Applications of Pentamethyl Phenyl Ketones in the Synthesis of Carbocycles and Heterocycles.



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By

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Declaration.

The work described herein is entirely my own, except where help is acknowledged from a specific person or a reference is given to a published source or thesis.



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Abstract.

Applications of Pentamethyl Phenyl Ketones in the Synthesis of Carbocycles and Heterocycles

A thesis submitted for the degree of **Doctor of Philosophy** by **Ciaran Lunt-Laurin**, St Hilda's College and the Chemistry Research Laboratory, Trinity term 2023.

Chapter 1: Introduction.

The introduction covers an overview of hydrogen borrowing and the types of hydrogen borrowing strategies. The challenges and advantages of hydrogen borrowing strategies. The structure of Ph* ketones and how this can be utilised in synthesis.

Chapter 2: Synthesis of piperidines by hydrogen borrowing.

Synthesis of C–C and C–N bond formation *via* hydrogen borrowing is well established. In this Chapter, we outline how Ph* ketone can be used to synthesise stable α-aminoketones allowing the two strategies to be combined to form piperidines *via* a [4+2] strategy in up to 66% yield.

Chapter 3: Synthesis of γ-lactones by alkylation with 1,2-diols.

In this Chapter, the synthesis of γ lactones is discussed using a hydrogen borrowing reaction followed by cleavage of Ph* ketone. Both reactions were performed in high yield, and by modifying the established Ph* cleavage conditions, lactones could be formed with 96% e.s.

Chapter 4: Synthesis of cyclohexenes by a Mukaiyama-Michael Addition and 1,5-Hydride Shift sequence. The synthesis of cyclohexenes by 1,5-hydride transfer is of ongoing interest to us. In this Chapter, we combine this reaction with Mukaiyama-Michael additions to access enantioenriched cyclohexenes. We then explore how tri-substituted THP rings behave, allowing us to access di-substituted cyclohexenes with both retention and inversion of the stereochemistry.

Chapter 5: Development of catalytic aluminium 1,5-hydride shift reactions.

Using (super)stoichiometric aluminium alkoxides in 1,5-hydride transfer reactions severely limits their synthetic utility. By preventing the condensation step, we were able to perform hydride transfers with 81% yield using 20 mol% loadings. We found that stepwise cyclisation allows access to the desired enone, skipped enone and chromenes.

Chapter 6: Experimental Procedures. This chapter contains all experimental procedures and structural information of compounds discussed in the chapters above.

Chapter 7: Appendix. This section summarises the group's understanding of aluminium's role in 1,5-hydride transfer. The X-ray crystal structures of compounds **3-58**, **4-138** and **4-165** can be found here.

References.

References for all chapters of the thesis are collated here.

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I've gone from a naïve first year to a cynical old man in F7 *via* a pandemic. Fortunately, I've had wonderful colleagues throughout my time there. I'd like to thank Roly Aaron and Chris who have constantly made people laugh, and Oscar, our iron-fisted lab enforcer. Tim Kwok and Danna are two of the most hard-working and intense chemists I've ever met, and working on the retrosynthesis competition with you both was great fun. Dani for tearing apart and rebuilding the HPLC. Hannah for her help and guidance when I began my work on aluminium chemistry. Jess, for tolerating our constant teasing. As well as Tim Jenkins and Teddy, who have brought optimism and light to every room they enter.

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Thank you to Mum, Dad and Charlotte, who have continuously supported me through my DPhil and undergraduate degree, even when you have no idea what I'm doing. I would also like to thank James, Gerard and Rory who were great housemates throughout my time in Oxford, and I miss living with you all.

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I pray I never hear Sia or Electro-swing again.

Abbreviations and Acronyms.

°C	—	Degrees celsius
2D	—	2-Dimensional
3D	—	3-Dimensional
Å	—	Angstrom
Ac	—	Acetyl
acac	—	Acetoacetate
aq.	—	Aqueous
Ar	—	A generic aromatic group
BArF	—	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BCF	—	Tris(pentafluorophenyl)borane
Bn	—	Benzyl
Bu	—	Butyl
Cat	—	Catalyst
COD	—	1,4-Cyclooctadiene
COSY	—	^{1}H-^{1}H Correlation spectroscopy
Cy	—	Cyclohexane
Cymene	—	1-(Propan-2-yl)-4-methyl-benzene
d.e.	—	Diastereomeric excess
d.r.	—	Diastereomeric ratio
DBU	—	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	—	1,2-Dichloroethane
DCM	—	1,1-Dichloromethane
DIBAL-H	—	Diisobutylaluminium hydride
DKR	—	Dynamic kinetic resolution
DMF	—	Dimethylformamide
DMF	—	*N,N*-Dimethylformamide
DMPS	—	Dimethylphenylsilyl
DMSO	—	Dimethylsulfoxide
Dppbz	—	1,2-Bis(diphenylphosphino)benzene
dppf	—	1,1′-Ferrocenediyl-bis(diphenylphosphine)
ds	—	Diastereospecificity
DTBM	—	2,6-di-*tert*-butylphenyl
E	—	A generic electrophile
e.e.	—	Enatiomeric excess
EDG	—	Electron donating group
eq.	—	Equivalents
es	—	Enantiospecificity
ESI	—	Electron spray ionisation
Et	—	Ethyl
Et al.	—	*Et allia* "and the rest"
EWG	—	Electron withdrawing group
FCC	—	Flash column chromatography
FTIR	—	Fourier-transform infra-red spectroscopy
g	—	Grams
HAT	—	Hydrogen atom transfer
HB	—	Hydrogen Borrowing
HFIP	—	Hexafluro-1,1,1,3,3,3-*iso*-propanol
HMBC	—	Heteronuclear multiple-bond correlation spectroscopy
HOMO	—	Highest occupied molecular orbital
HPLC	—	High performance liquid chromatography
h	—	Hours
HRMS	—	High resolution mass spectrometry
HSQC	—	Heteronuclear single-quantum correlation spectroscopy
HWE	—	Horner–Wadsworth–Emmons
Hz	—	Hertz
i	—	*Ipso*
i	—	*Iso*

Int	—	Intermediate
KHMDS	—	Potassium bis(trimethylsilyl)amide
L	—	Litre
LDA	—	Lithium diisopropylamide
LiHMDS	—	Lithium bis(trimethylsilyl)amide
LUMO	—	Lowest unoccupied molecular orbital
m	—	Meta
M	—	Moles per litre
Me	—	Methyl
Mes	—	2,4,6-Trimethylphenyl (Mesityl)
m	—	Milli
min	—	Minutes
MPV	—	Meerwein-Ponndorf-Verley
MS	—	Mass spectrometry
MS	—	Molecular sieves
MTBE	—	Methyl *tert*-butyl ether
n	—	Normal
NaHMDS	—	Sodium bis(trimethylsilyl)amide
NBD	—	N-bromosuccinamide
NMR	—	Nuclear magnetic resonance
NOESY	—	Nuclear Overhauser Effect Spectroscopy
Nu	—	A generic nucleophile
o	—	Ortho
p	—	Para
Ph	—	Phenyl
Ph*	—	2,3,4,5,6-Pentamethylphenyl
PMP	—	*Para*-methoxyphenyl ether
ppm	—	Parts per million
PPts	—	Pyridinium *p*-toluenesulfonate
Pr	—	Propyl
pTSA	—	Para tolluenesulfonic acid
quant	—	Quantitative
quat	—	Quaternary
R	—	A generic organic group
r.t.	—	Room temperature
R_f	—	Retardation factor
S	—	Selectivity factor
Sat	—	Saturated
sec	—	Secondary
SM	—	Starting material
t	—	*Tertiary*
t	—	Time
TES	—	Triethyl silyl
THF	—	Tetrahydrofuran
THP	—	Tetrahydropyran
TLC	—	Thin layer chromatography
TMB	—	1,3,5-Trimethoxybenzene
TMS	—	Trimethyl silyl
TON	—	Turn over number
Tr	—	Trityl, CPh_3
TS	—	Transition state
w.r.t.	—	with respect to
Xantphos	—	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)
μ	—	Micro

Chapter 1. Introduction.

This thesis covers a variety of interrelated topics. the introduction chapter covers: hydrogen borrowing (HB)[a] reactions which are explored during Chapters 2 and 3, and pentamethyl phenyl (Ph*) ketones, a functional group that acts as a masked ester with unique chemical properties, which are utilised throughout the thesis. Each Chapter has a specific introduction covering relevant concepts.

- Chapter 2: Discusses the application of HB in intermolecular ring formation reactions to form heterocycles and carbocycles.
- Chapter 3: Discusses the synthesis of lactones and lactams using a HB disconnection approach.
- Chapter 4: Discusses the synthesis of cyclohexenes in a [5+1] strategy developed by Donohoe and co-workers and gives an overview of 1,5-hydride transfer reactions and Mukaiyama-Michael reactions.
- Chapter 5: Discusses the numerous roles of aluminium reagents in 1,5-hydride transfer, aluminium catalysis and ongoing work towards enantioselective 1,5-hydride transfer.

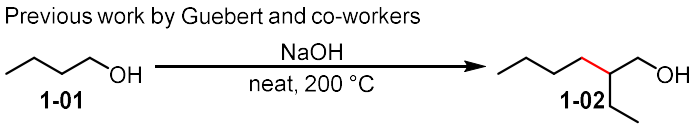
HB is a large topic and has recently been the subject of numerous reviews; Sabater and co-workers gave a general review of the field in 2018.[1] More focused perspectives have been provided by: Newton and co-workers, who accessed the recent industrial applications of the strategy;[2] Kempe and co-workers and Morrill and co-workers, who focussed on the use of earth-abundant metal catalysts;[3,4] Donohoe and co-workers outlined the control of absolute stereochemistry in HB, either *via* stereoretention or enantioselectivity;[5] finally, Krische and co-workers reviewed the use of alkenes and alkynes as pronucleophiles in hydrogen borrowing.[6,7]

1.1. Hydrogen Borrowing Catalysis Cycles.

HB is defined broadly as a one-pot reaction involving *in situ* substrate oxidation mediated by a catalyst that "stores" hydrogen, typically as a metal hydride. This generates a reactive species *in situ,* which can undergo various transformations. Hydrogen can then be "returned" to the substrate resulting in a redox-neutral process.

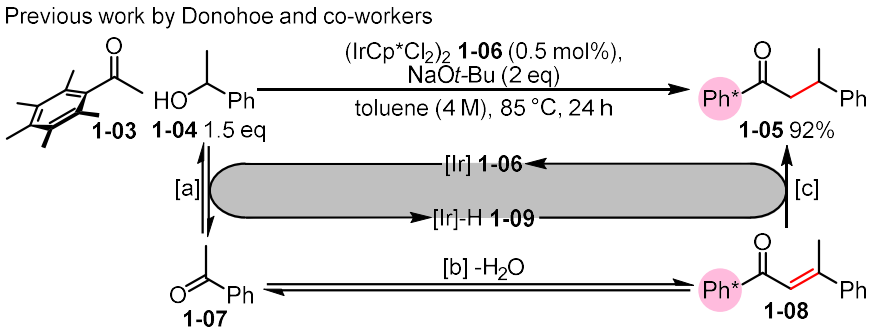
[a] In the literature both the terms "borrowing hydrogen" and "hydrogen auto transfer" are used as synonyms for HB. There is no technical distinction between these terms. "Hydrogen auto transfer" is not the same as "hydrogen atom transfer" (HAT).

The first reported HB reaction in the literature was described by Guebert and co-workers in 1909 (Scheme 1-1).[8] They discovered that butanol (**1-01**) dimerises when heated to 200 °C with NaOH to form the α-branched alcohol **1-02**.[9] The term HB was coined by Williams and co-workers in 2004.[10]



Scheme 1-1) The first hydrogen borrowing reaction was the Guebert reaction, performed in 1909. Yield not reported.[8]

The most common systems employ a three-step sequence involving: [a] catalyst **1-06** oxidising alcohol **1-04** (or "borrowing" the hydride) to form electrophile **1-07** and metal hydride **1-09**; [b] the intermediate **1-07** undergoes a condensation reaction with the ketone **1-03**, to form the hydride acceptor **1-08**; [c] the hydride is then "returned" to give the product **1-05** regenerating the catalyst **1-06** (Scheme 1-2). In C−C bond forming HB reactions, the reduction is generally irreversible and thermodynamically drives the reaction sequence.

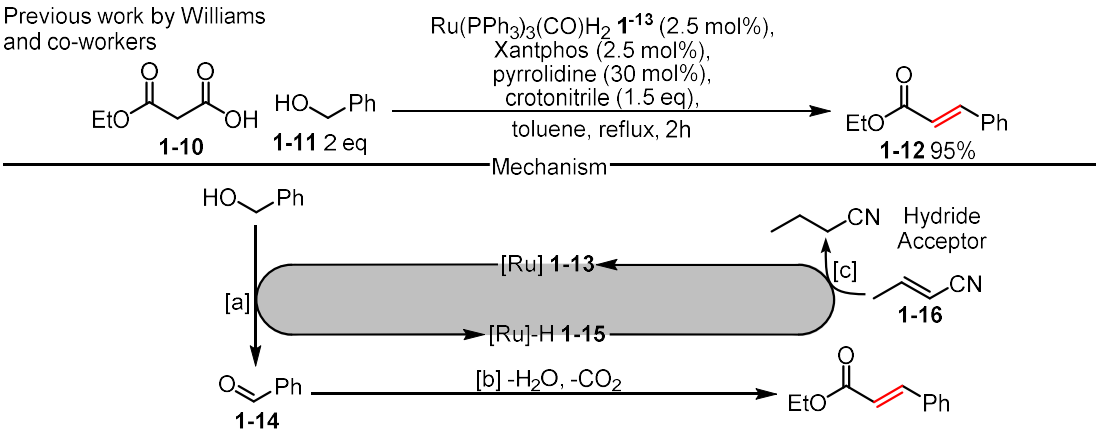


Scheme 1-2) Most hydrogen borrowing reactions involve [a] oxidation, [b] condensation followed by [c] reduction. Example performed by Donohoe and co-workers.[11]

1.1.1. Tandem Hydrogen Transfer Catalysis Reactions.

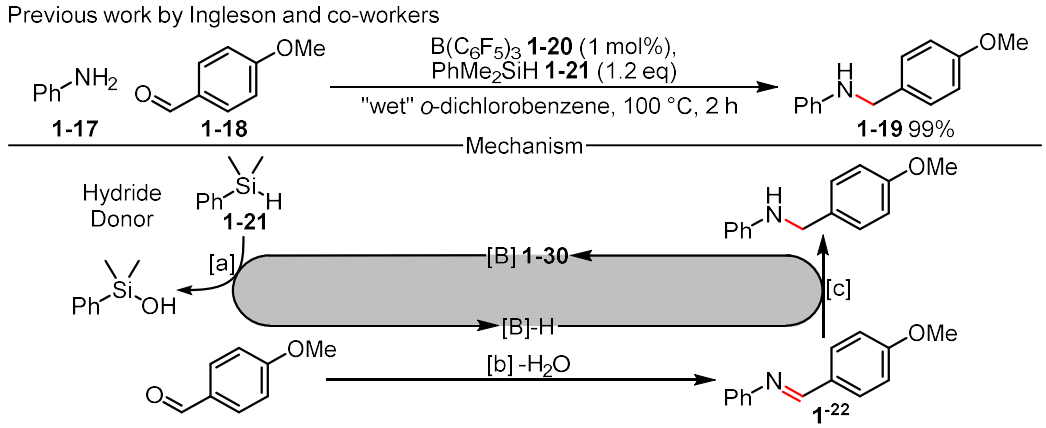
HB is a subset of tandem hydrogen transfer catalysis reactions. In this broader class of reactions, oxidation and reduction are decoupled. One of these substrates is generally a cheap and readily available reagent that acts as a sacrificial hydride acceptor (Scheme 1-3) or a hydride donor (Scheme 1-4) to access the desirable substrate.

For example, Williams and co-workers oxidised benzyl alcohol (**1-11**) to form the aldehyde **1-14** and subsequent alkene **1-12** in 95% yield (Scheme 1-3).[12–14] To regenerate the active Ru-complex **1-13**, the metal hydride **1-15** reduces crotononitrile **1-16**. Some reactions, referred to as "acceptorless hydride transfers", involve the direct release of H_2 using a proton as the hydride acceptor.[15–17]



*Scheme 1-3) The broader hydride transfer reaction class utilises the same mechanistic steps but with the hydride not being returned. William and co-workers used crotonitrile **1-16** as a sacrificial reagent to access the alkene **1-12**. [a] oxidation, [b] condensation and [c] reduction.*

Ingleson and co-workers developed a reductive amination of aldehyde **1-18** with aniline **1-17** to give the 2° amine **1-19** in 99% yield (Scheme 1-4).[18] Boron catalyst **1-20** acts as the hydride transfer reagent, with the sacrificial silane **1-21** acting as the hydride source.[a]



*Scheme 1-4) Xiao and co-workers used Silane **1-21** as a sacrificial reagent to access the amine **1-19**. [a] oxidation, [b] condensation and [c] reduction.*

1.1.2. Scope of Nucleophiles in Hydrogen Borrowing.

Various nucleophiles have been alkylated using the oxidation, condensation, reduction HB strategy, generating new C–C bonds (Figure 1-1). This includes condensations with; ketones,[19,20] 1,3-dicarbonyls,[21,22] malonates,[23,24] half esters,[25] nitriles,[26,27] nitroalkanes,[27] esters,[28] 2-oxoindoles,[23,26] amides,[28,29] pyrimidines,[30] barbiturates,[23,26,31] thioamides,[29] sulfones,[32] sulfonamides,[32,33][b] and phosphine oxides.[34] As seen in the Guebert reaction, alcohols can be oxidised *in situ* to act as the nucleophile as well as the electrophile.[35,36] Friedel-Craft reactions have allowed for the alkylation of aromatic rings such as indoles,[37,38]

[a] $B(C_6F_5)_3$ and silane are a common pair of reagents acting as a unique reductant. These are discussed in Section 2.7.3.
[b] Maji *et* al. discovered sulfones subsequently eliminates to form alkenes.[33]

phenols,[39] and pyrroles.[38] HWE reactions, instead of aldol condensations, allow for milder conditions to be used to alkylate; Ketones,[40] nitriles,[40] and esters.[40,41]

C–N bond formation has been developed in parallel to C–C bond formation. Alkylation of amines,[42–44] amides,[45] carbamates,[46] ureas,[47]a sulfinamides,[48–50] sulfonamides[51] and acyl hydrazines[52] have all been reported. By expelling triphenylphosphine oxide, iminophosphoranes[53] have been alkylated. C–S bond formation has also been demonstrated using thiol nucleophiles to generate thioethers using Pd nanoparticles as a catalyst.[54]

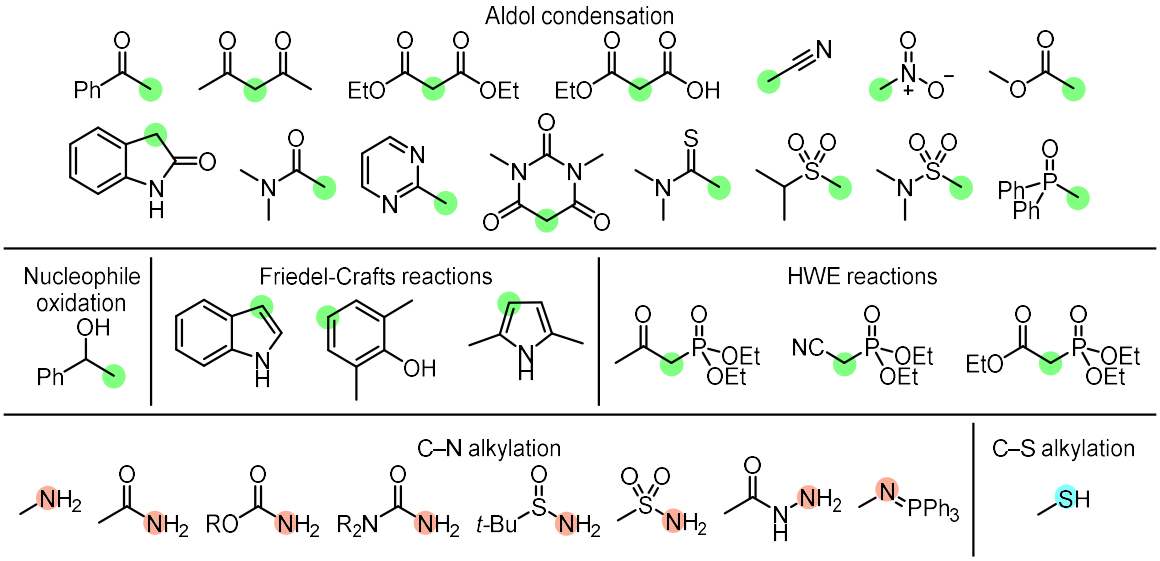
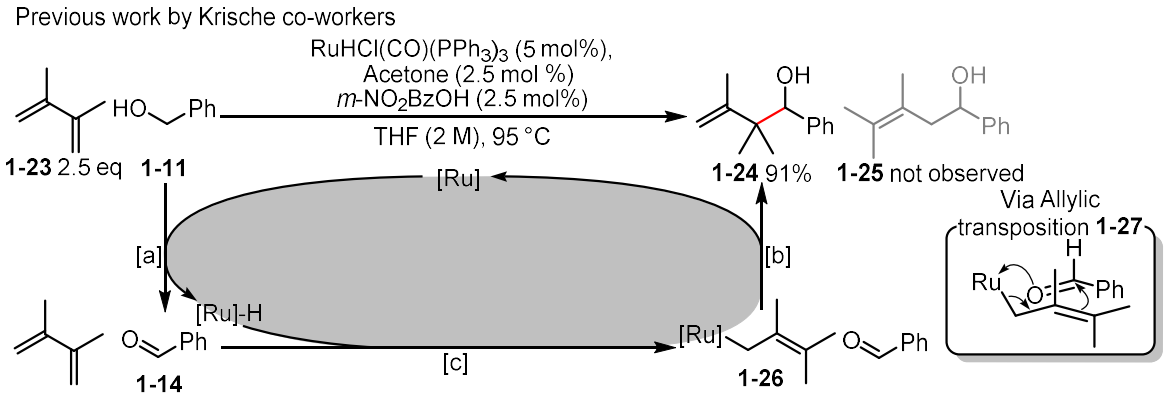


Figure 1-1) A diverse array of nucleophiles has been demonstrated in HB to form C–C, C–N and C–S bonds.

1.2. Oxidation, Reduction, Derivatisation Hydrogen Borrowing Cycles.

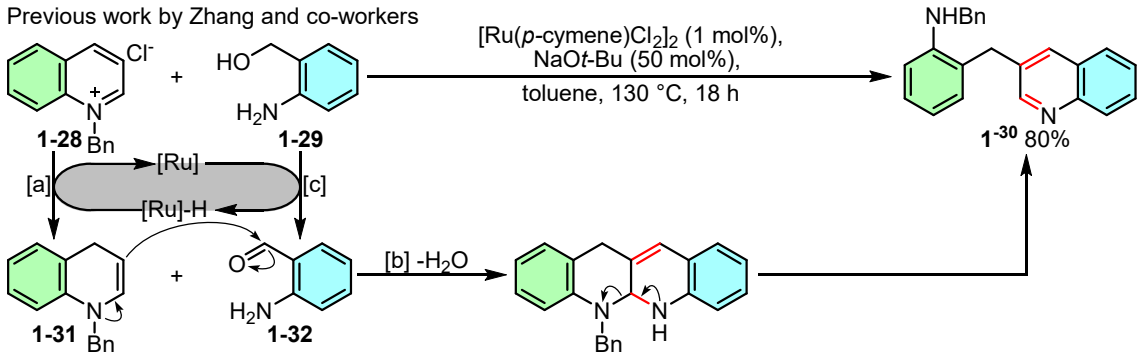
Whilst the HB cycle described above represents the most commonly reported HB reactions (Scheme 1-2), a smaller subset of reactions run through an oxidation, reduction, and alkylation sequence (Scheme 1-5). Krische and co-workers have explored this extensively, for example, in the synthesis of alcohol **1-24**: [a] the alcohol **1-11** is oxidised; [c] the Ru–H then inserts into the diene **1-23** *in situ* to form a metal alkyl in an η^1 fashion **1-26**; [b] the alkene is inserted into the aldehyde **1-14** by allylic transposition **1-27** to give the 2° alcohol **1-24** in 91% yield as a single regio isomer.

[a] Urea is most commonly used as an ammonia substitute instead of for the synthesis of urea compounds.



*Scheme 1-5) Krische and co-workers developed several alcohol alkylation methodologies that selectively form 2° alcohols, such as **1-53**. [a] oxidation, [b] alkylation, [c] reduction.*

Zhang and co-workers developed a similar HB strategy with pyridinium **1-28** acting as the hydride acceptor and alcohol **1-29** acting as a hydride donor (Scheme 1-6). Hydrogen transfer generates the active nucleophile **1-31** and electrophile **1-32** *in situ*. These substrates undergo condensation followed by transamination to give the product **1-30**.[42,55]



*Scheme 1-6) Zhang's hydrogen borrowing, Zincke sequence results in quinoline **1-30**.[42]*

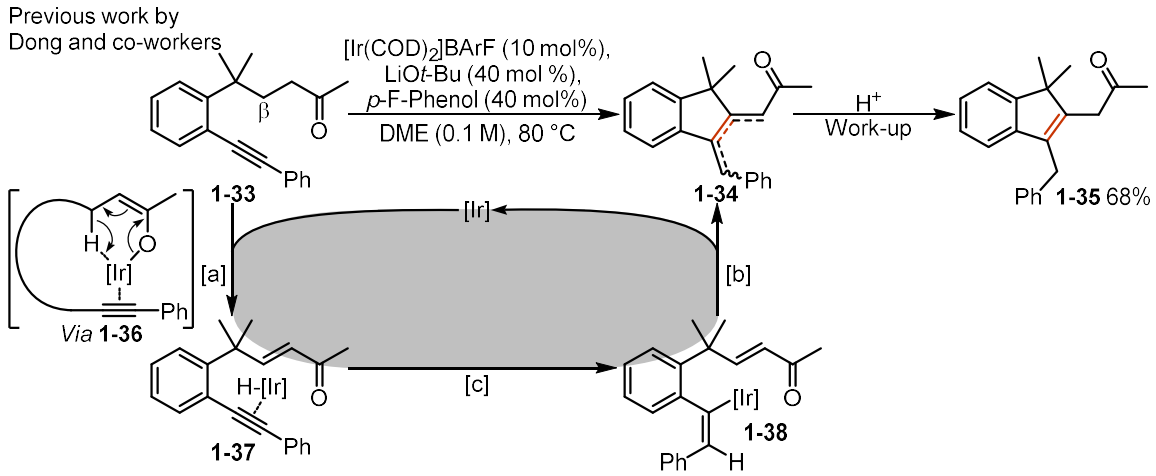
1.3. C-H Activation in Hydrogen Borrowing.

The selective oxidation of alcohols and amines makes up the majority of HB strategies reported. However, recent work has looked at weaker and more distant directing groups and undirected oxidation.

1.3.1. Ketone Directed C-H Activation.

By coordinating a "naked" Ir-species to an adjacent alkyne **1-36**, Dong and co-workers were able to oxidise ketone **1-33**[56–58] to form an enone **1-37** (Scheme 1-7).[59,60] The resulting Ir-H undergoes alkyne insertion to form the Ir–C complex **1-38,** followed by a Heck insertion to form the 5-membered ring **1-34**. The mixture of regioisomers converges to form the product **1-35** in 68% yield upon an acidic work-up. This work is notable in the context of HB, as irreversible enone reduction is usually the driving force of the reaction. The need for the naked

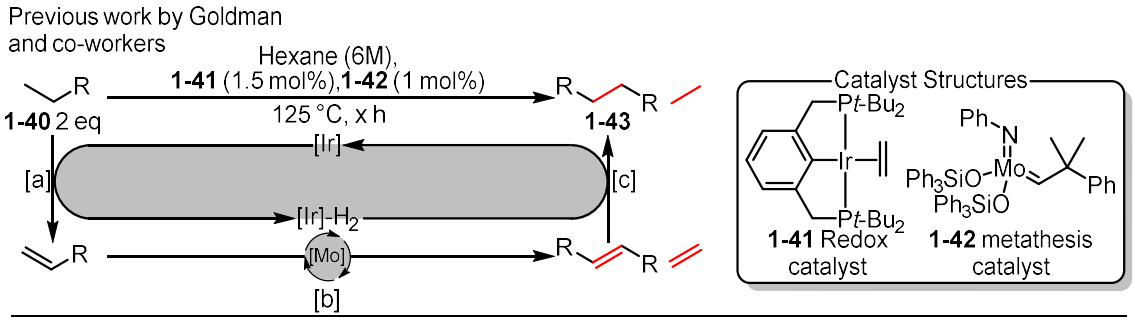
Ir-catalyst and intramolecular coordination is probably why this is not observed in other HB reactions.[61]a



*Scheme 1-7) Dong and co-workers were able to selectively activate the β-position of ketone **133** using Ir to form 5-membered ring **135**.[60] Published 2022.*

1.3.2. Undirected Oxidation.

Using the Ir-complex **1-41**, Goldman and co-workers have oxidised short-chain alkanes **1-40** (Scheme 1-8).[62,63] The subsequent alkenes undergo Molybdenum **1-42** mediated alkene metathesis. Reduction generates the alkane products **1-43**, which can undergo further HB reactions. The lack of selectivity (summarised in the Table below) is likely due to the intermediates undergoing unselective alkene chain walking.[64]b



Distribution of products (mM)

Time (h)	C_2	C_3	C_4	C_5	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}	C_{15}	Σ
6	123	123	105	183	131	73	70	47	10	4	2	1	0.3	872
24	233	233	191	319	234	133	122	81	22	9	5	2	1	1585
96	264	264	218	372	276	154	146	95	26	12	6	3	1	1837

*Scheme 1-8) Goldman and co-workers showed a dual catalytic system using Ir-complex **1-41** to undergo hydrogen borrowing and Mo-complex **1-42** to perform metathesis of the alkenes.[62,63]*

[a] Deuterium crossing experiments show that the Ir-H sits as a tightly bound complex **1-37** without intermolecular crossover.

[b] Product distribution given as a concentration in the solution of hexane. A clearly defined yield for this unselective process was not possible.

1.4. The Challenges and Advantages of Hydrogen Borrowing.

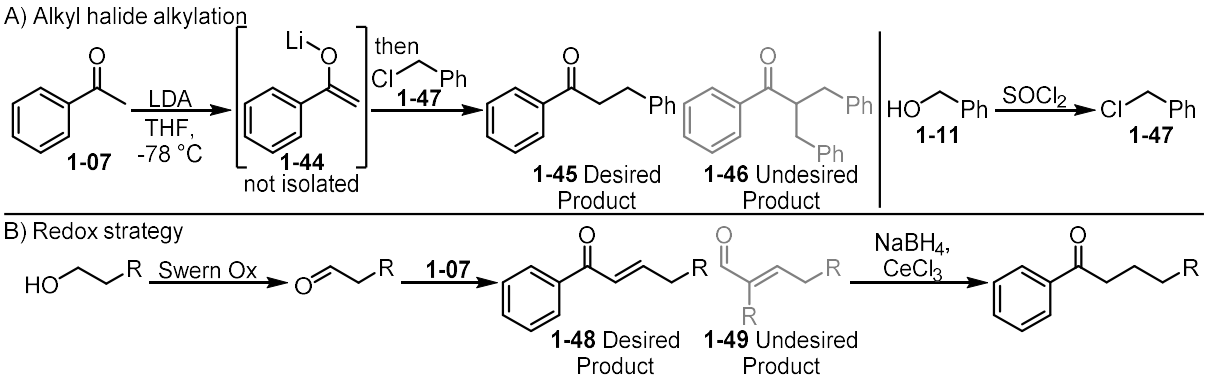
For a successful HB reaction, numerous reactions must occur within a single pot, at the same temperature and concentration, in the same solvent and in the presence of every other reagent (and product) in the sequence. Many species have roles in multiple steps; for example, the metal-hydride complex must be stable enough for oxidation to occur but sufficiently active for reduction to occur. This complexity significantly impedes rational reaction design. Whilst these challenges make HB intellectually interesting, its pursuit needs clear advantages to justify the work involved.

1.4.1. Efficiency and Environmental Impact.

HB reactions are generally highly atom efficient; most reactions produce water as the only by-product, with only catalytic loadings of the metal reagent being required.[a] By contrast, conventional alkyl halide alkylations require the controlled formation of enolates **1-44**, followed by the controlled addition of an alkyl halide such as **1-47**, all at cryogenic temperatures (Scheme 1-9 A). Alkyl halides and the reagents used to generate them, such as $SOCl_2$, are generally highly toxic.[65] Using alkyl halides has the potential for bis-alkylation **1-46**;[66] preventing bis-alkylation often requires the addition of HMPA, which is highly carcinogenic, as well as careful control of temperature and addition rates.[67]

Aldol condensation strategies require similar cryogenic conditions as well as stoichiometric oxidants and reductants (Scheme 1-9 B). Redox strategies prevent double alkylation; however, homocoupling side-products such as **1-49** can significantly complicate the reaction. When correctly designed, HB allows for a highly selective reaction which avoids these undesired side products (Scheme 1-12).

[a] The use of more abundant metals, as described by Kempe *et al.* and Morrill *et al.,* are motivated by the desire to further improve the environmental impact.[3,4]



Scheme 1-9) Classic strategies to alkylate ketones.

1.4.2. Self-Regulating Reaction Kinetics.

Although it is common for chemical reactions to consist of multiple-steps, HB kinetics have the metal catalytic cycle coupling the first and last step; because of this, the sum of all intermediate species stays below the initial loading of the catalyst.[a] Hence, HB reactions have short kinetic initiations and stable kinetic profiles until the starting material is almost entirely consumed, which prevents heat and gas release from rapidly spiking during reagent addition or as the reaction is heated up. From a process perspective, this makes reactions safe to perform.

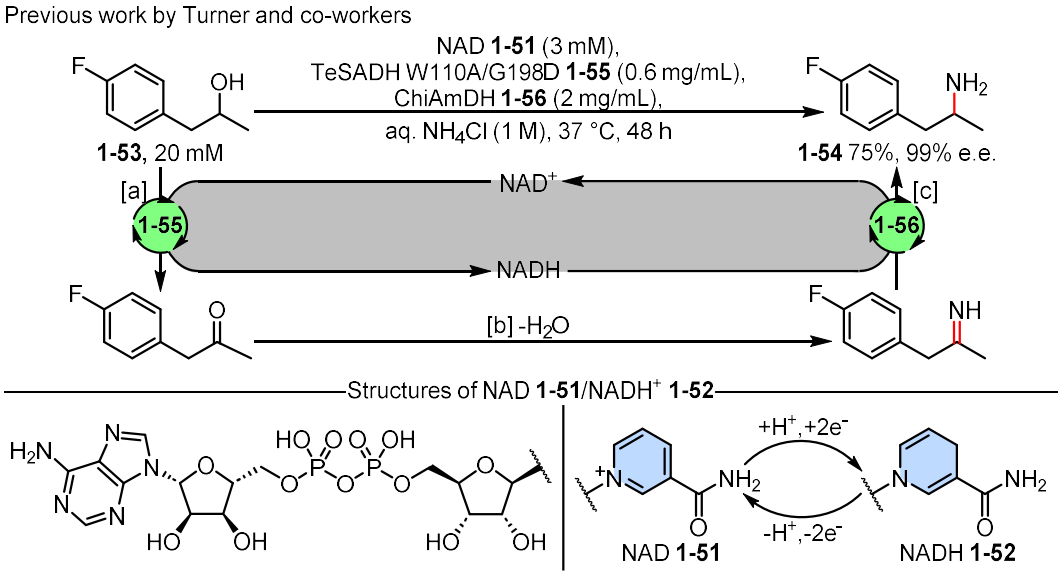
HB can be conceptualised as a chemical version of slow addition, with an aldehyde slowly being released. However, because the reformation of the oxidant is coupled to the rest of the reaction sequence, the oxidation rate changes depending on the rate of subsequent steps. Whether changes are due to the consumption of reagents during the reaction, changing the substrate or because of experimental variation. In principle, this should make reactions, once optimised, more reproducible.

1.5. Biochemical Hydrogen Borrowing.

The biological analogue of HB is the NADH **1-51** / NAD^+ **1-52** cycle which shuttles hydrides between substrates in cells (Scheme 1-10).[68] Synthetic biochemists have applied this cycle to make enzyme-mediated HB strategies.[43,69] For example, Turner and co-workers used NAD-mediated HB in the enantioselective synthesis of 1° amines, such as **1-54**, in 75% yield and 99% e.e., from alcohols **1-53**.

[a] This presumes an ideal reaction. Many reactions observe a small loss of hydrogen or metal hydrides react with residual O_2 resulting in increased build-up of the intermediates. This is normally compensated for by using a small excess of the alcohol in the reaction.

Because biochemical HB uses two enzymes and the NAD cycle instead of a transition metal, Turner was able to independently optimise the oxidation step, finding that a G198D mutation **1-55** of the wild-type enzyme increased the oxidation rate significantly.[70]



*Scheme 1-10) Turner and co-workers demonstrated the selective formation of the 1° amine **1-54** in 99% e.e. using bicatalysis.*

1.6. Structure and Reactivity of Ph* Ketones.

The Ph* ketone motif is of interest to the Donohoe group for several reasons: it has unique reactivity, which allows for new methods to be developed; it has a high propensity for crystallisation to aid purification and enhance enantiopurity; and can be cleaved to give access to more biologically relevant structures.[71] These properties arise from the steric clash of the *o*-Methyl groups twisting the aryl group out of the plane of the ketone resulting in a dihedral bond angle of 85° in the crystal structure of enone **1-57(*trans*)** (Figure 1-2). In some substrates, atropisomerism can be observed in the ^{1}H-NMR and ^{13}C-NMR spectra.

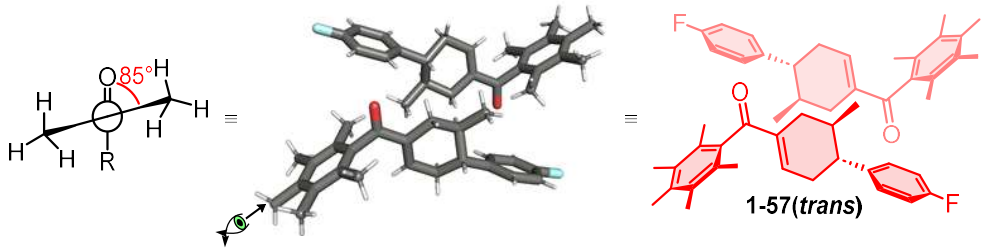
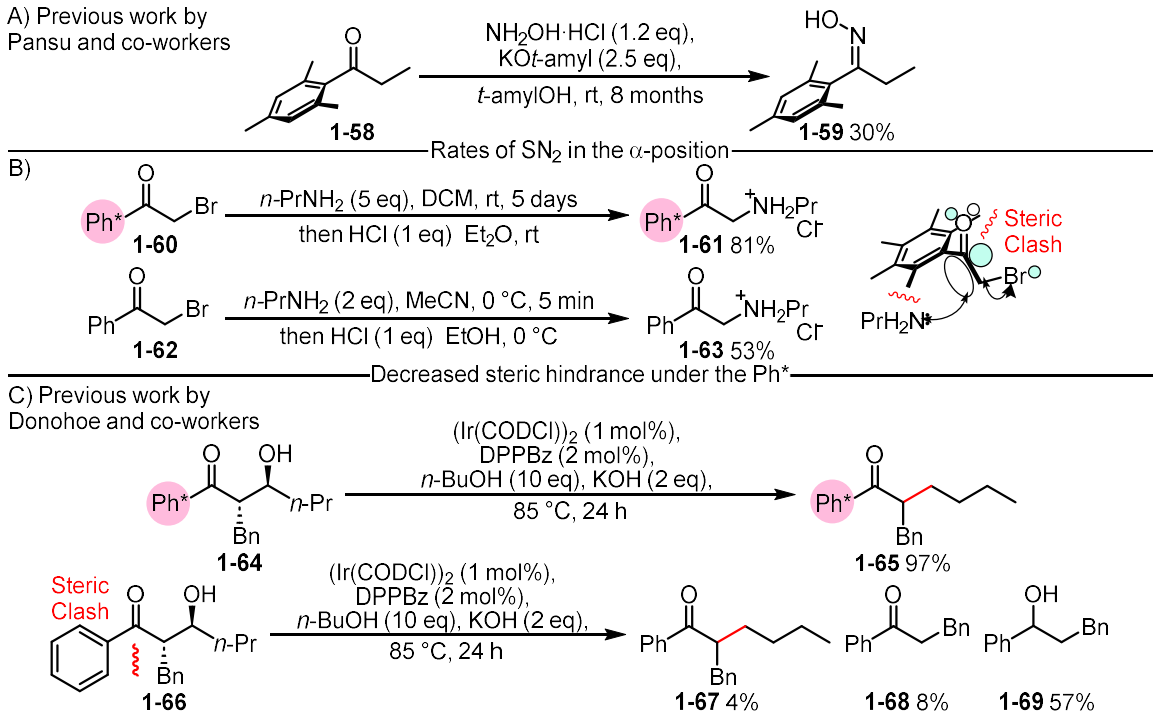


*Figure 1-2) Crystal structure of cyclohexene **1-57(trans)** taken from Section 4.15. The dihedral angle was measured to be 85°.*

1.6.1. General Reactivity of Ph* Ketones and their Analogues.

Pansu and co-workers found that the methyl groups prevented the electrophilic attack of the ketone **1-58** such that, under standard condensation conditions, the oxime **1-59** was formed in just 30% yield over 8 months (Scheme 1-11 A).[72] The effect of the ortho groups on the

α-position is more complex; whilst steric hindrance out of the ketone plane is much higher than phenyl analogues, steric hindrance in the plane of the ketone is much lower. Because of this, SN_2 substitution is much slower on the α-Br ketone **1-60** compared to the phenyl ketone analogue **1-62** (Scheme 1-11 B).[a] In contrast, E1cB elimination, which generates steric bulk specifically in the plane, occurs much faster using Ph* ketone **1-64** than the phenyl analogue **1-66**, which undergoes a retro-aldol reaction to give the ketone **1-68** and alcohol **1-69** (Scheme 1-11 C).[73]



*Scheme 1-11) The ortho-methyl groups sterically block the ketone and α-position. (A) Pansu and co-workers found only a 30% yield adding into ketone **1-58** after 8 months.[72] (B) The α-position is also significantly hindered; this could be observed in the relative rates of S_N2 in the α-position. (Discussed in section 2.3). (C) E1cB elimination is faster due to reduced steric clash in the plane of the ketone. Unpublished work.[73]*

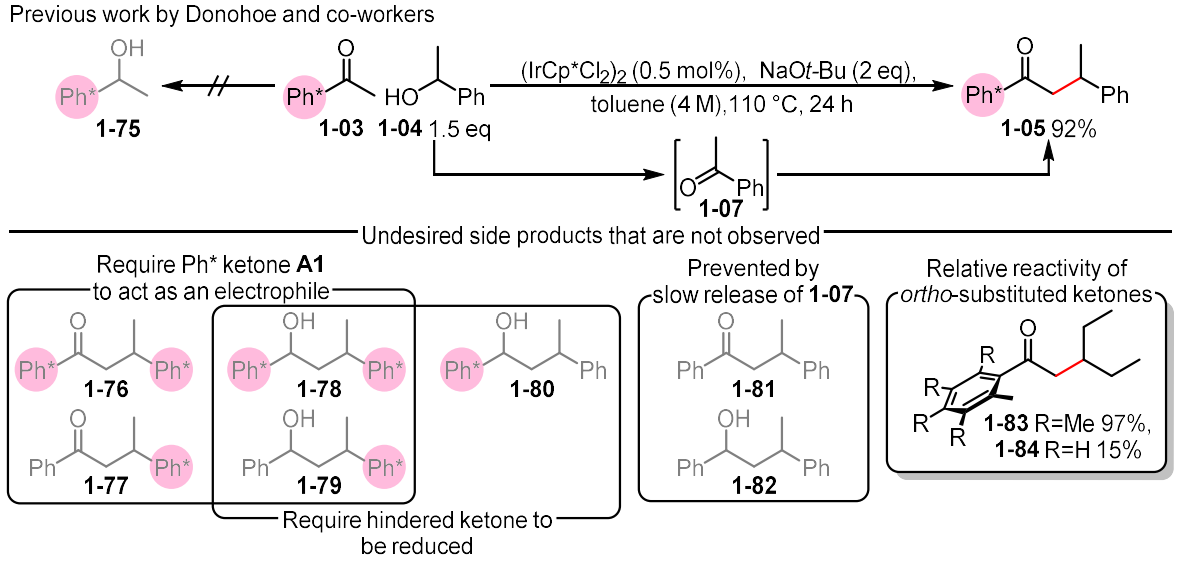
1.7. Application of Ph* Ketones in Hydrogen Borrowing.

2° Alcohols are challenging substrates in C–C bond-forming HB reactions due to the large number of products that can be formed (Scheme 1-12). Donohoe and co-workers employed Ph* methyl ketone (**1-03**) to significantly improve the reaction, allowing for the formation of a single product **1-05** in 92% yield.[11]

Since the Ph* group prevents the Nucleophilic attack of the ketone, ketones **1-76-1-79** cannot form, and since the group does not reduce, alcohols **1-75+1-78-1-80** cannot form either. Hence for the reaction to be successful, the HB system only needs to prevent the undesired

[a] Reaction developed during this research (see Section Synthesis of α-Amino Ph* Ketones.2.3).

homocoupling of **1-81**+**1-82**. By generating the ketone **1-07** *in situ,* the homocoupling can be outcompeted by a significant excess of the Ph* ketone **1-03**, even at the end of the reaction. Pentamethyl ketone **1-83** and ortho-methyl ketone **1-84** were synthesised in 97% and 15% yield, respectively, demonstrating the importance of *ortho*-substitution in achieving the desired reactivity.

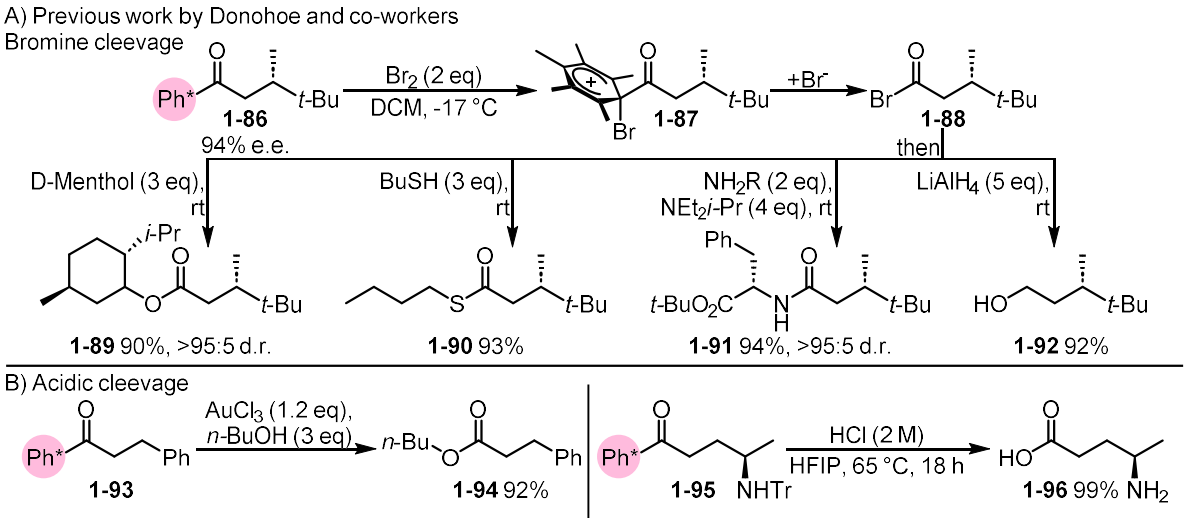


*Scheme 1-12) Donohoe and co-workers synthesised the ketone **1-05** selectively due to the numerous products that cannot form because of the Ph* ketones properties.*

Since this discovery, Ph* methyl ketone has subsequently been employed in numerous HB systems alongside a variety of metals, including K,[74] Co,[75] Mn[76] and Fe.[77] A chiral Ir-complex has also been shown to perform the reaction with enantioselective reduction.[19] This strategy was later extended to the formation of cyclic substrates, discussed in Sections 2.1.4 and 4.1.1.[20,78]

1.7.1. Cleavage of Ph* Methyl Ketone.

Donohoe and-co-workers discovered that the aryl group can be subsequently cleaved using bromine. Upon addition of bromine, the ring was found to react in the *ipso*-position to give the arenium cation **1-87,** which collapses to form the acylium ion and subsequent acetyl bromide **1-88**. Various nucleophiles were employed to subsequently trap the acetyl bromide to give derivatives **1-89-1-92** (Scheme 1-13 A).[19,79,80]. The *ipso*-addition into the arene is not believed to be selective; instead, it is believed to involve shuttling the different possible arenium ions until a stabilised cation can be eliminated. Lewis and Brønsted acids have also been proven to cleave the Ph* group (Scheme 1-13 B).

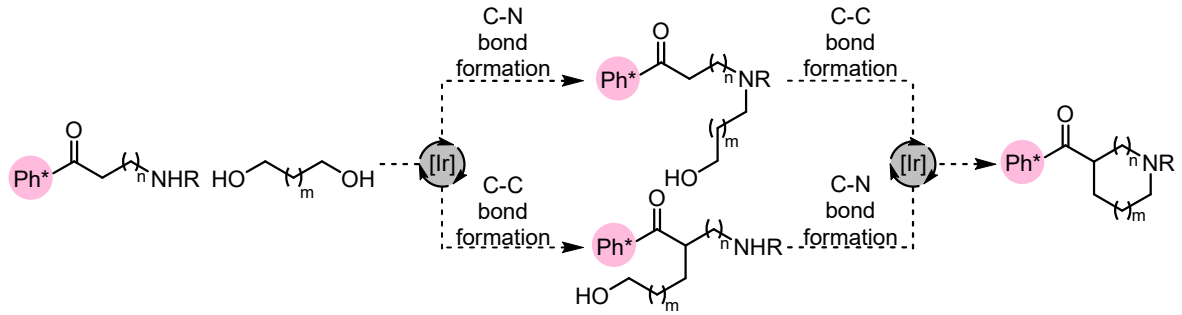


Scheme 1-13) Cleavage of the Ph can be done by either (A) brominating or (B) acidic conditions.*[19,79,80]

Chapter 2. Synthesis of Piperidines by Hydrogen Borrowing.

2.1. Introduction.

HB as a field is broadly split between C–C and C–N bond formation. In both of these areas, it has been established that two sequential HB cycles can be used to synthesise cyclic substrates in an [n+1] strategy. In this Chapter, we discuss the development of a strategy to combine C–C and C–N bond formation in a single system to synthesise N-heterocycles of various oxidation states and ring sizes (Scheme 2-1).



Scheme 2-1) Sequential HB reactions forming both a C–C and C–N bond as a potentially powerful approach to forming N-heterocyclic compounds.

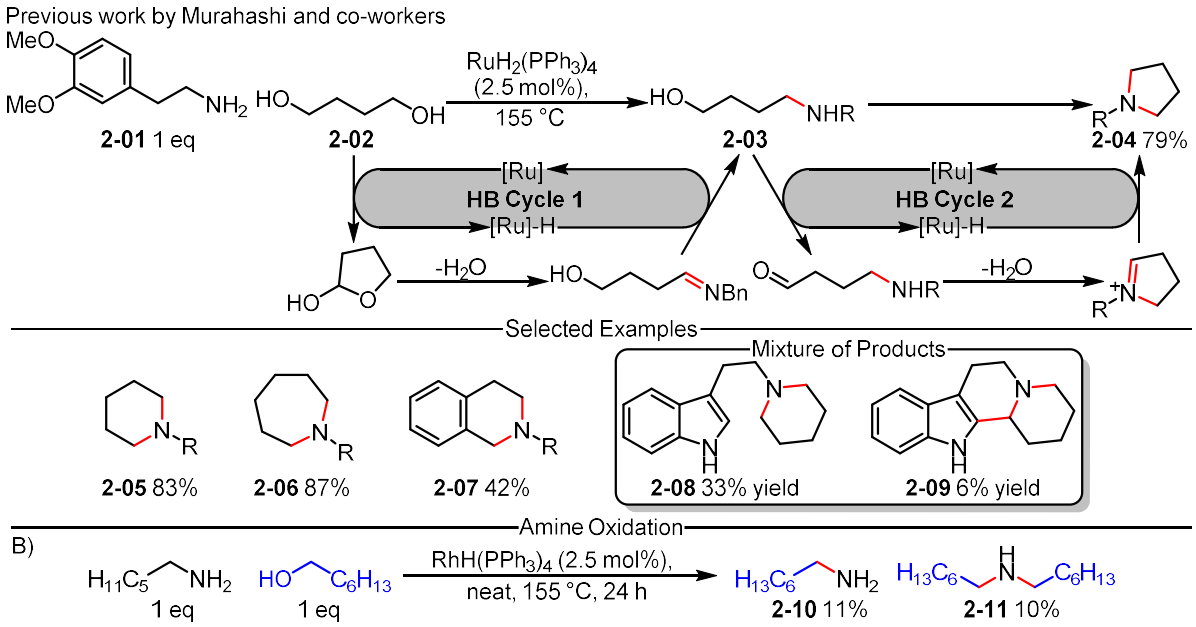
2.1.1. Sequential C–N Bond Formation for the Synthesis of N-Heterocycles.

This first example of a double HB cycle was performed by Grigg and co-workers in 1981, using Ru-catalysis to synthesise benzyl pyrrolidine from benzylamine and 1,4-butanediol.[81] Murahashi and co-workers expanded this concept to a broader set of heterocycles by a slight modification of the conditions which enabled them to synthesise pyrolidine **2-04** in 79% yield *via* the amino alcohol intermediate **2-03** (Scheme 2-2).[82] Under the same conditions they could synthesise; piperidine **2-05**, azepane **2-06** and tetrahydroisoquinoline **2-07**. In the presence of an indole group, they observed interception of the iminium intermediate by a Pictet-Spengler reaction to form the tetracyclic complex **2-09** as a minor product as well as the expected product **2-08**.[83]

HB reactivity was observed with numerous Ru and Rh-catalysts. However, when other catalysts were employed, such as $RhH(PPh_3)_4$, the undesired oxidation of amines resulted in the formation of a complex mixture, including undesired 1° amine **2-10** and 2° amine **2-11** (Scheme 2-2 B).[a] Using $RuH_2(PPh_3)_4$ resulted in selective oxidation, allowing high yields to be

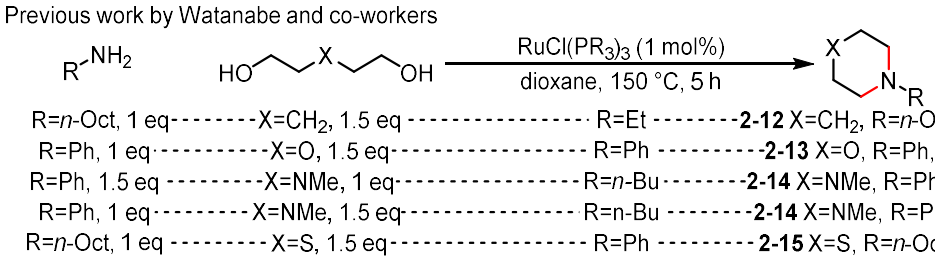
[a] Selective oxidation of amines is generally discussed in terms of isofunctional metathesis reactions due to the distinct challenges of thermodynamic product control. The subject was recently reviewed by Morandi and co-workers. with a very good summation of the principles of isofunctional reactions and the strategies that can be used to control selectivity.[284]

achieved with a 1:1 stoichiometry of the starting materials due to the stability of the C-N bonds under these conditions and the stability of the favourable entopy associated with ring formation.



*Scheme 2-2) (A) Murahashi and co-workers expanded sequential HB synthesis to a range of heterocycles beyond the piperidine previously demonstrated by Grigg. (B) Other catalysts, such as $RhH(PPh_3)_4$, oxidised amines and alcohols unselectively resulting in complex mixtures, including 1° amine **2-10** in 11% yield and 2° amine **2-11** in 10% yield.*[82]

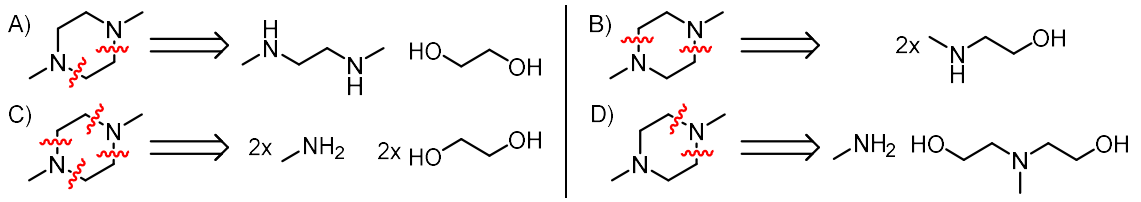
By incorporating heteroatoms into the diol backbone, Watanabe and co-workers were able to access morpholine **2-13** and piperazine **2-14** (Scheme 2-3).[84] Each substrate required extensive reoptimisation and the sulfur analogue **2-15** was not observed. Sulfides were suspected to poison the catalyst, an effect observed in multiple subsequent HB systems.[78,80]



*Scheme 2-3) Watanabe and co-workers successfully incorporated heteroatoms into the diol backbone giving access to numerous new heterocycles. NMR yields reported for piperidine **2-14**.*[84] *[a] Reaction run at 180 °C.*

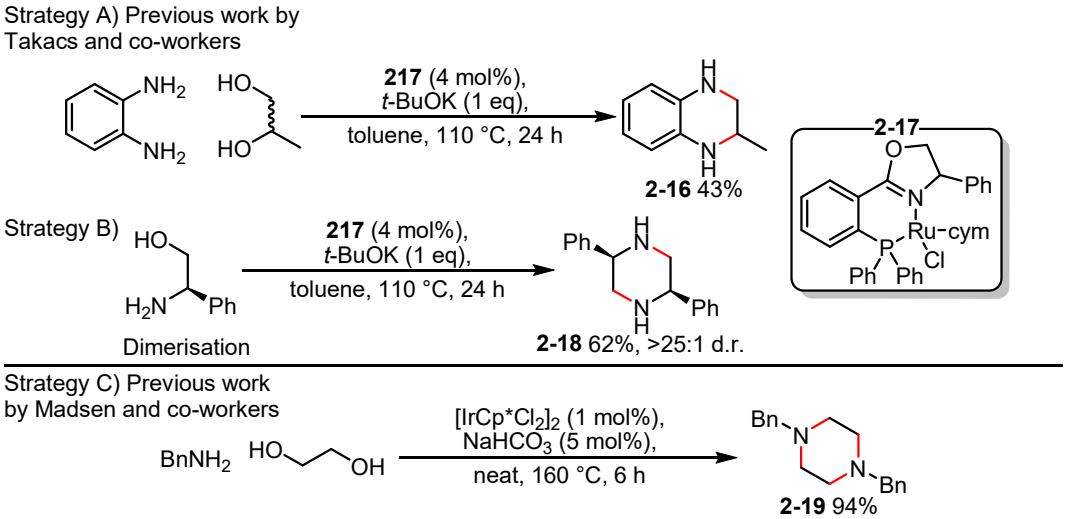
2.1.2. Strategic Diversity in the Synthesis of Piperazines.

Because of the two nitrogen atoms in a piperazine ring, the potential disconnection strategies are more diverse than the [n+1] strategy discussed above (Scheme 2-4). The utility of each disconnection strategy depends on the structure of the desired product and the availability of the starting materials.



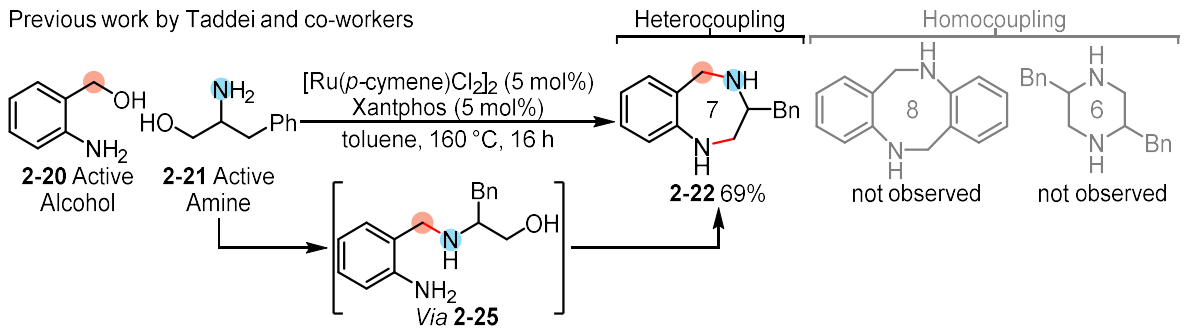
Scheme 2-4) Different retrosynthetic strategies can be applied to piperazines due to the four cleavable bonds in piperazines.

All four of these approaches have appeared numerous times in the literature. For example, Takacs and co-workers demonstrated strategies A and B using ruthenium complex **2-16** (Scheme 2-5 A+B).[85] It is worth noting that the aryl ring in piperazine **2-16** prevents disconnection strategies B, C or D. Madsen and co-workers successfully formed 4 C–N bonds in a single step to give the symmetrical piperazine **2-19** in 94% yield (Scheme 2-5 C).



*Scheme 2-5) (B and C) Takacs and co-workers demonstrated two disconnection strategies to synthesize piperazines **2-16** and **2-18**.*[85] *(C) Madsen and co-workers synthesised four of the six bonds in piperazine **2-19** in 94% yield.*[86]

Utilising the symmetry of a molecule can eliminate the need to perform selective *N*-alkylations; however, this is not possible for all substrates. Tadei and co-workers synthesised benzodiazepine **2-22** with a high degree of selectivity by activating one alcohol (C4) **2-20** for oxidation and one amine (C5) **2-21** for condensation, allowing for highly selective heterocoupling to give the amino alcohol intermediate **2-23** (Scheme 2-6).[87] The less active alcohol and amine can then close, driven by the entropically favourable intramolecular reactions, to give diazepane **2-22** in 69% yield. This is the type of regiocontrol we hoped to harness in our work.

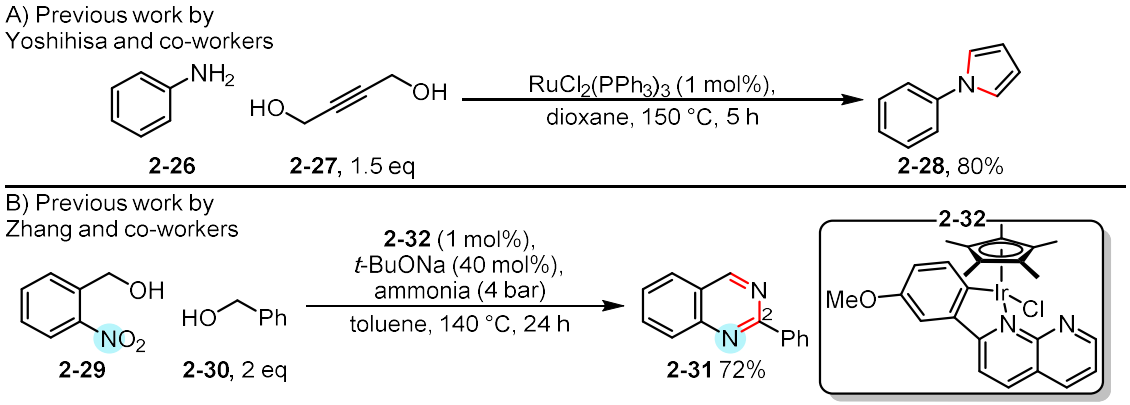


*Scheme 2-6) Taddei and co-workers used substrate control to give highly selective heterocoupling of amino alcohols **2-20**+**2-21**.*[87]

2.1.3. Hydrogen Borrowing in the Synthesis of Aromatic N-Heterocycles.

The return of the hydride by the metal catalyst means HB routes towards saturated compounds are far more common than routes to aromatic rings. Aromatic rings are more commonly synthesised by related oxidative hydride transfer processes (see Section 1.1.1), which either expel hydrogen or consume a sacrificial reductant.[16]

Yoshida and co-workers recognised that 1,4-diol **2-27** is isoelectronic to butanedial. When the diol was subjected to Ru-catalysed HB conditions, the alkyne isomerises to give the pyrrole **2-28** in 80% yield (Scheme 2-7 A).[88] Aryl nitro groups are often reduced under HB conditions, accepting three hydrides to form a 1° aniline *in situ* which can then act as an electrophile.[89] Whilst this often causes problems, Zhang and co-workers utilised this reduction to synthesise pyrimidines **2-31** from benzylic alcohols **2-29** and **2-30** (Scheme 2-7 B).[90]

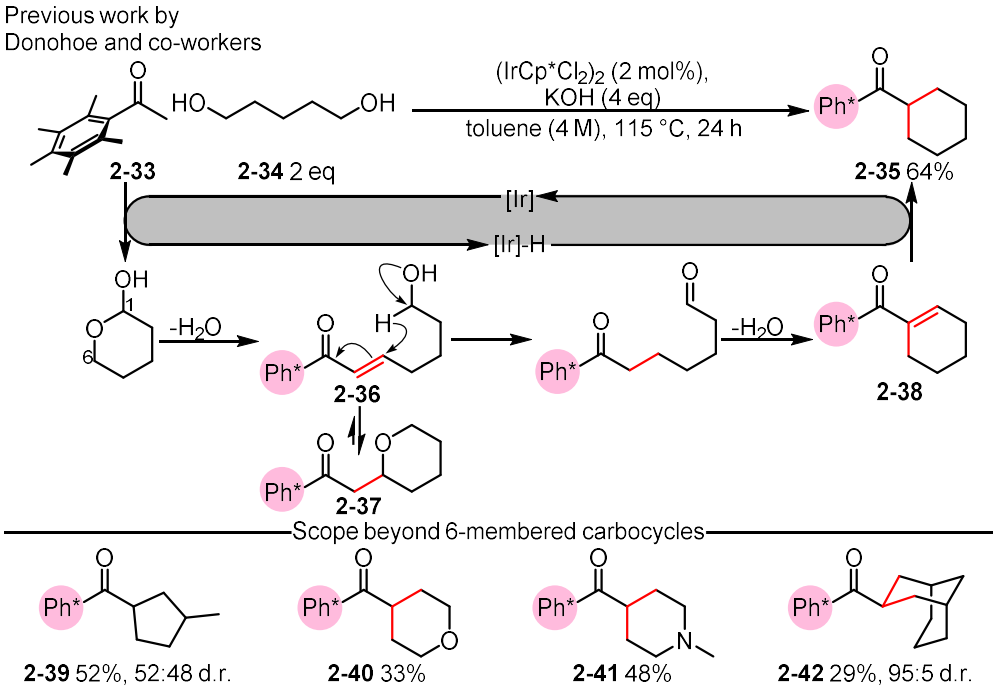


*Scheme 2-7) Yoshihisa and co-workers demonstrated that 1,4 butyne-diol **2-27** acts as a masked surrogate for butanedial.*[88]
Zhang and co-workers synthesised pyrimidine rings utilising a separate hydride acceptor.[90,91]

2.1.4. Sequential C–C Bond Formation for the Synthesis of Carbocycles.

Sequential C–C bond formation *via* HB was first achieved in 2018 by Donohoe and co-workers using Ph* methyl ketone (**2-33**) (Scheme 2-8).[20,92] Later mechanistic work found cyclohexanes **2-35** were not formed by a double metal catalysed hydrogen borrowing cycle but

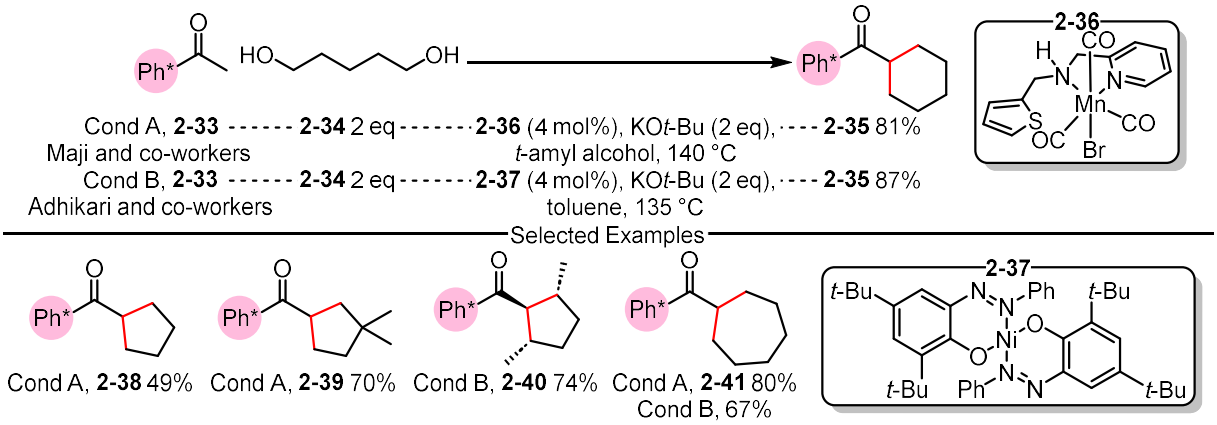
via a single cycle containing an intramolecular 1,5-hydride shift of the alcohol **2-36** before the hydride is returned to the enone **2-38**.[16,92,93]a The intermediate alcohol **2-36** was discovered to be in equilibrium with the THP **2-37**. The reaction showed good yields for a variety of cyclohexanes where as more modest yields were obtained for 5-membered rings **2-39**, heterocycles **2-40**+**2-41**, and bicycles **2-42**.[94]b



Scheme 2-8) Donohoe and co-workers demonstrated diol hydrogen borrowing with a ketone nucleophile allowing for a [5+1] cyclisation strategy to access cyclohexanes ***2-35****.*[16,92,93]

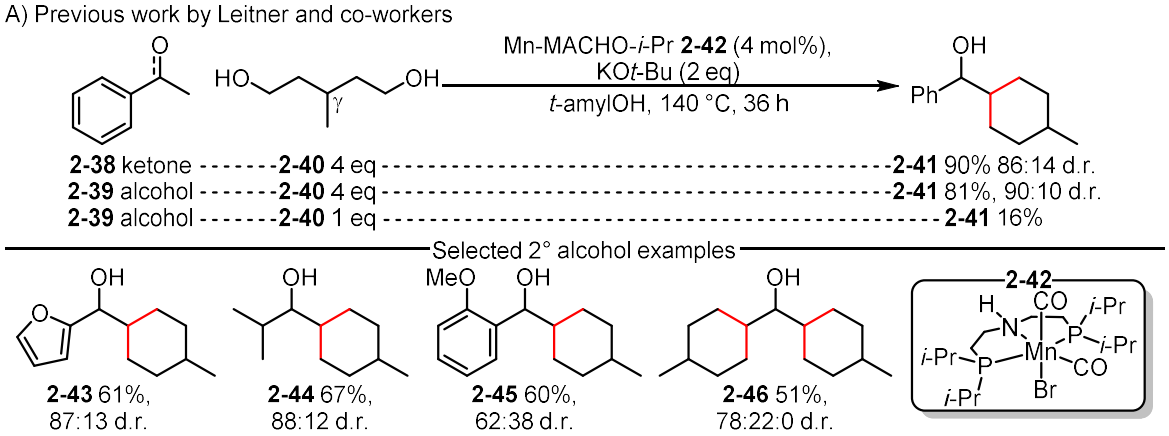
Since its discovery, Maji and co-workers developed Mn(I) complex **2-36** to catalyse the same cyclisation (Scheme 2-9, Cond A).[76,95] Having a hemilabile thiophene group on the catalyst **2-36** increased the rate of ligand exchange resulting in a significant increase in the yield.[96] For the same purpose, Adhikari and co-workers developed Ni-hydrazine catalyst **2-37** (Scheme 2-9, Cond B).[97–99] High yields were observed for the synthesis of cyclopentanes **2-38**-**2-40** and cycloheptane **2-41**. In addition, Donohoe and co-workers have also developed an enantioselective version of the [5+1] strategy, using a chiral Ir-complex to selectively reduce a pro-chiral enone.[20]

[a] The mechanism of this reaction is discussed in more depth in Section 4.1.1.
[b] Work in the group has attempted to improve the formation of piperidine **2-41** without significant improvements in yield.



*Scheme 2-9) Maji and co-workers developed Mn complex **2-36** which gave cycloheptane in 80% yield.[95] Adhikari and co-workers demonstrated cyclisation using nickel hydrazine complex **2-37**.[99]*

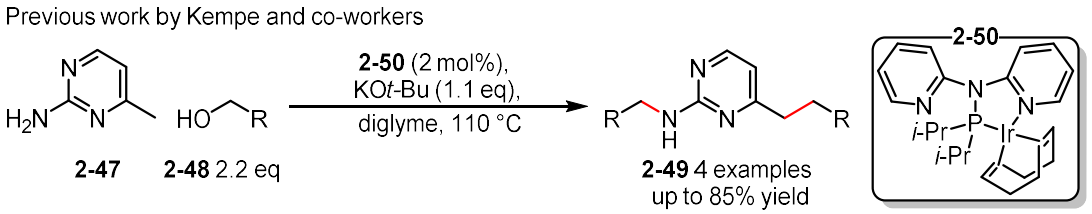
Leitneri and co-workers furthered the field by discovering a cyclisation methodology that does not require aryl *ortho*-methyl groups to protect the ketone (Scheme 2-10).[35] Employing either the ketone **2-38** or alcohol **2-39** gave the desired cyclohexane **2-41** in 90% and 81% yield, respectively. Controlling the reaction required a large excess of the diol **2-40** and was limited to unsubstituted or γ-substituted diols. This method allowed for the preparation of various cyclohexanes **2-43-2-45** as well as the tetra-alkylation of isopropanol to give **2-46**.



*Scheme 2-10) Leitner and co-workers demonstrated cyclisation with benzylic alcohol **2-39**.[35] Secondary alcohols were used in the formation of cyclohexanes **2-43-2-46**.*

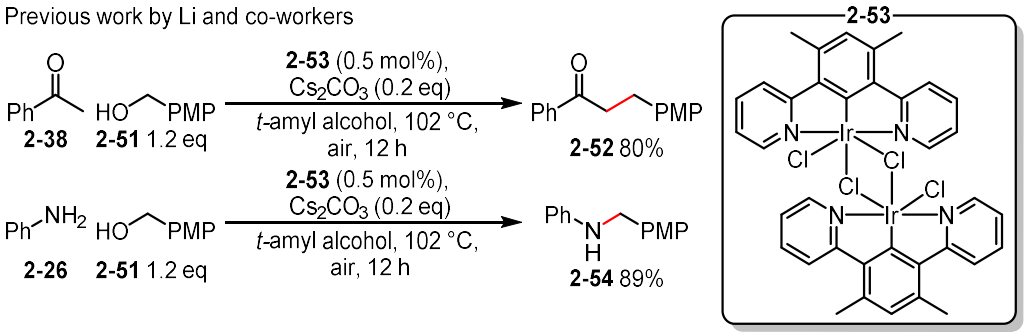
2.1.5. One-Pot Sequential C–C, C–N Bond Formation.

Kempe and co-workers were the first to observe C–C and C–N HB reactions in a single step (Scheme 2-11). Pyramidine **2-47** was alkylated in two positions in up to 85% yield to give pyramidine **2-49**.[30] The paper does not compare the relative rates of the two alkylations, and whilst this was not important in their process it was expected to be important in understanding and controlling our proposed system.



*Scheme 2-11) Kempe and co-workers successfully dialkylated pyrimidine **2-49** using the bidentate Iridium complex **2-50**.*[30]

Li and co-workers discovered that catalyst **2-53** could be employed in C–C and C–N HB reactions promoted by $CsCO_3$ (20 mol%) to form products **2-52**+**2-54**, respectively (Scheme 2-12).[100]. The group did not report any competition experiments between the nucleophiles or utilise this in a double alkylation strategy.



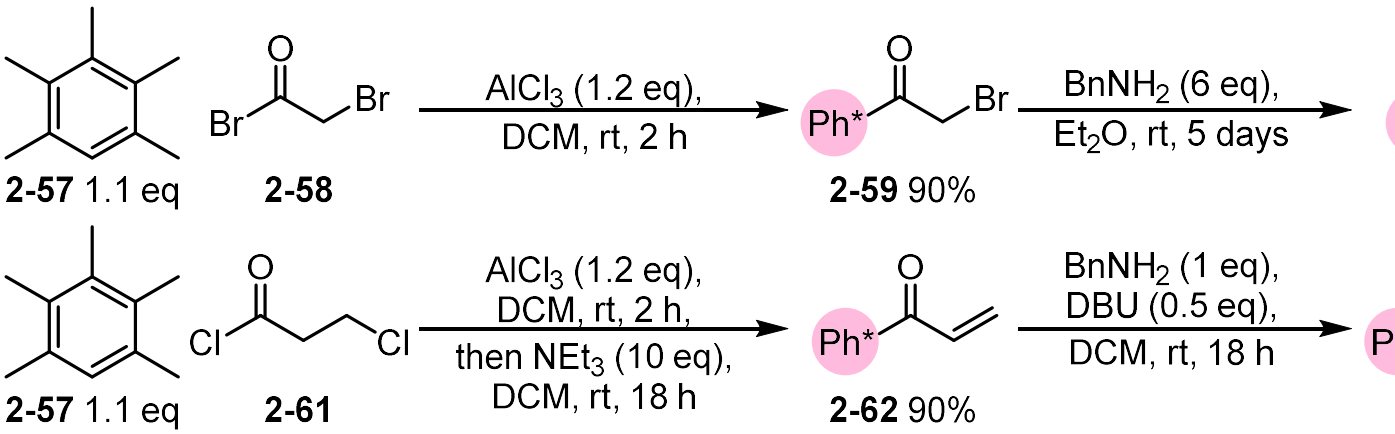
Scheme 2-12) Li and co-workers found that C–C and C–N bond formation could be performed under identical conditions using Cs_2CO_3 (0.2 eq) as a base.[100]

2.2. Aims and Objectives.

The synthesis of piperazines described above demonstrates how a choice of disconnections improves the utility of HB as a strategy (Scheme 2-4). The ability to form both C–C and C–N bonds in one pot could massively increase the strategic flexibility available to HB. Our initial aims were, therefore: (i) synthesise α and β-amino Ph*ketones as model bifunctional substrates and establish their stability; (ii) screen HB conditions to access the potential reactivity with 1,3 and 1,4-diols.

2.3. Synthesis of α-Amino Ph* Ketones.

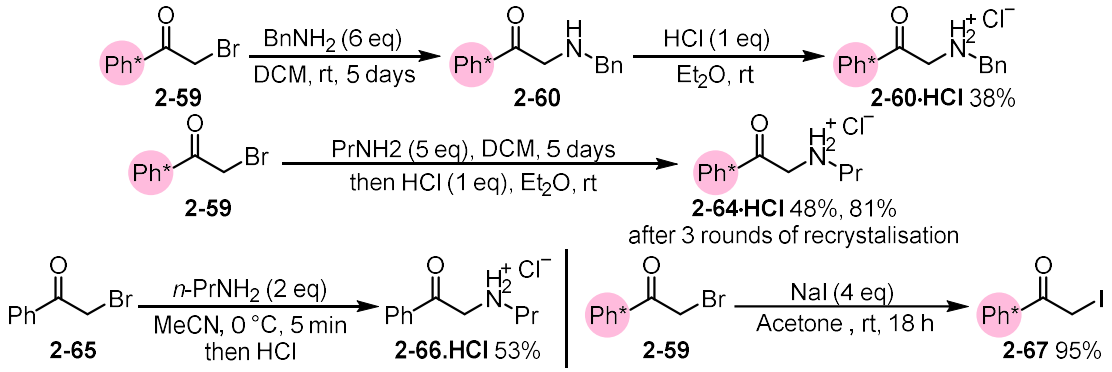
α-Bromoketone **2-59** and enone **2-62** were synthesised by Friedel-Crafts acylation in 90% and 78% yield, respectively; NEt_3 was used to drive the E1cB elimination to completion after work-up (Scheme 2-13). Mono-alkylation of benzylamine were observed to occur selectively, furnishing the α-amine **2-60** β-amine **2-63** in 60% and 44% yield, respectively.



*Scheme 2-13) Synthesis of the α and β-amine **2-60**+**2-63** were achieved in 54% and 35%, respectively over two steps.*

The amine **2-60** was bench stable for over 12 months. However, the combination of the polar amine and greasy Ph* group made purification by FCC challenging (Scheme 2-14). After removing excess benzylamine by FCC, the HCl salt of the impure material could be recrystallised to give the product **2-60.HCl** (Scheme 2-14). Excess amine could be removed under reduced pressure when using propylamine, which allowed the salt **2-64.HCl** isolated in 81% yield without FCC.

Alkylation of the phenyl analogue **2-65** was found to go to completion after 5 min at 0 °C and decomposed upon concentration under reduced pressure at rt.[101] Forming the salt allowed the product **2-66.HCl** to be isolated as a bench-stable solid in 53% yield. The α-iodo ketone **2-67** was synthesised *via* a Finkelstein reaction in 95% yield. However, using the α-iodoketone **2-67** in the amine S_N2 reaction or using iodide salts as an additive resulted in a complex mixture of impurities.



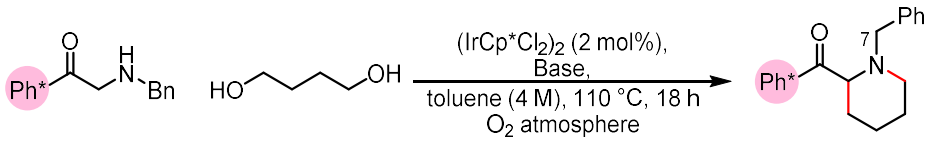
*Scheme 2-14) Forming the amine salt was found to be the best way of purifying the amine. With the phenyl analogue **2-66**, only the salt was stable during purification.*

2.3.1. Initial [4+2] Hydrogen Borrowing Cycle.

The *N*-benzyl containing substrate **2-60** was chosen as a model substrate due to the distinct AB pair expected to be observed in the desired product's **2-68** ^{1}H-NMR spectrum. 1,4-Butandiol

(**2-34**) was chosen to prevent the formation of regioisomers and diastereomers. Previous work suggested substituted diols would give higher yields after the initial optimisation.[20]

The desired product **2-68** was identified and successfully isolated in 7% yield using successive FCC, directed by the AB doublet observed in the crude ^{1}H-NMR spectrum (4.40 ppm (d, J = 12.4 Hz, C7H$_1$), 3.22 ppm (d, J = 12.4 Hz, C7H$_2$)) (Scheme 2-15). The conditions used had been optimised by Donohoe and co-workers, to form C–C bonds previously;[78] conditions that have previously formed C–N bonds gave no product.[20] Benzaldehyde was observed in the crude NMR. Whilst the yield was low (<10% in the initial reactions), the aldehyde was believed to be unstable under the HB conditions and formed in higher amounts than observed.[a]



C–C Bond forming conditions **2-60** ---------- **2-34** 2 eq ---------- KOH (4 eq) ---------- **2-68** 9% (7%)
C–N Bond forming conditions **2-60** ---------- **2-34** 2 eq ---------- K_2CO_3 (1.5 eq) ---------- not observed

*Scheme 2-15) The first successful piperidine **2-68** formation was observed using a strong base. Yield reported is a ^{1}H-NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. (Isolated yield).*

2.4. Optimisation.

Having successfully observed and isolated the piperidine **2-68**, we then sought to optimise the reaction conditions. The optimisation was performed on the propyl substrate **2-64·HCl** to reduce the amount of amine oxidation occurring.

2.4.1. Challenges in Interpreting the Optimisation.

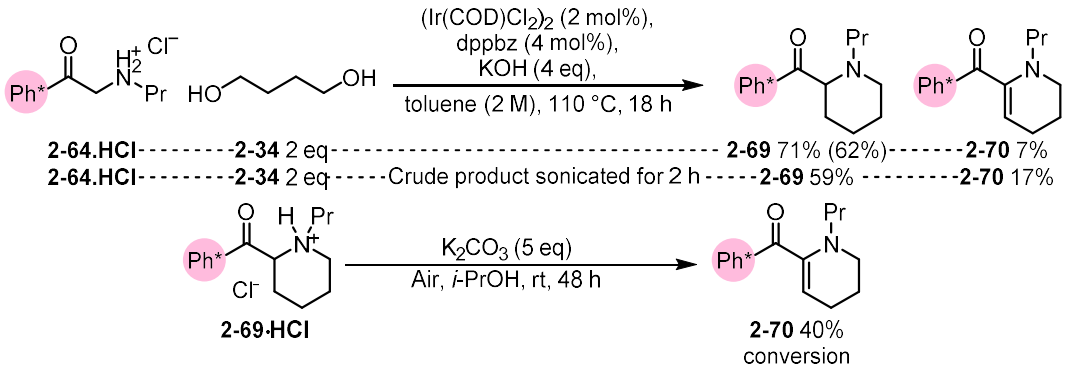
The optimisation of the system was complicated by the instability of the product **2-69** and the NMR standard, 1,1,2,2-tetrachloroethane, in the crude reaction mixture.

1,1,2,2-tetrachloroethane has been used reliably as an internal standard in similar work in the group.[102] In this reaction we found that the standard decomposed, presumably via E$_2$ elimination, when added after the reaction had been filtered through silica and concentrated. Hence 1,3,5-trimethoxy benzene (TMB) was used as an internal standard in further optimisation.

Concurrently, tetrahydropyridine **2-70** was observed in numerous reactions (Scheme 2-16). This compound was generally found in low yields and initially assumed to result from

[a] O_2 is generally believed to be highly reactive with metal hydrides, generating metal peroxides.[285] This process can poison the catalyst. However, if the peroxide species is unstable this can regenerate the active metal catalyst, which is beneficial if the intermediate species is decomposing and not generating the desired hydride acceptors.

incomplete reduction, similar to the cyclohexene **2-36** observed in previous HB reactions (See Scheme 2-8). It was later found that the product **2-69** was unstable to base under an air atmosphere and oxidised in the work-up, NMR tube and during FCC. Autooxidation was proven by sonicating the silica filtered crude material in $CDCl_3$ for 2 h resulting in approximately 17% conversion of the product **2-69** to the tetrahydropyridine **2-70**. When the amine salt **2-69.HCl** was subjected to mild base in an open flask over 48 h, 40% oxidation was observed without any major side products forming. Therefore, the combined yield of the products **2-69** and **2-70** was used to guide the optimisation.

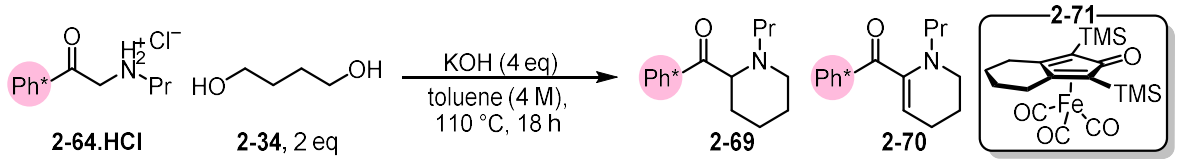


Scheme 2-16) Sonicating the crude material in air resulted in autooxidation of the desired product ***2-69****. Autooxidation could also be observed using K_2CO_3 in i-PrOH. Yields are ^{1}H-NMR yields calculated based on TMB as an internal standard. (Isolated yield). Conditions used were partially optimised conditions discussed in Section 2.4.2.*

2.4.2. Optimisation.

Screening a range of metal catalysts which have shown to be successful in previous research in the Donohoe group under a nitrogen atmosphere resulted in no product being isolated without Ir(I) (Table 2-1, Entry 1-5).[a] The use of Ir(I) with PBinol(NMe_2) **2-72** resulted in formation of the product in 19% isolated yield (Entry 6). However, the ligand decomposed to give binol which was only partially separable from the product. Under an oxygen atmosphere, the tetrahydro pyridine **2-70** formed in 8% yield.

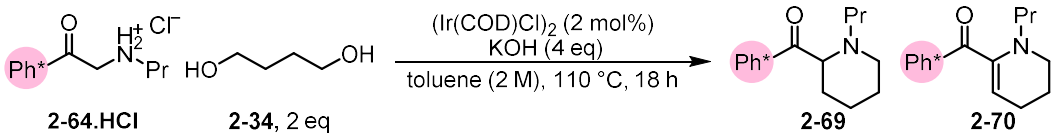
[a] Me_3NO oxidises the CO ligand of the air stable precatalyst **2-71** to form CO_2 and generate the active Fe(0) species. PPh_3 displaces the CO to activate the catalyst.



	Metal (mol%)	Ligand/Additive (mol%)	2-69 (%)	2-70 (%)
1	$(IrCp^*Cl_2)_2$ (2)		0	0
2	**2-71** (4)	$ONMe_3$ (5)	0	0
3	**2-71** (4)	PPh_3 (5)	0	0
4	Ru(*p*-cymene)Cl_2 (2)		0	0
5	RuMACHO (4)		0	0
6	$(Ir(COD)Cl)_2$ (2)	PBinol(NMe_2) **2-72** (8)	39[a](19)	3
7	$(Ir(COD)Cl)_2$ (2)[b]	PBinol(NMe_2) **2-72** (8)	0	8

*Table 2-1) Metal screening. The optimisation was performed on a 0.3 mmol scale. Yields are ^{1}H -NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. Catalyst **2-71** supplied by Hamish Hepburn. [a] Low yield was due to poor separation from binol. [b] O_2 balloon placed on the reaction.*

A broad selection of ligands were screened, monodentate ligands gave poor yields apart from the phosphoramidite **2-72** (Table 2-2, Entry 8). Bidentate phosphines gave a significantly higher yield. Due to the problems with 1,1,2,2-tetrachloroethane (described above), only the best ligands are reported below. dppbz was found to be the best ligand, giving the product in 62% isolated yield (Entry 11).[a]



	Ligand (mol%)	2-69 (%)	2-70 (%)
8	PCy_3 (8)	26	0
9	dppe (4)	(59)	n.d
10	dppf (4)	62 (57)	3
11	dppbz (4)	71 (62)	7 (10)

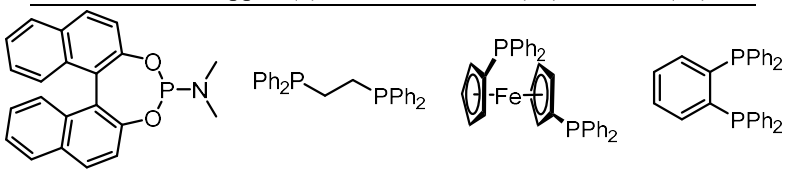
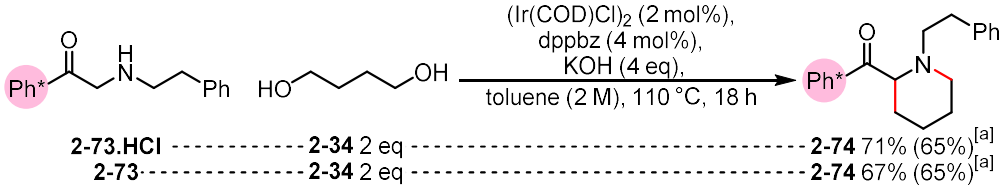


Table 2-2) Ligand screening. Reactions were performed on a 0.3 mmol scale. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (Isolated yield)

Both the chloride salt and free base of the amine **2-73** were subjected to the then-optimal HB conditions. The same isolated yields of piperidine **2-74** were obtained in both cases (Scheme

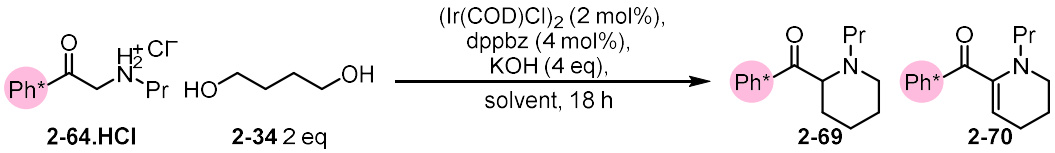
[a] The trend between mono and bidentate ligands was consistent across a large range of ligands these reactions were omitted due to the issues with 1,1,2,2-tetrachloroethane

2-17).[a] The ease of purification and the greater flowability of the amine salt compared to the respective free base meant the salts were used in subsequent experiments.



