C8H_3$), 18.8 (C6H), 3.1 ($C7_AH_2$), 3.0 ($C7_BH_2$).

***rac*-((1*R*,2*R*,4*R*)-2-Methyl-4-phenylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 614**



Ketone **329** (114 mg, 0.600 mmol), 3-phenylhexane-1,5-diol* (233 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 98:2→95:5) provided the title compound (140 mg, 67%, 94:6 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: *δ* 2.60–2.45 (2H, m, C4H and C1H, major

* Synthesised by Dr James Frost.

diastereoisomer), 2.85–2.77 (2H, m, C4H and C1H), minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was determined by *J*-coupling constant analysis. The peaks for the minor diastereoisomer could not be fully distinguished, so only the data for the major diastereoisomer is reported.

R_f = 0.34 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

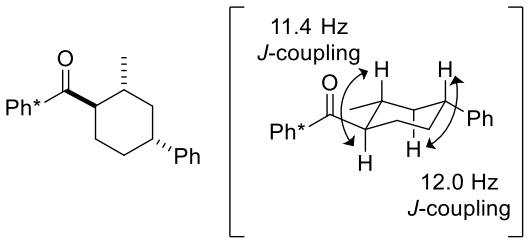
m.p. = 152–154 °C.

IR (film) ν_{max}/cm^{-1} 2925, 1688, 1602, 1494, 1450. 1381, 1310, 1260, 1155, 1104, 1069, 1029, 912.

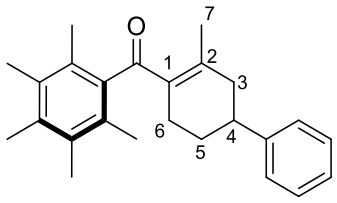
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.23 (2H, m, Ph), 7.15 (3H, d, *J* = 7.3 Hz, Ph), 2.58 (1H, tt, *J* = 12.0, 3.4 Hz, C4H), 2.54 (1H, td, *J* = 11.4, 3.3 Hz, C1H), 2.20 (3H, s, Ar-CH_3), 2.15 (6H, s, 2 × Ar-CH_3), 2.14–2.02 (1H, m, C2H), 2.12 (6H, s, 2 × Ar-CH_3) 2.01–1.84 (3H, m, C6H_{eq}H$_{ax}$, C3H_{eq}H$_{ax}$ and C5H_{eq}H$_{ax}$), 1.43–1.29 (2H, m, C6H$_{eq}$$H_{ax}$ and C5H$_{eq}$$H_{ax}$), 1.24 (1H, q, *J* = 12.0 Hz, C3H$_{eq}$$H_{ax}$), 1.11 (3H, d, *J* = 6.3 Hz, C7H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.0 (C=O), 146.9 (Ar-C), 139.7 (Ar-C), 135.7 (Ar-C), 133.2 (2C, 2 × Ar-C), 128.5 (4C, 2 × Ar-C and 2 × Ar-CH), 126.8 (2C, 2 × Ar-CH), 126.2 (Ar-CH), 59.0 (C1H), 43.8 (C4H), 42.5 (C3H_2), 34.1 (C5H_2), 33.0 (C2H), 30.0 (C6H_2), 21.0 (C7H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3).

HRMS (ESI+) Found $[M+H]^+$ = 349.2526; $C_{25}H_{33}O$ requires 349.2526, Δ 0.15 ppm.



(5-Methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 615



In the preparation of *ketone* **614** under **general procedure M**, the title compound (35 mg, 17%) was obtained as a white solid.

R_f = 0.18 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 125–126 °C

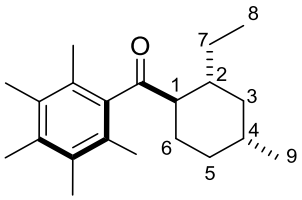
IR (film) ν_{max}/cm^{-1} 3027, 2925, 1668. 1619, 1601, 1495, 1452, 1421, 1377, 1352, 1307, 1265, 1229, 1207, 1168, 1092, 1069, 1028, 896.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.19 (2H, m, Ph), 7.18–7.08 (3H, m, Ph), 2.79–2.67 (1H, m, C4H), 2.44–2.25 (3H, m, C3$H_{eq}H_{ax}$ and C6$H_{eq}H_{ax}$), 2.22–2.13 (1H, m, C6$H_{eq}H_{ax}$), 2.17 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.01 (6H, s, 2 × Ar-CH_3), 1.96–1.80 (4H, m, C5$H_{eq}H_{ax}$ and C7H_3), 1.62 (1H, qd, *J* = 11.8, 5.1 Hz, C5$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.2 (C=O), 148.7 (C2), 146.4 (Ar-C), 141.4 (Ar-C), 135.4 (2C, 2 × Ar-C), 133.4 (2C, 2 × Ar-C), 133.3 (C1), 128.9 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-C), 127.2 (2C, 2 × Ar-CH), 126.7 (Ar-CH), 43.4 9 (C3H_2), 40.2 (C4H), 30.1 (C5H_2), 27.5 (C6H_2), 22.3 (C7H_3), 17.5 (2C, 2 × Ar-CH_3), 17.2 (Ar-CH_3), 16.4 (2C, 2 × Ar-CH_3).

HRMS (ESI+) Found $[M+H]^+$ = 374.2371; $C_{25}H_{31}O$ requires 374.2369, Δ 0.49 ppm.

***rac*-((1*R*,2*R*,4*R*)-2-Ethyl-4-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 616**



Ketone **329** (114 mg, 0.600 mmol), *diol* **611** (176 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 99:1→95:5) provided the title compound (108 mg, 60%, 93:7 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 2.41 (1H, ddd, *J* = 12.3, 10.6, 3.4 Hz, C1H, major diastereoisomer), 2.62 (1H, q, *J* = 5.8 Hz, C1H, minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was determined by *J*-coupling constant analysis. The peaks for the minor diastereoisomer could not be fully distinguished, so only the data for the major diastereoisomer is reported.

R_f = 0.60 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

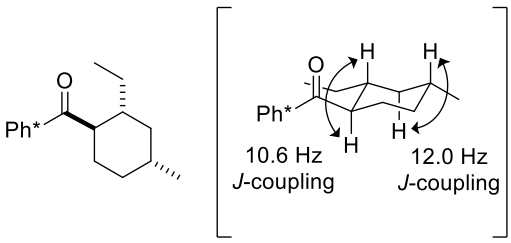
m.p. = 144–145 °C.

IR (film) ν_{max}/cm^{-1} 2916, 2872, 1683, 1451, 1377, 1303, 1267, 1110, 1066, 1017, 935.

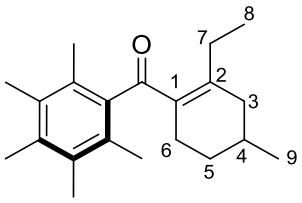
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.41 (1H, ddd, *J* = 12.3, 10.6, 3.4 Hz, C1H), 2.16 (3H, s, Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.05 (6H, s, 2 × Ar-CH_3), 1.96–1.82 (2H, m, C3$H_{eq}H_{ax}$ and C7H_AH_B), 1.79–1.70 (2H, m, C2H and C6$H_{eq}H_{ax}$), 1.61 (1H, m, C5$H_{eq}H_{ax}$), 1.34–1.23 (1H, m, C4H), 1.17 (1H, qd, *J* = 12.8, 3.5 Hz, C6$H_{eq}H_{ax}$), 1.00–0.92 (1H, m, C7H_AH_B), 0.89 (3H, *t*, *J* = 6.6 Hz, C8H_3), 0.81 (3H, d, *J* = 6.5 Hz, C9H_3), 0.74 (1H, qd, *J* = 13.0, 3.4 Hz, C5$H_{eq}H_{ax}$), 0.48 (1H, q, *J* = 12.0 Hz, C3$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 213.4 (C=O), 139.9 (Ar-C), 135.6 (Ar-C), 133.2 (4C, 4 × Ar-C), 58.1 (C1H), 39.2 (C2H), 39.1 (C3H_2), 35.3 (C5H_2), 32.1 (C4H), 30.0 (C6H_2), 27.2 (C7H_2), 22.7 (C9H_3), 18.1 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3), 11.8 (C8H_3).

HRMS (ESI+) Found $[M+H]^+$ = 301.2526; $C_{21}H_{33}O$ requires 301.2526, Δ –0.14 ppm.



(2-Ethyl-4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 617



In the preparation of *ketone* **616** under **general procedure M**, the title compound (46 mg, 27%) was obtained as a white solid.

R_f = 0.43 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 85–86 °C.

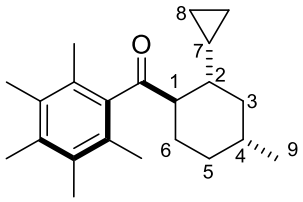
IR (film) ν_{max}/cm^{-1} 2923, 2872, 1667, 1637, 1456, 1420, 1380, 1305, 1263, 1200, 1170, 1117, 1070, 1016, 893.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.36–1.91 (20H, m, 5 × Ar-CH_3, C7H_AH_B, C6$H_{eq}H_{ax}$ and C3$H_{eq}H_{ax}$), 1.84–1.73 (1H, m, C3$H_{eq}H_{ax}$), 1.65–1.51 (2H, m, C5$H_{eq}H_{ax}$ and C4H), 1.13–1.01 (1H, m, C5$H_{eq}H_{ax}$), 0.94 (3H, t, *J* = 7.4 Hz, C8H_3), 0.89 (3H, d, *J* = 6.5 Hz, C9H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 203.9 (C=O), 153.8 (C2), 141.2 (Ar-C), 134.9 (Ar-C), 132.9 (2C, 2 × Ar-C), 132.0 (C1), 128.3 (2C, 2 × Ar-C), 40.4 (C3H_2), 31.0 (C5H_2), 28.4 (C4H), 28.2 (C7H_2), 27.1 (C6H_2), 21.6 (C9H_3), 17.2 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3), 12.9 (C8H_3).

HRMS (ESI+) Found $[M+H]^+$ = 299.2370; $C_{21}H_{31}O$ requires 299.2369, Δ 0.16 ppm.

***rac*-((1*R*,2*S*,4*R*)-2-Cyclopropyl-4-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone, 618**



Ketone **329** (114 mg, 0.600 mmol), *diol* **612** (190 mg, 1.20 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%) and KOH (135 mg, 2.40 mmol) were subjected to **general procedure M.** Purification by column chromatography (Pentane:Et_2O, 99:1→95:5) provided the title compound (70 mg, 37%, 91:9 d.r.) as a white solid. The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 2.56 (1H, ddd, J = 12.4, 10.6, 3.4 Hz, C1H, major diastereoisomer), 2.81 (1H, q, J = 5.2 Hz, C1H, minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was determined by J-coupling constant analysis. The peaks for the minor diastereoisomer could not be fully distinguished, so only the data for the major diastereoisomer is reported.

R_f = 0.51 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 124–126 °C.

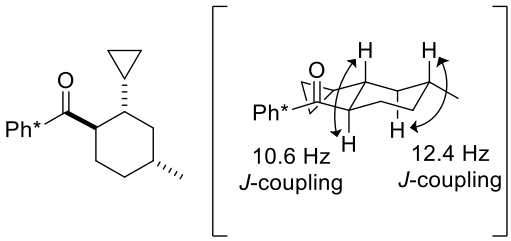
IR (film) ν_{max}/cm^{-1} 2919, 1692, 1454, 1382, 1353, 1303, 1263, 1171, 955.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.56 (1H, ddd, J = 12.4, 10.6, 3.4 Hz, C1H), 2.11 (3H, s, Ar-CH_3), 2.08–1.96 (12H, m, 4 × Ar-CH_3), 1.76–1.68 (2H, m, C3H_{eq}H$_{ax}$ and C6H_{eq}H$_{ax}$), 1.57–1.52 (1H, m, C5H_{eq}H$_{ax}$), 1.39–1.29 (1H, m, C2H), 1.27–1.15 (1H, m, C4H), 1.05 (1H, qd, J = 12.8, 3.5 Hz, C6H$_{eq}$$H_{ax}$), 0.75 (3H, d, J = 6.5 Hz, C9H_3), 0.65 (1H, qd, J = 12.7, 3.5 Hz, C5H$_{eq}$$H_{ax}$), 0.63 (1H, q, J = 12.4 Hz, C3H$_{eq}$$H_{ax}$), 0.58–0.42 (2H, m, C7H and C8H_AH$_B$), 0.37–0.23 (2H, m, C8H$_A$$H_B$ and C8'H_AH$_B$), 0.05– –0.05 (1H, m, C8'H$_A$$H_B$).

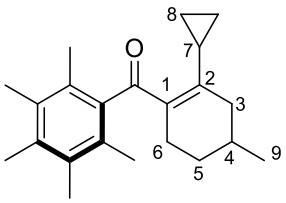
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.6 (C=O), 140.0 (Ar-C), 135.8 (Ar-C), 133.2 (4C, 4 × Ar-C), 58.5 (C1H), 40.3 (2C, C3H_2 and C2H), 34.9 (C5H_2), 32.1 (C4H), 30.4 (C6H_2), 22.6 (C9H_3), 18.0 (2C, 2 × Ar-

CH_3), 17.4 (Ar-CH_3), 16.2 (2C, 2 × Ar-CH_3), 6.4 (2C, C7H and C8_AH_2), 3.2 (C8_BH_2).