*Scheme 2-17) Using the free base **2-73** and ammonium chloride salts were both subjected to the partially optimised conditions. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (Isolated yield) [a] Trace amounts of the olefin were observed by NMR in both cases but were not isolated.*

Using toluene, benzene and *t*-BuOH as solvents gave the products with similar yields (Table 2-3, Entry 12-14). Toluene and *t*-BuOH were employed at 95 °C and 125 °C with reduced yields observed in all cases and higher decomposition (Entry 15-19). *t*-BuOH was chosen for future reactions due to the lower toxicity and the visually more homogeneous solution produced at 110 °.



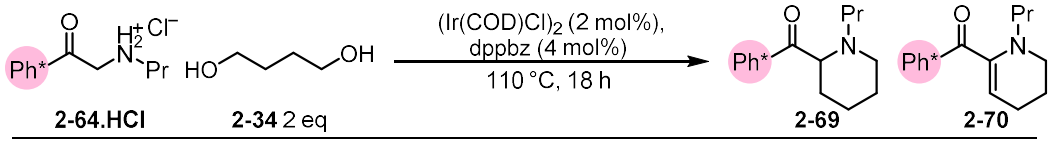
	Solvent (M)	Temperature (°C)	2-69 (%)	2-70 (%)
12	Toluene (2)	110	71 (62)	7
13	Benzene (2)	110	71 (61)	4
14	*t*-BuOH (2)	110	71 (62)	4
15	*m*-Xylene (2)	110	46	6
16	MeCN (2)	110	-	-
17	Dioxane (2)	110	47	4
18	H_2O (2)	110	-	-
19	-	110	48	1
20	Toluene (2)[a]	125	66	6
21	Toluene (2) [b]	95	38	5
22	*t*-BuOH (2) [a]	125	51	9
23	*t*-BuOH (2) [b]	95	51	4

Table 2-3) Solvent and base screening. Reactions were performed on a 0.3 mmol scale. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (Isolated yield). [a] Reaction run at 125 °C. [b] Reaction run at 95 °C.

Decreasing the base loading (Table 2-4, Entry 24-26) or base pKa (Entry 33) led to a sharp decrease in product formation with 9% combined yield using 2 eq of KOH. Using 5 eq of KOH saw an increase in the NMR yield of the reaction as well as a cleaner crude reaction mixture, although the isolated yield was not changed (Entry 28). Unsurprisingly, KO*t*-Bu gave the same

[a] Amine **273** was chosen as decomposition was observed during the isolation of the free base of amine **2-64** by FCC.

yield as KOH but was not used in future due to the increased cost. Changing the counterion to Na resulted in a significant decrease in the yield and purity of the crude material.[19,92]

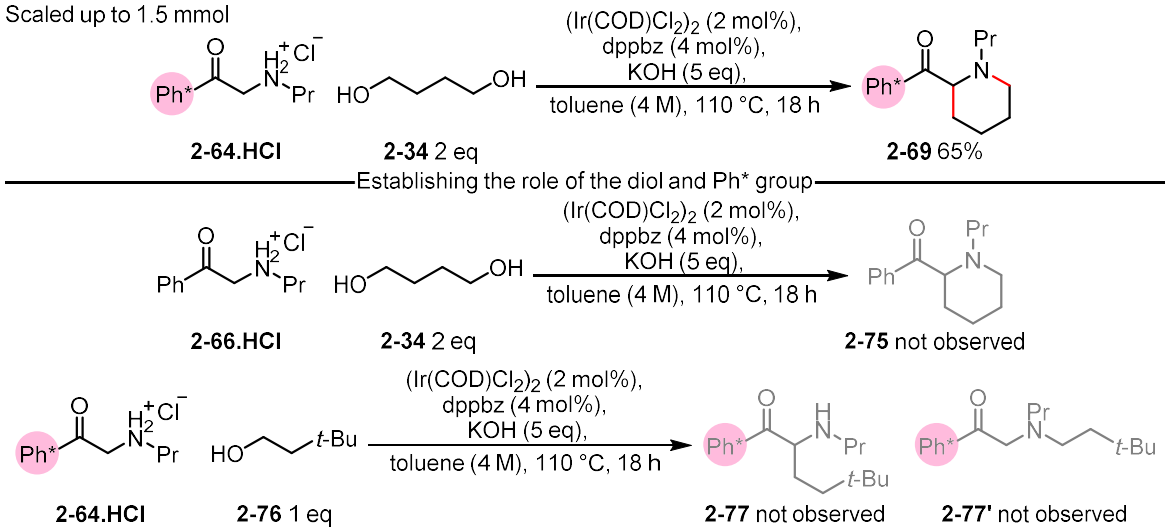


	Solvent (M)	Base (eq)	2-69 (%)	2-70 (%)
24	*t*-BuOH (2)	KOH (1)	0	1
25	*t*-BuOH (2)	KOH (2)	7	2
26	*t*-BuOH (2)	KOH (3)	21	7
27	*t*-BuOH (2)	KOH (4)	71 (62)	4
28	*t*-BuOH (2)	KOH (5)	79 (62)	3
29	*t*-BuOH (2)	NaOH (5)	36	4
30	*t*-BuOH (2)	KO*t*-Bu (5)	79	4
31	*t*-BuOH (2)	NaO*t*-Bu (5)	26	2
32	*t*-BuOH (2)	Na_2CO_3 (5)	-	-
33	*t*-BuOH (2)	K_2CO_3 (5)	-	-

Table 2-4) Solvent and base screening. Reactions were performed on a 0.3 mmol scale. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (Isolated yield).

The reaction could be performed on a 1.5 mmol scale without a decrease in the yield (Scheme 2-18). These optimal conditions were then taken further to explore the reaction scope.

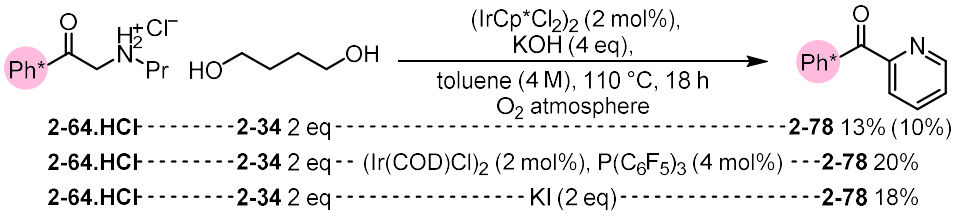
As expected, given the instability of the free base, the phenyl analogue **2-66.HCl** completely decomposed under the optimised conditions. Alcohol **2-76** was used to probe both the order of alkylations and as a potential strategy to form unnatural amino acids **2-77**. Under the optimised conditions, neither of the desired products **2-77** or **2-77'** could be isolated, a complex mixture of saturated and unsaturated species was formed in low yields and no products could be isolated or characterised.



Scheme 2-18) Scaling up the reaction resulted in the same isolated yield.

2.4.3. Aromatisation of the Piperidine product.

Under the initial conditions (Scheme 2-15), we were surprised to find the propyl substrate **2-64.HCl** aromatised to give the pyridine substrate **2-78** in 10% yield (Scheme 2-19). It is unclear why the propyl group behaves differently under these conditions. Using an electron-poor Ir(I) complex gave a modest increase in yield (20%). Surprisingly KI, which has previously been shown to increase the reductive capacity of Ir catalysts, resulted in an increased yield of the pyridine.[103]

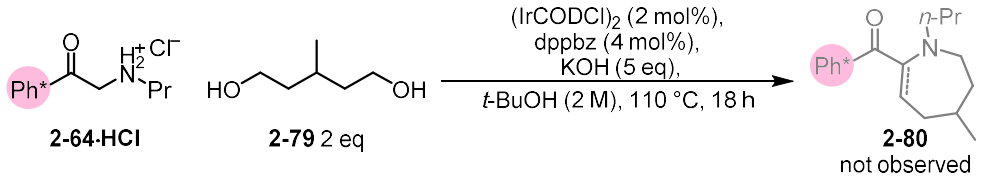


*Scheme 2-19) Subjecting amine **2-64·HCl** to the initial conditions resulted in aromatisation. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (Isolated yield) Piperidine **2-69** was not observed under these conditions.*

2.5. Substrate Scope.

2.5.1. [5+2] and [3+2] Cyclisation.

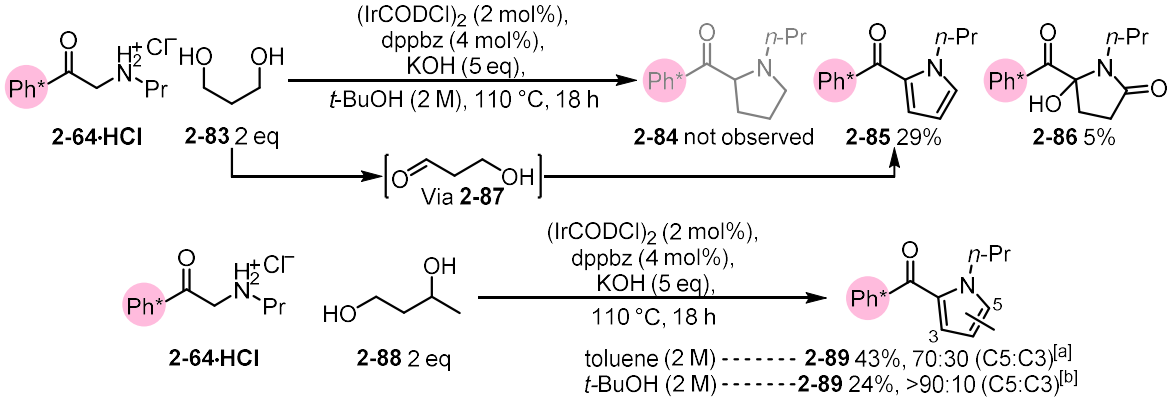
Hoping to extend the reactions to 7-membered ring formation, 1,5-pentanediol **2-79** was employed but the azepane **2-80** was not observed (Scheme 2-20).



*Scheme 2-20) 7-membered ring **2-80** was not observed.*

1,3-Diols are a challenge in HB reactions due to the aldehyde intermediate **2-86**, which can undergo competing E1cB elimination. When 1,3-propanediol **2-83** was subjected to the optimised conditions, the desired pyrrolidine **2-84** was not observed (Scheme 2-21). Instead, the pyrrole **2-85** was isolated in 29% yield. We were surprised to isolate the complex hemiaminal **2-86** as a stable species in 5% yield from a complex mixture of side products. Subjecting 1,3-butanediol (**2-88**) to the HB conditions in toluene, the pyrrole **2-89** was formed in modest yield and regioselectivity (43%, 70:30 r.r.). In *t*-BuOH, the regioselectivity was higher (>90:10) but with 24% isolated yield.[a]

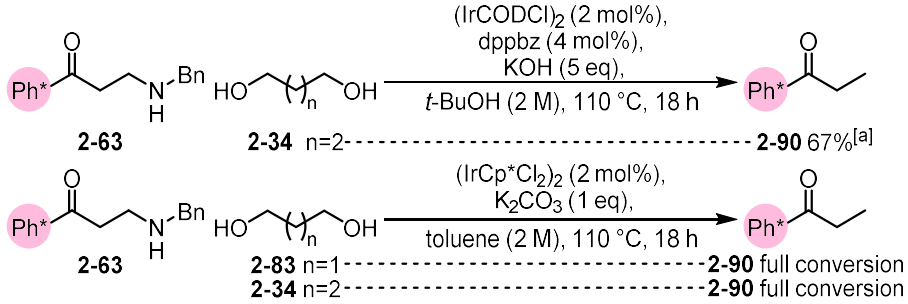
[a] Mechanism of the regioselectivity is discussed in Section 2.6.



*Scheme 2-21) 5-membered rings were observed to aromatise to form the pyrrole **2-85**. The substituted diol **2-88** gave poor regioselectivity in the ring formation. The regioisomeric ratio was measured in the crude NMR. Partial loss of the minor isomer was observed upon FCC. [a] Isolated in a 90:10 r.r. [b] Isolated in a 93:7 r.r.*

2.5.2. Use of β-Amino Ketones.

The β-amine **2-63** was not stable under the optimised conditions (Scheme 2-22). The substrate underwent E1cB elimination and reduction to give the ethyl ketone **2-90**. Using K_2CO_3 (1 eq) as the base still resulted in complete conversion to the ketone **2-90**. The successful isolation of **2-85** using 1,3-diol **2-83** compared to the result with β-amino ketone **2-63** under the same conditions shows how forming unstable species transiently significantly changes the reaction profile.

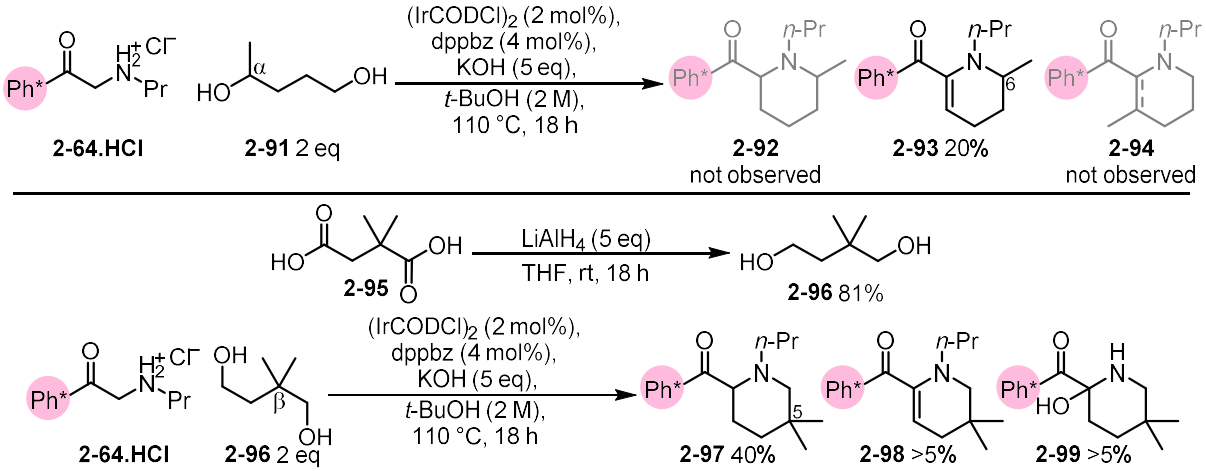


*Scheme 2-22) β-amine **263** underwent eliminated and subsequent reduction to give the ethyl ketone **2-90**. [a] Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard.*

2.5.3. Substituted [4+2] Cyclisation.

When subjected to the optimised conditions, α-methyl diol **2-91** resulted in a complex mixture with the 6-substituted olefin **2-93** as the only isolated product in 20% yield (Scheme 2-23). Efforts to minimise the crude's exposure to air did not result in the desired piperidine **2-92** being observed by NMR or TLC. The reaction appeared to be regioselective, with no 2,3-substituted species **2-94** being observed.

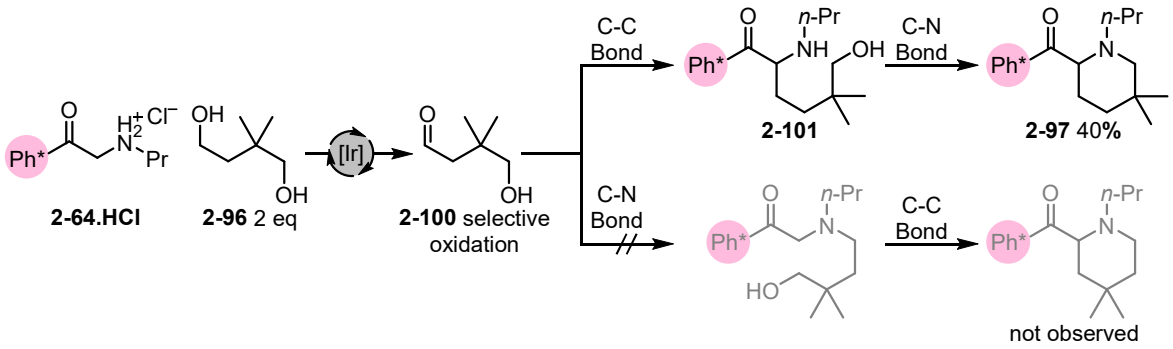
Diol **2-96** was synthesised by reducing the diacid **2-95** in 81% yield. The reaction of β-dimethyl substrate **2-96** again resulted in high regioselectivity with the desired product **2-97**, isolated in 40% yield, as well as the side products **2-98**+**2-99** which were isolated as single regioisomers.



*Scheme 2-23) The 2,6 substituted piperidine **2-92** was not observed. The β-dimethyl diol **2-96** gave high regioselectivity but with a modest yield.*

2.6. Mechanism of the Reaction.

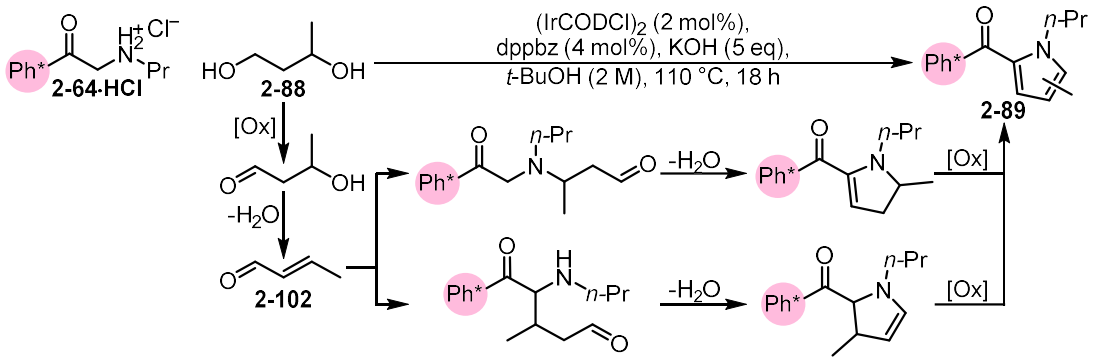
Whilst the yields of the substituted diols were disappointing, the regioselectivity of the ring formation allowed us to confirm the reaction pathway. Under similar conditions, 1,4-diol oxidation has been shown to be highly selective, forming the least hindered aldehyde as a single regioisomer, in this case **2-100** (Scheme 2-24).[104]a Since piperidine **2-97** is formed with high regioselectivity, the reaction appears to proceed *via* intermolecular C–C bond formation with amine **2-101**. This hypothesis is consistent with the initial hypothesis that the strong base required meant the C–C bond formation occurred intermolecularly (Scheme 2-15).



Scheme 2-24) Based on the regioselectivity of the reaction, C-C bond formation appears to occur first.

[a] No experiment to directly measure oxidation selectivity has been conceived. Oxidation selectivity was determined indirectly by comparison of a series of DKR reactions discovered by Daniella Cheang.

The regioselectivity of the 5-membered ring **2-89** appeared to be lower than that observed in the analogous 6-membered rings. It is possible that pyrrole formation occurs *via* enal **2-102** leading to different regioselectivity (Scheme 2-25).[a]



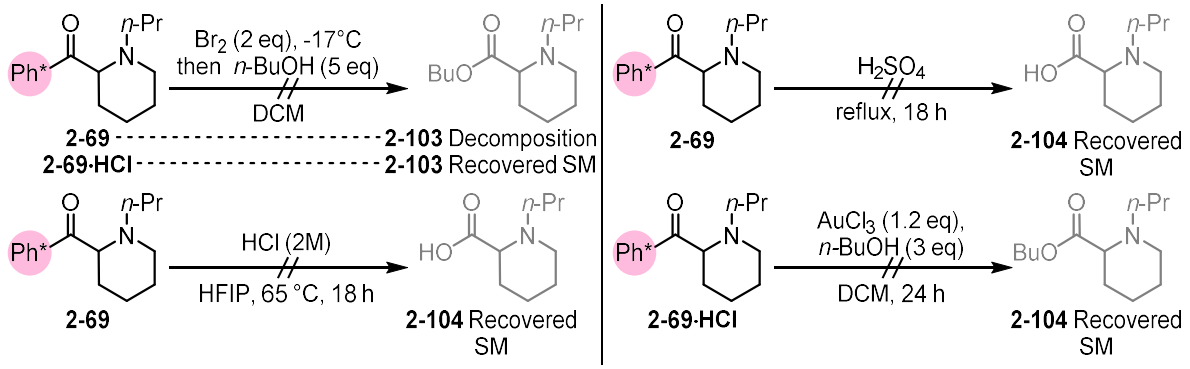
*Scheme 2-25) An alternative Pyrrole mechanism could go via an in situ enal **2-102** route.*

2.7. Cleavage of Ph* Methyl Ketone.

Given the lack of substrate scope under the optimised HB conditions, the Ph* cleavage with piperidine **2-84** was tested before considering reoptimisation.

2.7.1. Established Strategies.

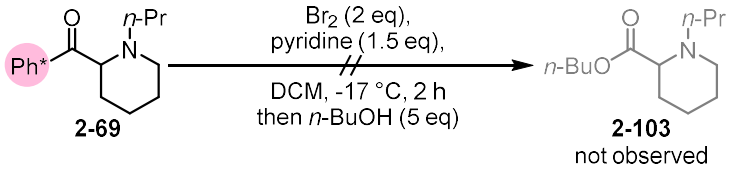
Several routes have already been established in the Donohoe group to cleave the Ph* moiety. Unfortunately, none of these methods produced the desired products (Scheme 2-26). Bromine conditions resulted in rapid decomposition of the product if the amine **2-69** was used or recovered starting material if the ammonium salt **2-69.HCl** was used. Under acidic conditions, no product was ever observed. The high barrier to forming two cations in close proximity was believed to prevent the desired cleavage.[b]



Scheme 2-26) Established conditions showed no sign of product formation.

[a] Hydrogen borrowing, involving the 1,4-addition into enals is the subject of extensive research by Rodriguez *et al*.[21,22] selective oxidation of 1° alcohols over 2° alcohols is discussed in section 4.1.1.
[b] γ-amino groups have been shown to be tolerated in the bromination conditions if protected as an amine salt (see Section 3.1.2).

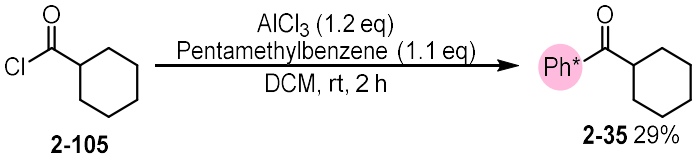
Using pyridine as an additive was found to significantly stabilise 3° alcohols during bromine-mediated cleavage (see Section 3.5.2). We were disappointed to find that this modification did not give the desired ester **2-103** (Scheme 2-27).



Scheme 2-27) Using pyridine additive did not improve the Ph ketone cleavage.*

2.7.2. New Cleavage Strategies.

Due to the oxidation and other side reactions that could occur with the piperidine **2-69**, new conditions were screened with the readily available α-branched ketone **2-35** (Scheme 2-28). Numerous acidic conditions and bromine analogues were screened to cleave the Ph* group. Whenever cleavage was observed, the conditions were tested on the piperidine **2-69**, which resulted in no cleavage being observed.



*Scheme 2-28) Ketone **2-35** was used as model substrates for Ph* cleavage.*

Since the Ph* ketone group has been shown to be nucleophilic due to the ketone being twisted out of the plane, we wondered if the substrate could be oxidised by photochemical or electrochemical methods. Using cyclic voltametry, irreversible oxidation was observed (E_P= 2.2 V and $E_{P/2}$= 1.73 V). These values suggested the substrate was within the range of established methods, with an oxidation potential similar to styrene **2-106 (**Figure 2-1).[105] Unfortunately, no product was observed when established oxidative photochemical conditions were tested.[106–108]a

[a] See SI for details.

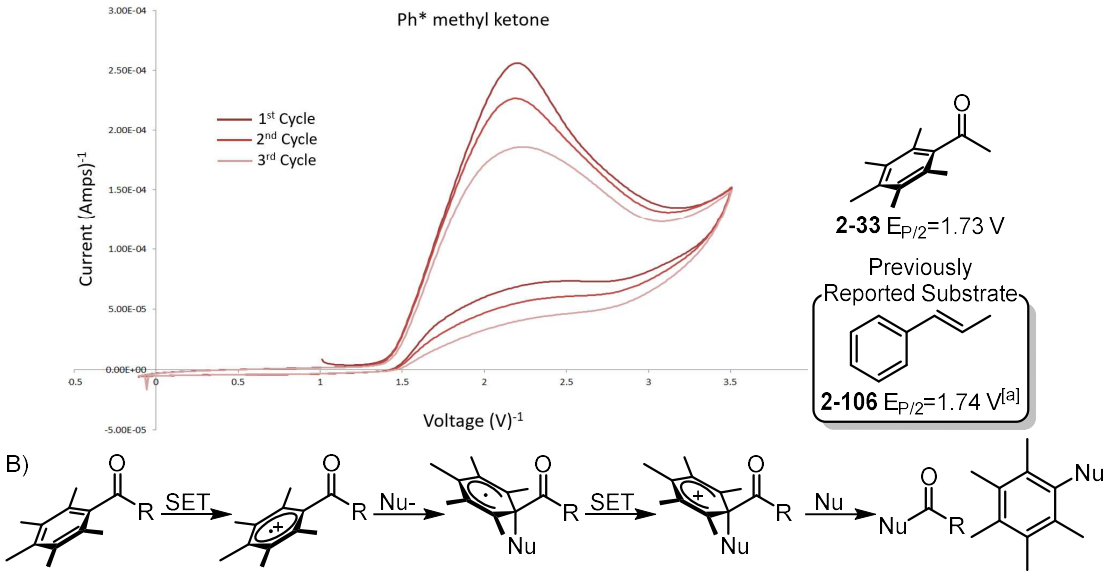
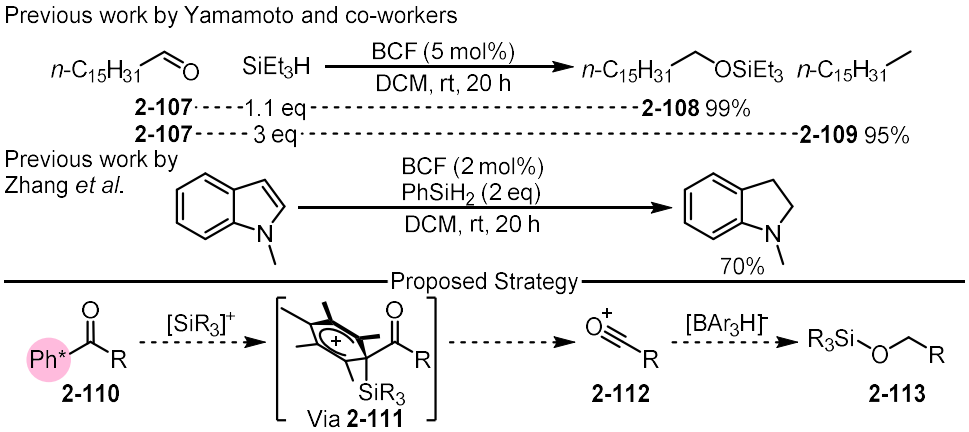


Figure 2-1) A) Cyclic voltammetry plot Ph ketone* ***2-33*** *in 0.1M tetrabutylammonium hexafluorophosphate DCM solution. $E_{P/2}$= 1.73 V measured according to the method by Nicewicz and co-workers.*[105] *[a] Voltage of styrene* ***2-106*** *reported by Nicewicz.*[105] *B) Proposed photchemical oxidation.*

2.7.3. Hydrosilane Cleavage.

Using tris(pentafluorophenyl)borane (BCF) in combination with a silane hydride source results in the formation of a "frustrated lewis pair", consisting of a silyl cation and borohydride anion. In combination, they act as a powerful reduction strategy, reducing carbonyls, such as **2-107** to form both silyl ethers, such as **2-108** and alkanes, such as **2-109** at rt (Scheme 2-29).[109,110] With the reduction of the ketone **2-110** prevented by the steric hindrance of the Ph* group, it was hoped that the arenium **2-111** would form *in situ*, leading to the desired retro-Friedel-Craft reaction and subsequent reduction to give the silyl ether **2-113**.

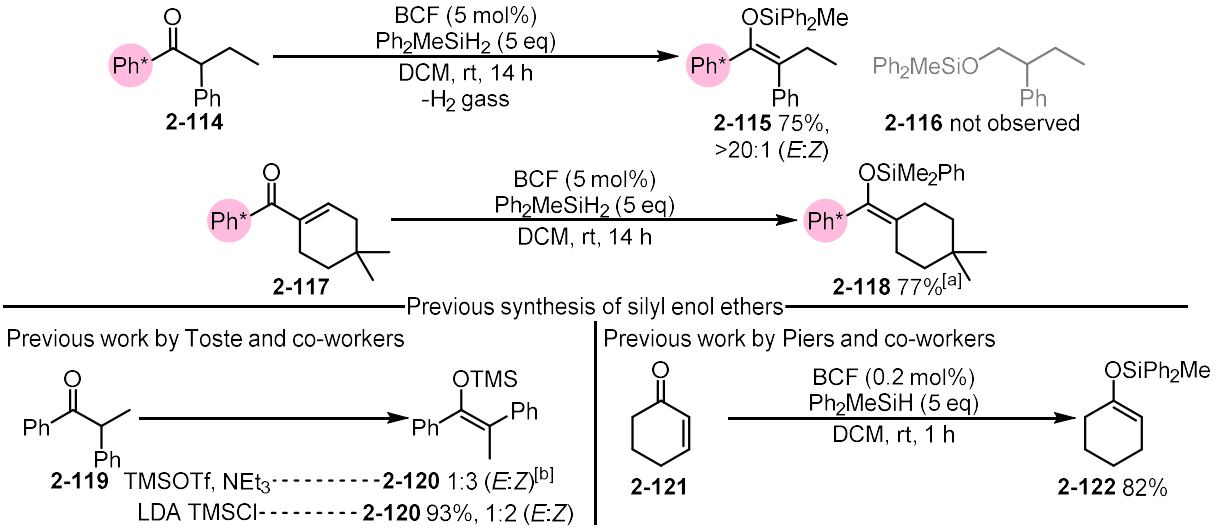


Scheme 2-29) Yamamato and co-workers were the first to report the use of BCF as a hydride transfer reagent.[110] *Zhang and co-workers performed a mild reduction of indoles as well as a variety of functional groups.*[111] Proposed cleavage when reduction could not occur.

Under these conditions, the ketone **2-114** was found to give the silyl enol ether **2-115** in 75% yield and a >20:1 *E*:*Z* ratio. The reaction was observed to go to completion after 4 h at rt; no

further reactivity was observed over 18 h at reflux (Scheme 2-30).[112] The alkene geometry, characterised by NOESY NMR, shows that the Ph group sits adjacent to the Ph* in the space created by the Ph* twisting out of the plane of the alkene. The formation of the phenyl silyl enol ether **2-120** has previously been shown to form with poor selectivity under kinetic or thermodynamic conditions.[113]

Under the same conditions, enone **2-117** was found to be reduced, giving the silyl enol ether **2-118** in 77% yield (Scheme 2-30). This transformation has previously been observed by Piers and co-workers, to synthesise silyl enol ether **2-122**.[114]



Scheme 2-30) With the Ph ketone **2-110**, deprotonation occured, giving the silyl enol ether **2-111** as the only isolated product. Enones were found to reduce to give the silyl enol ether **2-112**. Toste generated similar silyl enol ether **2-116** with modest selectivity.[113] Similar reactivity was observed by Piers and co-workers[114] [a] inseparable from siloxane impurity. [b] Yield not reported.*

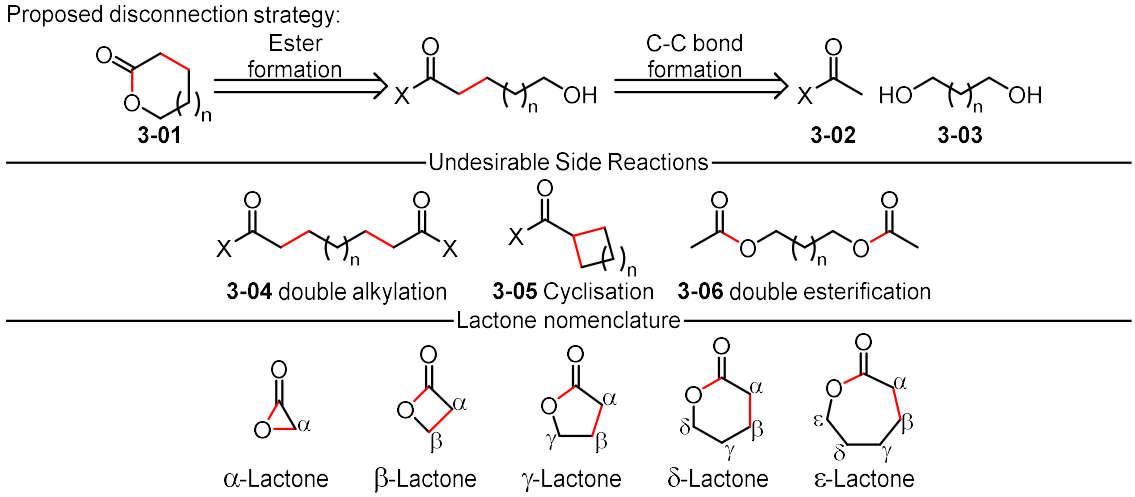
2.8. Conclusion

Whilst we were able to successful develop a novel piperidine strategy. Since we could not cleave the Ph* protecting group and the HB reactions gave poor yields when substituted diols were used, it was determined that efforts to reoptimise the HB reaction were not worth pursuing. Hence this project was not pursued further.

Chapter 3. Synthesis of γ-Lactones from 1,2-Diols.

3.1. Introduction.

The intermolecular synthesis of lactones such as **3-01** using HB, involves the formation of a C–C bond and a C–O bond (Scheme 3-1). In order to form complex substrates, the two alcohols of **3-03** must be differentiated to give both regioselectivity and to prevent the formation of unwanted products *via* double alkylation **3-04**, cyclisation **3-05** or double esterification **3-06**. In this work, we aimed to use 1,2-diols (n=0) to synthesise γ-lactones.



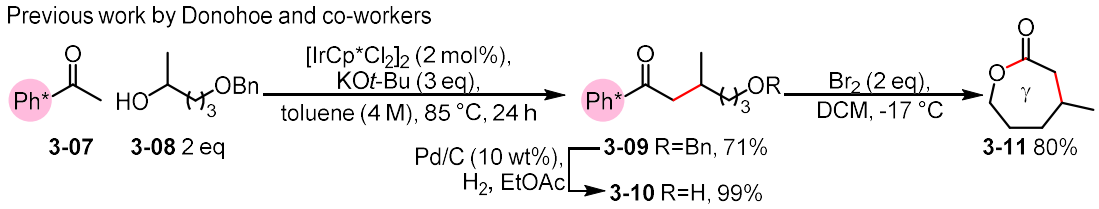
Scheme 3-1) Disconnection strategy to synthesise lactones via HB. Lactone nomenclature.

This project was subsequently taken on by Karan Lalwani as a Part II project: Where his results are discussed, he is explicitly acknowledged.

3.1.1. Lactone Synthesis Using Hydrogen Borrowing.

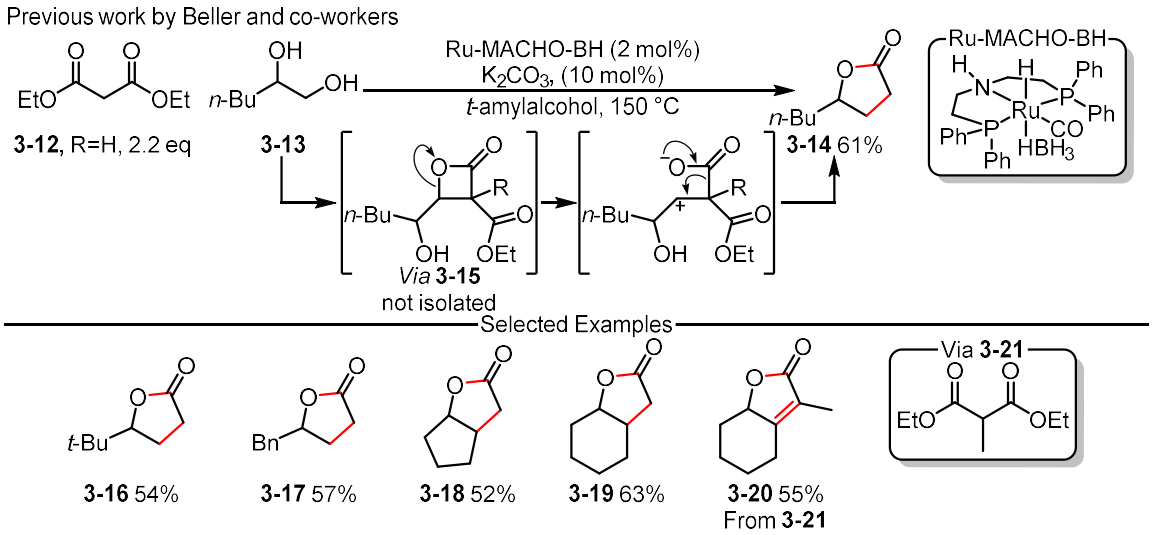
Three distinct strategies for synthesising lactones using HB in the literature have previously been reported.

By employing the mono-benzylated 1,5-diol **3-08**, Donohoe and co-workers alkylated Ph* methyl ketone **3-07** in 71% yield (Scheme 3-2) without modifying the previously discussed HB conditions (Scheme 1-12).[11] After hydrogenation to give the free alcohol **3-10** (99% yield), the Ph* group could be cleaved using bromine to afford the ε-lactone **3-11** in 80% yield.



*Scheme 3-2) Donohoe and co-workers cleaved the ether **3-09** to give the alcohol **3-10**. The ring was closed using bromine-mediated cleavage to give the lactone **311**.*[11]

Beller and co-workers alkylated 1,2-diols **3-13** with malonates **3-12**, followed by *in situ* transesterification to obtain the γ-lactone **3-14** in 61% yield (Scheme 3-3).[25] Regioselectivity could be controlled by selective oxidation of the 1° alcohols to give γ-substituted lactones (**3-14**+**3-16**+**3-17**) or by using symmetric 1,2-diols to give bicyclic substrates (**3-18**+**3-19**). Undesired double alkylation (Scheme 3-1) is prevented by intramolecular ring closure protecting the second alcohol.[a] The subsequent lactone is stable due to the low loading of K_2CO_3 employed. Based on the formation of tetra-substituted alkene **3-20** formed when the branched malonate **3-21** was employed, the reaction appears to proceed *via* a formal stereoretentive [2+2] cycloreversion of the β-lactone **3-15** and not an E1cB elimination.[115,116]b



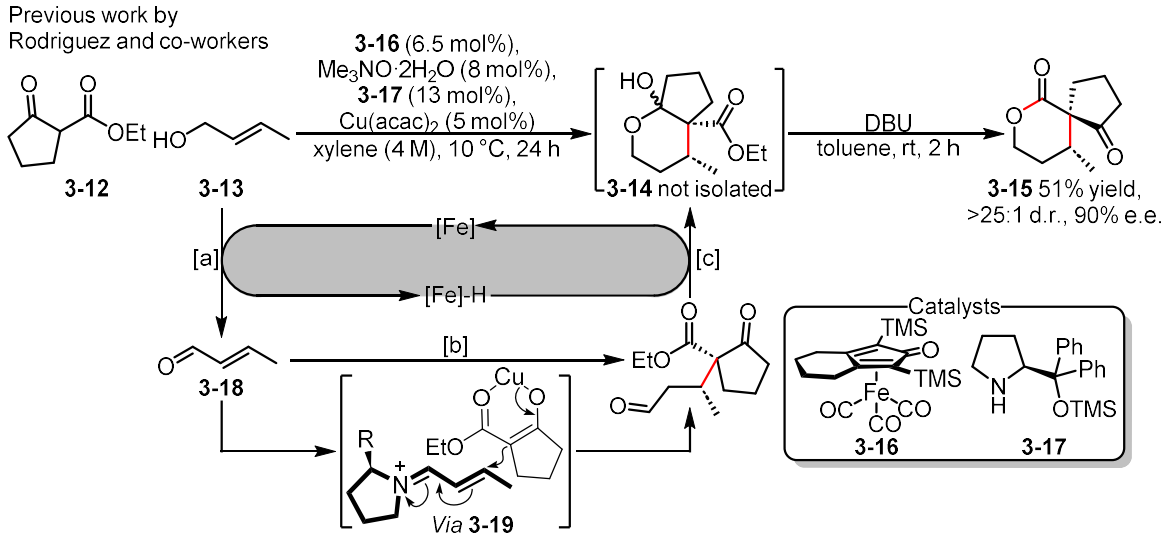
*Scheme 3-3) Beller and co-workers alkylated 1,2-diols, such as **3-13**, to synthesise γ-lactone via a stereoretentive [2+2] reaction. Neither absolute nor relative stereochemistry was reported.*[25]

Rodriguez and co-workers employed allyl alcohol **3-13** instead of a diol in their synthesis of lactone **3-15** (Scheme 3-4).[70] The allyl alcohol disconnection allows for a highly regioselective and chemoselective addition to the substrate. Upon oxidation, the aldehyde **3-18**

[a] Reversible oxidation of an alcohol under hydrogen transfer conditions with *insitu* enantioselective esterification of the alcohol has been used to perform a variety of dynamic kinetic resolution tactics, which has been the subject of a review by Rodriguez and co-workers.[286]

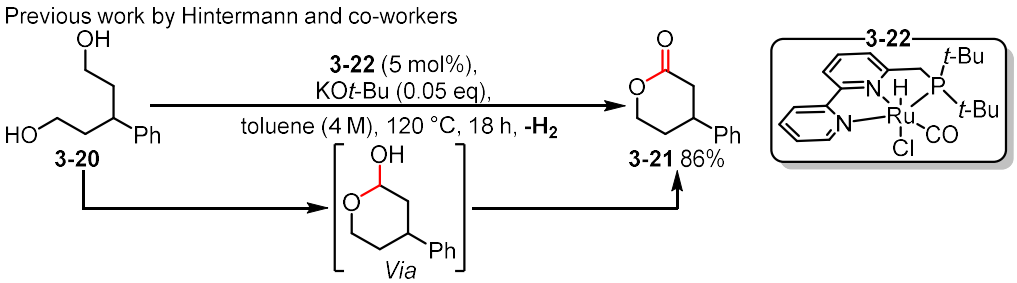
[b] Beller and co-workers. have also developed an analogous amination-transesterification strategy.[46] The communication of absolute stereochemistry in the reaction is the subject of Section 3.11.

undergoes enantioselective 1,4-addition **3-19** catalysed by the amine **3-20**. Upon reduction, the substrate sits as a hemiacetal **3-14**, which undergoes subsequent transesterification to afford the desired lactone **3-15** in 51% yield and 90% e.e.[a]



*Scheme 3-4) Rodriguez and co-workers synthesised the spirocyclic δ-lactones **3-15** via enantioselective 1,4-addition into the iminium **3-19**.*[70]

Although not a HB reaction, it is relevant to note that 1,5-diols are known to undergo oxidative acceptorless hydride transfer under HB conditions to form lactones if the lactol intermediate is not intercepted.[20,102] Hintermann and co-workers optimised this side reaction to oxidise the symmetric alcohol **3-20** giving the lactone **3-21** in 86% (Scheme 3-5).[15]b



*Scheme 3-5) Under HB conditions, diols can be oxidised to form lactones, such as **3-21**.*[15]

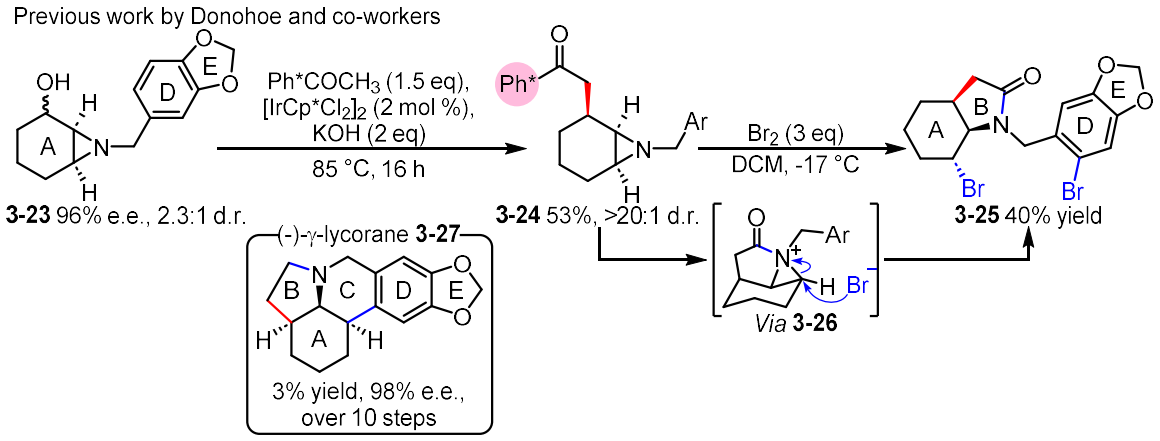
3.1.2. Alkylation using α-Amino Alcohols.

Alcohols with α-heteroatoms are challenging substrates to employ in HB catalysis, presumably due to the increased difficulty oxidising the alcohol.[37,117,118] However, Donohoe and co-workers demonstrated aziridine **3-23** could be used to alkylate Ph* methyl ketone (**3-07**) in 53% yield and >20:1 d.r. (Scheme 3-6).[119] Under the previously discussed bromine cleavage

[a] Rodriguez HB research specialises on 1,4-addition into *in situ* formed enal.[21,22,24,287]

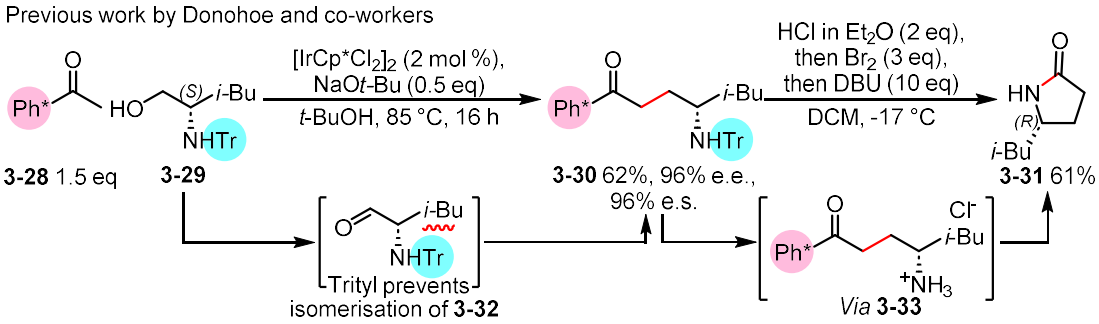
[b] Williams has utilised lactonisation as a source of hydrides in hydride transfer reactions.[288]

conditions (Scheme 1-13), it was found that the aziridine ring trapped the acylium ion to form the tricyclic intermediate **3-26**; the bromide anion then opened the aziridine to give the product **3-25** in 43% yield.



*Scheme 3-6)The synthesis of (-)-γ-lycorane **3-27** by Donohoe and co-workers used HB followed by Ph* cleavage to synthesise the γ-lactam intermediate **3-25**.*[119]

This approach was broadened to amino acid derivatives, such as **3-29** (Scheme 3-7).[80] When the trityl protection group was employed, alkylation gave the product **3-30** with high stereoretention of the α-stereocentre (62% yield, 96% es). For the amine to be tolerated during the Ph* cleavage, the protection group was switched *in situ*, forming the ammonium cation **3-33** allowed bromination to occur. Subsequently, deprotection initiated the ring closure to give the lactam **3-31** in 61% yield.[a]



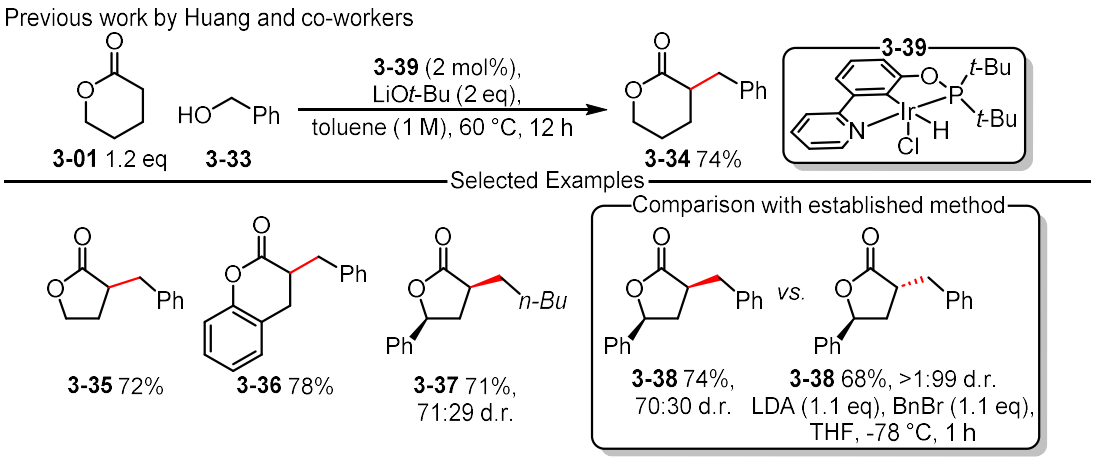
*Scheme 3-7) Donohoe and co-workers synthesised lactams, such as **3-31**, using a two-step strategy. The choice of protection group in each step was found to be vital to achieving both high yields and selectivity.*[80]

The tolerance of 1,2-amino alcohols, such as **3-29**, in both HB and Ph* cleavage made 1,2-diols an appealing set of substrates to employ in HB catalysis.

[a] A variety of the N-Heterocycles discussed in Chapter 2 can be oxidised to form lactams.[289–291]

3.1.3. The Derivatisation of Lactones Using Hydrogen Borrowing.

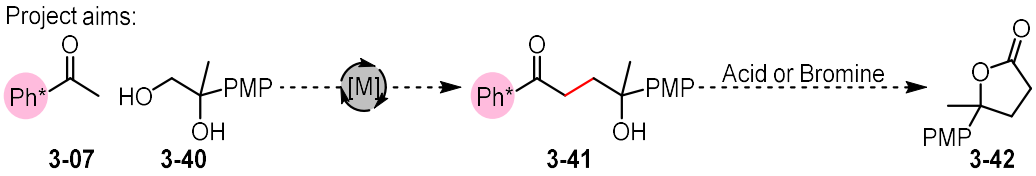
The alkylation and derivatisation of esters can be challenging due to the high pK_a of the α-protons and their tendency to hydrolyse under basic conditions. While esters have been alkylated in multiple HB systems,[28,41,120–123] the alkylation of lactones is very limited in the literature.[124,125] Huang and co-workers were able to successfully alkylate both δ and γ-lactones (**3-34**-**3-38**) using a relatively low reaction temperature (60 °C) to prevent hydrolysis (Scheme 3-8).[126] Notably, 3,5-substituted δ-lactone **3-36** was formed with modest *cis* selectivity (70:30 d.r.), which was inverted compared to the alkylation of the lithium enolate (>1:99 d.r.).[127]



Scheme 3-8) Huang and co-workers were able to alkylate both δ and γ-lactones.[126] No optimisation was reported.

3.2. Aims and Objectives.

Our initial research goal was to test the tolerance of 1,2-alcohols in HB catalysis (Scheme 3-9). We then wanted to test the viability of the Ph* group cleavage in the presence of the 3° alcohol.



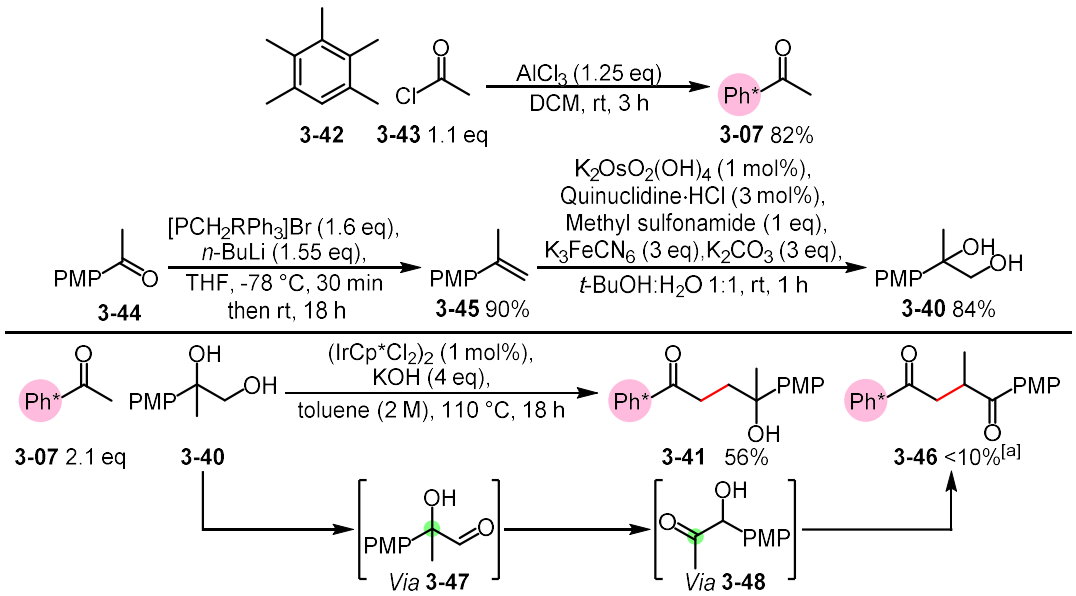
Scheme 3-9) Initial strategy towards γ-lactone.

3.3. Starting Material Synthesis and Preliminary Studies.

The desired model diol substrate **3-40** was synthesised cleanly by an olefination-dihydroxylation sequence (Scheme 3-10). The dihydroxylation was performed with a modified racemic Sharpless procedure. Methyl sulfonamide was used as an additive

promoting dihydroxylation of bulky alkenes, first outlined by Sharpless and co-workers.[128]a Moreover, Ph* methyl ketone (**3-07**) was synthesised in 82% yield *via* a Friedel-Crafts acylation.

HB conditions previously optimised by Donohoe and co-workers for forming cyclohexanes were chosen for initial screening (Scheme 2-8).[129] Under these conditions, alcohol **3-41** was isolated in 56% yield. Additionally, a small amount of the 1,4-diketone **3-46** was isolated, this was believed to occurred due to 1,2-aryl migration of the aldehyde intermediate **3-47** resulting in the formation and alkylation of ketone **3-47**.[130,131] During the subsequent optimisation, migration derivatives, such as **3-46**, were never observed in >10% yield.b



*Scheme 3-10) Initial reaction of the 1,2 diol. The two-step procedure to synthesise **3-40** was found to be a reliable and practical route to simple 1,2 diols and was used throughout this project. [a] The diketone **3-46** was isolated in less than 10% yield and could not be cleanly isolated.*

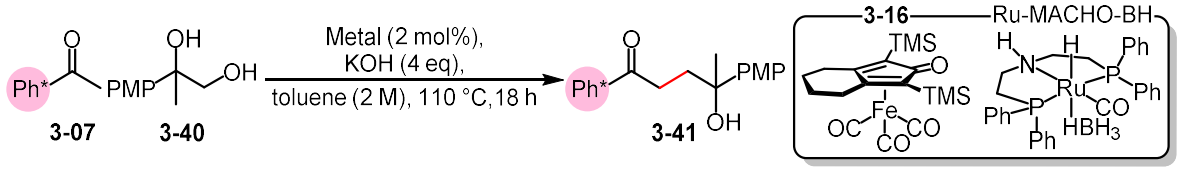
3.4. Optimisation of the Hydrogen Borrowing Reaction.

3.4.1. Initial Screening.

Initial optimisation was performed with an excess diol, which has been shown to give higher yields in previous HB reactions (Table 3-1).[19,20,92] A range of metals were also screened in the HB reaction, and Ru-MACHO (Entry 5) was found to be as efficient a catalyst as $(IrCp^*Cl_2)_2$,

[a] Methyl sulfonamide accelerates the hydrolysis of the Osmate ester which is the turnover limiting step.[292]
[b] Substrate controlled migration was observed (See Scheme 3-22).

giving the desired product **3-41** with 57% isolated yield with a lower cost.[a] Next, various bases were investigated; without an increase in yield being observed (Entry 6-11).

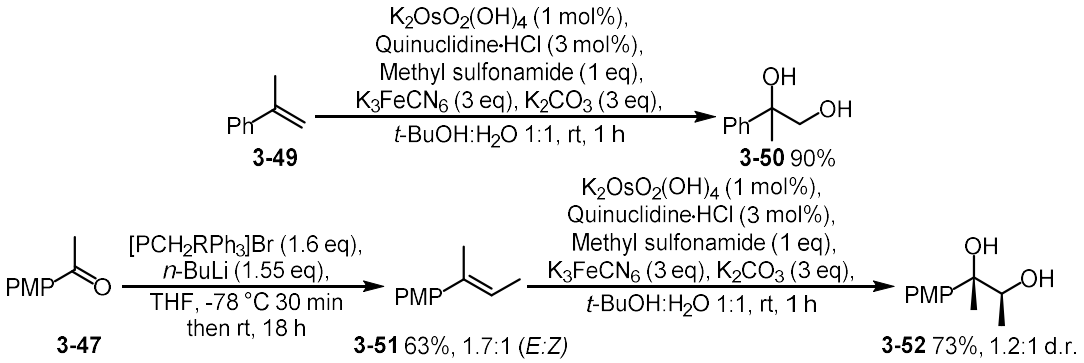


	3-07 (eq)	3-40 (eq)	Metal (mol%)	Additive (mol%)	Base (eq)	3-41 (%)
1	2	1	$(IrCp^*Cl_2)_2$ (1)	-	KOH (4)	56
2	1	1.25	$(IrCODCl)_2$ (1)	PPh_3 (4)	KOH (4)	10
3	1	1.25	$(Ru(p\text{-cymene})Cl)_2$ (1)	PPh_3 (4)	KOH (4)	10
4	1	1.25	**3-16** (2)	PPh_3 (2)	KOH (4)	-
5	1	1.25	Ru-MACHO (2)	-	KOH (4)	63(57)
6	1	1.25	Ru-MACHO (2)	-	KO*t*-Bu (4)	60
7	1	1.25	Ru-MACHO (2)	-	NaOH (4)	45
8	1	1.25	Ru-MACHO (2)	-	NaO*t*-Bu (4)	23
9	1	1.25	Ru-MACHO (2)	-	LiO*t*-Bu (4)	30
10	1	1.25	Ru-MACHO (2)	-	LiOH	38
11	1	1.25	Ru-MACHO (2)	-	LiHMDS[a]	37

Table 3-1) Metal screening. Yields are 1H-NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. (isolated yields). Metal loadings are constant for the monomeric metal species. Catalyst **3-16** was synthesised by Hamish Hepburn. The optimisation was performed on a 0.2 mmol scale. [a] LiHMDS added as a 1 M solution in toluene.

3.4.2. Oxidative-Cleavage of 1,2-Diols.

At this point in the optimisation, other diols were synthesised in order to explore the optimised conditions (Scheme 3-11). Phenyl alcohol **3-50** and 2° diol **3-52** were synthesised by the same method used above, with the alcohol **3-52** isolated in 46% yield over two steps in a 1.2:1 d.r.

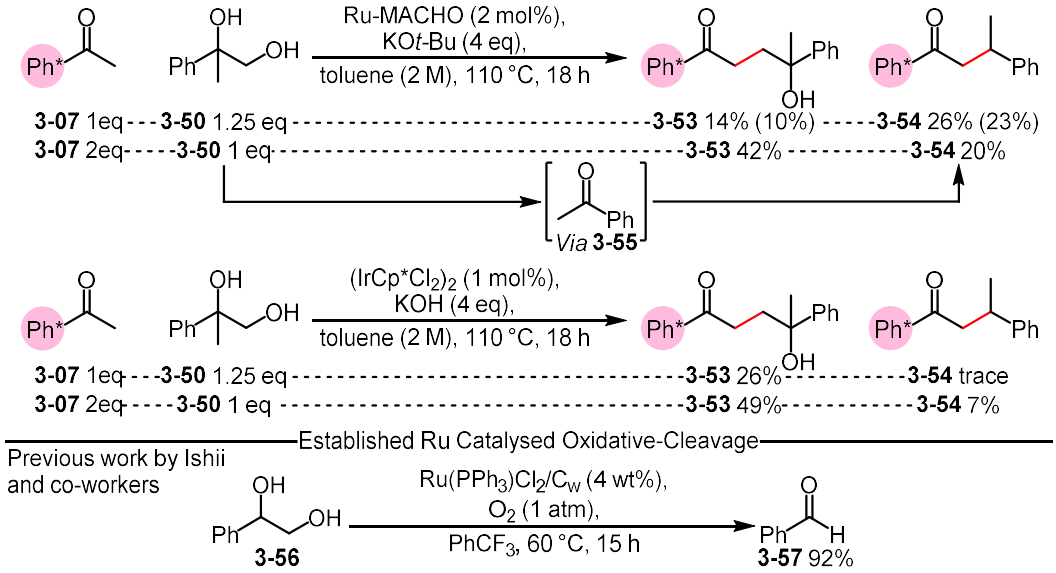


*Scheme 3-11) Synthesis of the diol substrates **3-50** and **3-52**.*

Despite the small change in structure, using alcohol **3-50** resulted in the formation of the desired product **353** in just 10% yield; instead, the major product was found to be ketone **3-54**, which

[a] Unreacted diols were discovered to be very prone to being acylated by EtOAC upon work up. This did not affect the purification of the reaction so the work up was not changed.

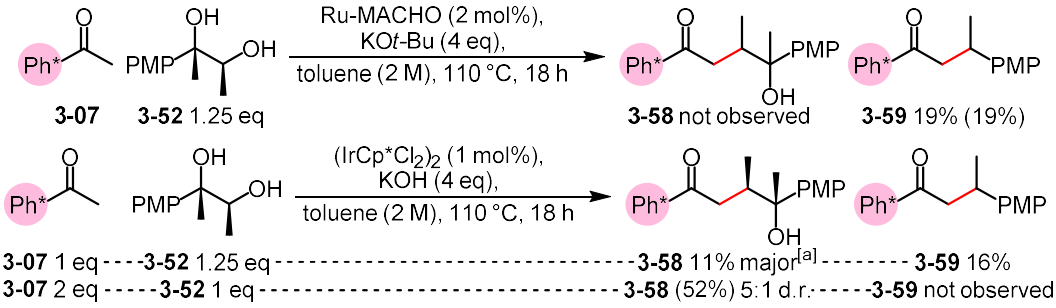
was formed in 23% yield (Scheme 3-12). This product was believed to form *via* oxidative-cleavage of the diol **3-50** resulting in acetophenone **3-55** being generated *in situ*. Ishii and co-workers previously discovered that ruthenium can promote oxidative-cleavage of 1,2-diols **3-56**, to aldehyde **3-57**.[132] Changing the reaction stoichiometry resulted in a significantly increased yield and selectivity, giving the desired product **3-53** in 42% yield. Reverting to the initial HB conditions, using $(IrCp^*Cl_2)_2$, gave a higher yield, regardless of which reagent was limiting. Hence, the reaction was reoptimised from this point using the phenyl alcohol **350** as a model substrate (Table 3-2).



*Scheme 3-12) Phenyl alcohol **3-50** showed significant glycol cleavage; this was reduced significantly using $(IrCp^*Cl_2)_2$. Yields reported are ^{1}H-NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. (isolated yields). Oxidative-cleavage was previously demonstrated by Ishi and co-workers*

Subjecting **3-52** to the Ru catalysed conditions resulted in the exclusive formation of the cleaved product **3-59** (Scheme 3-13). Under the Ir-mediated conditions, the product **3-58** was isolated in 11% yield.[a] Similar to the phenyl alcohol **3-50**, inverting the stoichiometry resulted in a dramatic increase in yield of product **3-58** (52%, 5:1 d.r.), with no oxidative-cleavage being observed.

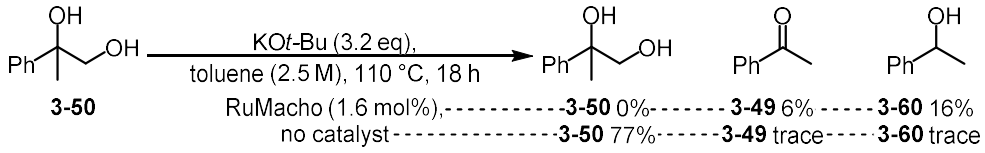
[a] The effects of the initial diol d.r. on the HB reaction as well as determination of the relative stereochemistry by X-ray crystallography is discussed in section 3.7.



*Scheme 3-13) Secondary alcohol **3-52** showed significant glycol cleavage; this was reduced significantly using $(IrCp^*Cl_2)_2$. Yields are ^{1}H -NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. [a] Relative stereochemistry of the product determined by X-ray crystallography. Minor isomer present, but yield could not be quantified.*

In order to determine whether the cleavage was metal-mediated, control reactions were run without Ph* ketone **3-07** (Scheme 3-14).[a] In the presence of Ru-MACHO, the diol was fully consumed and gave a complex mixture containing cleavage derivatives **3-49** and **3-60**. Without the Ru-complex, the diol **3-50** was reisolated without any significant by-product being observed.

Given that Ph* methyl ketone is not involved in the oxidation of **3-50**. The increase in yield and selectivity when excess ketone is used (Scheme 3-12) suggests that oxidative cleave occurs on the aldehyde intermediate, not the diol. Hence, increasing the rate of condensation should result in a more selective reaction.

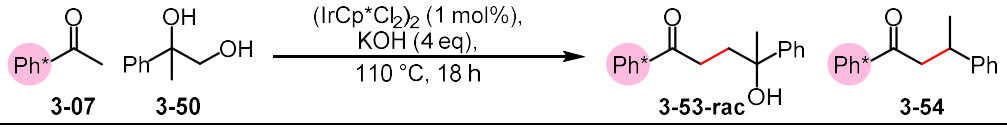


*Scheme 3-14) Control experiments demonstrate RuMacho is directly involved in the diol **3-50** decomposition. ^{1}H-NMR yields were calculated based on 1,1,2,2-tetrachloroethane as an internal standard.*

3.4.3. Reoptimisation in Order to Decrease Glycol Cleavage.

Having observed a significant side reaction when the phenyl diol **3-50** was used, the HB reaction was further investigated using the diol as the model substrate. Toluene and *t*-BuOH were found to be the best solvents for the reaction (Table 3-2, Entry 1-5). The effect of changing the concentration was then investigated, and the 4 M solution was found to be the most efficient, giving the product in 53% yield (Entry 6-12). Increasing the loading of the dimer to 2 mol% increased the product yield to 71% (Entry 16). Reducing the temperature to 100 °C gave the product in 86% yield (Entry 17); however, further decreasing the reaction temperature to 90 °C resulted in the yield dropping (Entry 18).

[a] The changes in equivalents and concentration in the control reactions are due to the values being w.r.t. to the alcohol **3-50** instead of the ketone **3-07**.

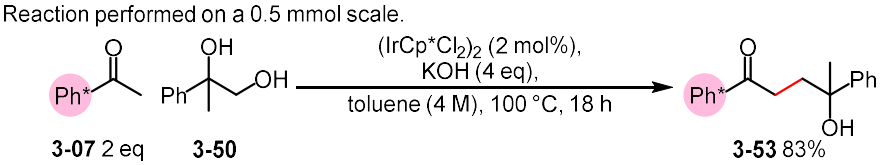


3-07 3-50 3-53-rac 3-54

	Catalyst (mol%)	Solvent (M)	Temp (°C)	3-53 (%)	3-54 (%)
1	$(IrCp^*Cl_2)_2$ (1)	Toluene (2)	110	49	7
2	$(IrCp^*Cl_2)_2$ (1)	*m*-Xylene (2)	110	29	15
3	$(IrCp^*Cl_2)_2$ (1)	Benzene (2)	110	35	7
4	$(IrCp^*Cl_2)_2$ (1)	*t*-BuOH (2)	110	47	10
5	$(IrCp^*Cl_2)_2$ (1)	Dioxane (2)	110	19	9
6	$(IrCp^*Cl_2)_2$ (1)	Toluene (0.5)	110	23	8
7	$(IrCp^*Cl_2)_2$ (1)	Toluene (1)	110	37	6
8	$(IrCp^*Cl_2)_2$ (1)	Toluene (3)	110	49	7
9	$(IrCp^*Cl_2)_2$ (1)	Toluene (4)	110	57(53)	6
10	$(IrCp^*Cl_2)_2$ (1)	Toluene (6)	110	51	7
11	$(IrCp^*Cl_2)_2$ (1)	Toluene (8)	110	47	3
12	$(IrCp^*Cl_2)_2$ (1)	-	110	25	10
13	$(IrCp^*Cl_2)_2$ (2)	Toluene (1)	110	67	5
14	$(IrCp^*Cl_2)_2$ (3)	Toluene (1)	110	62	6
15	$(IrCp^*Cl_2)_2$ (2)	Toluene (4)	120	72	3
16	$(IrCp^*Cl_2)_2$ (2)	Toluene (4)	110	71	4
17	$(IrCp^*Cl_2)_2$ (2)	Toluene (4)	100	86	Tr
18	$(IrCp^*Cl_2)_2$ (2)	Toluene (4)	90	69	2

Table 3-2) Solvent and concentration screening. Yields are ^{1}H-NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. (isolated yields).

Increasing the scale of the reaction from 0.2 mmol to 0.5 mmol had a minimal effect on the reaction and resulted in the desired product being isolated in 83% yield (Scheme 3-15).



3-07 2 eq **3-50** **3-53** 83%

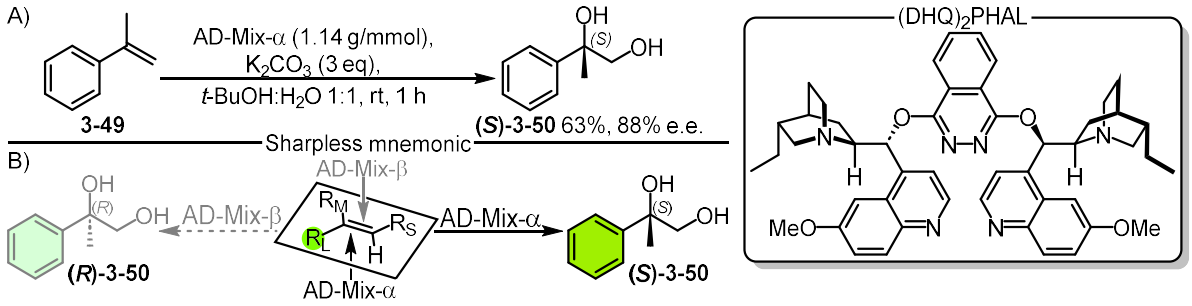
*Scheme 3-15) Scaling up the reaction gave the product **3-53** in 83% yield. Reaction performed on a 0.5 mmol scale.*

3.5. Enantioenriched Lactone Synthesis.

Before testing the cleavage of the Ph* protecting group, it was decided to synthesise an enantioenriched sample of ketone **3-53**, allowing measurement of racemisation of the acid labile tertiary alcohol centre during cleavage.

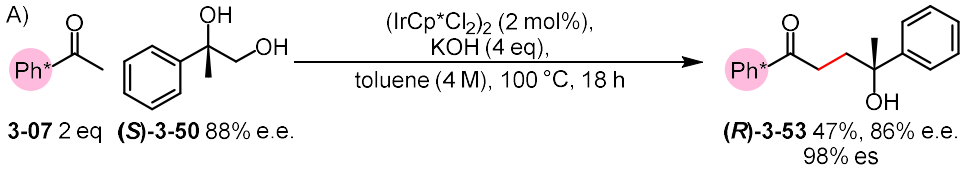
3.5.1. Synthesis of the Enantioenriched Ketone.

The required enantioenriched diol **(*S*)-3-50** was synthesised using Sharpless asymmetric dihydroxylation in 63% yield and 88% e.e. (Scheme 3-16 A).[133] The measured 86% e.e. is consistent with previous experimental work and Sharpless's mnemonic and guidelines for substrate tolerance (Scheme 3-16 B).[134,135]



Scheme 3-16) Sharpless dihydroxylation was a convenient route to the enantioenriched starting material. e.e. determined by HPLC.

Under the optimised conditions, the enantioenriched diol gave the product with 98% es as expected, albeit with significantly decreased yield compared to the racemic reaction (Scheme 3-17). The decreased yield compared to the racemic reaction was observed multiple times, suggesting that the difference was not due to an experimental error. Donohoe and co-workers previously saw a similar drop in yield using alcohols bearing an α-chiral aziridine;[119] As the reaction is not fully homogeneous, the difference in the racemic and enantioenriched diol's solubility may be effecting the relative polarity of the solution and relative concentration of the reagents, which.



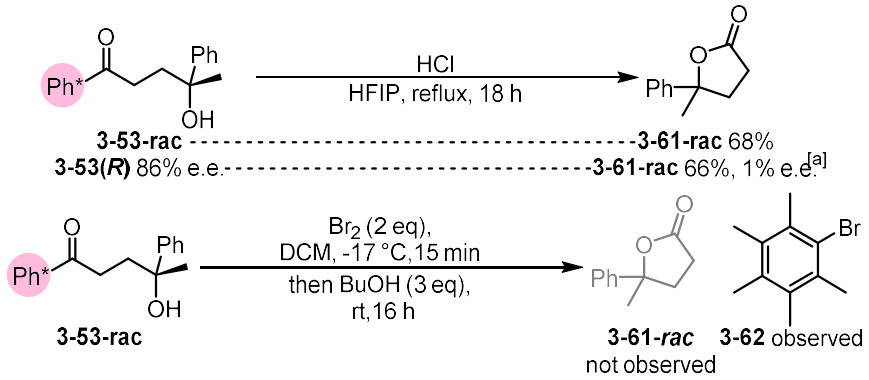
B) $es = \frac{[e.e.]_{Product}}{[e.e.]_{Starting\ Material}}$

*Scheme 3-17) [a] Enantioenriched diol **(S)-3-50** underwent HB with 98% es. [b] Enantiospecificity equation.*

3.5.2. Cleavage of the Ph* Protection Group.

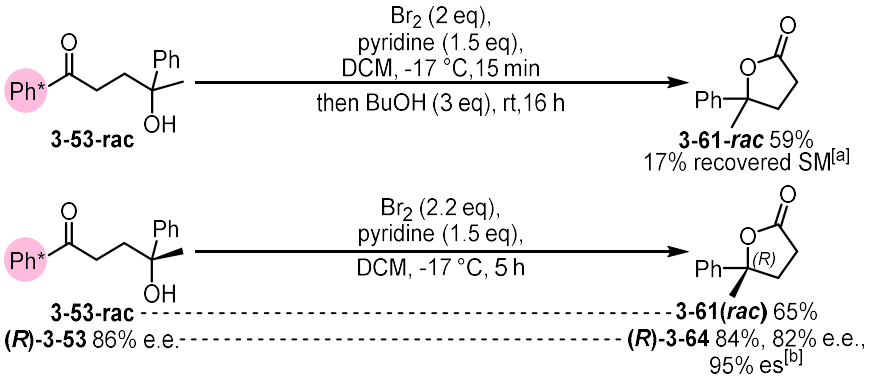
In order to selectively cleave the Ph* group, the formation of a 3° cation from the tertiary alcohol functionality needs to be prevented, in the starting material **3-53** and the product **3-61**. Under both acidic and bromine conditions, this may be challenging. In acidic conditions, HFIP is known to stabilise carbocation formation.[136,137] Under bromine cleavage conditions, C–N bond cleavage was previously observed *via* an S_N2 addition (Scheme 3-6).[119]

Under the previously optimised acidic conditions, the lactone **3-60-rac** was formed in 76% yield (Scheme 3-18).[94] When enantioenriched starting material was subjected to the same conditions, It was found that the lactone underwent almost complete racemisation. Under the previously optimised bromination conditions, a complex mixture was observed with consumption of the starting material and formation of the aryl bromide **3-62** (as observed by ^{1}H-NMR); however, no product **3-61** was observed.[11]



Scheme 3-18) Established cleavage strategies [a] Yield reported is a ^{1}H-NMR yield calculated based on 1,1,2,2-tetrachloroethane as an internal standard. e.e.'s determined by HPLC

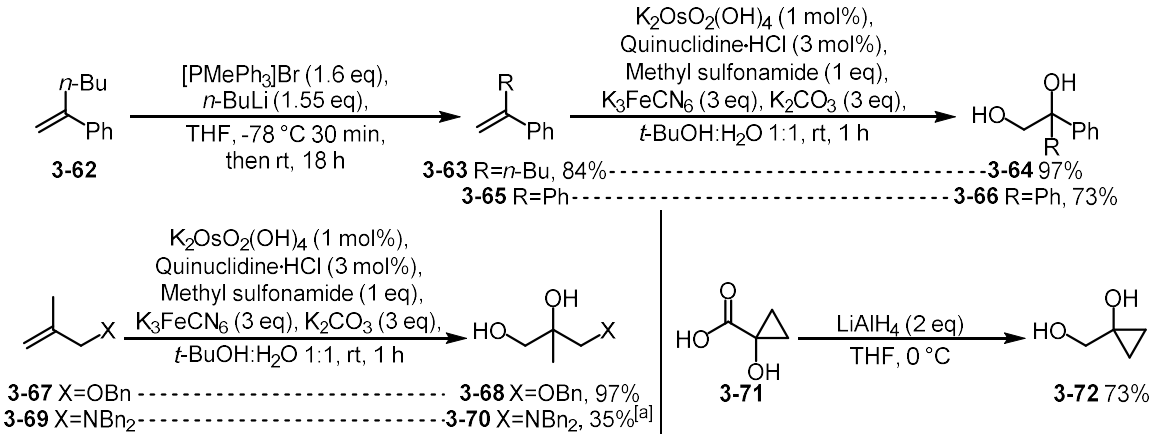
It was hypothesised that HBr, formed *in situ*, led to decomposition. Hence, 1.5 eq of pyridine was added, which resulted in the product **3-61** being formed in 59% yield (Scheme 3-19). Running the reaction for 5 h at -17 °C led to full consumption of the starting material **3-53** and gave the product in 65% yield. With enantioenriched starting material, we were pleased to achieve 95% es. This modification contrasts with the lactam synthesis previously reported, which required an acidic additive to prevent decomposition (Scheme 3-7).[80]



Scheme 3-19) With pyridine as an additive, lactonization occurred with high yield and enantiospecificity. [a] Recovered starting material ^{1}H-NMR yields calculated based on ratio with the product. [b] ^{1}H-NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard.

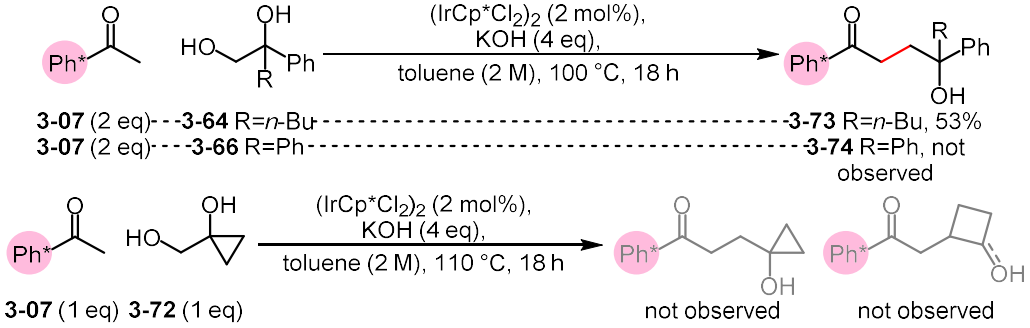
3.6. Substrate Scope of 1° Alcohols.

To further investigate the scope of 1° alcohols, 1,2-diols **3-64**, **3-66**, **3-68**, **3-70** and **3-71** were synthesised by dihydroxylation of the respective olefin substrates (Scheme 3-20). The cyclopropane containing diol **3-72** could be accessed by reducing the commercially available carboxylic acid **3-71**.



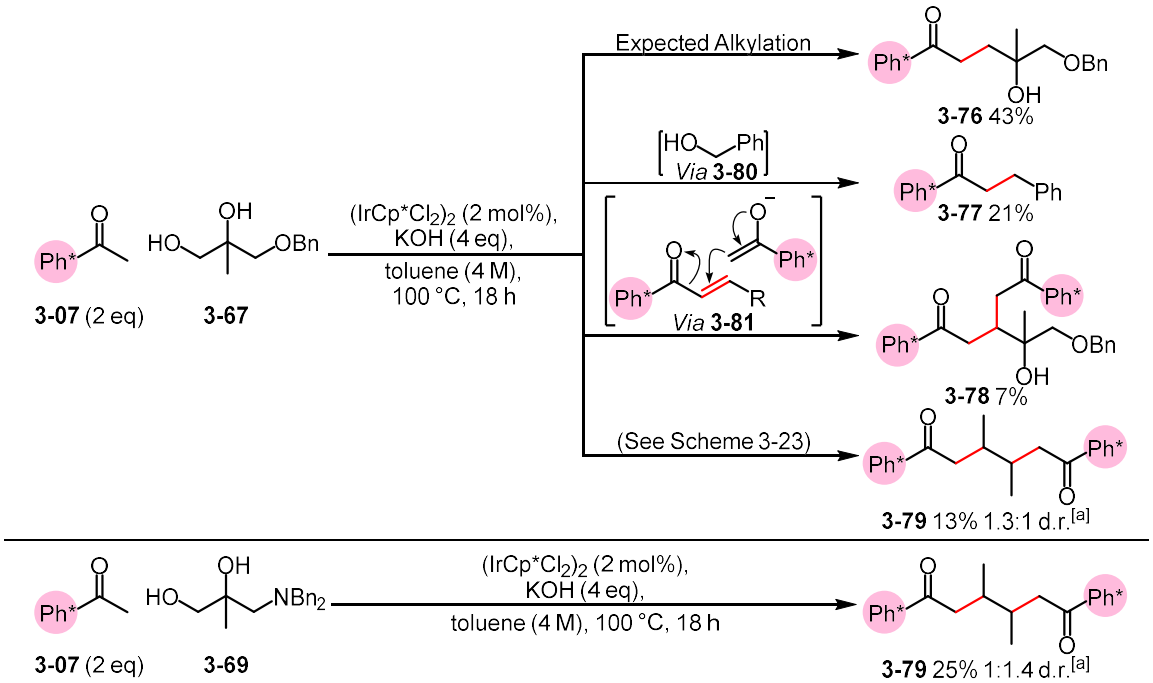
Scheme 3-20) Diols were synthesised from available olefins or carboxylic acids.[a] Reaction run for 5 days.

Alkylation, under the optimised conditions, with diol **3-64** was successful and the product **3-73**was isolated in 53% yield (Scheme 3-21). The larger diol **3-66** was found to be too hindered and gave no product **3-74**. Disappointingly, no products could be isolated from the HB reaction with cyclopropane **3-72**.



*Scheme 3-21) The n-butyl product **3-73** was isolated as a single product in 53% yield. No reaction was observed with the diphenyl substrate **3-66**.*

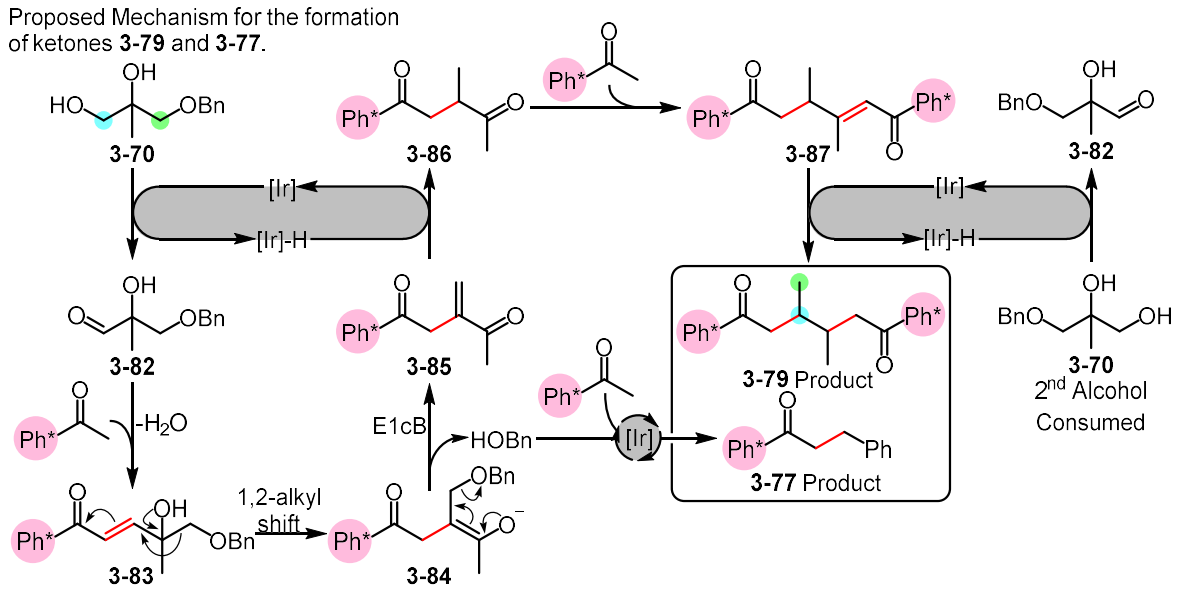
When the ether **3-68** was subjected to the optimised HB conditions, the desired product **3-76** was isolated in 43% yield (Scheme 3-22).[138] Alongside the desired product, three unexpected side products were isolated: cleavage of the benzyl group **3-80** resulted in the alkyl product **3-77** in 21% yield; the double addition product **3-78** was formed *via* interception of the enone intermediate **3-81** in 7% yield; finally, we were surprised to find that a second diketone **3-79** was formed in 13% yield. With the amino alcohol **3-70**, exclusive formation of the same diketone **3-79** in 25% yield was observed.



*Scheme 3-22) Alkylation was successful on the ether giving the product **3-76** in 43% yield. Alkylation of the amine **3-69** resulted exclusively in the rearranged product **3-79**. [a] Relative stereochemistry was not determined. The d.r. was determined based on the isolated product.*

The formation of **3-79** involves a complicated and unknown cascade. A tentative mechanism is proposed below (Scheme 3-23). We propose that the enone **3-83** undergoes a 1,2-alkyl migration stabilised by the adjacent heteroatom. The subsequent ketone **3-84** could then undergo E1cB elimination to give the enone **3-85** and BnOH, followed by reduction, to give diketone **3-86**, as observed previously (see Section 2.5.2). The diketone **3-86** can condense with Ph*methyl ketone **3-07** to give the enone **3-87**. The enone undergoes reduction by Ir-H to give the product **3-79** requiring a second alcohol **3-70** to act as a hydride donor. This mechanism could also explain why a large amount of BnOH was formed *in situ* leading to the ketone **3-77**.

If this mechanism is correct, two equivalents of the alcohol **3-70** are required to produce the product, meaning the yields are 26% and 50% with the alcohol and amine, respectively1. The proposed heteroatom-assisted migration is less common in the literature than aryl migration but has some literature precedent.[139,140]

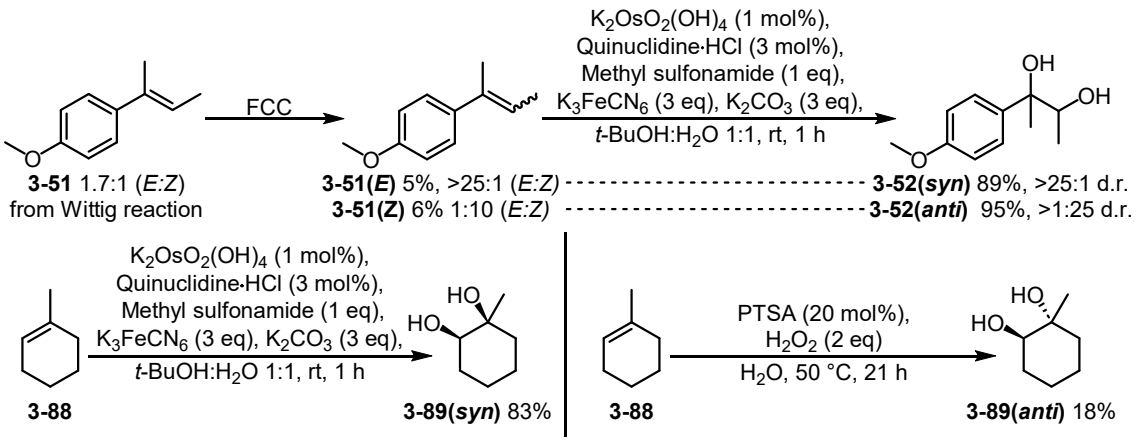


*Scheme 3-23) Proposed mechanism for the formation of HB products **3-79**+**3-77**.*

3.7. Reactions with 2° Diols.

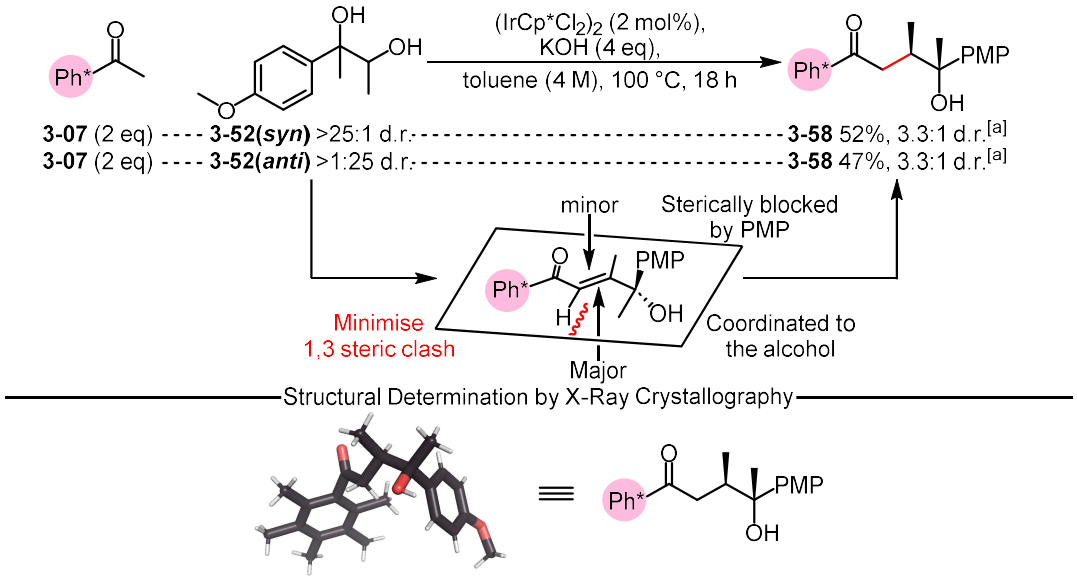
During optimisation of the HB reaction with 1,2-diols, the reactivity of the 2° alcohol **3-52** (Scheme 3-13) was examined with it present as a mixture of diastereomers in the starting material. It was decided to test whether the d.r. of the starting material affects the HB reaction. Since the stereocentre is lost during oxidation, it was initially suspected that the d.r. of the product would be unaffected; however, changing the oxidation rate or oxidative cleavage between diastereomers could significantly affect the yield.

The olefins **3-51** were separated by FCC (Scheme 3-24). Subsequent oxidation gave each diol **3-52** isomer in >25:1 d.r. Both the *syn* and *anti*-isomers of cyclohexane **3-88** were synthesised by stereoselective dihydroxylation of cyclohexene **3-89** in 83% and 18% yield, respectively. Stereochemistry of both the olefin and diol were determined based on comparison with literature results.