HRMS (ESI+) Found $[M+H]^+$ = 313.2525; $C_{22}H_{33}O$ requires 313.2526, Δ –0.17 ppm



(2-Cyclopropyl-4-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone, 619



In the preparation of *ketone* **618** under **general procedure M**, the title compound (38 mg, 20%) was obtained as a white solid.

R_f = 0.21 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

m.p. = 85–86 °C.

IR (film) ν_{max}/cm^{-1} 2921, 2871, 1660, 1631, 1594, 1455, 1419, 1377, 1303, 1265, 1197, 1171, 1102, 1072, 1007, 951.

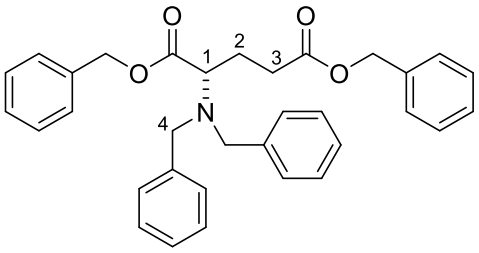
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.50 (1H, br s, C7H), 2.29–2.16 (1H, m, C6$H_{eq}H_{ax}$), 2.15 (3H, s, Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 2.08–1.97 (1H, m, C6$H_{eq}H_{ax}$), 2.03 (6H, s, 2 × Ar-CH_3), 1.78–1.66 (1H, m, C3$H_{eq}H_{ax}$), 1.64–1.56 (1H, m, C5$H_{eq}H_{ax}$), 1.51–1.40 (1H, m, C4H), 1.39–1.29 (1H, m, C3$H_{eq}H_{ax}$), 1.04 (1H, dtd, *J* = 12.8, 10.8, 5.6 Hz, C5$H_{eq}H_{ax}$), 0.86 (3H, d, *J* = 6.5 Hz, C9H_3), 0.68–0.61 (1H, m, C8H_AH_B), 0.56–0.46 (3H, m, C8H_AH_B and C8'H_AH_B).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 204.4 (C=O), 151.2 (C2), 141.5 (Ar-C), 134.8 (2C, 2 × Ar-C), 133.6 (Ar-C), 132.9 (2C, 2 × Ar-C), 128.4 (C1), 33.7 (C3H_2), 30.8 (C5H_2), 28.0 (C4H), 27.4 (C6H_2) , 21.6 (C9H_3),

17.3 (2C, 2 × Ar-CH_3), 16.9 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3), 14.6 (C7H), 6.4 ($C8_AH_2$), 5.2 ($C8_BH_2$).

HRMS (ESI+) Found $[M+H]^+$ = 311.2370; $C_{22}H_{31}O$ requires 311.2369, Δ 0.33 ppm.

Dibenzyl *N*,*N*-dibenzyl-L-glutamate, S4[135]



To a solution of L-glutamic acid (5.00 g, 34.0 mmol), K_2CO_3 (23.3 g, 136 mmol) and NaOH (2.72 g, 68.0 mmol) at 100 °C in water (60 mL) was added benzyl bromide (16.2 mL, 136 mmol) dropwise over 30 min. The reaction was monitored by TLC, and upon consumption of benzyl bromide, was cooled to RT. An oil formed on the surface, which was separated from the aqueous layer. The resulting aqueous layer was extracted with Et_2O (3 × 50 mL), the organic layers combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:EtOAc, 90:10), provided the title compound (2.25 g, 13%) as a colourless oil.

R_f = 0.18 (Pentane:EtOAc, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3031, 1729, 1495, 1454, 1377, 1260, 1154, 1076, 1028, 961.

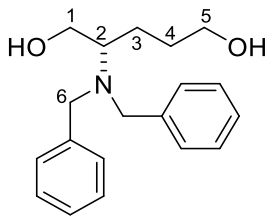
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.51–7.21 (20H, m, 4 × Ph), 5.32 (1H, d, *J* = 12.2 Hz, OC$H_A$$H_B$), 5.21 (1H, d, *J* = 12.2 Hz, OC$H_A$$H_B$), 5.10–4.95 (2H, m, OC'$H_A$$H_B$), 3.93 (2H, d, *J* = 13.7 Hz, 2 × C4$H_A$$H_B$), 3.55 (2H, d, *J* = 13.7 Hz, 2 × C4$H_A$$H_B$), 3.46 (1H, t, *J* = 7.7 Hz, C1H), 2.56 (1H, dt, *J* = 16.8, 7.0 Hz, C3$H_A$$H_B$), 2.40 (1H, dt, J = 16.3, 7.8 Hz, C3$H_A$$H_B$), 2.12 (2H, q, *J* = 7.5 Hz, C2$H_A$$H_B$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 172.9 (C=O), 172.3 (C=O), 139.3 (2C, 2 × Ar-C), 136.1 (Ar-C), 136.0 (Ar-C), 129.0 (4C, 4 × Ar-CH), 128.7 (2C, 2 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 128.6 (2C, 2 × Ar-CH), 128.5 (2C, 2 × Ar-CH), 128.4 (4C, 4 × Ar-CH), 128.3 (2C, 2 × Ar-CH), 127.2 (2C, 2 × Ar-CH), 66.3 (2C, 2 × OCH_2), 59.8 (C1H), 54.5 (2C, 2 × C4H_2), 30.7 (C3H_2), 24.3 (C2H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 508.2481; $C_{33}H_{34}NO_4$ requires 508.2482, Δ –0.30 ppm.

All spectroscopic data in agreement with that previously reported.[135]

(*S*)-2-(Dibenzylamino)pentane-1,5-diol, 622



To a solution of dibenzyl *N*,*N*-dibenzyl-L-glutamate **S4** (1.78 g, 3.50 mmol) in THF (21 mL) at 0 °C was added $LiAlH_4$ (531 mg, 14.0 mmol) portionwise. The reaction was slowly warmed to RT over 4 h. After this time, the reaction was quenched by careful dropwise addition of water (0.53 mL), $NaOH_{(aq)}$ (15% w/v, 0.53 mL) and water (1.6 mL). The reaction mixture was diluted with Et_2O (20 mL) and $MgSO_4$ added. The mixture was stirred vigorously for 30 mins then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) provided the title compound (1.03 g, 98%) as a colourless oil.

R_f = 0.28 (Pentane:Et_2O, 50:50), [$KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3352, 3028, 2936, 1494, 1453, 1363, 1249, 1207, 1131, 1027, 908.

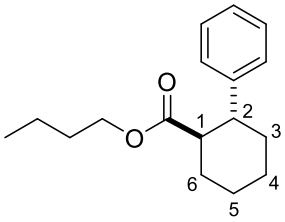
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.39–7.18 (10H, m, Ph), 3.74 (1H, dd, *J* = 10.9, 6.8 Hz, C1H_AH_B), 3.69 (4H, s, 2 × C6H_2), 3.55 (1H, dd, *J* = 11.0, 6.0 Hz, C1H_AH_B), 3.51–3.41 (2H, m, C5H_2), 2.70 (1H, quint., *J* = 6.5 Hz, C2H), 1.74–1.62 (2H, m, C3H_AH_B and C4H_AH_B), 1.57–1.40 (2H, m, C4H_AH_B and C3H_AH_B).

^{13}C NMR (CD_3OD, 101 MHz) δ = 141.5 (2C, 2 × Ar-C), 130.0 (4C, 4 × Ar-CH), 129.2 (4C, 4 × Ar-CH), 127.9 (2C, 2 × Ar-CH), 62.9 (C5H_2), 62.4 (C1H_2), 59.8 (C2H), 54.7 (2C, 2 × C6H_2), 31.1 (C4H_2), 24.8 (C3H_2).

HRMS (ESI$^+$) Found $[M+H]^+$ = 300.1954; $C_{19}H_{26}NO_2$ requires 300.1958, Δ –1.52 ppm.

All spectroscopic data in agreement with that previously reported.[136]

rac-Butyl (1*R*,2*R*)-2-phenylcyclohexane-1-carboxylate, 629



Ketone **579** (67 mg, 0.20 mmol), Br_2 (64 mg, 0.40 mmol) and *n*-butanol (45 mg, 0.60 mmol) were subjected to **general procedure N**. Purification by column chromatography (Pentane:Et_2O, 97:3) provided the title compound (49 mg, 94%, > 95:5 d.r.) as a colourless oil. The relative stereochemistry was determined by *J*-coupling constant analysis.

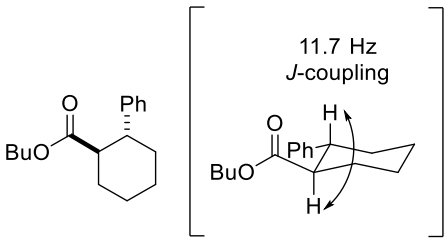
$\boldsymbol{R_f}$ = 0.29 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 3029, 2931, 2856, 1731, 1492, 1449, 1359, 1317, 1253, 1230, 1164, 1114, 1065, 1027, 951.

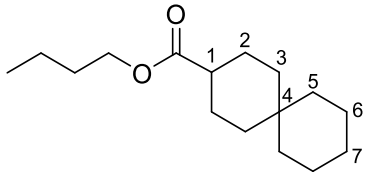
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.33–6.97 (5H, m, Ph), 3.79–3.67 (2H, m, OCH_2), 2.70 (1H, td, *J* = 11.5, 3.6 Hz, C2H), 2.50 (1H, td, *J* = 11.7, 3.5 Hz, C1H), 1.98–1.91 (1H, m, C6$H_{eq}$$H_{ax}$), 1.85–1.73 (3H, m, C3$H_{eq}$$H_{ax}$, C5$H_{eq}$$H_{ax}$ and C4$H_{eq}$$H_{ax}$), 1.53 (1H, qd, *J* = 12.7, 3.4 Hz, C6$H_{eq}$$H_{ax}$), 1.43–1.29 (3H, m, C3$H_{eq}$$H_{ax}$, C5$H_{eq}$$H_{ax}$ and C4$H_{eq}$$H_{ax}$), 1.29–1.16 (2H, m, OCH_2CH_2), 1.08–0.97 (2H, m, CH_3CH_2), 0.71 (3H, t, *J* = 7.3 Hz, CH_3CH_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 175.4 (C=O), 144.9 (Ar-C), 128.4 (2C, 2 × Ar-CH), 127.4 (2C, 2 × Ar-CH), 126.4 (Ar-CH), 63.8 (OCH_2), 50.4 (C1H), 46.9 (C2H), 34.4 ($C3H_2$), 30.6 (OCH_2CH_2), 30.3 ($C6H_2$), 26.4 ($C5H_2$), 25.5 ($C4H_2$), 19.0 (CH_3CH_2), 13.7 (CH_3CH_2).

HRMS (ESI+) Found $[M+Na]^+$ = 283.1667; $C_{17}H_{24}O_2Na$ requires 283.1669, Δ –0.63 ppm.



Butyl spiro[5.5]undecane-3-carboxylate, 630



Ketone **561** (65 mg, 0.20 mmol), Br_2 (64 mg, 0.40 mmol) and *n*-butanol (45 mg, 0.60 mmol) were subjected to **general procedure N**. Purification by column chromatography (Pentane:Et_2O, 99:1) provided the title compound (49 mg, 97%) as a colourless oil.

$\boldsymbol{R_f}$ = 0.45 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

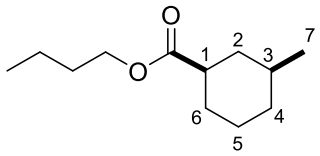
IR (film) ν_{max}/cm^{-1} 2925, 2846, 1732, 1449, 1391, 1315, 1295, 1275, 1198, 1162, 1149, 1063, 1024, 911.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.05 (2H, t, *J* = 6.6 Hz, OCH_2), 2.28–2.17 (1H, m, C1H), 1.75–1.53 (8H, m, 2 × C3$H_{eq}$$H_{ax}$, OCH_2CH_2 and 2 × C2$H_{eq}H_{ax}$), 1.46–1.33 (10H, m, C5$H_{eq}H_{ax}$, C7$H_{eq}H_{ax}$, C6$H_{eq}H_{ax}$, C6'$H_{eq}H_{ax}$ and CH_3CH_2), 1.23–1.19 (2H, m, C5'$H_{eq}H_{ax}$), 1.05 (2H, td, *J* = 12.8, 3.4 Hz, 2 × C3$H_{eq}H_{ax}$), 0.92 (3H, t, *J* = 7.4 Hz, CH_3CH_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 176.5 (C=O), 64.1 (OCH_2), 43.8 (C1H), 41.0 (C5'H_2), 35.8 (2C, 2 × C3H_2), 32.6 (C5H_2), 32.0 (C4), 30.9 (OCH_2CH_2), 27.0 (C7H_2), 24.2 (2C, 2 × C2H_2), 21.8 (C6H_2), 21.6 (C6'H_2), 19.3 (CH_3CH_2), 13.9 (CH_3CH_2).