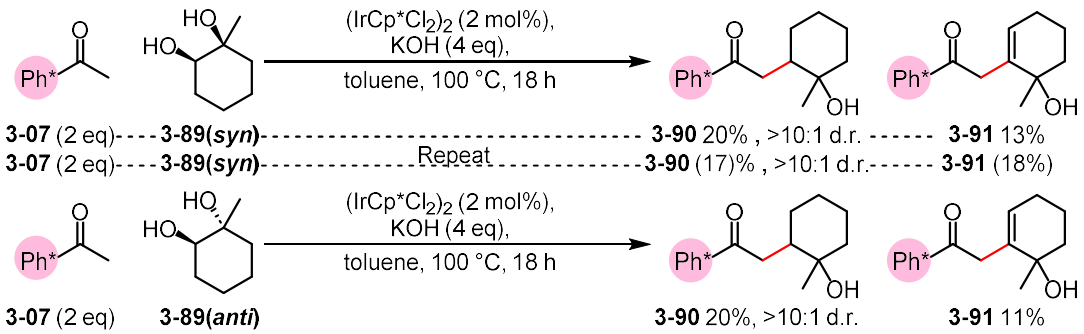
*Scheme 3-24) The 2° alcohol **3-52** and cyclic diol **3-89** were obtained as single diastereomers.*

Subjecting each separate diastereomer to the optimised conditions gave the product **3-58** with similar yields and d.r. (Scheme 3-25). The major isomer **3-58** was determined to be the *anti*-diastereomer by X-ray crystallography.[a] This stereochemistry is consistent with the final enone reduction occurring on the least hindered face of the major conformer and may involve coordination of the alcohol to the Ir-catalyst.



*Scheme 3-25) The d.r. of the starting material **3-52** did not affect the HB reaction. [a] ^{1}H -NMR yields calculated based on 11,22-tetrachloroethane as an internal standard. Major isomer determined by X-Ray crystallography from a single crystal of pure material. Olefins separated by FCC.*

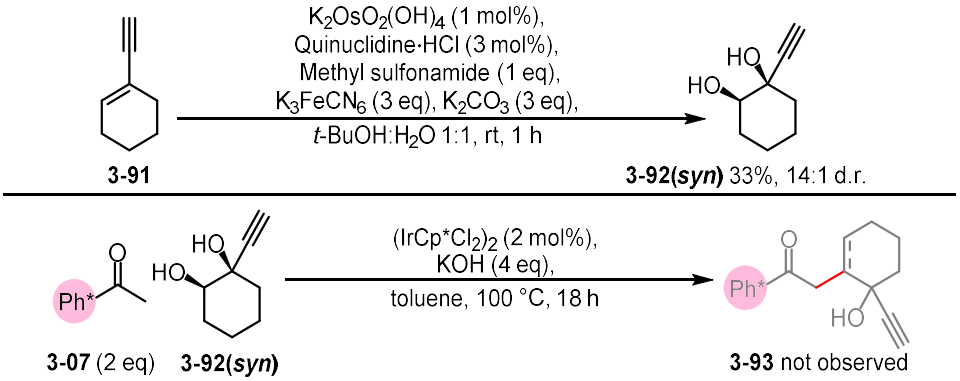
When subjected to HB conditions, both the diastereomers of diol **3-89** gave the same yield of the product **3-90** and the skipped enone **3-91** by NMR (Scheme 3-26). Repeating the *syn* reaction enabled the isolation of the products **3-90** and **3-91** in 18% and 17% yield, respectively.[b]



Scheme 3-26) Yields are ^{1}H-NMR yields calculated based on 1,1,2,2-tetrachloroethane as an internal standard. (Isolated yields). The relative stereochemistry of the product was not determined.

[a] Crystal sample formed from a diastereomerically pure sample of the product.
[b] Reaction required multiple attempts to cleanly isolate the products from the complex mixture.

It was hoped that alkynes, which are not often tolerated in HB reactions, could be protected by the steric bulk of an adjacent quaternary centre (Scheme 3-27).[1] Therefore, alcohol **3-92(*syn*)** was synthesised by dihydroxylation in 33% yield. When the alkyne **3-92(*syn*)** was subjected to the HB conditions, decomposition was observed, and only Ph* methyl ketone **3-07** was observed.

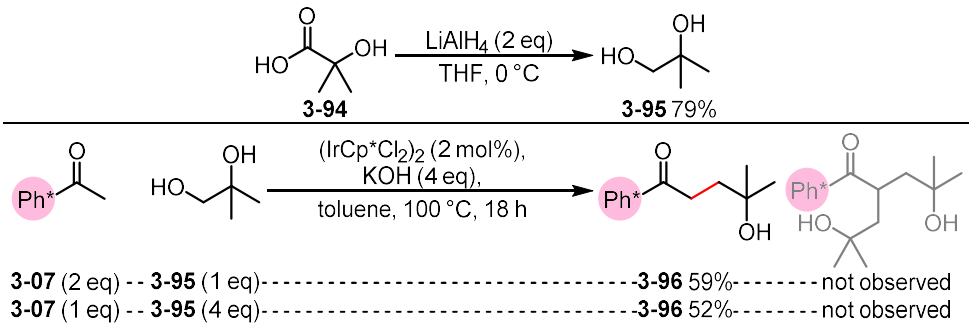


*Scheme 3-27) The adjacent quaternary centre was not found to prevent the decomposition of the alkyne **3-92**.*

3.8. Bis-Substitution of Ph* Methyl Ketone Under the Optimised Conditions.

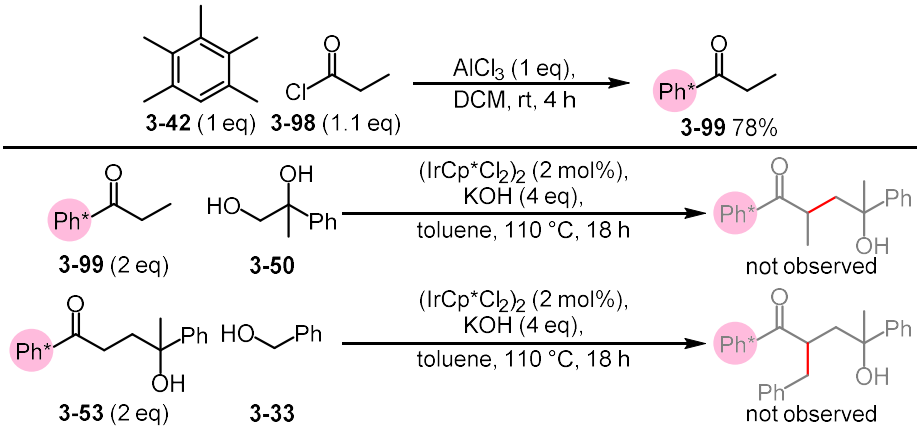
During the optimisation and scope of the HB reaction, we were surprised to observe no bis-alkylation reaction. It was thought that employing dimethyl alcohol **3-95** would encourage the bis-alkylation due to the reduced steric hindrance within the alkylated product **3-96** (Scheme 3-28).

The diol **3-95** was synthesised in 79% yield by reduction of the carboxylic acid **3-94**. Under the previously optimised conditions, the monoalkylated product **3-96** was isolated in 59% yield without bis-alkylation being observed. Using 4 eq of the alcohol resulted in the same product being isolated.



*Scheme 3-28) The small diol **395** did not undergo dialkylation even when 4 eq of the alcohol was employed. Yields of **3-96** w.r.t. to the limiting reagent in each case.*

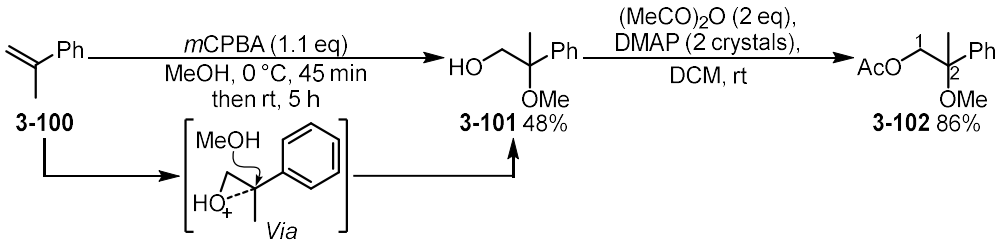
Having established that *bis*-alkylation does not occur under these conditions, it was decided to screen whether a sequential alkylation strategy could be employed with 1,2 diols. As a test substrate, Ph* ethyl ketone (**3-99**) was synthesised by Friedel-Crafts acylation (Scheme 3-29). No product was observed when ketone **3-99** was subjected to the HB procedure, or when the order of alkylations was reversed.[a] It may be that the steric bulk within the substrates is too large for bis-alkylation to occur.



*Scheme 3-29) Attempts to alkylate the α-branched substrate **3-99** and **3-53** gave no product.*

3.9. Effect of Alcohol Coordination on Hydrogen Borrowing Reactions.

In order to better understand the role of the α-alcohol in the HB reaction, the methylated substrate **3-102** was synthesised next (Scheme 3-30).[141] In order to confirm the regioselectivity of the epoxide opening, the free alcohol was acylated to give the product **3-102**. The shift of the adjacent C1 protons in the ^{1}H-NMR spectrum (3.66 ppm→4.19 ppm, 3.15 ppm→4.15 ppm) confirmed that the desired product had been formed.

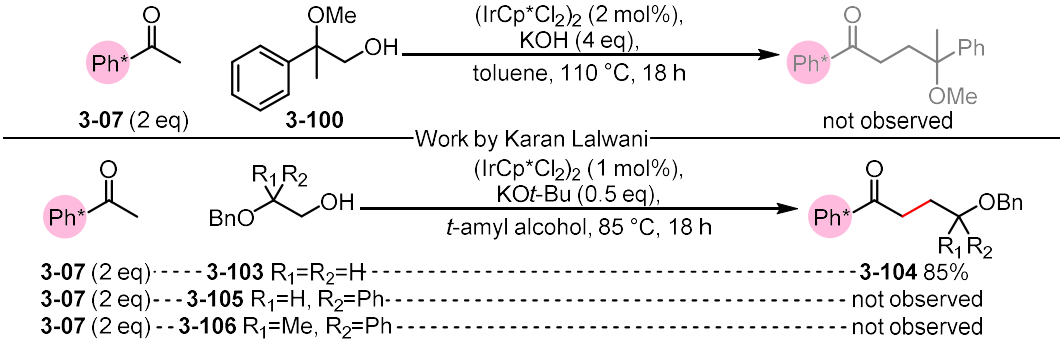


*Scheme 3-30) Synthesis of the 2-Methyalted substrate **3-101**.*

The O-methyl substituted ether **3-100** was found to completely prevent the HB reaction, which implies that the α-alcohol has an active role in the reaction (Scheme 3-31). Under reoptimised conditions, Karan Lalwani demonstrated that unsubstituted α-ether **3-103** could be tolerated in the reaction, giving the ketone **3-104**, but branched ethers **3-105**+**3-106** could not be tolerated

[a] Ongoing work using recently developed conditions. by Karan Lalwani has subsequently successfully alkylated alcohol **3-96** with BnOH.

under the same conditions. This data suggests that the free alcohol group is only required to overcome the steric hindrance of the α-centre.

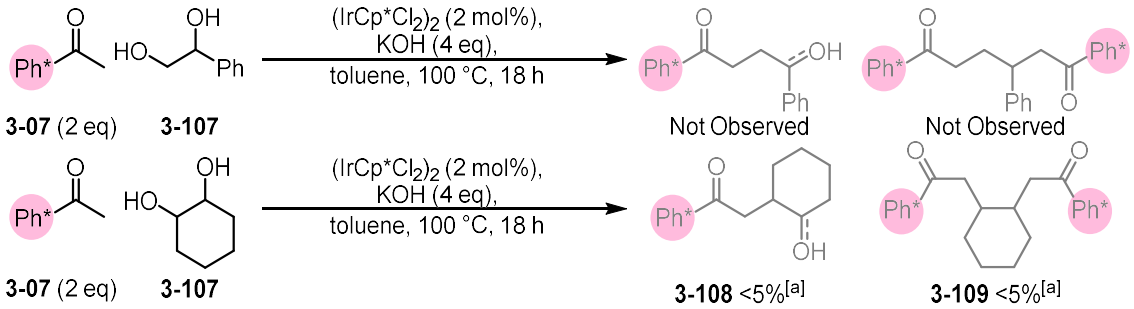


Scheme 3-31) Methylation of the 3° alcohol was found to prevent alkylation. Using the glycol ether, alkylated product ***3-104*** *was isolated in 85% yield by Karan Lalwani.*

Given the reactivity of the *n*-butyl substituted alcohol **3-73**, it seemed unlikely that this dramatic change in reactivity is entirely due to sterics. We tentatively suggest that the chelation of the diol and the intermediates to the Ir-catalyst increases the reactivity of the alcohols.[84]

3.10. 1,2-diols Without a 3° Alcohol Group.

Next, it was decided to explore whether the method could tolerate diols without a 3° centre. With the 1° alcohol **3-56**, a complex mixture was observed with no product formation (Scheme *3-32*). HB with cyclohexanediol **3-107** also resulted in a complex mixture, including what appeared to be the ketone **3-108** and diketone **3-109** in <5% yield, which was insufficient to allow structural elucidation.

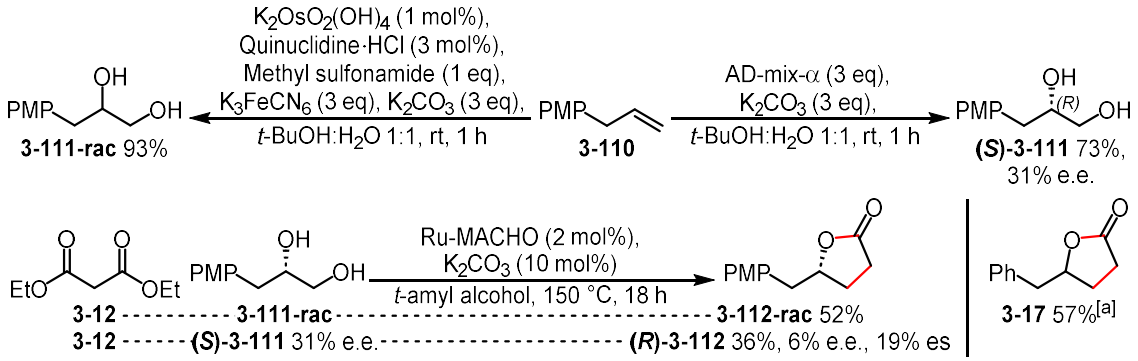


Scheme 3-32) Both alcohols gave complex mixtures under the optimised HB conditions.

3.11. Enantioretention in Beller's Lactone Strategy.

Beller's one-step lactone methodology, discussed previously, did not report how stereochemistry is communicated through the reaction sequence (Scheme 3-3).[25] Therefore, how the absolute stereochemistry of the alcohol **(*S*)-3-111** is communicated under their conditions was investigated.

Towards this end, the racemic and enantioenriched diols **3-111** were synthesised using the osmium dihydroxylation methods previously discussed (Scheme 3-33).[142] Under Beller's optimised conditions, the racemic product **3-112-rac** was isolated in 52% yield, consistent with the yield reported for **3-17**. Employing the enantioenriched diol **(*S*)-3-111** gave the product in 36% yield with 19% es.[143] Racemisation of the 2° alcohol could occur *via* direct oxidation of the alcohol or *via* epimerisation of the intermediates upon oxidation of the 1° alcohol as observed by Zhao and co-workers.[144]



Scheme 3-33) Under optimised conditions by Beller and co-workers, the α-stereocentre was found to undergo significant epimerisation. [a] Reaction reported by Beller and co-workers[25]

Chapter 4. Synthesis of Cyclohexenes by a Mukaiyama-Michael Addition and 1,5-Hydride Shift Sequence.

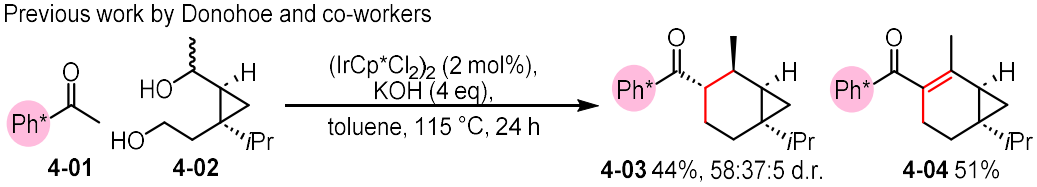
4.1. Introduction.

In order to expand on the previous synthesis of cyclohexenes within the Donohoe group, we aimed to develop new approaches to synthesising THP precursors, building on the work by Schneider and co-workers to synthesise enantioenriched THP rings. With these compounds in hand, we planned to explore how tri-substituted THP rings behave in 1,5-hydride transfer reactions.

Teodor Răzvan Mirescu (TRM) began this project; his work is described in Section 4.1.4.

4.1.1. The Synthesis of Cyclohexenes by Acceptorless Hydrogen Transfer

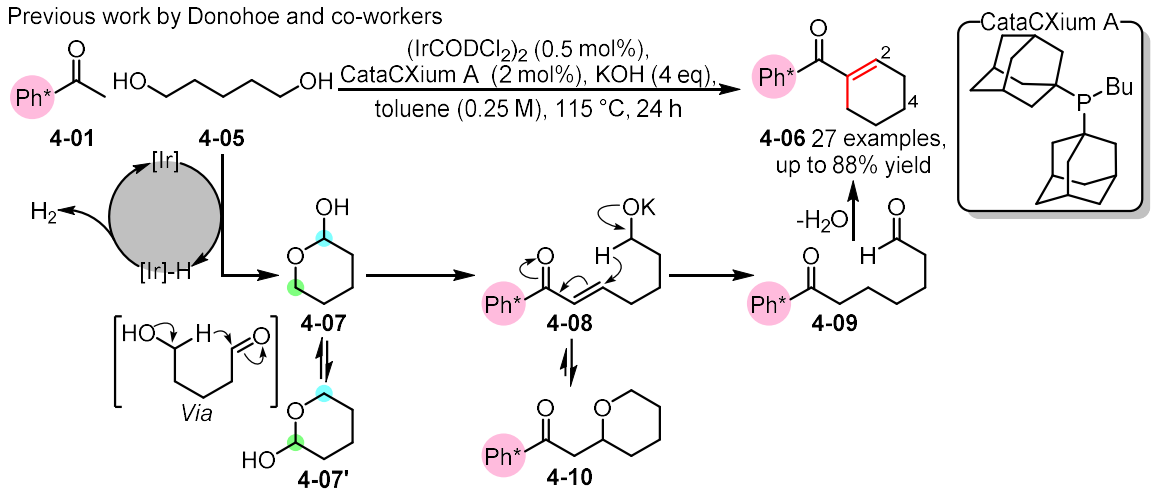
In Chapter 2, the synthesis of cyclohexanes, such as **4-03** *via* an [n+1] strategy using Ph* methyl ketone (**4-01**) and diols was discussed (Section 2.1.4).[20,92] In this research, the Donohoe group found that sterically hindered diols, such as cyclopropane **4-02**, were found to stall during the HB cycle, forming cyclohexene **4-04** in 51% yield (Scheme 4-1).



*Scheme 4-1) Cyclohexene side products, such as **4-04**, were formed during the synthesis of cyclohexanes **4-01** with hindered diols, such as **4-02**.* [20,92]

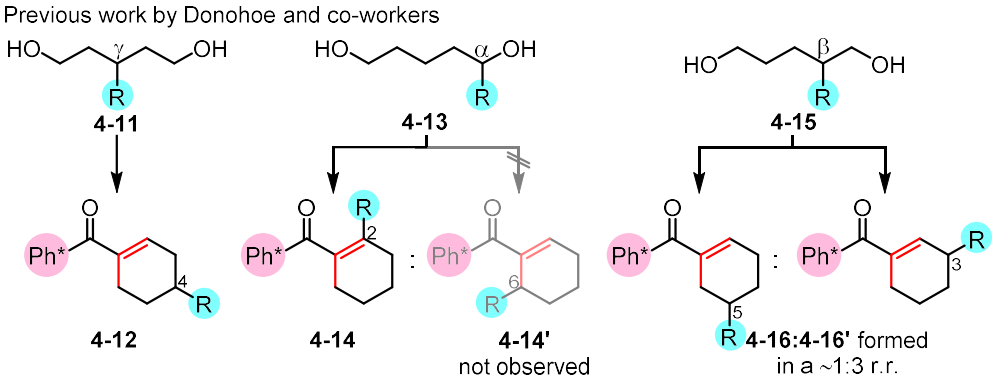
The method was re-optimised to selectively form the cyclohexene side product without substrate control (Scheme 4-2).[16] In both the cyclohexane and cyclohexene methodologies, the intermediate **4-08** was determined to undergo a 1,5-hydride transfer to form the dicarbonyl **4-09** instead of the expected Ir-mediated hydride transfer. A significant build-up of the off-cycle intermediate THP **4-10** was observed during the reaction.[a]

[a] Formation of the THP was observed by measuring the reaction profile using ^{1}H-NMR.



*Scheme 4-2) A) Numerous cyclohexenes were synthesised by Donohoe with substitution in the C2 and C4-positions. Cyclohexanes were demonstrated to be synthesised by the same route with reduction of the cyclohexene **4-06** by the Ir-H.*[16]

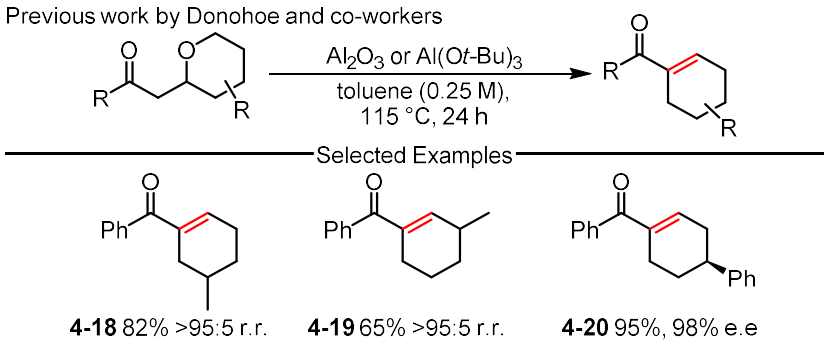
As the lactol intermediate **4-07/4-07'** undergoes a reversible 1,5-hydride transfer scrambling the regiochemistry or absolute stereochemistry (Scheme 4-3). Hence, when the diol was not symetrical: α-substituted diols **4-13** were found to give C2-substituted cyclohexenes **4-14** as a single regioisomer; and β-substituted diols **4-15** form a mixture of regioisomers forming both cyclohexene **4-16**+**4-16'**.



Scheme 4-3) Of the five possible di-substituted cyclohexenes, two could be synthesised with regioselectivity, and two were synthesised as a mixture of regioisomers.

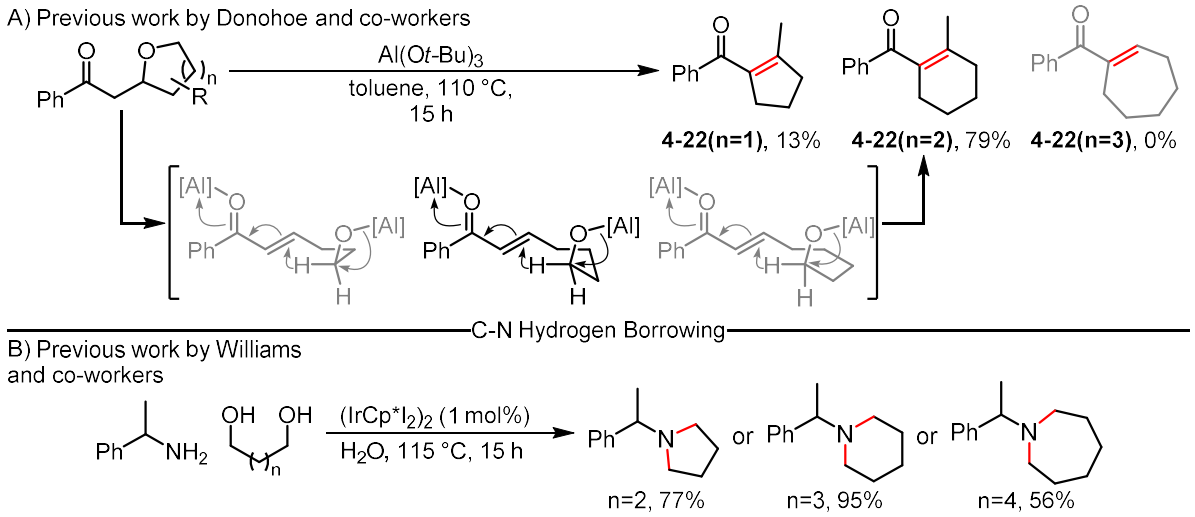
4.1.2. 1,5-Hydride Transfer Chemistry.

In order to prevent the undesired lactol interconversion via 1-5 hydride shift, the Donohoe group directly synthesised the intermediate THP. Investigation of THP reactivity led to aluminium reagents being found to be the best promoter for 1,5-hydride transfer to give the desired cyclohexenes (Scheme 4-4). By this approach, the **4-07/4-07'** interconversion could be successfully bypassed, allowing access to previously inaccessible highly regio (**4-18** + **4-19**) and enantioenriched (**4-20**) cyclohexenes.



*Scheme 4-4) Cyclohexenes were synthesised regioselectively **4-18**+**4-19** and enantioselectively **4-20** from substituted THP rings.*[16]

Intramolecular hydride transfers are well established in the literature, with 1-5 hydride transfers known to give higher yields than other chain lengths.[145–148] Hence, whilst the 6-membered ring **4-22(n=2)** could be obtained using aluminium promoted conditions in 79% yield, the 5-membered analogue **4-22(n=1)** forms in just 13% yield and 7-membered ring **4-22(n=3)** was not observed (Scheme 4-5 A). It is worth noting that this effect is not observed in amine HB; for example, Williams and co-workers demonstrated unsubstituted 5, 6 and 7-membered ring formation under HB conditions with high yields, suggesting a hydride shift is not part of the mechanistic pathway (77%, 95% and 56% yields, respectively, Scheme 4-5 B).[149]a



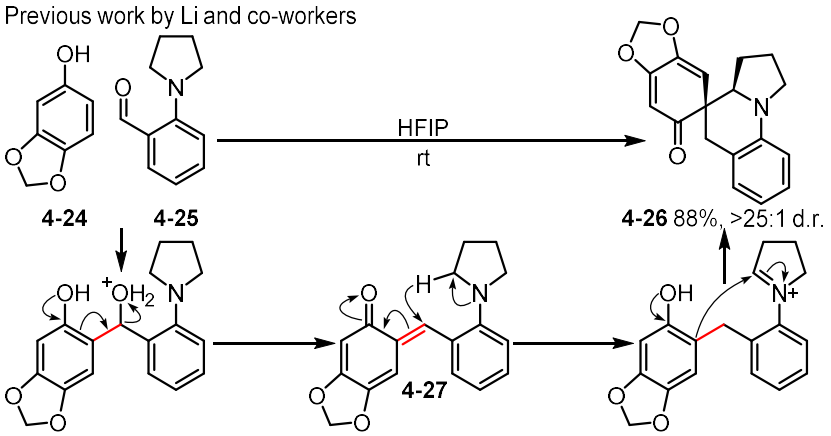
Scheme 4-5) (A) The Donohoe group found 1,N-hydride transfer to be highly ring size dependant.[16] *(B) In amine HB reactions, Williams and co-workers showed that ring size had relatively modest effects on the reaction yield.*[149]

The Donohoe group found that aluminium alkoxides and alumina were the most effective Lewis acids for this system; various other reagents are known to facilitate 1,5-hydride transfers in other systems.[150] These include; B,[151] Mg,[152] K,[153] Sc,[154] Fe,[155] Ti,[156] Mo,[157] Au[158]

[a] Regioselective reactions due to the formation of 6 membered intramolecular transitions states is also observed in hydrogen atom transfer (HAT) reactions.[293]

and Yb[152] as well as Bronsted acids.[159] Hydrides are usually activated by either an adjacent nitrogen, oxygen or bis-aryl activation.[146]a

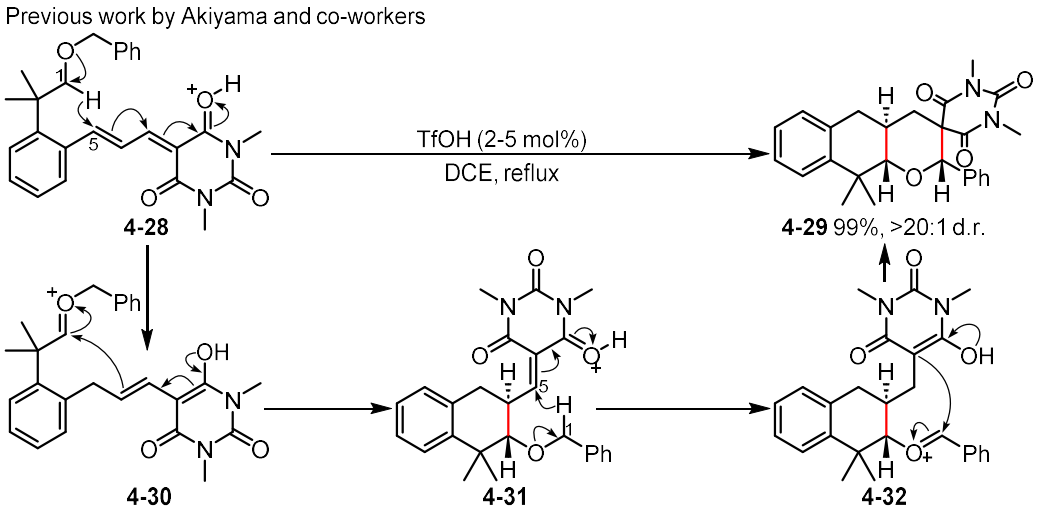
Whilst an extensive literature history is beyond the scope of this introduction, a few interesting and illustrative examples have been chosen. Li and co-workers discovered that aldehyde **4-25** can condense with phenol (**4-24**) *in situ* to form the highly activated enone **4-27** (Scheme 4-6).[160,161] The enone then undergoes 1,5-hydride transfer, with the subsequent iminium being trapped out to form the spirocycle **4-26**.



*Scheme 4-6) An example of N-activated hydride transfer. Li and co-workers generates the enone hydride acceptor in situ by condensation with the phenol **4-24**.* [160,161]

Akiyama and co-workers synthesised the diene **4-28** as an active substrate for a double 1,5-hydride transfer-cyclisation cascade (Scheme 4-7).[162] After the first acid-promoted 1,5-hydride transfer reaction forms the oxonium **4-30**, which then closes to form the bicycle **4-31**. Ring closing of **4-32** leads to forming the active 1,5-donor-acceptor arrangement *in situ,* allowing for the second 1,5-hydride transfer to occur, giving the THP **4-29** in 99% yield.

[a] C–H Activation isn't strictly necessary, given a sufficiently activated hydride-acceptor.[294,295] These reactions utilise highly reactive acceptors and rigid structures to drive the transfer.

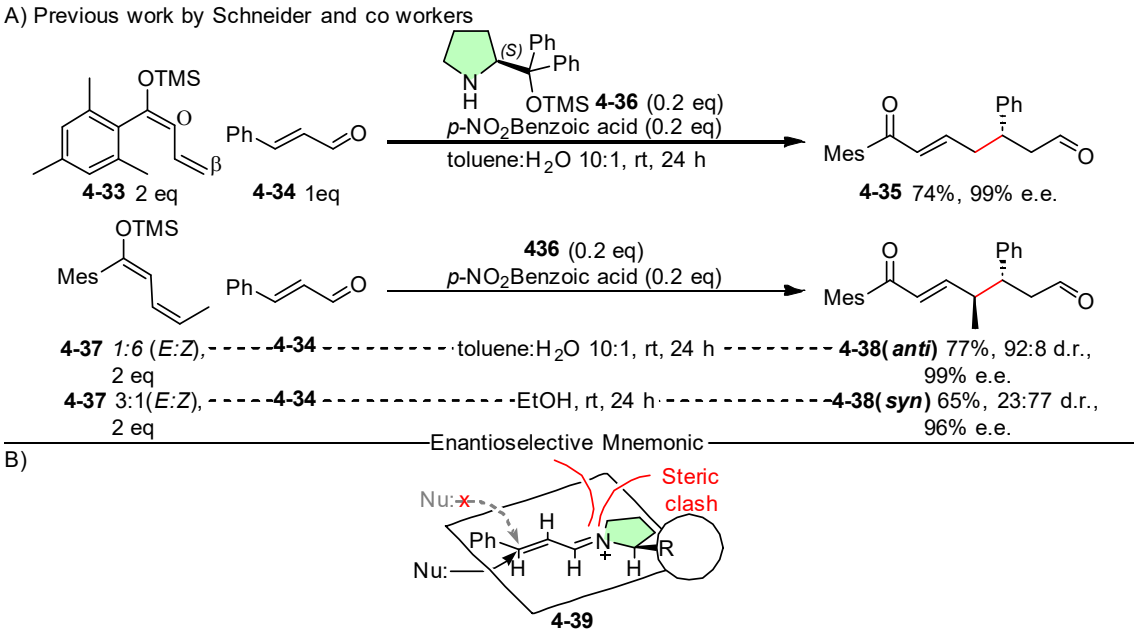


*Scheme 4-7) An example of O-activated hydride transfer into diene **4-28** by Akiyama. The first ring formation brings the groups close enough to trigger the second hydride transfer to form the tetracyclic substrate **4-29**.*[162]

4.1.3. The Vinylogous Mukaiyama-Michael Addition.

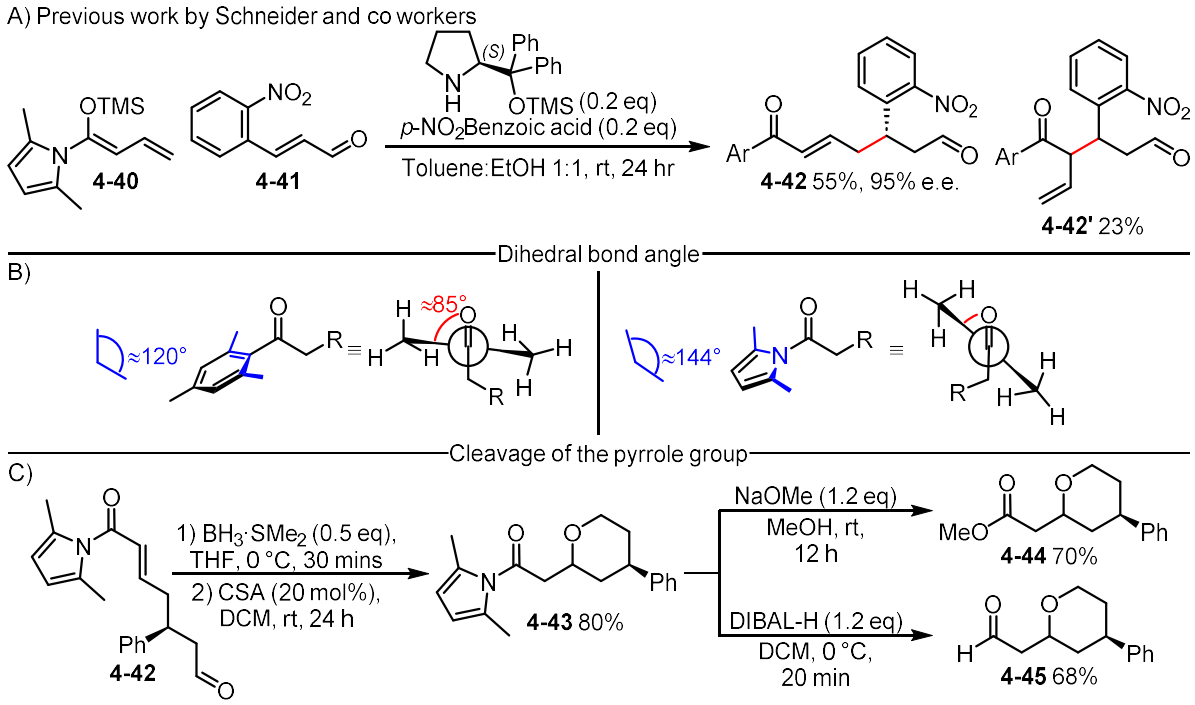
The Vinylogous Mukaiyama-Michael reaction, developed by Schneider and co-workers, appeared to be a promising approach to prepare enantioenriched THP rings and previously unexplored THP substitution patterns in the subsequent 1,5-hydride transfer reaction.[163] Schneider discovered that extended silyl enol ether **4-33** acts as an nucleophile exclusively through the γ-position (Scheme 4-8 A). The reaction with cinnamaldehyde (**4-34**) resulted in the formation of 1,7-dicarbonyl **4-35** in 74% yield and 99% e.e. Schneider also demonstrated that both the *E* and *Z* methyl substituted silyl enol ethers **4-37** could be tolerated with the two alkene geometries being communicated into the d.r. of the product **4-38** in 23:77 d.r. and 92:8 d.r., respectively. The *E* isomer of **4-37** was found to be less reactive and required using EtOH as a solvent to increase the reaction rate.

Since Macmillan and co-workers first discovered enantioselective 2° amine organocatalysis as a strategy to promote Diels-Alder reactions,[164] the strategy has been used to promote various reactions including; 1,3-dipolar cycloadditions,[165] epoxidations[166] and reductions[167]. Enantioselectivity is controlled by the activation of the aldehyde as an iminium **4-39** whilst sterically hindering one face for nucleophilic attack (Scheme 4-8 B).[168]



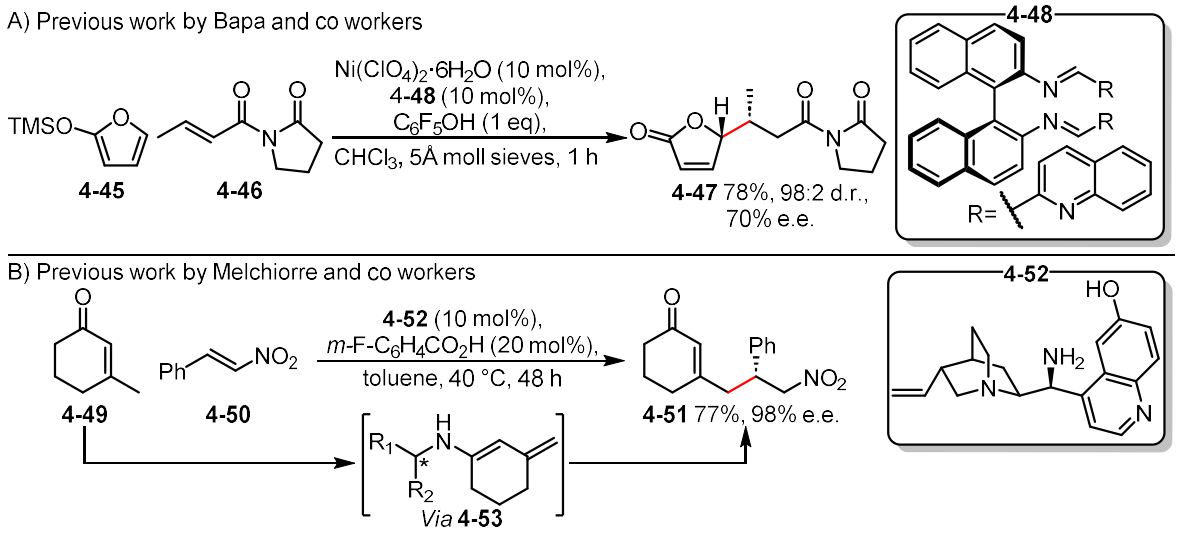
*Scheme 4-8) (A) Vinylogous Mukaiyama Michael reaction of acyclic dienyl silyl enol ethers **4-33**+**4-37** were designed by Schneider. They found that the d.r. of the starting material **4-37** is communicated into the product.*[163] *(B) Rigid iminium cation **4-39** allows controlled enantioselective addition to the enal in the C4-position.*

Schneider later developed a cleavable mesityl analogue **4-40**, which was found to alkylate with high enantioselectivity but modest regioselectivity in some cases, such as **4-42**/**4-42'** (95% e.e., 1:2 α:γ-selectivity, Scheme 4-9 A).[169] The modest α:γ selectivity during the Michael addition and the silyl enol ether **4-40** geometry suggests the wider bond angle between the methyl groups in the 5-membered ring results in a significantly less twisted aryl ring and hence less steric hindrance out of the plane of the molecule (Scheme 4-9 B). The twisted amide could be cleaved to form an ester **4-46** with NaOMe or an aldehyde **4-47** with DIBAL-H (Scheme 4-9 C).



*Scheme 4-9) (A) Schneider developed 2,4-Me$_2$-pyrrole as a cleavable Mesityl analogue. Alkylation is achieved with α-alkylation **4-42'** as a side product.[169] (B) Alkene geometry and Mukaiyama Michael reaction selectivity suggests the pyrrole sits more in the plan of the alkene. (C) Using the pyrolle group allows the group to be cleaved to form either an ester **4-44** or aldehyde **4-45**.*

Selective γ-alkylation of extended enolates has been a longstanding challenge within the literature. Bapa and co-workers found the silyloxyfuran **4-45** reacts selectively in the γ-position (Scheme 4-10 A).[170,171] The dicarbonyl electrophile **4-46** was activated by a chiral nickel complex **4-48** giving the ester **4-47** in 78% yield and 70% e.e. In contrast to Schneider, Melchiorre and co-workers' approach used amine catalysis **4-52** to activate the nucleophile instead of the electrophile (Scheme 4-10 B).[172] The condensation of the enone **4-49** forms the extended enamine **4-53** selectively, which then reacts through the γ-position to form the product **4-51** in 77% yield and 96% e.e.

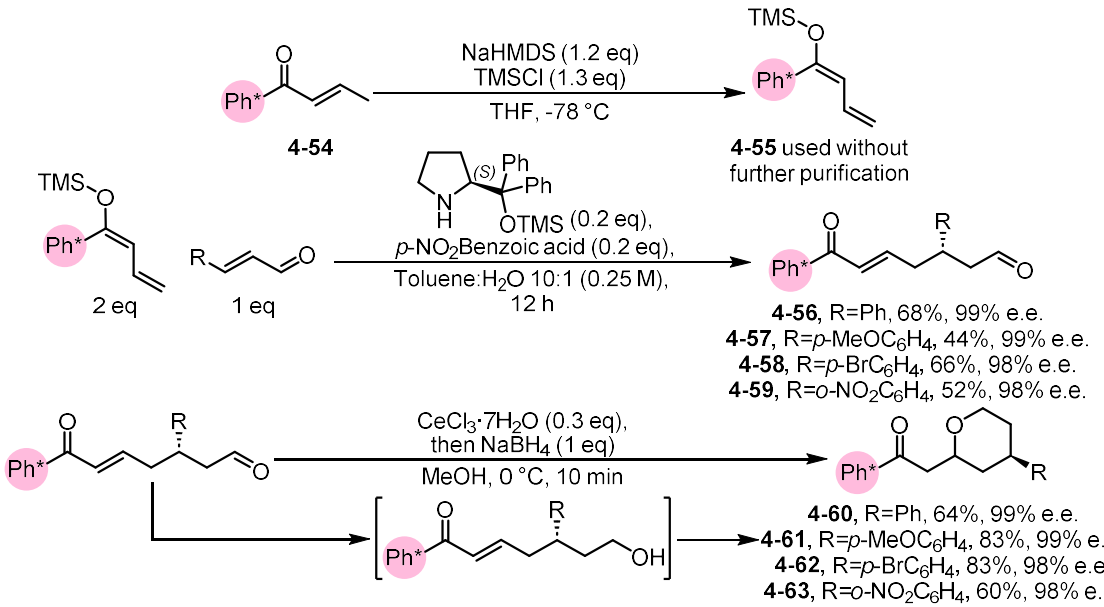


*Scheme 4-10) (A) Bapa and co-workers achieved regioselective γ-alkylation using Ni catalysis **4-48**.[170] (B) Melchiorre and co-workers achieved γ-alkylation using Cinchona alkaloid catalysis **4-52** to activate cyclohexenone **4-49**.[172]*

4.1.4. Initial Research by Teodor Răzvan Mirescu.

Within the group, TRM initiated work on this project. The extended silyl enol ether **4-55** was synthesised by trapping the extended enolate with TMSCl (Scheme 4-11). Due to the perceived instability of the product, the silyl enol ether was used without further purification. The Mukaiyama-Michael addition was performed on four cinnamaldehydes derivatives. The products **4-56-4-59** were isolated in 44%-68% yield with exclusive γ-alkylation in all cases. HPLC analysis could not separate the enantiomers for analysis; this was believed to be due to the substrate and isopropanol forming acetals and hemiacetals during separation.

Luche reduction conditions, designed to reduce enones in a 1,2-manner, gave the 2,4-substituted THP rings **4-60-4-63** in 60-83% yield (Scheme 4-11).[173] The reduction required careful monitoring to avoid the reduction of the enone; hence, the yield was found to be highly capricious. HPLC analysis allowed the e.e. of the THP rings and hence the aldehyde to be determined.



Scheme 4-11) Mukaiyama-Michael addition to functionalised cinnamaldehydes. Luche reduction of the aldehydes led to the desired THP products and allowed for determination of the product e.e. Racemat synthesised using piperidine as the 2° amine catalyst.

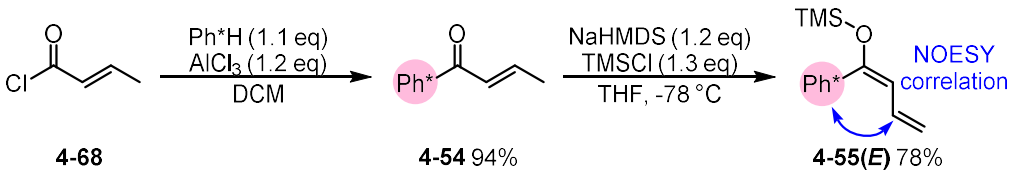
4.1.5. Initial Aims.

Building upon this work, our initial goal was to test and improve the reactions of silyl enol ether **4-55**. Once a small library of C4-substituted THP rings have been synthesised, we planned to subject them to 1,5-hydride transfer conditions to form the desired enantioenriched cyclohexene (see Section 4.2.2). After this, we aimed to functionalise the aldehyde (see Section 4.8).

Next, the objective was to introduce additional substituents in the Mukaiyama-Michael addition starting materials or by derivatising the products (see Section 4.7). This should give us access to a variety of tri-substituted THP products which can then be tested in the 1,5-hydride transfers (see Section 4.9).

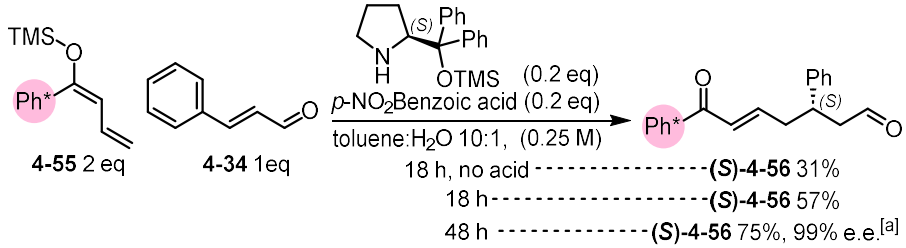
4.2. Reoptimisation of the Cyclohexene Reaction Sequence.

In order to synthesise the extended silyl enol ether **4-55(*E*)**, the acid chloride **4-68** was subjected to Friedel-Craft alkylation to give the enone **4-54** in 94% yield (Scheme 4-12). The silyl enol ether **4-55(*E*)** was then formed using NaHMDS. The silyl enol ether **4-55** was found to decomposed upon dry loading if it was not thoroughly dried. Once dried, purification by FCC (pentane) gave the pure product as a pale-yellow solid in 78% yield as a single isomer. The selectivity is driven by the low 1,3-steric clash with the Ph* in the plane of paper as observed in forming silyl enol ethers previously (See Section 2.7.3).



*Scheme 4-12) Silyl enol ether **4-55** was synthesised in 73% yield over two-steps as a single isomer.*

The Mukaiyama-Michael reaction was first tested using cinnamaldehyde (**4-34**). After 12 h, approximately 85% conversion of the aldehyde was observed by ^{1}H-NMR, with the product being isolated in 57% yield. Full consumption of the aldehyde was observed after 48 h and the product **(*S*)-4-56** was isolated in 75% yield (Scheme 4-13). The e.e. was determined *via* chiral HPLC analysis of the subsequent cyclohexene **4-67**, *vide infra*. Roland Armstrong provided the required racemic sample.[16]a



Scheme 4-13) Mukaiyama-Michael addition gave exclusive γ-alkylation over 48 h. [a] e.e. determined based on the subsequent cyclohexene product.

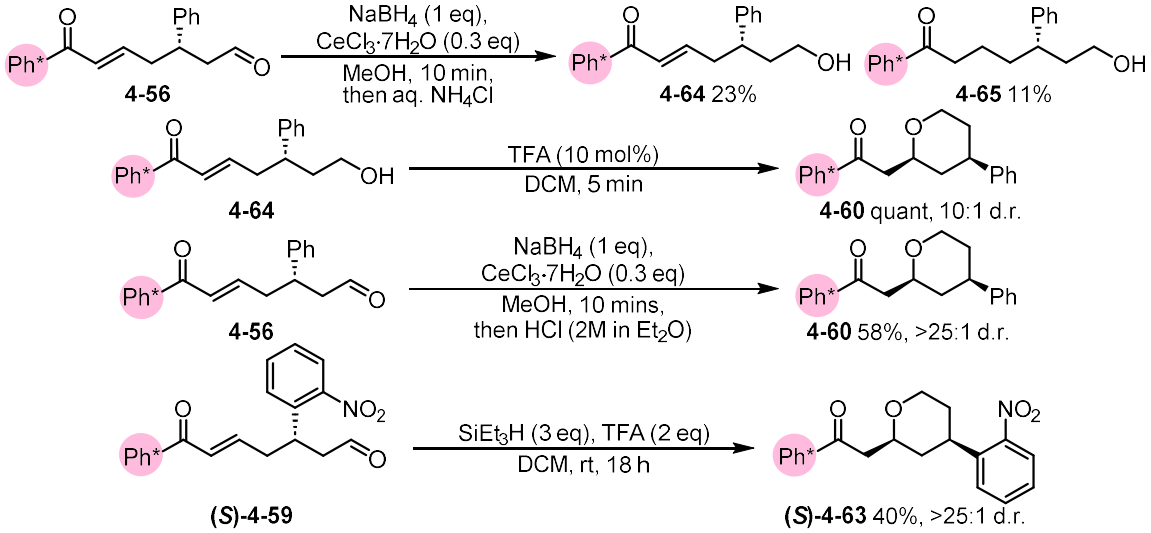
4.2.1. Selective Reductive Cyclisation.

With the aldehyde successfully synthesised, the Luche-type reduction was explored (Scheme 4-14). TRM's previous work did not discuss the conversion of the alcohol **4-64** intermediate to the THP **4-60**, implying the substrate rapidly cyclised during the work-up. However, in our hands, the reduction of the aldehyde **4-56** resulted in the formation of the alcohols **4-64**+**4-65** with only modest cyclisation of the enone observed during the quench, work-up and FCC. Pure alcohol **4-56** cyclised cleanly using TFA to give the desired THP **4-60**.[b] Under the same conditions, the crude material was found to undergo irreproducible partial cyclisation.

Several aqueous acids were screened to promote cyclisation during the quench, but they were found to result in irreproducible partial cyclisation due to the rapid precipitation of the products. Using HCl (2 M in Et_2O) resulted in no precipitation and gave clean conversion of the alcohol to the desired THP **4-60** in 58% yield. It was hoped that *in situ* cyclisation under acidic conditions would prevent over reduction. Silane reduction was observed to generate the THP

[a] The racemic substrate **4-67-rac** was synthesised via the aforementioned Ir-oxidative hydride transfer strategy.[16]
[b] Dropwise addition of DCM was used to solubilise the starting material

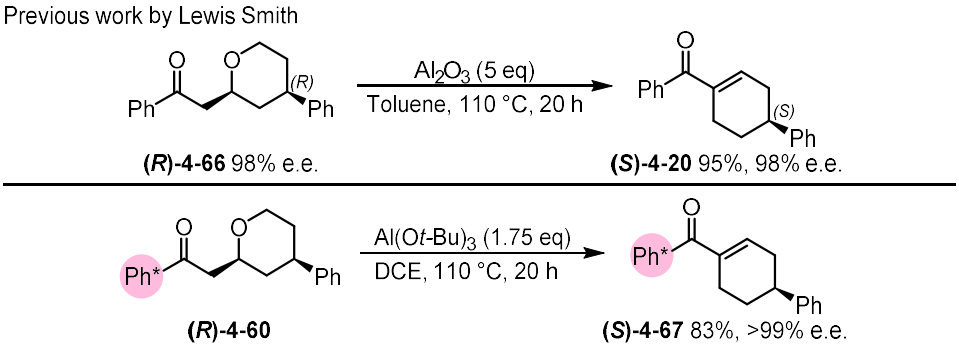
(*S*)-4-63 *in situ* in 40% yield without over-reduction being observed. However, the lower yield and reaction rate meant this was not pursued further.[174]



*Scheme 4-14) $NaBH_4$ reduction resulted in a mixture of alcohols **4-64** and **4-65**. The clean alcohol **4-64** could be rapidly closed using acid. HCl in Et_2O was an effective and clean reagent to quench the $NaBH_4$ and close the ring.*

4.2.2. 1,5-Hydride Transfer of the C4-Substituted Pyran.

Previously reported work showed that both Al(O*t*-Bu)$_3$ and Al_2O_3 give similar yields of cyclohexenes in both toluene and DCE. For the small scale of the reactions proposed, 1.75 eq of Al(O*t*-Bu)$_3$ in DCE was determined to be the most synthetically practical (Scheme 4-15).[30] Using these conditions, the desired cyclohexene **(*S*)-4-67** was isolated in 83% yield.

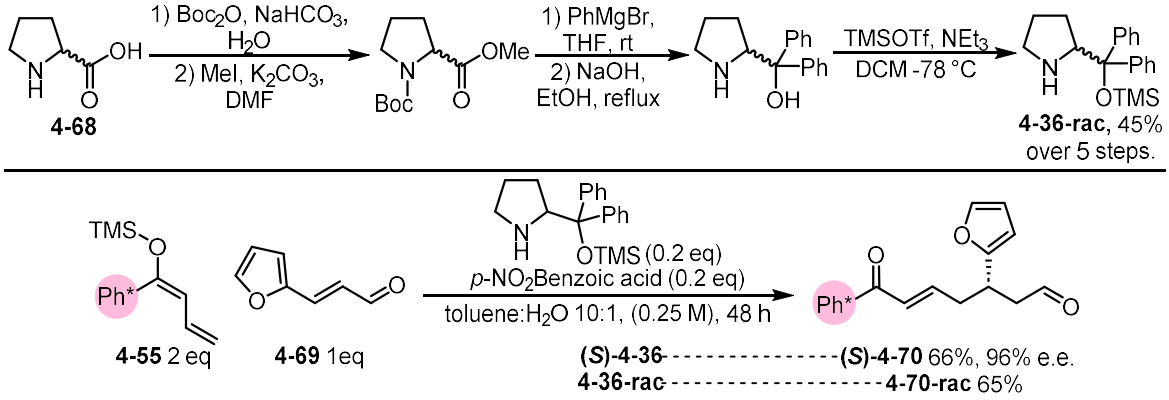


*Scheme 4-15) Cyclohexene **(S)-4-67** was cleanly synthesised by 1,5-hydride transfer.*

4.2.3. Synthesis of Racemic Aldehydes.

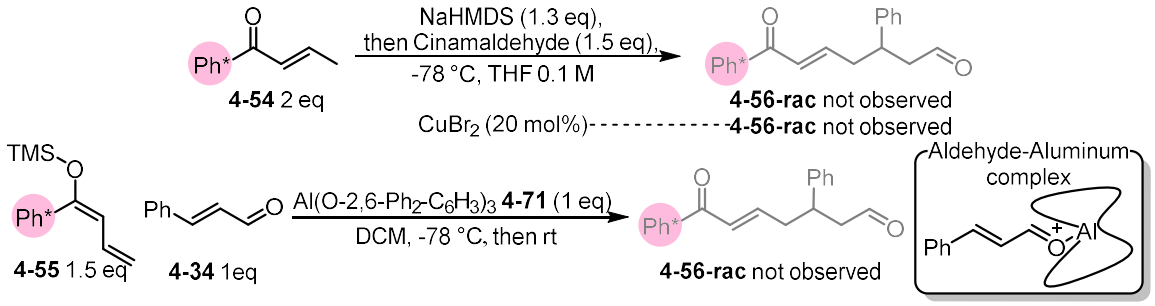
Piperidine, which had been used by TRM to synthesise the racemic substrates for HPLC analysis, was insufficient to activate *trans*-3-(2-furyl)acrolein (**4-69**), giving only a 9% yield of the dicarbonyl **4-70**. Yields below 15% were observed using a variety of readily available piperidines and solvents. Hence, Hayashi-Jørgensen catalyst (**4-36-rac**) was synthesised in 5 steps from racemic proline (**4-68**) (Scheme 4-16). The racemic substrate gave

clean conversion forming the product **(*S*)-4-70** in 65% yield. This route was used to make all subsequent racemates without further issues.



*Scheme 4-16) Synthesis of the racemic Hayashi-Jorgensen catalyst. The racemic and enantioenriched catalysts gave similar yields of the product **4-70**.*

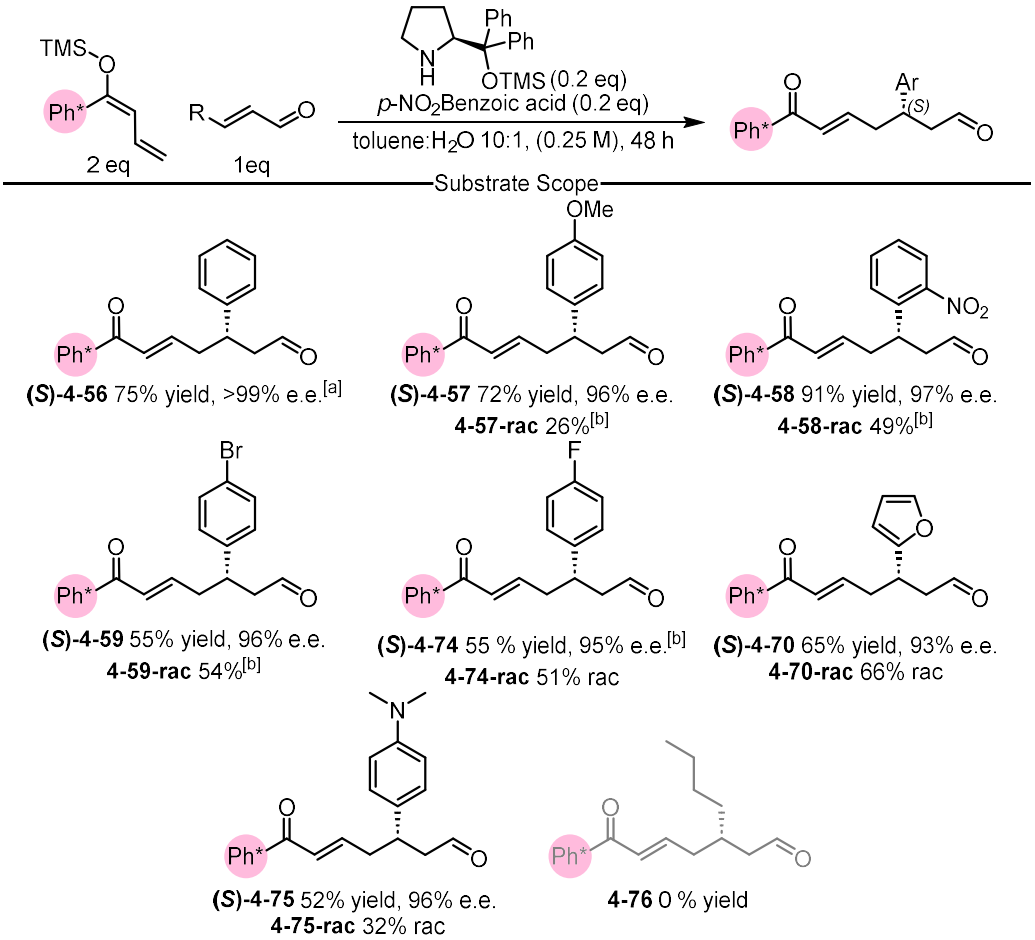
As an alternative approach, cinnamaldehyde (**4-34**) was directly added to the extended lithium enolate; however, no product was observed (Scheme 4-17). Yamato and co-workers previously developed an aluminium catalyst **4-71** to promote Mukaiyama-Michael additions with high regioselectivity. In our hands, this method could not be extended to silyl enol ether **4-55**.[175]



*Scheme 4-17) Directly using the extended enolate led to decomposition when adding cinnamaldehyde **4-34**. Yamamoto demonstrated selective 1,4-addition of aldehydes using bulky aluminium complex **4-71**.[175] The desired product was not observed using extended silyl enol ether **4-55** as a nucleophile.*

4.3. Scope of the Aldehyde Substrate in the Mukaiyama-Michael Reaction.

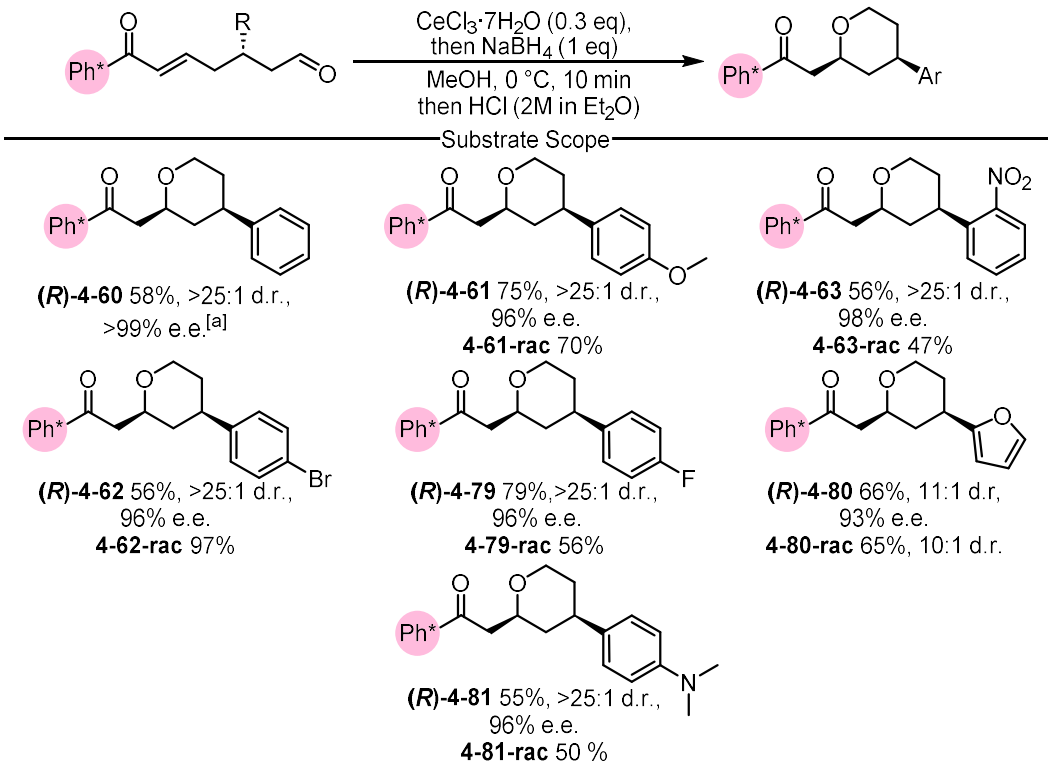
With a clear route to the enantioenriched and racemic aldehydes, various aldehydes were subjected to the Mukaiyama-Michael reaction (Scheme 4-18). Electron-poor substrates *o*-NO_2 **(*S*)-4-59** *p*-Br **(*S*)-4-58** and *p*-F **(*S*)-4-74** were well tolerated. Using both the furan **(*S*)-4-70** and *p*-NMe_2 **(*S*)-4-75**, small amounts of the aldehyde were recovered after 48 h. Enantioselectivity was high in all cases, as determined by HPLC analysis of the subsequent THP rings. We were disappointed to find that alkyl groups at the γ-position **4-76** could not be tolerated.



Scheme 4-18) Scope of C5-substituted 1,7-dicarbonyls. e.e., was determined by the measurement of the subsequent THP ring. [a] e.e. determined by the enantioenrichment of the subsequent cyclohexene. [b] (1.5 eq) of silyl enol ether used.

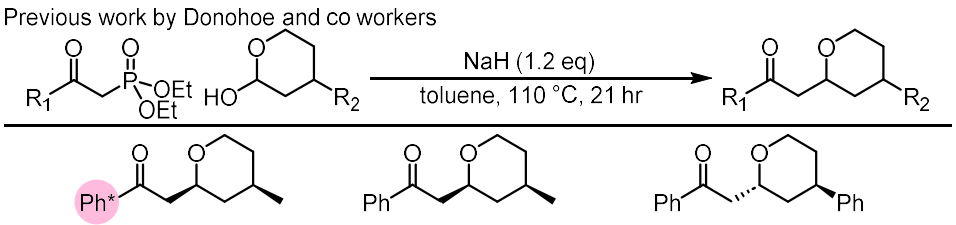
4.4. Scope of the Aldehyde Reduction.

With the aldehydes prepared, the substrates were reduced using the optimised conditions (Scheme 4-19). Yields varied between 51% and 79% yield. Ring closing gave the *cis* isomer of the THP as the major product in all cases. Stereochemistry was confirmed by *J*-coupling analysis and comparison with the previously synthesised compounds in the group. The furan **(*R*)-4-80** was the only species formed with an observable minor isomer (11:1 d.r.).



Scheme 4-19) Reduction of 1,7-dicarbonyls to form THP rings. [a] e.e. of THP ***(R)-4-60*** *determined by HPLC analysis of the subsequent cyclohexene.*

Previous work in the group used a HWE strategy to synthesise a 2,4-substituted THP ring, which gave lower diastereoselectivity when synthesising similar substrates (Scheme 4-20). The closest analogue **4-85(*trans*)** formed in 43:57 d.r. Since the C2-centre is lost during the hydride transfer, the cause of the higher selectivity was not investigated further.

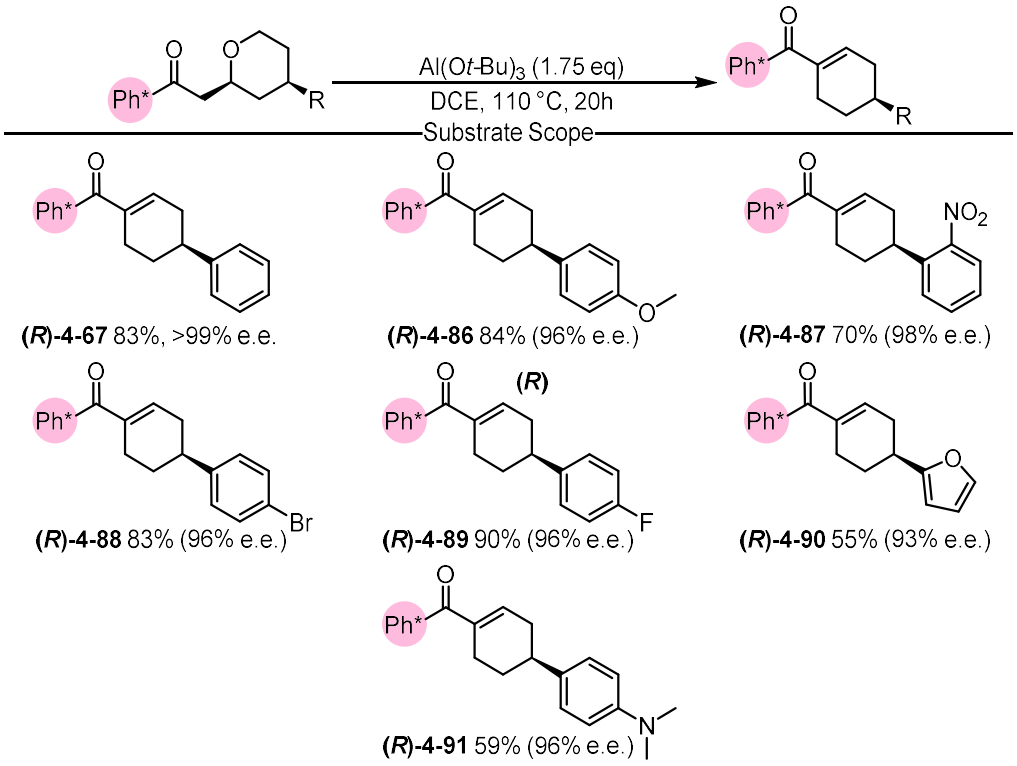


Scheme 4-20) HWE ring closing previously performed by Lewis Smith.[8]

4.5. Scope of C4-Substituted THP Rings in the 1,5-Hydride shift.

The cyclohexenes were generally synthesised in high yields of up to 95% (Scheme 4-21). As previously reported on similar compounds, the cyclohexene **(*R*)-4-67** was isolated in >99% e.e., suggesting no racemisation of the product during the 1,5-hydride transfer.[93] Only

the phenyl substrate **(*R*)-4-67** e.e. was measured directly. Retention of e.e. for other substrates was assumed by analogy.[a]



Scheme 4-21) Scope of 1,5-hydride shift reaction leading to the formation of C4-substituted cyclohexenes. (e.e. assumed to be the same as the starting material.)

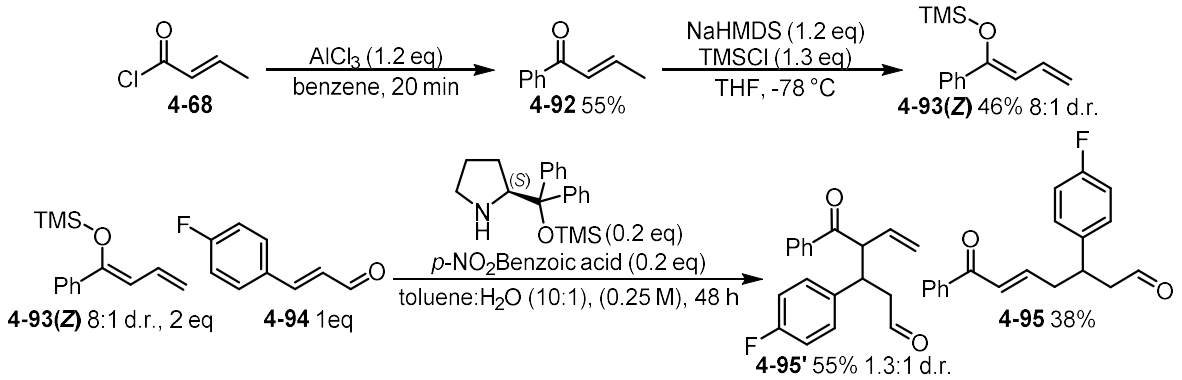
4.6. Assessing the Role of Ph* in α:γ-Regioselectivity.

In order to understand the importance of the Ph* to the Michael reactions regioselectivity, we determined to test the methodology with the phenyl analogue **4-92**.[176–178] Hence, silyl enol ether **4-93(*Z*)** was synthesised from the acid chloride **4-68** giving the product **4-93(*Z*)** in 25% yield and 8:1 d.r. over two steps (Scheme 4-22).[179]b

The Ph group has more steric hindrance in the plane of the ketone. Hence, the silyl enol ether **4-93(*Z*)** was the major isomer observed.[179] The extended silyl enol ether **4-93(*Z*)** was subjected to the organocatalysed conditions, which gave the products **4-95+4-95'** in a combined yield of 93% with poor α:γ-regioselectivity showing the Ph* motif is critical to determining regiocontrol.[c] Aleman and co-workers have previously described a similar

[a] All cyclohexene α_D values were determined to be non-zero.
[b] Alkene geometry assigned by *J*-coupling and using previously reported data.
[c] Relative and absolute stereochemistry of the products were not determined.

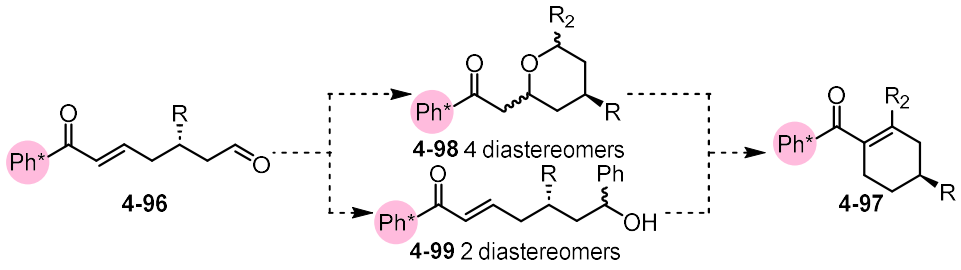
Mukaiyama-Michael reaction, using nitroalkenes as electrophiles, with high α-selectivity when using extended silyl enol ethers.[177]



Scheme 4-22) Effect of the Ph group on the regioselective addition. The absolute and relative stereochemistry of aldehydes **4-95** and **4-95'** were not determined. Silyl enol ether **4-93** was synthesised using the established route with inverted diastereoselectivity.*

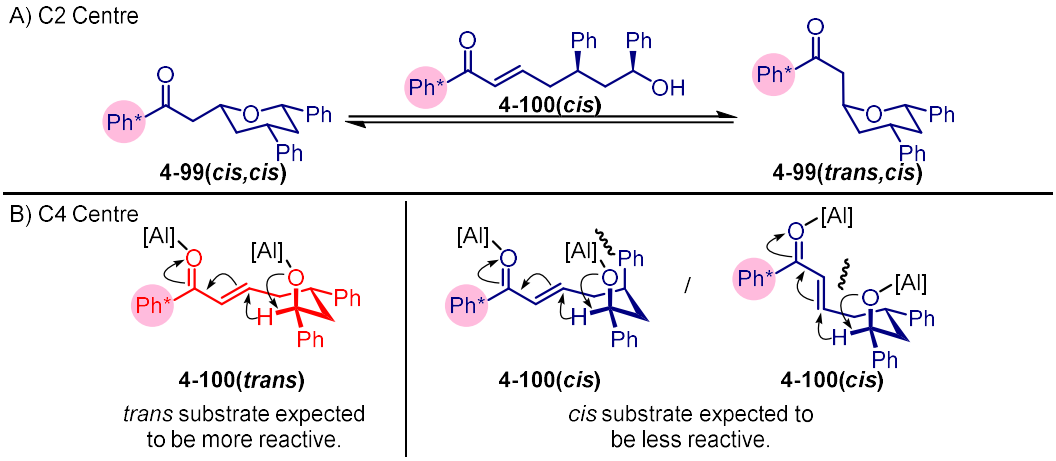
4.7. 2,4,6-Substituted THP Rings.

In order to further utilise the synthesised aldehydes **4-96**, a two-step alkylation, hydride transfer sequence was conceived (Scheme 4-23). If the strategy is successful, the four THP diastereomers **4-98** and the two alcohol diastereomers **4-99** will converge to form the tetra-substituted alkene **4-97**, negating the need to control the stereochemistry of the 1,2-addition. It was decided to first test and optimise the 1,5-hydride shift as a separate step, then optimise the alkylation, hoping to perform the sequence without purification of the intermediates.



*Scheme 4-23) Proposed alkylation of the aldehyde **4-96** is expected to form a mixture of 4 THP diastereomers **4-98**. These substrates would converge to a single cyclohexene **4-97**.*

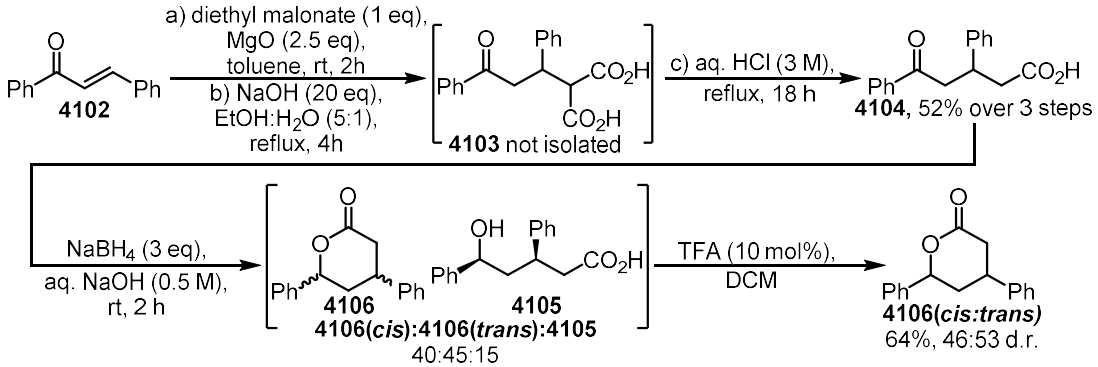
Whilst the C2-centre was expected to epimerise *in situ* (Scheme 4-24 A), the C6-centre is lost during the 1,5-hydride transfer (Scheme 4-24 B). For this reason, it was determined to synthesise and isolate the C4/C6-isomers separately, so their reactivity could be easily compared.



Scheme 4-24) (A) Reversible ring opening/closing was expected to epimerise the C2-position in situ. (B) The C6-position cannot be epimerised but is lost during the 1,5-hydride transfer. The trans substrates are expected to go via ***4-100(trans)****. The cis substrate requires groups to sit in the axial position via* ***4-100(cis)****.*

4.7.1. Synthesis of a Model 2,4,6-Substituted THP System.

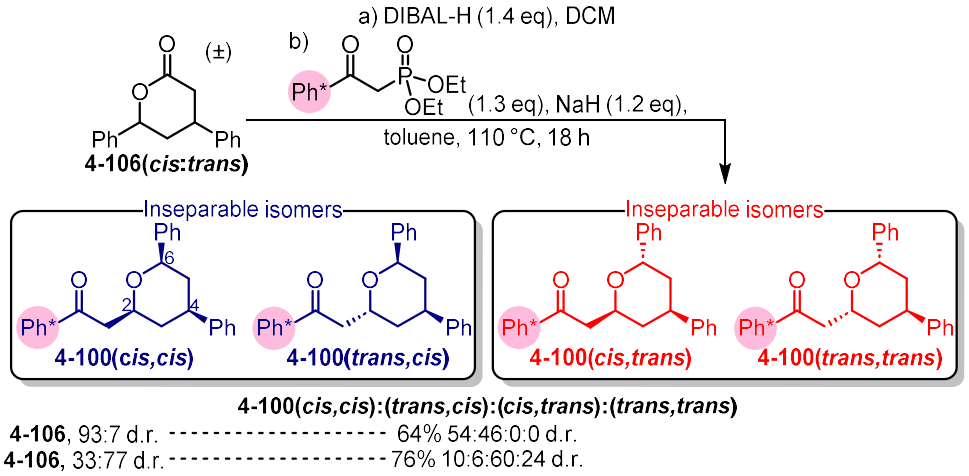
In order to access the desired THP rings on a large scale, lactone **4-106** was synthesised by the established HWE route from enone **4-102** (Scheme 4-25).[180] The ketone **4-104** was reduced to give a mixture of diastereomers. Whilst the *cis* isomer of the lactone **4-106** closed during the work-up, the *trans* isomer was initially isolated as a mixture of the ring opened product **4-105** and lactone **4-106(*trans*)**. The stereochemistry of the lactone diastereomers were determined by *J*-coupling and agreed with previous literature characterisation.[181] Crystallisation of a portion of the minor lactone isomer during FCC of the acid lactone mixture resulted in the isolation of the lactone **4-106(*cis*)** in 93:7 d.r.



Scheme 4-25) A) Synthesis of lactone ***4-106*** *from the readily available enone* ***4-102****.*

With the desired lactones in hand, the diastereomerically enriched lactones were subjected to DIBAL-H reduction followed by HWE olefination to give the THP in up to 76% yield over two steps (Scheme 4-26). FCC allowed the four diastereomers of the product **4-100** to be separated into two pairs of diastereomers. Each diastereomer could be characterised by *J*-coupling analysis, the initial d.r. of the lactone starting material and the epimerisation of the

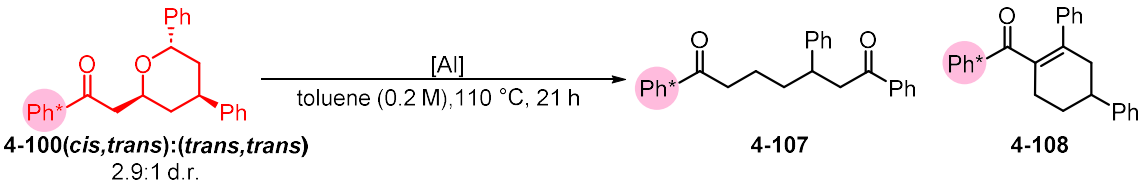
C2-centre in subsequent reactions. The two pairs were determined to be C2-epimers allowing the effect of the C4-C6 relationship to be clearly analysed.



*Scheme 4-26) HWE reaction allowed for the formation of the 4 diastereomers of the 2,4,6-substituted THP **4-100**.*

4.7.2. Optimisation of 1,5-Hydride Shifts with 2,4,6-Substituted THP Rings.

The *trans* isomers **4-100(*trans*)** (Table 4-1) and *cis* isomers **4-100(*cis*)** (Table 4-2) were both subjected to Al(O*t*-Bu)$_3$ and Al_2O_3 promoted conditions over 18 h in order to compare their relative reactivity. As predicted by the transition state model (Scheme 4-24), the *trans* isomers were found to be significantly more reactive. Al_2O_3 promoted 1,5-hydride transfer gave complete conversion of **4-100(*trans*)**, resulting in the diketone **4-107** in 91% yield (Table 4-1, Entry 2).



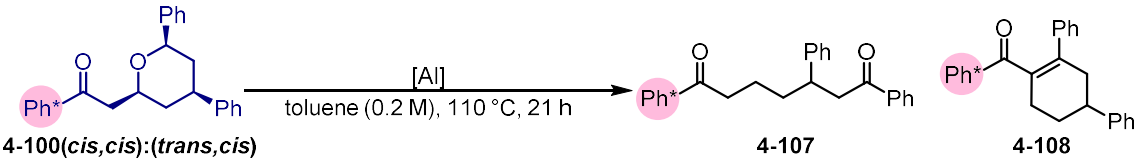
	Reagent	Temp (°C)	4-100 (%) recovered	4-100 d.r.[a]	4-107 (%)	4-108 (%)
1	Al(O*t*-Bu)$_3$ (1.75 eq)	110	25	1:1.9	70	5
2	Al_2O_3 (5eq)	110	0	-	91	9(9)

*Table 4-1) Optimisation of 1,5-hydride transfer with the cis 2,4,6-substituted THP **4-100**. Both the expected cyclohexene **4-108** and the diketone **4-107** were formed. [a] d.r. of the 2-4 relationship, no epimerisation of the 4-6 relationship was observed. Yields were determined using quantitative ^{1}H-NMR with TMB as an internal standard (isolated yield).*

With both Al(O*t*-Bu)$_3$ and Al_2O_3, only partial conversion of the THP **4-100(*cis*)** was observed over 18 h (13% and 64% conversion, respectively) (Table 4-2). With Al_2O_3, full epimerisation of the C2-centre was observed in the THP **4-100**. However, with Al(O*t*-Bu)$_3$, THP **4-100** was

recovered with a 2.8:1 d.r., which strongly suggests that THP ring opening is rate limiting when promoted by Al(O*t*-Bu)$_3$.[a]

Increasing the reaction temperature to 130 °C and changing the solvent to xylene successfully drove the reaction to completion, giving the diketone in 93% yield (Entry 3). Hoping to drive the condensation step, Na_2SO_4 was added as a desiccant, but this did not improve the reaction (Entry 4). Using Al(O*t*-Bu)$_3$ dramatically improved condensation, demonstrating that the aluminium complex facilitates the 1,5-hydride transfer and the subsequent condensation (Entry 5).[b]



4-100(*cis,cis*):(*trans,cis*) 1.2:1 d.r. **4-107** **4-108**

	Reagent	Temp (°C)	4-100 (%) Recovered	4-100 d.r.[a]	4-107 (%)	4-108 (%)
1	Al(O*t*-Bu)$_3$ (1.75 eq)	110	87	2.8:1	13	trace
2	Al_2O_3 (5eq)	110	36(34)	>25:1	60(54)	4
3	Al_2O_3 (5eq)[b]	130	0	-	93	7
4	Al_2O_3 (5eq)[b,c]	130	0	-	100	trace
5	Al(O*t*-Bu)$_3$ (3 eq)[b]	130	0	-	6	94(77)

*Table 4-2) Optimisation of 1,5-hydride transfer with the cis 2,4,6-substituted THP **4-100**. Both the expected cyclohexene **4-108** and the diketone **4-107** were formed. [a] d.r. of the 2-4 relationship, no epimerisation of the 4-6 relationship was observed. [b] Xylene is used as a solvent. [c] Na_2SO_4 25mg added. Yields were determined using quantitative ^{1}H-NMR with TMB as an internal standard (isolated yield).*

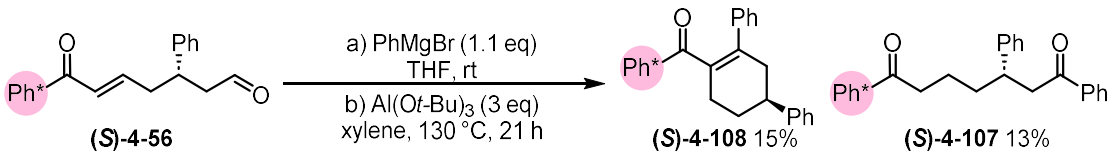
4.8. 1,2-Addition to Aldehydes.

Having developed more forcing conditions, that result in the less reactive *cis* substrates forming the desired cyclohexene, we could now look at 1,2-addition into the aldehyde.

4.8.1. Organometallic Addition.

Using aldehyde **(*S*)-4-56** as a model substrate, a variety of Grignard and organo-lithium species were screened as well as work-up and isolation procedures for the THP intermediates. The highest combined yield achieved was 28% over 2 steps by using PhMgBr (1.1 eq) and performing a solvent swap between the steps without work-up (Scheme 4-27). Unlike the purified starting material shown previously, complete cyclisation of the diketone **4-107** was not observed.

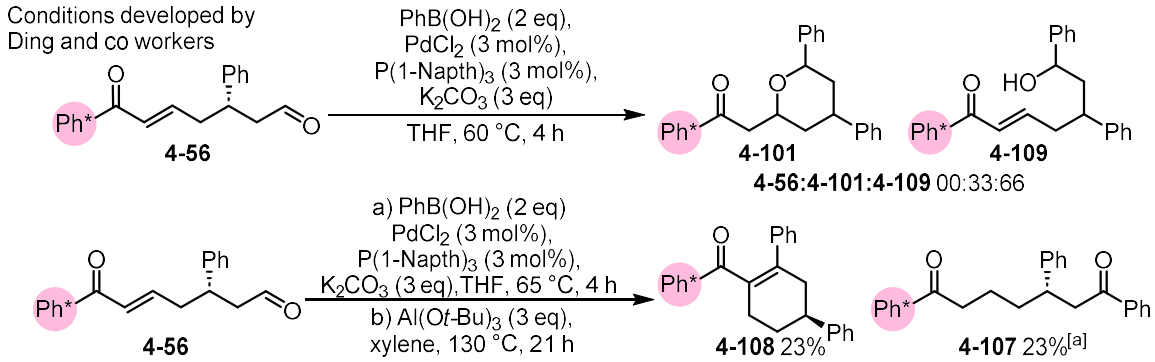
[a] RDS and other mechanistic details are discussed in Appendix 7.1.
[b] The isolation of diketone **4-107** without a subsequent condensation reaction led to exploring catalytic aluminium alkoxide loadings (See Chapter 5).



*Scheme 4-27) Cyclohexene **(S)-4-108** and diketone **(S)-4-107** were only formed in modest yield over two-steps. 0.1 mmol scale.*

4.8.2. 1,2-Addition of Boronic Acids.

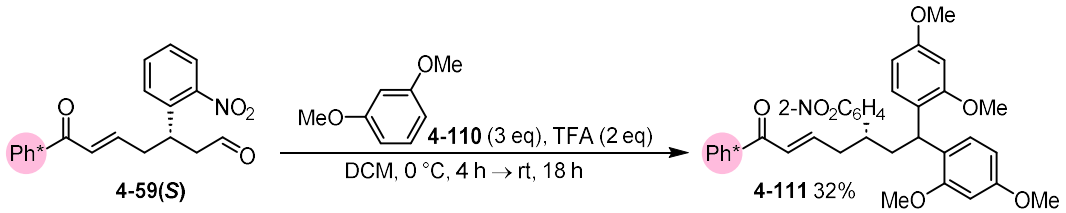
Optimisation of boronic acid coupling conditions allowed for the complete conversion of the starting material **4-56** using 2 eq of phenylboronic acid.[182–184] Whilst the THP **4-107** could not be cleanly isolated, subjecting the crude material to the 1,5-hydride transfer allowed the cyclohexene **4-108** to be isolated in 23% yield (Scheme 4-28). Diketone **4-107** was observed but could not be separated from an unknown impurity.



*Scheme 4-28) Literature conditions developed by Ding and co-workers[183] and Hu and co-workers[182] [a] A single unknown impurity could not be separated from the diketone. Yield of **4-107** is based on the 1:1 ratio of the two products in the crude.*

4.8.3. Friedel Craft Hydroxyalkylation.

It was hoped using a Friedel Craft hydroxy-alkylation method would prevent 1,4-addition into the enone. When using 1,3-dimethoxy benzene **4-110** as a nucleophile, no reactivity was observed at 0 °C. Upon warming the reaction to rt, a single product was observed to form by TLC over 18 h. The product was determined to be the tetra-aryl species **4-111**, formed in 32% yield (Scheme 4-29).

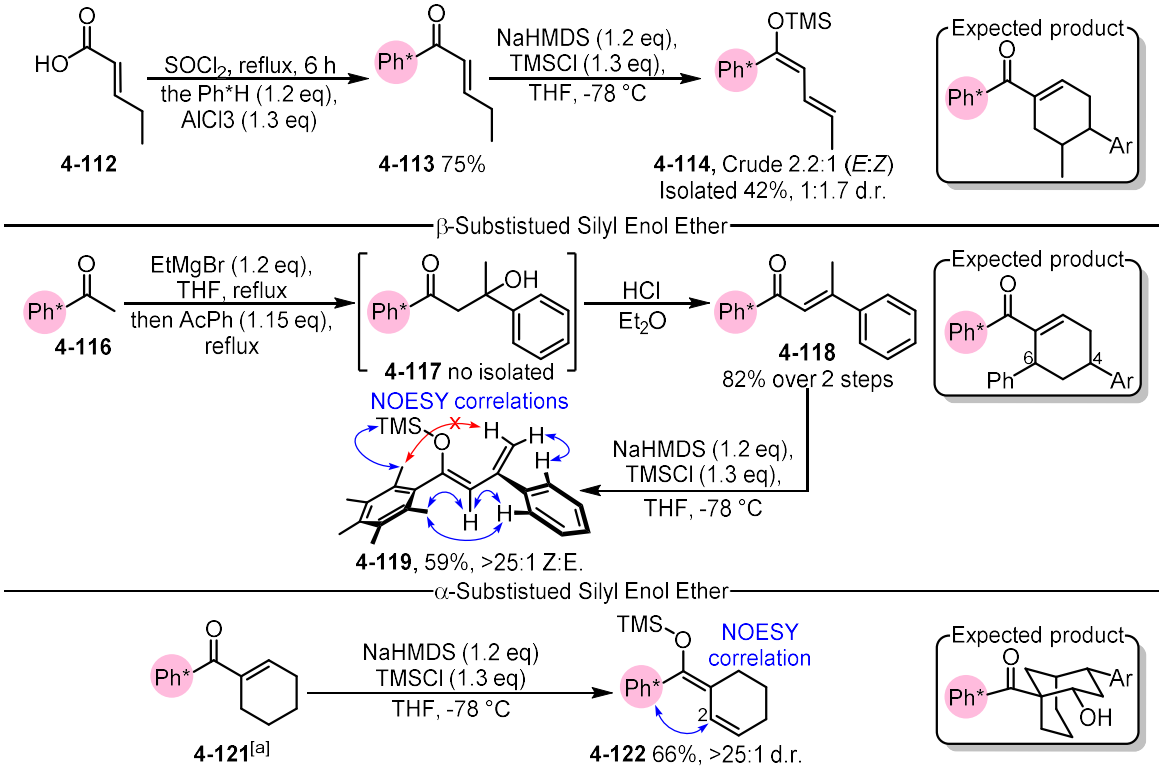


Scheme 4-29) Friedel-Craft bis-alkylation of the aldehyde **4-59**.

Having assessed numerous unsuccessful strategies to access enantioenriched 2,4,6-substituted THP rings from the 1,7-dicarbonyl, our focus moved to introducing further substitution *via* the Mukaiyama-Michael reaction.

4.9. Screening the Tolerance of Branched Substrates in the Mukaiyama-Michael Reaction.

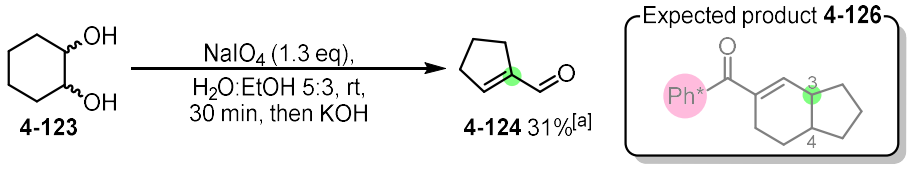
Schneider and co-workers had previously shown that both mesityl **4-37**[163] and pyrrole **4-40**[169] silyl enol ethers could tolerate a γ-Me group in the Mukaiyama-Michael reaction (Scheme 4-8). Therefore, α, β and γ-substituted silyl enol ethers **4-114**+**4-117**+**4-120** were synthesised as test substrates for the Michael addition (Scheme 4-30). γ-Substituted **4-114** was found to favour the *E*-isomer during the silylation reaction; however, the *Z*-isomer was found to be more stable during purification, resulting in the ratio appeared to invert upon FCC. The C1-alkene geometry of β-substituted silyl enol ether **4-118** was found to form exclusively as the *Z*-isomer based on the NOESY correlations. α-substituted silyl enol ether **4-120** was isolated as a single isomer with the stereochemistry determined by NOESY corelation.[a]



Scheme 4-30) Various silyl enol ethers were synthesised to probe the tolerance of the Mukaiyama Michael reaction. [a] Supplied by Roland Armstrong.

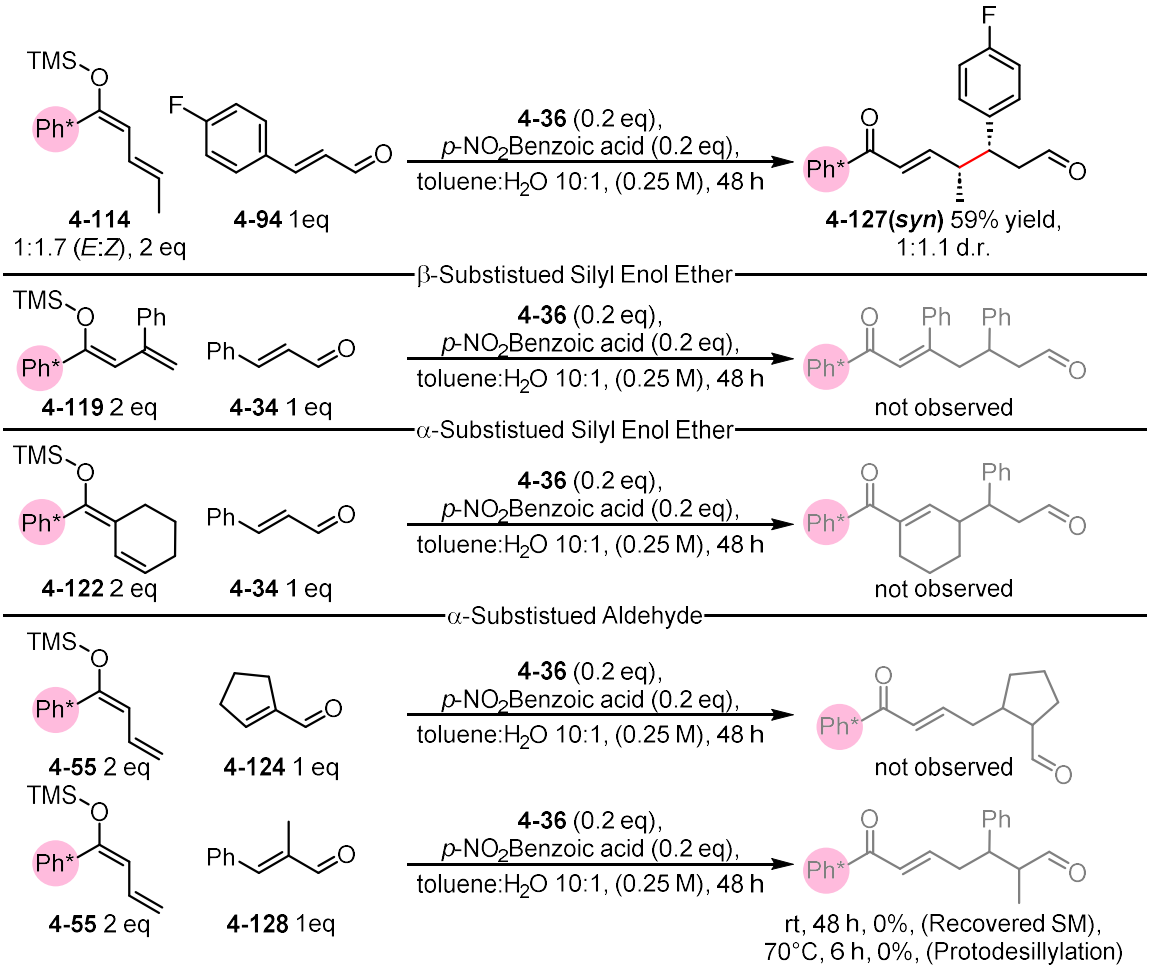
The cyclic substrate **4-124** is a privileged enal that can undergo 2° amine-catalysed Michael reactions despite containing an α-substituent (Scheme 4-31).[185–188] Hence, aldehyde **4-124** was synthesised to explore the possible synthesis of bicyclic substrates such as **4-126**.[189]

[a] α-Subsituents were not tolerated in previous 1,5-hydride transfer research by Teddy Smith.[296]



*Scheme 4-31) Synthesis of cyclopentene **4-124**, towards the synthesis of bicyclic cyclohexenes such as **4-126**. [a] 8% w/ pentane used without further purification.*

Next, the addition of these silyl enol ethers to an aldehyde under Mukaiyama-Michael conditions was examined; the product **4-127** was isolated in 59% yield and 1:1.1 d.r. (Scheme 4-32).[a] However, we were disappointed to find that all the other substrates were unreactive under these conditions, and the starting materials was recovered with modest decomposition after 48 h. When silyl enol ether **4-55** and aldehyde **4-128** were heated to 70 °C, the silyl enol ether decomposed rapidly without any product being observed. Therefore, we focussed our efforts on the chemistry of 4,5-substituted dicarbonyl **4-127(*syn*)**.



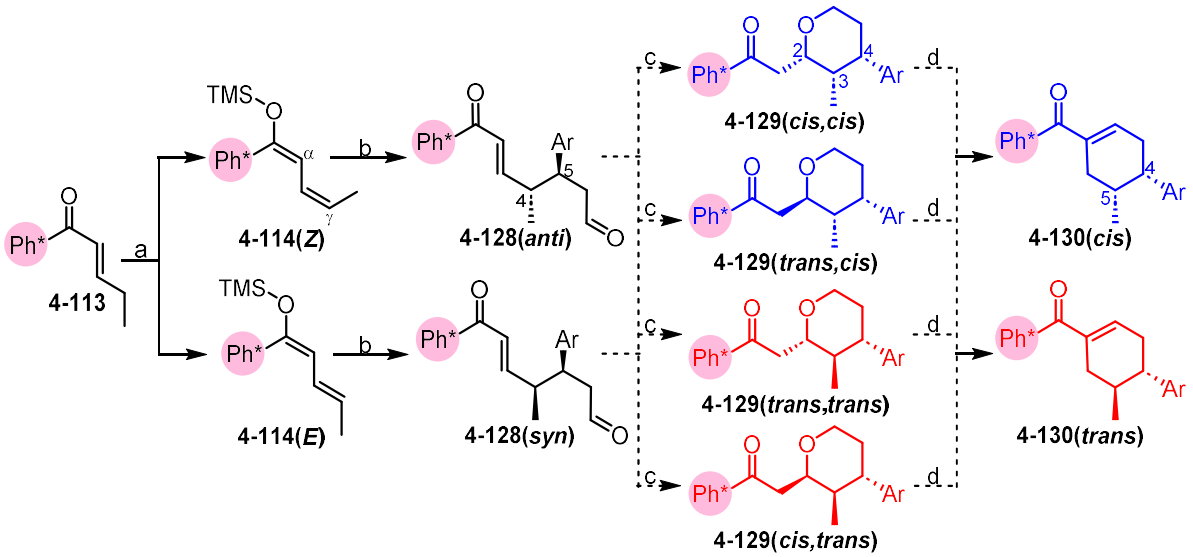
*Scheme 4-32) Only γ-substitution of the silyl enol ether **4-114** could be tolerated in the Mukaiyama Michael reaction.*

[a] Determination of absolute and relative stereochemistry of aldehyde **4-127** is discussed in section 4.12.

4.10. Considering Stereochemistry in 4,5-Substituted Cyclohexenes Synthesis.

Having established that the γ-methyl group can be tolerated in the Mukaiyama-Michael reaction, we considered how stereochemistry is communicated through the proposed reaction sequence (Scheme 4-33). The above work and Schneider's work (Scheme 4-8) strongly suggest that the C5-position of aldehyde **4-128** can be set enantioselectively by the amine catalyst **4-36** and then carried through to the cyclohexene **4-130** without difficulty. Schneider's work also demonstrated that the alkene geometry of silyl enol ether **4-114** determines the diastereoselectivity of the aldehyde **4-128** formation, with the *Z*-isomer selectively forming the anti-isomer of the aldehyde **4-128**.[163]

Hence, in order to achieve the overall aim of selectively synthesising the two cyclohexene diastereomers **4-130**, we needed to: (i) synthesise stereochemically pure silyl enol ether **4-114** (Step a), (ii) Test the stability of the methyl centre during the THP **4-129** ring formation (Step c) and (iii) explore how the C3-centre are communicated through the 1,5-hydride transfer reaction to form the cyclohexene **4-130** (Step d).

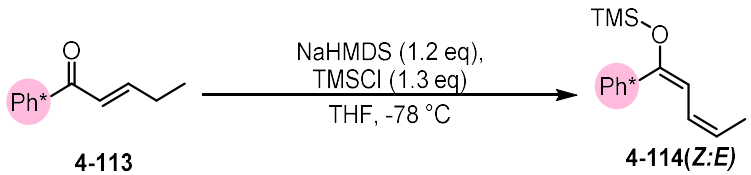


*Scheme 4-33) 4-Step sequence to form cyclohexene **4-130**. The nomenclature for the substitution patterns is used throughout the subsequent work. The THP rings are described by the cis/trans relationship of the C2 and C3-positions relative to the fixed C4 position.*

4.11. Controlling the Silyl Enol Ether Alkene Geometry.

Using Schneider's established conditions, our initial reaction gave the product **4-114** in 40% yield and 1:1.7 (*Z*:*E*) (Table 4-3, Entry 1). Due to the low polarity of the product, separation of

the isomers by FCC was not feasible.[a] Ensuring the silyl enol ether is thoroughly dried before dry loading allowed the product to be isolated without significant loss of the major isomer (Table 4-3, Entry 2). Increasing the addition time of the base and the TMSCl to 30 mins increased the selectivity to a 6.3:1 ratio (Entry 3). Inverting the order of addition reduced the selectivity significantly, giving the product in 1.7:1 ratio (Entry 4). On a 13 mmol scale, the crude material **4-114** (3.8:1 *Z*:*E*) could be recrystallised, giving the product in 31% yield and a 17:1 *Z*:*E* ratio.[92]

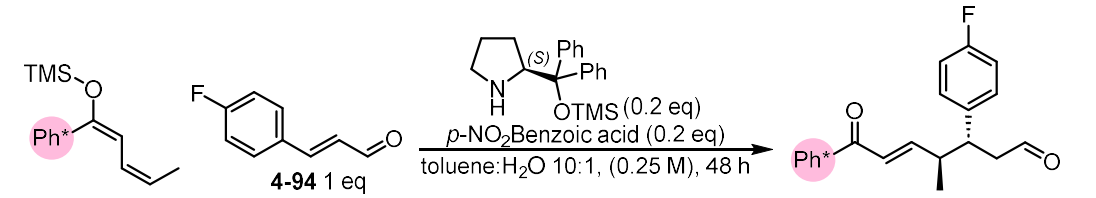


4-113 **4-114(*Z*:*E*)**

	Scale (mmol)	NaHMDS addition time (mins)	TMSCl addition time (mins)	4-114(*Z*:*E*)
1	9	5	5	2.2:1→(1:1.7)
2	8	5	5	2.4:1→(2.4:1)
3	1	30	30	6.3:1
4[a]	1	30	30	1.7:1
5	13	45	45	3.8:1→(17:1)[b]

*Table 4-3) Formation of silyl enol ether **4-114**. Crude d.r. reported (isolated d.r.). [a] Ketone added to base. [b] Purification by recrystallisation.*

Having obtained the material with high stereoselectivity, the silyl enol ether **4-114(*Z*)** was subjected to the conditions above, resulting in the isolation of the product **4-127(*anti*)** in 91% yield and 9:1 d.r. (Scheme 4-34). The aldehyde **4-127** diastereomers can be cleanly separated by FCC, allowing stereochemically pure material to be used in subsequent reactions.



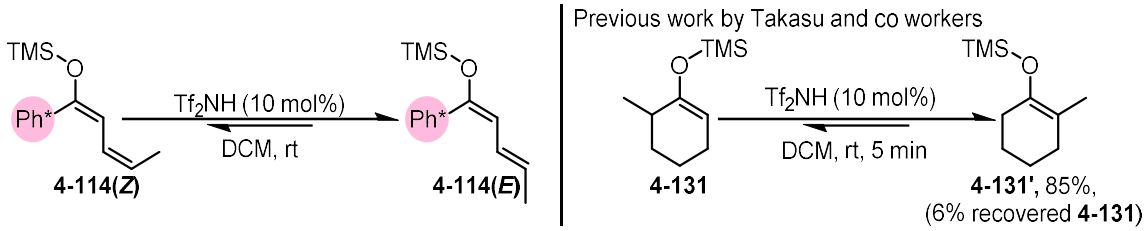
4-114(*E*) 2 eq, 1:1.7 ---------- **4-127(*syn*)** 59% yield, 1:1.1 d.r.
4-114(*Z*) 2 eq, 3.5:1 ---------- **4-127(*anti*)** 74% yield, 3.0:1 d.r.
4-114(*Z*) 2 eq, 17:1 ---------- **4-127(*anti*)** 91% yield, 9:1 d.r.
99% e.e. (92% e.e.)

*Scheme 4-34) p-F-cinnamaldehyde **4-94** reacting in the Mukaiyama-Michael reaction, diastereomers could be separated by FCC. Crude d.r. reported (e.e. of minor diastereomer). Stereochemistry was determined by analysis of the subsequent THP rings.*

It was hoped thermodynamic silylation conditions would result in the selective formation of the *E*-isomer; however, no product was observed using a variety of bases and solvents.[190,191] Takasu and co-workers previously discovered rapid equilibration of silyl enol ethers **4-131** and

[a] Rapid FCC was performed using 100% Pentane as a mobile phase and dry loaded silyl enol ether.

4-131' (Table 4-4).[192] Under these conditions, protodesilylation, instead of isomerisation, resulted in the isomeric ratio of the silyl enol ether **4-114** inverting.[193] It was subsequently found that control of the C3-centre could be performed in subsequent steps, so the synthesis of stereochemically enriched **4-114(*E*)** was not pursued further.

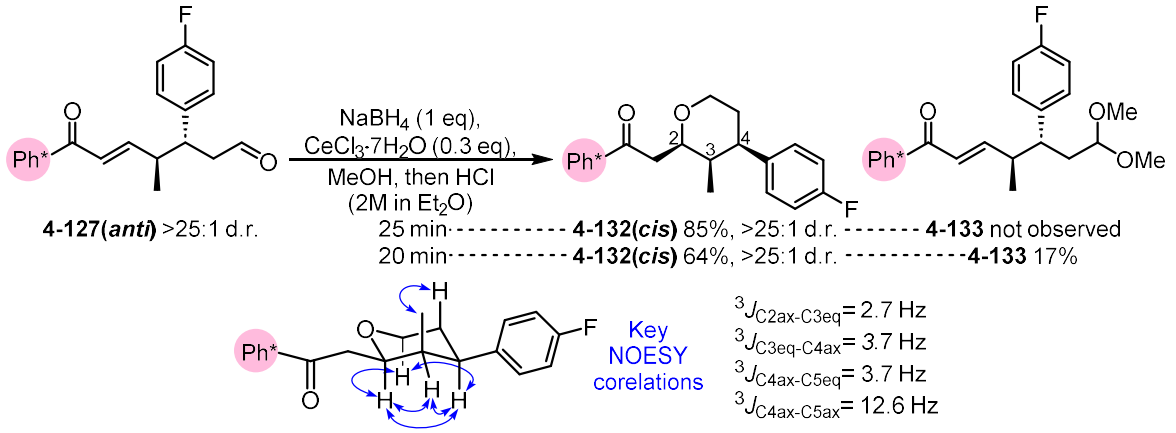


Time (min)	4-114 (%)	4-114 (*Z*:*E*)	4-113 (%)
0	100	2.4:1	-
12	37	1:2.7	63
77	32	1:2.6	68

*Table 4-4) Takasu and co-workers found that Tf_2NH promoted thermodynamic interconversion silyl enol ethers, such as **4-131**+**4-131'**. The extended silyl enol ether **4-114** was found to decompose, not isomerise, under these conditions. ^1H-NMR yields are calculated based on TMB as an internal standard.*

4.12. Formation of Tri-Substituted THP Rings.

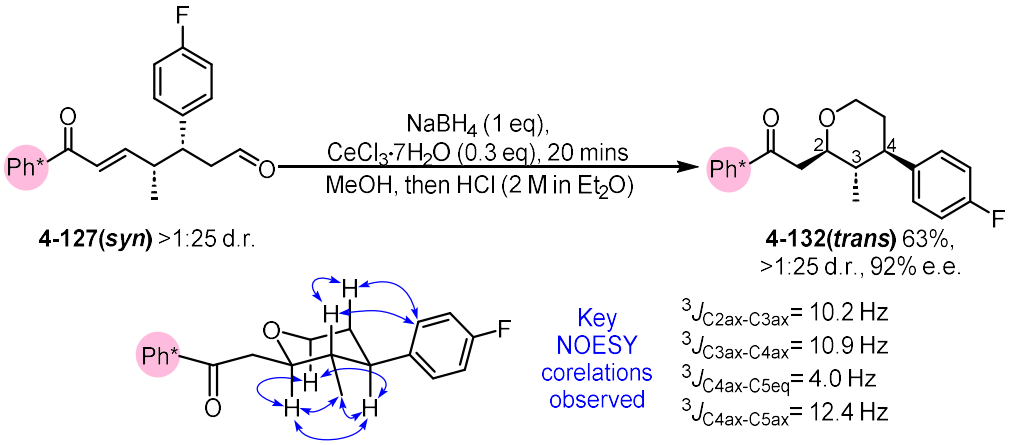
The reduction of the major aldehyde diastereomer **4-127** resulted in the clean formation of the THP **4-132** as a single diastereomer after 25 min (Scheme 4-35). *J*-couplings and NOESY couplings allowed us to determine the stereochemistry of THP **4-132(*cis*)** and the starting material. Quenching the reaction after 20 mins resulted in incomplete reduction and formation of the linear acetal **4-133** as a side product.



*Scheme 4-35) $NaBH_4$ reduction of the major aldehyde **4-127(anti)** followed by acid mediated cyclisation. The rigid structure allows for clear characterisation of the stereochemistry.*

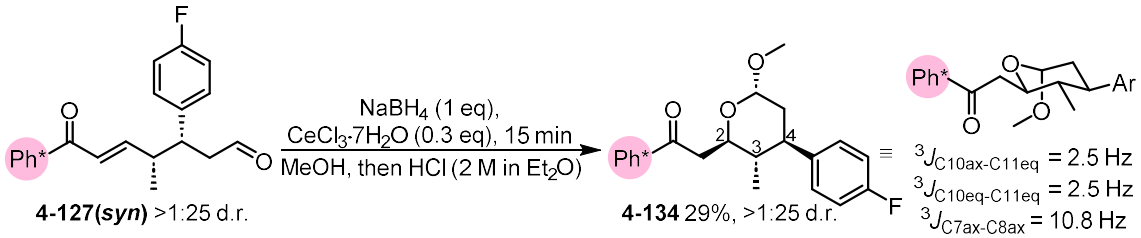
The reduction of the minor aldehyde **4-127(*syn*)** resulted in the formation of the THP **4-132(*trans*)** as a single diastereomer (Scheme 4-36). *J*-couplings and NOESY couplings suggest the THP **4-132(*trans*)** has the expected all equatorial conformation. Comparison of the ^{13}C-NMR shifts in the two diastereomers showed significant upshifts of the C5 peak

(24.5→34.5 ppm) and C3-Me peak (6.6→15.2 ppm) in the *trans* isomer consistent with previously reported conformational effects.[158]



*Scheme 4-36) $NaBH_4$ reduction of the minor aldehyde **4-127(syn)** followed by acid mediated cyclisation. The rigid structure allows for clear characterisation of the stereochemistry.*

The reduction of di-substituted aldehydes did not reliably reach completion in 20 min and resulted in acetal formation in numerous reactions. Whilst the linear acetal **4-133** could be easily separated from the desired product by FCC, cyclic acetals, such as **4-134**, were difficult or impossible to separate by FCC depending on the substituents (Scheme 4-37). The acetal **4-134** could not be cleanly separated from THP **4-132** and hence characterised when a decomposed batch of $NaBH_4$ was used in the reduction. In order to reliably get clean material, all reactions were run for 25 mins to prevent acetal contamination.[a]



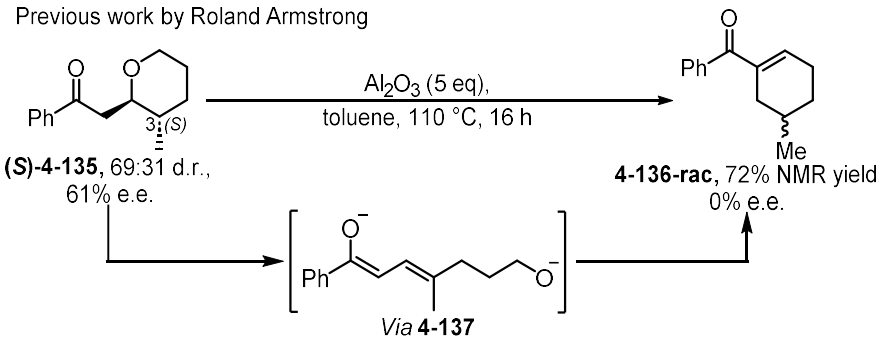
*Scheme 4-37) Cyclic acetal **4-134** was observed as a side product in numerous reductions. $NaBH_4$ was believed to have decomposed prior to addition.*

4.13. Initial 1,5-Hydride Transfer Reaction with 2,3,4-Substituted THP Rings.

Previously, D.r. R. Armstrong found that the 2,3-substituted enantioenriched THP **(*S*)-4-135** formed cyclohexene **4-136** in 72% yield as a racemic product under the previously optimised Al_2O_3 promoted conditions (Scheme 4-38).[b] It was proposed that racemisation occurred due to

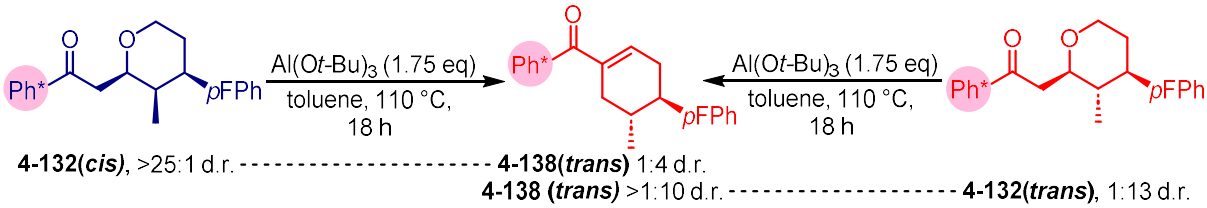
[a] Cyclic acetals were only observed when reducing the *syn* aldehyde isomers. Although this was not systematically investigated.
[b] Unpublished results by Roland Armstrong. Synthesis of the THP substrate discussed in Section 4.22.

formation of the extended enolate **4-137** before the 1,5-hydride transfer occurred. There was no attempt to optimise enantioretentive conditions for such 2,3-substituted THP rings.



*Scheme 4-38) D.r. Roland Armstrong showed that the C3-position of THP **4-135** would rapidly racemise during the Al_2O_3 mediated 1,5-hydride shift. Unpublished result.*

Hence, when each diastereomer of the THP **4-132** was subjected to Al(O*t*-Bu)$_3$ mediated transfer conditions, we were unsurprised to see epimerisation of the C3-centre, resulting in a single isomer of the cyclohexene **4-138(*trans*)** (Scheme 4-39).[a] The difference in the d.r. in the two reactions, suggests that epimerisation and 1,5-hydride transfer occur at comparable rates.



*Scheme 4-39) The C3-centre underwent stereoconvergence when cyclohexene **4-138** was synthesised from the THP epimers with Al(Ot-Bu)$_3$. Crude d.r. of cyclohexenes reported. Structures assigned by X-ray crystalography*

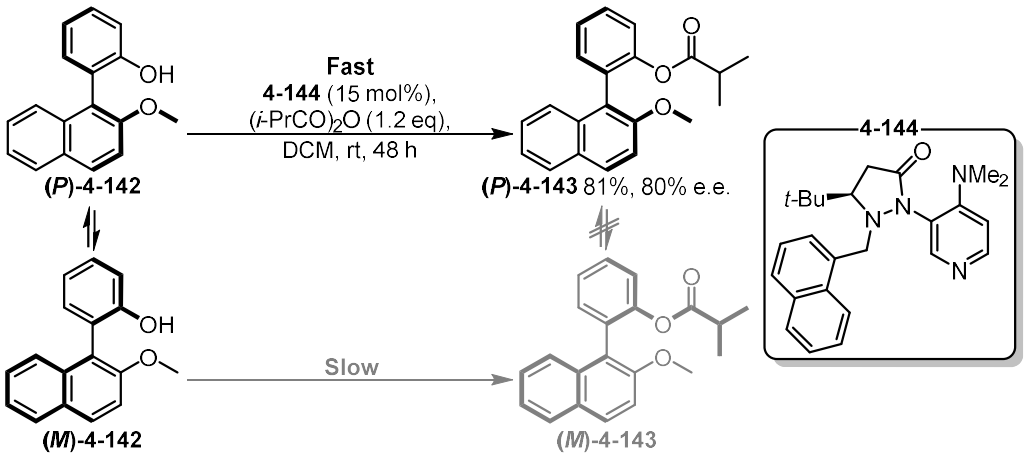
4.13.1. Mechanism of Epimerisation.

Based on these results, the two diastereomers of the THP **4-132** appear to interconvert through the extended enolate intermediate **4-146** before 1,5-hydride transfer occurs, locking the stereocentre and hence d.r. of the product in a diastereoselective dynamic kinetic resolution (DKR) (Scheme 4-41).[194,195]

This type of reaction has been described in the literature numerous times to control both the relative and absolute stereochemistry of substrates; for example, Sibi and co-workers demonstrated enantioselective esterification of phenol **4-142** to give the ester **4-143(*P*)** in 81% yield and 80% e.e. directed by the chiral DMAP analogue **4-144** (Scheme 4-40).[196] For high enantioselectivity to be achieved: the esterification must be highly selective; the

[a] The stereochemistry of cyclohexene **4-138** could not be confidently determined by ^{1}H-NMR methods. The crystal structure of **4-138** is shown in Section 4.15.

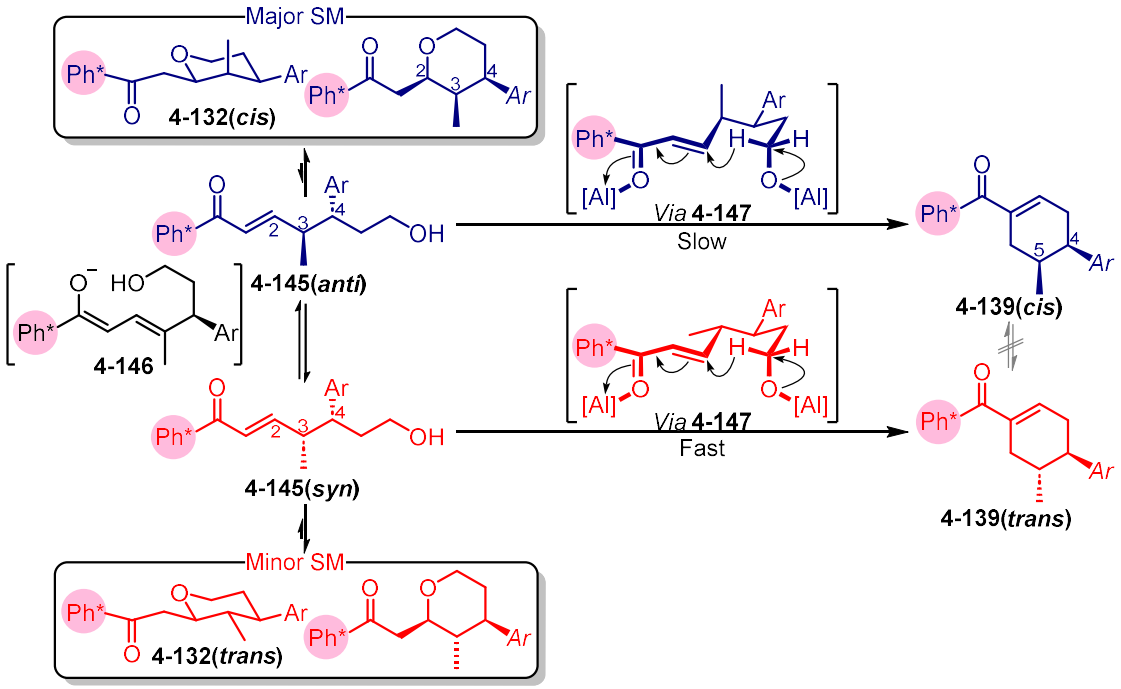
interconversion of the binol **4-142** must be faster than the disfavoured esterification; and the product **4-143(*P*)** must be stable w.r.t. to epimerisation.



*Scheme 4-40) Sibi and co-workers demonstrated a well-established DKR strategy reaction mediated by the DMAP analogue **4-144**.*[196]

In our proposed diastereoselective DKR, the mechanism is complicated because (Scheme 4-41):

- The 1,5-hydride transfer is substrate controlled, not catalyst controlled, with the *trans* isomer expected to be more reactive due to the all-equatorial conformation **4-147**.
- The equilibrium between the THP isomers **4-132** should heavily favour the *trans* isomer, which has all three groups in the equatorial position.
- Both epimerisation and 1,5-hydride transfer go *via* a shared alcohol intermediate **4-145**.

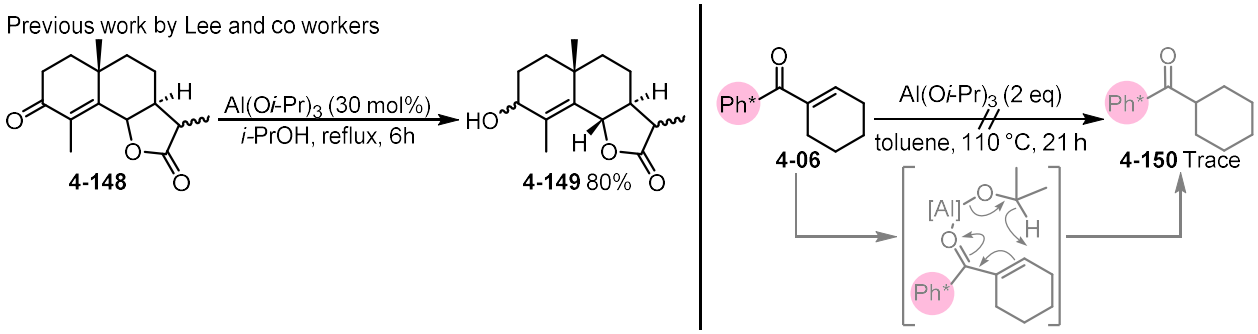


Scheme 4-41) Overview of the mechanism of interconversion during 1,5-hydride shifts. Initial results demonstrated that these processes happen with comparable rates under the previously optimised conditions.

Based on this, we decided to explore the behaviour of the stereochemically pure major THP **4-132(*cis*)**. By changing the epimerisation rate, the mechanism above suggests we could access the *trans* cyclohexene **4-139(*trans*)** by promoting epimerisation or the *cis* cyclohexene **4-139(*cis*)** by preventing epimerisation.[a]

4.13.2. Assessing the Potential for 1,4-MPV Reductions.

Generally MPV reactions with enones are known to be highly 1,2-selective (Scheme 4-42).[197–202] However, it was unclear if the properties of the Ph* ketone group would lead to intermolecular 1,4-reduction occurring.[b] When cyclohexene **4-06** was subjected to excess Al(O*i*-Pr)$_3$ over 21 h only trace cyclohexane **4-150** was observed. Hence, intermolecular transfers were disregard as a factor in the reaction profile.

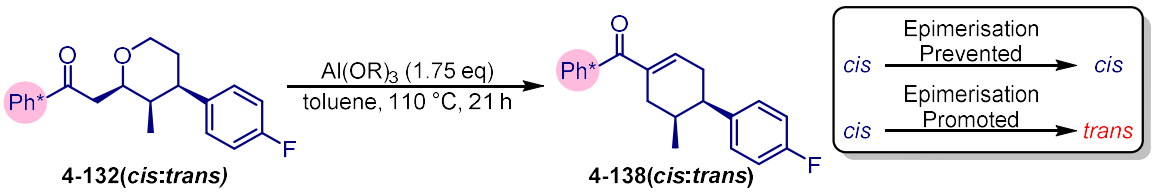


*Scheme 4-42) 1,2-Reduction of the terpene enone **4-148** was performed by Lee and co-workers Excess Al(Oi-Pr)$_3$ was chosen as a stress test for intermolecular reduction of the cyclohexenes. The stability of the product w.r.t. alcohols.*

4.14. Optimisation of 1,5-Hydride Transfer with 2,3,4-Substituted THP Rings.

Both retentive and epimerising conditions were optimised simultaneously, due to the changing d.r. of the starting material **4-132** and product **4-138** over time and variable conversion, the results was challenging to interpret (Table 4-5, Entry 1). The addition of KO*t*-Bu reduced both the epimerisation rate and conversion of the reaction (Entry 2). Pleasingly introducing phenol ligands (Entry 3-5) or HOCMe$_2$Ph (Entry 6) resulted in a high degree of stereoretention, with the phenol ligand giving the best d.r. (Entry 3) and HO-2,6-Me$_2$C$_6$H$_3$ giving better conversion (Entry 5).

[a] Computational kinetics are discussed in Section 4.23.
[b] Previously, we observed unique reactions with Ph* ketones and frustrated acid-base pairs when the rapid reduction normally observed is prevented by the *o*-methyl groups (see Section 2.7.3).

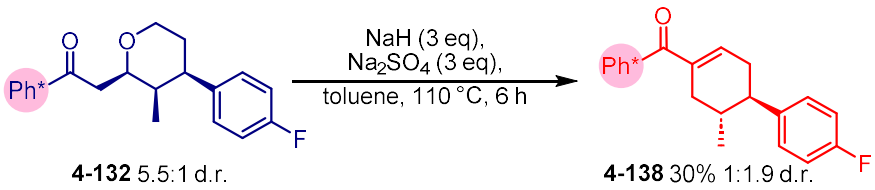


4-132(*cis*:*trans*) 4-138(*cis*:*trans*)

	R	4-132 Starting d.r.	4-132 Recovered Yield (%)	4-132 Recovered d.r.	4-138 Yield (%)	4-138 d.r.
1	*t*-Bu	5.5:1	27	1:2.0	40	1.1:1
2 [a]	*t*-Bu	5.5:1	63	1:1.0	10	1:01
3	Ph	13:1	28	13:1	40	9.0:1
4	2,6-$Me_2C_6H_3$	13:1	6	Cis[b]	63	8.0:1
5	4-$MeOC_6H_4$	13:1	60	14:1	12	Cis[b]
6	CMe_2Ph	13:1	0	—	63	6.0:1

Table 4-5) Screening of alcohol ligands. Yields are 1H -NMR yields calculated based on 1,3,5-trimethoxybenzene as an internal standard. [a] KOt-Bu 2 eq added. [b] Insufficient material to determine d.r.

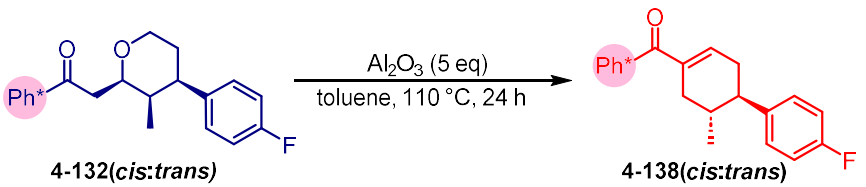
NaH has previously been used to initiate 1,5-hydride shifts. After NaH was added to the THP, the reaction was stirred for 10 mins at rt before heating (Scheme 4-43). The product was found to undergo only modest epimerisation giving the product **4-138** in 30% yield and 1:1.9 d.r. with decomposition of the remaining starting material.



4-132 5.5:1 d.r. **4-138** 30% 1:1.9 d.r.

Scheme 4-43) NaH mediated 1,5 hydride transfer resulted in modest interconversion. Yield is a 1H -NMR yield calculated based on 1,3,5-trimethoxybenzene as an internal standard.

Using Al_2O_3 to promote the reaction resulted in significant epimerisation of both the product **4-138** (1:4.0 d.r) and the recovered starting material **4-132** (1:5.8 d.r.) (Table 4-6, Entry 7). Repeating the reaction over 24 h gave the product in 64% yield but with no improvement in the d.r. (Entry 8). Reducing the temperature of the reaction to 80 °C resulted in a minimal hydride transfer being observed. However, the starting material underwent significant epimerisation to the *trans* product (Entry 9). Using the lower temperature to pre-equilibrate the starting material increased the d.r. of the product to 1:5.5 d.r and resulted in a high isolated yield (Entry 10).

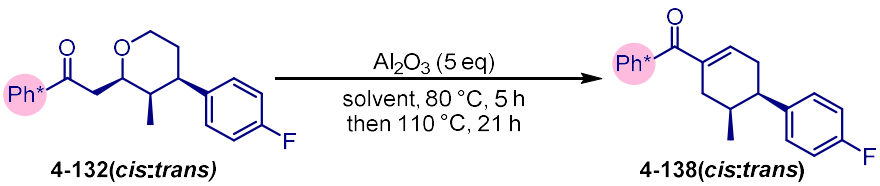


4-132(*cis*:*trans*) 4-138(*cis*:*trans*)

	Temp (°C)	4-132 Starting d.r.	4-132 Recovered Yield (%)	4-132 Recovered d.r.	4-138 Yield (%)	4-138 d.r.
7[a]	110	5.5:1	34	1:5.8	35	1:4.0
8	110	5.5:1	7	*trans*[b]	64	1:3.9
9	80	5.5:1	70	1:2.3	8	1:3.0
10	80, 5 h, then 110, 24 h	5.5:1	0	—	90(92)	1:5.5

Table 4-6) Alumina-mediated transfer conditions. [a] 21 h reaction time. [b] Major product annotated insufficient material to determine d.r. with any accuracy. (Isolated yield).

Using Al_2O_3, we next screened a variety of solvents resulting in significantly higher retention in both the starting material and product then had been observed in toluene (Table 4-7, Entry 11-13). Using Al(O*t*-Bu)$_3$ in DCE gave the desired product with a significant degree of retention (4.3:1 d.r.) and 70% isolated yield (Entry 14). Whilst solvent changes did not improve the epimerisation reaction, we hoped this would therefore improve the retention conditions. Conversion using Al(OPh)$_3$ was irreproducible; however, using 5 eq of Al(O-2,6-$Me_2C_6H_3$), which had given better conversion in our initial results (Entry 4), 99% diasterospecificity (ds) and full conversion was achieved reproducibly (Entry 15). The ligand could not be separated by FCC, washing the crude with aq. KOH removed some of the ligand but was not sufficient to purify the cyclohexene **4-138**. These results were the best retentive conditions we were able to achieve although the purification needed to be reoptimised (see Section 4.14.1).[a]



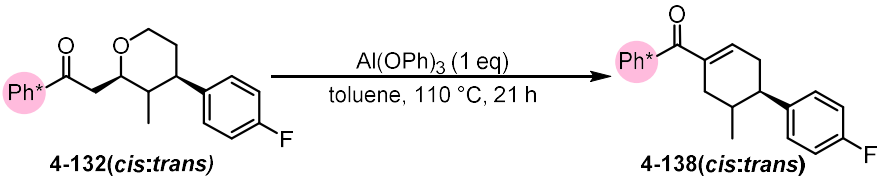
4-132(*cis*:*trans*) 4-138(*cis*:*trans*)

	R (Solv)	4-132 Starting d.r.	4-132 Recovered Yield (%)	4-132 Recovered d.r.	4-138 Yield (%)	4-138 d.r.
11	Al_2O_3 (DCE)	20:1	100	2.7:1	—	—
12	Al_2O_3 (PhCl)	20:1	91	1.7:1	8	1:1
13	Al_2O_3 (*t*-BuOH)	20:1	40	1.2:1	60	1.3:1
14[a]	Al(O*t*-Bu)$_3$ (DCE)	20:1	—	—	100 (70)	4.3:1
15[b]	Al(O2,6-MeC_6H_3)$_3$ (DCE)	4.8:1	—	—	N.d.	4.7:1

Table 4-7) Solvent screening. Conversions reported (isolated yield).[a] Al(Ot-Bu)$_3$ (1.75 eq),110 °C, 24 h. [b] Al(O2,6-$Me_2C_6H_3$)$_3$ (5 eq), 110 °C, 24 h.

[a] Separation of the ligand is discussed in Section 4.14.1.

Subjecting both the *cis* and *trans* isomer to $Al(OPh)_3$ mediated transfer resulted in the product being isolated with retention (Table 4-8, Entry 16+17). This demonstrates that the phenol ligand gave the desired retention by preventing the epimerisation, as predicted by the initial model.

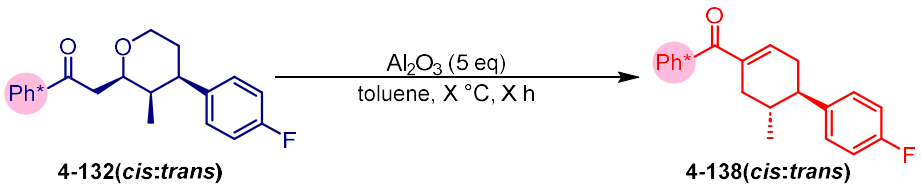


4-132(*cis*:*trans*) **4-138(*cis*:*trans*)**

	R	4-132 Starting d.r.	4-132 Recovered Yield (%)	4-132 Recovered d.r.	4-138 Yield (%)	4-138 d.r.
16	Ph	20:1	n.d.	12:1	(51)	15:1 (6.5:1)
17	Ph	1:25	n.d.	1:25	(49)	1:25

Table 4-8) Subjecting the trans isomer to $Al(OPh)_3$ promoted conditions did not result in formation of the cis product. (Isolated yield/d.r.)

Our previous best inversion result (Entry 5) used 5.5:1 d.r. starting material **4-132**. It was determined to repeat these results with pure *cis* starting material and a longer equilibration period. In this way the product was isolated in 83% yield and 6.6:1 d.r. (Table 4-9, Entry 18). Subsequent results with the furan analogue **4-180** showed better conversion and reproducibility running the reaction at 110 °C**.** Running the model substrate **4-138** at 110 °C had only a small effect on the yield and d.r. (Entry 19) These conditions were hence used in subsequent examples. Running the reaction with water-saturated toluene did not affect the reaction (Entry 20).[a]



4-132(*cis*:*trans*) **4-138(*cis*:*trans*)**

	Temp	4-132 Starting d.r.	4-132 Recovered Yield (%)	4-132 Recovered d.r.	4-138 Yield (%)	4-138 d.r.
18	80 °C 16 h then 110 °C 24 h	>25:1	—	—	(83)	1:6.6
19	110 °C 21 h	>25:1	—	—	100 (93)	1:5.3
20[a]	110 °C 21 h	>25:1	—	—	100 (90)	1:5.8

Table 4-9) Solvent screening. Conversions reported (isolated yield).[a] Water saturated toluene.

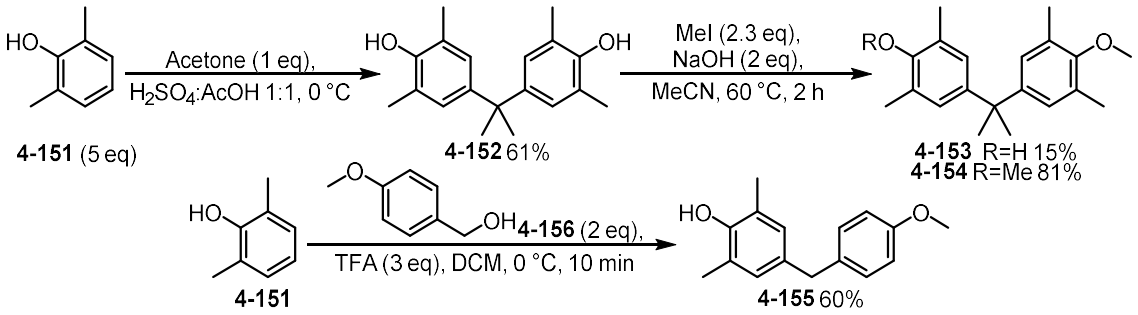
[a] A 1:1 mixture of water and toluene were stirred for 20 mins and the layers separated.

4.14.1. Isolation of Cis Cyclohexenes.

Under the optimised stereoretentive conditions (Table 4-7, Entry 15), the ligand could not be separated from the product by FCC or using NaOH washes. Hence, alternate strategies to purify the *cis* isomer were investigated.

4.14.2. Ligand Modification.

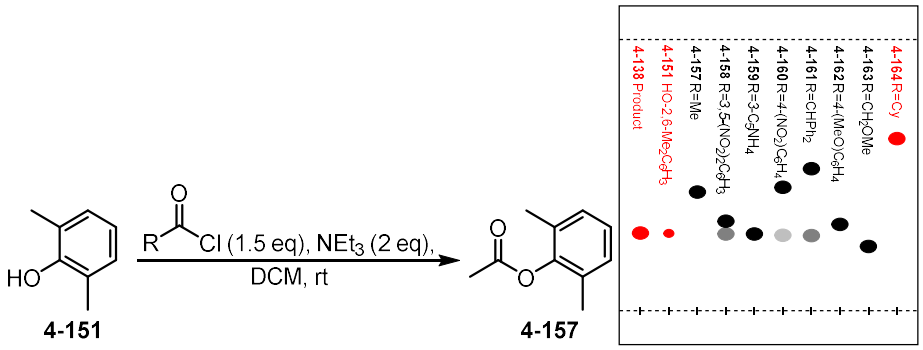
It was hoped that adding a *p*-substituent to the ligand could increase its polarity allowing for easy separation by FCC. Ligand **4-153**, synthesised by dimerisation, was found to have the same polarity as the starting material **4-151**, so was not tested (Scheme 4-44). Ligand **4-155**, synthesised by Friedel-Craft alkylation, was found to be sufficiently polar to separate from the product. Under the previously optimised conditions, using ligand **4-155** resulted in significant decomposition, with only trace product being observed.



*Scheme 4-44) Synthesis of 2,4,6-substituted phenol ligands **4153** and **4155**.*

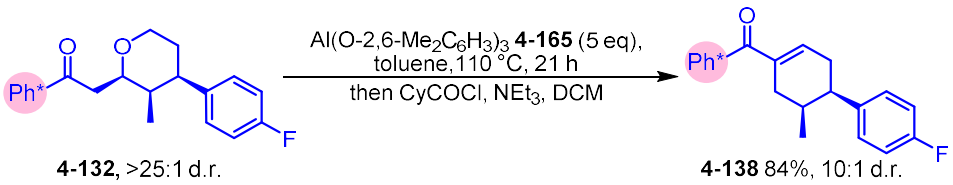
4.14.3. Acylation of the Phenol.

Given the large change in reactivity observed with ligand **4-155**, it was determined to explore an alternative work-up strategy instead. acylation of the phenol was determined as a reaction that would reduce the phenol's polarity significantly without changing the cyclohexene **4-138**. Several commercial acid chlorides were assessed, looking for clean phenol conversion and a significant change in the polarity (Scheme 4-45). Both R=Me **4-157** and R=Cy **4-164** gave clean conversion with a large decrease in polarity. The cyclohexane gave the best separation and was hence taken further.



Scheme 4-45) Screening acid chlorides to access which compounds could be best separated. R_f values were measured in Pentane:Et_2O (93:7).

Following the optimised procedure, aluminium salts were filtered through silica and the crude was concentrated. In the crude mixture, the phenol could be acylated using cyclohexanecarbonyl chloride which allowed for the product **4-138** to be cleanly isolated in 84% yield and 10:1 d.r (Scheme 4-46).



Scheme 4-46) Acylation of the ligand with CyCOCl allowed for the successful purification of the desired cyclohexene ***4-138****.*

4.15. X-Ray Conformation of the Stereochemistry of the 4,5-Substituted Cyclohexenes.

Both diastereomers of enone **4-138**, have key ^{1}H-NMR peaks in the aryl methyl region, meaning *J*-couplings could not be interpreted. In order to unambiguously assign the stereochemistry, the *trans* isomer was crystallised (Figure 4-1). The cyclohexene **4-138(*trans*)** was found to exist as a dimer with both aryl rings twisted out of the plane of the enone.

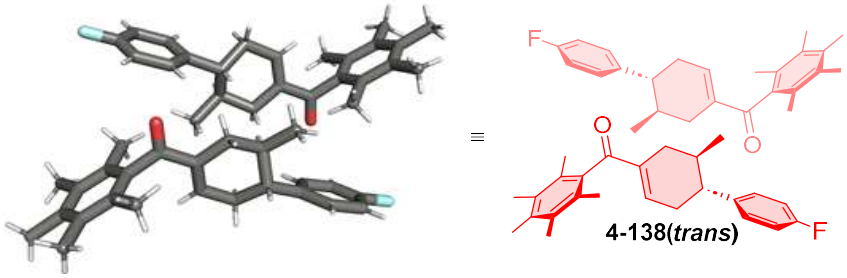


Figure 4-1) Crystal structure confirming the structure of the trans *isomer of cyclohexene* ***4-138****.*

During the substrate scope Al(O-2,6-$Me_2C_6H_3$)$_3$ was found to crystallise in a 0.34 M DCE solution over 48 h. The crystal structure contains two similar dimeric structures with the bridging ligands sitting equidistant from the adjacent metal centres (1.8 Å or 1.8 Å, respectively). The cycle appears to be planar with bond angles of (80.2° or 79.3°) at the

aluminium centres and (99.8° or 100.7°) at the oxygen centres.[a] This is consistent with the reported structure of Al(O*t*-Bu)$_3$ and not the monomeric structure of Al(O-2,6-Ph$_2$C$_6$H$_3$)$_3$ **4-71** previously reported by Yamamoto.[175]

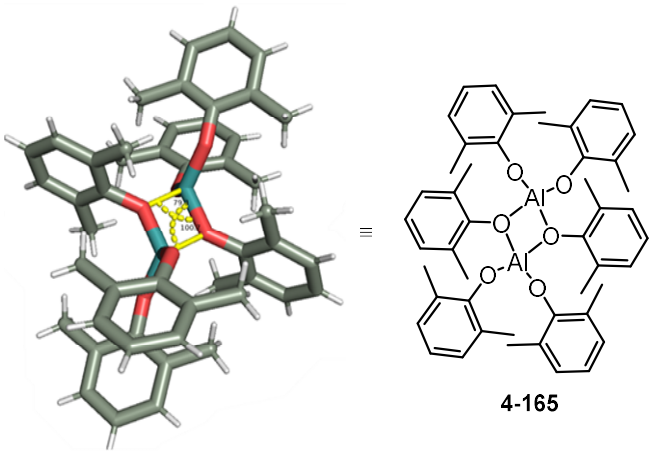


*Figure 4-2) Al(O-2,6-Me$_2$C$_6$H$_3$)$_3$ **4-165** sits as a dimeric pair in the crystal structure.*

4.16. Deuterium Incorporation in the 2,3,4-Substituted THP Rings.

In order to better understand the epimerisation process, the *cis* substrate **4-132** was subjected to NaO*t*-Bu in D$_4$-methanol at 50 °C over 2 h (Figure 4-3). In the ^{1}H-NMR spectrum, no *trans*-THP **4-132** was observed. ^{2}D incorporation was observed in the C7-position, resulting in a C2 doublet (4.28 ppm d, *J*= 2.14 Hz), suggesting the starting material forms enolates under these conditions but not extended enolates.

[a] Dimerisation of aluminium alkoxides is discussed in the Appendix.

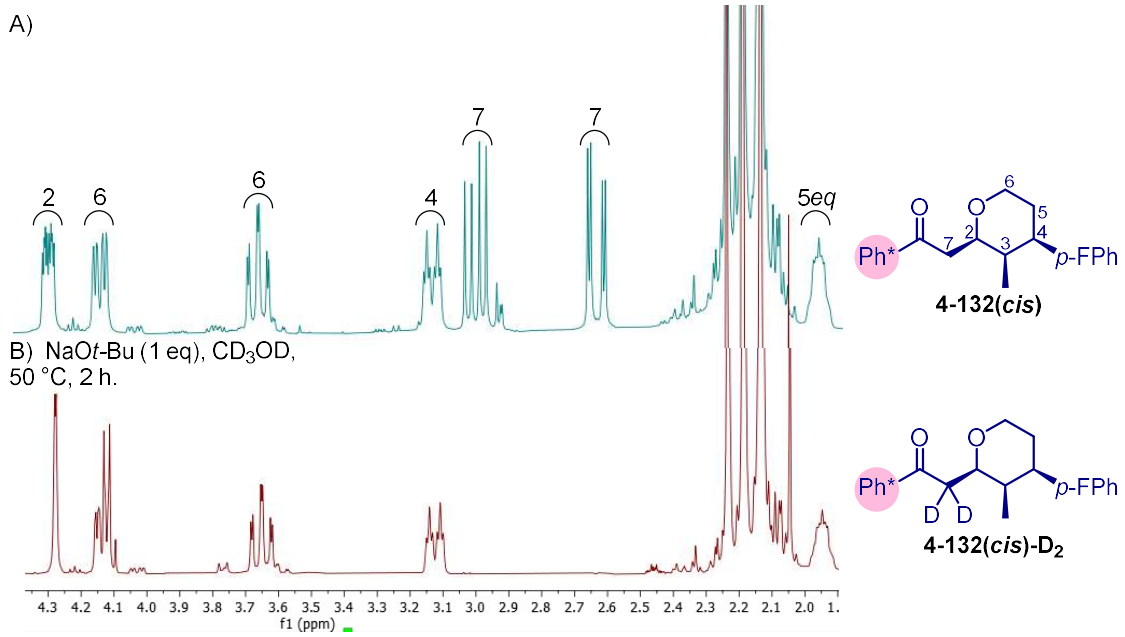


*Figure 4-3) The THP **4-132(cis)** isomer was stable when subjected to NaOt-Bu at 50 °C. A) Cis substituted THP. B) NaOt-Bu (1 eq), Methanol-D_4, 50 °C, 2 h.*

With 4 eq of NaO*t*-Bu at 75 °C (Figure 4-4), the C7-position again underwent full ^{2}D incorporation. Epimerisation was observed, resulting in 22:78 d.r. with full ^{2}D incorporation in the C3-position of both diastereomers resulting in the splitting of the C4 position changing accordingly ($C4_{cis}$ (3.12 ppm, dd, *J*= 12.9, 3.5 Hz) and $C4_{trans}$ (2.39 ppm, dd, *J*= 12.3, 4.1 Hz)).

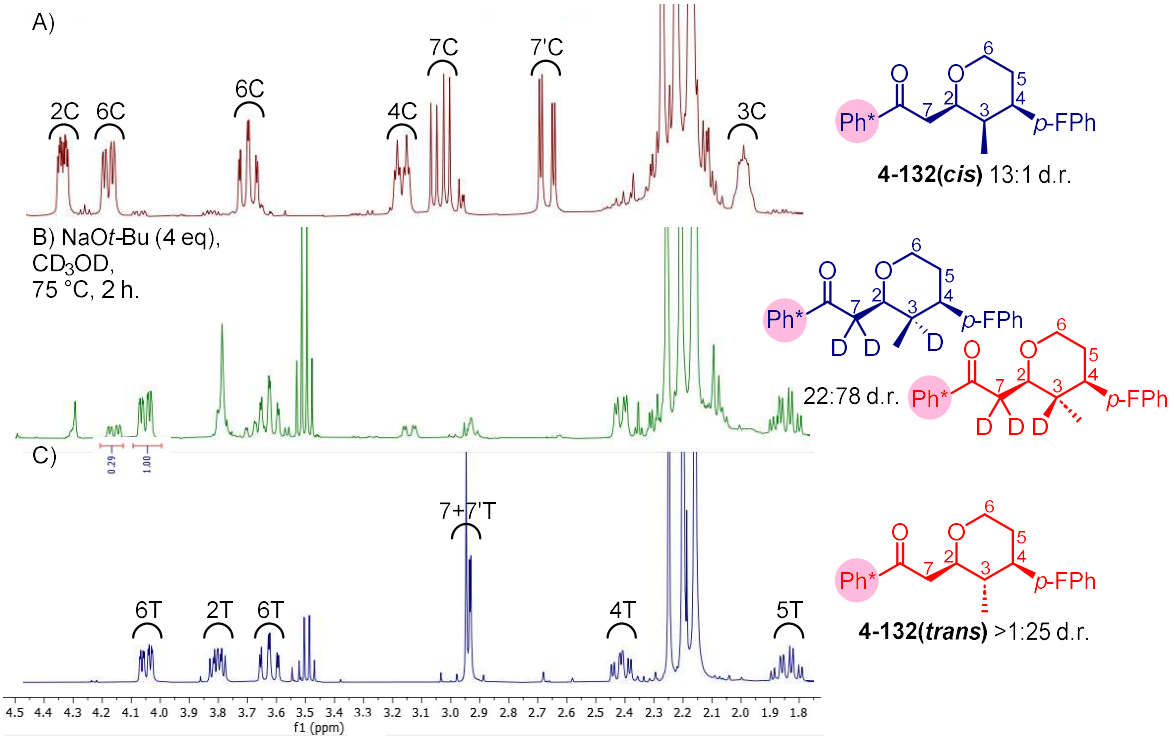
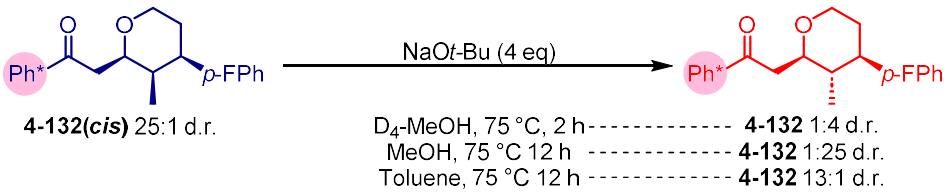


*Figure 4-4)Epimerisation of the C3-centre could be directly observed at 75 °C A) 2,3,4-cis substituted THP **4-132**. B) NaOt-Bu (4 eq), Methanol-D_4, 75 °C, 2 h. C)2,3,4-trans substituted THP **4-132**.*

The conditions shown above are significantly different to the optimised 1,5-hydride transfer conditions. Changing the solvent to toluene demonstrates that Brønsted-base mediated epimerisation requires a protic solvent to stabilise the dianion and is not the cause for epimerisation under the optimised conditions (Scheme 4-47).[a]

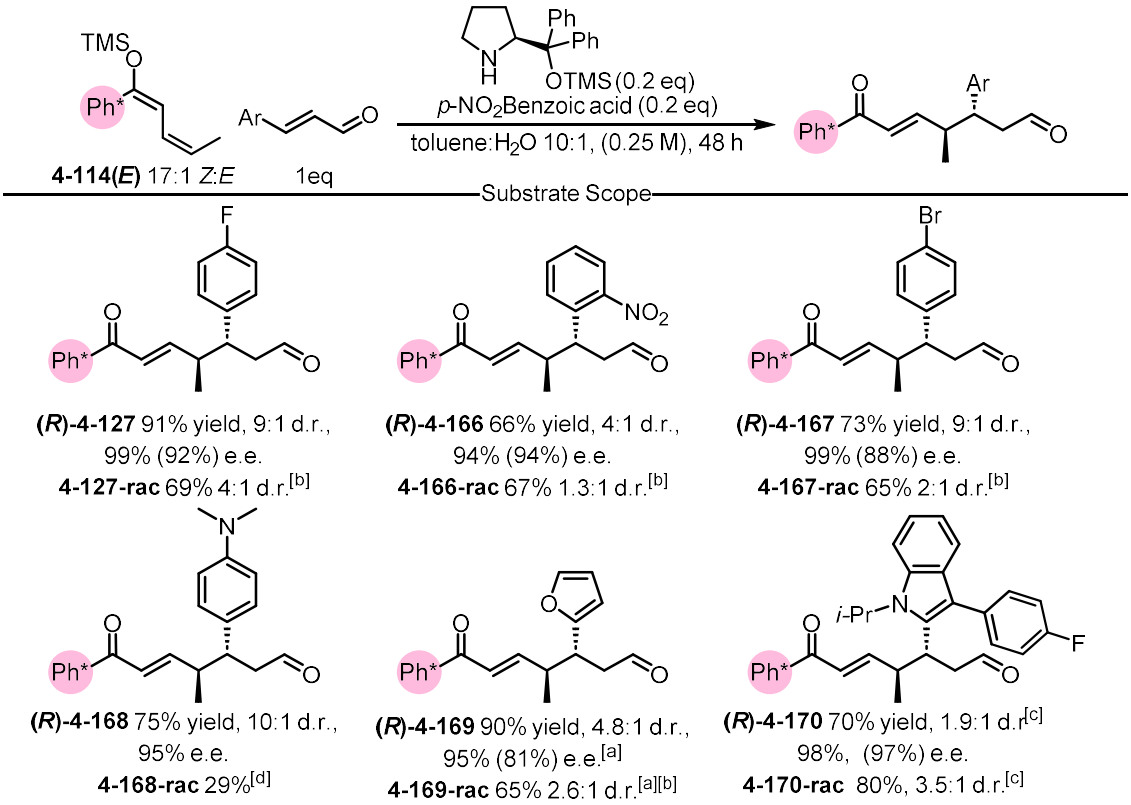


*Scheme 4-47) Epimerisation of the C3-centre in the THP **4-132** was found to be highly solvent dependent.*

4.17. Scope of the Vinylogous Mukaiyama-Michael Reaction.

With the sequence fully optomised, six examples of the Mukaiyama-Michael reaction were performed; in all six cases, the reaction was performed with good yield and e.e., determined *vide infra* by HPLC analysis of the subsequent THP rings (Scheme 4-48). The d.r. of the reaction was more variable, ranging from 1.9:1 to 9:1 d.r. Larger substituents **4-166**+**4-170** were found to be less selective, as well as the less bulky furan **4-169**. The diastereomers could generally be separated using FCC. The furan **4-169** was found to be inseparable, and the minor diastereomer of the aniline **4-168** could not be cleanly isolated. The reactions to generate racemic substrates were performed using a 2:1 (*Z*:*E*) mixture of the silyl enol ether **4-114** allowing easier access to the minor isomer, resulting in lower yields and d.r. in all cases.

[a] Repeating the epimerisation was found to be irreproducible.



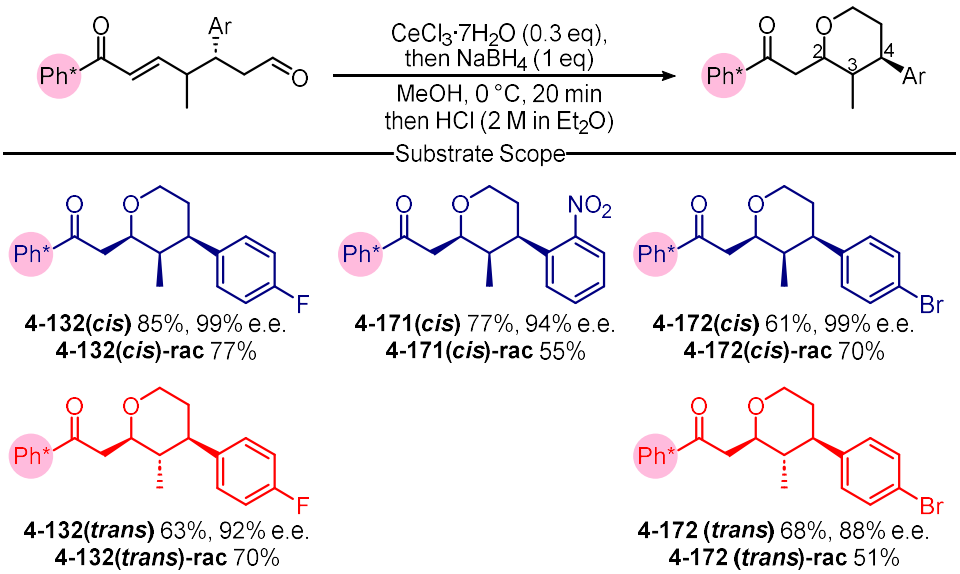
Scheme 4-48) Synthesis of di-substituted aldehydes via the Mukaiyama-Michael reaction. Major e.e. (Minor e.e.). [a] inseparable diastereomers. [b] Starting material 2:1 E:Z. [c] Isolated d.r., crude not determined. [d] isolated pure major isomer. e.e determined by HPLC analysis of the subsequent THP rings

Both diastereomers of indole **4-170** have significant peak broadening in the NMR spectra due to the hindered rotation around the C–C bonds. This prevented us from determining the diastereoselectivity of the reaction from the crude mixture. The subsequent THP ring **4-175** (see Section 4.18), which has the alkyl chain conformationally locked, has minimal peak broadening.[a]

4.18. Synthesis of the 2,3,4-Substituted THP Ring by Reduction.

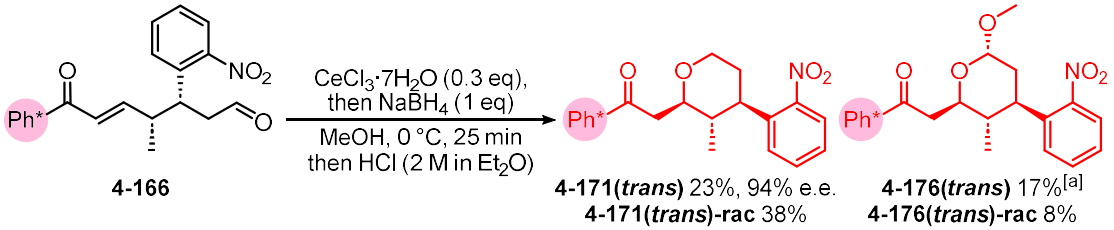
Due to the difficulty in measuring the reduction rate *in situ*, the yield of the reduction was found to be somewhat irreproducible, resulting in a large difference in yield between the enriched and racemic reductions. Whilst both diastereomers of THPs **4132,4171+4172** were isolated as single diastereomers by NMR, trace amounts of the C3 epimer were large enough to prevent determination of the e.e in the HPLC traces (Scheme 4-49). In order to determine the absolute stereochemistry, the diastereomers as well as the enantiomers were separated by HPLC.[b]

[a] Structure was atropisomeric and was analysed using VT NMR in C_6D_6 at 333 °K.
[b] Where necessary, different HPLC conditions were used to separate each pair of enantiomers. See SI for details



*Scheme 4-49) Reductive cyclisation of 2,3,4-substituted pyrans **4-132, 4-171+4-172**, no epimerisation of the C3-centre was observed.*

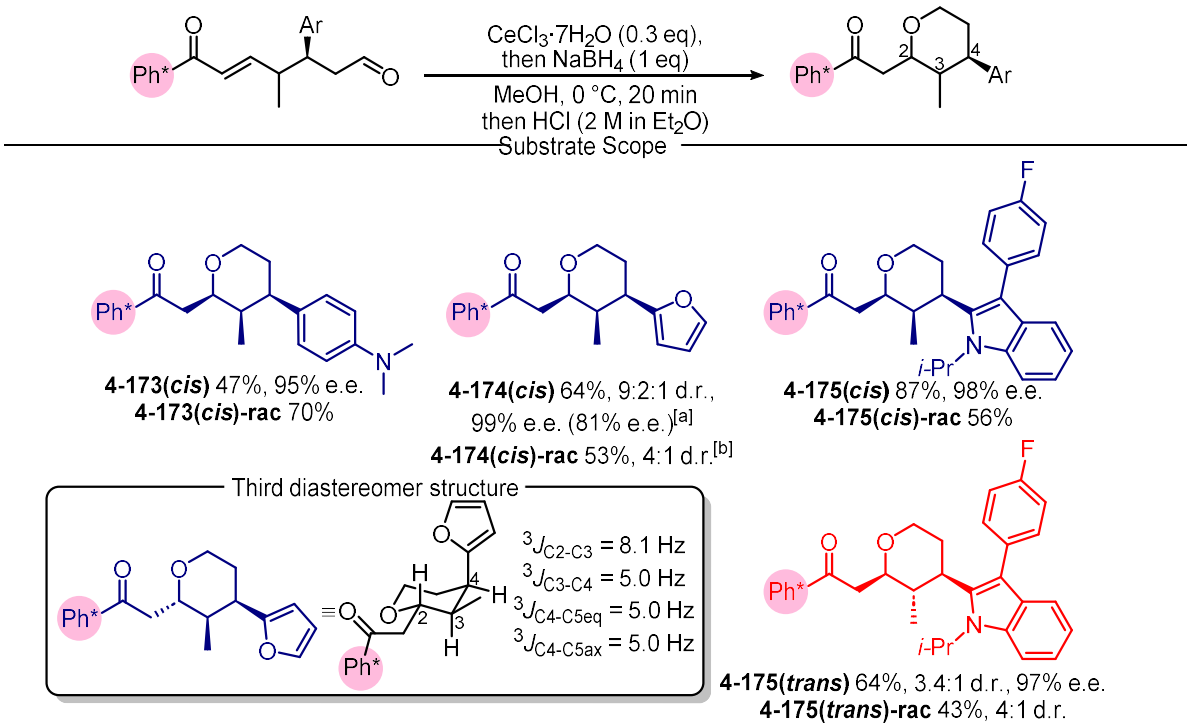
THP **4-166** was found to be significantly slower to reduce (Scheme 4-50). The reaction gave a mixture of the THP **4-171(*trans*)** and acetal **4-176(*trans*)** after 25 mins which could not be fully separated by FCC. Small samples of this substrate were separated by prep TLC for the purpose of HPLC analysis.



*Scheme 4-50) The THP **4-171** could only be isolated in modest yield. [a] e.e. not determined, no mechanism for racemisation is known.*

The furan **4-174** was found to give a mixture of 3 diastereomers (Scheme 4-51 A). The third diastereomer could be separated by FCC and was characterised as the THP **4-174(*cis*,*trans*)** by *J*-couplings analysis.[a] Indole **4-175(*trans*)** also formed a mixture of diastereomer, the stereochemistry of the minor diastereomer, believed to be the C2 epimer, could not be determined.

[a] The A-value of phenyl = 3 kcal/mol. a value for furan could not be found.[297]



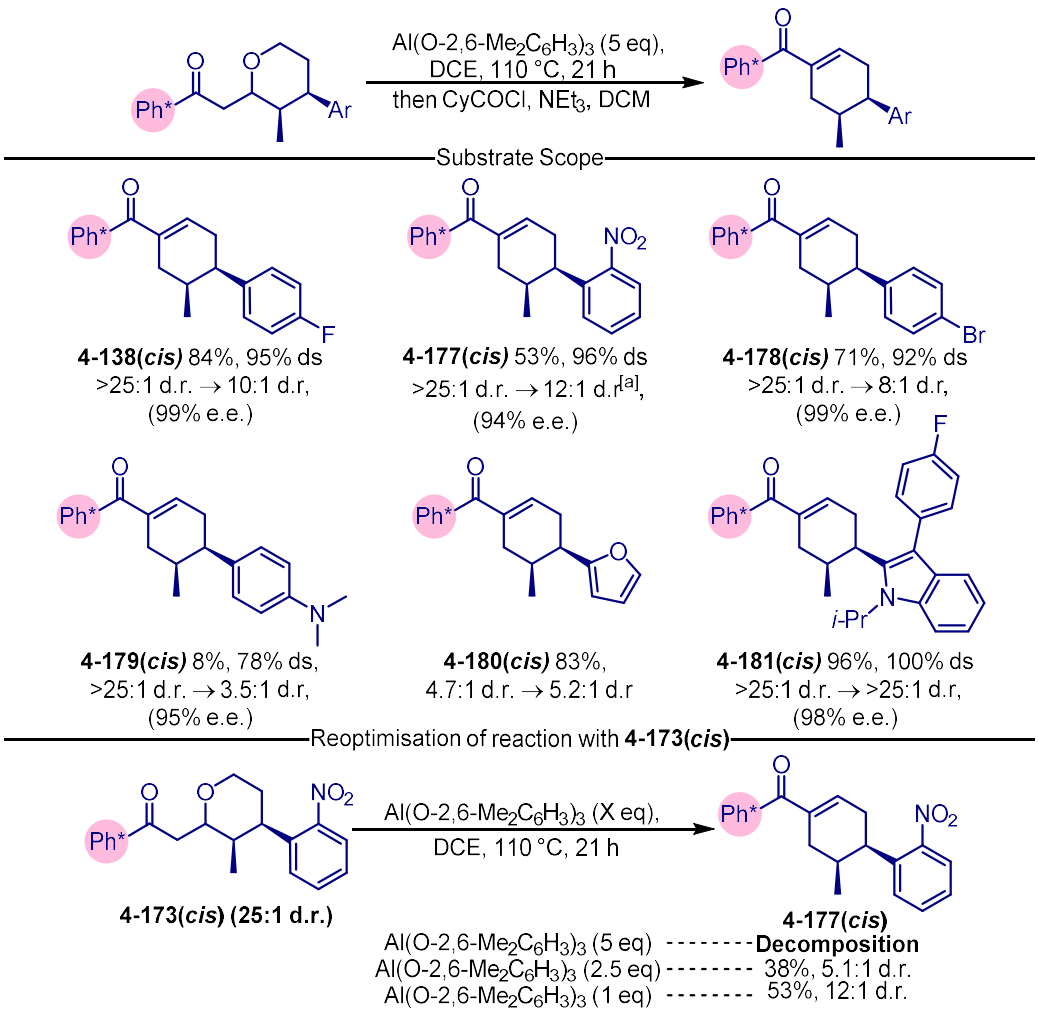
*Scheme 4-51) Further examples of reductive cyclisation of 2,3,4-substituted pyrans **4-173-4-175**, no epimerisation of the C3-centre was observed. (Minor enanatiomer).The 3rd diastereomer of THP **4-174(trans,cis)** could be determined by J-coupling [a] 4.8:1 d.r. SM Starting material. [b] 5.0:1 d.r. starting material.*

4.19. Scope of 1,5-Hydride Transfer with Stereoretention.

Given the preliminary results in Section 4.13, we were delighted to find high yields and diastereospecificity (above 90%) with most substrates (Scheme 4-52). The worst substrate under the retentive conditions was the aniline substrate **4-179(*cis*)**, isolated in 58% yield and 78% d.s. The furan underwent 1,5-hydride transfer with a small increase in the stereochemical enrichment, which we could not explain.

We were initially disappointed to find that *o*-NO_2 THP **4-177(*cis*)** decomposed under standard conditions. Poor mass recovery had not generally been observed in these reactions, including in the formation of the similar cyclohexene **4-87** (see Section 4.5). Reducing the aluminium loading to 2.5 eq and 1 eq resulted in the product forming 38% and 53% yield, respectively. The increase in both yield and d.r. suggests that the cyclohexene decomposed after formation, with the *cis* isomer being less stable and hence decomposing faster.[a]

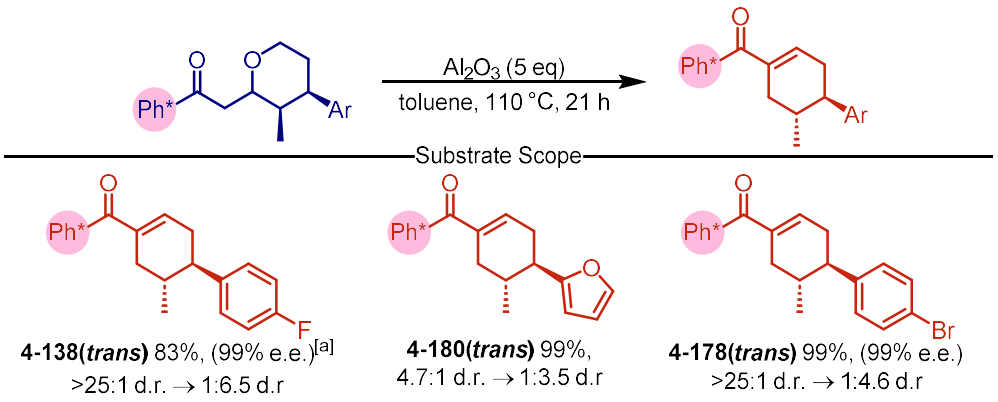
[a] The e.e. of the enone was assumed to be directly communicated from the starting materials, consistent with the previously discussed work (see Section 4.5) In the case of furan **4174** the two diastereomers have different e.e. and the value for the resulting enones has not been determined. This is also the case for the inversion conditions.



Scheme 4-52) Scope of stereoretentive 1,5-hydride transfer. [a] Al(O-2,6-Me$_2$C$_6$H$_3$)$_3$ (1 eq), isolated as a single isomer. e.e. determined vide infra from the starting material.

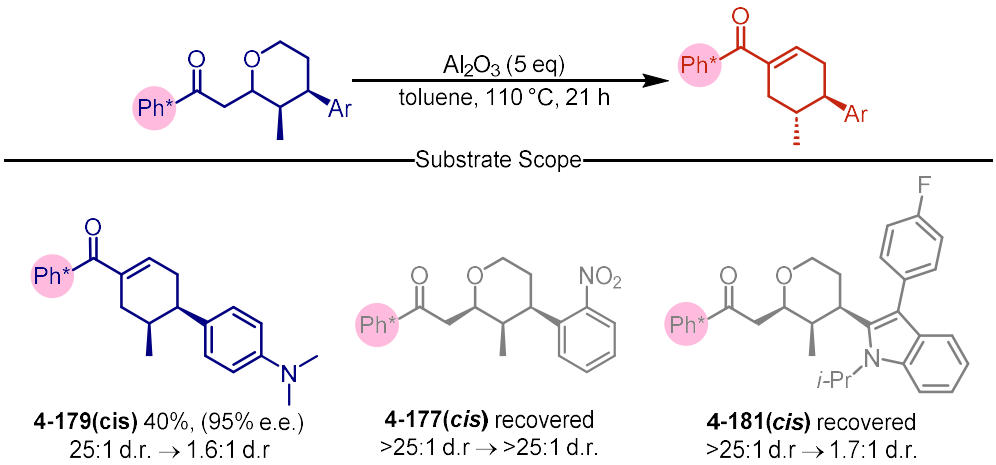
4.20. Scope of 1,5-Hydride Transfer with Stereoinversion.

Whilst the reactions using the retentive transfer conditions had been generally successful, the inversion conditions were not as reliable. Three substrates **4-138**+**4180**+**4-178** gave high yields and inversion (Scheme 4-53).



Scheme 4-53) Successful stereoinversion of the cis-THP substrates. [a] 80 °C 5 h, then 110 °C 18 h. e.e. determined vide infra from the starting material.

Under the same conditions, the aniline **4-179(*cis*)** gave only 40% yield of the product without inversion of the stereochemistry (Scheme 4-54). The two ortho-substituted aryl substrates were unreactive, giving the recovered starting material. With the *o*-NO_2 substrate **4-177**, the starting material was recovered without epimerisation of the C3-Centre. With the indole **4-181**, partial epimerisation occurs. The reason these substrates were unreactive is unclear; the lack of epimerisation of recovered **4-177** is indicative that ring opening was not occurring; which is surprising as ring opening under alumina conditions this appeared to be faster with the 2,4,6-substituted THP **4-100** (Table 4-2).[a]

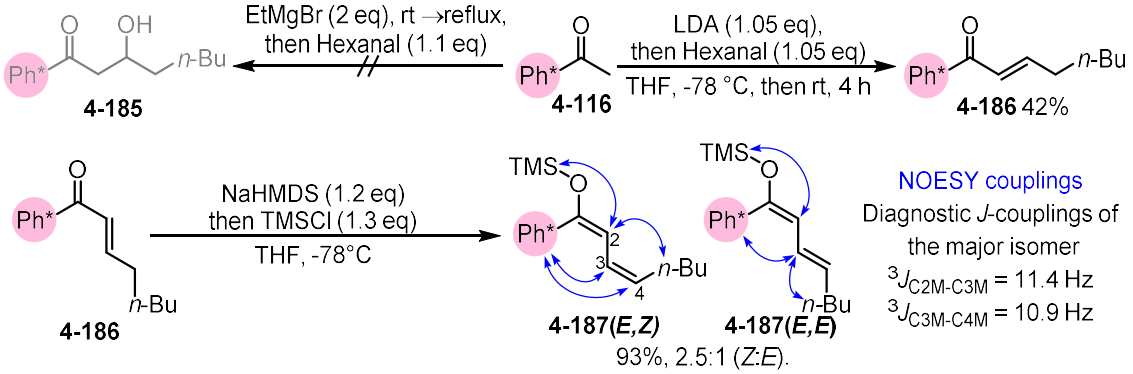


*Scheme 4-54) Failed stereoinversion of the cis-THP substrates. Epimerisation of THP rings **4-177**+**4-181** was determined by analysis of the ^{1}H-NMR without isolation. The percentage recovery of the THP rings was not determined. e.e. determined vide infra from the starting material.*

4.21. Tolerance of an *n*-Butyl γ-Substituents.

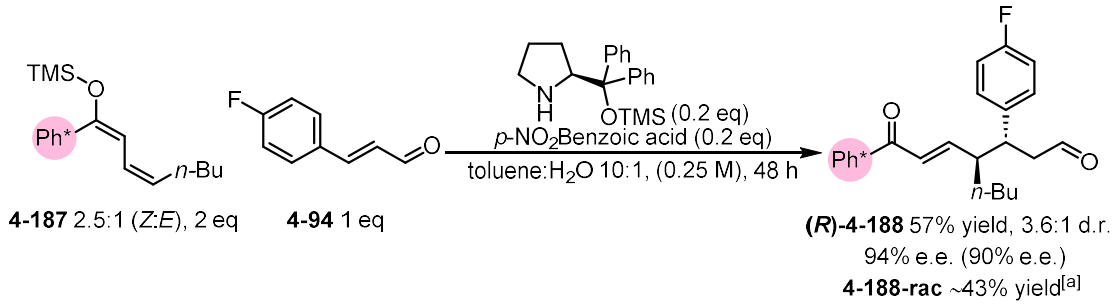
Having explored the C4-position, we decided to test whether a larger group can be tolerated in the C5-position of the cyclohexene (Scheme 4-55).[b] We initially found the previously utilised condensation conditions did not give the desired aldol product **4-185** (Scheme 4-30). Using LDA as a base allowed us to obtain the enone **4-186** in 42% yield at -78 °C. The silyl enol ether **4-187** was successfully synthesised in 93% yield with modest selectivity (2.5:1 d.r.).[c] The major and minor isomers were found to be (*E,Z*) and (*E,E*), respectively, based on the *J*-couplings and NOESY couplings consistent with the Me adduct **4-114**.

[a] Both reactions were repeated without the enone being observed.
[b] Schneider's work does not discuss anything other than Methyl groups in the γ-position.[163]
[c] No attempt to purify the silyl enol ether by recrystallisation was made.



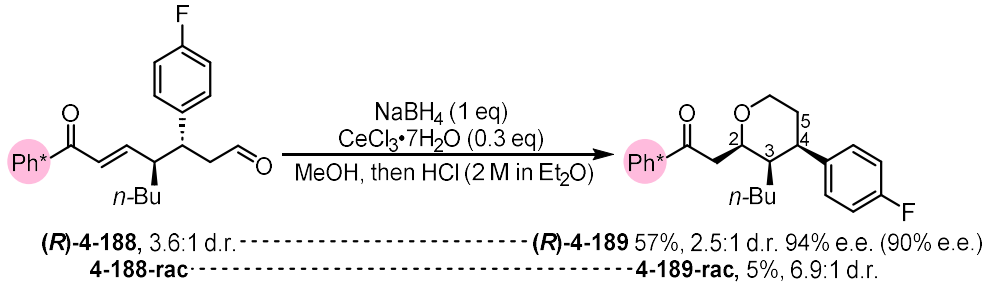
*Scheme 4-55) Synthesis of the enone **4-119** and silyl enol ether **4-120**.*

Given the disappointing initial screening of silyl enol ethers outlined in Section 4.9, we were pleased to isolate the desired aldehyde **4-188** in 57% yield and 3.6:1 d.r. without a significant drop in the e.e. (94% and 90% respectively, determined by HPLC analysis of the subsequent THP) (Scheme 4-56).[a]



*Scheme 4-56) Mukaiyama-Michael reaction with the n-butyl substrate. (Minor e.e.). [a] 1 eq of Silyl enol ether **4-187**. e.e. determined by HPLC analysis of the subsequent THP.*

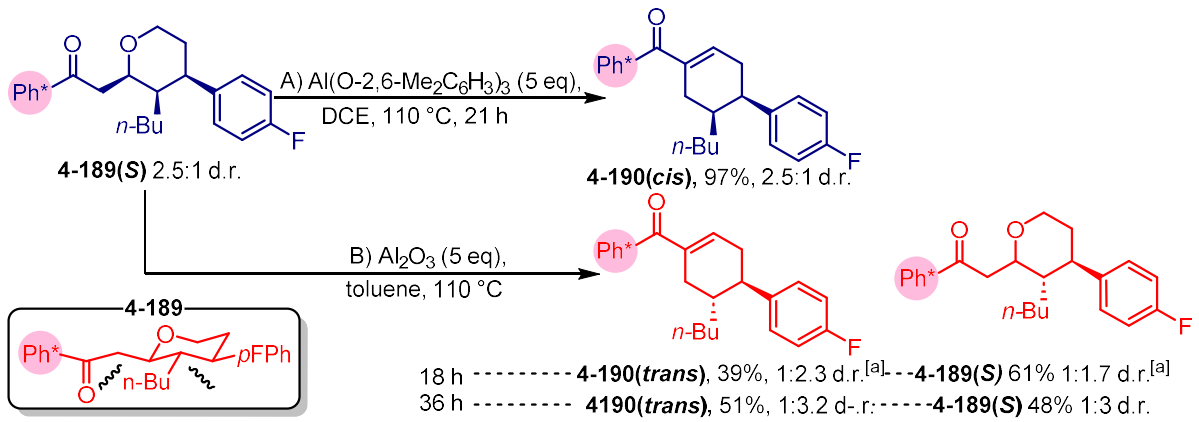
The aldehyde **(*R*)-4-188** reduction using the established Luche conditions gave the desired product **4-189** in 57% yield and 2.5:1 d.r. (Scheme 4-57). Under the same conditions, a complex mixture was isolated from the reduction of the racemic material. The impurities could not be identified and lacked the methoxy singlet previously observed in the cyclic acetal **4-134**. A small amount of the clean THP could be isolated by repeated FCC for HPLC analysis (Scheme 4-37).



*Scheme 4-57) Reduction of the aldehyde **4-188** was performed with both enantioenriched and racemic aldehyde allowing for the determination of enantioselectivity.*

[a] Aldehyde **4-188-rac** was subjected to reduction without the d.r. being determined.

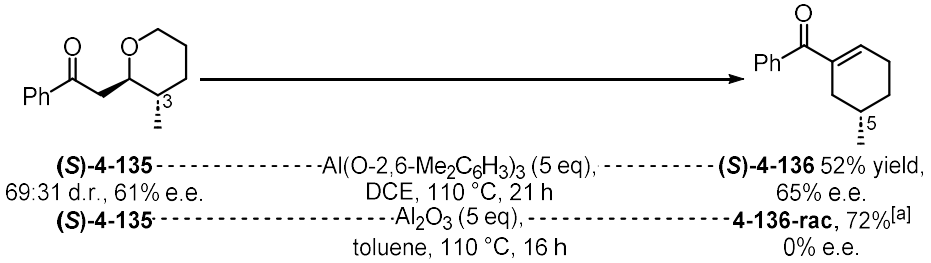
Under the retentive 1,5-hydride transfer conditions, the substrate was found to give the product **4-190(*cis*)** in 97% yield and with full stereoretention (Scheme 4-58). Under the inversion conditions, only partial conversion was observed after 18 h; the crude was resubjected for a further 24 hours with only modest further conversion. The unreacted THP **(*S*)-4-189** was recovered with partial inversion. Assuming the NMR conversion is accurate, from 18-36 h, the product was formed in >10:1 d.r., Whilst this is only an approximation, it strongly indicates that the epimerisation rate is the limiting factor in selectivity.



*Scheme 4-58) Stereoretentive and stereoinversion with the n-Butyl substituted THP **(S)-4-189** [a] NMR conversion, the material was resubmitted for a further 24 h. e.e of the cyclohexenes not determined*

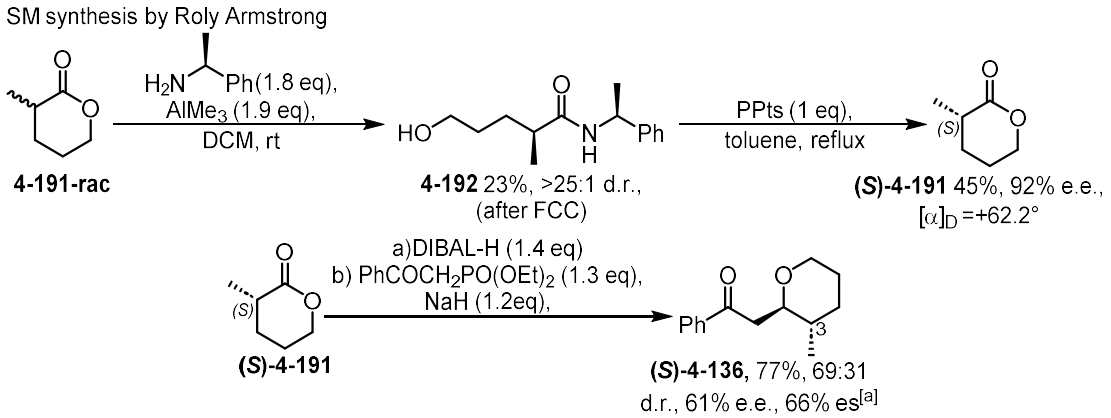
4.22.Revisiting Enantioretention in the C3-Position.