HRMS (ESI+) Found $[M+H]^+$ = 253.2162; $C_{16}H_{29}O_2$ requires 253.2162, Δ –0.08 ppm.

***rac*-Butyl (1*R*,3*S*)-3-methylcyclohexane-1-carboxylate, 631**



Ketone **493** (55 mg, 0.20 mmol), Br_2 (64 mg, 0.40 mmol) and *n*-butanol (45 mg, 0.60 mmol) were subjected to **general procedure N**. Purification by column chromatography (Pentane:Et_2O, 99:1) provided the title compound (38 mg, 96%, 92:8 d.r.) as a colourless oil. The d.r. was determined

by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: 2.28 (1H, tt, *J* = 12.1, 3.5 Hz, C1H, major diastereoisomer), 2.61 (1H, quint., *J* = 5.0 Hz, C1H, minor diastereoisomer). The relative stereochemistry of the major diastereoisomer was determined by *J*-coupling constant analysis. The peaks for the minor diastereoisomer could not be fully distinguished, so only the data for the major diastereoisomer is reported.

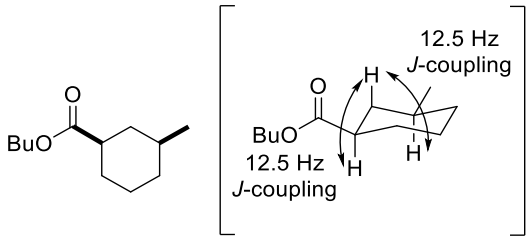
R_f = 0.41 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2929, 2866, 1733, 1458, 1378, 1304, 1259, 1217, 1179, 1138, 1090, 1021, 969.

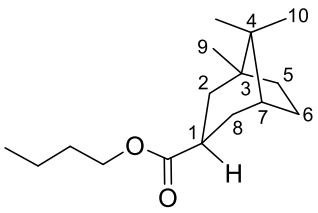
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.05 (2H, t, *J* = 6.7 Hz, OCH_2), 2.28 (1H, tt, *J* = 12.1, 3.5 Hz, C1H), 1.97–1.86 (2H, m, C2H_{eq}H$_{ax}$ and C6H_{eq}H$_{ax}$), 1.81–1.74 (1H, m, C5H_{eq}H$_{ax}$), 1.70–1.63 (1H, m, C4H_{eq}H$_{ax}$), 1.66–1.54 (2H, m, OCH_2CH_2), 1.44–1.33 (3H, m, CH_3CH_2 and C3H), 1.32–1.24 (2H, m, C5H$_{eq}$$H_{ax}$ and C6H$_{eq}$$H_{ax}$), 1.04 (1H, q, *J* = 12.5 Hz, C2H$_{eq}$$H_{ax}$), 0.93 (3H, t, *J* = 7.4 Hz, CH_3CH_2), 0.90 (3H, d, *J* = 6.6 Hz, C7H$_3$), 0.85 (1H, qd, *J* = 12.3, 3.6 Hz, C4H$_{eq}$$H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 176.4 (C=O), 64.1 (OCH_2), 43.8 (C1H), 37.6 (C2H$_2$), 34.6 (C4H$_2$), 32.2 (C3H), 30.9 (OCH_2CH_2), 28.8 (C6H$_2$), 25.7 (C5H$_2$), 22.8 (C7H$_3$), 19.3 (CH_3CH_2), 13.9 (CH_3CH_2).

HRMS (ESI+) Found $[M+H]^+$ = 199.1693; $C_{12}H_{23}O_2$ requires 199.1693, Δ 0.29 ppm.



rac-Butyl (1*S*)-1,8,8-trimethylbicyclo[3.2.1]octane-3-carboxylate, 632



(2,3,4,5,6-pentamethylphenyl)((1*S*)-1,8,8-trimethylbicyclo[3.2.1]octan-3-yl)methanone * (65 mg, 0.20 mmol), Br_2 (64 mg, 0.40 mmol) and *n*-butanol (45 mg, 0.60 mmol) were subjected to **general procedure N**. Purification by column chromatography (Pentane:Et_2O, 99:1) provided the title compound (48 mg, 95%, > 95:5 d.r.) as a colourless oil. The relative stereochemistry was determined by using key nOe correlations from 2D NOESY data.

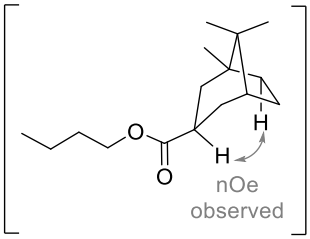
R_f = 0.48 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$].

IR (film) ν_{max}/cm^{-1} 2951, 2873, 1732, 1468. 1390, 1367, 1331, 1296, 1236, 1183. 1157, 1110, 1063, 1023.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.05 (2H, t, *J* = 6.7 Hz, OCH_2), 2.64 (1H, tt, *J* = 12.5, 6.4 Hz, C1H), 1.98–1.89 (1H, m, C8$H_A$$H_B$), 1.88–1.80 (1H, m, C6$H_A$$H_B$), 1.78–1.68 (2H, m, C2$H_A$$H_B$ and C7H), 1.65–1.45 (5H, m, C5$H_A$$H_B$, OCH_2CH_2 and C8$H_A$$H_B$), 1.44–1.27 (4H, m, CH_3CH_2, C6$H_A$$H_B$ and C2$H_A$$H_B$), 0.94 (3H, s, C9$H_3$, C10$H_3$ *or* C10'H_3), 0.93 (3H, t, *J* = 7.5 Hz, CH_3CH_2), 0.84 (3H, s, C9H_3, C10H_3 *or* C10'H_3), 0.83 (3H, s, C9H_3, C10H_3 *or* C10'H_3).

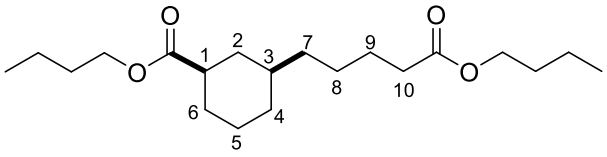
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 176.9 (C=O), 64.2 (OCH_2), 45.4 (C7H), 42.7 (C3 *or* C4), 42.5 (C3 *or* C4), 38.1 (C2H_2), 37.1 (C1H), 35.4 (C5H_2), 30.9 (OCH_2CH_2), 30.7 (C8H_2), 26.6 (C6H_2), 24.6 (C9H_3, C10$_A$$H_3$ *or* C10$_B$$H_3$), 21.0 (C9$H_3$, C10$_A$$H_3$ *or* C10$_B$$H_3$), 19.3 ($CH_3CH_2$), 18.7 (C9$H_3$, C10$_A$$H_3$ *or* C10$_B$$H_3$), 13.9 ($CH_3CH_2$).

HRMS (ESI+) Found $[M+H]^+$ = 253.2162; $C_{16}H_{29}O_2$ requires 253.2162, Δ –0.08 ppm.



* Synthesised by Dr Roly Armstrong.

***rac*-Butyl (1*R*,3*S*)-3-(5-butoxy-5-oxopentyl)cyclohexane-1-carboxylate, 633**



5-(3-(2,3,4,5,6-pentamethylbenzoyl)cyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one [*] (49 mg, 0.10 mmol), Br_2 (64 mg, 0.40 mmol) and *n*-butanol (45 mg, 0.60 mmol) were subjected to **general procedure N**. Purification by column chromatography (Pentane:Et_2O, 90:10) provided the title compound (34 mg, 99%, > 95:5 d.r.) as a colourless oil. The relative stereochemistry was determined by *J*-coupling constant analysis.

R_f = 0.18 (Pentane:Et_2O, 90:10), [UV, $KMnO_4$].

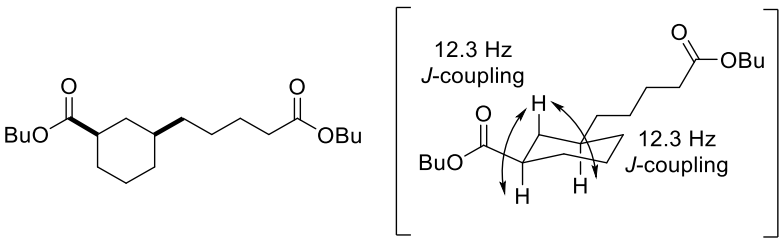
IR (film) ν_{max}/cm^{-1} 2932, 2859, 1733, 1462, 1248, 1176, 1064.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.06 (2H, t, *J* = 6.7 Hz, OCH_2), 4.05 (2H, t, *J* = 6.7 Hz, OCH_2), 2.28 (2H, t, *J* = 7.5 Hz, C10H_2), 2.26 (1H, tt, *J* = 12.1, 3.7 Hz, C1H), 1.97–1.89 (2H, m, C2$H_{eq}$$H_{ax}$ and C6$H_{eq}$$H_{ax}$), 1.81–1.75 (1H, m, C5$H_{eq}$$H_{ax}$), 1.71 (1H, br. d, *J* = 13.0 Hz, C4$H_{eq}$$H_{ax}$), 1.63–1.55 (6H, m, 2 × OCH_2CH_2 and C9H_2), 1.43–1.17 (11H, m, C8H_2, C7H_AH_B, C3H, C6$H_{eq}H_{ax}$, C5$H_{eq}H_{ax}$ and 2 × CH_3CH_2), 1.01 (1H, q, *J* = 12.3 Hz, C2$H_{eq}H_{ax}$), 0.92 (6H, t, *J* = 7.4 Hz, 2 × CH_3CH_2), 0.83 (1H, qd, *J* = 12.7, 3.6 Hz, C4$H_{eq}H_{ax}$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 176.4 (C=O), 174.1 (C=O), 64.3 (OCH_2), 64.2 (OCH_2), 43.7 (C1H), 37.0 (C7H_2), 36.9 (C3H), 35.7 (C2H_2), 34.5 (C10H_2), 32.5 (C4H_2), 30.8 (2C, 2 × OCH_2CH_2), 29.2 (C6H_2), 26.4 (C8H_2), 25.6 (C5H_2), 25.3 (C9H_2), 19.3 (2C, 2 × CH_2CH_3), 13.9 (CH_2CH_3), 13.8 (CH_2CH_3).

HRMS (ESI+) Found $[M+Na]^+$ = 363.2502; $C_{20}H_{36}O_4Na$ requires 363.2506, Δ –1.18 ppm.

[*] Synthesised by Dr Roly Armstrong.


O
O
BuO
OBu
12.3 Hz
J-coupling
O
OBu
H
O
BuO
H
H
12.3 Hz
J-coupling

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Appendix 1: X-ray Crystallographic Data for Compound 476

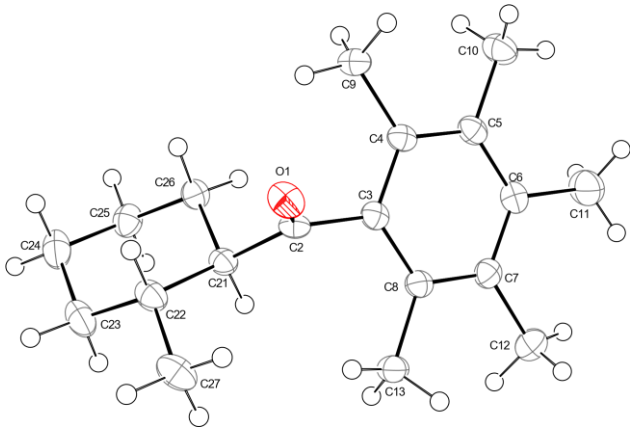
CIF file is provided on the accompanying CD.

Table 1. Crystal data and structure refinement for **476**.

Empirical formula	C19 H28 O	
Formula weight	272.43	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.6845(2) Å	α = 111.787(4)°.
	b = 11.8639(4) Å	β = 97.794(3)°.
	c = 12.9651(6) Å	γ = 96.038(3)°.
Volume	792.84(6) $Å^3$	
Z	2	
Density (calculated)	1.141 Mg/m^3	
Absorption coefficient	0.512 mm^{-1}	
F(000)	300	
Crystal size	0.41 x 0.24 x 0.05 mm^3	
Theta range for data collection	3.739 to 75.981°.	
Index ranges	-7<=h<=6, -14<=k<=14, -16<=l<=16	
Reflections collected	11800	
Independent reflections	3256 [R(int) = 0.043]	
Completeness to theta = 73.701°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.76	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2419 / 0 / 181	
Goodness-of-fit on F^2	0.9910	
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1162	
R indices (all data)	R1 = 0.0498, wR2 = 0.1255	
Largest diff. peak and hole	0.26 and -0.22 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **476**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7906(2)	-1948(1)	1459(1)	31
C(2)	6402(3)	-1394(1)	1917(1)	22
C(3)	6558(3)	-25(1)	2198(1)	21
C(4)	8513(3)	801(1)	2989(1)	22
C(5)	8662(3)	2066(1)	3241(1)	25
C(6)	6847(3)	2493(1)	2711(1)	27
C(7)	4878(3)	1662(1)	1929(1)	25
C(8)	4752(3)	396(1)	1657(1)	22
C(9)	10456(3)	364(1)	3586(1)	27
C(10)	10796(3)	2944(2)	4084(2)	34
C(11)	7040(4)	3857(2)	2972(2)	45
C(12)	2893(3)	2103(2)	1358(2)	35
C(13)	2741(3)	-504(1)	746(1)	27
C(21)	4451(2)	-2018(1)	2315(1)	23
C(22)	3945(3)	-3426(1)	1695(1)	28
C(23)	2205(3)	-3995(2)	2243(2)	35
C(24)	3074(3)	-3605(2)	3508(2)	36
C(25)	3505(3)	-2210(2)	4111(1)	30
C(26)	5286(3)	-1623(1)	3601(1)	26
C(27)	2953(3)	-3832(2)	437(2)	38