As discussed in Section 4.13, the 2,3-substituted THP **(*S*)-4-135** was previously shown to fully racemise during Al_2O_3 mediated 1,5-hydride transfer, giving **4-136-rac** in 72% yield (Scheme 4-59). On a small scale, substrate **(*S*)-4-135** was subjected to the optimised Al(O-2,6-$Me_2C_6H_3$)$_3$, giving the product **4-136** in 52% yield and 65% e.e. The slight increase in e.e. was believed to be experimental error.



Scheme 4-59) Using the reoptimised conditions lead to complete stereoretention of the C3 position. Reaction performed on a 0.025 mmol scale. [a] Reaction performed by Roly Armstrong. ^{1}H -NMR yields were calculated based on TMB as an internal standard.

Dr Armstrong synthesised the enantioenriched lactone **(*S*)-4-136** by resolution of the amide **4-192** in 23% yield >25:1 d.r. (Scheme 4-60).[a] The DIBAL-H-HWE sequence gave access to the desired THP **4-135** in 77% yield but only 66% es. Improving this step is hence the main limit to accessing enantioenriched 5-substituted cyclohexenes.



*Scheme 4-60) Synthesis of enantioenriched 2,3 THP **4-136**. [a] Enantioenrichment was the same in both diastereomers.*

4.23. Assessing the Kinetics of the Epimerisation Reaction.

Having optimised the diastereoselective DKR mechanism we wanted to revisit the proposed mechanism for the stereoinversion,

Two factors to determine the stereoselectivity were proposed; the THP equilibrium and the relative rates of the 1,5-hydride transfer reaction (see Section 4.13.1). Since both mechanisms predict the same major product, we looked to computational kinetics for a secondary effect that could differentiate the two mechanisms.[203]

Two kinetic models were made, solving the linear rate equations by using quadrature rule numerical integration:[b] a 4-component model representing a general diastereoselective DKR reaction (Section 4.23.1); and a 6-component model including the open chained intermediates which are specific to our system (Section 4.23.5). As outlined below, the six-component methodology demonstrates that the THP equilibrium cannot be the driving force of the reaction selectivity and must be predominantly controlled by the enone equilibria and kinetics of the 1,5-hydride transfer.

[a] The absolute stereochemistry of lactone **(*S*)-4136** was determined by comparing the $[\alpha]_D$ value with previous work by Evans *et al.* Who characterized the structure by analysis of crystalline derivatives.[298]

[b] Quadrature rule integration is the classic methodology where the rates of formation and consumption of every species are calculated at a single time point. These rates are presumed to be constant for a "time step" and then the values are recalculated.

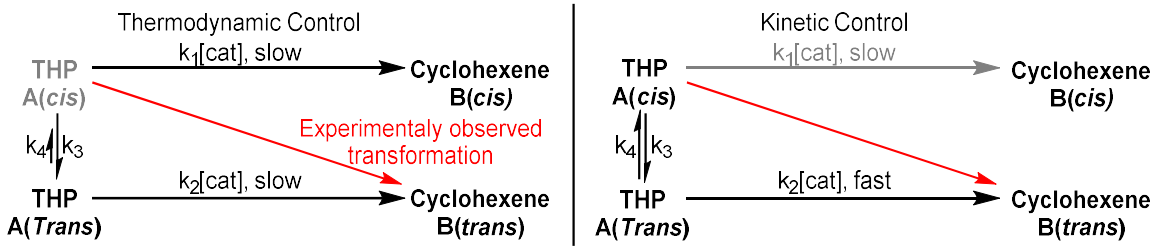
4.23.1. Four-Component Model DKR System.

Our initial model used four compounds, representing the freely interconverting isomers of the THP **A** and the irreversible formation of the two isomers of the cyclohexene **B** (Scheme 4-61).[a] Since Al_2O_3 and not an alkoxide promotes the reaction, consumption of the catalysis was not considered. Mathematically, d.e. is much easier to plot and manipulate; positive d.e. here corresponds to the *cis* isomer and negative d.e. corresponds to the *trans* isomer.

The model was set up to simultaneously perform the integration with variable d.e. of the THP **A** starting material from +100% d.e. (*cis,* pink) to -100% d.e. (*trans,* brown) allowing us to observe the effect of the starting material on the product (Figure 4-5 + Figure 4-6).

In order to look at how the two factors change the reaction kinetics, constraints were placed on the variables representing the extremes where only one factor is involved.[b]

- k_1=k_2 corresponds to Equilibrium control.
- k_3=k_4 corresponds to Kinetic resolution.



$$\frac{d[A(cis)]}{dt} = k_4[A(trans)] - k_3[A(cis)] - k_1[cat][A(cis)]$$

$$\frac{d[A(trans)]}{dt} = -k_4[A(trans)] + k_3[A(cis)] - k_2[cat][A(tran)]$$

$$\frac{d[B(cis)]}{dt} = k_1[cat][A(cis)]$$

$$\frac{d[B(trans)]}{dt} = k_2[cat][A(trans)]$$

Scheme 4-61) Kinetic model of the hydride transfer conditions and associated equations.

[a] Integrations were performed using Microsoft Excel.

[b] The specific plots shown below were chosen to allow the system to run to completion over 5000 time steps and are consistent with the experimental values observed when p-Br substrate **4-172(*cis*)** was subjected to the optimised conditions giving the Cyclohexene **4-178(*trans*)** in 98% yield and d.r. of 1:4.6 d.r. (-64% d.e.) (Scheme 4-53).

4.23.2. $k_1=k_2$. Equilibrium Controlled Reaction.

First, equilibrium control was modelled (Figure 4-5). As expected, exponential rate curves were calculated for the starting material consumption (Figure 4-5 A) and product formation (Figure 4-5 C). The rate of product formation is independent of the initial d.e. as expected.

In order to replicate the experimental results, equilibration must happen rapidly w.r.t. to the 1,5-hydride transfer and strongly favour the *trans* isomer (Figure 4-5 B). The product is initially formed with the same d.e. as the initial SM d.e. and tends towards the equilibrium SM d.e. over time without reaching it (Figure 4-5 D).

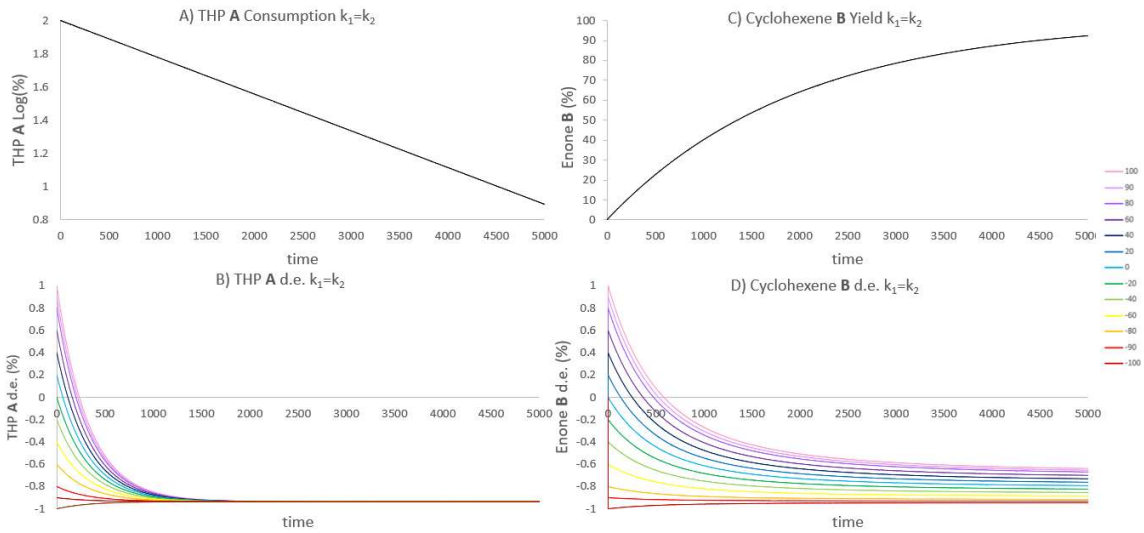


Figure 4-5) Model kinetics where $k_1=k_2$ (non-selective 1,5-hydride transfer). Values used: [cat]=1.7 mol%, $k_1=k_2=3$, $k_3=30$, $k_4=1$, time step=10000. Each line represents a different stating d.e. (%)

4.23.3. $k_3=k_4$. Kinetic Resolution Controlled Reaction.

Under Kinetic control, regardless of the initial enrichment, the SM tends towards the same equilibrium ratio (in this example 31% d.e.), not 0% d.e.[a] due to the *trans*-THP being consumed by the 1,5-hydride transfer reaction at a higher rate than the *cis* isomer (Figure 4-6 B). Until the THP d.e. reaches equilibria the reaction rate does not follow the exponential curve. Like with the equilibrium controlled system, the product **B** is initially formed with the same d.e. as the initial SM and converges towards the same value (Figure 4-6 D).

[a] This mathematics of this system is the same as an enantioselective DKR.

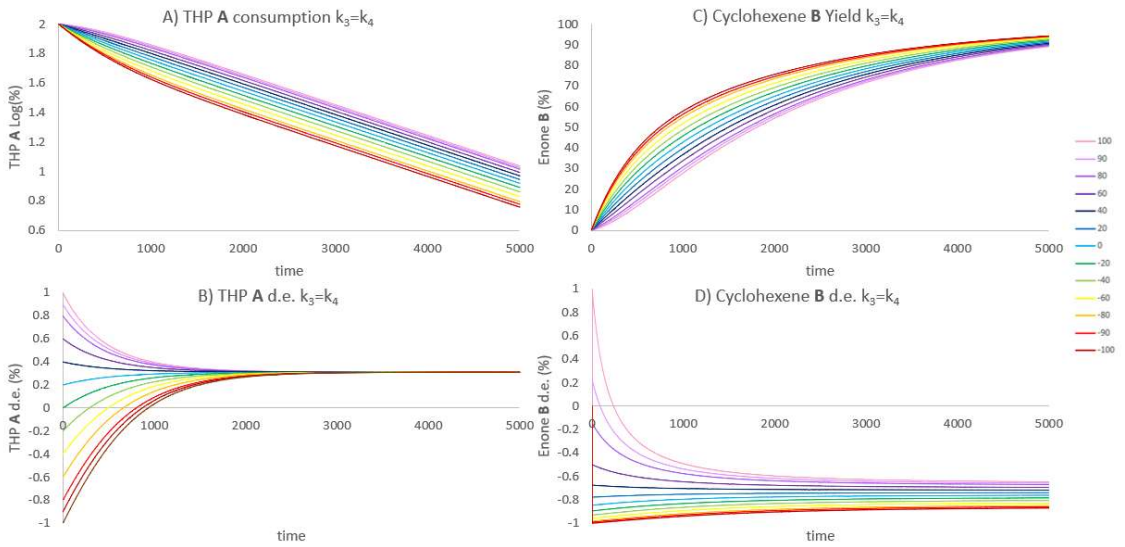


Figure 4-6) Model kinetics with $k_3=k_4$ (non-selective equilibria). Values used: [cat]=1 mol%, $k_1=1$ $k_2=12$, $k_3=8$, $k_4=8$, time step=10000. Each line represents a different *stating d.e. (%).*

The relative rates between the equilibrium and 1,5-hydride shift are important in both regimes. For example, keeping all the other variables the same but decreasing the epimerisation rate by 37% results in the product forming with -54% d.e. instead of -64% d.e (Figure 4-7). This decrease in the product d.e. occurs both because; the initial starting material d.e. takes longer to reach equilibria, resulting in a larger effect of the starting material d.e on the resulting product (22% range increases to 34%) and the THP equilibriates at 44% d.e. instead of 31% d.e.

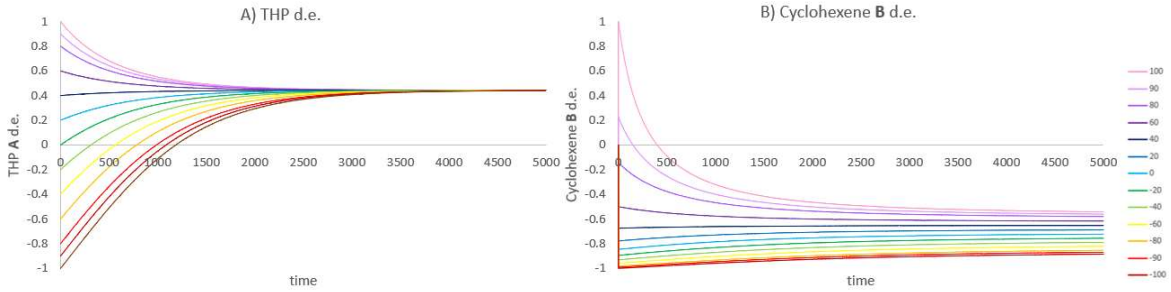


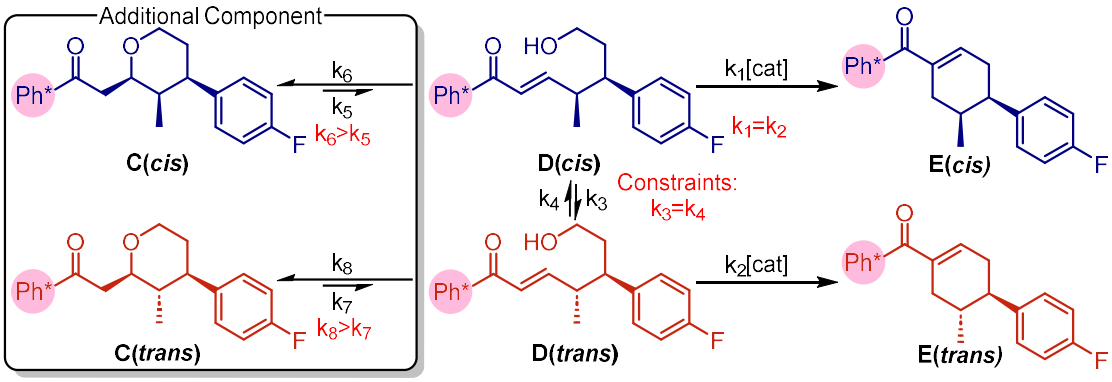
*Figure 4-7) d.e. of the starting material **A** and product **B**. Model kinetics with $k_3=k_4$ (non-selective equilibria). Values used: [cat]=1 mol%, $k_1=1$, $k_2=12$, $k_3=5$, $k_4=5$, time step=10000. Each line represents a different stating d.e. (%).*

4.23.4. Comparison.

The 4-component model suggests that the two factors can be differentiated by measuring the d.e. of the recovered THP **A** (Figure 4-5 B) and (Figure 4-6 B). An equilibrium-controlled model predicts that the recovered SM **A** should have a lower d.e. than the product. A kinetically controlled model predicts a higher d.e. (more *cis*) as the *trans* isomer is rapidly consumed. The data collected during the optimisation indicates equilibrium control is the larger effect; although a more detailed reaction profile would need to be measured to confirm this.

4.23.5. Six-Component Model DKR System.

The simple model described above does not consider how epimerisation occurs. The major problem that was envisaged with this simplification is that the open alcohols **D** act as a common intermediate for the epimerisation and 1,5-hydride transfer (Scheme 4-62).[204,205]



$$\frac{d[\boldsymbol{C}(cis)]}{dt} = k_6[\boldsymbol{D}(cis)] - k_5[\boldsymbol{C}(cis)]$$

$$\frac{d[\boldsymbol{C}(trans)]}{dt} = k_8[\boldsymbol{D}(trans)] - k_7[\boldsymbol{C}(trans)]$$

$$\frac{d[\boldsymbol{D}(cis)]}{dt} = k_5[\boldsymbol{C}(cis)] - k_6[\boldsymbol{D}(cis)] + k_4[\boldsymbol{D}(trans)] - k_3[\boldsymbol{D}(cis)] - k_1[cat][\boldsymbol{D}(cis)]$$

$$\frac{d[\boldsymbol{D}(trans)]}{dt} = k_7[\boldsymbol{C}(trans)] - k_8[\boldsymbol{D}(trans)] - k_4[\boldsymbol{D}(trans)] + k_3[\boldsymbol{D}(cis)] - k_2[cat][\boldsymbol{D}(trans)]$$

$$\frac{d[\boldsymbol{E}(cis)]}{dt} = k_1[cat][\boldsymbol{D}(cis)]$$

$$\frac{d[\boldsymbol{E}(trans)]}{dt} = k_2[cat][\boldsymbol{D}(trans)]$$

Scheme 4-62) Introducing ring opening into the system requires the kinetics of six compounds and eight steps. Additional terms in the equations are highlighted in blue.

The 4-component model indicated the THP equilibration is the largest factor controlling the reaction. We aimed to see if this form of stereocontrol could still occur when epimerisation and hydride transfer share the same intermediate. Hence, constraints were placed on the eight variables.

- The substrates preferentially sit as the THP rings, not the alcohols $k_6>k_5$ and $k_8>k_7$.
- The equilibrium ratio between the alcohol diastereomers (**D**) is not very selective ($k_3 \approx k_4$). For the sake of this discussion, this was fixed as ($k_3=k_4$).
- The initial starting material is purely *cis*.

The lowest product (**E**) d.e. under these constraints was found to be 0% and the experimentally observed inversion could not be observed using any set of inputs. Hence, according to this

model, the THP equilibrium cannot be the system's primary cause of the reactions diastereoselectivity.[a]

Whilst this appears to be true for all values, it is worth considering a few specific cases to illustrate why this is the case.

4.23.6. Rapid Epimerisation, $k_1=k_2$, $k_3=k_4$.

If epimerisation is rapid relative to the hydride transfer, the alcohols **D** equilibrate to ~0% d.e (Figure 4-8, Red). The cyclohexene **E** (Green) enrichment is due to the initial product formation before the THP and alcohol reach equilibrium. Under the example conditions, the final cyclohexene **E** (Green) d.e. was calculated to be 18%. As the rate of epimerisation increases, the conversion of the product that occurs before the THP-alcohol system reaches equilibrium decreases, and hence the final d.e. of the product tends towards 0%.

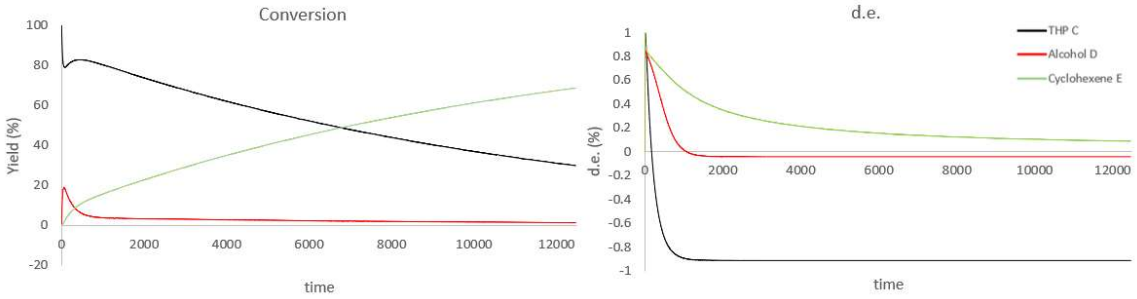


Figure 4-8) Yields and d.e. based on the model described in Scheme 4-62 where $k_1=k_2$ is slow and $k_3=k_4$. Values used: cat=2 mol%, $k_1=k_2=1$, $k_3=k_4=20$, $k_5=10$, $k_6=20$, $k_7=5$, $k_8=200$, time step=1000.

4.23.7. Slow Epimerisation, $k_1=k_2$, $k_3=k_4$.

In the plots below, the system is modelled with three equilibration rates, with the slowest shown in green and the fastest in purple (Figure 4-9). When the equilibration is slow, and reaches dynamic equilibria, the alcohol **D** is consumed before it can epimerise; hence the d.e. of the THP drives the reaction selectivity. However, experimentally the *trans* product can be formed even if the initial THP **C** has +100% d.e. (*cis*). With this constraint, the d.e. of the THP **C** and alcohol **D** does not reached equilibrium (negative d.e. is reached at ~t=4000 after conversion is already ~80%). This results in the final d.e. of the cyclohexene being +ve.

As the rate of epimerisation is increased (Figure 4-9, Blue and Purple), the d.e. of the THP **C** and alcohol **D** reach steady-state faster; however, the THP equilibrium d.e. tends towards 0% as the system moves towards the "Rapid Epimeriation" mode previously described.

[a] The THP equilibrium can still affect the product d.r. but not determine it.

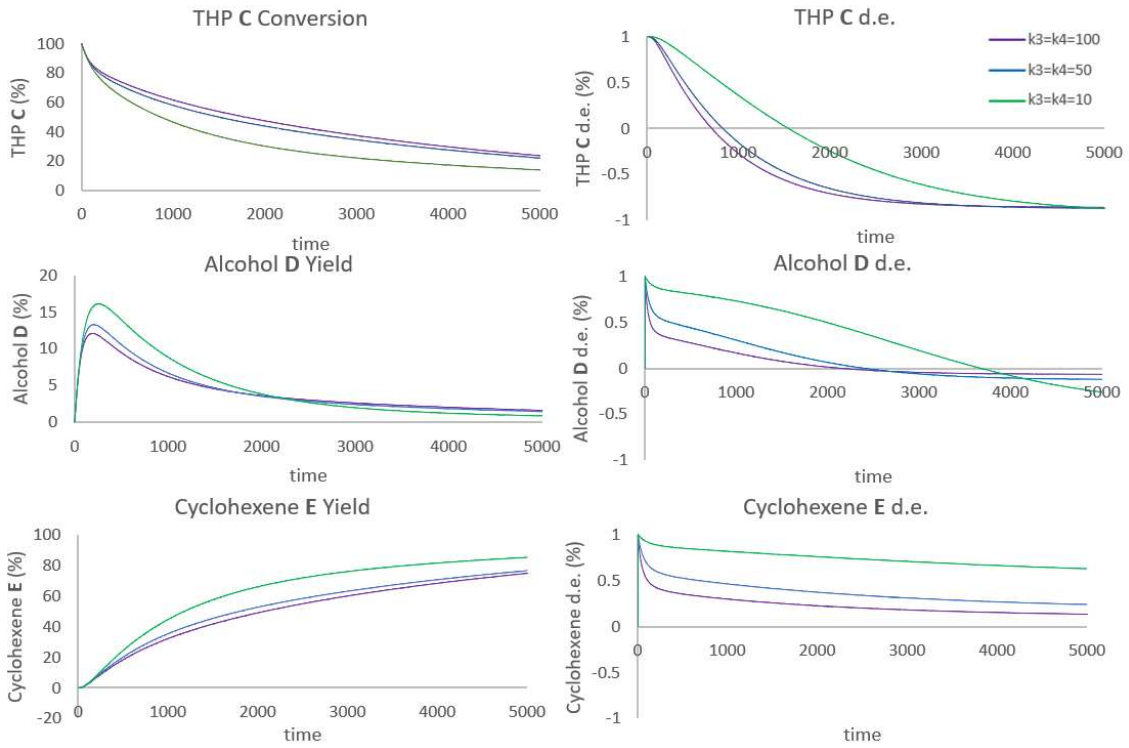
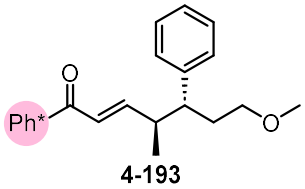


Figure 4-9) Kinetic plots showing variable equilibration rates k_3=k_4 = 10, 50 and 100. Values used: cat=18 mol%, k_1=k_2=1, k_5=10, k_6=20, k_7=5, k_8=200, time step=5000.

These examples show why the experimental values cannot be replicated under these constraints. Hence, according to this model, the THP equilibrium cannot be the driving force of the reactions selectivity.

4.23.8. Comparison of the Models.

The 6-component model directly contradicts the conclusions reached based on the general 4-component model. We believe this is a far better representation of the reaction in question. Hence, our kinetic models lead us to eliminate the THP **4-132** equilibration as the determining factor in selectivity. Instead, the system must be controlled by a combination of the alcohol equilibrium, which cannot be directly measured, and the selectivity 1,5-hydride transfer. Given this conclusion, we suggest that future DKR work should investigate ethers, such as **4-193**, to increase the relative epimerisation rate (Figure 4-10).

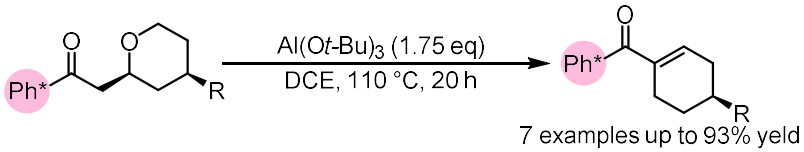


4-193

*Figure 4-10) Ether **4-193** is a promising substrate for future DKR research.*

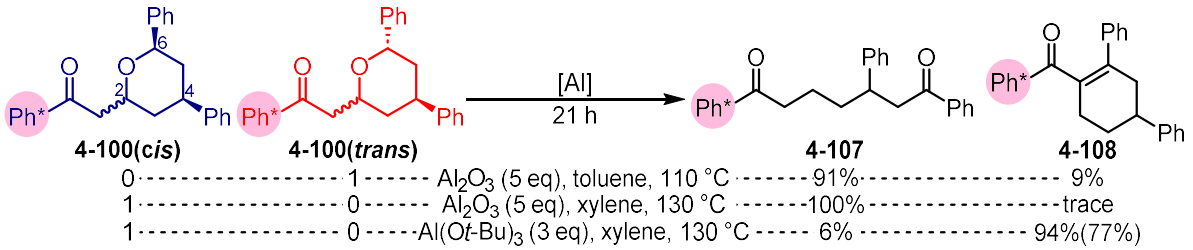
4.24. Summary.

Our first aim was to build upon TRM's initial THP synthesis. the yields and reliability of each step were improved and seven examples of 1,5-hydride transfer were performed in up to 93% yield with high enantioselectivity (Scheme 4-63).



Scheme 4-63) Synthesis of C4-substituted cyclohexenes.

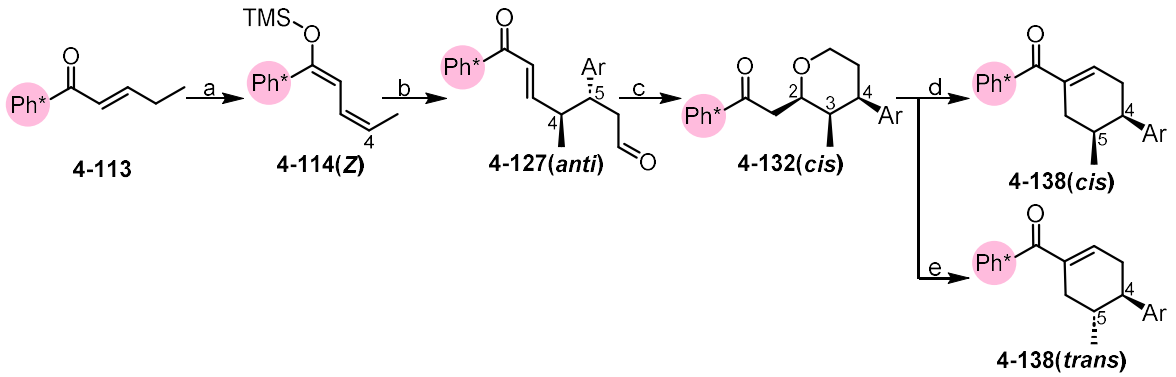
By synthesising the 2,4,6-substituted THP ring **4-100**, the mechanism of the 1,5-hydride shift was probed (Scheme 4-64). The 4,6-*cis* relationship was found to significantly impede the 1,5-hydride shift as predicted by the cyclic transition state model. This reaction could be pushed to completion using elevated temperature. It was found that the choice of Lewis-acid allowed for a highly selective divergent product formation of either diketone **4-107** or cyclohexene **4-108**.



*Scheme 4-64) 2,4,6-substituted THP ring **4-100** closure was shown to have different kinetics depending on the diastereomer used. The choice of aluminium reagent allows for the selective formation of two products divergently. ^{1}H -NMR yields were calculated using TMB as an internal standard (isolated yield).*

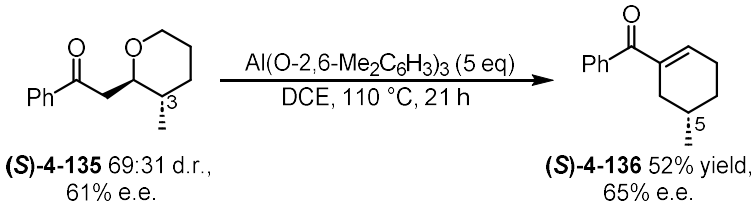
The selective formation of the diketone **4-107** inspired later work discussed in Chapter 5. A general route towards the 2,4,6-substituted THP ring **4-100** by 1,2-addition to aldehydes **4-56** was unsuccessful, resulting in complex mixtures that could not be driven through a two-step sequence.

It was found enriched alkene **4-114(*Z*)** could be accessed by utilising the high crystallinity of the Ph* group. This allowed for the enantio and diastereoselective formation of the 1,7-dicarbonyl **4-117(*anti*)**. Using the 2,3,4-substituted THP ring **4-132(*cis*)**, a pair of stereodivergent routes were developed to access both cyclohexene **4-138** isomers (Scheme 4-65).



*Scheme 4-65) Strategy to obtain the desired cyclohexenes. Ar= 4-F-C_6H_4. [a] NaHMDS, TMSCl, THF, -78 °C. [b] cinnamaldehyde, Hayashi Jorgensen catalyst **4-68**, p-NO_2-benzoic acid, toluene:H_2O 10:1. [c] $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, then HCl (2M in Et_2O). [d]$Al(O\text{-}2,6\text{-}Me_2C_6H_3)_3$, DCE, 110 °C. [e] Al_2O_3, toluene, 110 °C.*

The insights into epimerisation of the C3-position allowed us to synthesise **(*S*)-4-136** with high stereoretention (Scheme 4-66).



Scheme 4-66) Enantioretentive 1,5-hydride transfer.

4.25. Further work.

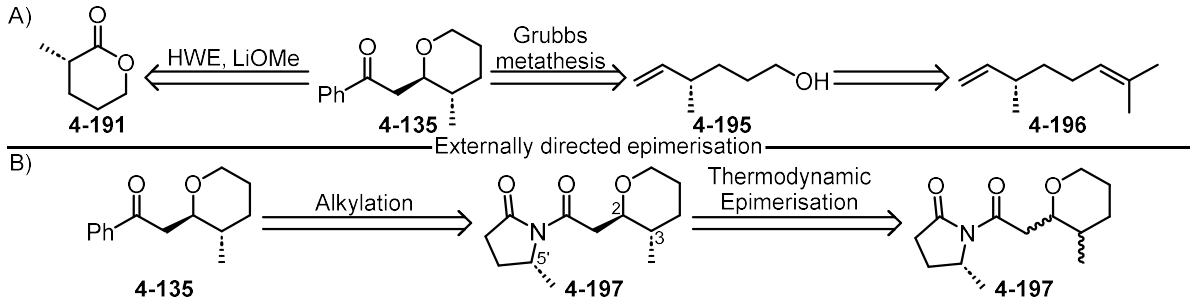
Outlined below are two avenues of interest. (i) Developing a route to enantioenriched C3-substituted THP rings, which would allow for the optimised stereoretention conditions to be fully utilised (Scheme 4-59). (ii) Exploring tri-substituted substrates with the directing group in other positions around the ring (Scheme 4-53).

4.25.1. Developing a Substrate Scope for the Enantioretention of the C3-Centre.

The enantiopurity of cyclohexene **4-136** is limited by the 65% e.s. observed in the HWE olefination used to synthesise the THP **4-135** (Scheme 4-60). Enantiospecificity may be improved using the rt HWE conditions used in Section 5.5.2. The established metathesis strategy, which avoids subjecting the THP **4-135** to strong bases is also a promising strategy (Scheme 4-67 A).[206][a]

[a] The desired starting material alkene **4-195** has previously been synthesised by Waldmann *et al*. from (R)-citronellene **4-196** on a large scale.[206]

More ambitiously, we envisage utilising a cleavable directing group to direct C3-epimerisation. Elman's auxiliary **4-197** seems a promising target, using the fixed C5'-centre to direct the C2 and C3-centre in THP **4-135** (Scheme 4-67 B).[a]

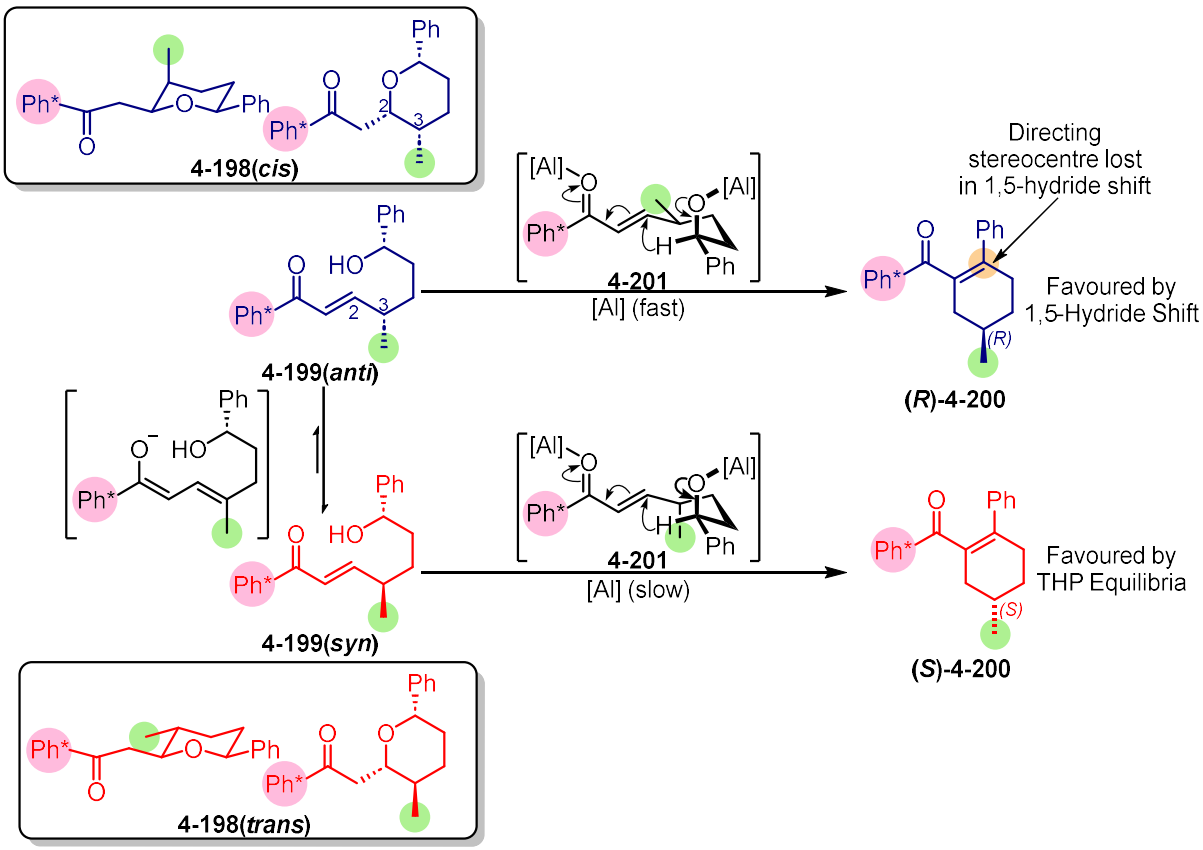


*Scheme 4-67) Approaches to enantioenriched 2,3-substituted THP ring **4-135**. A) Potential application of established routes. B) Epimerisation of the C3-centre could be utilised to create enantioenriched material instead of losing it if directed by a cleavable auxiliary group.*

4.25.2. 2,3,6-Substituted THP Rings.

Having demonstrated the ability to direct the C3-centre from the C4-centre, exploring using directing groups in other positions may be of interest. The substitution pattern that seems most exciting to us is the 2,3,6-substituted THP ring **4-198**, because the C6 directing group is lost during the hydride transfer. Considering the mechanism, we believe the 2,3,6-substituted THP ring would behave differently from the current work (Scheme 4-68); instead of the 1,5-hydride transfer and THP equilibria cooperating to favour a single product, the two factors conflict. The dynamic kinetic resolution of the 1,5-hydride transfer reaction would favour cyclohexene **(*R*)-4-200**, whilst pre-equilibration followed by stereoretentive 1,5-hydride transfer conditions would favour cyclohexene **(*S*)-4-200** from the same mixed starting material.

[a] Oxazolidines have been used as hydride acceptors in the past.[299]



*Scheme 4-68 Mechanism of C3 epimerisation when considering the proposed 2,3,6-THP **4-198**. Based on our understanding of the 2,3,4-THP system.*

Chapter 5. The Development of Catalytic Aluminium Promoted 1,5-Hydride Shift Reactions.

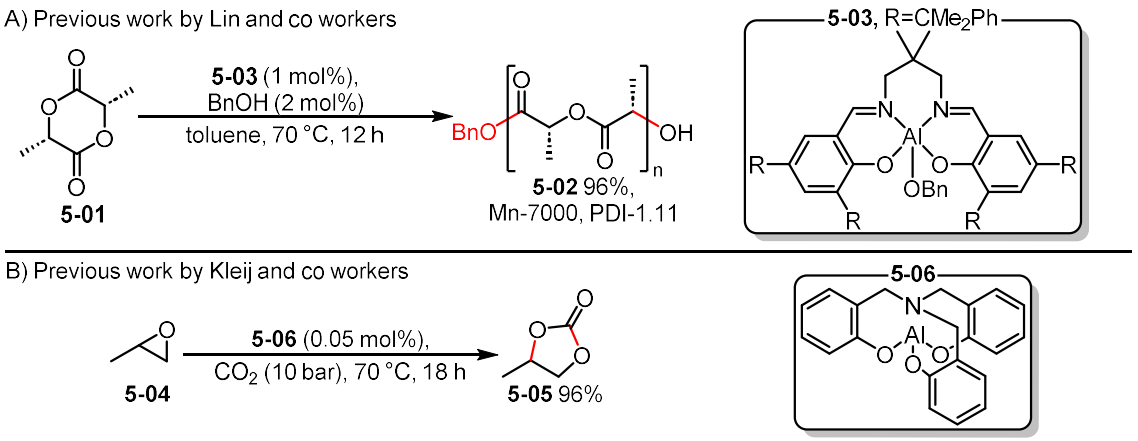
5.1. Introduction.

Ongoing work within the group has established the feasibility of enantioselective 1,5-hydride transfer reactions. This exciting work requires stoichiometric loadings of a complex chiral aluminium-based reagent (Scheme 5-5). In order to support this work, we decided to explore the role of aluminium in more detail in order to develop a system with *catalytic* aluminium loadings. This could greatly increase the synthetic utility of the current and subsequent enantioselective strategies.

Work in this Chapter was performed concurrently with work by Jingyan Hou on enantioselective hydride transfers. Her experimental findings are shown where relevant.

5.1.1. Established Aluminium Catalysis in Organic Synthesis.

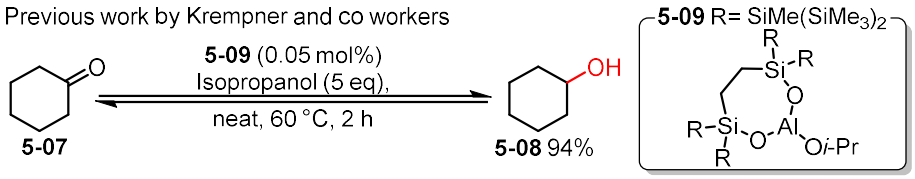
In the literature, aluminium-(III) complexes have been used as catalysts in numerous systems. For example, Lin and co-workers reported that Al Salen complex **5-03** promoted transesterification of esters **5-01** to give the polyester **5-02** (Scheme 5-1 A).[207] Kleij and co-workers discovered that alkoxide **5-06** could open epoxide **5-04** and trap the resulting zwitterion with CO_2 to give the cyclic carbonate **5-05** (Scheme 5-1 B).[208]



*Scheme 5-1) Various aluminium alkoxide catalysts have been shown in the literature. (A) Lin and co-workers used Al-Salen complexes **5-03** to catalyse transesterification.[207] (B) Kleij and co-workers. form carbonate **5-05** by epoxide **5-04** opening with carbon dioxide activation.[208]*

The Meerwein-Ponndorf-Verley (MPV) reaction uses aluminium alkoxides to reversibly catalyse hydride transfer between alcohols, such as isopropanol and ketones **5-07**, driven by the evaporation of acetone.[209] Krempner and co-workers developed the catalyst aluminium

alkoxide **5-09,** which allowed them to perform MPV reactions with just 0.05 mol% loading (Scheme 5-2).[210]a



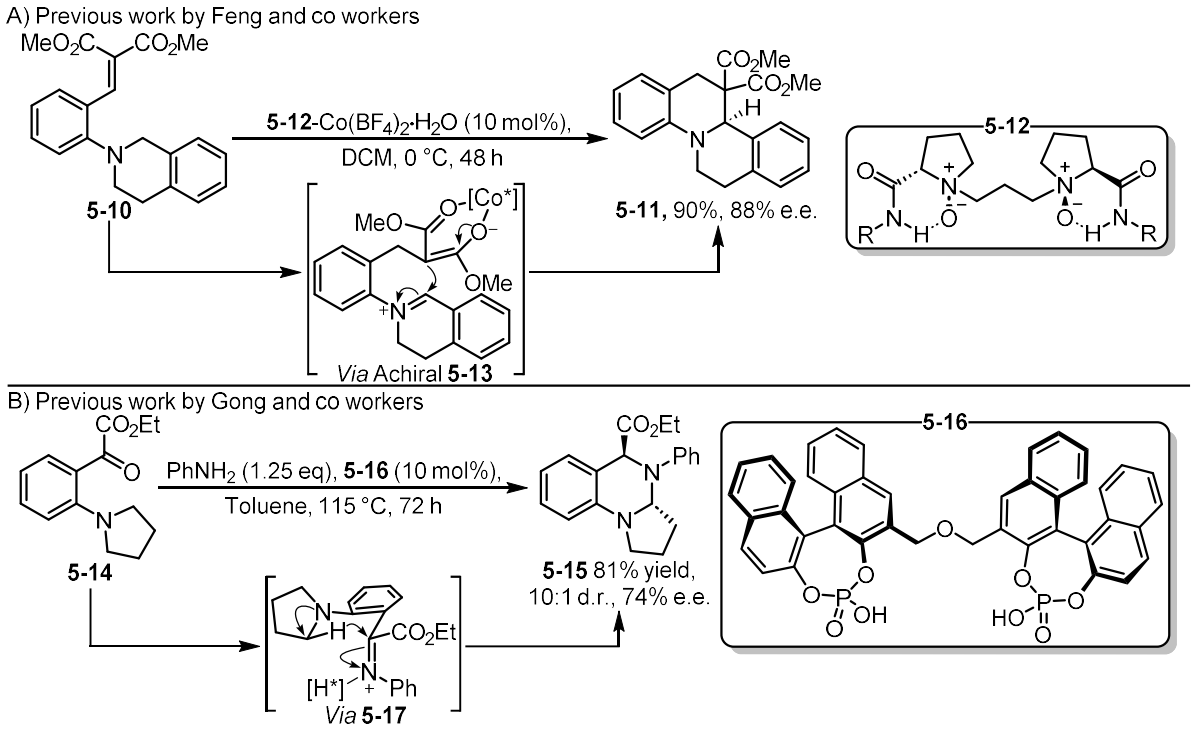
Scheme 5-2) Krempner and co-workers performed MPV reactions with 0.05 mol% catalyst loading.[210]

5.1.2. Enantioselective 1,5-Hydride Transfer Reactions.

Enantioselective 1,5-hydride transfer sequences have been previously reported in the literature, with the most common strategies involving ring closing being the enantiodetermining step in the methodology.[211,212] For example, Feng and co-workers promoted the synthesis of amine **5-11** under cobalt **5-12** catalysed conditions. The amine **5-10** underwent 1,5-hydride transfer to generate the achiral iminium **5-13**, followed by an enantioselective imino-aldol-cyclisation (Scheme 5-3 A).[213]b Gong and co-workers reported the enantioselective synthesis of aminal **5-15** in 81% yield with 10:1 d.r. and 74% e.e *via* a phosphoric acid **5-16** promoted enantioselective 1,5-hydride transfer of imine **5-14** (Scheme 5-3 B).[214]

[a] Asymmetric MPV reactions are discussed in two reviews by Node and co-workers. and Garg and co-workers.[300,301]

[b] Wang and co-workers. summarised this subset of enantioselective 1,5-hydride transfer reactions in 2013.[302]

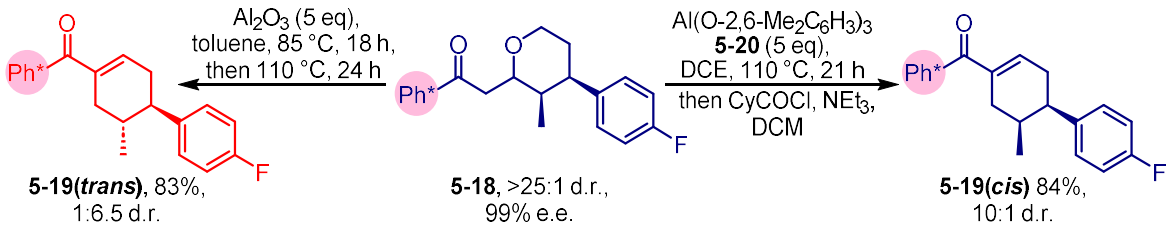


*Scheme 5-3) (A) Feng and co-workers synthesised tetrahydro isoquinoline **5-11** by an enantioselective ring closing step after the 1,5-hydride shift.*[213] *(B) Gong and co-workers demonstrated an enantioselective hydride transfer to set the C4-centre in the aminal **5-15**.*[214]

5.1.3. Current Work on Cyclohexene Synthesis in the Donohoe Group.

As discussed in Section 4.19, the initial aluminium-promoted 1,5-hydride transfer reaction greatly improved the diversity of cyclohexenes that could be selectively accessed compared to the original Ir-catalysed oxidation strategy.[16] Initially Al(O*t*-Bu)$_3$ and Al_2O_3 were chosen as readily available reagents to promote the reaction.

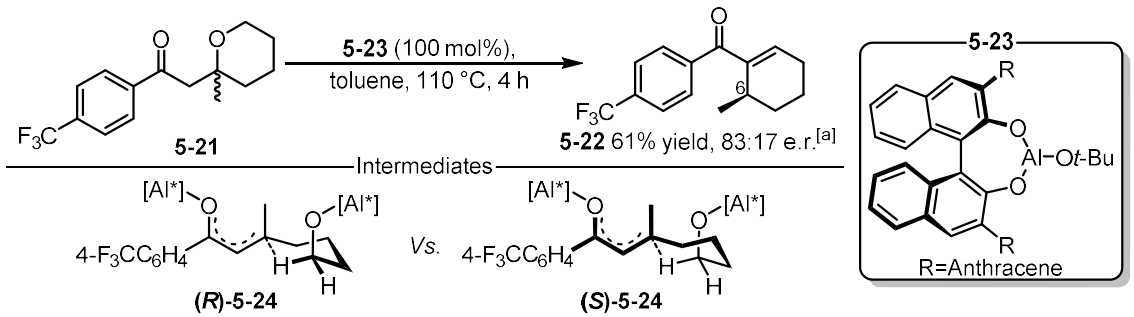
Subsequently, in Chapter 4, both cyclohexene isomers **5-19** were synthesised in a stereodivergent manner by modifying the aluminium complex used (Section 4.19, Scheme 5-4). The sterically hindered complex **5-20** required to achieve high diastereoretention resulted in a more challenging purification afterwards, requiring the ligand to be acylated in some cases; however, the reagent is still inexpensive.



Scheme 5-4) Ligand effect on C8 epimerisation during the 1,5-hydride transfer.

An enantioselective 1,5-hydride shift has been established within the Donohoe group, which was initially discovered by Lewis Smith and then developed by Jingyan Hou. In this reaction,

the aluminium-complex **5-23** was shown to direct the reduction of the tri-substituted enone *via* the cyclic transition state **(*R*)-5-24** to form the cyclohexene **5-22** in 61% yield and 83:17 e.r. (Scheme 5-5).



*Scheme 5-5) Catalyst-controlled C6 enantioenrichment using the binol-derived aluminium complex **5-22**. [a] Absolute stereochemistry not determined.*

Going forward, the desire to synthesise more complex cyclohexene substrates, including *via* kinetic resolutions and DKR reactions, will likely require more complex aluminium reagents to be employed, which require multi-step synthetic sequences to access. Achieving catalytic Al loadings is hence highly desirable to benefit both the ongoing research and future projects.[194,215,216]

5.2. Mechanistic Analysis.

Experimental data, using 2,4,6-substituted THP rings (Section 4.7.2), strongly suggests that aluminium performs numerous roles in the reaction (Scheme 5-6):

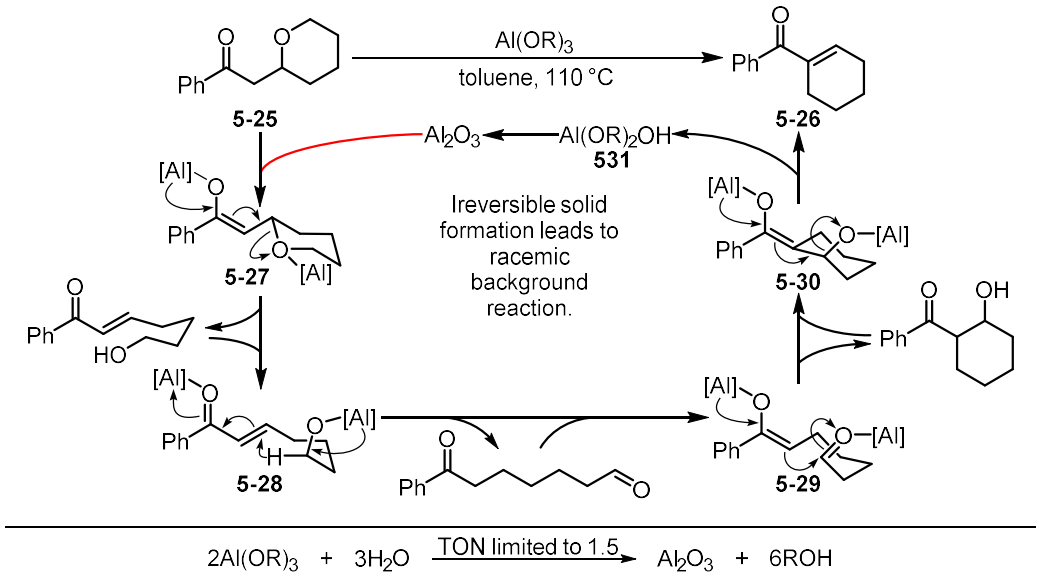
i) The THP ring opening **5-27**.

ii) The 1,5-hydride transfer **5-28**.

iii) The Aldol reaction **5-29**.

iv) The 2nd E1cB elimination **5-30** of the activated hydroxide leaving group.

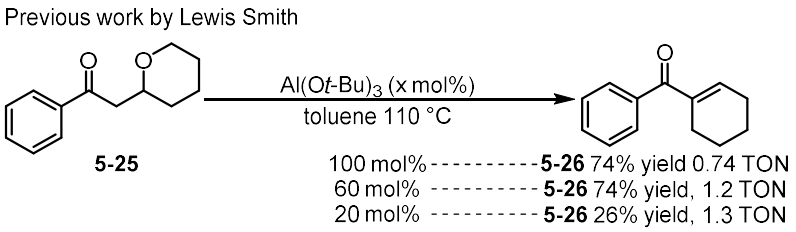
Our experimental data was supported by DFT computational analysis of the 1,5-hydride transfer by Ming Kit Sze.[217] In all four steps, the aluminium is suspected to enthalpically stabilise the anionic intermediates and reduce the entropic barrier by preorganising the structure.



Scheme 5-6) The proposed mechanism shows all of the potential roles of aluminium during the reaction.

After the second E1cB elimination, we suspected that aluminium alkoxide **5-31** irreversibly forms Al_2O_3 and related precipitates.[a] A white precipitate can be observed within seconds at rt when water is added dropwise to a solution of Al(O*t*-Bu)$_3$ in toluene (as well as being observed during 1,5-hydride transfer reactions).[218]b

This hypothesis is consistent with the results found by Lewis Smith previously. He discovered that dropping the loading of Al(O*t*-Bu)$_3$ to 60 mol% had no effect on the yield, but with loadings below this there was a significant drop in the yield of the cyclohexene **5-26** (Scheme 5-7).[219] It is worth noting that the Al_2O_3 by-product is itself capable of catalyzing 1,5-hydride shifts resulting in an undesired background reaction with different selectivity compared to the initial aluminium alkoxide.



Scheme 5-7) Lewis Smith demonstrated Al(Ot-Bu)$_3$ could not turnover in the current system.

5.3. Aims.

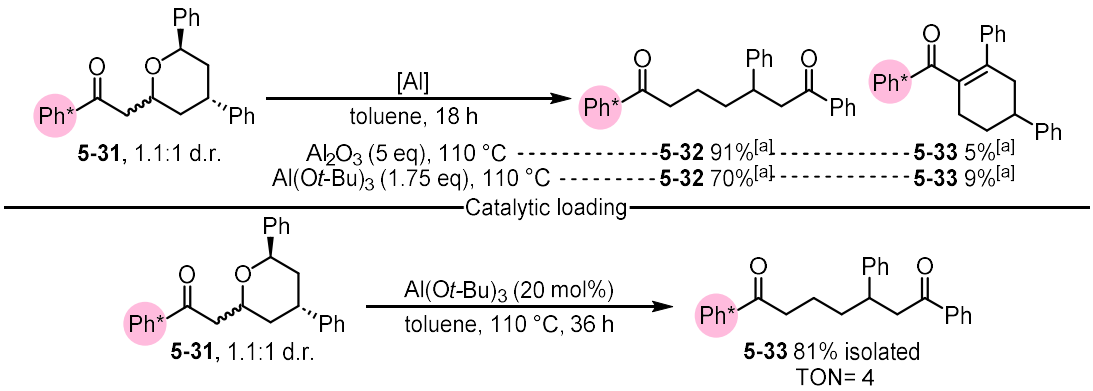
Based on our understanding of the 1,5-hydride transfer mechanism, we aimed to achieve 1,5-hydride transfer reactions with catalytic aluminium loadings by using substrate control to

[a] Inorganic chemists have characterised a number of different types of alumina and alumina hydrate species as well as $Al_wO_x(OH)_y(OR)_z$ complexes. All of these are referred to as alumina or Al_2O_3 here.[303,304]
[b] More detailed mechanistic analysis is discussed in the appendix section 7.1.

prevent the condensation of the diketone **5-28** and thus prevent the decomposition of the aluminium alkoxide reagent.

5.4. Testing the Hypothesis with 2,4,6-Substituted THP Rings.

When exploring the chemistry of 2,4,6-substituted THP ring **5-31(*cis*)**, we previously found that condensation of the diketone intermediate did not occur in significant quantities at 110 °C, resulting in the isolation the diketone **5-32** in up to 91% yield (Scheme 5-8). Cyclisation of this substrate, to form **5-33**, was observed when both elevated temperature (130 °C) and Al(O*t*-Bu)$_3$ were used. Hence, the reaction of THP **5-31** was performed with 20 mol% of Al(O*t*-Bu)$_3$ at 110 °C for 36 h.[a] We were delighted to find that under these conditions, complete conversion to diketone **5-32** was observed, and the product was isolated in 81% yield (TON=4). This successful result proves the hypothesis that water formation in the condensation is the cause of the alkoxide decomposition.



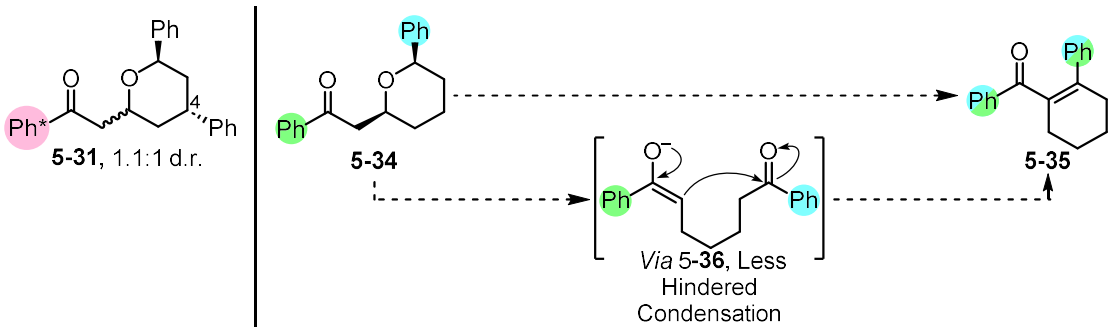
Scheme 5-8) Initial results using 2,4,6-substituted THP rings. 1,5-Hydride shift using 20 mol% Al(Ot-Bu)$_3$. [a] Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard.

5.5. Optimisation of Dicarbonyl Formation.

5.5.1. Selection of a Model Substrate.

In order to further explore the catalytic reaction manifold, an alternative model substrate, THP **5-34**, was chosen (Scheme 5-9). Removing the C4-Ph group removes the need to control the relative stereochemistry in the starting material, which we have previously shown has a significant effect on the substrate reactivity. Replacing the Ph* group with a Ph was expected to make condensation faster due to the reduced steric hindrance of the electrophile **5-36**, which was thought to allow us to more clearly examine the effect of changing the conditions on condensation. The symmetry of the substrate also means only one cyclohexene **5-35** is formed.

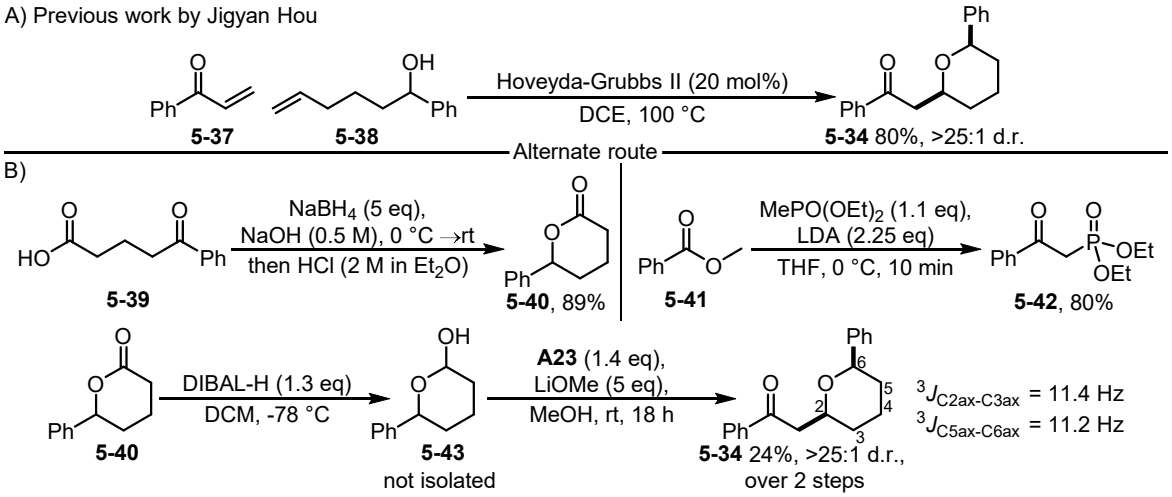
[a] Because of the high concentration and instability of the aluminium complex the reaction was not monitored by TLC



*Scheme 5-9) The model substrate **5-34** was chosen for future reactions.*

5.5.2. Substrate Synthesis.

Given the large amount of material desired, the alkene metathesis of the olefins **5-37**+**5-38**, using Hoveyda-Grubs catalyst (20 mol)%, was replaced (Scheme 5-10 A).[93] Reduction of the ketone **5-39** gave the lactone **5-40** in 89% yield by,[220] and the phosphite **5-42** was made by alkylation of the benzoyl ester (**5-41**) (Scheme 5-10 B).[16] The reduction-olefination sequence previously used in the group only gave 10% yield of the THP **5-34**. However mild olefination conditions developed by Maegawa and co-workers gave the desired product **5-34** in 24% yield over two steps.



*Scheme 5-10) (A) previously reported synthesis of THP **5-34**. (B) HWE route to synthesise the THP **534**.*

5.5.3. Optimisation of Diketone Formation.

With the model substrate **5-34** in hand, we began optimising the reaction, aiming to maximise conversion of the starting material and selectivity of the diketone **5-36** over the cyclohexene **5-35**. Using stoichiometric Al(O*t*-Bu)$_3$, gave a 69% combined yield with a 66:33 ratio of open diketone **5-36** to cyclohexene **5-35** (Table 5-1, Entry 1). With 20% loading, the total yield decreased to 40% with a product ratio of 63:37 (Entry 2). Lowering the catalyst loading or the

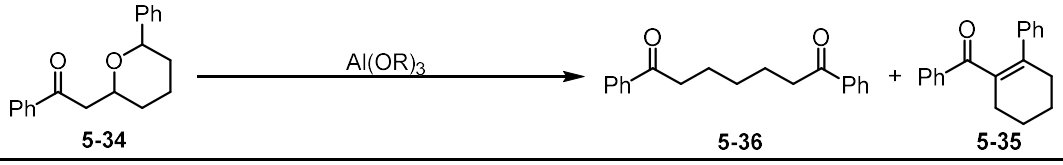
temperature led to <5% yield. Increasing the concentration led to a combined yield of 50% after 20 h (TON 2.5, Entry 6).

It was thought the addition of *t*-BuOH as a proton source could quench enolate **5-45**, preventing condensation. Although high selectivity was observed, the yield was diminished to 15% (Entry 7). Increasing the concentration resulted in a 51% combined yield with more modest selectivity (75:25, Entry 8).

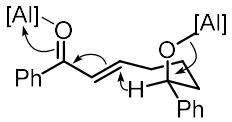
The HO-2,6-$Me_2C_6H_3$ ligand, which was previously found to reduce the formation of extended enolates,[a] was tested to improve selectivity (Entry 9). The diketone **5-36** was formed as the only product with only 30% yield. Increasing the concentration to 0.33 M maintained the selectivity but did not increase yield (Entry 10). Despite the lack of condensation, further conversion was not observed over 36 h (Entry 11).

Increasing the concentration was key to increasing the TON (Entry 6), giving 50% yield compared to 69% with a stoichiometric Al loading. Conditions using *t*-BuOH as a cosolvent (Entry 8) were taken forward and those described in Entry 10, which gave a modest yield but complete chemoselectivity.

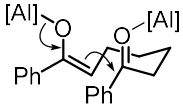
[a] Measured by the epimerisation of a thermodynamically unstable 3°centre. Discussed in Chapter 4.



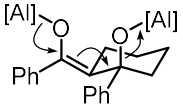
5-34 5-36 5-35



5-44 Desired reaction



5-45 Undesired reaction



5-46 Undesired reaction

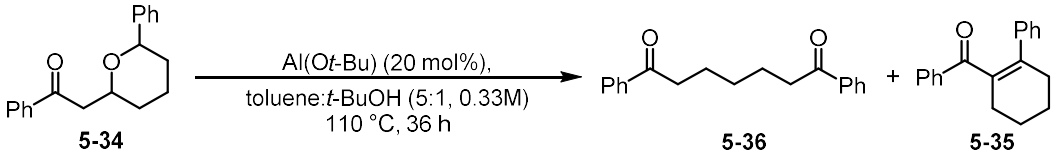
	Al(OR)$_3$ (mol%)	Solvent System (M)	Temp (°C)	Time (h)	5-34 (%)	5-36 (%)	5-35 (%)	Σ(5-35-5-36) (%)	TON
1	*t*-Bu (100)	toluene (0.1)	110	18	-	46	23	69	0.7
2	*t*-Bu (20)	toluene (0.09)	110	36	34	25	15	40	2
3	*t*-Bu (5)	toluene (1.05)	110	36	74	4	-	4	0.2
4	*t*-Bu (20)	DCE:toluene (4:1) (0.1)	90	20	92	2	-	2	0.1
5	*t*-Bu (20)	toluene (0.1)	90	20	89	3	2	5	0.3
6	*t*-Bu (20)	toluene (0.33)	110	20	30	30	20	50	2.5
7	*t*-Bu (20)	toluene:*t*-BuOH (20:1) (0.09)	110	20	85	14	1	15	0.75
8	*t*-Bu (20)	toluene:*t*-BuOH (5:1) (0.33)	110	20	26	38	13	51	2.5
9	2,6-$Me_2C_6H_3$ (20)	toluene (0.1)	110	20	40	30	trace	30	1.5
10	2,6-$Me_2C_6H_3$ (20)	toluene (0.33)	110	20	49	25	-	25	1.3
11	2,6-$Me_2C_6H_3$ (20)	toluene (0.33)	110	36	56	18	-	18	0.9

Table 5-1) Optimisation of catalytic 1,5 hydride shift. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard.

5.5.4. Screening of Desiccants.

With the condensation partially suppressed, we wondered if additives would mop up water allowing condensation to occur without the catalyst being destroyed;[a] hence, several known solid desiccants were added (Table 5-2). In all cases, yields decreased and no cyclohexene **5-35** was observed. It was unclear why adding desiccants resulted in decreased formation of the cyclohexene **5-35**.

[a] Entry 6 and 8 resulted in approximately the same yield and selectivity. The higher selectivity at low concentration (Entry 2 and 7) made Entry 8 more promising

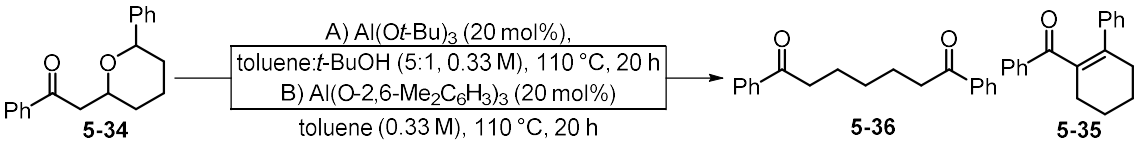


5-34 5-36 5-35

	Additive	5-34 (%)	5-36 (%)	5-35 (%)	Σ(5-35-5-36) (%)	TON
12	-	26	38	13	51	2.5
13	3Å Molecular Sieves[a,b]	59	30	-	30	1.5
14	4Å Molecular Sieves[a,b]	59	30	-	30	1.5
15	LiCl[a,b]	76	7	-	7	0.4

Table 5-2) Screening of inactive desiccants. NMR yields given based on TMB as an internal standard. [a] Heated under vacuum at 225 °C, 18 h. [b] Stored under vacuum at 110 °C. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard.

Subsequently, $MgSO_4$, Ti(O*t*-Bu)$_4$, and triethyl orthoacetate were chosen as they might directly mediate the E1cB elimination (Table 5-3). Previous research had shown that similar Mg, and Ti complexes did not mediate the 1,5-hydride transfer conditions.[94] These reagents were added to the *t*-BuOH cosolvent conditions and the chemoselective aluminium phenoxide conditions. The yields were generally observed to decrease significantly, using triethyl orthoacetate led to the formation of complex olefin(s), which could not be isolated (Entry 21). Unfortunately, the screening of external desiccants led to no increase in the TON or chemoselectivity.



5-34 5-36 5-35

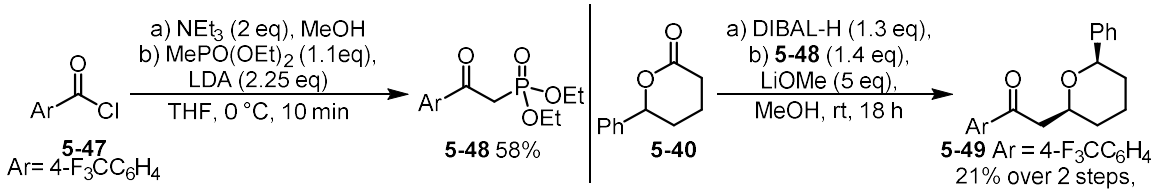
	Conditions	Desiccant (eq)	5-34 (%)	5-36 (%)	5-35 (%)	Σ(5-35-5-36) (%)	TON
16	A	$MgSO_4$ (4)	78	18	-	18	0.9
17	A	Ti(O*t*-Bu)$_4$(1)	75	17	-	17	0.8
18	A	Triethyl orthoacetate (1)	85	-	-	-	-
19	B	$MgSO_4$ (4)	89	3	-	3	0.2
20	B	Ti(O*t*-Bu)$_4$(1)	15	38	15	52	2.6
21	B	Triethyl orthoacetate (1)	36[a]	-	-	-	-

Table 5-3) Screening of active desiccants. Yields are ^{1}H -NMR yields calculated based on 1,3,5-trimethoxybenzene as an internal standard. [a] substrate reacted to form an unknown olefin specie(s).

5.5.5. The Effect of EWG on the 1,5-Hydride Shift Reaction.

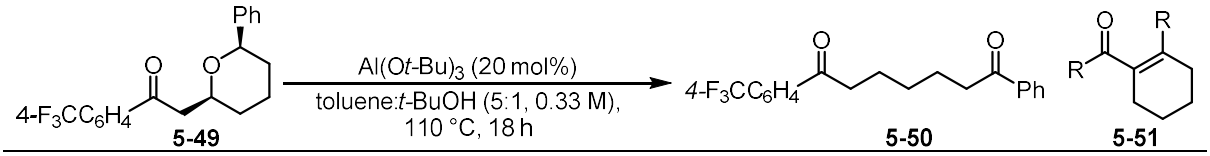
In the optimisation of the enantioselective 1,5-hydride shift by Jingyan Hou, it was found that the introduction of an electron-withdrawing *p*-CF_3 group to the aryl ketone of the 2,3-substituted THP **5-21** resulted in a significant increase in the reaction rate (Scheme 5-5).[6] Therefore, we decided to synthesise **5-49** to see if this effect benefited this 2,6-substituted

system.[a] The HWE reagent **5-48** was synthesised in 58% yield, followed by the reduction-olefination sequence to form the THP **5-40** in 21% yield over two steps as a single diastereomer (Scheme 5-11). The relative stereochemistry was determined by *J*-coupling.



*Scheme 5-11) Synthesis of the p-CF_3 substituted THP **5-49**.*

The substrate **5-49** was submitted to the previously optimised conditions under a range of temperatures, no sign of reactivity was observed below 110 °C (Table 5-4, Entry 22-24). At 110 °C, some product was formed with good regioselectivity but poor yield (Entry 25). Given the high selectivity, the reaction was repeated over 36 h, which resulted in products **5-50**+**5-51** in 58% yield and 70:30 selectivity. The cyclohexene **5-51** forms a 58:42 mixture of regioisomers, likely due to the lack of steric differentiation (Entry 26).[b]



Entry	Temp (°C)	Time (h)	5-49 (%)	5-50 (%)	5-51 (%)	Σ(5-50-5-51) (%)	TON
22	50	18	100	-	-	-	-
23	70	18	100	-	-	-	-
24	90	18	100	-	-	-	-
25	110	18	61[a]	17[a] (18)	-	(18)	1
26	110	36	41	42(39)	17(17%)[b]	58(56)	2.9

*Table 5-4) Temperature screening of the p-CF_3 substituted THP **5-49**. ^{1}H-NMR Conversions reported. [a] Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (isolated yields) [b] 1.4:1 r.r. One isomer was isolated as a mixture with the starting material.*

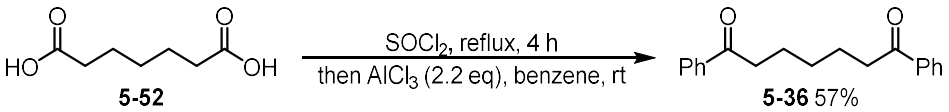
The addition of the p-CF_3 aryl group resulted in a modest increase in yield compared to the unsubstituted substrate **5-34** but with a significant decrease in the reaction rate. The clear difference between this result and the ongoing work by Jingyan Hou suggests the substitution pattern affects the mechanism (see Section 7.1.3).

[a] Introducing a substituent to the ring breaks the symmetry of the diketone and greatly increases the complexity of any cyclohexene. Selective diketone ring closing, without the use of Ph*, is an unsolved problem in the group and beyond the scope of this report.

[b] The *p*-CF_3 ketone was the major regioisomer. Ratio determined based on isolated material. See SI for details.

5.6. Condensation of Diketones to Form Cyclohexenes.

To access the catalytic strategy to access the desired cyclohexenes, we need to establish ring closing conditions for the diketone **5-36**. For screening purposes, the diketone was synthesised on an 8 mmol scale by a double Friedel-Craft reaction of diacid **5-52** in 57% yield (Scheme 5-12).



*Scheme 5-12) Synthesis of 1,7 diketone **536** by Friedel Craft.*

The diketone **5-36** was submitted to 300 mol% Al(O*t*-Bu)$_3$ conditions giving the cyclohexene in 26% yield; freshly generated reagent improved conversion significantly (Table 5-5, Entry 2). Consumption of the starting material required higher loading (500 mol%) over 24 h to give the product in 53% yield (Entry 5).

In order to access alternatives to aluminium alkoxides, various literature conditions were screened (Entry 7-15). The conditions reported in the literature consistently returned the starting material **5-36** without significant reactivity (Entries 7-14). Interestingly, a highly non-polar. novel product **5-53** was cleanly formed when the diketone was subjected to *p*-TSA. The ^{1}H and ^{13}C-NMR spectra showed desymmeterisation of one of the Ph rings, consumption of the carbonyls and two distinctive electron-poor aryl carbons observed (140.4, 143.3 ppm). The product was determined to be chromene **5-53**, formed in 63% yield.



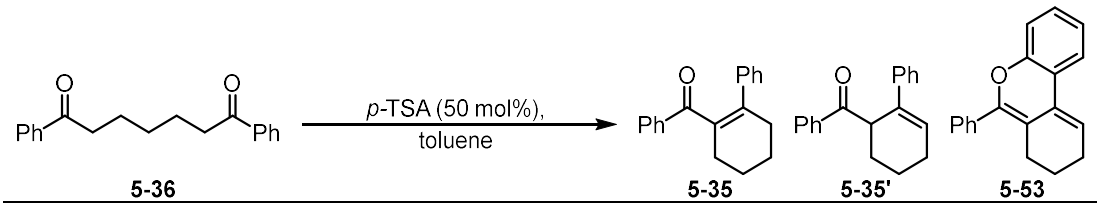
5-36 5-35 5-53

	Reagent (mol%)	Solvent	Temp (°C)	Time (h)	5-36 (%)	5-35 (%)	5-53 (%)
1	Al(O*t*-Bu)$_3$ (300)	Xylene	130	18	47	20	-
2	Al(O*t*-Bu)$_3$ (100) [a]	Toluene	110	18	46	23	-
3	Al(O*t*-Bu)$_3$ (200) [a]	Toluene	110	18	29	46	-
4	Al(O*t*-Bu)$_3$ (500) [a]	Toluene	110	18	12	53	-
5	Al(O*t*-Bu)$_3$ (500) [a,b]	Toluene	110	24	-	(53)	-
6[221]	KO*t*-Bu (200)	Ethanol	80	18	31	-	-
7	Piperidine (100)	Ethanol	80	18	74	8	-
8	Piperidine (100)	Ethanol[c]	80	18	70	-	-
9[222]	HCl (25% solv.)	THF	50	18	73	5	-
10[223]	KOH (120)	DCE	80	18	70	-	-
11[224]	KOH (120)	Dioxane	80	18	56	-	-
12[225]	KOH (60)[d]	THF:H_2O (1:1)	80	18	63	-	-
13[226]	*t*-BuOK (140)	THF:*t*-BuOH (4:1)	80	18	-	-	-
14[227]	*p*TSA.H_2O (50)[b]	Toluene	80	18	-	-	(63)

Table 5-5) Exploration of known condensation cyclisation conditions. 0.1 mmol scale. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (Isolated yields). [a] Fresh Al(Ot-Bu)$_3$ generated from AlMe$_3$ [b] 0.3 mmol, [c] NaSO$_4$ (2.8 eq) added . [d]NBu$_4$OH (3mg) added.

5.6.1. Acid-Catalysed Cyclisation.

Believing the chromene **5-53** was a derivative of the desired enone **5-35**, the temperature and reaction time were reduced (Table 5-6). Reduction of the temperature to 60 °C gave the skipped enone **5-35'** as the major product in 16% yield (Entry 16). Running the reaction for 8 h resulted in formation of skipped enone **5-35'** in 41% yield, with modest formation of the two other products in a 1:7:1 ratio (Entry 17). Sparging the reaction with argon before heating gave both the skipped enone **5-35'** and chromene **5-53** forming in 39% yield after 18 h (Entry 18).

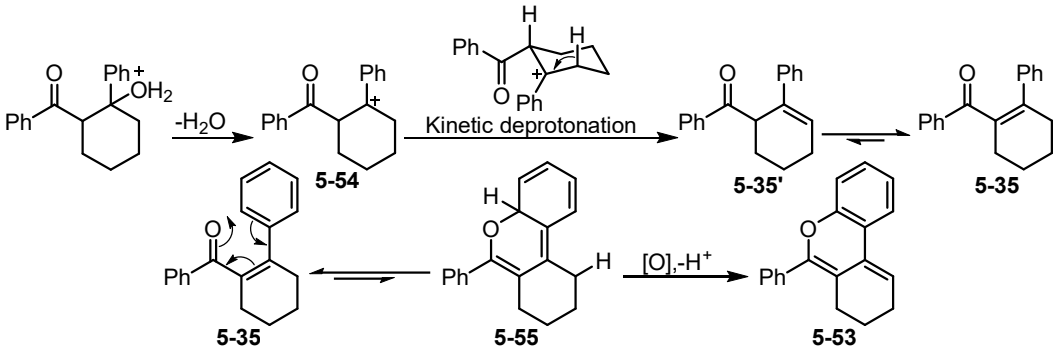


5-36 5-35 5-35' 5-53

	Temp (°C)	Time (h)	5-36 (%)	5-35 (%)	5-35' (%)	5-53 (%)
14	80	18	-	-	-	(63)
15	40	18	72	-	-	-
16	60	18	49	2	16	-
17	80	8	18	6	41	6
18	80[a,b]	18	-	(13)	(39)	(39)

Table 5-6) Optimisation of the acid mediated diketone ring closing. [a] 0.3 mmol. [b] Reaction sparged with argon. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. (isolated yields)

Based on these results, we hypothesise that under acidic conditions, formation of the skipped enone **5-35'** proceeds *via* E_1 elimination of the cation **5-54** (Scheme 5-13). From there, the alkene thermodynamically isomerises to form enone product **5-35**. The formation of chromene **5-53** appears to result from a proton-mediated oxa-6π electrocyclisation of **5-35** and subsequent oxidation of **5-55** acting as a thermodynamic sink to drive the reaction.[228–230]a



*Scheme 5-13) Proposed mechanism for the formation of the skipped enone **5-35'** and chromene **5-53**.*

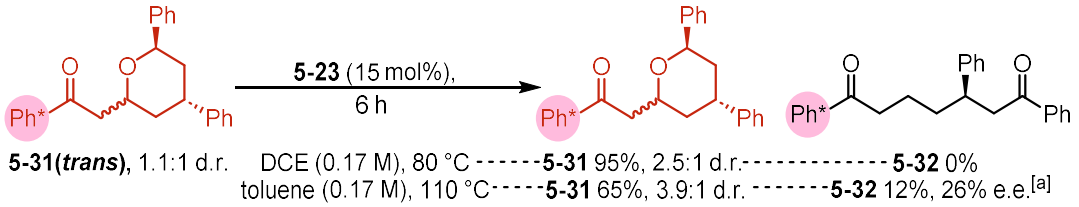
5.7. Further Work.

We were pleased to demonstrate a catalytic version of the previously reported THP rearrangement for the first time and experimentally validate the reason why stoichiometric aluminium reagents are generally needed. However, this approach is limited to a narrow subset of 2,6-substituted THP rings where the condensation step is most hindered. We propose that further work should aim to: (i) apply enantioselective conditions to this class of substrates, (ii) Look at alternate condensates as a general strategy to perform catalytic reactions.

[a] A review of the biological relevance of chromenes by Lee and co-workers was published in 2020.[305]

5.7.1. Enantioselective Kinetic Resolution.

In the future a kinetic resolution of THP **5-31(*trans*)** could be used to synthesise enantioenriched ketone **5-32**. In toluene at 110 °C, the desired diketone **5-32** was afforded in 12% yield and 26% e.e., which equates to an S-factor of 1.8 (Scheme 5-14).[231] In this preliminary result, we were pleased to demonstrate that modest enantioselectivity could be achieved without any modification of the established conditions or catalyst design and may be of interest for future research.



Scheme 5-14) Proof of principal for the kinetic resolution of the C4 position. Yields are ^{1}H -NMR yields calculated based on TMB as an internal standard. [a] Absolute stereochemistry was not determined.

5.7.2. Piperidine Substrates.

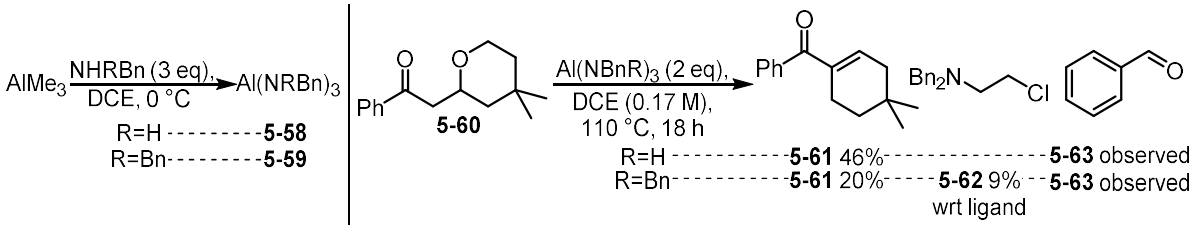
An alternative to preventing condensation from happening altogether would be to change the molecule released in the condensation. Weinreb and co-workers have previously synthesised aluminium amide complexes and found them to be soluble and stable in aprotic organic solvents.[232] Based on this, we are interested to see whether analogously substituted piperidines **5-56** could be used as substrates; the resulting amine condensate would result in a traceless formation of the desired cyclohexene **5-57** without the undesired water formation (Scheme 5-15).



*Scheme 5-15) piperidines, such as **5-56**, could undergo 1,5-hydride shifts without producing water in situ.*

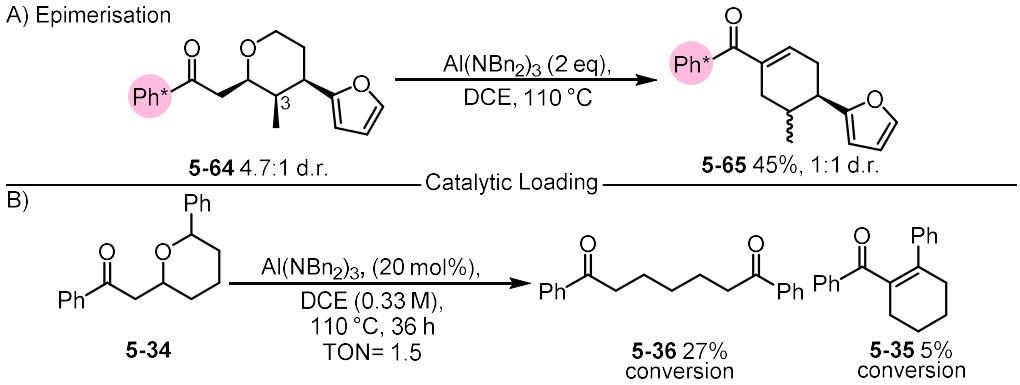
The resulting aluminium-amide complex, whilst being soluble, may not promote the 1,5-hydride transfer reaction. To evaluate this concern, $AlMe_3$ was amidated using aluminium amides **5-58** and **5-59** (Scheme 5-16). With the 2° amine, the desired product **5-61** was formed in 46% yield. The ligand was observed to react with the solvent *in situ* to give the tertiary amine

5-62. The 1° amine showed partial conversion, with 20% isolated yield. Benzaldehyde (**5-63**) was observed by ^{1}H-NMR in both reactions.[a]



Scheme 5-16) Aluminium-amide complexes were observed to promote 1,5-hydride transfer.

$Al(NBn_2)_3$ **5-59** was subsequently used to promote 1,5-hydride transfer with the 2,3,4 and 2,6-substituted THP rings **5-64+5-34** previously discussed. Furan **5-65** was isolated in 45% yield in a 1:1 d.r. (Scheme 5-17 A). 32% conversion of the 2,6-substituted THP was observed using 20 mol% loading of the aluminium catalyst (TON=1.5, Scheme 5-17 B).[150] In both reactions, the results were worse than with the previously optimised conditions.



Scheme 5-17) Effect of aluminium amide on the previously explored epimerisation of the C3 centre (A) and the catalytic system (B).

As well as suggesting that piperidines **5-56** are feasible substrates, this preliminary work demonstrates that aluminium amides are capable of promoting 1,5hydride transfer. This could be valuable for future work as nitrogen-based ligands allow for a wide variety of new, easily accessible chiral aluminium complexes to be synthesised, which can easily access the space around the aluminium centre (Figure 5-1).

[a] Benzaldehyde was observed in 7% NMR yield w.r.t. $Al(NBn_2)_3$ **5-59**. As discussed previously in section 2.4.2 the stability of aldehydes generated at high temperatures means the amount of aldehyde generated is likely much higher.

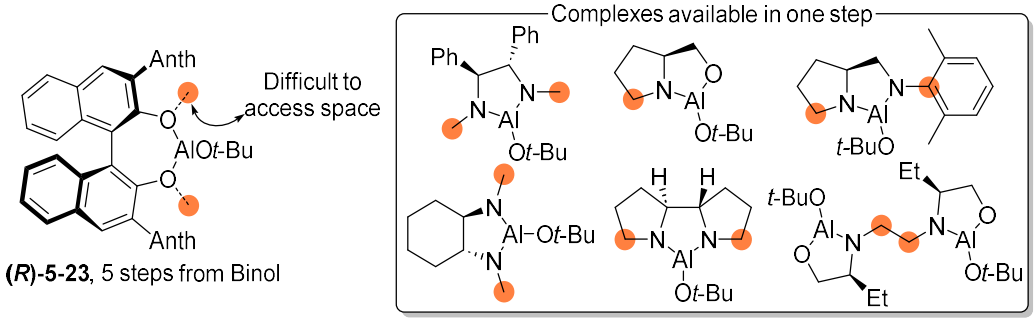


Figure 5-1) A) Readily accessible aluminium amide complexes could be used to control stereochemistry or develop new reactivity.

Chapter 6. Experimental Procedures.

6.1. General Methods.

All procedures were performed under a N_2 atmosphere unless stated otherwise.

6.1.1. Reagents and Starting Materials.

DCM, Et_2O, toluene, MeCN, benzene, chloroform, methanol, pyridine, DMF and triethylamine were purified by filtration through activated alumina columns employing the method of Grubbs and co-workers[233] KOH and NaOH were freshly ground before immediate use. Cinnamaldehyde, butanal and hexanal were distilled before use. Benzyl bromide was filtered through a plug of K_2CO_3 before use. All other reagents were used as supplied. Brine refers to a saturated solution of sodium chloride.

When catalytic loadings of aluminium alkoxides where employed: toluene, after being purified by the method above,[233] was stored over 4 Å molecular sieves for at least 48 h before use (referred in the text as dry); *t*-BuOH anhydrous ≥ 99.5% supplied by Sigma Aldrich was used as supplied.

6.1.2. Handling of α-Keto Piperidines.

Piperidines were found to oxidise during the work up, FCC as well as when the crude was dissolved in $CDCl_3$ for NMR analysis. Samples should be allowed to fully cool to rt before microwave vials are opened. The resulting viscous oil and solid mixture was dissolved in a mixture of DCM and EtOAc and filtered through silica as soon as possible. FCC was performed without analysis of the solution to minimise the amount of time the sample was exposed to silica. Tetrahydropyridines, observed to form during FCC were collected alongside the desired piperidine.

6.1.3. Temperature Control.

Reactions were heated using a silicon oil bath with automated temperature control and verified with an alcohol thermometer. Cooling to 0 °C was performed with an ice bath. Cooling to -78 °C was performed using excess dry ice bath at -78 °C if the reaction time was under 8 h. Cooling to temperatures between 0 and -30 °C for less than 90 mins was achieved *via* an acetone with dry ice bath and regulated by addition of acetone and dry ice. For longer time periods, cooling was controlled by an EK90 immersion cooler. Oil baths were preheated unless stated otherwise.

6.1.4. NMR Yields and Conversions.

Conversions refer to relative integrals of diagnostic peaks. All structures were either previously isolated within the group or commercially available. NMR standards were added after workup and the crude being concentrated under reduced pressure. 1,1,2,2-tetrachloroethane was added directly *via* microsyringe. 1,3,5-Trimethoxy benzene was weighed into a 5 mL volumetric flask and dissolved into $CDCl_3$ to give a stock solution of known concentration. The lid was sealed with parafilm and used within 3 days.

6.1.5. Flash Column Chromatography.

FCC was carried out using Merck Geduran® Silicagel (40-63 μm particle size) or Merck Geduran® Silicagel (15-40 μm particle size). Amines were purified on pre-basified silica which was prepared as follows; silica (400 g), Et2O (500 mL) and triethylamine (5 mL) were combined in a 1 L beaker and stirred for 15 mins. The solvent was allowed to evaporate overnight, and the resulting silica could be stored in a sealed bottle. Analytical thin layer chromatography was carried out using pre-coated, aluminium backed plates (Merck Kieselgel 60 F254). Visualisation was achieved with ultraviolet irradiation (254 nm) and staining with solutions of potassium permanganate or vanillin as appropriate.

Potassium permanganate solution was made by dissolving potassium permanganate (2.5 g), potassium carbonate (13 g) and sodium hydroxide (0.63 g) in water (250 mL).

Vanillin solution was made by dissolving 4-hydroxy-3-methoxybenzaldehyde (15 g), glacial acetic acid (1.5 mL) and concentrated sulfuric acid (1.5 mL) in ethanol (250 mL).

6.1.6. Naming and Numbering of Compounds.

Compound names were generated using the computer software ChemDraw according the to the International Union of Pure and Applied Chemistry (IUPAC) guidelines. The unnecessary numbering is removed from the pentamethyl Ph* group. The numbering shown on structures has been used to aid NMR assignment, Numbering was chosen to allow for an ease of comparison between similar compounds or compounds in a sequence and does not necessarily correspond with the systematic name. Compounds that are not assigned a compound number in the main text are labelled S1-1, S1-2 etc.

6.1.7. NMR Spectroscopy.

^{1}H-NMR spectroscopy was carried out using either a Bruker AVC500 (500 MHz), AV400 (400 MHz), DPX400 (400 MHz), AV600 (600 MHz) NEO600 (600 MHz) spectrometer using the residual non-deuterated solvent signal as the internal reference. Chemical shifts are quoted in ppm, 123 based on appearance rather than interpretation.

^{1}H-NMR spectra are reported as follows: *^{1}H-NMR* (*spectrometer frequency, solvent) δ_H: chemical shift/ppm (coupling constant, number of protons, assignment) ppm*. The assignment refers to the numbering scheme shown in the diagrams prefacing each experimental procedure. The multiplicity is abbreviated in the following way: s = singlet; d = doublet; t = triplet; q = quartet; quint. = quintet; sept. = septet; m = multiplet; br = broad.

^{13}C-NMR spectroscopy was carried out using the same machines described above. Using the central resonance of the solvent signal as refrence. ^{13}C-NMR spectra are reported as follows: *^{13}C-NMR* (*spectrometer frequency, solvent) δ_C: chemical shift/ppm (couplings, assignment*) ppm. Assignments given refer to a combination of the numbering schemes shown along with other generic labels. A variety of additional spectroscopic techniques including COSY, HSQC, HMBC and NOESY were used to assign the one-dimensional spectra as necessary.

If two carbon peaks fully overlap a single value is given and two carbons are assigned e.g. 38.0 (C9M+C9m) ppm, if 2 distinct peaks are observed, but have the same shift to 1 d.p., two peaks are listed with the same value 200.5 (C11M), 200.5 (C11m) .