Appendix 2: X-ray Crystallographic Data for Compound 493

CIF file is provided on the accompanying CD.

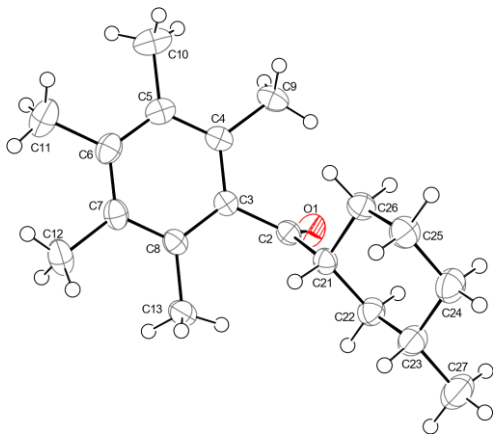
Table 1. Crystal data and structure refinement for **493**.

Empirical formula	C19 H28 O	
Formula weight	272.43	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.53540(10) Å	α = 111.824(3)°.
	b = 12.5708(3) Å	β = 101.376(2)°.
	c = 13.1465(4) Å	γ = 96.846(2)°.
Volume	813.70(4) $Å^3$	
Z	2	
Density (calculated)	1.112 Mg/m^3	
Absorption coefficient	0.499 mm^{-1}	
F(000)	300	
Crystal size	0.38 x 0.20 x 0.11 mm^3	
Theta range for data collection	3.753 to 75.048°.	
Index ranges	-6<=h<=6, -15<=k<=15, -16<=l<=16	
Reflections collected	29230	
Independent reflections	3315 [R(int) = 0.046]	
Completeness to theta = 72.046°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.95 and 0.54	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3315 / 0 / 181	
Goodness-of-fit on F^2	1.0001	
Final R indices [I>2sigma(I)]	R1 = 0.0571, wR2 = 0.1578	
R indices (all data)	R1 = 0.0630, wR2 = 0.1656	
Largest diff. peak and hole	0.44 and -0.30 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **493**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3212(2)	3666(1)	6528(1)	44
C(2)	5263(3)	3523(1)	6924(1)	29
C(3)	5511(3)	2474(1)	7202(1)	27
C(4)	4510(3)	2345(1)	8057(1)	30
C(5)	4810(3)	1380(2)	8322(1)	35
C(6)	6151(3)	573(1)	7752(2)	37
C(7)	7137(3)	708(1)	6894(1)	34
C(8)	6775(3)	1653(1)	6598(1)	29
C(9)	3126(3)	3226(2)	8695(1)	39
C(10)	3666(4)	1219(2)	9223(2)	54
C(11)	6488(4)	-460(2)	8055(2)	57
C(12)	8618(4)	-136(2)	6277(2)	47
C(13)	7655(3)	1757(1)	5615(1)	36
C(21)	7645(3)	4434(1)	7232(1)	29
C(22)	7447(3)	5142(1)	6516(1)	37
C(23)	9820(3)	6090(2)	6868(2)	42
C(24)	10326(4)	6890(2)	8129(2)	47
C(25)	10560(3)	6209(2)	8870(2)	41
C(26)	8213(3)	5244(1)	8504(1)	35
C(27)	9582(5)	6770(2)	6126(2)	60

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z



Appendix 3: X-ray Crystallographic Data for Compound 495

CIF file is provided on the accompanying CD.

Table 1. Crystal data and structure refinement for **495**.

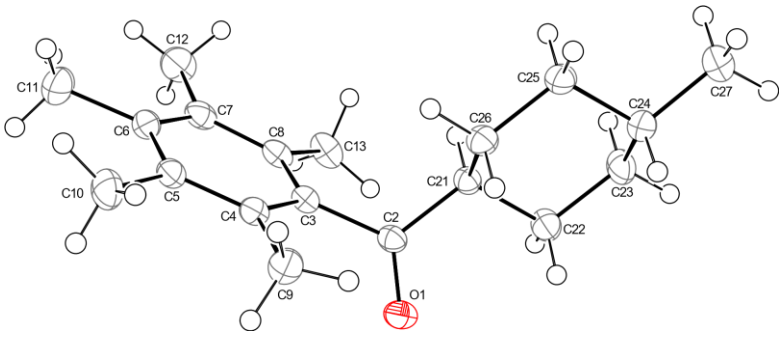
Empirical formula	C19 H28 O	
Formula weight	272.43	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.54610(10) Å	α = 90°.
	b = 11.6681(3) Å	β = 90°.
	c = 24.5455(7) Å	γ = 90°.
Volume	1588.40(7) $Å^3$	
Z	4	
Density (calculated)	1.139 Mg/m^3	
Absorption coefficient	0.511 mm^{-1}	
F(000)	599.995	
Crystal size	0.75 x 0.05 x 0.03 mm^3	
Theta range for data collection	4.195 to 76.279°.	
Index ranges	-6<=h<=6, -13<=k<=14, -30<=l<=30	
Reflections collected	23399	
Independent reflections	3287 [R(int) = 0.060]	
Completeness to theta = 76.279°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.45	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3287 / 0 / 182	
Goodness-of-fit on F^2	1.0020	
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.0892	
R indices (all data)	R1 = 0.0375, wR2 = 0.0924	
Absolute structure parameter	0.1(3)	
Largest diff. peak and hole	0.20 and -0.15 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **495**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4537(2)	3202(1)	4162(1)	33
C(2)	6457(2)	3487(1)	3967(1)	21
C(3)	6926(2)	3369(1)	3360(1)	21
C(4)	5589(2)	4042(1)	2995(1)	22
C(5)	6027(2)	3931(1)	2435(1)	24
C(6)	7822(3)	3182(1)	2246(1)	26
C(7)	9167(2)	2527(1)	2617(1)	26
C(8)	8666(2)	2594(1)	3177(1)	23
C(9)	3696(3)	4874(1)	3195(1)	29
C(10)	4506(3)	4610(1)	2039(1)	33
C(11)	8232(3)	3076(1)	1637(1)	37
C(12)	11192(3)	1750(1)	2432(1)	36
C(13)	9929(3)	1799(1)	3573(1)	30
C(21)	8416(2)	4033(1)	4313(1)	21
C(22)	8003(3)	3835(1)	4921(1)	28
C(23)	9939(3)	4424(1)	5263(1)	30
C(24)	10110(3)	5707(1)	5141(1)	26
C(25)	10522(2)	5884(1)	4530(1)	25
C(26)	8555(2)	5326(1)	4188(1)	24
C(27)	12096(3)	6283(2)	5471(1)	39