6.1.8. Assignment of Ph* Ketone.

The chemical shifts of the Ph* Methyl and Ph* 4° peaks were found to be consistent in numerous ketone structures. The peaks were assigned using HMBC couplings and found to be consistent across multiple structure (Figure 6-1). Subsequent assignment was done by comparison. Assignment is consistent with NOESY couplings when these were obtained as well as atropisomeric splitting.

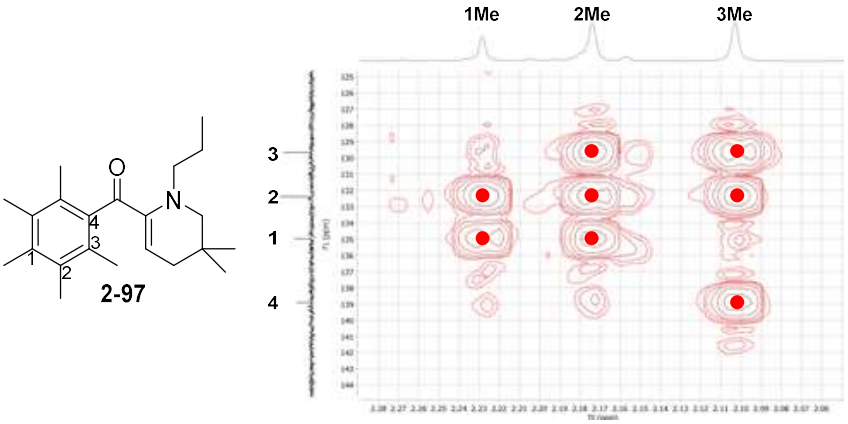


*Figure 6-1) HMBC of the enone **2-97**.*

Relevant ^{1}H and ^{13}C peaks in enone **2-97** are described below.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.23 (s, 3H, C1Me), 2.17 (s, 6H, C2Me), 2.10 (s, 6H, C3Me) ppm.

^{13}C NMR δ_C (126 MHz, $CDCl_3$) δ_C: 139.0 (C4), 135.1 (C1), 132.5 (C2), 129.8 (C3) ppm.

6.1.9. Infared Spectroscopy.

Infrared spectra samples were prepared as a neat film and were recorded using a Bruker Tensor 27 FTIR spectrometer. Spectra are reported as follows: FTIR(film)= *absorption maxima/cm^{-1}*.

6.1.10. High Performance Liquid Chromatography (HPLC).

HPLC analysis was preformed using an Agilent 1260 Infinity II instrument, equipped with Chiralcel® and Chiralpak® columns (250mm x 4.6 mm, particle size 5 µm) and appropriate guard columns (4 mm x 10 mm, particle size 5 µm) and a diode array detector. Enantiomeric samples were compared to an authentic sample of the corresponding racemic compound.

6.1.11. High Resolution Mass Spectroscopy.

High resolution mass spectrometry (HRMS) was carried out by staff at the Oxford University Mass Spectrometry Research Facility. Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with Waters Equity liquid chromatography system using an eluent of 10:89.9:0.1 water:methanol:formic acid and a flow rate of 0.2 mL min^{-1}. The system was operated using a heated electrospray

(HESI-II) probe with a resolution of 50,000 FWHM. Conditions were adjusted to maximise sensitivity, and the system was calibrated on the day of analysis to have an accuracy of better than 5 ppm for 24 hours following external calibration. Instrument control and data processing were carried out using Agilent MassHunter software. The mass reported is that containing the most abundant isoptopes and is within 5 ppm of the calculated mass, unless otherwise stated. HRMS values are quoted as a mass to charge ratio (m/z) in Daltons, rounded to 4 decimal places and within 5 ppm of the calculated value.

6.1.12. Optical Rotation.

Specific optical rotation was measured on a Schmidt Haensch Unipol L2000 Polarimeter, using a 100 mm quartz glass mictrotube (volume 1 cm^3) at the sodium D line (λ= 589.3 nm) and at 25 °C. $[\alpha]_D^{25}$ values have units $10^{-1}deg.cm^2g^{-1}$. The solvent used is quoted in parentheses, along with the concentration, C, which has units $10^{-2}.g.mL^{-1}$.

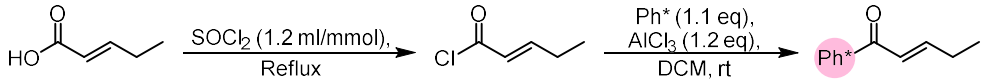
6.1.13. X-Ray Crystallography.

Single crystal X-ray diffraction was recorded by Amber Thompson using a Nonius Kappa CCD diffractometer or Oxford Diffraction/Agilent Supernovae A. Crystal structure images presented were produced using the computer software pyMol.

6.2. General Reactions and Procedures.

General Procedures described below are given as specific examples. In section 7.3-7.7, either a full procedure is given or the changes to the general procedure are described as well as the characterisation of products.

6.2.1. General Procedure 2A: Synthesis of Acid Chlorides and Subsequent Friedel-Craft Acylation.



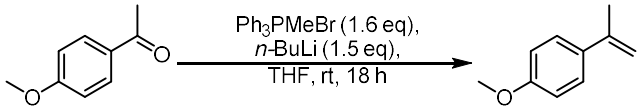
(E)-1-(pentamethylphenyl)pent-2-en-1-one (**4-54**)

Based upon a modified literature procedure.[234]

To pent-2-enoic acid (2.1 mL, 21 mmol) was added $SOCl_2$ (25 mL, 1.2 mL/mmol) dropwise at rt under rapid stirring. After 30 mins, once gas evolution had stopped, the reaction was heated to reflux (80 °C) for 4 h. The reaction was concentrated under reduced pressure with gaseous $SOCl_2$ filtered through a KOH trap. The acid chloride was used without purification.

To a solution of the crude acid chloride dissolved in DCM (250 mL) was added pentamethyl benzene (3.42 g, 23.1 mmol, 1.1 eq) followed by $AlCl_3$ (3.63 g, 27.3 mmol, 1.3 eq). After 40 mins, the solution was quenched by pouring the solution over ice (c.a. 100 g). The layers were separated and the aqueous layer was extracted with DCM (3 x 40 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane: Et_2O, 99:1→98:2) gave the desired enone **4-54** as a pale yellow solid (3.60 g, 15.6 mmol, 75%).

6.2.2. General Procedure 3A: Olefination of Ketones.



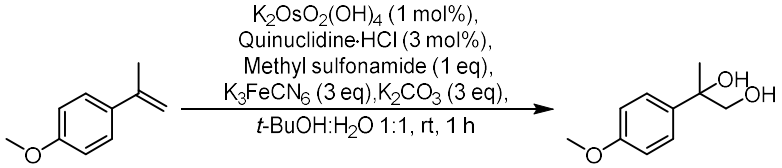
1-Methoxy-4-(prop-1-en-2-yl)benzene (**3-45**)

Based on the procedure by Lin and co-workers[235]

To a stirred solution of methyltriphenylphosphonium bromide (1.91 g, 5.33 mmol, 1.6 eq) in THF (33 ml) was added *n*-BuLi (2.0 mL, 2.5 M in THF, 5.2 mmol, 1.5 eq) dropwise at -78 °C. The solution was warmed to rt for 30 mins, and then the p-methoxy phenyl methyl ketone (600 mg, 3.33 mmol, 1 eq) was added portionwise. After 18 h, the reaction was quenched with aq. NH_4Cl (20 mL, sat) dropwise at 0 °C. The product was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by FCC (Pentane: EtOAc, 94:6→75:25) to give the desired product (445 mg, 3.00 mmol, 90%).

The characterisation of the product is below.

6.2.3. General Procedure 3B: Racemic Dihydroxylation.

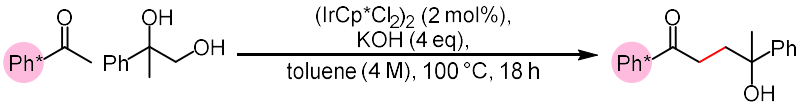


2-(4-methoxyphenyl)propane-1,2-diol (**3-40**)

To a stirred solution of the alkene (1.30 g, 8.78 mmol, 1 eq), quinucliodine·HCl (39 mg, 0.26 mmol, 3 mol%), K_2CO_3 (3.6 g, 26 mmol, 3 eq), $K_2Fe(CN)_6$ (8.7 g, 26 mmol, 3 eq) and methyl sulfonamide (837 mg, 8.80 mmol, 1 eq) in *t*-BuOH: H_2O (88 mL, 4:1) was added $K_2OsO_2(OH)_4$ (32 mg, 0.088 mmol, 1 mol%). After 18 h, upon consumption of the olefin, the product was extracted with Et_2O (5 x 30 mL). The combined organic layers were washed with aq. NaOH (4 x 10 mL, 2 M), dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by FCC (Pentane: EtOAc, 94:6→75:25) to give the diol as a waxy white solid (1.18 g, 6.48 mmol, 74%).

The characterisation of the product is below.

6.2.4. General Procedure 3C: Optimised Hydrogen Borrowing Conditions with 1,2-Diols.

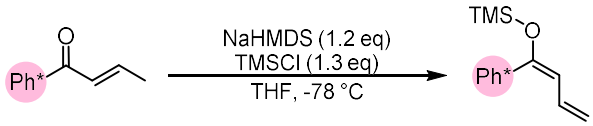


4-hydroxy-1-(pentamethylphenyl)-4-phenylpentan-1-one (**3-53**)

1,2-diol **3-50** (76 mg, 0.50 mmol, 1 eq), $(IrCp^*Cl_2)_2$ (8.0 mg, 0.01 mmol, 2 mol%), freshly ground KOH (112 mg, 2.00 mmol, 4 eq) and Ph* methyl ketone (190 mg, 1.00 mmol, 2 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times. Toluene (125 µL) was added, and the reaction was heated to 100 °C. After 18 h, the reaction was cooled to rt, diluted with EtOAc (5 mL) and flushed through a silica plug with EtOAc. The solution was concentrated under reduced pressure to give the crude product. The product was isolated using FCC (Pentane:Et_2O 98:2) to give the product **3-53** (135 mg, 0.415 mmol, 83%).

The characterisation of the product is below.

6.2.5. General Procedure 4A: Synthesis of Silyl Enol Ethers.



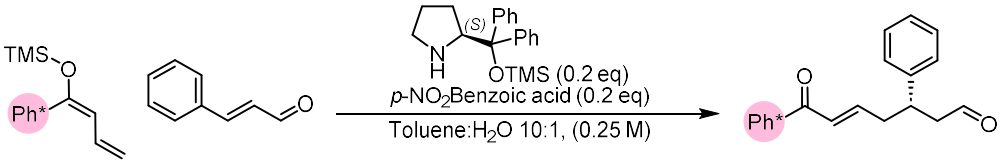
(E)-trimethyl((1-(pentamethylphenyl)buta-1,3-dien-1-yl)oxy)silane (**4-55**)

To a solution of enone **4-54** (1.30 g, 6.01 mmol) in THF (150 mL) was added NaHMDS (6.5 mL, 2 M in THF, 13 mmol, 2 eq) dropwise over 45 min using a syringe pump at -78 °C. After 30 min, a solution of TMSCl (1.7 mL, 7.8 mmol, 1.3 eq) was added dropwise over 3 h using a syringe pump, maintaining the temperature. After 1 h, the reaction was quenched with aq. NH_4Cl (10 mL, sat) and warmed to rt. The mixture was diluted with Et_2O (150 mL) and Brine (100 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were partially concentrated by reduced pressure until water became immiscible, the mixture was diluted with Et_2O (50 mL) and the aqueous layer was separated. The organic extract was dried with Na_2SO_4 and the crude was concentrated under reduced pressure and purified by FCC (Pentane)[a] to give the product **4-55** as a pale-yellow solid (1.14 g, 3.96 mmol, 66%).

The characterisation of the product is below.

[a] Compound could only be purified by dry loading, residual THF or Et_2O prevented purification. Residual water was found to lead to complete decomposition of the product.

6.2.6. General Procedure 4B: Mukaiyama-Michael Reaction.



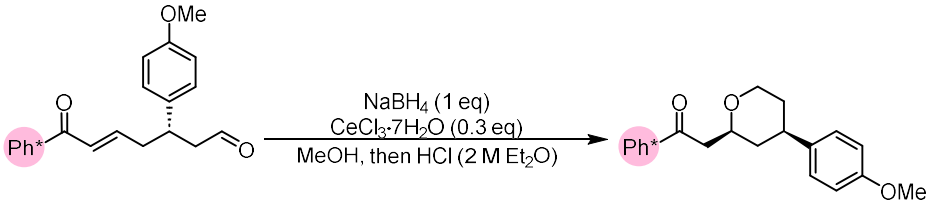
(E)-7-oxo-7-(pentamethylphenyl)-3-phenylhept-5-enal (**4-56**)

Based on a modified procedure by Schneider and co-workers[163]

Hayashi Jørgensen catalyst (***S*** or **rac**) (78 mg, 0.24 mmol, 20 mol%), *p*-NO_2benzoic acid (80 mg, 0.24 mmol, 20 mol%), silyl enol ether **4-55** (692 mg, 2.40 mmol, 2 eq), cinnamaldehyde (158 mg, 1.20 mmol, 1 eq) were dissolved in toluene and H_2O (4.8 mL, 10:1, 0.25 M). After 48 h, the mixture was diluted in EtOAc (20 mL) and H_2O (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extract was dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane: Et_2O, 80:20→75:25) gave the desired aldehyde **4-56** as a clear oil (313 mg, 0.898 mmol, 75%, 99% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent enone.

The characterisation of the product is below. The racemic substrates were synthesised using the same conditions, with racemic Hayashi Jørgensen catalyst.

6.2.7. General Procedure 4C: Reductive Cyclisation of 1,7-Dicarbonyls.



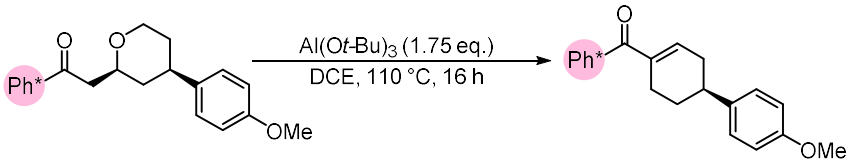
2-(4-(4-methoxyphenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-61**)

To a solution of the aldehyde **4-60** (75 mg, 0.20 mmol, 1 eq) was added MeOH (5 mL), followed by dropwise addition of DCM under rapid stirring until the solution was homogeneous. At 0 °C, $CeCl_3 \cdot 7H_2O$ (22 mg, 0.06 mmol, 0.33 eq) was added, followed by $NaBH_4$ (8 mg, 0.2 mmol, 1 eq) after 5 mins. After 12 mins, for 2,4-substituted THP, or 25 mins, for 2,3,4-substituted THPs, HCl (1 mL, 2M in Et_2O) was added dropwise, and the solution was allowed to warm to rt.[a] After 16 h, the solution was diluted with Et_2O (30 mL) and H_2O (15 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane: Et_2O, 90:10) gave the desired THP **4-61** as a waxy solid (56 mg, 0.15 mmol, 75%).

The characterisation of the product is below.

[a] Starting material can appear to be consumed by TLC but be observed after quenching, this is believed to be due to acetal and hemiacetals forming in situ. Quenching the reaction before the reaction has gone to completion can lead to inseparable cyclic acetal side products.

6.2.8. General Procedure 4D: 1,5-Hydride Shift with 2,4-Substituted THP rings.



(4'-methoxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-86**)

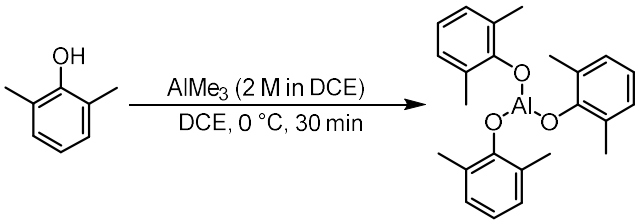
Based on a modified procedure by Donohoe and co-workers[94]

To a microwave vial was added THP **4-61** (31 mg, 0.086 mmol, 1 eq) and Al(O*t*-Bu)$_3$ (43 mg, 0.18 mmol, 1.75 eq). The flask was evacuated and flushed with N_2 four times, DCE (2 mL) was added *via* syringe and the suspension was heated to 110 °C. After 21 h, the reaction was cooled to rt and diluted with EtOAc (2 mL). The suspension was filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude product was purified by FCC (Pentane: Et_2O, 98.5:1.5) to give the desired product **4-86** (25 mg, 0.069 mmol, 69%).

The characterisation of the product is below.

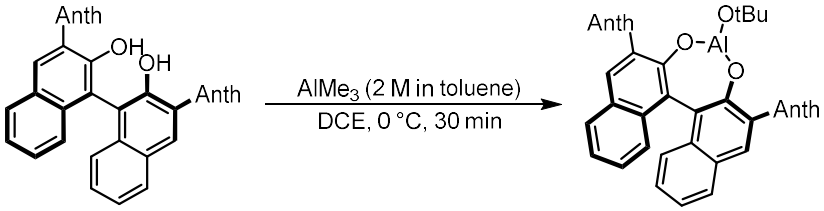
6.2.9. General Procedure 4E: Synthesis of Aluminium Alkoxides.

Monodentate Species.



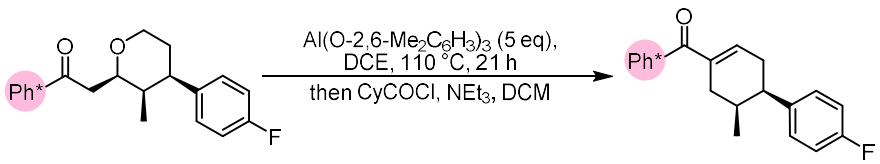
To a solution of 2,6 dimethylphenol (1.83 mg, 15.0 mmol, 3 eq) in DCE (12 mL) was added $AlMe_3$ (2.5 mL, 2 M in toluene, 5.0 mmol, 1 eq) cooled to 0 °C. After 30 mins, the aluminium alkoxide **4-71** was used as a 0.34 M solution without further purification.

Bidentate Species.



To a solution of binol **S6-01** (32 mg, 0.050 mmol, 1 eq) and *t*-BuOH (3.7 mg, 0.05 mmol, 1 eq) in toluene (950 µL) was added $AlMe_3$ (50 µL, 1 M in toluene, 0.05 mmol, 1 eq) dropwise at 0 °C. After 30 mins, the solution was warmed to rt. After a further 30 mins, aluminium alkoxide **5-23** was used as a 0.05 M solution without further purification.

6.2.10. General Procedure 4F: Stereoretentive 1,5-Hydride shift of 2,3,4-Substituted THP Rings.



(4'-fluoro-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4138**)

A solution of $Al(O\text{-}2,6\text{-}Me_2C_6H_3)_3$ (0.34 M) in DCE was synthesised using General Method 4E.

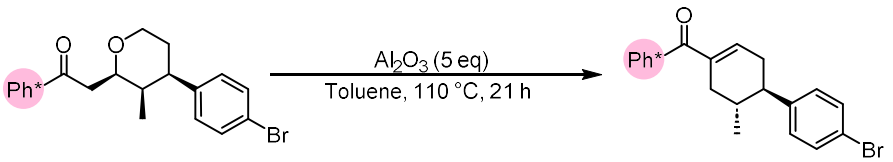
The THP **4-132** (27 mg, 0.070 mmol, >25:1 d.r., 1 eq) was added to a microwave vial and flushed with N_2 four times. $Al(O\text{-}2,6\text{-}Me_2C_6H_3)_3$ (1 mL, 0.34 M in DCE, 0.35 mmol, 5 eq) was added *via* a syringe, and the solution was heated to 110 °C. After 21 h, the reaction was cooled to rt and diluted with EtOAc (2 mL). The suspension was filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product.

If necessary, based on TLC analysis, the crude material was dissolved in DCM (1 mL) and NEt_3 (15 µL, 0.11 mmol, 1.5 eq), and Cyclohexane carbonyl chloride (15 mL, 0.11 mmol, 1.5 eq) were added sequentially at rt. After 5 h, the reaction was quenched with aq. HCl (5 mL, 1 M), the layers were separated, and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic extracts were washed with aq. K_2CO_3 (2 x 5 mL), dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product.

The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4-138** as an inseparable mixture of isomers (23 mg, 0.063 mmol, 89%, 13:1 d.r.).

The characterisation of the product is below.

6.2.11. General Procedure 4G: Stereoinversion 1,5-Hydride Shift of 2,3,4-Substituted THP Rings.



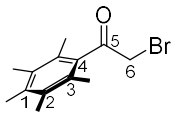
(4'-bromo-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-178**)

The THP **4-172** (20 mg, 0.045 mmol, >1:25 d.r., 1 eq) and Al_2O_3 (23 mg, 0.23 mmol, 5 eq) were added to a microwave vial and flushed with N_2 four times. Toluene (250 µL) was added *via* syringe, and the suspension was heated to 110 °C and stirred at 450 rpm. After 21 h, the reaction was cooled to rt and diluted with EtOAc (2 mL). The suspension was filtered through a silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4-178** as an inseparable mixture of isomers (19 mg, 0.045 mmol, 99%, 1:4.6 d.r.).

The characterisation of the product is below.

6.3. SI for Chapter 2.

6.3.1. Starting Materials.



2-Bromo-1-(pentamethylphenyl)ethan-1-one (**2-59**)

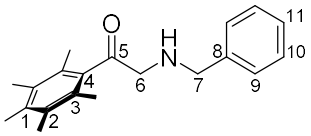
2-bromoacetyl bromide (6.7 mL, 77 mmol, 1.1 eq), Pentamethyl benzene (10.0 g, 67.5 mmol, 1 eq) and $AlCl_3$ (11.2 g, 84.9 mmol, 1.25 eq) were subjected to General Procedure 2A to give the product **2-59** as a dull white powder (16.3 g, 60.5 mmol, 90%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.28 (s, 2H, C6), 2.25 (s, 3H, C1Me), 2.19 (s, 6H, C3Me), 2.12 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 201.2 (C5), 137.1 (C4), 136.9 (C1), 133.5 (C2/C3), 128.4 (C2/C3), 38.2 (C6), 17.7 (C3Me), 16.9 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 271.05177, $C_{13}H_{17}O^{81}Br$ calculated 271.05151, Δ = 1 ppm.

FTIR (film) = 2935, 2362, 1717, 1396, 1101, 657 cm^{-1}.



2-(Benzylamino)-1-(pentamethylphenyl)ethan-1-one (**2-60**, free base)

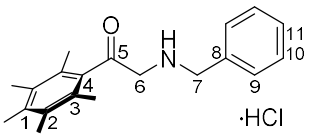
To a solution of α-bromoketone **2-59** (2.0 g, 7.4 mmol, 1 eq) in Et_2O (4.8 mL) was added benzylamine (4.8 mL, 45 mmol, 6 eq) at rt resulting in a white precipitate. After 5 days, the reaction was diluted with Et_2O (30 mL), and quenched with aq. K_2CO_3 (100 mL, sat). The phases were separated and the aqueous layer was extracted with DCM (5 x 20 mL). The combined organic layers were concentrated under reduced pressure and purified by FCC to give the product **2-60** as a yellow wax (1.32 g, 4.46 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39 – 7.30 (m, 4H, C9+C10), 7.28 – 7.22 (m, 1H, C11), 3.92 (s, 2H, C6), 3.71 (s, 2H, C7), 2.22 (s, 3H, C1Me), 2.16 (s, 6H, C2Me), 2.05 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.0 (C5), 139.7 (C4), 138.3 (C1), 136.1 (C2), 133.3 (C3), 128.6 (C9/C10), 128.3 (C9/C10), 128.1 (C8), 127.3 (C11), 60.4 (C6), 53.3 (C7), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 296.20059, $C_{20}H_{26}ON$ calculated 296.20089, Δ = 1 ppm.

FTIR (film) = 3659, 2981, 1684, 1383, 1262, 954, 699 cm^{-1}.



2-(Benzylamonium chloride)-1-(pentamethylphenyl)ethan-1-one **(2-60·HCl)**

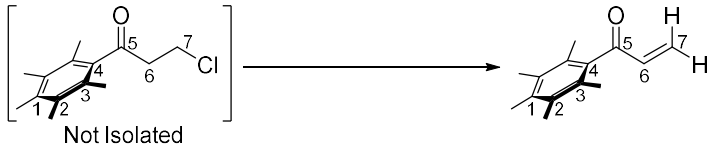
To a solution of α-amino ketone **2-60** (1.72 g, 5.80 mmol, 1 eq) in Et_2O (20 mL) and HCl (2.9 mL, 2 M in Et_2O, 5.8 mmol, 1 eq) was added dropwise at 0 °C. The pale-yellow precipitate was filtered off, washed with Et_2O at 0 °C. The precipitate was dried under reduced pressure to give the product **2-60·HCl** (726 mg, 2.18 mmol, 38%).

^{1}H NMR (400 MHz, D_4-Methanol) δ_H: 7.59 – 7.53 (m, 2H, Ar), 7.52 – 7.46 (m, 3H, Ar), 4.33 (s, 2H, C7), 4.31 (s, 2H, C6), 2.26 (s, 3H, C1Me), 2.21 (s, 6H, C2Me), 2.11 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, D_4-Methanol) δ_C: 204.0 (C5), 138.3 (C4), 136.6 (C1), 134.6 (C2), 132.3 (C8), 131.1 (Ar), 130.9 (Ar), 130.4 (Ar), 129.3 (C3), 57.5 (C6), 51.9 (C7), 17.3 (C3Me), 16.9 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 296.20059, $C_{20}H_{26}ON$ calculated 296.20089, Δ = 1 ppm.

FTIR (film) = 2906, 2703, 1713, 1416, 669 cm $^{-1}$.



1-(Pentamethylphenyl)prop-2-en-1-one (**2-62**) *via* 3-chloro-1-(pentamethylphenyl)propan-1-one (**S2-01**)

2-bromoacetyl bromide (5.6 mL, 58.0 mmol, 1.1 eq) Pentamethylbenzene (8.00 g, 54.0 mmol, 1 eq) and $AlCl_3$ (7.86 g, 60.0 mmol, 1.02 eq) was subjected to General Procedure 2A to give a crude mixture of the enone **2-62** and β-Cl ketone **S2-01**.

β-Cl ketone was not isolated. Diagnostic ^{1}H NMR peaks reported bellow for reference.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.05 – 2.78 (m, 4H, C6+C7), 2.16 (s, 3H, C1Me), 2.11 (s, 6H, C2Me), 2.04 (s, 6H, C3Me) ppm.

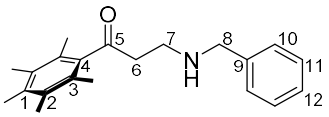
The crude mix was dissolved in DCM (55 mL) and NEt_3 (7.4 mL) and allowed to stir for 18 h. The solution was diluted in DCM (200 mL) and washed with aq. HCl (2 x 50 mL, 1 M). The solid was purified by FCC to give the product **2-62** as a dull white powder (8.50 g, 42.1 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.57 (dd, *J* = 17.6, 10.4 Hz, 1H, C6), 6.06 (dd, *J* = 10.4, 1.1 Hz, 1H, C7H$_{tr}$), 5.88 (dd, *J* = 17.6, 1.1 Hz, 1H, C7H$_{cis}$), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C3Me), 2.06 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, CDCl^3) δC: 203.6 (C5), 138.9 (C6), 137.3 (C4), 135.7 (C1), 133.0 (C2), 132.5 (C7), 129.1 (C3), 17.5 (C3Me), 16.9 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 203.14322, $C_{14}H_{19}O$ calculated 203.14304, Δ = 1 ppm.

FTIR (film) = 2990, 2928, 1653, 1394, 1312 1189, 978cm^{-1}.



3-(Benzylamino)-1-(pentamethylphenyl)propan-1-one (**2-63**)

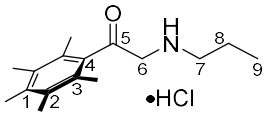
To a solution of propenone **2-62** (1.5 g, 7.4 mmol, 1.2 eq) in DCM (4 mL) was added benzylamine (690 µL, 5.9 mmol, 1 eq) and DBU (450 µL, 2.9 mmol, 0.5 eq) sequentially. After 18 h, upon consumption of the enone by TLC, the reaction was diluted with EtOAc (20 mL) and aq. $NaHCO_3$ (20 mL, sat). The phases were separated, the aqueous layer was extracted with EtOAc (4 x 15 mL), and the combined organic layers were concentrated under reduced pressure. The crude was purified by FCC (DCM:NEt_3, 99:1) to give the product **2-63** as an orange solid (1.03 g, 3.24 mmol, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.29 – 7.22 (m, 4H, C10/C11), 7.20 – 7.15 (m, 1H, C12), 3.76 (s, 2H, C8), 2.93 (td, *J* = 6.2, 1.1 Hz, 2H, C6/C7), 2.84 (td, *J* = 6.1, 1.2 Hz, 2H, C6/C7), 2.15 (s, 3H, C1Me), 2.10 (s, 6H, C3Me), 2.03 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 211.9 (C5), 140.4 (C4/C9), 140.3 (C4/C9), 135.6 (C1), 133.2 (C2), 128.5 (C10/C11), 128.2 (C10/C11), 127.4 (C3), 127.0 (C12), 54.4 (C8), 45.9 (C6/C7), 43.8 (C6/C7), 17.3 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 310.2165, $C_{21}H_{28}NO$ calculated 310.2165, Δ = 0 ppm.

FTIR (film) = 2923, 2360, 1697, 1494, 1127, 736, 698 cm^{-1}.



2-(Propylammonium chloride)-1-(pentamethylphenyl)ethan-1-one (**2-64**)

To a solution of α-bromoketone **2-59** (10.0 g, 37.2 mmol, 1 eq) in Et_2O (20 mL) was added propylamine (15.2 mL, 186 mmol, 5 eq) at rt resulting in a white precipitate. After 5 days, the reaction was quenched with aq. K_2CO_3 (100 mL, sat). The phases were separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layers were concentrated under reduced pressure to give the crude product.

The crude product was dissolved in Et_2O (50 mL) at 0 °C, and HCl (18.6 mL, 2 M in Et_2O, 37.2 mmol) was added dropwise. The pale yellow precipitate was filtered and recrystallized from EtOH (reflux to rt), the crystals were washed with cold EtOH and dried to give the ammonium chloride **2-64·HCl** (5.1 g, 17.9 mmol, 48%). By concentrating the mother liquor and recrystallizing two further times, the total isolated product could be increased to (8.56 g, 30.2 mmol, 81%).[a]

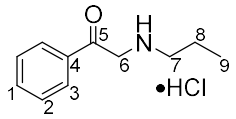
[a] Dropwise addition of Et_2O (≈2 mL) was used to initiate crystal growth if no growth was observed to form after 1 h.

^{1}H NMR (400 MHz, d_6DMSO) δ_H: 9.26 (s, 2H, NH), 4.22 (brs, 2H, C6), 3.35 (brs, 2H, C7), 2.95 – 2.80 (m, 2H, C8), 2.19 (s, 3H, C1Me), 2.14 (s, 6H, C2Me), 2.07 (s, 6H, C3Me), 1.69 (h, J = 7.5 Hz, 2H, C8), 0.92 (t, J = 7.5 Hz, 3H, C9) ppm.

^{13}C NMR (101 MHz, d_6DMSO) δ_C: 203.6 (C5), 136.2 (C4), 135.9 (C1), 132.8 (C2), 127.9 (C3), 56.7 (C6), 48.1 (C7), 19.1 (C8), 17.0 (C3Me), 16.5 (C1Me), 15.7 (C2Me), 11.1 (C9) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 248.20099, $C_{16}H_{25}ON$ calculated 248.20089, Δ = 0.5 ppm.

FTIR (film) = 2709, 2361, 2342, 1711, 1471, 667 cm^{-1}.



1-Phenyl-2-(propylamonium)ethan-1-one chloride (**2-66·HCl**)

Based on the literature procedure.[101]

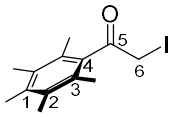
To a solution of 2-bromoacetophenone (1.50 g, 7.54 mmol, 1 eq) in CH_3CN (3 mL) was added a solution of propylamine (1.2 mL, 15 mmol, 2 eq) in CH_3CN (2.25 mL) dropwise at 0 °C to give a dark red solution. After 5 mins, upon consumption of the ketone by TLC, the reaction was diluted with Et_2O (75 mL) and the precipitate was filtered. The majority of the solvent was removed under a stream of N_2 at 0 °C to give a crude oil.[a] Without warming the crude to rt, the crude was diluted with Et_2O (40 mL) and HCl (3.75 mL, 7.50 mmol, 2 M in Et_2O, 1 eq) was added dropwise, resulting in a white precipitate and green solution. The solid was filtered and washed with cold Et_2O (15 mL) to give a clear white solid. The product was purified by recrystallization in EtOH (≈50 mL) to give the product as a clear white solid (850 mg, 3.98 mmol, 53%).

^{1}H NMR (400 MHz, D_6DMSO) δ_H: 9.20 (s, 2H, NH_2), 8.05 – 7.97 (m, 2H, C3), 7.80 – 7.71 (m, 1H, C1), 7.61 (t, J = 7.8 Hz, 2H, C2), 4.79 (t, J = 5.4 Hz, 2H, C6), 2.97 – 2.86 (m, 2H, C7), 1.72 (hex, J = 7.5 Hz, 2H, C8), 0.93 (t, J = 7.5 Hz, 3H, C9) ppm.

^{13}C NMR (101 MHz, D_6DMSO) δ_C: 192.5 (C5), 134.7 (C4), 133.7 (C1), 129.1 (C2), 128.2 (C3), 52.1 (C6), 48.5 (C7), 18.8 (C8), 11.0 (C9) ppm.

Data in agreement with previous literature.[236]

[a] Attempts to concentrate the product under reduced pressure at rt resulted in complete decomposition of the amine to form a black tar.



2-Iodo-1-(pentamethylphenyl)ethan-1-one (**2-67**)

α-Bromoketone **2-65** (1.00 g, 3.70 mmol 1 eq) and NaI (2.2 g, 15 mmol, 4 eq) were dissolved in Acetone (8 mL). After 18 h, the mixture was diluted in DCM (25 mL) and water (20 mL) and, the organic layer was extracted, the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated without further purification to give the product **2-67** as a pale orange powder (1.10 g, 3.48 mmol, 95%).

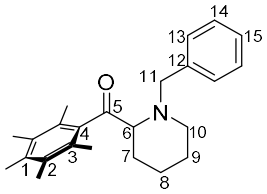
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.25 (s, 2H, C6), 2.25 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.15 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 201.9 (C5), 137.1 (C4), 136.7 (C1), 133.5 (C2), 128.3 (C3), 18.1 (C3Me), 16.9 (C1Me), 16.2 (C2Me), 12.2 (C6) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 317.03979, $C_{x3}H_{17}OI$ calculated 317.03968, Δ = 0.5 ppm.

FTIR (film) = 2926, 2361, 2341, 1709, 1386, 1091, 931, 646 cm^{-1}.

6.3.2. Heterocycles.



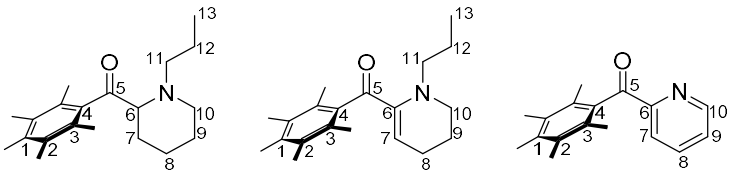
(1-Benzylpiperidin-2-yl)(pentamethylphenyl)methanone (**2-68**)

Aminoketone **2-60** (89 mg, 0.30 mmol, 1 eq), $(IrCp^*Cl_2)_2$ (4.8 mg, 0.006 mmol, 2 mol%) and KOH (68 mg, 1.2 mmol, 4 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, and the reaction was placed under a balloon of O_2. 1,4-Butandiol (50 µL, 0.60 mmol, 2 eq) and toluene (75 µL) were added, and the vial was stirred at 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in CH_2Cl_2 (2 x 6 mL) and EtOAc (4 x 6 mL), which was run through a silica pad. The solution was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:Et_2O, 90:10) to give the product as a yellow solid (7 mg, 0.021 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H, C13), 7.36 – 7.30 (m, 2H, C14), 7.25 (m, 1H, C15), 4.40 (d, *J* = 12.4 Hz, 1H, C11H_1), 3.54 (dd, *J* = 9.1, 3.9 Hz, 1H. C6), 3.22 (d, *J* = 12.4 Hz, 1H, C11H_2), 3.08 (dt, *J* = 11.6, 4.5 Hz, 1H, C10H_1), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.18 (s, 6H, C3Me), 2.09 (ddd, *J* = 11.4, 8.9 , 3.7 Hz, 1H, C10H_2) 1.85 – 1.77 (m, 1H, C7H_1), 1.76 – 1.68 (m, 1H, C8H_1), 1.67 – 1.55 (m, 1H, C7H_2), 1.55 – 1.40 (m, 2H, C9), 1.38 – 1.21 (m, 1H, C8H_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.9 (C5), 139.7 (C4), 138.4 (C1), 136.0 (C2), 133.0 (C3), 129.4 (C13), 128.3 (C14), 127.0 (C15), 72.6 (C6), 60.1 (C11), 51.2 (C10), 28.0 (C7), 25.0 (C9), 24.3 (C8), 18.2 (C3Me), 17.0 (C1Me), 16.2 (C2Me) ppm. C12 peak not observed.

LRMS: ESI$^+$ found $[M+H]^+$ = 350.2.



(Pentamethylphenyl)(1-propylpiperidin-2-yl)methanone (**2-69**) Pentamethylphenyl)(1-propyl-1,4,5,6-tetrahydropyridin-2-yl)methanone (**2-70**) (Pentamethylphenyl)(pyridin-2-yl)methanone (**2-78**)

Piperidine

Aminoketone **2-66·HCl** (426 mg, 1.50 mmol, 1 eq), $(IrCODCl)_2$ (20.0 mg, 0.03 mmol, 2 mol%), dppbz (5.4 mg, 0.06 mmol, 4 mol%) and KOH (85 mg, 7.5 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times. 1,4-Butandiol (270 µL, 3.0 mmol, 2 eq) and *t*-BuOH (150 µL) were added, and the vial was stirred at 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 6 mL) and EtOAc (4 x 6 mL), which was run through a silica pad. The crude was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:Et_2O, 90:10) to give the product **2-69** as a yellow solid (274 mg, 0.91 mmol, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.36 (dd, J = 10.2, 3.1 Hz, 1H, C6), 3.26 (dtd, J = 11.6, 4.0, 1.0 Hz, 1H, C10H_1), 3.03 (ddd, J = 11.7, 9.2, 7.2 Hz, 1H, C11H_1), 2.23 (s, 3H, C1Me), 2.17 (s, 13H, C2Me+C3Me+C11H_2), 2.03 – 1.93 (m, 1H, C10H_2), 1.76 – 1.67 (m, 2H, C7H_1+C9H_1), 1.67 – 1.61 (m, 2H, C12), 1.61–1.55 (m, 2H, C8), 1.55 – 1.47 (m, 1H, C7H_2), 1.21 – 1.07 (m, 1H, C9H_2), 0.85 (t, J = 7.4 Hz, 3H, C13) ppm.

^{13}C NMR δ_C (126 MHz, $CDCl_3$) δ_C: 210.3 (C5), 138.3 (C4), 135.9 (C1), 133.2 (br, C2), 130.6-128.1 (vbr, C3), 73.3 (C6), 57.9 (C11), 51.5 (C10), 28.3 (C7), 25.1 (C9), 24.5 (C8), 20.7 (C12), 18.1 (br, C3Me), 16.9 (C1Me), 16.2 (br, C2Me), 12.1 (C13) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 302.2478, $C_2H_{32}ON^+$ calculated 302.2479, Δ = 0.5 ppm.

FTIR (film) = 2980, 2889, 1657, 1381, 1265, 1155, 1073 cm^{-1}.

Tetrahydropyridine

Aminoketone **2-66·HCl** (89 mg, 0.30 mmol, 1 eq), $(IrCODCl)_2$ (4 mg, 0.006 mmol, 2 mol%), $P(OPh)_3$ (7.4 mg, 0.06 mmol, 4 mol%) and KOH (67 mg, 1.2 mmol, 4 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, and a balloon of oxygen was added. 1,4-Butandiol (50 µL, 0.60 mmol, 2 eq) and toluene (75 µL) were added, and the vial was stirred at 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 6 mL) and EtOAc (4 x 6 mL), which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:Et_2O, 95:5) to give the product **2-70** as a yellow solid (4.1 mg, 0.014 mmol, 5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 4.2 Hz, 1H, C7), 3.08 – 3.02 (m, 2H, C10), 3.02–2.95 (m, 2H, C11), 2.23 (s, 3H, C1Me), 2.17 (s, 6H, C2Me), 2.08 (s, 8H, C3Me+C8), 1.74 – 1.62 (m, 4H, C9+C12), 0.91 (t, *J* = 7.4 Hz, 3H, C13) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 200.0 (C5), 148.1 (C6), 138.5 (C4), 135.1 (C1), 132.5 (C2), 129.7 (C3), 125.0 (C7), 54.5 (C11), 48.2 (C10), 24.3 (C8), 22.1 (C12), 19.2 (C9), 17.5 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 11.7 (C13) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 300.2322, $C_{20}H_{30}NO$ calculated 300.2322, Δ = 0.0 ppm.

FTIR (film) = 2959, 2923, 2871, 1656, 1380, 1175, 1077 cm^{-1}.

Pyridine

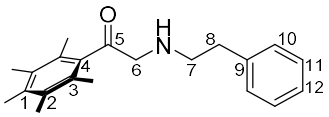
Aminoketone **2-66·HCl** (89 mg, 0.30 mmol, 1 eq), $(IrCp^*Cl_2)_2$ (4.8 mg, 0.006 mmol, 2 mol) and KOH (67.3 mg, 1.2 mmol, 4 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, and a balloon of oxygen was added. 1,4-Butandiol (50 µL, 0.60 mmol, 2 eq) and toluene (75 µL) were added, and the vial was stirred at 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 6 mL) and EtOAc (4 x 6 mL), which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:EtOAc, 90:10) to give the product **2-78** as a yellow solid (10 mg, 0.39 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.71 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H, C10), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H, C7), 7.89 (td, *J* = 7.7, 1.8 Hz, 1H, C8), 7.45 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H, C9), 2.26 (s, 3H, C1Me), 2.21 (s, 6H, C2Me), 2.02 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.5 (C5), 154.5 (C6), 150.2 (C10), 137.7 (C7), 137.1 (C4), 136.1 (C1), 132.9 (C2), 129.2 (C3), 127.0 (C9), 123.3 (C8), 17.8 (C3Me), 17.0 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 254.15402, $C_{17}H_{20}NO$ calculated 254.15394, Δ = 0.5 ppm.

FTIR (film) = 2981, 2361, 1679, 1314, 893 cm^{-1}.



2-(Phenylethylamino)-1-(pentamethylphenyl)ethan-1-one (**2-73**)

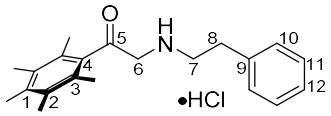
To a solution of α-bromoketone **2-59** (2.0 g, 7.4 mmol, 1 eq) in Et_2O (4.8 mL) was added phenethylamine (4.7 mL, 37 mmol, 5 eq), resulting in the formation of a white precipitate. After 5 days, the reaction was diluted with Et_2O (20 mL) and aq. K_2CO_3 (60 mL, sat). The phases were separated, and the aqueous layer was extracted with DCM (3 x 40 mL). The combined organic layers were concentrated under reduced pressure and purified by FCC to give a thick white wax (1.01 g, 3.54 mmol 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 – 7.27 (m, 2H, C11), 7.28 – 7.18 (m, 3H, C10+C12), 3.74 (s, 2H, C6), 3.02 – 2.94 (m, 2H, C7), 2.87 (t, *J* = 7.2 Hz, 2H, C8), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.10 (s, 6H, C3Me) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 209.8 (C5), 139.8 (C4), 138.2 (C1), 136.0 (C2), 133.2 (C3), 128.8 (C10), 128.5 (C11), 128.0 (C9), 126.3 (C12), 61.4 (C6), 51.1 (C7), 36.7 (C8), 17.2 (C3Me), 16.7 (C1Me), 15.9 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 310.21640, $C_{21}H_{28}ON$ calculated 310.21654, Δ = 0 ppm.

FTIR (film) = 2117, 1754, 1683, 1239, 1050 cm^{-1}.



2-(Phenylethylammonium chloride)-1-(pentamethylphenyl)ethan-1-one (**2-73·HCl**)

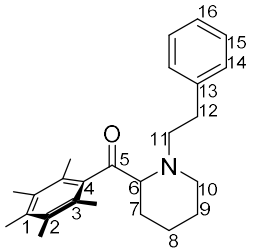
To a solution of the α-amino ketone **2-73** (309 mg, 1.00 mmol, 1 eq) in Et_2O (4 mL), was added HCl (550 µL, 2 M in Et_2O 1.1 eq) dropwise and cooled to 0 °C. The resulting pale-yellow precipitate was filtered off and dried under reduced pressure to give the product **2-73·HCl** (299 mg, 0.86 mmol, 86%), which was used without further purification.

^{1}H NMR (400 MHz, d_6DMSO: D_3COD 2:1) δ_H: 7.41 – 7.33 (m, 2H, C11), 7.29 (m, 3H, C10+C12), 4.34 (s, 2H, C6), 3.30 – 3.22 (m, 2H, C7/C8), 3.09 – 2.99 (m, 2H, C7/C8), 2.23 (s, 3H, C1Me), 2.17 (s, 6H, C2Me), 2.11 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, d_6DMSO: d_4Methanol, 2:1) δ_C: 204.8 (C5), 138.4 (C4), 138.0 (C1), 137.0 (C2), 134.4 (C3), 130.2, 130.1, 129.5 (C9), 128.4, 58.1 (C6), 49.0 (C7), 33.1 (C8), 18.2 (C3Me), 17.6 (C1Me), 16.8 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 310.21640, $C_{21}H_{28}ON$ calculated 310.21654, Δ = 0 ppm.

FTIR (film) = 3390, 3330, 2980, 2753, 1707, 892, 748.1, 697 cm^{-1}.



(Pentamethylphenyl)(1-phenethylpiperidin-2-yl)methanone (**2-77**)

Aminoketone **2-73·HCl** (100 mg, 0.29 mmol, 1 eq), $(IrCODCl)_2$ (4.0 mg, 0.006 mmol, 2 mol%), dppbz (5.4 mg, 0.012 mmol, 4 mol%) and KOH (68 mg, 1.2 mmol, 4 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times. 1,4-Butandiol (50 µL, 0.60 mmol, 2 eq) and toluene (150 µL) were added, and the vial was stirred at 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 4 mL) and EtOAc (4 x 4 mL), which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:Et_2O, 90:10 → 65:35) to give the product as a white solid (68 mg, 0.19 mmol, 65%).

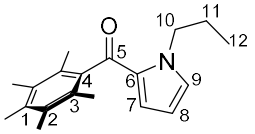
^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.23 – 7.14 (m, 4H, C14+C15), 7.13 – 7.08 (m, 1H, C16), 3.38 (dd, *J* = 10.1, 3.1 Hz, 1H, C6), 3.31 (dt, *J* = 11.5, 4.1 Hz, 1H, $C10H_1$), 3.24 (td, *J* = 11.6, 5.5 Hz, 1H, $C11H_1$), 2.01 (ddd, *J* = 13.2, 11.1, 5.5 Hz, 1H, $C12H_1$), 3.00–2.90 (m, 1H, $C12H_2$), 2.39 (td, *J* = 11.3, 5.5 Hz, 1H, $C11H_2$), 2.14 (s, 3H, C1Me), 2.08 (s, 6H, C2Me/C3Me), 2.06 (s, 6H, C2Me/C3Me), 2.18-2.10 (m, 1H, $C10H_2$), 1.72 – 1.62 (m, 2H, $C7H_1$+$C8H_2$), 1.60 – 1.51 (m, 2H, $C9H_1$+$C9H_2$), 1.51 – 1.42 (m, 1H, $C7H_2$), 1.25 – 1.12 (m, 1H, $C8H_2$) ppm.

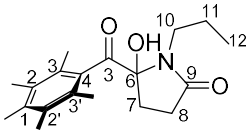
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.4 (C5), 140.6 (C13), 138.0 (C4), 136.0 (C1), 133.2 (br, C2/C3), 128.9 (C15), 128.4 (C14), 126.0 (C16), 73.1 (C6), 57.8 (C11), 51.8 (C10), 34.7 (C12), 28.3 (C7), 25.1 (C9), 24.4 (C8), 18.2 (br, C3Me), 16.9 (C1Me), 16.2 (br, C2Me) ppm. C2/C3 peak not observed.

HRMS: ESI^+ found $[M+H]^+$ = 364.26331, $C_{25}H_{34}NO$ calculated 364.26349, Δ = 0.5 ppm.

FTIR (film) = 2980.6, 1696, 1453, 1382, 908, 728, 699 cm^{-1}.

Note. Trace unsaturated product was observed in the crude 5.69 (t, 4.27 Hz, 1H) ppm. Using the amino ketone **273** (89 mg, 0.29 mmol, 1 eq) gave the product **277** as a white solid (69 mg, 0.19 mmol, 65%).





(Pentamethylphenyl)(1-propyl-1H-pyrrol-2-yl)methanone (**2-85**) 5-hydroxy-5-(pentamethylbenzoyl)-1-propylpyrrolidin-2-one (**2-86**)

Aminoketone **2-66·HCl** (85 mg, 0.30 mmol, 1 eq), 1,3-propandiol (45 mg, 0.60 mmol, 2 eq), $(IrCODCl)_2$ (4.0 mg, 0.006 mmol, 2 mol%), dppbz (5.4 mg, 0.012 mmol, 4 mol%) and KOH (84 mg, 1.5 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times. *t*-BuOH (150 µL) was added, and the vial was stirred at 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 4 mL) and EtOAc (4 x 4 mL) which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (Pentane:Et_2O, 90:10 → 65:35) to give the pyrrole **285** as a white solid (25 mg, 0.88 mmol, 29%). The column was flushed with EtOAc to give the crude hemiaminal, which was further purified by FCC to give the hemiaminal **2-86** (5.0 mg, 0.015 mmol, 5%).

Pyrrole

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.92 (t, *J* = 2.1 Hz, 1H, C9), 6.36 (dd, *J* = 4.0, 1.8 Hz, 1H, C7), 6.03 (dd, *J* = 4.0, 2.4 Hz, 1H, C8), 4.46 (t, *J* = 7.2 Hz, 2H, C10), 2.26 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.09 (s, 6H, C3Me), 1.90 (h, *J* = 7.4 Hz, 2H, C11), 0.96 (t, *J* = 7.4 Hz, 3H, C12) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 191.1 (C5), 139.4 (C4), 135.0 (C1), 132.5 (C2/C3), 131.6 (C6), 131.0 (C9), 129.4 (C2/C3), 123.6 (C7), 108.3 (C8), 51.4 (C10), 24.9 (C11), 17.6 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 11.2 (C12) ppm.

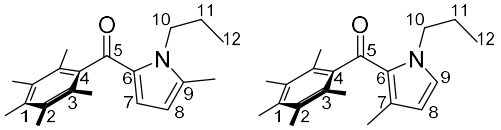
HRMS: ESI$^+$ found $[M+H]^+$ = 284.20096, $C_{19}H_{26}ON$ calculated 284.20089, Δ = 0 ppm.

FTIR (film) =2929, 1629, 1467, 1396, 1073, 863, 715 cm^{-1}.

Hemiaminal

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.33 (ddd, *J* = 13.8, 10.8, 5.5 Hz, 1H. C10H_1), 2.84 (ddd, *J* = 13.9, 10.7, 5.2 Hz, 1H, C10H_2), 2.43 – 2.33 (m, 1H, C7H_1), 2.22 (s, 3H, C1Me), 2.22 – 2.17 (m, 1H, C8H_1), 2.17 (s, 3H, C2Me/C3Me), 2.16 (s, 3H, C2'Me/C3'Me), 2.06 (s, 3H, C2Me/C3Me), 1.96 (s, 3H, C2'Me/C3'Me), 1.94 – 1.88 (m, 1H, C8H_2), 1.89 – 1.81 (m, 1H, C7H_2), 1.76 – 1.63 (m, 1H, C11H_1), 1.53 – 1.40 (m, 1H, C11H_2), 0.89 (t, *J* = 7.4 Hz, 3H, C12) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 210.2 (C5), 175.4 (C9), 137.9 (C4), 136.1 (C1), 133.9 (C3), 133.1 (C3'), 128.4 (C2), 128.0 (C2'), 71.0 (C6), 43.0 (C10), 30.6 (C7), 29.8 (C8), 23.1 (C11), 19.1 (C2Me/C3Me), 18.0 (C2'Me/C3'Me), 16.8 (C1Me), 16.4 (C2Me/C3Me), 16.1 (C2'Me/C3'Me), 11.8 (C12) ppm.



(5-methyl-1-propyl-1H-pyrrol-2-yl)(pentamethylphenyl)methanone and (3-methyl-1-propyl-1H-pyrrol-2-yl)(pentamethylphenyl)methanone (**2-89**)

Amino ketone **2-66·HCl** (85 mg, 0.30 mmol, 1 eq), 1,3 butanediol (50 µL, 0.59 mmol, 2 eq), $(IrCODCl)_2$ (4.0 mg, 0.006 mmol, 2 mol%), dppbz (5.4 mg, 0.012 mmol, 4 mol%) and KOH (84 mg, 1.5 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, *t*-BuOH (150 µL) was added, and the vial was heated to 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in CH_2Cl_2 (2 x 4 mL) and EtOAc (4 x 4 mL), which was run through a silica pad and the reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (Pentane:Et_2O, 90:10) to give the pyrrole **2-89** as a waxy solid (21 mg, 0.71 mmol, 24%, 13:1, C5:C3).

8:1 r.r. measured in the Crude ^{1}H NMR.

C5-Methyl

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.29 (d, *J* = 4.0 Hz, 1H, C7), 5.84 (d, *J* = 4.0 Hz, 1H, C8), 4.51 – 4.38 (m, 2H, C10), 2.30 (s, 3H, C9Me), 2.25 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.09 (s, 6H, C3Me), 1.84 (qd, *J* = 7.4, 1.8 Hz, 2H, C11), 1.00 (t, *J* = 7.4 Hz, 3H, C12) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 189.9 (C5), 139.7 (C4/C6), 139.0 (C4/6), 134.7 (C1), 132.4 (C2), 131.5 (C9), 129.4 (C3), 123.5 (C7), 108.8 (C8), 47.1 (C10), 24.4 (C11), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 12.6 (C9Me), 11.4 (C12) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 320.1984, $C_{20}H_{27}NONa$ calculated 320.1985, Δ = 0.28 ppm.

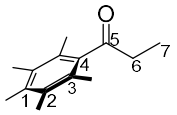
FTIR (film) = 2970, 1684, 1483, 1466, 862, 757, 668 cm^{-1}.

C3-Methyl

Under the same procedure in toluene (150 µL) gave the product (39 mg, 0.13 mmol, 43%, 4:1 r.r.) with minor impurities, repeated attempts to isolate the minor isomer were unsuccessful diagnostic peaks from the mixture reported below.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.74 (d, *J* = 2.4 Hz, 1H, C9), 5.81 (d, *J* = 2.4 Hz, 1H, C8), 0.90 – 0.84 (t, *J* = 7.4 Hz, 3H, C12). ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 130.0 (C9), 111.0 (C8), 52.3 (C10), 24.7 (C11), 11.1 (C12). ppm.



1-(Pentamethylphenyl)propan-1-one (**2-90**)

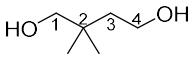
Aminoketone **2-63** (92 mg, 0.30 mmol, 1 eq), $(IrCODCl)_2$ (4.0 mg, 0.006 mmol, 2 mol%), dppbz (5.4 mg, 0.012 mmol, 4 mol%) and KOH (68 mg, 1.5 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated four times and flushed with N_2. 1,3-propanediol (45 µL, 0.56 mmol, 1.9 eq) and toluene (150 µL) was added, and the vial was heated to 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 4 mL) and EtOAc (4 x 4 mL), which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The yield of propanone **2-90** was determined to be 67% by ^{1}H-NMR using 1,2,3-trimethoxybenzene (16.8 mg, 0.10 mmol) as an internal standard. An analytical quantity of the product was isolated by FCC for characterisation purposes.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.69 (q, J = 7.2 Hz, 2H, C6), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.09 (s, 6H, C3Me), 1.20 (t, J = 7.2 Hz, 3H, C7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.9 (C5), 140.9 (C4), 135.5 (C1), 133.2 (C2), 127.5 (C3), 38.9 (C7), 17.4 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 7.7 (C7) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 227.14085, $C_{14}H_{20}ONa$ calculated 227.14064, Δ = 1 ppm.

FTIR (film) = 2362, 2342, 1698 cm^{-1}.



2,2-dimethylbutane-1,4-diol (**2-96**)

Quench based on the literature procedure.[237]

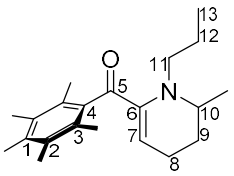
To a solution of the diacid **2-95** (4.0 g, 27 mmol, 1 eq) in Et_2O (40 mL) was added $LiAlH_4$ (3.2 g, 81 mmol, 3 eq) portion-wise at 0 °C. After 18 h, the reaction was diluted with Et_2O (40 mL) and cooled to 0 °C, the reaction was quenched sequentially with H_2O (3.4 mL), aq. NaOH (6.7 mL, 2 M) and H_2O (10 mL). The mixture was dried with $MgSO_4$, and the solids were filtered and washed with Et_2O (40 mL). The combined filtrate was concentrated under reduced pressure and columned using FCC (DCM:MeOH, 90:10) to give the diol as a viscous oil (1.76 g, 16.9 mmol, 63%).[a]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.78 – 3.62 (m, 2H, C4), 3.51 – 2.92 (m, 2H, C1), 1.72 – 1.33 (m, 2H, C3), 0.92 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_c: 71.5 (C1), 58.9 (C4), 42.9 (C3), 35.1 (C2), 25.1 (C2Me) ppm.

Data in agreement with previous literature.[238]

[a] In order to remove the solvent, the vial should be placed at a 45 ° angle and the solvent removed under a stream of N_2 such that the oil flows.



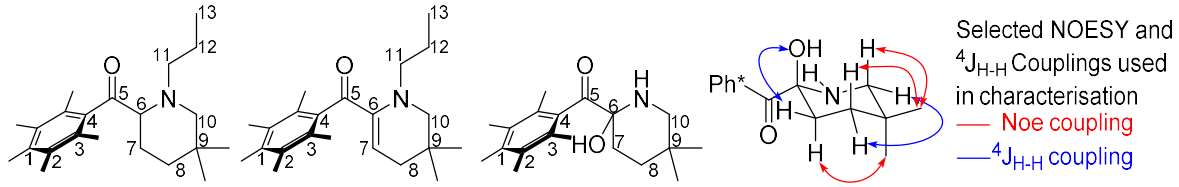
(6-Methyl-1-propyl-1,4,5,6-tetrahydropyridin-2-yl)(pentamethylphenyl)methanone (**2-93**)

Aminoketone **2-66·HCl** (85 mg, 0.30 mmol, 1 eq), 1,4-pentandiol (63 mg, 0.60 mmol, 2 eq), $(IrCODCl)_2$ (4.0 mg, 0.006 mmol, 2 mol%), dppbz (5.4 mg, 0.012 mmol, 4 mol%) and KOH (84 mg, 1.5 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated four times and flushed with N_2. *t*-BuOH (150 µL) was added, and the vial was heated to 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 4 mL) and EtOAc (4 x 4 mL), which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:Et_2O, 90:10) to give the tetrahydropyridine **2-93** as a white solid (19 mg, 0.061 mmol, 20%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: δ 5.71 (ddd, *J* = 4.6, 3.5, 1.0 Hz, 1H, C7), 3.29 (qt, *J* = 6.8, 3.4 Hz, 1H, C10), 3.14 (ddd, *J* = 13.6, 10.5, 6.0 Hz, 1H C11H_1), 2.90 (ddd, *J* = 13.6, 10.3, 4.5 Hz, 1H, C11H_2), 2.26 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.16 – 2.04 (m, 8H, C3Me+C8), 1.80 – 1.69 (m, 1H, C12H_1) 1.71 – 1.56 (m, 1H, C9H_1+C12H_2), 1.54 – 1.48 (m, 1H, C9H_2), 1.04 (d, *J* = 6.8 Hz, 3H, C10Me), 0.94 (t, *J* = 7.4 Hz, 3H, C13) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 200.8 (C5), 145.6 (C6), 138.8 (C4), 135.0 (C1), 132.5 (C2), 129.5 (C3), 124.4 (C7), 54.5 (C11), 50.7 (C10), 23.5 (C9), 22.5 (C12), 20.2 (C8), 17.7 (C10Me), 17.5 (Ph*Me), 16.8 (Ph*Me), 16.0, (Ph*Me), 11.6 (C13) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 314.24777, $C_{21}H_{32}ON$ calculated 314.24784, Δ = 0 ppm.



(5,5-Dimethyl-1-propylpiperidin-2-yl)(pentamethylphenyl)methanone (**2-97**), (5,5-Dimethyl-1-propyl-1,4,5,6-tetrahydropyridin-2-yl)(pentamethylphenyl)methanone (**2-98**) and (2-Hydroxy-5,5-dimethylpiperidin-2-yl)(pentamethylphenyl)methanone (**2-99**)

Aminoketone **2-66·HCl** (85 mg, 0.30 mmol, 1 eq), 1,4-diol **2-96** (71 mg, 0.60 mmol, 2 eq), $(IrCODCl)_2$ (4.0 mg, 0.006 mmol, 2 mol%), dppbz (5.4 mg, 0.012 mmol, 4 mol%) and KOH (84 mg, 1.5 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times. *t*-BuOH (150 µL) was added, and the vial was heated to 110 °C. After 18 h, the reaction was cooled to rt, and the solid dissolved in DCM (2 x 4 mL) and EtOAc (4 x 4 mL), which was run through a silica pad. The reaction was concentrated under reduced pressure to give a viscous brown oil. The crude was purified by FCC (pentane:Et_2O, 90:10) to give the piperidine **2-97** (28 mg, 0.085 mmol, 28%) and hemiaminal **2-99** (3.3 mg, 0.010 mmol, 3%). Purification of the tetrahydropyridine **2-98** (7.4 mg crude) was done with subsequent prep TLC.

Tetrahydropyridine

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.22 (t, *J* = 4.6 Hz, 1H, C7), 3.37 – 3.24 (m, 2H, C11), 2.76 (t, *J* = 1.5 Hz, 2H, C10), 2.23 (s, 3H, C1Me), 2.17 (s, 6H, C2Me), 2.10 (s, 6H, C3Me), 1.83 (dt, *J* = 4.7, 1.5 Hz, 2H, C8), 1.70 (h, *J* = 7.5 Hz, 2H, C12), 0.95 – 0.91 (m, 9H, C9Me+C13).ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 199.2 (C5), 146.2 (C6), 139.0 (C4), 135.1 (C1), 132.5 (C2), 129.8 (C3), 117.2 (C7), 60.2 (C10), 54.1 (C11), 37.9 (C8), 28.6 (C9), 26.9 (C9Me), 22.4 (C12), 17.6 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 11.6 (C13) ppm.

LRMS: ESI^+ found $[M+H]^+$ 328.2.

Piperidine

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.33 (dd, *J* = 7.7, 5.8 Hz, 1H, C6), 3.05 (ddd, *J* = 11.7, 9.0, 6.7 Hz, 1H, $C11H_{eq}$), 2.83 (dd, *J* = 11.3, 1.7 Hz, 1H, $C10H_{eq}$), 2.23 (s, 3H, C1Me), 2.17 (s, 13H, C2Me+C3Me+$C11_{ax}$), 1.81 (d, *J* = 11.4 Hz, 1H, $C10H_{ax}$), 1.68 – 1.62 (m, 2H, C7), 1.62 – 1.50 (m, 2H, C12), 1.39 (dtd, *J* = 11.2, 5.1, 1.5 Hz, 1H, $C8H_{eq}$), 1.11 (dt, *J* = 13.1, 7.5 Hz, 1H, $C8H_{ax}$), 1.01 (s, 3H, $C9Me_1$), 0.94 (t, *J* = 7.4 Hz, 3H C13), 0.89 (s, 3H, $C9Me_2$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ_C:211.2 (C5), 138.5 (C4), 135.9 (C1), 133.2 (br, Ar), 73.4 (C6), 62.8 (C10), 57.0 (C11), 37.3 (C8), 30.2 (C9), 28.7 (C9Me), 25.9 (C9Me), 25.3 (C7), 20.9 (C12), 18.2 (br, C3Me), 17.0 (C1Me), 16.2 (br, C2Me), 12.0 (C13) ppm. C3 could not be observed.

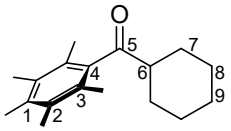
Hemiaminal

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.80 – 3.76 (d, *J* = 10.9 Hz, 1H, C10H_{ax}), 3.60 (d, *J* = 2.2 Hz, 1H, OH), 3.25 (dd, *J* = 10.9, 2.5 Hz, 1H, C10H_{eq}), 2.26 (s, 3H, C1Me), 2.21 (s, 3H, C2Me), 2.20 (s, 3H, C2Me), 2.18 (s, 3H, C3Me), 2.10 (s, 3H, C3Me), 1.99 (tdd, *J* = 13.7, 5.0, 2.5 Hz, 1H, C7H_{eq}), 1.72 (td, *J* = 13.4, 4.4 Hz, 1H, C8H_{ax}), 1.67-1.58 (m, 1H, C7H_{ax}), 1.36 (ddt, *J* = 13.0, 4.9, 2.6 Hz, 1H, C8H_{eq}), 0.94 (s, 3H,C9Me_1), 0.85 (s, 3H, C9Me_2) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 209.9 (C5), 136.1 (C1/C4), 136.0 (C1/C4), 133.3 (C2), 133.1 (C2), 129.4 (C3), 128.7 (C3), 95.4 (C6), 71.2 (C10), 31.8 (C7), 29.5 (C9), 27.2 (C9Me_2), 26.6 (C8), 22.9 (C9Me_1), 18.8 (C3Me), 18.5 (C3Me), 16.9 (C1Me), 16.2 (C2Me), 16.1 (C2Me) ppm.

HRMS: APCI$^+$ found $[M\text{-}OH]^+$= 328.2634, $C_{22}H_{34}ON$ calculated 328.2635, Δ = 0.5 ppm.

FTIR (film) = 2980, 2889, 1657, 1381, 1265, 1155, 1073cm^{-1}.



Cyclohexyl(pentamethylphenyl)methanone (**2-35**)

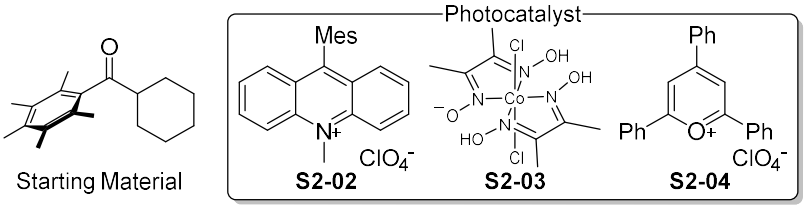
Pentamethylbenzene (2.50 g, 37.2 mmol, 1 eq), acid chloride **2-105** (5.5 mL, 41 mmol, 1.1 eq) and $AlCl_3$ (3.95 g, 46.5 mmol, 1.25 eq) was subjected to General Procedure 2A to give the product as a dull white solid (2.76 g, 10.7 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.61 (tt, *J* = 11.9, 3.3 Hz, 1H, C6), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.09 (s, 6H, C3Me), 1.97 – 1.89 (m, 2H, C7H_1), 1.84 – 1.76 (m, 2H), 1.68 (m, 1H), 1.49 – 1.36 (m, 2H, C7H_2), 1.31 – 1.16 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 215.1 (C5), 140.4 (C4), 135.5 (C1), 133.2 (C2), 128.3 (C3), 53.3 (C6), 28.4 (C7), 26.1 (C8), 26.1 (C9), 18.1 (C3Me), 16.9 (C1Me), 16.2 (C2Me) ppm.

Data in agreement with literature.[234]

6.3.3. Cleavage.



Photochemical activation of electron rich arene systems is a popular method of C–H activation that involves cleavage of an arenium cation to release a proton. It was hoped that under the same conditions an acylium cation could instead be released and trapped by a nucleophile *in situ*. In all cases, neither the desired product or the cleaved Ph* group could be observed (Table 6-1).

	Conditions	Result
1	Pyrazole (3 eq), **S2-02** (7 mol%), **S2-03** (8 mol%), MeCN, hv, 24 h.[106,108]	Decomposition
2	**S2-02** (5 mol%), HBr (1.25 eq), DCE O_2, hv, 72 h.[107]	SM recovered.
3	Pyrazole (3 eq), **S2-02** (7 mol%), TEMPO (10 mol%), DCE, O_2, hv, 48 h.[239]	SM recovered.
4	Pyrazole (3 eq), **S2-02** (7 mol%), **S2-03** (8 mol%), MeCN, hv, 24 h.[239]	SM recovered.
5	**S2-04** (10 mol%), Pyrazole (2 eq), DDQ (20 mol%), *t*-BuONO (20 mol%), MeCN, O_2, hv, 48 h.[240]	SM recovered.
6	**S2-04** (10 mol%),$CO(NH_2)_2$ (2 eq), DDQ (20 mol%), *t*-BuONO (20 mol%), MeCN, O_2, hv, 48 h.[240]	SM recovered.
7	**S2-04** (10 mol%),$PhCONH_2$ (2 eq), DDQ (20 mol%), *t*-BuONO (20 mol%), MeCN, O_2, hv, 48 h.[240]	SM recovered.
8	**S2-04** (10 mol%), $(PhSO_2)NH_2$ (2 eq), DDQ (20 mol%), *t*-BuONO (20 mol%), MeCN, O_2, hv, 48 h.[240]	SM recovered.

Table 6-1) Screened conditions for photo induced Ph* cleavage.

Light Source: Ledxon Modular 9009083 LED, Single 5050, 14.4 W, Blue purchased from the Farnell Company: http://pl.farnell.com/ledxon/9009083/led-single-5050-14-4w-blue/dp/2214013

Cyclic voltametry measurements

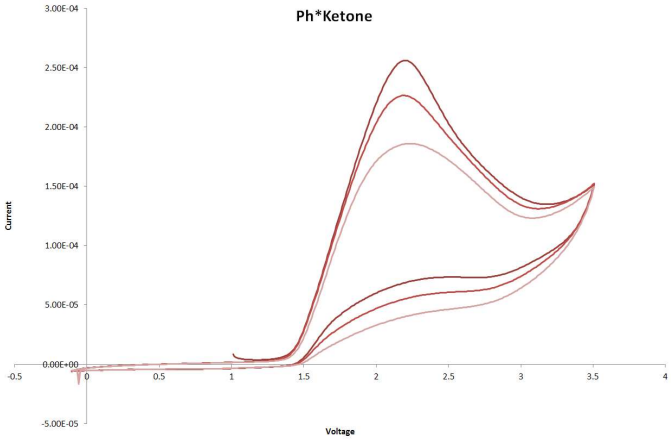
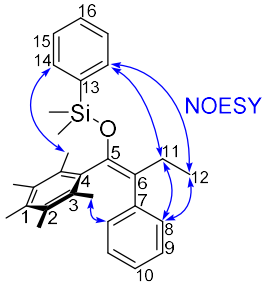


Figure 6-2) Cyclic voltammetry of Ph methyl Ketone*

Cyclic voltammetry of Ph* ketone **3-07** in 0.1M tertbutylamonium hexaflurophosphate DCM solution. E_p= 2.2 V, $E_{p/2}$= 1.73 V based on literature interpretation of irreversible cyclic voltammograms.[241] Oxidative potential causes the formation of a pale pink solution at ≈1.4 V.



(Z)-Dimethyl((1-(pentamethylphenyl)-2-phenylbut-1-en-1-yl)oxy)(phenyl)silane (**2-111**)

Based on literature procedure.[110]

In a Schlenk tube, ketone **2-110** (24 mg, 0.10 mmol, 1eq.) and BCF (2.6 mg, 5 µmol, 5%) were dissolved in DCM (1 mL) under a N_2 atmosphere. Dimethylphenylsilane (46 µl, 0.30 mmol, 3eq) was added dropwise to the solution over 5 mins. The solution was allowed to stir at rt until effervescence stopped. The reaction was then refluxed for a further 14 h. The reaction was diluted with Et_2O (10 mL) and washed through a silica pad with Et_2O (4 x 5 mL). The crude was concentrated under reduced pressure and purified by FCC to give the product **2-110** (32 mg, 0.074 mmol, 74%, >20:1 dr)

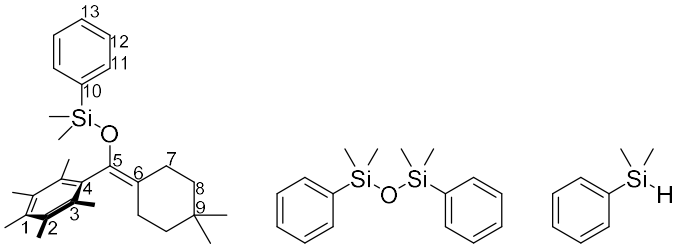
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.43 – 7.35 (m, 3H, C14+C16), 7.33 – 7.28 (m, 2H C15), 7.08 – 7.03 (m, 2H, C9), 7.02 – 6.96 (m, 3H, C8+C10), 2.75 (q, J = 7.5 Hz, 2H, C11), 2.17 (s, 3H, C1Me), 2.04 (s, 6H, C2Me), 1.99 (s, 6H, C3Me), 1.13 (t, J = 7.4 Hz, 3H, C12), 0.16 (s, 2H, $SiMe_2$) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 145.3 (C6), 141.3 (C7), 138.2 (C13), 135.0 (C4), 134.2 (C1), 133.4 (C14), 132.1 (C2), 131.9 (C3), 129.3 (C16), 128.7 (C8), 127.4 (C9/C15), 127.4 (C9/C15), 125.2 (C10), 124.2 (C5), 24.6 (C11), 18.3 (C3Me), 16.8 (C1), 16.5 (C2Me), 13.3 (C12), -0.7 ($SiMe_2$) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ 429.2609, $C_{29}H_{37}OSi$ calculated 429.2608, Δ = 0.0 ppm.

FTIR (film) = 2961, 1645, 1261, 1177, 1118, 264, 698 cm^{-1}.

Repeating the reaction with 6 eq of silane over 60 h did not result in further reactivity.



((4,4-Dimethylcyclohexylidene)(pentamethylphenyl)methoxy)dimethyl(phenyl)silane (**2-114**)

Based on literature procedure.[110]

In a Schlenk tube, enone **2-113** (57 mg, 0.20 mmol, 1eq.) and BCF (5 mg, 0.01 mmol, 5 mol%) were dissolved in DCM (0.1 mL). dimethylphenylsilane (92 µl, 0.60 mmol, 3 eq) was added dropwise over 5 mins. The solution was allowed to stir at rt for 30 mins and then heated to reflux for a further 14 h. The reaction was diluted with Et_2O (10 mL) and washed through a silica pad with Et_2O (4 x 5 mL). The product was concentrated and purified by FCC (pentane) to give the product **2-114** as an oil, contaminated by the disiloxane and silyl hydride 1:0.3:0.3 (87 mg, 77% w/w, 0.17 mmol, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.50 – 7.47 (m, 1.3H, C13+imp), 7.35 – 7.22 (m, 5.6H, C11+imp), 7.21 – 7.14 (m, 2H C14), 2.46 – 2.35 (m, 2H, C11), 2.15 (s, 3H, C1Me), 2.05 (s, 6H, C2Me), 1.98 (s, 6H, C3Me), 1.74 – 1.61 (m, 2H, C11), 1.35 – 1.28 (m, 2H, C10), 1.12 – 1.03 (m, 2H, C8), 0.86 (s, 6H, C9Me), 0.33 (s, 1.8H, SilylhydrideMe$_2$), 0.28 (s, 4H, SiloxaneMe$_2$), 0.03 (s, 6H, SiMe$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_c: 139.7 (C5), 138.6 (C12), 135.2 (C4), 134.0 (C1), 133.4 (C14), 132.5 (C2), 132.0 (C3), 129.2 (C155), 127.9, 127.9, 127.4 (C13), 118.7 (C6), 40.1 (C8/C10), 40.0 (C8/C10), 30.5 (C9), 28.3 (C9Me), 25.2 (C7), 22.6 (C11), 18.0 (C3Me), 16.8 (C1Me), 16.6 (C2Me), -0.7 (SiMe$_2$) ppm.

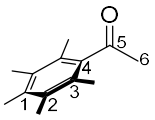
HRMS: ESI$^+$ found $[M+H]^+$ 421.2920, $C_{28}H_{41}OSi$ calculated 421.2921, Δ = 0.0 ppm.

Ratio calculated by integration of the SiMe peaks. Impurities omitted for clarity.

Impurites in agreement with literature.[242]

6.4. SI for Chapter 3.

6.4.1. Initial Results and Optimisation.



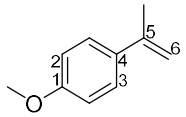
(Pentamethylphenyl)ethan-1-one (**3-07**)

Pentamethylbenzene (12.5 g, 84.3 mmol, 1 eq), acetyl chloride (6.6 mL, 93 mmol, 1.1 eq) and $AlCl_3$ (14.0 g, 105 mmol, 1.25 eq) were subjected to General Procedure 3A to give the product **3-07** as a white flakey solid (13.2 g, 69.3 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.38 (s, 3H, C6), 2.16 (s, 3H, C1Me), 2.12 (s, 6H, C2Me), 2.06 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.3 (C5), 141.0 (C4), 135.5 (C1), 133.2 (C2), 127.1 (C3), 33.3 (C6), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

Data in agreement with previous literature.[234]



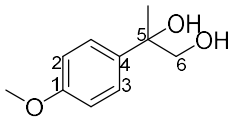
1-Methoxy-4-(prop-1-en-2-yl)benzene (**3-45**)

[PMePPh$_3$]Br (1.91 g, 5.33 mmol, 1.6 eq) and *p*-methoxy phenyl methyl ketone (600 mg, 3.33 mmol, 1 eq) were subjected to General Procedure 3A to give the product **3-45** as a clear oil (445 mg, 3.00 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: δ 7.46 – 7.37 (m, 2H, C3), 6.89 – 6.83 (m, 2H, C2), 5.28 (d, J = 1.5 Hz, 1H, C6H$_{cis}$), 4.99 (q, J = 1.4 Hz, 1H, C6H$_{trans}$), 3.82 (s, 3H, OMe), 2.13 (dd, J = 1.4, 0.7 Hz, 2H, C5Me) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 159.5 (C1), 142.7 (C6), 133.9 (C5), 126.8 (C3), 113.7 (C2), 110.8 (C4), 55.4 (OMe), 22.1 (C5Me) ppm.

Data in agreement with previous literature.[243]



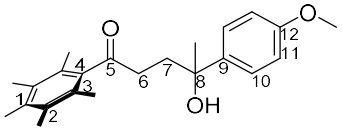
2-(4-methoxyphenyl)propane-1,2-diol (**3-47**)

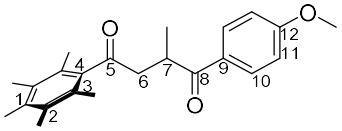
Alkene **3-45** (1.3 g, 8.8 mmol, 1 eq) was subjected to General Procedure 3B to give the desired diol **3-47** as a clear oil (1.18 g, 6.48 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.40 – 7.33 (m, 2H, C3), 6.97 – 6.80 (m, 2H, C2), 3.80 (s, 3H, OMe), 3.76 (dq, J = 10.6, 2.1 Hz, 1H, C6H$_1$), 3.60 (dq, J = 11.1, 1.9 Hz, 1H, C6H$_2$), 1.60 – 1.31 (m, 3H, C5Me) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 158.8 (C1), 137.2 (C4), 126.5 (C3), 113.9 (C2), 74.7 (C5), 71.3 (C6), 55.4 (OMe), 26.2 (C5Me) ppm.

Data in agreement with previous literature.[244]





4-hydroxy-4-(4-methoxyphenyl)-1-(pentamethylphenyl)pentan-1-one (**3-41**) and 1-(4-methoxyphenyl)-2-methyl-4-(pentamethylphenyl)butane-1,4-dione (**3-46**)

1,2-diol **3-40** (36 mg, 0.20 mmol, 1 eq), $(IrCp^*Cl_2)_2$ (1.6 mg, 0.002 mmol, 1 mol%), KOH (45 mg, 0.80 mmol, 4 eq) and Ph* methyl ketone (80 mg, 0.42 mmol, 2.1 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, toluene (100 µL) was added, and the reaction was heated to 115 °C. After 18 h, the reaction was cooled to rt, diluted with EtOAc (5 mL) and flushed through a silica plug with EtOAc (3x 5 mL). The solution was concentrated under reduced pressure to give the crude product. The crude was purified using FCC (Pentane:Et_2O 98:2 → 95:5) to give the diketone **3-46** (7 mg, <10%) and the product **3-41** (40 mg, 0.11 mmol, 56%).

Alcohol

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.27 (d, *J* = 8.9 Hz, 2H, C10), 6.78 (d, *J* = 8.8 Hz, 2H, C11), 3.72 (s, 3H, OMe), 2.59 (ddd, *J* = 19.3, 7.7, 6.9 Hz, 1H, $C6H_1$), 2.52 (ddd, *J* = 19.3, 7.4, 6.0 Hz, 2H, $C6H_2$). 2.27 – 2.12 (m, 2H, C7), 2.12 (s, 3H, C1Me), 2.06 (s, 6H, C2Me), 1.90 (s, 6H, C3Me), 1.51 (s, 3H, C8Me) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 213.3 (C5), 158.3 (C12), 140.4 (C4/C9), 139.4 (C4/C9), 135.4 (C1), 133.0 (C2), 127.2 (C3), 126.0 (C10), 113.6 (C11), 73.8 (C8), 55.3 (OMe), 41.2 (C6), 37.0 (C7), 31.4 (C8Me), 17.1 (C3Me), 16.6 (C1Me), 15.9 (C2Me) ppm.

HRMS: ESI+ found [M+Na]+ = 377.2087, $C_{23}H_{30}O_3Na$ calculated 377.2087, Δ = 0 ppm.

FTIR (film) = 3471, 2980, 1693, 1510, 1247, 1178, 1033, 833 cm^{-1}

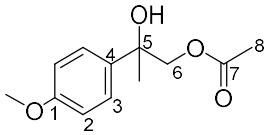
Diketone

The compound could not be cleanly isolated; key diagnostic peaks and mass spec are reported. Higher yields of the side product were not observed during the optimisation.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.97 (d, *J* = 8.9 Hz, 2H, C10), 6.90 (d, *J* = 8.9 Hz, 2H, C11), 4.07-3.97 (pd, *J* = 8.3, 4.6 Hz, 1H, C7), 3.43 (dd, *J* = 19.4, 8.3 Hz, 1H, $C6H_1$), 2.79 (dd, *J* = 19.4, 4.6 Hz, 1H, $C6H_2$) 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.13 (s, 6H, C3Me), 1.26 (d, *J* = 7.2 Hz, 3H, C7Me) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 130.9 (C10), 113.9 (C11), 55.6 (OMe), 49.5 (C6), 35.3 (C7), 18.2 (C7Me), 17.1 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI+ found [M+Na]+ = 375.1931, $C_{23}H_{28}O_3Na$ calculated 375.1931, Δ = 0 ppm.



2-hydroxy-2-(4-methoxyphenyl)propyl acetate **S3-01**

During optimisation, when the alcohol did not run to completion, esterification of the alcohol was observed due to the work-up. Isolation of the ester **S3-01** is reported below.

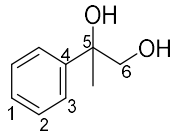
1,2-diol **3-40** (49 mg, 0.25 mmol, 1.25 eq) Fe-complex **3-16** (1.7 mg 0.004 mmol, 0.02 eq), PPh_3 (1 mg, 0.004 mmol, 0.02 eq) KOH (45 mg, 0.80 mmol, 4 eq) and Ph* methyl ketone (38 mg, 0.20 mmol, 1 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, toluene (100 µL) was added, and the reaction was heated to 115 °C. After 18 h, the reaction was cooled to rt, diluted with EtOAc (5 mL) and flushed through a silica plug with EtOAc (3 x 5 mL). The solution was concentrated under reduced pressure to give the crude product. The crude was purified using FCC (Pentane:Et_2O 98:2) to give the ester **S3-01** (10 mg, 0.045 mmol, 17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48 – 7.33 (m, 2H, C3), 7.01 – 6.78 (m, 2H, C2), 4.28 (d, J = 11.4 Hz, 1H, C6H$_1$), 4.18 (d, J = 11.4 Hz, 1H, C6H$_2$), 3.82 (s, 3H, OMe), 2.07 (s, 3H, C8), 1.56 (s, 3H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 171.2 (C7), 159.0 (C1), 136.5 (C4), 126.4 (C3), 113.8 (C2), 73.5 (C5), 72.0 (C6), 55.4 (OMe), 26.7 (C5Me), 21.0 (C8) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ $C_{12}H_{15}O_3$ = 207.1019 calculated 207.1016, Δ = 1.57 ppm.

FTIR (film) ν= 2981, 2360, 1739, 1514, 1382, 1249, 1035, 833 cm^{-1}.



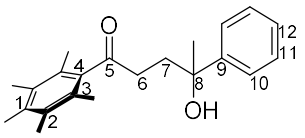
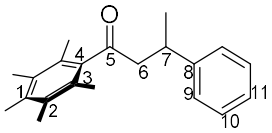
2-phenylpropane-1,2-diol (**3-50**)

The Styrene **3-49** (830 mg, 7.00 mmol) was subjected to General Procedure 3B to give the desired diol **3-50** (954 mg, 6.27 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43 – 7.33 (m, 2H, C3), 7.33 – 7.26 (m, 2H, C2), 7.23 – 7.17 (m, 1H, C1), 3.69 (ddt, J = 11.3, 3.9, 1.9 Hz, 1H, C6H$_1$), 3.53 (ddt, J = 11.4, 3.5, 1.6 Hz, 1H, C6H$_2$), 2.41 (s, 2H, OH), 1.44 (dd, J = 3.3, 1.7 Hz, 3H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 145.1 (C4), 128.5 (C2), 127.3 (C1), 125.2 (C3), 75.0 (C5), 71.2 (C6), 26.1 (C5Me) ppm.

Data in agreement with previous literature.[245]

4-hydroxy-1-(pentamethylphenyl)-4-phenylpentan-1-one (**3-53**) and 1-(pentamethylphenyl)-3-phenylbutan-1-one (**3-54**)

1,2-diol **3-50** (38 mg, 0.25 mmol, 1.25 eq), RuMacho (2.4 mg 0.004 mmol, 0.02 eq), KOH (45 mg, 0.80 mmol, 4 eq) and Ph* methyl ketone (38 mg, 0.20 mmol, 1 eq) were added to a microwave vial. The sealed vial was evacuated, flushed with N_2 four times, and heated to 115 °C. After 18 h, the reaction was cooled to rt, diluted with EtOAc (5 mL) and flushed through a silica plug with EtOAc (3x 5 mL). The solution was concentrated under reduced pressure to give the crude product. The crude was purified using FCC (Pentane:Et_2O 98:2) to give the β-branched substrate **3-54** (6mg, 0.2 mmol, 10%) and ketone **3-53** (14 mg, 0.043 mmol, 20%).

β-Branched ketone

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.26 – 7.16 (m, 4H, C9+C10), 7.14 – 7.09 (m, 1H, C11), 3.47 (dq, *J* = 14.2, 7.0 Hz, 1H, C7), 2.95 (dd, *J* = 18.9, 5.7 Hz, 1H, C6H_1), 2.86 (dd, *J* = 18.9, 7.7 Hz, 1H, C6H_2), 2.14 (s, 3H, C1Me), 2.08 (s, 6H, C2Me), 1.92 (brs, 6H, C3Me), 1.31 (d, *J* = 7.0 Hz, 3H, C7Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.2 (C5), 146.8 (C8), 140.5 (C4), 135.4 (C1), 133.1 (C2), 128.6 (C9/C10), 127.4 (C3), 127.2 (C9/C10), 126.3 (C11), 53.9 (C6), 34.3 (C7), 22.5 (C8Me), 17.0 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

Data in agreement with previous literature.[11]

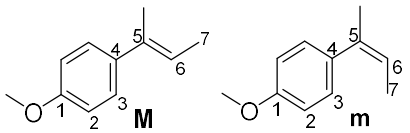
Alcohol

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48 – 7.43 (m, 2H, C10), 7.37 – 7.31 (m, 2H, C11), 7.26 – 7.20 (m, 1H, C12), 2.91 (brs, 1H, OH), 2.69 (dt, *J* = 19.4, 7.3 Hz, 1H, C6H_1), 2.61 (ddd, *J* = 19.4, 7.3, 5.9 Hz, 1H, C6H_2), 2.35 (dt, *J* = 14.4, 7.2 Hz, 1H, C7H_1), 2.26 (ddd, *J* = 14.6, 7.7, 5.9 Hz, 1H, C7H_2), 2.21 (s, 3H, C1Me), 2.15 (s, 6H, C2Me), 1.98 (s, 6H, C3Me), 1.62 (s, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 213.4 (C5), 147.3 (C9), 140.5 (C4), 135.5 (C1), 133.1 (C2), 128.3 (C11), 127.3 (C3), 126.7 (C12), 125.0 (C10), 74.1 (C8), 41.2 (C6), 37.1 (C7), 31.5 (C8Me), 17.1 (C3Me), 16.7 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$= 347.1979 $C_{22}H_{28}O_2Na$ calculated 347.1982 calculated, Δ = 0.74 ppm.

FTIR (film) ν= 2980, 2360, 1696, 1447, 1070, 763, 702 cm^{-1}.



(E)-1-(but-2-en-2-yl)-4-methoxybenzene (**3-51**) and (Z)-1-(but-2-en-2-yl)-4-methoxybenzene (**3-51**)

Mixed Isomers

p-Methoxy acetophenone (500 mg, 3.32 mmol, 1 eq) and [PPh_3Et]Br (1.91 g, 5.33 mmol, 1.6 eq) were subjected to General Procedure 3B to give the desired olefin (338 mg, 2.89 mmol, 63%, 1.7:1 *E*:*Z*)

Single Isomers

p-Methoxy acetophenone (1.80 g, 12.0 mmol, 1 eq) and [PPh_3Et]Br (5.0 g, 13.6 mmol, 1.3 eq) were subjected to General Procedure 3B. The crude was purified by FCC to give the major E isomer (120 mg, 0.72 mmol, >25:1 *E*:*Z*, 6%) and minor Z isomer (87 mg, 0.54 mmol, 1:10 *E*:*Z*, 5%).

Major (*E*)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.31 (d, *J* = 8.8 Hz, 2H, C3), 6.85 (d, *J* = 8.9 Hz, 2H, C2), 5.78 (dddd, *J* = 8.2, 6.8, 5.4, 1.4 Hz, 1H, C6), 3.81 (s, 3H, OMe), 2.00 (t, *J* = 1.2 Hz, 3H, C5Me), 1.78 (dd, *J* = 6.8, 1.1 Hz, 1H, C7).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 158.5 (C1), 136.8 (C4/C5), 135.0 (C4/C5), 126.6 (C3), 121.0 (C6), 113.7 (C2), 55.4 (OMe), 15.7 (C5Me), 14.4 (C7) ppm.

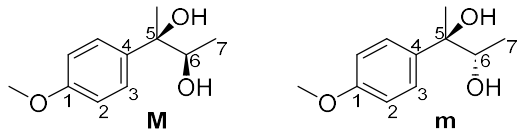
Data in agreement with previous literature.[246]

Minor (*Z*)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.14 (d, *J* = 8.8 Hz, 2H, C3), 6.88 (d, *J* = 8.8 Hz, 2H, C2), 5.53 (qq, *J* = 6.9, 1.5 Hz, 1H, C6), 3.82 (s, 3H OMe), 2.23 – 1.92 (m, 3H, C5Me), 1.61 (dd, *J* = 6.9, 1.5 Hz, 3H, C7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 158.2 (C1), 136.3 (C4/C5), 134.3 (C4/C5), 129.3 (C3), 121.3 (C6), 113.5 (C2), 55.4 (OMe), 25.6 (C5Me), 15.1 (C7) ppm.

Data in agreement with previous literature.[246]



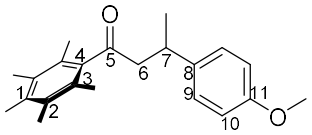
(*syn*:*anti*)-2-(4-methoxyphenyl)butane-2,3-diol (**3-52**)

The olefin (1.03 g, 6.32 mmol 1.7:1 *E*:*Z*) was subjected to General Procedure 3B to give the desired diol (745 mg, 4.59 mmol, 73%, 1.2:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.42 – 7.37 (m, 1.6H, C3m), 7.37 – 7.31 (m, 2H, C3M), 6.92– 6.85 (m, 3.6H, C2M+C2m), 3.96 (q, *J* = 6.4 Hz, 0.8H, C6m), 3.87 (q, *J* = 6.5 Hz, 1H, C6M), 3.81 (s, 5.4H, OMeM+m), 1.59 (s, 3H, C5MeM), 1.49 (s, 2.4H, C5Mem), 1.12 (d, *J* = 6.4 Hz, 2.4H, C7m), 0.98 (d, *J* = 6.5 Hz, 3H, C7M) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 158.9 (C1m), 158.7 (C1M), 137.9 (C4M), 136.7 (C4m), 126.9 (C3m), 126.8 (C3M), 113.8 (C2m), 113.6 (C2M), 76.7 (C5m), 76.3 (C5M), 74.6 (C6m), 74.4 (C6M), 55.4 (OMem), 55.4 (OMeM), 26.6 (C5Mem), 23.2 (C5MeM), 17.8 (C7m), 16.7 (C7M) ppm.

Data in agreement with previous literature.[247]



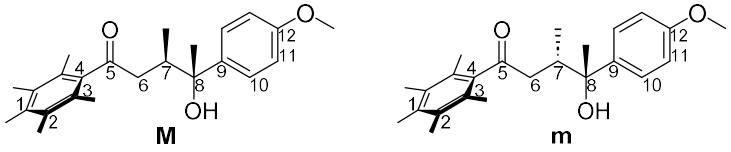
3-(4-methoxyphenyl)-1-(pentamethylphenyl)butan-1-one (**3-59**)

1,2-diol **3-40** (49 mg, 0.25 mmol, 1.25 eq) RuMacho (2.4 mg 0.004 mmol, 0.02 eq), KO*t*-Bu (45 mg, 0.80 mmol, 4 eq) and Ph* methyl ketone (38 mg, 0.20. mmol, 1 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times and the reaction was heated to 115 °C. After 18 h, the reaction was cooled to rt, the mixture was flushed through a silica plug with EtOAc and concentrated under reduced pressure. The product was isolated using FCC (Pentane:Et_2O 98:2) to give the β-branched ketone **3-59** (12 mg, 0.037 mmol, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.17 (d, *J* = 8.6 Hz, 2H, C9), 6.83 (d, *J* = 8.7 Hz, 2H, C10), 3.79 (s, 3H, OMe), 3.50 (td, *J* = 7.2, 6.0 Hz, 1H, C7), 2.99 (dd, *J* = 18.8, 5.9 Hz, 1H, C6H_1), 2.90 (dd, *J* = 18.9, 7.5 Hz, 1H, C6H_2), 2.22 (s, 3H, C1Me), 2.16 (s, 6H, C2Me), 1.99 (s, 6H, C3Me), 1.35 (d, *J* = 7.0 Hz, 3H, C7Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.4 (C5), 158.1 (C11), 140.6 (C4/C8), 139.0 (C4/C8), 135.5 (C1), 133.2 (C2), 128.1 (C9), 127.5 (C3), 113.9 (C10), 55.4 (OMe), 54.2 (C6), 33.5 (C7), 22.7 (C7Me), 17.0 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

Data in agreement with previous literature.[74]



Molecular Weight: 368.52

4-hydroxy-4-(4-methoxyphenyl)-3-methyl-1-(pentamethylphenyl)pentan-1-one (**3-58**)

1,2-diol **3-52** (36 mg, 1.2:1, 0.2 mmol, 1 eq), $(IrCp^*Cl_2)_2$ (1.6 mg, 0.002 mmol, 1 mol%), KOH (45 mg, 0.80 mmol, 4 eq) and Ph* methyl ketone (76 mg, 0.40 mmol, 2 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, toluene (100 µL) was added and the reaction was heated to 115 °C. After 18 h, the reaction was cooled to rt diluted with EtOAc (5 mL), flushed through a silica plug with EtOAc (3x 5 mL) and the solution was concentrated under reduced pressure to give the crude product. The crude was purified using FCC (Pentane:Et_2O 98:2 → 95:5) to give the desired product as a mixture of diastereomers **3-58** (38 mg, 0.10 mmol, 52%, 5:1 d.r.)[a] Further FCC gave the major isomer as a single isomer (21 mg, 0.057 mmol, 28% >25:1 d.r.) and a mixture of diastereomers (17 mg, 0.046 mmol, 23%, 1.7:1 d.r.)

Major isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39 – 7.33 (m, 2H, C10), 6.89 – 6.83 (m, 2H, C11), 3.81 (s, 3H, OMe), 2.83 (dd, *J* = 19.5, 2.3 Hz, 1H, C6H$_1$), 2.69 – 2.56 (m, 1H, C7), 2.50 (dd, *J* = 19.4, 8.3 Hz, 1H, C6H$_2$), 2.20 (s, 3H, C1Me), 2.13 (s, 6H, C2Me), 1.89 (brs, 6H, C3Me), 1.52 (s, 3H, C8Me), 1.15 (d, *J* = 6.7 Hz, 3H, C7Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.2 (C5), 158.3 (C12), 140.4 (C4/C9), 140.4 (C4/C9), 135.3 (C1), 133.0 (C2), 127.2 (C3), 126.2 (C10), 113.5 (C11), 76.1 (C8), 55.3 (OMe), 48.7 (C6), 38.7 (C7), 27.2 (C8Me), 16.7 (C3Me), 16.6 (C1Me), 15.9 (C2Me), 15.0 (C7Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 391.2253, $C_{24}H_{32}O_3Na$ calculated, 391.224 Δ = 2.38 ppm.

FTIR (film) ν= 2981, 2888, 1383, 1251, 1152, 1073, 954 cm^{-1}

Relative stereochemistry determined by Xray crystallography, see Section 8.

Minor Isomer.

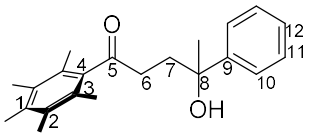
Characterised from the mixture.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1H NMR (400 MHz, CDCl3) δH: 7.40 – 7.31 (m, 2H, C10), 6.90 – 6.80 (m, 2H, C11), 3.86 – 3.76 (m, 3H, OMe), 2.93 (dd, J = 19.5, 2.9 Hz, 1H, C6H$_1$), 2.69 – 2.56 (m, 1H, C7), 2.40 (dd, J = 19.5, 8.3 Hz, 1H, C6H$_2$), 2.22 (s, 3H, C1Me), 2.16 (s, 6H, C2Me), 2.01 (brs, 6H, C3Me), 1.58 (s, 3H, C8Me), 1.02 (d, J = 6.8 Hz, 3H, C7Me) ppm.

[a] Crude d.r. could not be determined.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.0 (C5), 158.5 (C12), 140.4 (C4), 135.5 (C1), 133.2 (C2), 127.9 (C3), 127.0 (C10), 113.4 (C11), 76.0 (C8), 55.4 (OMe), 48.6 (C6), 39.2 (C7), 27.4 (C8Me), 17.0 (C3Me), 16.8 (C1Me), 16.2 (C7Me) 16.0 (C2Me) ppm.

FTIR (film) ν= 3469, 2981, 1737, 1514, 1373, 1249, 1035, 756 cm^{-1}.

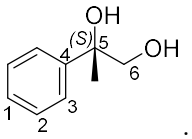


4-hydroxy-1-(pentamethylphenyl)-4-phenylpentan-1-one (**3-53**)

1,2-diol **3-50** (76 mg, 0.50 mmol, 1 eq) $(IrCp^*Cl_2)_2$ (8 mg 0.01 mmol, 0.02 eq), KOH (112 mg, 2.00 mmol, 4 eq) and Ph* methyl ketone (38 mg, 0.20 mmol, 1 eq) was subjected to General Procedure 3C to give the product **3-53** (135 mg, 0.415 mmol, 83%).

Data in agreement with the procedure above.

6.4.2. Control of Absolute Stereochemistry and Ph* Cleavage.



(S)-2-phenylpropane-1,2-diol (**3-50**)

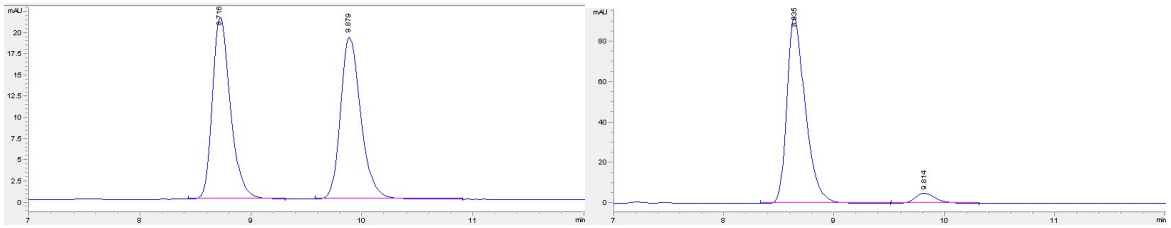
Under a N_2 atmosphere, a mixture of Olefin **3-49** (230 µL, 1.5 mmol, 1 eq), AD-mix-α (1.7 g), K_2CO_3 (620 mg, 4.5 mmol, 3eq) and $K_2OsO_2(OH)_4$ (6 mg, 0.015 mmol, 0.01 eq) was cooled to 0 °C and dissolved in *t*-BuOH:H_2O (15 mL, 1:1). After 18 h, upon consumption of the olefin, the product was extracted with Et_2O (5 x 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude was purified by FCC (Pentane: EtOAc, 94:6→75:25) to give the diol as a viscous oil (145 mg, 0.95 mmol, 63%, 88% e.e.)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43 – 7.33 (m, 2H, C3), 7.33 – 7.26 (m, 2H, C2), 7.23 – 7.17 (m, 1H, C1), 3.69 (ddt, *J* = 11.3, 3.9, 1.9 Hz, 1H, $C6H_1$), 3.53 (ddt, *J* = 11.4, 3.5, 1.6 Hz, 1H, $C6H_2$), 2.41 (s, 2H, OH), 1.44 (dd, *J* = 3.3, 1.7 Hz, 3H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 145.1 (C4), 128.5 (C2), 127.3 (C1), 125.2 (C3), 75.0 (C5), 71.2 (C6), 26.1 (C5Me) ppm.

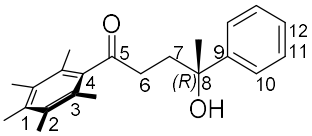
$[\alpha]_D^{25}$ = 11.4° (C=0.4)

Chiral HPLC: (Chiralpak IA with Guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 230 nm, 10 µL injection).



	Racemic		Enantioenriched	
Time (min)	8.7	9.9	8.6	9.8
Area (%)	50	50	94	6

Data in agreement with previous literature.[245]



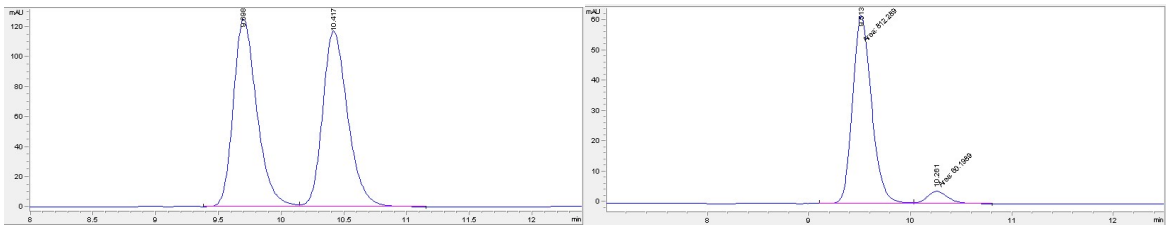
(*R*)-4-hydroxy-1-(pentamethyl phenyl)-4-phenylpentan-1-one **3-53**

Diol **(*S*)-3-50** (181 mg, 1.19 mmol 1 eq) was subjected to General Procedure 3C to give the desired product **(*R*)-3-53** (182 mg, 0.56 mmol, 47%).

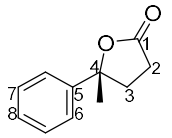
Data in agreement with that reported above.

$[\alpha]_D^{25}$ = -0.8 ° (C= 1.0, $CHCl_3$)

Chiral HPLC: (Chiralpak IA with Guard, 2% IPA, 98% hexane, 1.0 mL/min, 25 o C, λ = 230 nm, 10 µL injection).



	Racemic		Enantioenriched	
Time (min)	9.7	10.4	9.5	10.3
Area (%)	50	50	93	7



(*R*)-5-methyl-5-phenyldihydrofuran-2(3H)-one (**3-61**)

Acidic cleavage

Enantioenriched

To a stirred solution of ketone **3-53** (32 mg, 0.10 mmol) in HFIP (0.83 mL) was added conc. HCl (0.17 mL) dropwise, and the solution was heated to 65 °C. After 18 h, the solution was diluted with DCM (10 mL) and H_2O (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (4 x 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. 1,1,2,2-tetrachloroethane (10 µL, 0.094 mmol) was added as a reference. ^{1}H-NMR yield was determined to be 66%. An aliquot of the crude was purified by prep TLC to allow the lactone e.e. to be determined (2% e.e.).

Racemic

To a stirred solution of ketone **3-53** (16 mg, 0.049 mmol) in HFIP (0.44 mL) was added conc. HCl (0.07 mL) dropwise, and the solution was heated to 65 °C. After 18 h, the solution was diluted with DCM (10 mL) and H_2O (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (4 x 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by FCC (Pentane;Et_2O 98:2) to give the desired lactone **3-61** as a clear oil (6.7 mg, 0.034 mmol 68%)

Bromination conditions

Enantioenriched

To a rapidly stirred solution of ketone **353** (40 mg, 0.13 mmol) and pyridine (17 µL, 0.19 mmol, 1.5 eq) in DCM (625 µL), cooled to -17 °C using a cryostat, was added bromine (15 µL, 0.29 mmol, 2.2 eq) dropwise. After 5 h, upon consumption by TLC, the reaction was quenched with aq. NaS_2O_3 (1 mL, sat). After 30 mins, the solution was diluted with DCM (10 mL) and H_2O (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (4x 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. 1,1,2,2-tetrachloroethane (10 µL, 0.094 mmol) was added as a reference. ^{1}H-NMR yield was determined to be 84%. An aliquot of the crude was purified by prep TLC to allow the lactone e.e. to be determined (82% e.e.).

Racemic

To a rapidly stirred solution of ketone **3-53** (32 mg, 0.099 mmol) and pyridine (11 µL, 0.14 mmol, 1.5 eq) in DCM (500 µL), cooled to -17 °C using a cryostat, was added bromine (10 µL, 0.2 mmol, 2 eq) dropwise. After 5 h, upon consumption by TLC, the reaction was quenched with aq. NaS_2O_3 (1 mL, sat). After 30 mins, the solution was diluted with DCM (10 mL) and H_2O (5 mL), the layers were separated, and the aqueous layer was extracted with DCM (4x 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by FCC (Pentane;Et_2O 98:2) to give the desired lactone **3-61** as a clear oil (12 mg, 0.068 mmol 68%).

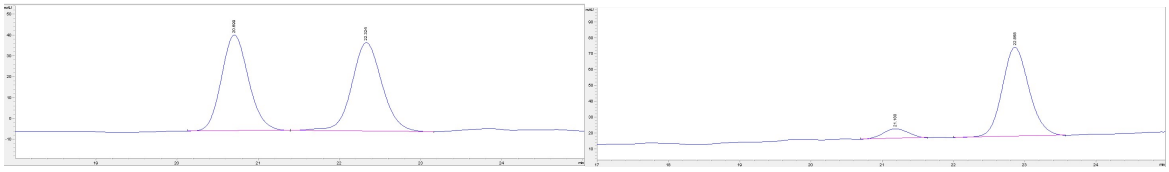
The crude NMR showed a clean mixture of the lactone and pentamethylphenyl bromide in a 1:1 ratio.

Lactone

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39 – 7.36 (m, 4H, C6+C7), 7.34 – 7.27 (m, 1H, C8), 2.68 – 2.58 (m, 1H), 2.56 – 2.37 (m, 3H), 1.73 (s, 3H, C4Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 176.6 (C1), 144.5 (C5), 128.8 (C6/C7), 127.8 (C8), 124.2 (C6/C7), 87.1 (C4), 36.3 (C3), 29.6 (C5Me), 29.1 (C2) ppm.

Chiral HPLC: (Chiralpak IC with Guard, 2% IPA, 98% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 µL injection).



	Acidic cleavage		Bromine cleavage	
Time (min)	20.7	22.3	21.2	22.9
Area (%)	49	51	9	91

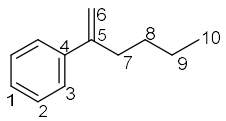
Data in agreement with previous literature.[248]

Phenyl Bromide

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.37 (s, 6H), 2.20 (s, 6H), 2.13 (s, 3H) ppm. The material was observed in the crude mixture but not isolated.

Data in agreement with previous literature.[234]

6.4.3. Substrate Scope.



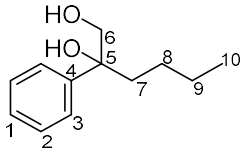
hex-1-en-2-ylbenzene (**3-63**)

Ketone **3-62** (1.0 mL, 6.0 mmol) and Ph_3PMeBr (2.80 g, 7.8 mmol, 1.3 eq) were subjected to General Procedure 3A to give the product **3-63** (806 mg, 5.03 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37 – 7.33 (m, 2H, C3), 7.29 – 7.24 (m, 2H, C2), 7.22 – 7.17 (m, 1H, C1), 5.20 (d, J = 1.6 Hz, 1H, $C6H_{cis}$), 4.99 (q, J = 1.4 Hz, 1H, $C6H_{trans}$), 2.48 – 2.40 (m, 2H, C7), 1.42 – 1.34 (m, 2H, C8), 1.33 – 1.24 (m, 2H, C9), 0.84 (t, J = 7.2 Hz, 3H, C10) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 148.9 (C4/C5), 141.7 (C4/C5), 128.4 (C3), 127.4 (C1), 126.2 (C2), 112.1 (C6), 35.2 (C7), 30.6 (C8), 22.6 (C9), 14.1 (C10) ppm.

Data in agreement with previous literature.[249]



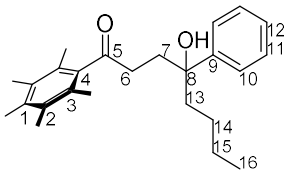
2-phenylhexane-1,2-diol (**3-64**)

The alkene **3-63** (480 mg, 3.00 mmol, 1 eq) was submitted to General Procedure 3B to give the product **3-63** (564 mg, 2.90 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43 – 7.33 (m, 4H, C2+C3), 7.31 – 7.23 (m, 1H, C1), 3.88 – 3.77 (m, 1H, $C6H_1$), 3.73 – 3.60 (m, 1H, $C6H_2$), 2.10 (brs, 2H, OH) 1.86 – 1.72 (m, 2H, C7), 1.35 – 1.17 (m, 3H), 1.08 – 0.97 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H, C10). ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 143.7 (C4), 128.5 (C2/C3), 127.1 (C1), 125.7 (C2/C3), 77.4 (C5), 70.8 (C10), 38.4 (C6), 25.3, 23.2, 14.1 (C9) ppm.

Data in agreement with previous literature.[250]



4-hydroxy-1-(pentamethylphenyl)-4-phenyloctan-1-one (**3-73**)

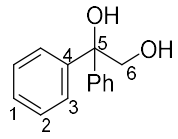
Pentametyl benzene (114 mg, 0.599 mmol, 2 eq) and diol **3-64** (58 mg, 0.30 mmol, 1 eq) was subjected to General Procedure 3C to give the product **3-73** (57 mg, 0.16, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.41 – 7.36 (m, 2H, C10), 7.34 – 7.28 (m, 2H, C11), 7.23 – 7.17 (m, 1H, C12), 2.65 (dt, J = 19.5, 7.4 Hz, 1H, $C6H_1$), 2.54 (ddd, J = 19.6, 7.0, 5.6 Hz, 1H, $C6H_2$), 2.36 (dt, J = 14.4, 7.2 Hz, 1H, $C7H_1$), 2.24–2.13 (m, 1H, $C7H_2$), 2.18 (s, 3H, C1Me), 2.12 (s, 6H, C2Me), 1.95 (s, 6H, C3Me), 1.85 (m, 2H, C13), 1.43 – 1.18 (m, 3H, $C14H_1$+C15), 1.11 – 0.96 (m, 1H, $C14H_2$), 0.84 (t, J = 7.3 Hz, 3H, C16). ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 213.6 (C5), 145.7 (C4), 140.3 (C1), 135.4 (C2), 133.0 (C3), 128.1 (C11), 127.2 (C9), 126.3 (C12), 125.4 (C10), 76.4 (C8), 43.9 (C13), 40.9 (C6), 35.8 (C7), 25.7 (C14), 23.1 (C15), 17.0 (C3Me), 16.6 (C1Me), 15.9 (C2Me), 14.0 (C16) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ $C_{25}H_{34}O_2Na$ = 389.2453 calculated, 389.2451 Δ = 0.5 ppm.

FTIR (film) ν= 3504, 2955, 2341, 195, 1447, 912, 737 cm^{-1}.



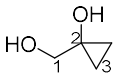
1,1-diphenylethane-1,2-diol (**3-66**)

Olefin **3-65** (1.44 g, 8.00 mmol) was subjected to General Procedure 3B to give the desired diol **3-66** as a white solid (1.06 g, 4.94 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48 – 7.41 (m, 4H, C3), 7.38 – 7.32 (m, 4H, C2), 7.30 – 7.24 (m, 2H, C1), 4.18 (d, *J* = 5.7 Hz, 2H, C6), 3.20 – 3.14 (m, 1H, OH), 1.86 (d, *J* = 6.8 Hz, 1H, OH) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 144.0 (C4), 128.6 (C2), 127.6 (C1), 126.5 (C3), 78.7 (C5), 69.6 (C6) ppm.

Data in agreement with previous literature.[251]



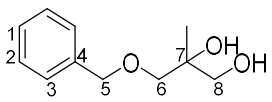
1-(hydroxymethyl)cyclopropan-1-ol (**3-72**)

To a solution of carboxylic acid **3-71** (700 mg, 6.85 mmol, 1 eq) in THF (25 mL) was added $LiAlH_4$ (520 mg, 13.7 mmol, 2 eq) portion-wise at 0 °C. After 10 min, the solution was heated to reflux. After 5 h, upon consumption of the starting material by TLC, the reaction was cooled to 0 °C and quenched with H_2O (7 mL), aq. NaOH (7 mL, 1 M) and H_2O (21 mL). After stirring for 30 min, the product was extracted with DCM (4 x 25 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (DCM:MeOH, 95:5) gave the desired diol **3-72** as a pale yellow oil (438 mg, 4.97 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.63 (s, 2H, C1), 0.88 – 0.76 (m, 2H, $C3H_1$), 0.68 – 0.50 (m, 2H, $C3H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 69.1 (C1), 56.8 (C2), 11.8 (C3) ppm.

Data in agreement with previous literature.[252]



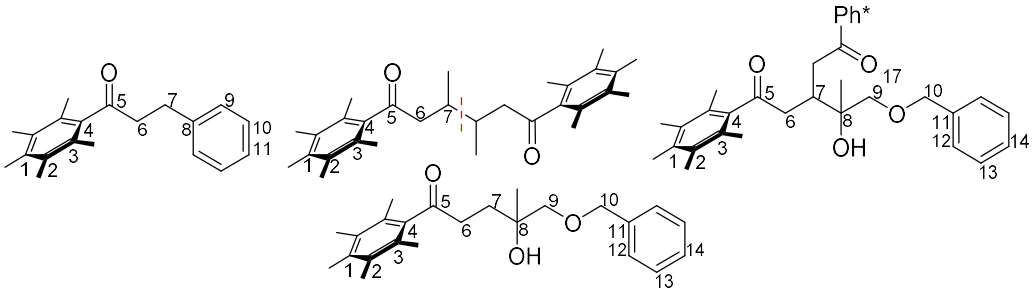
3-(benzyloxy)-2-methylpropane-1,2-diol (**3-68**)

Allyl ether **3-67** (510 mg, 3.14 mmol) was subjected to General Procedure 3B to give the diol **3-68** (568 mg, 2.89 mmol, 97%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39 – 7.28 (m, 5H, C1-C3), 4.57 (d, *J* = 12.0 Hz, 1H, $C5H_1$), 4.54 (d, *J* = 12.0 Hz, 1H, $C5H_2$), 3.64 (d, *J* = 11.1 Hz, 1H. $C6H_1$), 3.51 (d, *J* = 9.1 Hz, 1H, $C8H_1$), 3.45 (d, *J* = 10.9 Hz, 1H $C6H_2$), 3.43 (d, *J* = 9.5 Hz, 1H, $C8H_2$), 2.35 (brs, 2H, OH), 1.15 (s, 3H, C7Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 137.8 (C4), 128.7 (C2/C3), 128.1 (C1), 127.8 (C2/C3), 76.4 (C6), 73.9 (C5), 72.0 (C7), 68.7 (C8), 21.5 (C7Me) ppm.

Data in agreement with previous literature.[253]



5-(benzyloxy)-4-hydroxy-4-methyl-1-(pentamethylphenyl)pentan-1-one (**3-77**) and 1-(pentamethylphenyl)-3-phenylpropan-1-one (**3-79**) and 3,4-dimethyl-1,6-bis(pentamethylphenyl)hexane-1,6-dione (**3-78**) and 3-(1-(benzyloxy)-2-hydroxypropan-2-yl)-1,5-bis(pentamethylphenyl)pentane-1,5-dione (**3-76**) and

Diol **3-68** (59 mg, 0.30 mmol) was subjected to General Procedure 3C. Purification by FCC gave four products; the phenyl propanone **3-77** (18 mg, 0.064 mmol, 21%), 1,6-diketone **3-79** (17 mg, 0.039 mmol, 13%, 1.3:1 d.r.), 1,5-diketone **3-78** (11 mg, 0.020 mmol, 7%) and the desired alcohol **3-76** (47 mg, 0.13 mmol, 43%).

Benzylpropanone

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.35 – 7.25 (m, 4H, C9+C10), 7.24 – 7.18 (m, 1H, C11), 3.14 – 3.06 (m, 2H, C6), 3.05 – 3.00 (m, 2H, C7), 2.25 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.07 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 211.0 (C5), 141.2 (C4/C8), 140.6 (C4/C8), 135.6 (C1), 133.2 (C2), 128.6 (C9/C10), 128.6 (C9/C10), 127.5 (C3), 126.2 (C11), 47.2 (C6), 29.5 (C7), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

Data in agreement with previous literature.[234]

1,6-Diketone

1H NMR (400 MHz, CDCl3) δH: 2.72 (dd, J = 18.9, 2.8 Hz, 1H, $C6H_1M$), 2.64 (dd, J = 18.7, 3.0 Hz, 0.75H, $C6H_1m$), 2.62 – 2.46 (m, 1.75H, $C6H_2M$+$C6H_2m$), 2.41 – 2.28 (m, 1.75H, C7M+C7m), 2.24 (s, 5.25H, C1MeM+C1Mem), 2.19 (s, 6H, C2Me), 2.18 (s, 6H, C2Me), 2.11 (s, 6H, C3MeM), 2.08 (s, 4.5H, C3Mem), 1.05 (d, J = 6.5 Hz, 2.25H, C7Mem), 0.98 (d, J = 6.6 Hz, 3H, C7MeM) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.8 (C5M), 210.7 (C5m), 140.7 (C4M+C4m), 135.4 (C1m), 135.4 (C1M), 133.1 (C2m), 133.1 (C2M), 127.3 (C3m), 127.3 (C3M), 50.8 (C6M), 49.5 (C6m), 32.3 (C7m), 32.0 (C7M), 17.1 (C3Me), 17.1 (C3Me), 17.0 (C7Mem), 16.7 (C1MeM+C1Mem), 15.9 (C2MeM+C2Mem) + (C7MeM) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ $C_{30}H_{43}O_2$ = 435.3265 calculated, 435.3258 Δ = 1.7 ppm.

FTIR (film) ν= 2981, 2360, 1702, 1382, 1252, 1382, 954, 762 cm^{-1}.

1,5-Diketone

No attempt to differentiate the C1-C6 chains has been made.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 – 7.26 (m, 5H, C12-C14), 4.59 (d, J = 12.2 Hz, 1H, $C10H_1$), 4.54 (d, J = 12.2 Hz, 1H, $C10H_2$), 3.47 – 3.33 (m, 3H, C7+C9), 3.14-3.04 (m, 2H, $C6H_1$+C6'H_1), 2.87 (dd, J = 19.9, 3.9 Hz, 1H, $C6H_2$), 2.63 (dd, J = 19.7, 8.9 Hz, 1H, $C6H_2$), 2.24 (s, 3H, C1Me), 2.22 (s, 3H, C1Me), 2.19 (s, 6H, ArMe), 2.18 (s, 6H, ArMe), 2.16 (s, 6H, ArMe), 2.05 (s, 6H, ArMe), 1.09 (s, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.3 (C5), 211.0 (C5), 140.5 (C4), 140.3 (C4), 138.2 (C11), 135.6 (C1), 135.6 (C1), 133.2 (2xC2), 128.5 (C12/C13), 127.9 (2xC3), 127.8 (C12/C13), 127.5 (C14), 77.0 (C9), 73.8 (C8/C10), 73.8 (C8/C10), 47.1 (C6), 46.9 (C6), 33.5 (C7), 21.0 (C8Me), 17.2 (C3Me), 17.2 (C3Me), 16.8 (C1Me), 16.8 (C1Me), 16.1 (C2Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 579.3453 $C_{37}H_{49}O_4Na$ calculated, 579.3445 Δ = 1.41 ppm.

FTIR (film) ν= 2360, 1701, 912, 736 cm^{-1}.

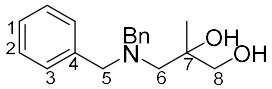
Desired Product

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.42 – 7.27 (m, 5H, C12-C14), 4.57 (s, 2H, C10), 3.37 (d, J = 9.0 Hz, 1H $C9H_1$), 3.34 (d, J = 9.0 Hz, 1H, $C9H_2$), 2.92 – 2.75 (m, 2H, C6), 2.56 (s, 1H, OH), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.10 (s, 6H, C3Me), 2.14 – 2.04 (m, 1H, $C7H_1$), 1.87 (ddd, J = 14.3, 9.4, 6.0 Hz, 1H, $C7H_2$), 1.19 (s, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.6 (C5), 140.9 (C4), 138.2 (C11), 135.5 (C1), 133.2 (C2), 128.6 (C3), 127.9 (C12/C13), 127.8 (C12/C13), 127.4 (C14), 77.7 (C9), 73.6 (C10), 71.5 (C8), 40.4 (C6), 32.1 (C7), 24.1 (C8Me), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ 269.2437 = $C_{24}H_{33}O_3$ calculated, 269.2424 Δ = 3.5 ppm.

FTIR (film) ν= 3657, 2981, 2889, 2360, 1699, 1382, 1093, 757, 699 cm^{-1}.



3-(dibenzylamino)-2-methylpropane-1,2-diol **(3-70**)

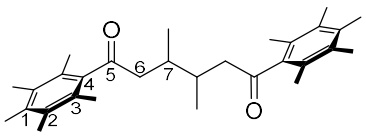
Alkene **3-69** (750mg, 2.98 mmol) was subjected to General Procedure 3B for 5 days to give the desired diol **3-70** (299 mg, 1.05 mmol, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.41 – 7.28 (m, 10H, C1-C3), 3.99 (d, J = 13.2 Hz, 2H, $C5H_1$), 3.44 (d, J = 13.2 Hz, 2H, $C5H_2$), 3.29 (dd, J = 11.1, 1.5 Hz, 1H, $C8H_1$), 3.21 (d, J = 11.1 Hz, 1H, $C8H_2$), 2.76 (d, J = 13.9 Hz, 1H, $C6H_1$), 2.61 (dd, J = 13.9, 1.5 Hz, 1H, $C6H_2$), 1.62 (brs, 2H, OH), 1.00 (s, 3H, C7Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 138.3 (C4), 129.5 (C2/C3), 128.7 (C2/C3), 127.7 (C1), 71.9 (C7), 70.2 (C8), 61.5 (C6), 60.9 (C5), 24.0 (C7Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ $C_{19}H_{23}NO_2Na$ = 308.1612 calculated, 308.1621 Δ = 2.93 ppm.

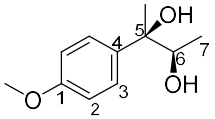
FTIR (film) ν= 3403, 1452, 1266, 1047, 737, 700 cm^{-1}.



3-(1-(benzyloxy)-2-hydroxypropan-2-yl)-1,5-bis(pentamethylphenyl)pentane-1,5-dione (**3-79**)

Amine **3-70** (85 mg, 0.30 mmol) was subjected to General Procedure 3C to give the 1,6-diketone **3-79** (32 mg, 0.074 mmol, 25%, 1:1.4 d.r.).[a]

Data in agreement with the procedure above.

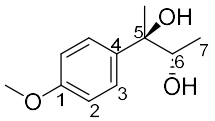


(*syn*)-2-(4-methoxyphenyl)butane-2,3-diol (**352**)

The olefin **Ax(*E*)** (87 mg, 0.54 mmol) was subjected to General Procedure 3B to give the desired diol **352** (101 mg, 0.514 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37 – 7.31 (m, 2H, C3), 6.91 – 6.85 (m, 2H, C2), 3.87 (q, *J* = 6.5 Hz, 1H, C6), 3.81 (s, 3H, OMe), 1.59 (s, 3H, C5Me), 0.98 (d, *J* = 6.5 Hz, 3H, C7) ppm.

Data in agreement with the procedure above.



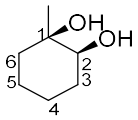
(*anti*)-2-(4-methoxyphenyl)butane-2,3-diol (**3-52**(***anti***))

The olefin **3-51(*E*)** (120 mg, 0.739 mmol) was subjected to General Procedure 3B to give the desired diol **3-52(*anti*)** (130 mg, 0.662 mmol, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.42 – 7.37 (m, 2H, C3), 6.92 – 6.86 (m, 2H, C2), 3.96 (q, *J* = 6.4 Hz, 1H, C6), 3.81 (s, 3H, OMe), 1.49 (s, 3H, C5Me), 1.12 (d, *J* = 6.4 Hz, 3H, C7) ppm.

Data in agreement with the procedure above.

[a] 50% if the mechanism proposed is correct, which requires a second alcohol to act as a hydride source.

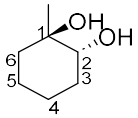


(±-syn)-1-methylcyclohexane-1,2-diol (**3-89**(***syn***))

1-Methyl cyclohexene (590 µL, 5.0 mmol) was subjected to General Procedure 3B to give the desired product **3-89** (544 mg, 4.18 mmol, >25:1 d.r., 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.34 (dd, J = 9.2, 3.9 Hz, 1H, C1), 1.75 – 1.41 (m, 5H), 1.39 – 1.20 (m, 3H), 1.19 (s, 3H, C1Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 74.9 (C1), 71.7 (C2), 37.0, 30.6, 26.7 (C1Me), 23.3, 21.7 ppm.



(±-anti)-1-methylcyclohexane-1,2-diol (**3-89**(***anti***))

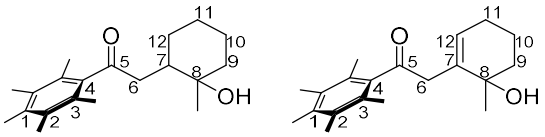
Based on procedure by Alfonso and co-workers[254]

PTSA (345 mg, 2.00 mmol, 0.2 eq) was dissolved in H_2O_2 (610 µL, 30% in H_2O, 20 mmol, 2 eq) at rt. After 5 min, cyclohexene **3-88** (1.2 mL, 10 mmol, 1 eq) was added, and the solution was heated to 50 °C. After 26 h, upon consumption of the alkene by TLC, the reaction was cooled to rt and quenched with aq. Na_2CO_3 (5 mL, sat) and aq. NaS_2O_3 (10 mL, sat). The product was extracted with DCM (4 x 10 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (DCM:MeOH, 90:10) gave the desired diol **3-89** as a pale yellow oil (233 mg, 1.78 mmol, >1:25,18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.49 (dd, J = 10.6, 4.4 Hz, 1H, C2), 1.91 – 1.82 (m, 1H), 1.82 – 1.66 (m, 4H, 2xOH), 1.66 – 1.58 (m, 1H), 1.44 – 1.27 (m, 4H), 1.20 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 77.4 (C2), 74.1 (C1), 38.8, 31.2, 24.2, 23.4, 19.8 (C1Me) ppm.

Data in agreement with previous literature.[254]



2-(2-hydroxy-2-methylcyclohexyl)-1-(pentamethylphenyl)ethan-1-one (**3-90**) and 2-(6-hydroxy-6-methylcyclohex-1-en-1-yl)-1-(pentamethylphenyl)ethan-1-one (**3-91**)

Diol **Ax(*syn*)** was subjected to General Procedure 3C to give the unsaturated product **3-91** (16 mg, 0.053 mmol, 18%) and saturated product **3-90** (15 mg, 0.05 mmol, 17%, >10:1 d.r.).

Olefin

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.59 (t, *J* = 3.8 Hz, 1H, C12), 3.70 (brs, 1H, OH) 3.62 (ddd, *J* = 19.7, 2.0, 1.0 Hz, 1H, $C6H_1$), 3.46 (d, *J* = 18.8 Hz, 1H, $C6H_2$), 2.24 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.16 (s, 6H, C3Me), 2.23-2.14 (m, 1H, $C11H_1$) 2.11 – 1.97 (m, 1H $C11H_2$), 1.96 – 1.82 (m, 2H, $C9H_1$+ $C10H_1$), 1.78 – 1.60 (m, 2H, $C9H_2$+ $C10H_2$), 1.29 (s, 3H, 8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 213.6 (C5), 140.4 (C4), 135.8 (C1/C7), 135.4 (C1/C7), 133.3 (C2), 130.5 (C12), 127.4 (C3), 69.3 (C8), 50.1 (C6), 39.4 (C10), 27.5 (C8Me), 26.1 (C11), 19.8 (C9), 17.4 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found [M-H]= 301.2173 $C_{20}H_{29}O_2$ calculated 301.2173 calculated, Δ = 0.00 ppm.

FTIR (film) ν= 3449, 2981, 2360, 2341, 1692, 1392, 937, 759 cm^{-1}.

Saturated

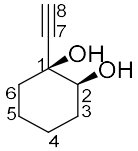
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.11 (dd, *J* = 19.3, 3.6 Hz, 1H, $C6H_1$), 2.45 (dd, *J* = 19.2, 8.3 Hz, 1H, $C6H_2$), 2.30-2.15 (m, 1H, C7), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.11 (s, 6H, C3Me), 1.96 – 1.86 (m, 1H, $C12H_1$), 1.83 – 1.76 (m, 1H), 1.75 – 1.63 (m, 2H), 1.52 – 1.30 (m, 3H), 1.17 – 1.08 (m, 1H, $C12H_2$), 1.07 (s, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.3 (C5), 140.9 (C4), 135.5 (C1), 133.2 (C2), 127.4 (C3), 72.3 (C8), 47.0 (C6), 43.1, 42.5 (C7), 30.9 (C12), 25.9, 24.4, 20.6 (C8Me), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ $C_{20}H_{30}O_2Na$ = 325.2139 calculated, 325.2138 Δ = 0.29 ppm.

FTIR (film) ν= 3480, 2981, 2361, 1699, 1382, 1155, 954, 759 cm^{-1}.

Small impurities were observed by ^{1}H-NMR (~5%) 3.03 (dd, *J*=19.8, 3.3 Hz, $C6H_1$), 2.62 (dd, *J*= 19.8, 7.8 Hz, $C6H_2$) ppm, which was suspected to be the minor isomer, although no other peaks could be observed.



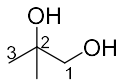
(±-syn)-1-ethynylcyclohexane-1,2-diol (**3-92**)

Cyclohexene **3-91** (590 μL, 5.0 mmol) was subjected to General Procedure 3B to give the desired product **3-92** (233 mg, 1.66 mmol, 33%, 14:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.12 (ddd, *J* = 12.1, 6.8, 1.5 Hz, 0.1H, C2m), 3.73 (dd, *J* = 8.3, 3.9 Hz, 1H, C2M), 2.48 (s, 1H, C8), 2.43 (brs, 2H, OH), 2.10 – 2.00 (m, 1H, $C6H_1$), 1.82 – 1.73 (m, 1H, $C3H_1$), 1.72 – 1.61 (m, 3H, $C3H_2$+$C4H_1$+$6H_2$), 1.61 – 1.52 (m, 1H, $C5H_1$), 1.52 – 1.43 (m, 1H, $C5H_2$), 1.39 – 1.17 (m, 1H, $C4H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 86.6 (C7), 75.5 (C2m), 74.2 (C2), 72.7 (C8), 70.1 (C1), 39.6 (m), 35.7 (C6), 29.8 (m), 28.6 (C3), 27.7 (m), 23.5 (m), 22.1 (C4), 21.0 (C5) ppm.

Data in agreement with previous literature.[255]



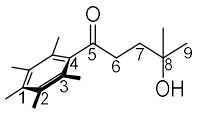
2-methylpropane-1,2-diol (**3-95**)

To a solution of the acid **3-94** (1.3 mL, 11 mmol, 1 eq) in THF (50 mL) was added $LiAlH_4$ (835 mg, 22.0 mmol, 2 eq) portion-wise at 0 °C. After 10 mins, the reaction was heated to reflux. After 5 h, upon consumption by TLC, the reaction was cooled to 0 °C and quenched with H_2O (0.85 mL), aq NaOH (0.85 mL, 1 M) and H_2O (2.1 mL). After stirring for 30 mins, the suspension was filtered, and the filtrate was dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (DCM: MeOH, 95:5) gave the desired diol **3-95** as a clear oil (781 mg, 8.67 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.43 (s, 2H, C1), 1.96 (brm, 2H, OH), 1.22 (s, 6H, C3) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 71.2 (C2), 71.1 (C1), 25.9 (C3) ppm.

Data in agreement with previous literature.[252]



4-hydroxy-4-methyl-1-(pentamethylphenyl)pentan-1-one (**3-96**)

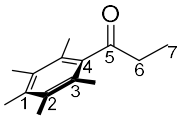
Diol **39-5** (23 mg, 0.25 mmol, 1 eq) was subjected to General Procedure 3C to give the desired product **3-96** as a waxy solid (39 mg, 0.15 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.83 (t, J = 7.5 Hz, 2H, C6), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.11 (s, 6H, C3Me), 1.93 (t, J = 7.5 Hz, 2H, C7), 1.26 (s, 6H, C9) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 212.9 (C5), 140.8 (C4), 135.6 (C1), 133.2 (C2), 127.4 (C3), 70.2 (C8), 40.9 (C6), 36.5 (C7), 29.6 (C9), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ $C_{17}H_{26}O_2Na$ = 285.1820 calculated, 285.1825 Δ = 1.77 ppm.

FTIR (film) ν= 3495, 2981, 2889, 1692, 1382, 1155, 938, 737 cm^{-1}.



1-(pentamethylphenyl)propan-1-one (**3-99**)

propionyl chloride (0.96 mL, 11 mmol) was subjected to General Procedure 2A to give the desired ketone **3-99** as a white solid (1.77 g, 8.66 mmol, 78%).

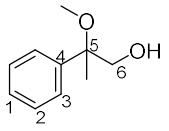
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.69 (q, *J* = 7.2 Hz, 2H, C6), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.09 (s, 6H, C3Me), 1.20 (t, *J* = 7.2 Hz, 3H, C7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 212.9 (C5), 140.9 (C4), 135.5 (C1), 133.2 (C2), 127.5 (C3), 38.9 (C7), 17.4 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 7.7 (C7) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 227.14085, $C_{14}H_{20}ONa$ calculated 227.14064, Δ = 1 ppm.

FTIR (film) = 2362, 2342, 1698 cm^{-1}.

Data in agreement with previous isolation.



2-methoxy-2-phenylpropan-1-ol (**3-100**)

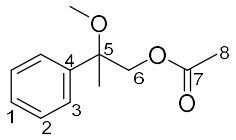
Based on the procedure by Garber and co-workers[141]

To a solution of mCPBA (1.3 g, 7.7 mmol, 1.1 eq) in MeOH (14 mL) at 0 °C was added styrene **3-49** (910 μL, 7.0 mmol, 1 eq) dropwise over 10 min. The solution was then allowed to warm to rt. After 2 h, an additional portion of mCPBA (1.3 g, 7.7 mmol, 1.1 eq) was added. After 5 h, the reaction was quenched using aq. $Na_2S_2O_3$ (10 mL, sat). After 30 mins, upon full quenching of the peroxide determined by starch paper, the reaction was diluted with Et_2O (40 mL) and H_2O (20 mL) and the layers were separated. The organic layer was washed with aq. NaOH (2 M) until residual carboxylic acid was removed, as measured by TLC. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC to give the diol **3-100** (564 mg, 3.39 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.41 – 7.34 (m, 4H, C2+C3), 7.34 – 7.25 (m, 1H, C1), 3.66 (d, *J* = 11.1 Hz, 1H, $C6H_1$), 3.51 (d, *J* = 11.1 Hz, 1H, $C6H_2$), 3.15 (s, 3H, OMe), 1.62 (s, 3H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 142.1 (C4), 128.5 (C2/C3), 127.6 (C1), 126.7 (C2/C3), 79.8 (C5), 71.6 (C6), 50.7 (OMe), 19.5 (C5Me) ppm.

Data in agreement with previous literature.[256]



2-methoxy-2-phenylpropyl acetate **(3-101**)

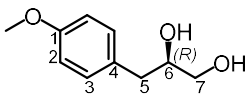
To a solution of ether **3-100** (50 mg, 0.30 mmol) and DMAP (3 crystals) in DCM (10 mL) was added acetic anhydride (57 µL, 0.60 mmol, 2 eq) dropwise. Upon consumption of the ether by TLC, the reaction was quenched with aq. $NaHCO_3$ (15 mL, sat), the layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC to give the diol **3-101** (55 mg, 0.26 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 – 7.33 (m, 4H, C2+C3), 7.32 – 7.25 (m, 1H, C1), 4.19 (d, J = 11.4 Hz, 1H, C6H$_1$), 4.15 (d, J = 11.5 Hz, 1H, C6H$_2$), 3.13 (s, 3H, OMe), 2.05 (s, 3H, C8), 1.61 (s, 3H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 170.9 (C7), 141.5 (C4), 128.5 (C2/C3), 127.8 (C1), 126.6 (C2/C3), 78.1 (C5), 70.9 (C6), 50.8 (OMe) , 21.0 (C8), 20.2 (C5Me). ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 231.0995 $C_{12}H_{16}O_3Na$ calculated 231.0992, Δ = 1.43 ppm.

FTIR (film) ν= 2985, 1743, 1448, 1384, 1243, 1076, 1042, 913, 845, 702 cm^{-1}.



(R)-3-(4-methoxyphenyl)propane-1,2-diol **(3-111**)

Enantioenriched

Under an atmosphere of N_2 a mixture of olefin **3-110** (230 µL, 1.5 mmol, 1 eq), AD-mix-α (1.7 g), K_2CO_3 (620 mg, 4.5 mmol, 3 eq) and $K_2OsO_2(OH)_4$ (6 mg, 0.015 mmol, 0.01 eq) was cooled to 0 °C and dissolved in *t*-BuOH:H_2O (15 mL, 1:1) after 30 min the reaction was warmed to rt. After 18 h, upon consumption of the olefin by TLC, the product was extracted with Et_2O (5 x 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude was purified by FCC (Pentane: EtOAc, 94:6→75:25) to give the diol **3-111** as a viscous oil (198 mg, 1.08 mmol, 73%, 31% e.e.).

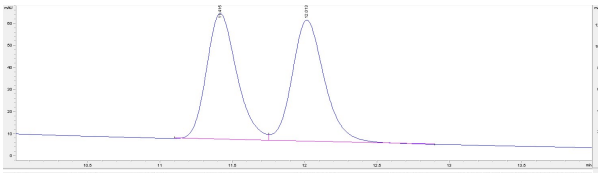
Racemic

Olefin **3-110** (460 µL, 3.0 mmol) was subjected to General Procedure 3B to give the diol **3-111** (507 mg, 2.78 mmol, 93%).

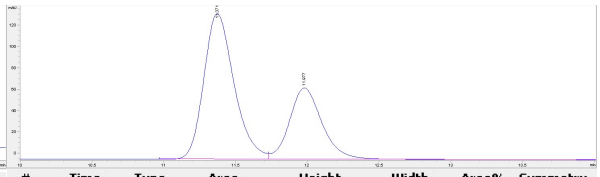
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.14 (d, J = 8.6 Hz, 2H, C3), 6.86 (d, J = 8.6 Hz, 2H, C2), 3.95 – 3.88 (m, 1H, C6), 3.80 (s, 3H, OMe), 3.70 (ddd, J = 11.1, 3.3, 0.7 Hz, 1H, C7H$_1$), 3.52 (ddd, J = 11.1, 6.9, 0.6 Hz, 1H, C7H$_2$), 2.76 (dd, J = 13.8, 5.4 Hz, 1H, C5H$_1$), 2.69 (dd, J = 13.8, 7.9 Hz, 1H, C5H$_2$), 1.76 (brs, 1H OH), 1.72 (brs, 1H, OH) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 158.6 (C1), 130.4 (C3), 129.7 (C4), 114.3 (C2), 73.2 (C6), 66.2 (C7), 55.4 (OMe), 39.0 (C5) ppm.

Chiral HPLC: (Chiralpak IA with Guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 230 nm, 10 µL injection).

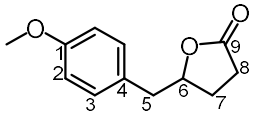


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.415	BV	836.6	57.3	0.2242	49.342	0.776
2	12.013	VBA	858.9	55.2	0.2375	50.658	0.787



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.371	BV	2001	136.7	0.2248	65.383	0.759
2	11.977	VB	1059.4	66.9	0.2386	34.617	0.783

Data in agreement with previous literature.[257]



5-(4-methoxybenzyl)dihydrofuran-2(3H)-one **3-113**

Based on the literature procedure.[25]

Racemic

1,2-diol **3-111-*rac*** (55 mg, 0.30 mmol, 1 eq), RuMacho (3.6 mg, 0.06 mmol, 0.02 eq), K_2CO_3 (4.4 mg, 0.03 mmol, 0.1 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, *t*-amyl alcohol (0.3 mL) and diethyl malonate (90 µL, 0.6 mmol, 2 eq) were added, and the reaction was heated to 115 °C. After 18 h, the reaction was cooled to rt; the mixture was flushed through a silica plug with EtOAc (5 mL) and concentrated under reduced pressure. The product was isolated using FCC (Pentane:Et_2O 95:5) to give the product **3-113** (32 mg, 0.16 mmol, 52%).

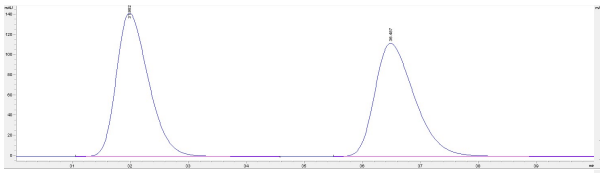
Enantioenriched

1,2-diol **(*R*)-3-111** (55 mg, 0.30 mmol, 1 eq), RuMacho (3.6 mg, 0.06 mmol, 0.02 eq), K_2CO_3 (4.4 mg, 0.03 mmol, 0.1 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, *t*-amyl alcohol (0.3 mL) and diethyl malonate (90 µL, 0.6 mmol, 2 eq) were added, and the reaction was heated to 115 °C. After 18 h, the reaction was cooled to rt; the mixture was flushed through a silica plug with EtOAc (5 mL) and concentrated under reduced pressure. The product was isolated using FCC (Pentane:Et_2O 95:5) to give the product **3-113** (22 mg, 0.11 mmol, 36%, 6% e.e., 19% es).

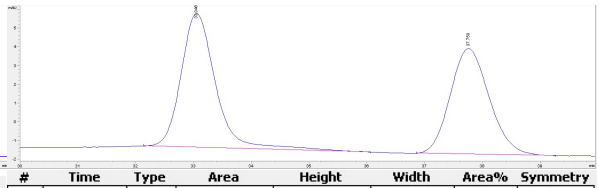
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.14 (d, J = 8.6 Hz, 1H, C3), 6.85 (d, J = 8.7 Hz, 1H, C2), 4.70 (ddt, J = 7.4, 6.8, 6.0 Hz, 1H, C6), 3.79 (s, 3H OMe), 3.00 (dd, J = 14.2, 5.9 Hz, 1H, $C5H_1$), 2.88 (dd, J = 14.1, 6.2 Hz, 1H, $C5H_2$), 2.50 – 2.30 (m, 2H, $C8H_1$+$C8H_2$), 2.28 – 2.19 (m, 1H, $C7H_1$), 2.00 – 1.87 (m, 1H, $C7H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 177.2 (C9), 158.8 (C1), 130.6 (C3), 128.0 (C4), 114.2 (C2), 81.1 (C6), 55.4 (OMe), 40.6 (C5), 28.8 (C8), 27.1 (C7) ppm

Chiral HPLC: (Chiralpak ID with Guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 230 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	31.982	BB	5507.3	142.5	0.597	50.535	0.664
2	36.487	BB	5390.6	112.5	0.737	49.465	0.631

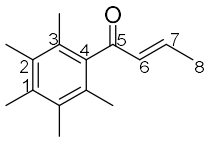


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	33.046	BB	298.8	7.2	0.6083	52.971	0.745
2	37.75	BB	265.3	5.6	0.674	47.029	0.843

Data in agreement with literature procedure.[258]

6.5. SI for Chapter 4.

6.5.1. Reoptimisation of Model Reactions.



(E)-1-(pentamethylphenyl)but-2-en-1-one (**4-54**)

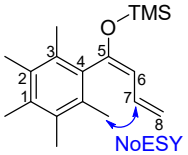
crotonyl chloride (2.57 g, 27.0 mmol, 1 eq), pentamethyl benzene (4.00 g, 27.0 mmol, 1 eq) and $AlCl_3$ (4.67 g, 35.1 mmol, 1.3 eq) were subjected to General Procedure 2C. Purification by FCC (Pentane: Et_2O, 99:1→98:2) gave the desired enone **4-54** as a pale yellow solid (4.30 g, 19.9 mmol, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.48 (dq, *J* = 15.8, 6.7 Hz, 1H, C7), 6.33 (dq, *J* = 15.7, 1.5 Hz, 1H, C6), 2.24 (s, 3H, C1Me), 2.18 (s, 6H, C2Me/C3Me), 2.06 (s, 6H, C2Me/C3Me), 1.89 (dd, *J* = 6.7, 1.5 Hz, 3H, C8) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.1 (C5), 146.9 (C7), 137.2 (C4), 134.4 (C1), 133.8 (C6), 131.9 (C2/C3), 128.0 (C2/C3), 17.6 (C9), 16.5 (C2Me/C3Me), 15.8 (C1Me), 15.1(C2Me/C3Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 217.1594, $C_{15}H_{21}O$ calculated 217.1587, Δ = 3.2 ppm.

FTIR (film) = 2980, 2918, 2361, 2341, 1650, 1433, 1382, 1313, 1273, 1190, 968 cm^{-1}.



(Z)-trimethyl((1-(pentamethylphenyl)buta-1,3-dien-1-yl)oxy)silane (**4-55**)

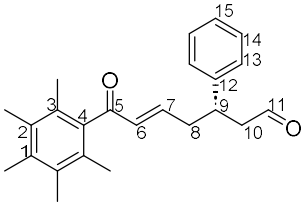
Enone **4-54** (1.30 g, 6.01 mmol) was subjected to General Procedure 4A to give the product as a pale-yellow solid **4-55** (1.14 g, 3.96 mmol, 66%) which was stored at 0 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.85 – 5.68 (m, 2H, C6+C7), 5.05 – 4.88 (m, 1H, $C8H_1$), 4.71 – 4.57 (m, 1H, $C8H_2$), 2.24 (s, 3H, C1Me), 2.20 (s, 6H, C2Me/C3Me), 2.19 (s, 6H, C2Me/C3Me), 0.18 (d, *J* = 0.8 Hz, 9H, TMS) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 154.6 (C5), 135.0 (C1/C4), 134.5 (C1/C4), 134.3 (C6/C7), 132.4 (C2/C3), 131.7 (C2/C3), 111.5 (C6/C7), 111.1 (C8), 17.6 (C2Me/C3Me), 16.9 (C1Me), 16.6 (C2Me/C3Me), 0.7 (TMS) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 311.1802, $C_{18}H_{28}OSiNa$ calculated 311.1802, Δ = 0.1 ppm.

FTIR (film) = 2981, 2889, 2360, 2341, 1635, 1381, 1252, 1169, 868, 843 cm^{-1}.



(E)-7-oxo-7-(pentamethylphenyl)-3-phenylhept-5-enal (**4-56**)

Silyl enol ether **4-55** (692 mg, 2.40 mmol, 2 eq) and cinnamaldehyde (158 mg, 1.20 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-56** as a viscous oil (313 mg, 0.898 mmol, 75%, 99% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent enone.

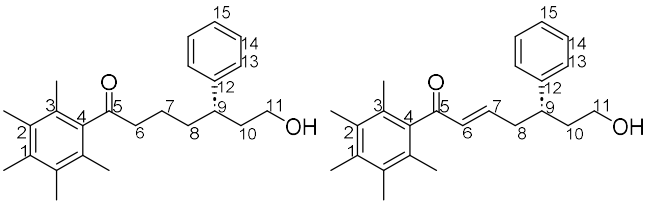
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.60 – 9.55 (m, 1H, C11), 7.22 – 7.16 (m, 2H, C14), 7.15 – 7.09 (m, 1H, C15), 7.05 – 6.99 (m, 2H, C13), 6.18 (ddd, *J* = 15.9, 7.4, 6.3 Hz, 1H, C7), 6.10 (d, *J* = 15.9 Hz, 1H, C6), 3.25 (dq, *J* = 8.8, 6.9 Hz, 1H, C9), 2.71 (ddd, *J*= 17.3, 7.5, 1.7 Hz, 1H, C10), 2.65 (ddd, *J*= 17.2, 7.0, 1.6 Hz, 1H, C10'), 2.53 (dtd, *J* = 14.5, 6.2, 0.9 Hz, 1H, C8), 2.44 (ddd, *J* = 14.6, 8.7, 7.4 Hz, 1H, C8'), 2.15 (s, 3H, C1Me), 2.07 (s, 6H, C2Me/C3Me), 1.83 (brs, 6H, C2Me/C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.8 (C11), 200.8 (C5), 149.0 (C7), 142.3 (C12), 137.7 (C1/C4), 135.4 (C1/C4), 135.1 (C6), 132.9 (C2/C3), 128.9 (C14), 128.8 (C2/C3), 127.4 (C13), 127.2 (C15), 49.9 (C10), 39.3 (C8), 39.1 (C9), 17.4 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 349.2162, $C_{24}H_{29}O_2$ calculated 349.2162, Δ = 0.03 ppm.

FTIR(Film) =2980, 2888, 2360, 2341, 1651, 1461, 1381, 953 cm^{-1}.

$[\alpha]_D^{25}$ =-16.8 (C=1.0, $CHCl_3$)



7-hydroxy-1-(pentamethylphenyl)-5-phenylhept-1-one (**4-65**) and (*E*)-7-hydroxy-1-(pentamethylphenyl)-5-phenylhept-2-en-1-one (**4-65**)

To a solution of aldehyde **4-56** (52 mg, 0.15 mmol, 1 eq) and $CeCl_3{\cdot}7H_2O$ (18 mg, 0.048 mmol, 0.33 eq) in MeOH (1 mL) was added $NaBH_4$ (5.7 mg, 0.15 mmol, 1 eq) at 0 °C. After 20 mins, upon consumption of the starting aldehyde by TLC, the reaction was quenched with aq. NH_4Cl (7 mL, sat). The solution was diluted with Et_2O (10 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. Purification by FCC (Pentane:Et_2O, 85:15) gave the saturated alcohol **4-65** (6 mg, 0.017 mmol, 11%) and unsaturated alcohol **4-66** (12 mg, 0.03 mmol, 23%)

Saturated substrate

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.34 – 7.25 (m, 2H, C14), 7.24 – 7.16 (m, 3H, C13+C15), 3.54 (m, 1H, C11), 3.50 – 3.42 (m, 1H, C11'), 2.80 – 2.69 (m, 1H, C9), 2.68 – 2.52 (m, 2H, C6), 2.22 (s, 3H, C1Me), 2.17 (s, 6H, C2Me), 2.04 (s, 6H, C3Me), 2.01 – 1.79 (m, 2H, C10), 1.77 – 1.65 (m, 2H, C8), 1.65 – 1.53 (m, 2H, C7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 211.9 (C5), 144.7 (C12), 140.8 (C4), 135.5 (C1), 133.2 (C2/C3), 128.7 (C14), 127.8 (C13), 127.4 (C2/C3), 126.5 (C15). 61.3 (C11), 45.6 (C6), 42.6 (C9), 39.7 (C10), 36.4 (C8), 21.3 (C7), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 353.2486, $C_{24}H_{33}O_2$ calculated 353.2475, Δ = 3.08 ppm.

FTIR(Film)= 3350, 2980, 2888, 2360, 1463, 1161, 953 cm^{-1}.

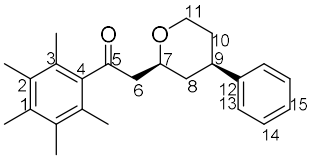
$[\alpha]_D^{25}$ =-4.7 (C=0.5, $CHCl_3$)

Unsaturated substrate

Product slowly cyclised during work up, flash column chromatography and in $CDCl_3$, Low levels of the THP were observed in the product.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.21 – 7.16 (m, 2H, C14), 7.15 – 7.06 (m, 1H, C15), 7.03 – 6.98 (m, 2H, C13), 6.21 (ddd, *J* = 15.9, 7.6, 6.5 Hz, 1H, C7), 6.10 (dt, *J* = 15.8, 1.0 Hz, 1H, C6), 3.50 – 3.43 (m, 1H, C11), 3.42 – 3.32 (m, 1H, C11), 2.86 – 2.76 (m, 1H, C9), 2.56 – 2.39 (m, 2H, C8), 2.14 (s, 1H), 2.07 (s, 3H), 1.93 – 1.67 (m, 8H, C3Me +C10) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.0 (C5), 150.4 (C7), 143.3 (C7), 137.9, 135.3, 134.6 (C6), 132.8, 128.9, 128.7, 128.7, 127.7, 126.9, 126.8, 60.8 (C11), 41.8 (C9), 39.9 (C8), 39.1 (C10), 17.4 (br, C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.



1-(pentamethylphenyl)-2-(4-phenyltetrahydro-2H-pyran-2-yl)ethan-1-one (**4-60**)

Reduction

Aldehyde **4-56** (24 mg, 0.069 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 93:7) gave the product **4-60** as a waxy solid (14 mg, 0.040 mmol, 58%).

Ring closure

To a solution of alcohol **4-64** (12 mg, 0.034 mmol, 1 eq) in DCM (5 mL) was added CSA (3 g, 0.012 mmol, 35 mol%). After 5 mins, the solution was washed with aq. $NaHCO_3$ (2 x 5 mL, sat), dried with $NaSO_4$, and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-60** as a waxy solid (10 mg, 0.028 mmol, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37 – 7.29 (m, 2H, C14), 7.26 – 7.19 (m, 3H, C13+C15), 4.13 (m, 2H, C7+C11), 3.77 (m, 0.1H, m), 3.71 – 3.62 (m, 1H, C11), 3.20 (dd, *J* = 17.7, 6.4 Hz, 0.1H, C6m), 3.04 (dd, *J* = 17.9, 6.8 Hz, 1H, C6), 2.89 (m, 1H, C9), 2.75 (dd, *J* = 17.9, 5.2 Hz, 1H, C6'), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.12 (s, 6H, C3Me), 2.06 – 1.98 (m, 1H, $C8H_1$), 1.85 – 1.74 (m, 2H, $C10H_1$+$C10H_2$), 1.50 (td, *J* = 12.5, 11.1 Hz, 1H, $C8H_2$) ppm.

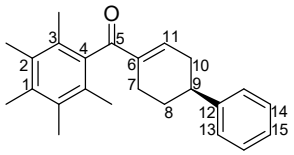
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.5 (C5), 145.7 (C12), 140.4 (C4), 135.7 (C1), 133.3 (C2/C3), 128.7 (C14), 127.7 (C2/C3), 126.9 (C13), 126.5 (C15), 73.3 (C7), 68.4 (C11), 52.3 (C6), 41.8 (C9), 39.6 (C8), 33.3 (C10), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 351.2319, $C_{24}H_{31}O_2$ calculated 351.2319, Δ = 0.11 ppm.

FTIR(Film)= 2981, 2360, 2341, 1458, 1252, 1153, 1083, 954, 736 cm^{-1}.

$[\alpha]_D^{25}$ =19.2 (C=0.5, $CHCl_3$)

Data in agreement with literature.[94]



(pentamethylphenyl)(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)methanone (**4-67**)

THP **4-60** (9 mg, 0.026 mmol, 1 eq) was subjected to General Procedure 4D. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-67** as a waxy solid (8 mg, 0.024 mmol, 92%, >99% e.e.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.35 – 7.29 (m, 2H, C14), 7.25 – 7.19 (m, 3H, C13+C15), 6.59 – 6.55 (m, 1H, C11), 2.90 – 2.80 (m, 1H, $C9H_1$), 2.80 – 2.71 (m, 1H, $C7H_1$), 2.56 – 2.37 (m, 2H, $C7H_2$+$C10H_1$), 2.37 – 2.26 (m, 1H, $C10H_2$), 2.25 (s, 3H, C1Me), 2.20 (s, 6H, C2me), 2.16 – 2.08 (m, 1H, $C8H_2$), 2.06 (s, 3H, C3Me), 2.05 (s, 3H, C3Me), 1.88 – 1.74 (m, 1H, $C8H_2$).ppm.

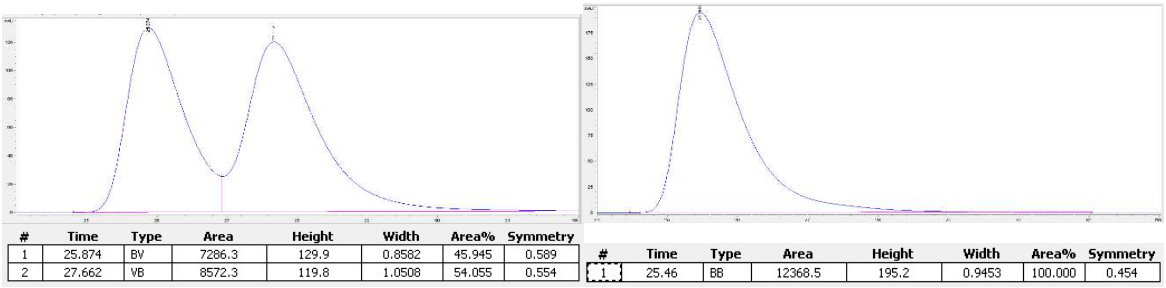
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 146.1, 144.7 (C11), 140.6, 138.2 (C4), 135.2 (C1), 132.8 (C2), 129.3 (C3), 129.2 (C3), 128.7 (C14), 127.0 (C13), 126.5 (C15), 39.6 (C9), 34.4 (C10), 29.5 (C8), 23.2 (C7), 17.7 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 333.2211, $C_{24}H_{29}O$, calculated 333.2213 Δ = 0.59 ppm.

FTIR (film) = 3734, 2361, 2341, 1653, 1559, 668 cm^{-1}.

$[\alpha]_D^{25}$ = -44.4 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak ID with guard, 0.5% IPA, 99.5% hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 µL injection).

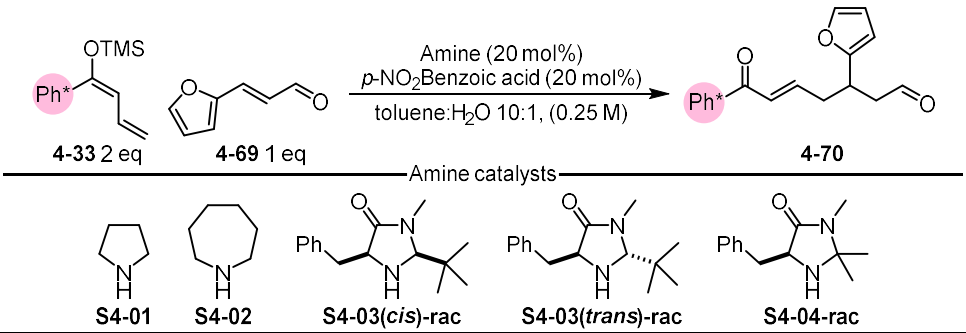


#	Time	Type	Area	Height	Width	Area%	Symmetry
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2	27.662	VB	8572.3	119.8	1.0508	54.055	0.554

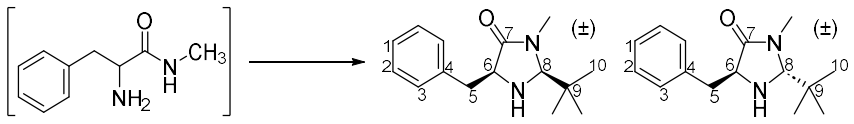
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.46	BB	12368.5	195.2	0.9453	100.000	0.454

6.5.2. Synthesis of Racemic Substrates.

Various catalysts and solvents were screened to access the racemic substrate **4-70**. In all cases, the yield was below 12%.



Modification	Yield (%)	Modification	Yield (%)
S4-01 (20 mol%)	9	**S4-01** (40 mol%)	10
S4-02 (20 mol%)	12	**S4-01** (20 mol%) in EtOH	6
S4-03(*cis*)-rac (20 mol%)	0	**S4-01** (20 mol%) in CH_3CN:H_2O, 10:1	2
S4-03(*trans*)-rac (20 mol%)	6	**S4-01** (20 mol%) in DCM	4
S4-04 (20 mol%)	3	-	-



(*cis*) and (*trans*)-5-benzyl-2-(tert-butyl)-3-methylimidazolidin-4-one (**S4-03**)

Based on the procedure by Gilmour and co-workers[259]

To a solution of (*rac*)-phenylalanine (1.65 g, 10.0 mmol, 1 eq) in MeOH (4 mL) was added $SOCl_2$ (880 µL, 12 mmol, 1.2 eq) over 15 mins at 0 °C and the reaction was heated to reflux. After 18 h, the solution was cooled to rt and concentrated under reduced pressure to give a white solid. The solid was dissolved in $MeNH_2$ (5 mL, 8 N in EtOH). After 23 h, the solution was concentrated under reduced pressure and dissolved in DCM (30 mL) and brine (30 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extract was dried with Na_2SO_4 to give the crude oil **S4-05** (1.43 g, 8.02 mmol, 80%), which was used without further purification.

Diagnostic peaks of the amide are described below.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.88 (ddd, J = 6.7, 4.3, 1.7 Hz, 1H), 3.84 (d, J = 1.8 Hz, 1H), 3.14 (dd, J = 14.1, 4.3 Hz, 1H), 2.96 – 2.88 (m, 4H) ppm.

A solution of the crude amine (496 mg, 2.78 mmol, 1eq), pivaldehyde (550 µL, 5.1 mmol, 1.8 eq) and $Yb(OTf)_3$ (25 mg, 0.040 mmol, 1.5 mol%) in $CHCl_3$ (40 mL) was heated to reflux and allowed to stir overnight. After 18 h, the solution was cooled to rt, quenched with water (25 mL), and the layers were separated. The aqueous layer was extracted with DCM (4 x 10 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude was purified by FCC (Pentane: EtOAc, 70:30) to give the *cis* isomer **S4-03(*cis*)** (119 mg, 0.48 mmol, 17% yield) and *trans* isomer **S4-03(*trans*)** (299 mg, 1.21 mmol, 43% yield)

Cis

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.26 – 7.20 (m, 2H, C2), 7.18 – 7.14 (m, 3H, C1+C3), 3.79 (m, 1H, C6), 3.74 (d, J = 1.8 Hz, 1H, C8), 3.05 (dd, J = 14.1, 4.3 Hz, 1H, $C5H_1$), 2.88 – 2.78 (m, 4H, $C5H_2$+NMe), 0.84 (s, 9H, C10) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 175.4 (C7), 137.6 (C4), 129.6 (C3), 128.7 (C2), 126.8 (C1), 83.5 (C8), 59.6 (C6), 38.7 (C5), 37.9 (C9), 31.5 (NMe), 25.7 (C10) ppm.

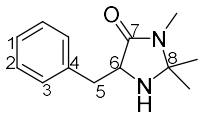
Data in agreement with literature.[259]

Trans

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.26 – 7.10 (m, 5H, Ar), 3.98 (d, J = 1.5 Hz, 1H, C8), 3.69 – 3.60 (m, 1H, C6), 3.08 (dd, J = 13.8, 3.9 Hz, 1H, C5), 2.90 – 2.81 (m, 4H, $C5H_2$+NMe), 0.76 (s, 9H, C10) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 175.3 (C7), 137.9 (C4), 129.6 (C3), 128.6 (C2), 126.6 (C1), 82.5 (C8), 59.4 (C6), 38.3 (C5), 35.1 (C9), 30.7 (NMe), 25.3 (C10) ppm.

Data in agreement with literature.[259]



(±)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (**S4-04**)

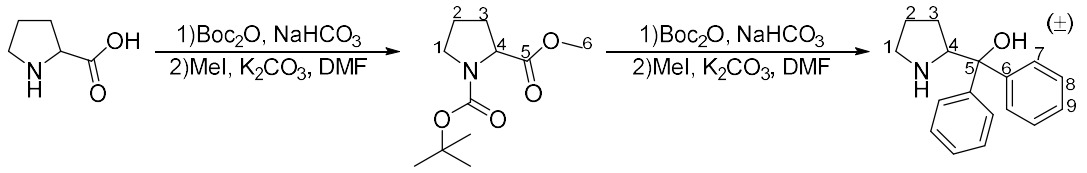
Based on the procedure by Gilmour and co-workers[259]

To a solution of the crude amine **S4-05** (496 mg, 2.78 mmol, 1 eq) in MeOH (6 mL) was added acetone (1.1 mL, 15 mmol, 5 eq) and NEt_3 (330 µL, 2.4 mmol, 0.8 eq) at rt and the reaction was heated to 65 °C. After 18 h, the product was diluted with DCM (30 mL) and water (25 mL), the layers were separated, and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude was purified by FCC (Pentane:EtOAc, 70:30) to give the product **S4-04** (376 mg, 1.72 mmol, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.32 – 7.25 (m, 2H, C2), 7.25 – 7.17 (m, 3H C1+C3), 3.78 (dd, *J* = 6.9, 4.5 Hz, 1H, C6), 3.14 (dd, *J* = 14.2, 4.5 Hz, 1H, C5H$_1$), 3.00 (dd, *J* = 14.2, 6.8 Hz, 1H, C5H$_2$), 2.74 (s, 3H, NMe), 1.25 (s, 3H, C8Me$_1$), 1.15 (s, 3H, C8Me$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 173.5 (C7), 137.3 (C4), 129.6 (C3), 128.7 (C2), 126.9 (C1), 75.7 (C8), 59.4 (C6), 37.4 (C5), 27.4 (C8Me$_1$), 25.4 (C8Me$_2$), 25.3 (NMe) ppm.

Data in agreement with literature.[259]



diphenyl(pyrrolidin-2-yl)methanol (**S4-06**)

Based on the procedures by Schmalz and co-workers[260]

To a rapidly stirring solution of (*rac*)-proline (1.96 g, 17.0 mmol, 1 eq) in aq $NaHCO_3$ (26 mL, sat) was added Boc_2O (4.30 mL, 18.7 mmol, 1.1 eq) in THF (8 mL + 2 x 0.5 mL). After 18 h, the THF was removed under reduced pressure and diluted with aq. HCl (30 mL, 3 M). The aqueous layer was extracted with EtOAc (4 x 20 mL), and the combined organic extract was dried with Na_2SO_4 and concentrated *in vacuo*.

To a solution of the crude amine and K_2CO_3 (2.58 g, 18.7 mmol, 1.1 eq) in DMF (43 mL) was added iodomethane (1.8 mL, 34 mmol, 2 eq) dropwise over 5 min at 0 °C. After 25 min, the solution was filtered through Celite® and the precipitate was washed with Et_2O (350 mL). The solution was washed with brine (10 x 20 mL), and the combined organic extract was dried with Na_2SO_4 and concentrated *in vacuo* to give the crude, which was used without further purification.

Boc-protected ester sits as a 1:1.5 mixture of rotamers. Diagnostic peaks are described below.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.32 (dd, *J* = 8.6, 3.3 Hz, 1H, C4), 4.21 (dd, *J* = 8.5, 4.2 Hz, 1.5H, C4'), 3.71 (s, 4.5H, OMe), 3.60 – 3.30 (m, 4.5H, C1) ppm.

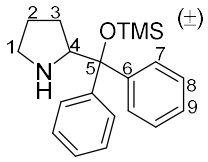
To a solution of PhMgBr (51 mL, 1 M in THF, 51 mmol, 3 eq) was added the crude ester in THF (34 + 3 x 0.5 mL) over 30 mins at rt. After 90 mins, upon consumption of the SM by TLC, the solution was cooled to 0 °C and quenched with aq. NH_4Cl (20 mL, sat). The reaction was warmed to rt and diluted with Et_2O (100 mL) and water (40 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude alcohol product.

The crude alcohol and NaOH (6.8 g, 170 mmol, 10 eq) were dissolved in ethanol (85 mL) and heated to reflux. After 2 h, the crude was cooled to rt and concentrated under reduced pressure. The crude was dissolved in Et_2O (200 mL), and the solution was washed with brine (3 x 30 mL) and concentrated under reduced pressure to give the crude product. Purification by FCC gave the desired pyrrolidine **S4-06** as a viscous oil (2.04 g, 8.05 mmol, 47% over 4 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.54 – 7.48 (m, 2H, C7), 7.46 – 7.40 (m, 2H, C7'), 7.26 – 7.16 (m, 4H, C8), 7.14 – 7.02 (m, 2H, C9), 4.19 (t, J = 7.6 Hz, 1H, C4), 2.96 (ddd, J = 9.3, 6.6, 5.1 Hz, 1H, C1H_1), 2.87 (dt, J = 9.4, 7.4 Hz, 1H, C1H_2), 1.72 – 1.43 (m, 4H, C2+C3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 148.2 (C6), 145.5 (C6), 128.4 (C8), 128.1 (C8), 126.6 (C9), 126.5 (C9), 126.0 (C7), 125.7 (C7), 77.4 (C5), 64.7 (C4), 46.9 (C1), 26.4 (C2/C3), 25.6 (C2/C3) ppm.

Data in agreement with literature.[261]



2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**4-36**)

Based on the procedures by Schmalz and co-workers[260]

To a solution of pyrrolidine **S4-06** (2.04 g, 8.05 mmol, 1 eq) and imidazole (1.63 g, 24.2 mmol, 3 eq) in DCM (20 mL) was added TMSCl (2.5 mL, 20 mmol, 2.5 eq) dropwise at rt. After 12 h, the solution was diluted with MTBE (50 mL) resulting in rapid precipitation. The solution was filtered, and the filtrate was washed with water (3 x 10 mL) and Brine (2 x 10 mL). The combined organic extract was dried with Na_2SO_4 and concentrated *in vacuo* to give the desired pyrrolidine **4-36** (2.46 g, 7.56 mmol, 93%), which was used in subsequent reactions without further purification.

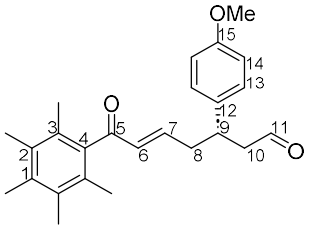
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.66 – 7.62 (m, 2H, C7), 7.57 – 7.52 (m, 2H, C7'), 7.50 – 7.37 (m, 6H), 4.22 (t, J = 7.4 Hz, 1H, C4), 3.09 – 2.90 (m, 2H, C1), 1.84 – 1.70 (m, 3H, C2H_1+C3H_1+C3H_2), 1.62 – 1.50 (m, 1H, C2H_2), 0.09 (s, 9H, TMS) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 146.9 (C6), 145.9 (C6'), 128.5 (C7), 127.8, 127.7, 127.7, 127.0, 126.9, 83.3 (C5), 65.6 (C4), 47.3 (C1), 27.7 (C3), 25.2 (C2), 2.3 (TMS) ppm.

The material contains trace silyl impurities. ^{1}H = 0.35 (s), 0.28 (s), 0.25 (s) ppm. ^{13}C = 0.3, -0.3 ppm.

Data was in agreement with previous literature.[188]

6.5.3. Scope of the Vinylagous Mukaiyama-Michael Reaction.



(E)-3-(4-methoxyphenyl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-57**)

Enantioenriched

Silyl enol ether **4-55** (577 mg, 2.00 mmol, 2 eq) and *p*-MeO-cinnamaldehyde (162 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-57** as a waxy oil (272 mg, 0.719 mmol, 72%, 96% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-55** (433 mg, 1.50 mmol, 2 eq) and *p*-MeO-cinnamaldehyde (162 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B for 24 h. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-57** as a waxy oil (98 mg, 0.26 mmol, 26%).

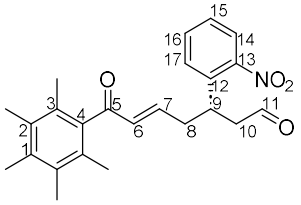
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.91 (t, *J* = 1.7 Hz, 1H, C11), 7.28 (d, *J* = 8.7 Hz, 2H, C13), 7.07 (d, *J* = 8.7 Hz, 2H, C14), 6.53 (ddd, *J* = 15.8, 7.4, 6.4 Hz, 1H, C7), 6.44 (d, *J* = 15.8 Hz, 1H, C6), 4.04 (s, 3H, OMe), 3.60 – 3.49 (m, 1H, C9), 3.01 (ddd, *J* = 17.0, 9.5, 1.8 Hz, 1H, $C10H_1$), 2.95 (dd, *J* = 10.2, 1.7 Hz, 1H, $C10H_2$), 2.84 (dtd, *J* = 14.4, 6.2, 0.9 Hz, 1H, C8), 2.74 (m, 1H, $C8H_2$), 2.49 (s, 3H, C1Me), 2.42 (s, 6H, C2Me), 2.18 (brs, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.7 (C5), 200.9 (C11), 158.5 (C15), 149.0 (C7), 137.7 (C4), 135.3 (C1), 134.9 (C6), 134.2 (C12), 132.7 (C2/C3), 128.7 (C2/C3), 128.3 (C13), 114.2 (C14), 55.3 (OMe), 49.9 (C10), 39.4 (C8), 38.3 (C9), 17.3 (C3Me), 16.7 (C1Me), 15.9 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 379.2261, $C_{25}H_{31}O_3$ calculated 379.2268, Δ = 1.85 ppm.

FTIR (film) = 3000, 1718, 1653, 1514, 1275,1035, 832, 759,651 cm^{-1}

$[\alpha]_D^{25}$ = 21.4 (C=1.0, $CHCl_3$)



(E)-3-(2-nitrophenyl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-59**)

Enantioselective

Silyl enol ether **4-55** (1.1 g, 3.8 mmol, 2 eq) and *o*-NO_2-cinamaldehyde (354 mg, 1.89 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-59** as a waxy oil (684 mg, 1.74 mmol, 91%, 97% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-55** (433 mg, 1.50 mmol, 2 eq) and *o*-NO_2-cinnamaldehyde (177 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B for 24 h. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-59** as a waxy oil (196 mg, 0.498 mmol, 49%).

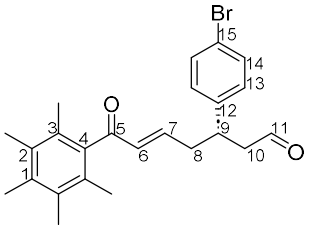
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.70 (t, *J* = 1.4 Hz, 1H, C11), 7.81 (dd, *J* = 8.1, 1.4 Hz, 1H, C14), 7.61 (td, *J* = 7.7, 1.4 Hz, 1H, C16), 7.49 – 7.36 (m, 2H, C15+C17), 6.28 (dd, *J* = 15.9, 6.3 Hz, 1H, C7), 6.22 (d, *J* = 15.6 Hz, 1H, C6), 4.04 – 3.92 (m, 1H, C9), 2.92 (ddd, *J* = 17.6, 7.1, 1.4 Hz, 1H, C10H_1), 2.83 (ddd, *J* = 17.7, 6.9, 1.4 Hz, 1H, C10H_2), 2.79 – 2.63 (m, 2H, C8), 2.28 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 1.99 (s, 3H, C3Me_1), 1.81 (s, 3H, C3Me_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.7 (C5), 199.4 (C11), 150.2 (C13), 147.7 (C7), 137.4 (C4), 136.7 (C1), 135.7 (C6), 135.6 (C2/C3), 133.0 (C16), 132.9 (C2/C3), 128.7 (C12), 128.6 (C15/C17), 128.0 (C15/C17), 124.7 (C14), 49.6 (C10), 38.3 (C8), 33.0 (C9), 17.3 (br, C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 394.2015, $C_{24}H_{28}NO_4$ calculated 394.2013, Δ = 0.53 ppm.

FTIR (film) = 2981, 2360, 2341, 1652, 1525, 911, 732 cm^{-1}

$[\alpha]_D^{25}$ = -1.3 (C=0.5, $CHCl_3$)



(E)-3-(4-bromophenyl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-58**)

Enantioenriched

Silyl enol ether **4-55** (460 mg, 1.60 mmol, 2 eq) and *p*-Br-cinamaldehyde (169 mg, 0.801 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-58** as a waxy oil (188 mg, 0.440 mmol, 55%, 96% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-55** (433 mg, 1.50 mmol, 2 eq) and *p*-Br-cinnamaldehyde (211 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B for 24 h. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-58** as a waxy oil (231 mg, 0.541 mmol, 54%).

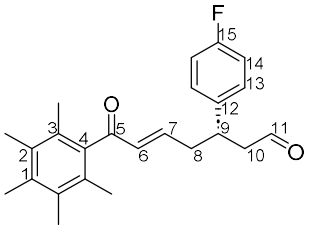
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.55 (t, *J* = 1.4 Hz, 1H, C11), 7.29 (d, *J* = 8.4 Hz, 2H, C14), 6.88 (d, *J* = 8.4 Hz, 2H, C13), 6.18 – 6.02 (m, 2H, C6+C7), 3.21 (dq, *J* = 9.1, 6.9 Hz, 1H, C9), 2.66 (ddd, *J*= 17.4, 7.4, 1.5 Hz, 1H, C10H_1) 2.62 (ddd, *J*= 17.4, 6.9, 1.5 Hz, 1H, C10H_2), 2.50 (dt, *J* = 14.7, 5.9 Hz, 1H, C8H_1), 2.43 – 2.32 (ddd, *J*=14.5, 9.0, 6.4 Hz, 1H, C8H_2), 2.13 (s, 3H, C1Me), 2.06 (s, 6H, C2Me), 1.80 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.6 (C5), 200.1 (C11), 148.3 (C7), 141.4 (C12), 137.7 (C4), 135.5 (C1), 135.2 (C6), 132.9 (C2), 132.0 (C14), 129.2 (C13), 128.8 (C3), 120.9 (C15), 49.8 (C10), 39.0 (C8), 38.5 (C9), 17.4 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI^+ not found.

FTIR (film) = 2981, 2360, 2341, 1722, 1684, 732 cm^{-1}.

$[\alpha]_D^{25}$ = 23.6 (C=0.5, $CHCl_3$)



(E)-3-(4-fluorophenyl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-74**)

Enantioentiched

Silyl enol ether **4-55** (54 mg, 0.19 mmol) and *p*-F-cinamaldehyde (19 mg, 0.13 mmol) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-74** as a waxy oil (26 mg, 0.071 mmol, 55%, 95% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-55** (288 mg, 1.00 mmol, 2 eq) and *p*-F-cinamaldehyde (75 mg, 0.5 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-74** as a waxy oil (93 mg, 0.25 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.65 (t, *J* = 1.5 Hz, 1H, C11), 7.10 – 7.03 (m, 2H, C14), 7.00 – 6.92 (m, 2H, C13), 6.24 (ddd, *J* = 15.9, 7.0, 6.0 Hz, 1H, C7), 6.17 (d, *J* = 15.9 Hz, 1H, C6), 3.34 (dq, *J* = 9.1, 6.9 Hz, 1H), 2.80 – 2.67 (m, 2H, C10), 2.65 – 2.55 (m, 1H, C8), 2.48 (ddd, *J* = 14.5, 8.9, 7.0 Hz, 1H, C8), 2.23 (s, 3H, C1Me), 2.15 (s, 6H, C2Me), 1.90 (s, 6H, C3Me) ppm.

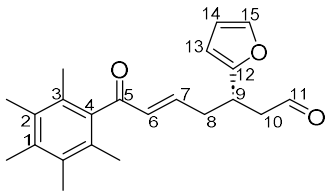
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.6 (C5), 200.4 (C11), 161.8 (d, *J*= 245.6 Hz, C14), 148.5 (C7), 138.1 (d, *J*= 3.3 Hz, C12), 137.7 (C1), 135.5 (C4), 135.2 (C6), 132.9 (C2/3), 129.0 (d, *J* = 21.3 Hz, C14) 128.8 (C2/3), 115.7 (d, *J*= 8.0 Hz, C13) 50.0 (C10), 39.3 (C8), 38.3 (C9), 17.3 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -115.6 ppm.

HRMS: ESI^+ found $[M+H]^+$ =367.2068, $C_{24}H_{28}FO_2$ calculated 367.2068, Δ = 0.0 ppm.

FTIR(Film)= 3645, 2860, 1462, 1383, 1252 cm^{-1}.

$[\alpha]_D^{25}$ = -19.6° (C=0.5, $CHCl_3$)



(E)-3-(furan-2-yl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-70**)

Enantioselective

Silyl enol ether **4-55** (577 mg, 2.00 mmol, 2 eq) and trans-3-(2-Furyl)acrolein (122 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-70** as a waxy oil (227 mg, 0.65 mmol, 65%, 93% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-55** (288 mg, 1.00 mmol, 2 eq) and trans-3-(2-Furyl)acrolein (61 mg, 0.50 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-70** as a waxy oil (100 mg, 0.30 mmol, 60%).