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z



Appendix 4: X-ray Crystallographic Data for Compound 515

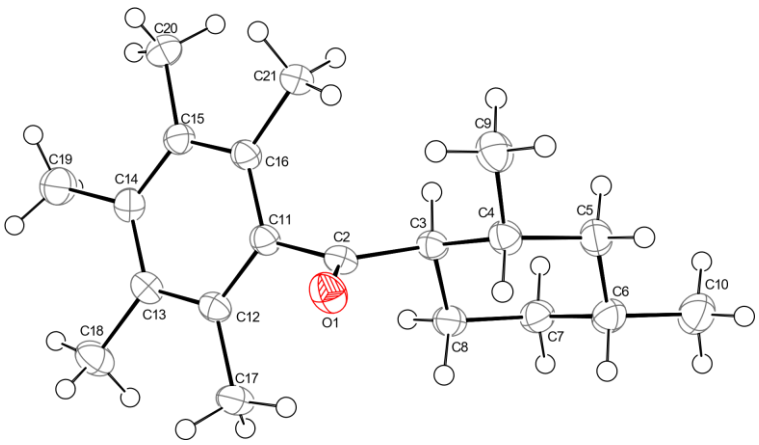
CIF file is provided on the accompanying CD.

Table 1. Crystal data and structure refinement for **515**.

Empirical formula	C20 H30 O	
Formula weight	286.46	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.5564(2) Å	α = 60.847(4)°.
	b = 13.1890(5) Å	β = 78.478(3)°.
	c = 13.3683(5) Å	γ = 88.408(3)°.
Volume	835.56(6) $Å^3$	
Z	2	
Density (calculated)	1.139 Mg/m^3	
Absorption coefficient	0.508 mm^{-1}	
F(000)	316	
Crystal size	0.30 x 0.09 x 0.01 mm^3	
Theta range for data collection	3.850 to 75.917°.	
Index ranges	-6<=h<=6, -16<=k<=16, -16<=l<=16	
Reflections collected	18964	
Independent reflections	3452 [R(int) = 0.050]	
Completeness to theta = 74.399°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.63	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3452 / 0 / 190	
Goodness-of-fit on F^2	1.0036	
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.1291	
R indices (all data)	R1 = 0.0556, wR2 = 0.1400	
Largest diff. peak and hole	0.36 and -0.22 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **515**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8246(2)	2987(1)	3813(1)	33
C(2)	6658(2)	2993(1)	3300(1)	25
C(3)	4698(2)	3866(1)	3081(1)	24
C(4)	4304(2)	4330(1)	3953(1)	28
C(5)	2640(3)	5332(1)	3589(1)	31
C(6)	3570(3)	6324(1)	2336(1)	33
C(7)	3813(3)	5836(1)	1493(1)	31
C(8)	5548(2)	4863(1)	1801(1)	28
C(9)	3239(3)	3373(1)	5206(1)	34
C(10)	1894(3)	7319(1)	2023(2)	42
C(11)	6696(2)	2183(1)	2796(1)	24
C(12)	8665(2)	2313(1)	1890(1)	26
C(13)	8760(2)	1522(1)	1468(1)	28
C(14)	6886(3)	623(1)	1935(1)	29
C(15)	4880(2)	520(1)	2819(1)	27
C(16)	4827(2)	1282(1)	3274(1)	25
C(17)	10671(3)	3292(1)	1351(1)	31
C(18)	10963(3)	1651(2)	529(1)	38
C(19)	7025(3)	-256(1)	1511(2)	42
C(20)	2780(3)	-407(1)	3306(1)	35
C(21)	2813(2)	1089(1)	4311(1)	29



Appendix 5: X-ray Crystallographic Data for Compound 594b

CIF file is provided on the accompanying CD.

Table 1. Crystal data and structure refinement for **594b**.

Empirical formula	C12 H18 O2	
Formula weight	194.27	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 7.8379(2) Å	α = 90°.
	b = 9.8399(2) Å	β = 90°.
	c = 28.2494(7) Å	γ = 90°.
Volume	2178.71(9) $Å^3$	
Z	8	
Density (calculated)	1.184 Mg/m^3	
Absorption coefficient	0.624 mm^{-1}	
F(000)	848	
Crystal size	0.25 x 0.20 x 0.05 mm^3	
Theta range for data collection	6.267 to 76.083°.	
Index ranges	-9<=h<=6, -11<=k<=12, -35<=l<=35	
Reflections collected	10994	
Independent reflections	2262 [R(int) = 0.045]	
Completeness to theta = 74.561°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.68	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1883 / 0 / 127	
Goodness-of-fit on F^2	1.0093	
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.1077	
R indices (all data)	R1 = 0.0456, wR2 = 0.1118	
Largest diff. peak and hole	0.23 and -0.23 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **594b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5291(2)	5404(1)	6486(1)	22
C(2)	5070(2)	6205(1)	6888(1)	26
C(3)	4145(2)	5728(2)	7273(1)	32
C(4)	3435(2)	4438(2)	7264(1)	33
C(5)	3669(2)	3626(2)	6869(1)	33
C(6)	4592(2)	4103(2)	6484(1)	28
C(7)	6242(2)	5945(1)	6056(1)	22
C(8)	5048(2)	6031(2)	5626(1)	25
C(9)	3446(2)	6841(2)	5722(1)	28
O(10)	2563(1)	7068(1)	5289(1)	33
C(11)	7864(2)	5102(1)	5957(1)	23
C(12)	9111(2)	5198(2)	6371(1)	28
C(13)	8741(2)	5484(1)	5493(1)	25
O(14)	9201(1)	6900(1)	5475(1)	25

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z #2 x+1/2,-y+3/2,-z+1