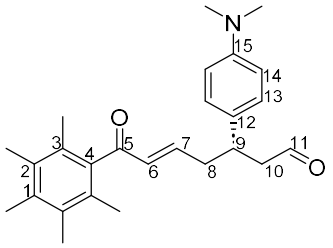
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.70 (t, *J* = 1.5 Hz, 1H, C11), 7.27 (dd, *J* = 1.9, 0.8 Hz, 1H, C15), 6.37 – 6.27 (m, 1H, C7), 6.28 – 6.22 (m, 2H, C6+C14), 5.97 (dt, *J* = 3.2, 0.8 Hz, 1H, C13)), 3.47 (p, *J* = 6.9 Hz, 1H, C9), 2.79 (ddd, *J* = 17.4, 7.5, 1.7 Hz, 1H, C10), 2.66 (ddd, *J* = 17.4, 6.5, 1.5 Hz, 1H, C10), 2.61 – 2.54 (m, 2H, C8), 2.23 (s, 3H, C1Me), 2.17 (s, 6H,C2Me), 1.99 (s, 6H,C3Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.7 (C5), 200.2 (C11), 155.3 (C12), 148.2 (C7), 141.8 (C15), 137.9 (C4), 135.5 (C1), 135.2 (C6), 132.9 (C2), 128.9 (C3), 110.2 (C14), 106.1 (C13), 47.2 (C10), 36.8 (C8), 32.6 (C9), 17.5 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 339.1956, $C_{22}H_{27}O_3$ calculated 339.1955, Δ = 0.37 ppm.

FTIR (film) = 2980, 2360, 1653, 1525, 1382, 1161, 954 cm^{-1}.

$[\alpha]_D^{25}$ = -27.7° (C=0.5, $CHCl_3$)



(E)-3-(4-(dimethylamino)phenyl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-75**)

Enantioenriched

Silyl enol ether **4-55** (577 mg, 2.00 mmol) and *p*-NMe_2-cinamaldehyde (177 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-75** as a waxy oil (205 mg, 0.52 mmol, 52% 96% e.e.). Enantioselectivity was determined by HPLC analysis of the subsequent THP

Racemic

Silyl enol ether **4-55** (288 mg, 1.00 mmol, 2 eq) and *p*-NMe_2-cinamaldehyde (88 mg, 0.50 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-75** as a waxy oil (62 mg, 0.16 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.64 (t, *J* = 1.8 Hz, 1H, C11), 6.95 (d, *J* = 8.7 Hz, 1H, C13), 6.63 (d, *J* = 8.7 Hz, 2H, C14), 6.28 (dt, *J* = 15.8, 7.0 Hz, 1H, C7), 6.19 (d, *J* = 15.8 Hz, 1H, C6), 3.23 (ddd, *J* = 14.6, 8.0, 6.4 Hz, 1H, C9), 2.91 (s, 6H, NMe_2), 2.73 (ddd, *J* = 17.1, 8.0, 2.0 Hz, 1H, C8), 2.66 (ddd, *J* = 16.8, 6.8, 1.8 Hz, 1H, C8), 2.60 – 2.37 (m, 2H, C10), 2.22 (s, 3H, C1Me), 2.16 (s, 6H, C2Me), 1.93 (brs, 6H, C3Me) ppm.

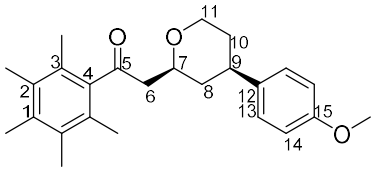
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.9 (C5), 201.5 (C11), 149.7 (C7), 137.8 (C4), 135.4 (C1), 134.9 (C6), 132.8 (C2/C3), 128.9 (C2/C3), 128.1 (C13), 113.0 (C14), 50.0 (C10), 40.8 (NMe_2), 39.7 (C8), 38.4 (C9), 17.4 (C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 392.2595, $C_{26}H_{34}NO_2$ calculated 392.2584, Δ = 2.78 ppm.

FTIR (film) = 2981, 2360, 2341, 1652, 1524, 732 cm^{-1}.

$[\alpha]_D^{25}$ = -3.3 (C=0.5, $CHCl_3$)

6.5.4. Reduction.



(*cis*)-2-(4-(4-methoxyphenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-61**)

Enantioenriched

Aldehyde **4-57** (75 mg, 0.20 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 93:7) gave the product **4-61** as a waxy solid (56 mg, 0.15 mmol, 75%, 96% e.e.).

Racemic

Aldehyde **4-57** (81 mg, 0.21 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-61** as a waxy solid (55 mg, 0.14 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.18 – 7.12 (m, 2H), 6.89 – 6.84 (m, 2H), 4.15 – 4.07 (m, 2H), 3.80 (s, 3H), 3.70 – 3.60 (m, 1H), 3.03 (dd, *J* = 17.9, 6.8 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.75 (dd, *J* = 18.0, 5.3 Hz, 1H), 2.23 (s, 3H), 2.18 (s, 6H), 2.12 (s, 6H), 1.99 (dt, *J* = 13.0, 2.7 Hz, 1H), 1.75 (td, *J* = 9.6, 3.9 Hz, 2H), 1.45 (td, *J* = 12.4, 10.9 Hz, 1H). ppm.

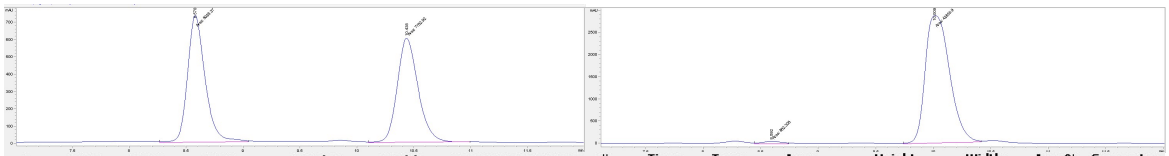
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.5 (C5), 158.2 (C15), 140.4 (C4), 138.0 (C12), 135.7 (C1), 133.3 (C2/C3), 127.8 (C14), 127.7 (C2/C3), 114.1 (C13), 73.2 (C7), 68.4 (C11), 55.4 (C16), 52.3 (C6), 40.9 (C9), 39.9 (C8), 33.5 (C10), 17.2 (C2Me), 16.8 (C3Me), 16.1 (C1Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 381.2419, $C_{25}H_{33}O_3$ calculated 381.2424, Δ = 1.38 ppm.

FTIR (film) = 1382, 1249, 1084, 940cm^{-1}.

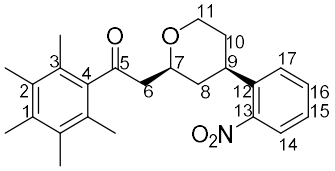
$[\alpha]_D^{25}$ = 17.7 (C=0.25, $CHCl_3$)

Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.578	MM	8026.4	738.5	0.1811	50.770	0.758
2	10.438	MM	7782.9	604.3	0.2147	49.230	0.796

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.592	MM	862.3	68.5	0.2098	1.975	0.91
2	10.009	MM	42805.9	2900.9	0.2459	98.025	0.661



(*cis*)-2-(4-(2-nitrophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-63**)

Enantioenriched

Aldehyde **4-59** (33 mg, 0.084 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-63** as a waxy solid (16 mg, 0.041 mmol, 50%, 97% e.e.).

Racemic

Aldehyde **4-59** (224 mg, 0.569 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 90:10) gave the product **4-63** as a waxy solid (106 mg, 0.268 mmol, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.67 (dd, *J* = 8.1, 1.4 Hz, 1H, C14), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H, C16), 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H, C17), 7.27 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, C15), 4.08 – 3.99 (m, 2H, C7+C11H_1), 3.64 – 3.54 (m, 1H, C11H_2), 3.33 (ddt, *J* = 12.0, 8.7, 3.6 Hz, 1H, C9), 2.95 (dd, *J* = 17.5, 7.4 Hz, 1H, C6H_1), 2.66 (dd, *J* = 17.6, 4.6 Hz, 1H, C6H_2), 2.16 (s, 3H, C1Me), 2.11 (s, 6H, C2Me), 2.05 (s, 6H, C3Me), 2.00 – 1.87 (m, 1H, C8H_1), 1.79 – 1.69 (m, 2H, C10H_1+C10H_2), 1.57 – 1.48 (m, 1H, C8H_2) ppm.

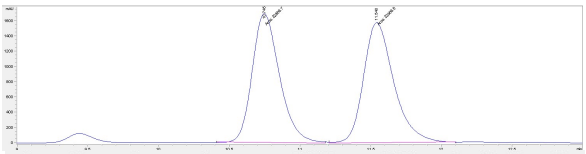
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.0 (C5), 150.0 (C13), 140.3 (C4), 139.2 (C1), 135.7 (C2/C3), 133.3 (C2/C3), 132.8 (C16), 128.3 (C17), 127.7 (C12), 127.2 (C15), 124.3 (C14), 73.1 (C7), 68.1 (C11), 52.0 (C6), 38.6 (C8), 36.5 (C9), 33.0 (C10), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 418.1988 $C_{24}H_{30}NO_4$ calculated 418.1989, Δ = 0.2 ppm.

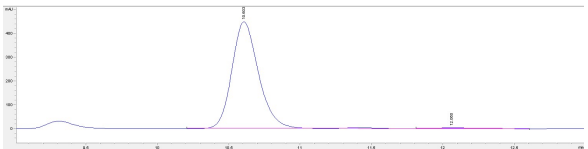
FTIR (film) = 1524, 1419, 1163, 953, 669 cm^{-1}.

$[\alpha]_D^{25}$ = 19.2 (C=0.5, $CHCl_3$)

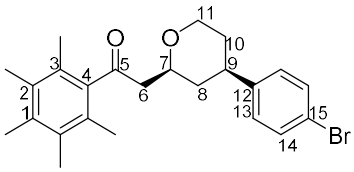
Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.745	MM	22866.7	1695.8	0.2247	49.246	0.76
2	11.54	MM	23566.6	1579.7	0.2486	50.754	0.745



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.603	BV R	5955.7	450.1	0.2	98.657	0.785
2	12.06	VB E	81.1	4.5	0.2642	1.343	0.639



Molecular Weight: 429.40

(*cis*)-2-(4-(4-bromophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-62**)

Enantioenriched

Aldehyde **4-58** (149 mg, 0.349 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 90:10) gave the product **4-62** as a waxy solid (84 mg, 0.196 mmol, 56%, 96% e.e.).

Racemic

Aldehyde **4-58** (153 mg, 0.358 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 90:10) gave the product **4-62** as a waxy solid (150 mg, 0.349 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 (d, J = 8.4 Hz, 2H, C14), 7.10 (d, J = 8.4 Hz, 2H, C13), 4.15 – 4.07 (m, 2H, C7+C11H_1), 3.69 – 3.59 (m, 1H, C11H_2), 3.04 (dd, J = 18.0, 6.7 Hz, 1H, C6H_1), 2.91 – 2.81 (m, 1H, C9), 2.74 (dd, J = 18.0, 5.3 Hz, 1H, C6H_2), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.12 (s, 6H, C3Me), 1.99 (dq, J = 12.7, 2.0 Hz, 1H, C8H_1), 1.80 – 1.70 (m, 2H, C10H_1+C10H_2), 1.51 – 1.40 (m, 1H, C8H_2).ppm.

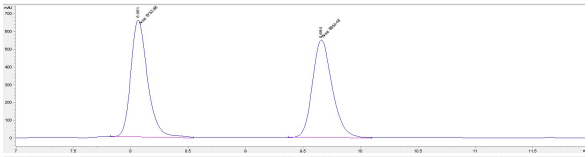
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.4 (C5), 144.7 (C15), 140.3 (C4), 135.7 (C1), 133.3 (C2/C3), 131.8 (C14), 128.7 (C13), 127.6 (C2/C3), 120.2 (C12), 73.1 (C7), 68.2 (C11), 52.1 (C6), 41.3 (C9), 39.4 (C8), 33.1 (C10), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 451.1251, $C_{24}H_{29}BrO_2Na$ calculated 391.2044, Δ = 3.44 ppm.

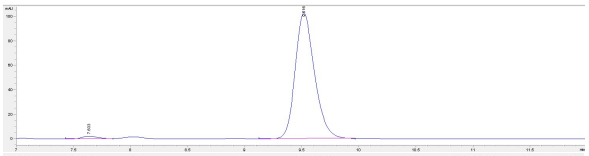
FTIR (film) = 2981, 2889, 2360, 2341, 1383, 1153, 954 cm^{-1}.

$[\alpha]_D^{25}$ = 17.9 (C=0.5, $CHCl_3$)

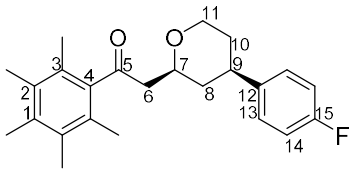
Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.061	MM	6754	661.2	0.1702	50.367	0.74
2	9.654	MM	6655.5	552.3	0.2008	49.633	0.794



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.633	BV	23.2	2.2	0.1547	1.886	0.68
2	9.516	BB	1208.8	102.7	0.1794	98.114	0.76



(*cis*)-2-(4-(4-fluorophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-79**)

Enantioenriched

Aldehyde **4-74** (29 mg, 0.079 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-79** as a waxy solid (23 mg, 0.062 mmol, 79% 95% e.e.).

Racemic

Aldehyde **4-74** (91 mg, 0.25 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-79** as a waxy solid (53 mg, 0.14 mmol, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.21 – 7.15 (m, 2H, C13), 7.04 – 6.97 (m, 2H, C14), 4.16 – 4.08 (m, 2H, C7+C11H_1), 3.70 – 3.61 (m, 1H, C11H_2), 3.04 (dd, J = 18.0, 6.8 Hz, 1H, C6H_1), 2.94 – 2.81 (m, 1H, C9), 2.75 (dd, J = 18.0, 5.3 Hz, 1H, C6H_2), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.12 (s, 6H, C3Me), 2.00 (dt, J = 13.4, 3.0 Hz, 1H, C8H_1), 1.82 – 1.72 (m, 2H, C10H_1+C10H_2), 1.49 – 1.39 (m, 1H, C8H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.3 (C5), 161.4 (d, J = 244.1 Hz, C15), 141.3 (C4), 140.2 (C1), 135.6 (C2/C3), 133.1 (C2/C2), 128.1 (d, J = 7.9 Hz, C13), 127.5 (C12), 115.3 (d, J = 21.0 Hz, C14), 73.0 (C7), 68.2 (C11), 52.0 (C6), 40.9 (C9), 39.6 (C10), 33.3 (C8), 17.1 (C3Me), 16.7 (C1Me), 15.9 (C2Me) ppm.

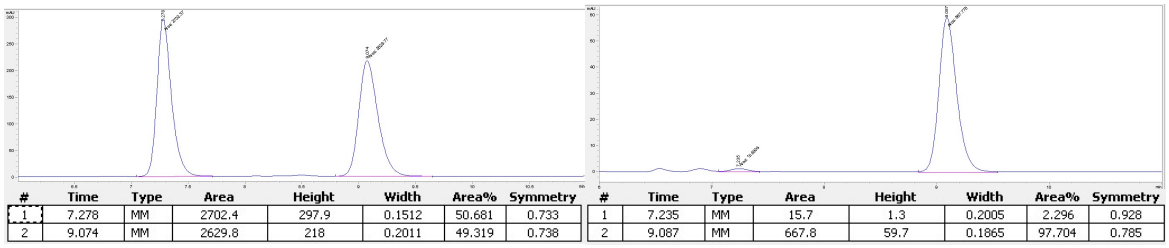
^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -116.9 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 391.2846, C24H29O_2FNa calculated 391.2044, Δ = 3.44 ppm.

FTIR (film) = 1701, 1490, 1083, 1010 cm^{-1}.

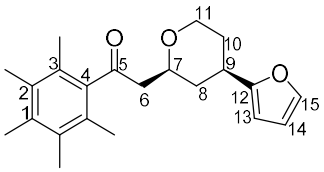
$[\alpha]_D^{25}$ = 9.9 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.278	MM	2702.4	297.9	0.1512	50.681	0.733
2	9.074	MM	2629.8	218	0.2011	49.319	0.738

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.235	MM	15.7	1.3	0.2005	2.296	0.928
2	9.087	MM	667.8	59.7	0.1865	97.704	0.785



(*cis*)-2-(4-(furan-2-yl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-80**)

Enantioenriched

Aldehyde **4-70** (74 mg, 0.21 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-80** as a waxy solid (47 mg, 0.14 mmol, 69%, 11:1 d.r. 93% e.e.).

Racemic

Aldehyde **4-70** (44 mg, 0.13 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-80** as a waxy solid (29 mg, 0.085 mmol, 73%, 10:1 d.r.).

^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.32 (dd, *J* = 1.8, 0.8 Hz, 1H, C15), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H, C14), 5.99 (dt, *J* = 3.2, 0.9 Hz, 1H, C13), 4.14 – 4.04 (m, 2H, C7+C11H_1), 3.62 (ddd, *J* = 12.4, 11.6, 2.3 Hz, 1H, C11H_2), 3.09 – 2.94 (m, 2H, C6H_1+C9), 2.74 (dd, *J* = 17.9, 5.1 Hz, 1H, C6H_2), 2.23 (s, 3H, C1Me), 2.21-2.10 (m, 1H, C8H_1) 2.18 (s, 6H, C2Me), 2.13 (s, 6H, C3Me), 1.90 (ddq, *J* = 13.3, 3.9, 2.0 Hz, 1H, C10H_1), 1.71 (dtd, *J* = 13.3, 12.3, 4.6 Hz, 1H, C10H_2), 1.44 (td, *J* = 12.6, 11.3 Hz, 1H, C8H_2) ppm.

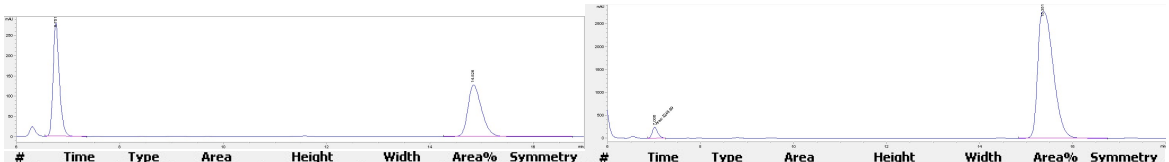
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.4 (C5), 158.9 (C12), 141.1 (C15), 140.4 (4), 135.7 (C1), 133.3 (C2+C3), 127.7 (C2+C3), 110.1 (C14), 103.4 (C13), 72.6 (C7), 67.8 (C11), 52.1 (C6), 36.8 (C8), 35.0 (C9), 30.8 (C10), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 341.2123, C22H29O3 calculated 341.2111, Δ = 3.44 ppm.

FTIR (film) = 3662, 2980, 1692, 1462, 1382, 1267, 1155, 737 cm^{-1}.

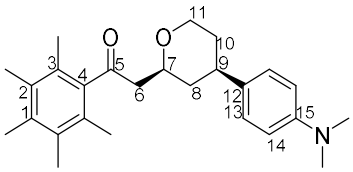
$[\alpha]_D^{25}$ = -4.2 (C=0.3, $CHCl_3$)

Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.751	VB	2368.5	281.1	0.1283	50.065	0.711
2	14.826	BB	2362.4	128.2	0.2829	49.935	0.664

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.006	MM	2246.9	252.7	0.1482	3.379	0.78
2	15.351	BB	64243.6	2781.7	0.3614	96.621	0.519



(*cis*)-2-(4-(4-(dimethylamino)phenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-81**)

Enantioenriched

Aldehyde **4-75** (105 mg, 0.268 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-81** as a waxy solid (58 mg, 0.15 mmol, 55%, 96% e.e.).

Racemic

Aldehyde **4-75** (62 mg, 0.16 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-81** as a waxy solid (31 mg, 0.079 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.12 (d, J = 8.7 Hz, 2H, C13), 6.73 (d, J = 8.2 Hz, 2H, C14), 4.15 – 4.08 (m, 2H, C7+C11H_1), 3.69 – 3.60 (m, 1H, C11H_2), 3.03 (dd, J = 17.9, 6.8 Hz, 1H, C6H_1), 2.93 (s, 6H, NMe_2), 2.84-2.75 (m, 1H, C9), 2.75 (dd, J = 17.9, 5.2 Hz, 1H, C6H_2), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.12 (s, 6H, C3Me), 1.98 (dq, J = 13.3, 2.2 Hz, 1H, C8H_1), 1.80 – 1.71 (m, 1H, C10H_1+C10H_2), 1.51 – 1.40 (m, 1H, C8H_2) ppm.

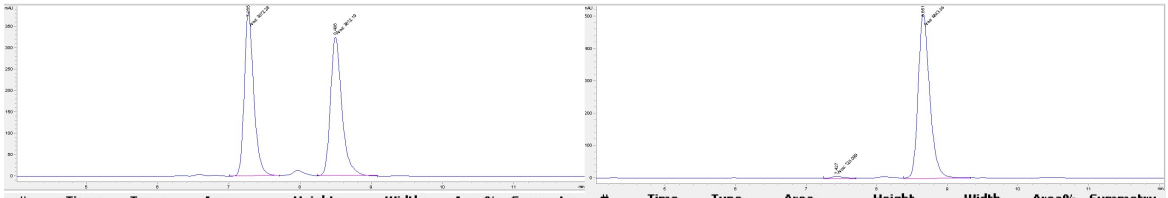
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.6 (C5), 140.5, 135.6, 133.2, 127.7, 127.5 (C13), 113.1 (br, C14), 73.3 (C7), 68.5 (C11), 52.3 (C6), 41.0 (br, NMe_2), 40.7 (C9), 40.0 (C8), 33.5 (C10), 17.2 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 394.2746, $C_{26}H_{36}NO_2$ calculated 394.2741, Δ = 1.37 ppm.

FTIR (film) = 2981, 2889, 2360, 2341, 2699, 1522, 1382, 1082, 732 cm^{-1}.

$[\alpha]_D^{25}$ = 9.8 (C=0.25, $CHCl_3$)

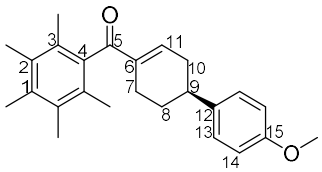
Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.265	MM	3572.3	384.7	0.1548	49.722	0.753
2	8.486	MM	3612.2	324.5	0.1855	50.278	0.733

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.427	MM	125.1	8	0.2612	2.096	0.593
2	8.651	MM	5843.6	509.1	0.1913	97.904	0.734

6.5.5. 1,5-Hydride Shift.



(4'-methoxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-86**)

THP **4-61** (31 mg, 0.086 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-86** as a waxy solid (25 mg, 0.069 mmol, 84%).

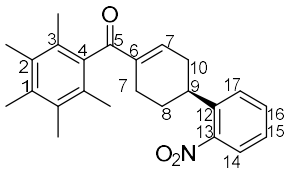
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.14 (d, J = 8.7 Hz, 2H, C13), 6.86 (d, J = 8.7 Hz, 2H, C14), 6.59 – 6.53 (m, 1H, C11), 3.80 (s, 3H, OMe), 2.86 – 2.69 (m, 2H, C7H_1+C9), 2.52 – 2.34 (m, 2H, C7H_2+C10H_1), 2.34 – 2.14 (m, 1H, C10H_2), 2.25 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.13-2.01 (m, 1H, C8H_1), 2.06 (s, 3H, C3Me_1), 2.05 (s, 3H, C3Me_2), 1.76 (dtd, J = 12.9, 11.1, 5.3 Hz, 1H, C8H_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 158.2 (C15), 144.8 (C11), 140.6 (C6), 138.3 (C1/C12), 138.2 (C1/C12), 135.2 (C4), 132.8 (C2), 129.3 (C3), 129.2 (C3), 127.8 (C13), 114.0 (C14), 55.4 (OMe), 38.7 (C9), 34.6 (C10), 29.7 (C8), 23.2 (C7), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 363.2316, $C_{25}H_{31}O_2$ calculated 363.2319, Δ = 0.72 ppm.

FTIR (film) = 3734, 3260, 2341, 1653, 1513, 1248, 1181, 668 cm^{-1}.

$[\alpha]_D^{25}$ = 36.7 (C=0.5, $CHCl_3$)



(2'-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-87**)

THP **4-63** (8.7 mg, 0.023 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-87** as a waxy solid (5.9 mg, 0.16 mmol, 70%).

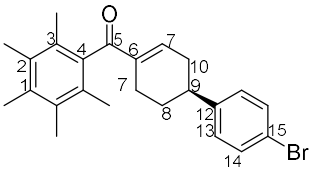
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.68 (dd, *J* = 8.1, 1.4 Hz, 1H, C14), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H, C16), 7.37 (dd, *J* = 8.0, 1.4 Hz, 1H, C17), 7.29 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, C15), 6.56 – 6.40 (m, 1H, C11), 3.25 (dddt, *J* = 13.2, 8.0, 5.3, 2.8 Hz, 1H, C9), 2.80 – 2.68 (m, 1H, $C7H_1$), 2.55 (dtt, *J* = 19.6, 5.2, 1.9 Hz, 1H, $C10H_1$), 2.36 (m, 1H, $C7H_2$), 2.27 – 2.15 (m, 1H, $C10H_2$), 2.17 (s, 3H, C1Me), 2.12 (s, 6H, C2Me), 2.07 – 1.95 (m, 1H, $C8H_1$) 1.98 (d, *J* = 2.4 Hz, 6H, C3Me), 1.80 (dtd, *J* = 12.9, 11.5, 5.2 Hz, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.9 (C5), 143.5 (C11), 140.4, 139.8, 137.9, 135.2, 132.7 (C16), 127.9 (C17), 127.1 (C15), 124.1 (C14), 34.3 (C9), 33.9 (C10), 28.9 (C8), 23.0 (C7), 17.5 (br, C3Me), 16.7 (C1Me), 16.0 (C2Me) ppm. C13 not observed, NMR sample contaminated by acetone.

HRMS: ESI^+ found $[M+H]^+$ = 378.2068, $C_{24}H_{28}NO_3$ calculated 378.2064, Δ = 1.13 ppm.

FTIR(Film)= 2360 1653 1524 912 767 669 cm^{-1}.

$[\alpha]_D^{25}$ = -15.9 (C=0.5, $CHCl_3$)



(4'-bromo-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-88**)

THP **4-62** (43 mg, 0.10 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-88** as a waxy solid (34 mg, 0.083 mmol, 83%).

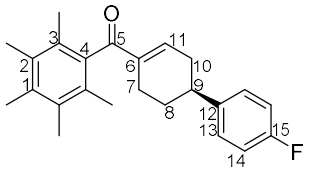
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.35 (d, *J* = 8.5 Hz, 2H, C14), 7.02 (d, *J* = 8.5 Hz, 2H, C13), 6.51 – 6.43 (m, 1H, C11), 2.79 – 2.62 (m, 2H, C9+$C7H_1$), 2.44 – 2.29 (m, 2H, $C7H_2$+$C10H_1$), 2.24 – 2.08 (m, 1Hm $C10H_2$), 2.17 (s, 3H, C1Me), 2.12 (s, 6H, C2Me), 2.06 – 1.92 (m, 1H, $C8H_1$), 1.97 (s, 3H, $C3Me_1$), 1.96 (s, 3H, $C3Me_2$), 1.77 – 1.63 (dtd, *J* = 13.0, 11.0, 5.3 Hz, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.2 (C5), 145.0 (C12), 144.1 (C11), 140.6 (C6), 138.1 (C4), 135.3 (C1), 132.8 (C2), 131.7 (C14), 129.3 (C3), 129.2 (C3), 128.7 (C13), 120.1 (C12), 39.0 (C9), 34.1 (C10), 29.3 (C8), 23.0 (C7), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 44.1328, $C_{24}H_{28}OBr$ calculated 411.1318, Δ = 2.42 ppm.

FTIR (film) = 3745, 2361, 2341, 1653, 1636, 668 cm^{-1}.

$[\alpha]_D^{25}$ = 38.9 (C=0.5, $CHCl_3$)



(4'-Fluro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-89**)

THP **4-79** (9 mg, 0.024 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-89** as a waxy solid (8.0 mg, 95 w/w%, 0.022 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.17 (dd, *J* = 8.6, 5.5 Hz, 2H, C13), 6.99 (t, *J* = 8.7 Hz, 2H, C14), 6.60 – 6.51 (m, 1H, C11), 2.83 (ddd, *J* = 13.0, 8.4, 2.9 Hz, 1H, C9), 2.79 – 2.71 (m, 1H, $C7H_1$), 2.52 – 2.36 (m, 1H, $C7H_2$+$C10H_1$), 2.32 – 2.19 (m, 1H, $C10H_2$), 2.24 (s, 3H, C1Me), 2.19 (s, 3H, C2Me) 2.12 – 2.02 (m, 1H, $C8H_1$) 2.05 (d, *J* = 4.2 Hz, 3H, C3Me), 1.77 (dtd, *J* = 12.9, 11.1, 5.3 Hz, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 144.3 (C11), 141.7, 141.7, 140.6, 138.2, 135.3, 132.8, 129.3 (d, *J* = 12.9 Hz, C12), 128.3 (d, *J* = 7.8 Hz, C13), 115.4 (d, *J* = 21.0 Hz, C14), 38.8 (C9), 34.5 (C10), 29.6 (C8), 23.2 (C7), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm. C15 not observed, Sample contained acetone (29.8 ppm) <5%.

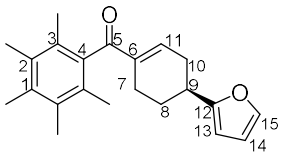
^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -117.0 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 351.2113, $C_{24}H_{28}OF$ calculated 251.2119, Δ = 1.63 ppm.

FTIR(Film)= 1814, 1649, 1636, 1510, 1223, 912, 739 cm^{-1}.

$[\alpha]_D^{25}$ =-2.65 (C=0.2, $CHCl_3$)

Data in agreement with literature.[30]



(4-(furan-2-yl)cyclohex-1-en-1-yl)(pentamethylphenyl)methanone (**4-90**)

THP **4-80** (31 mg, 0.91 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-90** as a waxy solid (16 mg, 0.050 mmol, 55%).

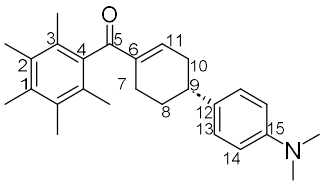
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.32 (dd, *J* = 1.8, 0.8 Hz, 1H, C15), 6.52 (ddt, *J* = 4.6, 3.0, 1.3 Hz, 1H, C11), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H, C14), 6.00 (dt, *J* = 3.2, 0.9 Hz, 1H, C13), 3.03 – 2.92 (m, 1H, C9), 2.73 – 2.62 (m, 1H, $C7H_1$), 2.62 – 2.50 (m, 1H, $C10H_1$), 2.49 – 2.28 (m, 2H, $C7H_2$+$C10H_2$), 2.26-2.18 (1H, m, $C8H_1$), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.04 (s, 3H, $C3Me_1$), 2.01 (s, 3H, $C3Me_2$), 1.77 (dtd, *J* = 13.2, 10.6, 5.5 Hz, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.2 (C5), 158.9 (C12), 143.6 (C11), 141.2 (C15), 140.5 (C6), 138.1 (C4), 135.2 (C1), 132.8 (C2), 129.3 (C3), 129.2 (C3), 110.1 (C13), 103.8 (C14), 32.7 (C9), 31.1 (C10), 27.1 (C8), 22.2 (C7), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 323.2009, $C_{22}H_{27}O_2$ calculated 323.2006, Δ = 1.05 ppm.

FTIR(Film)= 2981, 2889, 1655, 1384, 1252, 1151, 996 cm^{-1}.

$[\alpha]_D^{25}$ = 26.2 (C=0.5, $CHCl_3$)



(4'-(dimethylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-91**)

THP **4-81** (39 mg, 0.10 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-91** as a waxy solid (22 mg, 0.059 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.11 (d, *J* = 8.7 Hz, 2H, C13), 6.73 (d, *J* = 8.2 Hz, 2H, C14), 6.63 – 6.53 (m, 1H, C11), 2.93 (s, 6H, NMe_2), 2.80 – 2.71 (m, 2H, C9+$C7H_1$), 2.51 – 2.33 (m, 2H, $C7H_2$+$C10H_1$), 2.33-2.17 (m, 1H, $C10H_2$), 2.25 (s, 3H, C1Me), 2.20 (s, 3H, C2Me), 2.14-2.01 (m, 1H, $C8H_1$), 2.06 (s, 3H, C3Me), 2.06 (s, 3H, C3Me), 1.76 (dtd, *J* = 12.9, 11.2, 5.2 Hz, 1H, $C8H_2$) ppm.

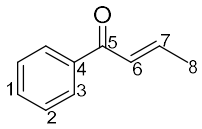
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.4 (C5), 145.1 (C11), 140.6 (C6), 138.3 (C4), 135.1 (C1), 132.8 (C2+C12), 132.7 (C2+C12), 129.3 (C3), 129.2 (C3), 127.5 (C13), 113.2 (br, C14), 41.0 (br, NMe_2), 38.5 (C9), 34.7 (C7), 29.8 (C8), 23.3 (C10), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 398.2444, $C_{26}H_{33}NONa$ calculated 398.2454, Δ = 2.61 ppm.

FTIR (film) = 3744, 23691, 2341, 1651, 1637, 803, 668cm^{-1}.

$[\alpha]_D^{25}$ =-38.9 (C=0.5, $CHCl_3$)

6.5.6. The Role of Ph* in α:γ-Regioselectivity.



(E)-1-phenylbut-2-en-1-one (**4-92**)

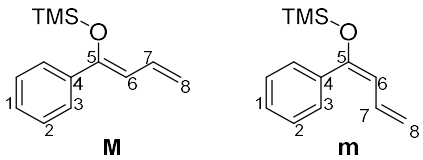
Based on a procedure by Natscheim and co-workers[262]

To a rapidly stirring solution of $AlCl_3$ (1.5 g, 12 mmol, 1.2 eq) in Benzene (6.5 mL) was added (*E*)-but-2-enoyl chloride (960 µL, 10 mmol, 1 eq) dropwise over 20 mins at rt. After 15 mins, the solution was diluted with DCM (25 mL) and poured over ice (ca. 100 g). The layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. Purification by FCC (Pentane: Et_2O, 95:5) gave the desired enone **4-92** as a clear oil (802 mg, 5.49 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.92 (d, *J* = 7.1 Hz, 2H, C3), 7.58 – 7.52 (m, 1H, C1), 7.50 – 7.42 (m, 2H, C2), 7.08 (dq, *J* = 15.3, 6.7 Hz, 1H, C7), 6.91 (dq, *J* = 15.5, 1.6 Hz, 1H, C6), 2.00 (ddd, *J* = 6.8, 1.6, 0.8 Hz, 3H, C8) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 190.9 (C5), 145.2 (C7), 138.1 (C4), 132.7 (C1), 128.6 (C2+C3), 127.7 (C6), 18.7 (C8) ppm.

Data in agreement with literature.[179]



(Z)-trimethyl((1-phenylbuta-1,3-dien-1-yl)oxy)silane (**4-93**)

The enone **4-92** (780 mg, 5.34 mmol, 1 eq) was subjected to General Procedure 4A. Purification by FCC (Pentane) gave the product as a clear oil (532 mg, 2.43 mmol, 46%, 8:1 d.r.).

Major

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 (d, *J* = 6.9 Hz, 2H, C3), 7.18 – 7.04 (m, 3H, C1+C2), 6.57 (ddd, *J* = 17.1, 10.8, 10.3 Hz, 1H, C7), 5.88 (dt, *J* = 10.8, 0.7 Hz, 1H, C6), 5.05 (ddd, *J* = 17.1, 2.0, 0.8 Hz, 1H, $C8H_{cis}$), 4.86 (ddd, *J* = 10.3, 2.0, 0.8 Hz, 1H, $C8H_{trans}$), -0.00 (s, 9H, TMS) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 150.5 (C5), 138.4 (C4), 132.1 (C7), 128.3 (C2), 128.2 (C1), 125.6 (C3), 114.7 (C8), 112.1 (C6), 0.7 (TMS) ppm.

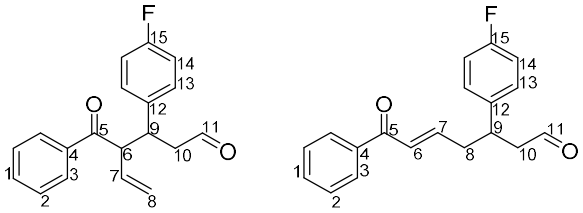
Data in agreement with literature.[179]

Minor

Minor isomer could not be fully characterised, Diagnostic peaks are reported below.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.31 (ddd, *J* = 16.9, 11.1, 10.2 Hz, 1H), 5.67 – 5.48 (m, 1H), 4.68 (ddd, *J* = 10.3, 2.0, 0.8 Hz, 1H) ppm.

Data in agreement with literature.[179]



(E)-3-(4-fluorophenyl)-7-oxo-7-phenylhept-5-enal (**4-95'**) and 4-benzoyl-3-(4-fluorophenyl)hex-5-enal (**4-95**)

Silyl enol ether **4-93** (174 mg, 0.797 mmol, 2 eq) and cinnamaldehyde (60 mg, 0.40 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the α-alkylated product **4-95'** as a pale orange oil (65 mg, 0.21 mmol, 55%, 1.3:1 d.r.) and the γ-alkylated product **4-95** as a pail orange oil (45 mg, 0.15 mmol, 38%).

The major and minor isomers of the α-alkylated products could be further separated by FCC for the purposes of characterisation. Major diastereomer (31 mg), and minor diastereomer (15 mg), respectively.

α-Substituted Minor

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.63 (dd, *J* = 2.4, 1.2 Hz, 1H, C11), 7.74 (dd, *J* = 8.4, 1.3 Hz, 2H, C3), 7.51 – 7.45 (m, 1H, C1), 7.36 (t, *J* = 7.6 Hz, 2H, C2), 7.20 (dd, *J* = 8.7, 5.4 Hz, 2H, C14), 6.87 (t, *J* = 8.7 Hz, 2H, C13), 5.86 (dt, *J* = 17.3, 9.7 Hz, 1H, C7), 5.35-25 (m, 2H, $C8H_{cis}$+$C8H_{trans}$), 4.39 (t, *J* = 9.6 Hz, 1H, C6), 3.92 (td, *J* = 9.9, 4.4 Hz, 1H, C9), 2.98 (ddd, *J* = 17.1, 4.5, 1.3 Hz, 1H, $C10H_1$), 2.75 (ddd, *J* = 17.1, 10.0, 2.4 Hz, 1H, $C10H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 201.0 (C11), 199.5 (C5), 161.7 (d, *J* = 245.3 Hz, C15), 137.4 (d, *J* = 3.3 Hz, C12), 136.9 (C4), 135.3 (C7), 133.3 (C1), 129.7 (d, *J* = 8.0 Hz, C14), 128.6 (C2), 128.2 (C3), 121.1 (C8), 115.6 (d, *J* = 21.3 Hz, C13), 58.2 (C6), 47.5 (C10), 40.9 (C9) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -115.6 ppm.

HRMS: ESI^+ found $[M+H]^+$ = 319.1099, $C_{19}H_{17}FO_2Na$ calculated 319.1105, Δ = 1.83 ppm.

FTIR (film) = 2981, 2360, 2341, 1723, 1676, 1448, 1223, 668 cm^{-1}.

α-Substituted Major

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.60 (dd, *J* = 2.2, 1.3 Hz, 1H, C11), 8.03 – 7.96 (m, 2H, C3), 7.65 – 7.56 (m, 1H, C1), 7.49 (dd, *J* = 8.3, 6.9 Hz, 2H, C2), 7.13 (dd, *J* = 8.7, 5.4 Hz, 2H, C14), 6.98 (t, *J* = 8.7 Hz, 2H, C13), 5.65 (ddd, *J* = 17.2, 10.2, 9.0 Hz, 1H, C7), 5.06 (dd, *J* = 10.2, 1.2 Hz, 1H, $C8H_{Trans}$), 4.98 (dt, *J* = 17.2, 1.0 Hz, 1H, $C8H_{Cis}$), 4.37 (t, *J* = 8.9 Hz, 1H, C6), 3.89 (td, *J* = 8.8, 5.5 Hz, 1H, C9), 2.83 (ddd, *J* = 17.1, 5.5, 1.4 Hz, 1H, $C10H_1$), 2.75 (ddd, *J* = 17.0, 8.8, 2.2 Hz, 1H, $C10H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 200.7 (C11), 199.9 (C5), 161.9 (d, *J* = 245.6 Hz, C15), 136.8 (C4), 136.3 (d, *J* = 3.4 Hz, C12), 134.7 (C7), 133.6 (C1), 130.1 (d, *J* = 7.9 Hz, C14), 128.9 (C2), 128.7 (C3), 120.0 (C8), 115.6 (d, *J* = 21.3 Hz, C13), 56.6 (C6), 48.0 (C10), 41.5 (C9) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -115.4 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 297.1272, $C_{19}H_{18}FO_2$ calculated 297.1285, Δ = 4.50 ppm.

FTIR (film) = 2981, 2360, 2341, 1723, 1676, 1511, 1224, 836, 702, 668 cm^{-1}.

γ-Substituted

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.72 – 9.66 (m, 1H, C11), 7.80 (dt, *J* = 6.9, 1.4 Hz, 2H, C3), 7.60 – 7.49 (m, 2H, C1), 7.44 (t, *J* = 7.5 Hz, 2H, C2), 7.21 – 7.14 (m, 2H, C14), 7.01 (t, *J* = 8.6 Hz, 2H, C13), 6.90 – 6.72 (m, 2H, C6+C7), 3.46 (p, *J* = 7.2 Hz, 1H, C9), 2.81 (dd, *J* = 7.2, 1.6 Hz, 2H, C10), 2.73 – 2.53 (m, 2H, C8) ppm.

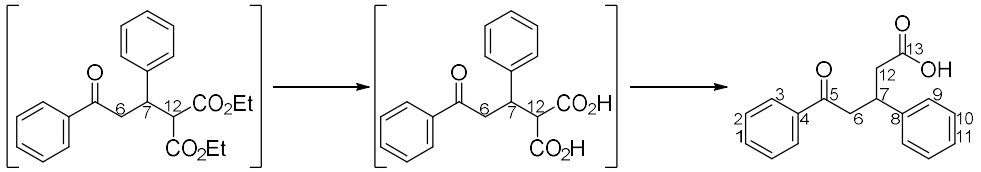
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 200.5 (C11), 190.4 (C5), 161.7 (d, *J* = 245.6 Hz, C15), 145.4 (C7), 138.2 (d, *J* = 3.3 Hz, C12), 137.6 (C4), 132.8 (C1), 128.9 (d, *J* = 8.0 Hz, C14), 128.6 (C2+C3), 128.5 (C2+C3), 128.3 (C6), 115.7 (d, *J* = 21.3 Hz, C13), 49.7 (C10), 39.5 (C8), 38.4 (C9) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -115.6 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 297.1285, $C_{19}H_{18}FO_2$ calculated 297.1285, Δ = 0.13 ppm.

FTIR (film) = 2981, 2360, 2342, 1718, 1510, 1224, 668 cm^{-1}.

6.5.7. 2,4,6-Substituted THP Systems.



5-oxo-3,5-diphenylpentanoic acid (**4-104**)

To a solution of 1,3-diphenylpropenone (3.12 g, 15.0 mmol, 1 eq) and MgO (1.5 g, 38 mmol, 2.5 eq) in toluene (150 mL) was added diethylmalonate (2.3 mL, 15 mmol, 1 eq) dropwise at rt under rapid stirring. After 2 h, upon consumption of the enone by TLC, the suspension was filtered and the solid was washed with DCM (40 mL). The filtrate was concentrated under reduced pressure to give the crude product used without further purification.

Key peaks of the crude diester intermediate:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.81 (d, *J* = 9.7 Hz, 1H, C12), 3.54 (dd, *J* = 16.7, 4.7 Hz, 1H, $C6H_1$), 3.45 (dd, *J* = 16.7, 9.1 Hz, 1H, $C6H_2$) ppm.

Data in agreement with literature.[263]

The crude material and freshly ground NaOH (12 g, 300 mmol, 20 eq) was dissolved in EtOH (150 mL) and water (30 mL). Once the solid was fully dissolved, the solution was heated to reflux. After 8 h, upon consumption of the malonate by TLC, the reaction was allowed to cool to rt and the aqueous solution washed with Et_2O (4 x 40 mL). The solution was acidified with aq. HCl (3 M) to pH=2 to give a white precipitate. The precipitate was dissolved and extracted with EtOAc (5 x 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude, which was used without further purification.

Key peaks of the crude Diacid intermediate:

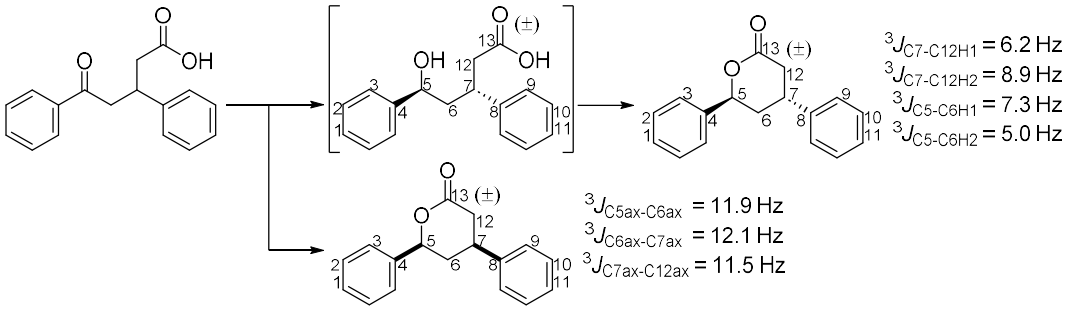
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.21 (td, *J* = 8.3, 5.4 Hz, 1H, C7), 3.94 (dd, *J* = 8.6, 0.7 Hz, 1H, C12), 3.68 – 3.59 (m, 1H, $C6H_1$), 3.54 (dd, *J* = 17.2, 8.3 Hz, 1H, $C6H_2$) ppm.

The crude product and LiCl (1.9 g, 45 mmol, 3 eq) were dissolved in DMSO (25 mL) and water (680 µL, 38 mmol, 2.5 eq) and heated to 140 °C. After 4 h, upon consumption of the SM by TLC, the solution was cooled to rt. The solution was diluted in DCM (100 mL) and washed with aq. HCl (3 x 15 mL, 1.5 M). The organic layer was dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product. The crude product was purified by FCC (5:95 EtOAc:Pent to 30:58:2 EtOAc:Pent:AcOH) to give the acid **4-104** (2.09 g, 7.79 mmol, 52% over 3 steps).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 12.07 (s, 1H, CO_2H), 7.94 – 7.90 (m, 2H, C3), 7.61 (tt, *J* = 7.4, 1.3 Hz, 1H, C1), 7.49 (dd, *J* = 8.3, 7.0 Hz, 2H, C2), 7.32 – 7.28 (m, 2H, C9), 7.24 (dd, *J* = 8.4, 6.8 Hz, 2H, C10), 7.14 (tt, *J* = 7.2, 1.4 Hz, 1H, C11), 3.67 (m, 1H, C7), 3.46 (dd, *J* = 17.2, 7.8 Hz, 1H, $C12H_1$), 3.37 (dd, *J* = 17.1, 6.4 Hz, 1H, $C12H_2$), 2.70 (dd, *J* = 15.8, 6.4 Hz, 1H, $C6H_1$), 2.57 (dd, *J* = 15.8, 8.5 Hz, 1H, $C6H_2$) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ_C: 198.4 (C5), 172.9 (C13), 143.8 (C4), 136.7 (C8), 133.1 (C1), 128.6 (C2), 128.1 (C10), 127.9 (C3), 127.5 (C9), 126.2 (C11), 44.0 (C6), 40.4 (C12), 37.2 (C7) ppm.

Data in agreement with literature.[264]



(4,6 trans)-4,6-diphenyltetrahydro-2H-pyran-2-one and (4,6 cis)-4,6-diphenyltetrahydro-2H-pyran-2-one (**4-106**)

To a solution of acid **4-104** (2.09 g, 7.79 mmol, 1 eq) in aq. NaOH (60 mL, 0.5 M) was added $NaBH_4$ (900 mg, 24.0 mmol, 3 eq) portion-wise at 0 °C. After rapid effervescence stopped, the reaction was then warmed to rt. After 2 h, upon consumption of the SM by TLC, the reaction was cooled to 0 °C and carefully quenched with dropwise addition of aq. HCl (2 M) until the reaction reached pH=2.[a] The reaction was then warmed to rt and allowed to stir for 2 h. The product was extracted with EtOAc (5 x 20 mL), the combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product as a mixture of the lactone **4106(*cis:trans*)** and alcohol **4-105** (15:40:45). Purification by FCC (Pentane: Et_2O, 80:20) resulted in precipitation of white crystals in the column fractions which were filtered and washed with cold pentane to give the desired lactone **4-106(*cis:trans*)** (434 mg, 1.72 mmol, 24% 93:7 d.r.) and a mixture of lactone **4-106(*cis:trans*)** and alcohol **4-105** (22:44:33).

To a solution of the mixed product in DCM (50 mL) was added TFA (110 μL, 1.4 mmol) dropwise at rt. After 20 mins, upon consumption of the alcohol by TLC, the reaction mixture was washed with aq. $NaHCO_3$ (3 x 10 mL, sat). The organic extract was dried with Na_2SO_4, and concentrated *in vacuo.* Purification by FCC (Pentane:Et_2O, 80:20) gave the lactone **4-106(*cis:trans*)** (820 mg, 3.25 mmol, 41% 23:77 d.r.).

The combined yield was **4-106(*cis:trans*)** (1.25 g, 4.97 mmol, 64%, 46:53 d.r).

***Cis* isomer**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.35 – 7.24 (m, 7H, Ar), 7.23 – 7.13 (m, 3H,Ar), 5.39 (dd, *J* = 11.9, 3.0 Hz, 1H, C5), 3.31 (tdd, *J* = 11.9, 6.0, 3.7 Hz, 1H, C7), 2.98 (ddd, *J* = 17.9, 6.0, 2.0 Hz, 1H, $C12H_{eq}$), 2.61 (dd, *J* = 17.8, 11.5 Hz, 1H, $C12H_{ax}$), 2.34 (dddd, *J* = 14.1, 3.7, 3.0, 2.0 Hz, 1H, $C6H_{eq}$), 1.98 (dt, *J* = 14.1, 12.0 Hz, 1H, $C6H_{ax}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 170.6 (C13), 142.7 (C8), 139.6 (C4), 129.2, 128.8, 128.6, 127.5, 126.6, 125.9, 81.9 (C5), 39.1 (C6), 38.1 (C7), 37.8 (C12) ppm.

Data in agreement with previous literature.[181]

Trans isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.33 – 7.07 (m, 10H, Ar), 5.44 (dd, *J* = 7.2, 5.0 Hz, 1H, C5), 3.20 (dq, *J* = 8.5, 6.2 Hz, 1H, C7), 2.83 (ddd, *J* = 17.3, 6.2, 0.7 Hz, 1H, $C12H_1$), 2.73 (dd, *J* = 17.3, 8.9 Hz, 1H, $C12H_2$), 2.30 – 2.24 (m, 2H, C6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 171.3 (C13), 142.8 (C4), 139.7 (C8), 129.1, 128.8, 128.3, 127.3, 126.7, 125.6, 78.8 (C5), 37.4 (C6), 36.5 (C12), 34.3 (C7) ppm.

Data in agreement with previous literature. [181]

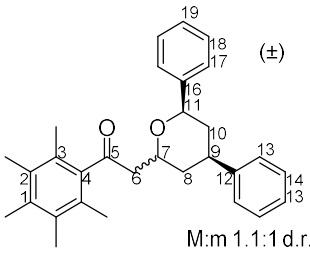
[a] Significant H_2 gas release observed. Rate of gas release was observed to rapidly increase part way through the quenched. Quench should be performed with caution.

Open chain

The open chain was isolated as a single isomer alongside both lactone isomers only peaks that could be observed in the mixture are described below. stereochemistry was assigned based on the lactone ratio upon ring closing

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.51 (t, *J* = 6.9 Hz, 1H, C5), 2.22 (ddd, *J* = 13.8, 8.6, 7.1 Hz, 1H, $C6H_1$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3 (C13), 143.7, 143.4, 128.6, 127.9, 127.5, 126.8, 126.3, 72.5 (C5), 45.0 (C6), 41.0 (C12), 38.5 (C7) ppm.



2,4,6-diphenyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-100**)

Based on the procedure by Donohoe and co-workers[94]

To a stirred solution of lactone **4-106-(cis)** (434 mg, 1.72 mmol, 1 eq, 93:7 d.r) in DCM (3.4 mL, 0.5 M), was added Dibal-H (2.4 mL, 1 M in hexane, 2.4 mmol, 1.4 eq) dropwise at -78 °C. After 2 h, upon completion by TLC, the solution was quenched with aq. Rochelle salt (3.4 mL, 2 mL/mmol, sat) and allowed to stir at rt for 30 mins. The product was diluted with DCM (20 mL), the layers were separated, and the aqueous layer was extracted with DCM (6 x 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Aluminium salts and diols were removed by FCC (Pentane:Et_2O, 50:50) and the product (372 mg) was used without further purification.

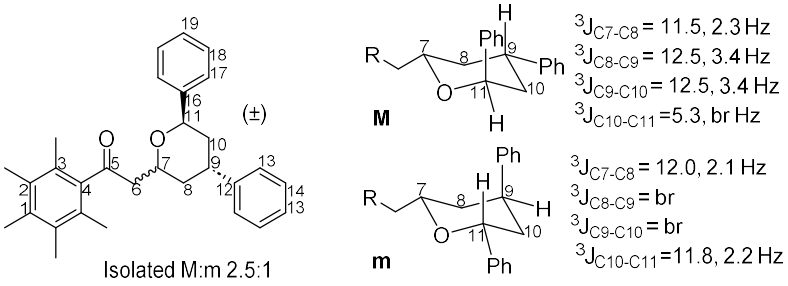
To a solution of diethyl benzoylmethylphosphonate (667 mg, 2.04 mmol, 1.2 eq) in toluene (10 mL) was added NaH (70 mg, 2.9 mmol, 1.7 eq) at rt. After 30 mins, a solution of the crude lactol (372 mg) in toluene (3 x 0.5 mL) was added, and the reaction was heated to reflux. After 18 h, the reaction was cooled to rt, and the reaction was quenched with water (10 mL) and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in *vacuo* to give the crude product. The crude was purified by FCC (Pentane:Et_2O 95:5), to give an inseparable mixture of THP isomers **4-100(*cis,cis*):(*trans,cis*)** (462 mg, 1.08 mmol, 64%, 1.2:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.31 – 7.20 (m, 11H) 7.19 – 7.10 (m, 8H) 4.96 (q, *J* = 6.3 Hz, 0.8H, C7m), 4.56 (ddd, *J* = 13.2, 11.3, 2.1 Hz, 1.8H, C11M+C11m), 4.31 (dddd, *J* = 12.6, 7.1, 5.4, 1.9 Hz, 1H, C7M), 3.31 (dd, *J* = 17.4, 5.9 Hz, 0.8H, $C6mH_1$), 3.17 (dd, *J* = 17.4, 7.6 Hz, 0.8H, $C6mH_2$), 3.12 (dd, *J* = 18.0, 6.7 Hz, 1H, $C6MH_1$), 3.11 – 2.95 (m, 1.8H, C9M+C9m) 2.76 (dd, *J* = 18.0, 5.4 Hz, 1H, $C6MH_2$), 2.16 (s, 2.4H,C1Me), 2.15 (s, 3H, C1Me), 2.10 (s, 4.8H, C2Me), 2.08 (s, 6H, C2Me), 2.05 (s, 4.8H, C3Me), 2.03 (s, 6H, C3Me), 2.20-2.0 (m, 2.8H, $C8H_1M$+$C8H_2m$+C10H1M))2.00 – 1.90 (m, 1.6H, $C8H_2m$+$C10H_1m$), 1.76 – 1.56 (m, 1.8H, $C10MH_2$+$C10mH_2$), 1.53 – 1.41 (m, 1H, $C8H_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.5 (C5), 209.4 (C5), 145.4 (M), 145.2 (m), 142.9 (M), 142.7 (m), 140.5 (M), 135.8 (m), 135.6 (M), 133.4 (m), 133.2 (M), 128.8 (m), 128.7 (M), 128.5 (m), 128.3 (M), 127.7 (m), 127.6 (m), 127.6 (M), 127.3 (M), 127.0 (M), 126.8 (m), 126.7 (m), 126.6 (M), 126.1 (m), 125.8 (M), 79.5 (C11M), 73.5 (C7M), 73.1 (C11m), 69.6 (C7m), 52.2 (C6M), 46.9 (C6m), 42.1 (C9M), 41.3 (C10m), 40.9 (C10M), 39.0 (C8M), 37.0 (C9m), 36.0 (C8m), 17.4 (C2Mem), 17.2 (C2MeM), 16.8 (C1MeM+C1Mem), 16.1 (C3Mem), 16.1 (C3MeM) ppm.

HRMS: ESI^+ found $[M+Na]^+$ = 449.2442, $C_{30}H_{34}O_2Na$ calculated 449.2451, Δ = 2.02 ppm.

FTIR(Film)= 2360, 2341, 1725, 1709, 1450, 1383, 1068 cm^{-1}.



2,4,6-diphenyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-100**)

Based on the procedure by Donohoe and co-workers[94]

To a stirred solution of lactone **4-106-(*trans*)** (434 mg, 1.72 mmol, 1 eq, 23:77 d.r) in DCM (3.4 mL, 0.5 M), was added Dibal-H (2.4 mL, 1 M in hexane, 2.4 mmol, 1.4 eq) dropwise at -78 °C. After 2 h, upon completion by TLC, the solution was quenched with aq. Rochelle salt (3.4 mL, 2 mL/mmol, sat) and allowed to stir at rt for 30 mins. The product was diluted with DCM (20 mL), the layers were separated, and the aqueous layer was extracted with DCM (6 x 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Aluminium salts and diols were removed by FCC (Pentane:Et_2O, 50:50) and the crude product (506 mg) was used without further purification.

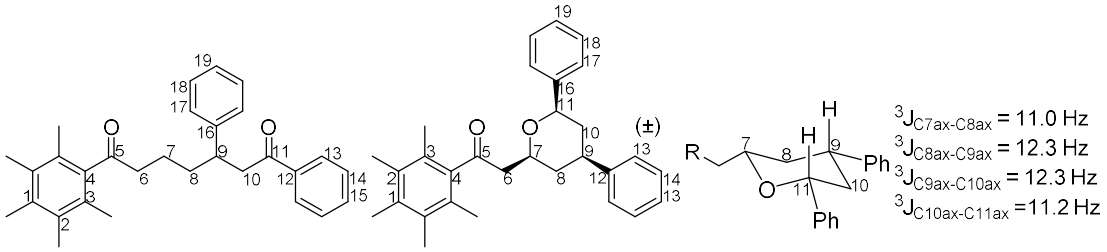
To a solution of the diethyl benzoylmethylphosphonate (730 mg, 2.24 mmol, 1.3 eq) in toluene (10 mL) was added NaH (77 mg, 3.2 mmol, 1.9 eq) at rt. After 30 min, a solution of the crude lactol (506 mg) in toluene (3 x 0.5 mL) was added, and the reaction was heated to reflux. After 18 h, the reaction was cooled to rt, and the reaction was quenched with water (10 mL) and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in *vacuo* to give the crude product. The crude was purified by FCC (Pentane:Et_2O 95:5) to give the product THP **4-100(*cis,cis*):(*cis,trans*):(*cis,trans*):(*trans,trans*)** (561 mg, 1.31 mmol, 76%, 1.7:1:10:4 d.r.). FCC allowed two isomers to be separated to give a mixture of THP 4-**100(*cis,trans*):(*trans,trans*)** (257 mg, 0.603 mmol, 35%, 2.9:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.53 – 7.47 (m, 2H, 2xM), 7.44 (dt, *J* = 8.3, 1.1 Hz, 0.7H, 2xm), 7.40 – 7.30 (m, 2.7H, 2xM+2xm), 7.28 – 7.21 (m, 4.05H, 3xM+3xm), 7.20 – 7.12 (m, 4.05H, 3xM+3xm), 5.20 (brd, *J* = 5.2 Hz, 1H, C11M), 4.54 (dd, *J* = 11.7, 2.2 Hz, 0.35H, C11m), 4.46 (dtd, *J* = 12.0, 6.2, 2.0 Hz, 0.35H, C7m), 4.31 (dddd, *J* = 11.5, 7.0, 4.6, 2.3 Hz, 1H, C7M), 3.36 (br, 0.35H, C9m), 3.09 (dd, *J*= 18.1, 6.1 Hz, 0.35H, $C6H_1m$), 3.05 (dd, *J*= 18.5, 6.6 Hz, 1H, $C6H_1M$), 2.90 (tt, *J* = 12.5, 3.4 Hz, 1H, C9M), 2.74 (dd, *J* = 18.1, 6.1 Hz, 0.35H, $C6H_2m$), 2.62 (dd, *J* = 18.5, 4.6 Hz, 1H, $C6H_2M$), 2.48 (ddt, *J* = 13.8, 3.5, 1.8 Hz, 1H, $C10H_1M$), 2.40 (dq, *J* = 13.5, 2.0 Hz, 0.35H, C10H1m), 2.29 (dq, *J* = 13.9, 2.2 Hz, 0.35H, $C8H_1m$), 2.16 (s, 3H, C1MeM), 2.15 (s, 1.05H,C1Mem), 2.11 (s, 6H, C2MeM), 2.09 (s, 2.1H, C2Mem), 2.07 (brs, 6H, C3MeM), 2.02 (brs, 2.1H, C3Mem) 2.20-1.90 (m, 1.35H, $C8H_2m$+ $C10H_2M$ 1.87 – 1.80 (m, 1.35H. $C8H_1M$+$C10H_2m$), 1.58 – 1.44 (m, 1H, $C8H_2M$). ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.7 (C5m), 209.3 (C5M), 145.8 (M), 143.4 (m), 143.3 (m), 140.6 (M), 140.3 (M), 135.6 (M), 135.6 (m), 133.2 (M), 133.2 (m), 129.2 (M), 128.8 (M), 128.7 (m), 128.4 (m), 128.3 (m), 128.1 (m), 127.6 (m), 127.3 (m), 127.1 (M), 127.0 (M), 126.9 (M), 126.6 (M), 126.1, 125.8, 75.1 (C11m), 73.9 (C11M), 69.4 (C7m), 65.9 (C7M), 52.6 (C6m), 52.2 (C6M), 39.7 (C8M), 38.5 (C8m), 36.4 (C9M), 35.4 (C9m), 34.7 (C10m), 34.0 (C10M), 17.3 (C3Mem), 17.2 (C3MeM), 16.8 (C1MeM+C1Mem), 16.1 (C2MeM+C2Mem) ppm.[a]

HRMS: ESI^+ found $[M+H]^+$ = 427.2636, $C_{30}H_{35}O_2$ calculated 427.2632, Δ = 1.02 ppm.

FTIR(Film)= 2980, 2360, 1709, 1383, 1581, 1153, 1071, 954 cm^{-1}.



7-(pentamethylphenyl)-1,3-diphenylheptane-1,7-dione (**4-107**) 2,4,6-diphenyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-100**)

THP **4-100(*cis,cis*):(*cis,trans*)** (64 mg, 0.15 mmol, 1:1.1 d.r., 1 eq) and Al_2O_3 (76 mg, 0.75 mmol, 5 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, anhydrous toluene (750 µL) was added, and the suspension was heated to 110 °C. After 21 h, the reaction was cooled to rt and diluted with EtOAc (2 mL), the suspension was filtered through a SiO_2 plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5→95:5) to give the diketone **4-107** (34 mg, 0.080 mmol, 53%) and THP **4-100(*cis,cis*):(*cis,trans*)** (22 mg, 0.051 mmol, 34%, >25:1 d.r.).

[a] 1 minor quaternary peak not observed believed to be under the major isomer

Diketone

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.84 – 7.77 (m, 2H, C13), 7.49 – 7.41 (m, 1H, C15), 7.39 – 7.31 (m, 2H, C14), 7.24 – 7.14 (m, 4H, C17+C18), 7.14 – 7.08 (m, 1H, C19), 3.35 – 3.25 (m, 1H, C9), 3.24 – 3.14 (m, 2H, C10), 2.60 (dt, *J* = 18.5, 7.3 Hz, 1H, $C6H_1$), 2.51 (dt, *J* = 18.5, 7.3 Hz, 1H, $C6H_2$), 2.14 (s, 3H, C1Me), 2.08 (s, 6H, C2Me), 1.95 (s, 6H, C3Me), 1.80 – 1.61 (m, 2H, C8), 1.59 – 1.48 (m, 2H, C7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 211.8 (C11), 199.0 (C5), 144.5 (C4), 140.8 (C12), 137.3 (C1), 135.4 (C16), 133.1 (C2/C3), 133.1 (C15), 128.7 (C14+C18), 128.2 (C13), 127.7 (C17), 127.4 (C2/C3), 126.6 (C19), 45.9 (C10), 45.4 (C6), 41.2 (C9), 35.7 (C8), 21.3 (C7), 17.3 (C3), 16.8 (C1), 16.0 (C2) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 427.2631, $C_{30}H_{35}O_2$ calculated 427.2632, Δ = 0.014 ppm.

FTIR(film)= 2981, 2360, 2341, 1691, 1450, 1382, 1205, 1001 cm$^{-1.}$

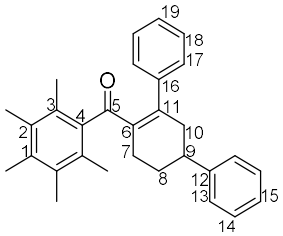
THP (cis:cis)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.38 – 7.28 (m, 5H), 7.27 – 7.18 (m, 5H), 4.63 (dd, *J* = 11.2, 2.0 Hz, 1H, C11), 4.39 (dddd, *J* = 11.0, 7.1, 5.5, 1.9 Hz, 1H, C7), 3.20 (dd, *J* = 17.9, 6.7 Hz, 1H, $C6H_1$), 3.10 (tt, *J* = 12.3, 3.7 Hz, 1H, C9), 2.84 (dd, *J* = 17.9, 5.4 Hz, 1H, $C6H_2$), 2.23 (s, 3H, C3Me), 2.17 (s, 6H, C2Me), 2.11 (s, 6H, C1Me), 2.20-2.00 (m, 2H, $C8H_1$+$C10H_1$) 1.70 (ddd, *J* = 13.5, 12.3, 11.1 Hz, 1H, $C10H_2$), 1.63 – 1.48 (m, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.6 (C5), 145.4, 142.9, 140.5, 135.6, 133.2, 128.7, 128.3, 127.7, 127.3, 127.0, 126.6, 125.8, 79.4 (C11), 73.4 (C7), 52.1 (C6), 42.1 (C9), 40.9 (C10), 39.0 (C8), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 449.2461, $C_{30}H_{34}O_2Na$ calculated 449.2461, Δ = 1.02 ppm.

FTIR(film)= 2360.4, 1693,1068, 988.5 cm$^{-1.}$



(pentamethylphenyl)(1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-yl)methanone (**4-108**)

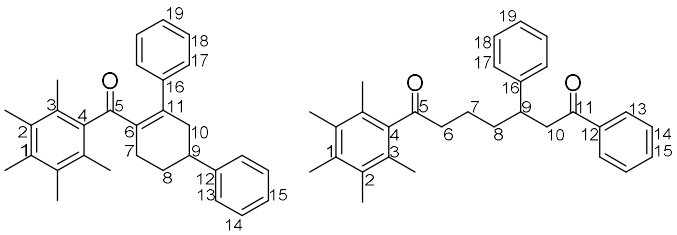
THP **4-100** (128 mg, 0.300 mmol, 1 eq) and Al(O*t*-Bu)$_3$ (221 mg, 0.898 mmol, 3 eq) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, anhydrous xylene (4 mL) was added *via* syringe, and the suspension was heated to 130 °C. After 21 h, The reaction was cooled to rt and diluted with EtOAc (2 mL). The suspension was filtered through a SiO_2 plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4-108** (94 mg, 0.23 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.33 – 7.28 (m, 2H, C14), 7.27 – 7.23 (m, 2H, C13), 7.20 (tt, *J* = 7.0, 1.5 Hz, 1H, C15), 6.92 – 6.86 (m, 3H, C17+C19), 6.76 – 6.70 (m, 1H, C18), 3.02 – 2.90 (m, 2H), 2.63 – 2.41 (m, 1H), 2.23 – 2.14 (m, 1H), 2.01 (s, 3H, C1Me), 1.95 (s, 6H), 1.94 (s, 6H), 1.93 – 1.82 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 151.1 (C11), 145.7, 142.3, 140.7, 136.1, 134.8, 132.2, 128.6 (2x), 126.9, 126.7, 126.5, 126.1, 125.9, 44.2, 40.3 (C9), 29.6, 26.6, 18.2 (C3Me), 16.5 (C1Me), 15.7 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 409.2512, $C_{30}H_{33}O$ calculated 409.2526, Δ = 3.41 ppm.

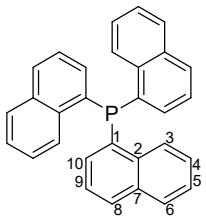
FTIR(film)= 3358, 2680, 2360, 1380, 1161, 1131, 953 cm^{-1}.



(pentamethylphenyl)(1',2',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-yl)methanone (**4-108**) and 7-(pentamethylphenyl)-1,3-diphenylheptane-1,7-dione (**4-107**)

To a solution of aldehyde **4-56** (34 mg, 0.098 mmol, 1 eq) in THF (2 mL) was added PhMgBr (110 µL, 1M in THF, 0.11 mmol, 1 eq) dropwise at 0 °C and warmed to rt. After 2 h, the solvent was removed under a flow of N_2 at rt. To the crude material was added Al(O*t*-Bu)$_3$ (74 mg, 0.30 mmol, 3 eq) and xylene (1 mL) before heating the reaction to 130 °C. After 21 h, the reaction was cooled to rt and diluted with EtOAc (2 mL); the suspension was filtered through a SiO_2 plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the cyclohexene **4-108** (6.4 mg, 0.016 mmol, 16%) and diketone **4-107** (5.4 mg, 0.013 mmol, 13%).

Data in agreement with values reported above.



tri(naphthalen-1-yl)phosphane (**S4-06**)

Based on the procedure by Lakhdar and co-workers[265]

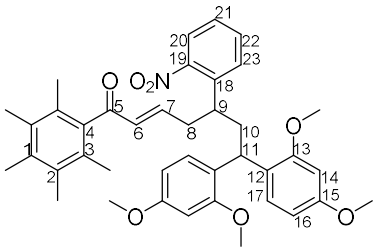
To a solution of 1-bromonapthalene (6.8 g, 33 mmol, 3.3 eq) in THF (90 mL) was added *n*-BuLi (13 mL, 2.5 M in hexane, 33 mmol, 3.3 eq) dropwise over 5 mins at -78 °C. After 1 h, keeping the reaction at -78 °C, PCl_3 (870 µL, 10 mmol, 1 eq) was added dropwise over 10 mins, and the reaction was warmed to 0 °C. After 5 h, the precipitate was filtered and washed with THF (2 x 5 mL, 0 °C). The solid was dissolved in DCM (30 mL) and washed sequentially with aq. NH_4Cl (15 mL, sat) and aq. $NaHCO_3$ (15 mL, sat). The organic layer was dried with $NaSO_4$ concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O, 97:3) to give the phosphine **S4-06** (411 mg, 1.00 mmol, 10%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.54 (dd, *J* = 8.4, 4.5 Hz, 1H, C3), 7.90 (d, *J* = 8.2 Hz, 1H, C6), 7.85 (dt, *J* = 8.4, 1.1 Hz, 1H, C8), 7.51 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, C5), 7.43 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H, C4), 7.29 – 7.21 (m, 1H, C9), 6.96 (ddd, *J* = 7.1, 4.9, 1.2 Hz, 1H, C10) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 135.9 (d, *J* = 23.7 Hz, C1), 133.7 (d, *J* = 4.8 Hz, C10), 133.6 (C7), 133.0 (d, *J* = 10.8 Hz, C2), 129.8 (C8), 128.8 (d, *J* = 2.1 Hz, C6), 126.4 (C3/C4), 126.3 (C3/C4), 126.0 (C5), 125.8 (C9) ppm.

^{31}P-NMR (162.0 MHz, $CDCl_3$) δ_P: -33.1 ppm.

Data in agreement with previous literature.[265]



(E)-7,7-bis(2,4-dimethoxyphenyl)-5-(2-nitrophenyl)-1-(pentamethylphenyl)hept-2-en-1-one (**4-111**)

To a solution of the aldehyde **4-59** (39 mg, 0.99 mmol) and 1,3-dimethoxybenzene **4-110** (41 mg, 0.30 mmol, 3 eq) in DCM (2 mL) was added TFA (15 µL, 0.20 mmol, 2 eq) dropwise, at 0 °C. After 3 h, the reaction was warmed to rt. After 18 h, upon consumption of the starting material by TLC, the reaction was diluted with DCM (10 mL) and H_2O (10 mL), the layers were separated, and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude was purified by FCC (Pentane: Et_2O, 95:5) to give the product **4-111** (26 mg, 0.032 mmol, 32% yield).

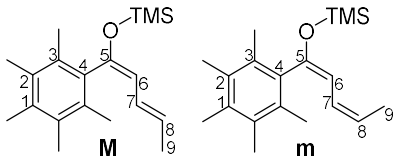
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.66 (dd, *J* = 8.1, 1.3 Hz, 1H, C20), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H, C22), 7.44 (dd, *J* = 8.0, 1.4 Hz, 1H, C23), 7.30 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H, C21), 6.93 (d, *J* = 9.1 Hz, 1H, C17), 6.87 (d, *J* = 8.3 Hz, 1H, C17'), 6.38 – 6.31 (m, 4H, C13+C13'+C16+C16'), 6.27 (dt, *J* = 15.9, 7.3 Hz, 1H, C7), 6.15 (d, *J*= 15.9 Hz, 1H, C6), 4.33 (dd, *J* = 9.0, 6.6 Hz, 1H, C11), 3.77 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.31 – 3.20 (m, 1H, C9), 2.66 – 2.55 (m, 2H, C8), 2.32-2.1 (m, 2H, C10), 2.22 (s, 3H, C1Me), 2.15 (s, 6H, C2Me), 1.98 (brs, 3H, C3Me), 1.76 (brs, 3H, C3Me') ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.2 (C5), 159.2, 159.2, 158.2, 158.0, 150.6 (C19), 150.1 (C7), 138.6 (C4), 137.7 (C1), 135.3 (C2), 135.0 (C6), 132.8 (C3), 132.2 (C21), 129.1 (C23), 128.8 (C17/17'), 128.7 (C18), 128.6 (C17/17'), 126.9 (C22), 125.0 (C12/C12'), 124.0 (C20), 123.7 (C12/C12'), 104.1 (C14/C14'), 103.9 (C14/C14'), 98.9 (C16/C16'), 98.9 (C16/C16'), 55.5 (OMe), 55.4 (OMe), 55.4 (OMe), 55.4 (OMe), 40.0 (C10), 39.6 (C8), 36.8 (C9), 33.6 (C11), 17.3 (br, C3), 16.8 (C1), 16.0 (C2) ppm.

HRMS= ESI$^+$ found $[M+H]^+$ = 652.3269, $C_{40}H_{46}NO_7$ calculated 652.3269, Δ = 0.02 ppm.

FTIR(film) = 2980, 1653, 1612, 1526, 1505, 1209, 1039, 912, 736 cm.$^{-1}$

6.5.8. Silyl Enol Ether Scope.



trimethyl(((1E,3E/Z)-1-(pentamethylphenyl)penta-1,3-dien-1-yl)oxy)silane (**4-114**)

The enone **4-113** (1.38 g, 6.00 mmol, 1 eq) was subjected to General Procedure 4B. to give the crude product (2.2:1 *E*:*Z*) Purification by FCC (Pentane) gave the product as a waxy solid (768 mg, 2.53 mmol 42%, 1:1.7 *E*:*Z*).

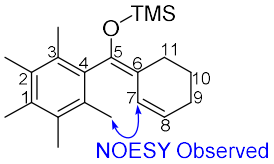
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.98 (dd, *J* = 11.4, 1.1 Hz, 0.5H, C6m), 5.72 – 5.66 (m, 1H, C6M), 5.48 – 5.45 (m, 2H, C7M+C8M), 5.41 (tt, *J* = 11.1, 1.7 Hz, 0.5H, C7m), 5.10 (dqd, *J* = 10.9, 7.0, 1.1 Hz, 0.5H, C8m), 2.25 (s, 3H, C1MeM), 2.24 (s, 1.5H, C1Mem), 2.22 (s, 6H, C2MeM), 2.21 (s, 3H, C2Mem), 2.19 (s, 9H, C3MeM+C3Mem), 1.72 (dd, *J* = 7.0, 1.7 Hz, 1.5H, C9m), 1.62 – 1.60 (m, 1.2H, C9M), 0.18 (s, 9H, TMSM), 0.16 (s, 4.5H, TMSm).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 153.4 (C5m), 151.5 (C5M), 134.9 (C4M+m), 134.5 (C1M+m), 132.4 (C2M+C2m), 131.9 (C3M), 131.8 (C3m), 128.1 (C7M), 126.1 (C7m) , 123.6 (C8M), 120.5 (C8m), 111.0 (C6M), 106.5 (C6m), 18.3 (C9M), 17.7 (C3MeM), 17.7 (C3Mem), 17.0 (C1MeM), 16.9 (C1Mem), 16.7 (C2MeM), 16.6 (C2Mem), 13.4 (C9m), 0.7 (TMSM), 0.7 (TMSm) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 303.2146, $C_{19}H_{31}OSi$ calculated 303.2139, Δ = 2.40 ppm.

FTIR(film) = 298, 2889, 2360, 2341, 1382, 1252, 1165, 965 cm^{-1}.

Product of Mukaiyama-Michael reaction reported in next section.



(E)-(cyclohex-2-en-1-ylidene(pentamethylphenyl)methoxy)trimethylsilane (**4-122**)

The enone **4-121** (1.03 g, 4.02 mmol, 1 eq) was subjected to General Procedure 4A. Purification by FCC (Pentane) gave the product as a waxy pale yellow solid (867 mg, 2.63 mmol, 66%).

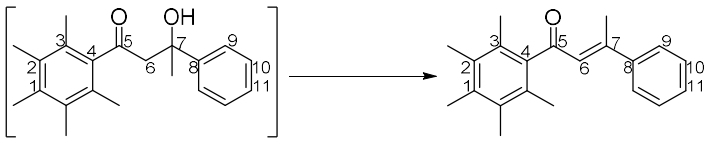
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.59 (dt, *J* = 10.0, 1.9 Hz, 1H, C7), 5.44 (dt, *J* = 10.0, 4.1 Hz, 1H, C8), 2.54 (dd, *J* = 6.9, 5.8 Hz, 2H, C711), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.16 (s, 6H, C3Me), 2.11 (tdd, *J* = 6.1, 4.1, 1.9 Hz, 2H, C9), 1.74 (p, *J* = 6.2 Hz, 2H, C10), -0.11 (s, 9H, TMS) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 145.0 (C5), 134.5 (C1/C4), 134.5 (C1/C4), 132.6 (C2/C3), 132.2 (C2/C3), 126.6 (C7), 124.6 (C8), 117.0 (C6), 25.8 (C9), 23.6 (C11), 22.7 (C10), 18.3 (C3Me), 16.9 (C1Me), 16.6 (C2Me), 0.9 (TMS) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 329.2306, $C_{21}H_{33}OSi$ calculated, 329.2295 Δ = 3.27 ppm

FTIR(Film)= 2981, 2889, 1639, 1382, 1280, 1179, 1071, 872 cm^{-1}.

Cyclohexene **4121** was synthesised by Roland Armstrong.



(E)-1-(pentamethylphenyl)-3-phenylbut-2-en-1-one (**4-118**)

Based on the literature procedure by Donohoe and co-workers[73]

To a stirred solution of Ph* methyl ketone (**4-116**) (1.33 g, 7.00 mmol, 1 eq) in Et_2O (21 mL) was added EtMgBr (2.8 mL, 3M in Et_2O, 8.4 mmol, 1.2 eq) was added dropwise over 90 mins at rt, and the solution was heated to 90 °C. The solution was cooled to rt, a solution of acetophenone (940 µL, 8.1 mmol, 1.15 eq) in THF (7 + 2 x 0.5 mL) was added dropwise and then the reaction was heated to reflux. After 24 h, the solution cooled to rt and poured over ice (ca. 100 g), the aqueous layer was separated, and the organic extract was dried with Na_2SO_4. The solution was concentrated under reduced pressure to give the crude aldol product, which was used without further purification.[a]

The diagnostic peaks of the ^{1}NMR are described below.

[a] The crude was initially dissolved in Et_2O (10 mL) and conc. HCl (7 mL) and heated to reflux overnight. No conversion or decomposition was observed after 24 h. The reaction was cooled to rt and the reaction was quenched with water (10 mL) the aqueous layer was separated. The organic extract was dried with Na_2SO_4. The crude was concentrated under reduced pressure and subjected to the alternate conditions above.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 – 7.39 (m, 2H, C9), 7.27 (dd, *J* = 8.5, 7.0 Hz, 2H, C10), 7.19 – 7.13 (m, 1H, C11), 3.28 (d, *J* = 18.9 Hz, 1H, C6H$_1$), 3.11 (d, *J* = 18.9 Hz, 1H, C6H$_2$), 2.14 (s, 3H, C1Me), 2.08 (s, 6H, C2me), 1.90 (brs, 6H, C3 Me), 1.56 (s, 3H, C7Me) ppm.

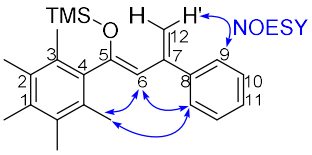
Data in agreement with literature.[73]

To a solution of the crude aldol product in toluene (7 mL) was added Ac_2O (1.3 mL, 14.0 mmol, 2 eq) and NEt_3 (1.10 mL, 7.9 mmol 1.1 eq) sequentially at rt and the mixture was heated to 60 °C. After 8 h, upon consumption of the alcohol by TLC, the reaction was cooled to rt, diluted with Et_2O (40 mL) and quenched with aq. $NaHCO_3$ (40 mL, sat). The organic layer was extracted and washed sequentially with aq. $NaHCO_3$ (2 x 10 mL, sat) and aq. HCl (2 x 10 mL, sat) was dried with Na_2SO_4. The solution was concentrated under reduced pressure and purified by FCC (Pentane:Et_2O 98:2) to give the desired enone **4-118** (1.67 g, 5.71 mmol, 82%, single isomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.47 – 7.40 (m, 2H, C10), 7.32 – 7.26 (m, 3H, C9+C11), 6.63 (q, *J* = 1.2 Hz, 1H, C6), 2.53 (d, *J* = 1.3 Hz, 3H, C7Me), 2.18 (s, 3H, C1Me), 2.13 (s, 6H, C2Me), 2.10 (s, 6H, C3Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 201.7 (C5), 154.3 (C7), 142.5 (C4/C8), 141.8 (C4/C8), 135.4 (C1), 133.2 (C2/C3), 129.4 (C11), 128.7 (C9), 128.2 (C2/C3), 126.7 (C6+C9), 18.4 (C7Me), 17.3 (C3Me), 16.9 (C1Me), 16.1 (C2Me) ppm.

Data in agreement with literature.[73]



(Z)-trimethyl((1-(pentamethylphenyl)-3-phenylbuta-1,3-dien-1-yl)oxy)silane (**4-119**)

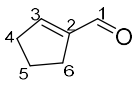
The enone **4-118** (877 mg, 3.00 mmol, 1eq) was subjected to General Procedure 4A. Purification by FCC (Pentane), gave the product **4-119** as a clear oil (642 mg, 1.76 mmol, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48 – 7.43 (m, 2H, C9), 7.36 – 7.28 (m, 2H, C10), 7.27 – 7.21 (m, 1H, C11), 5.73 (ddt, *J* = 3.0, 2.2, 0.9 Hz, 1H, C12H), 5.39 (dt, *J* = 3.6, 1.6 Hz, 1H C12H'), 5.26 – 5.22 (m, 1H, C6), 2.34 (d, *J* = 3.1 Hz, 6H, C2Me/C3Me), 2.26 (d, *J* = 2.6 Hz, 3H, C1Me), 2.22 (d, *J* = 2.6 Hz, 6H, C2Me/C3Me), -0.16 (s, 9H, TMS) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 151.9 (C5), 143.9 (C8), 143.7 (C7), 137.1 (C4), 135.0 (C1), 132.6 (C2), 132.0 (C3), 128.0 (C9), 127.0 (C10), 126.9 (C11), 113.8 (C7), 110.6 (C6), 18.7 (C2Me/C3Me), 16.9 (C1Me), 16.6 (C2Me/C3Me), 0.7 (TMS) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 365.2277, C24H33OSi calculated 365.2295, Δ = 5.00 ppm.

FTIR (film) = 2981, 2889, 2361, 2341, 2382, 1251, 1158, 842 cm^{-1}.



cyclopent-1-ene-1-carbaldehyde
Molecular Weight: 96.13

cyclopent-1-ene-1-carbaldehyde (**4-124**)

Based on previous literature procedure.[188]

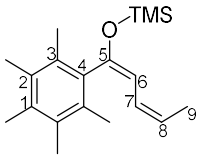
To a rapidly stirring, biphasic mixture of 1,2 cyclohexane diol **4-123** (1.16 g, 10.0 mmol, 1 eq, mixed isomers) in Et_2O:water (5:3, 40 mL) was added $NaIO_4$ (2.8 g, 13 mmol, 1.3 eq) at rt. After 30 mins, aq. KOH (4 mL, 20 w/w%) was added. After 2 h, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. Purification by FCC (Pentane: Et_2O, 80:20) gave the desired enal **4-124** as a clear liquid in pentane (327 mg, 92 w/w%, 3.13 mmol, 31%).[a] Due to the volatility of the product, the solution was used without further concentration.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.79 (s, 1H, C1), 6.86 (ttd, J = 2.5, 1.8, 0.6 Hz, 1H, C3), 2.64 – 2.57 (m, 2H, C4), 2.57 – 2.47 (m, 2H, C6), 1.99 (dt, J = 15.6, 7.5 Hz, 2H, C5) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 189.9 (C1), 153.1 (C3), 148.1 (C2), 33.8 (C4), 28.5 (C6), 23.1 (C5) ppm.

Data in agreement with literature.[189]

6.5.9. Synthesis of the Model Enantioenriched 2,3,4-substituted THP Rings.



$^3J_{C6\text{-}C7}$ = *11.4* Hz
$^3J_{C6\text{-}C8}$ = *10.9* Hz
$^3J_{C7\text{-}C8}$ = *1.1* Hz

trimethyl(((1E,3Z)-1-(pentamethylphenyl)penta-1,3-dien-1-yl)oxy)silane (**4-114**)

To a solution of enone **4-113** (2.30 g, 10.0 mmol, 1eq) in THF (250 mL) was added NaHMDS (6.0 mL, 12 mmol, 1.2 eq) dropwise over 30 min using a syringe pump at -78 °C. After 15 mins, a solution of TMSCl (1.65 mL, 13.0 mmol, 1.3 eq) in THF (4.5 mL) was added dropwise over 45 mins using a syringe pump, maintaining the temperature. After 1 h, the reaction was quenched with aq. NH_4Cl (10 mL, sat) and warmed to rt. The mixture was diluted with Et_2O (150 mL) and brine (100 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were partially concentrated by reduced pressure until water became immiscible, the mixture was diluted with Et_2O (50 mL) and the aqueous layer was separated. The organic extract was dried with Na_2SO_4. The crude was concentrated under reduced pressure to give the crude product (3.8:1, *Z*:*E*). The sample was purified by recrystallisation in hot MeOH to give the product **4-114** as a pale yellow crystal (950 mg, 3.14 mmol, 31%, 17:1 *Z*:*E*).

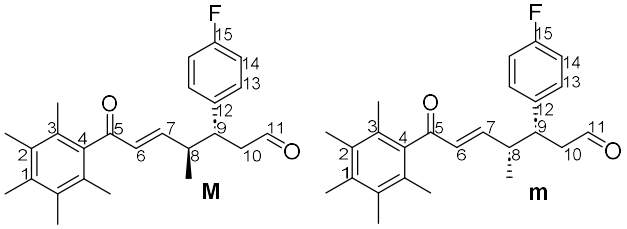
[a] Boiling point previously reported at 10 Torr at 40 °C. yield adjusted for w/w% pentane.[306]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.98 (dd, *J* = 11.4, 1.1 Hz, 1H, C6), 5.41 (tt, *J* = 11.1, 1.7 Hz, 1H, C8), 5.10 (dqd, *J* = 10.9, 7.0, 1.1 Hz, 1H, C8), 2.24 (s, 3H, C1Me), 2.21 (s, 6H, C2Me), 2.19 (s, 6H, C3Me), 1.72 (dd, *J* = 7.0, 1.7 Hz, 3H, C9M), 0.16 (s, 9H, TMSM) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 153.4 (C5), 134.9 (C4), 132.4 (C2), 131.8 (C3), 126.1 (C7), 120.5 (C8), 106.5 (C6), 17.7 (C3Me), 16.9 (C1Me), 16.6 (C2Me), 13.4 (C9), 0.7 (TMS) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 303.2146, $C_{19}H_{31}OSi$ calculated 303.2139, Δ = 2.40 ppm.

FTIR (film) = 298, 2889, 2360, 2341, 1382, 1252, 1165, 965 cm^{-1}.



Major-(4,5 anti)-3-(4-fluorophenyl)-4-methyl-7-oxo-7-(pentamethylphenyl)hept-5-enal (**4-127**)

Enantioenriched

Silyl enol ether **4-114** (302 mg, 1.00 mmol, 17:1 *E*:*Z*, 2 eq) and p-F-cinnamaldehyde (75 mg, 0.50 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-127** as a The major and minor isomers could be isolated as single diastereomers in (160 mg, 0.420 mmol, 84%, 99% e.e.), (13 mg, 0.034 mmol, 7%, 92% e.e.), respectively.

Racemic

Silyl enol ether **4-114** (453 mg, 1.50 mmol, 2:1 *E:*Z, 2 eq) and cinnamaldehyde (113 mg, 0.753 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-127** as a waxy oil (197 mg, 0.518 mmol, 69%, 4:1 d.r.). The major and minor isomers could be isolated as single diastereomers in (129 mg, 0.339 mmol, 45%), (44 mg, 0.12 mmol, 16%), respectively.

Major

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.60 (t, *J* = 1.7 Hz, 1H, C11), 6.98 (ddt, *J* = 8.2, 5.2, 2.5 Hz, 2H, C14), 6.94 – 6.87 (m, 2H, C13), 6.22 – 6.15 (m, 1H, C7), 6.12 (d, *J* = 15.7 Hz, 1H, C6), 3.16 (ddd, *J* = 8.8, 7.4, 5.8 Hz, 1H, C9), 2.83 – 2.69 (m, 2H, C10), 2.63 (h, *J* = 6.9 Hz, 1H, C8), 2.23 (s, 3H, C1Me), 2.16 (s, 6H, C2Me), 1.90 (vbrs, 6H, C3Me), 1.05 (d, *J* = 6.8 Hz, 3H, C8Me).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.6 (C5), 200.5 (C11), 161.7 (d, *J* = 245.8 Hz, C15), 153.5 (C7), 137.7 (C4), 136.7 (d, *J* = 3.4 Hz, C12), 135.4 (C1), 133.0 (C6), 132.7 (C2/C3), 129.6 (d, *J* = 7.9 Hz, C13), 128.5 (C2/C3), 115.4 (d, *J* = 21.3 Hz, C14), 47.3 (C10), 44.0 (C9), 42.0 (C8), 17.6 (C8Me), 17.2 (C3Me), 16.7 (C1Me), 15.9 (C2Me) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -115.55 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 381.2227, $C_{25}H_{30}FO_2$ calculated 381.2224, Δ = 0.69 ppm.

FTIR(film)= 3734, 2980, 2360,2341, 1724, 1653, 1510 cm.$^{-1}$

$[\alpha]^{24}$= -10.6 (c= 0.5, CHCl3).

Minor

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.54 (t, *J* = 1.6 Hz, 1H, C11), 7.12 – 7.04 (m, 2H, C14), 6.97 (t, *J* = 8.6 Hz, 2H, C13), 6.35 – 6.31 (m, 2H, C6+C7), 3.07 (td, *J* = 8.9, 5.5 Hz, 1H, C9), 2.80 – 2.63 (m, 2H, C10), 2.56 (dqt, *J* = 8.3, 6.5, 3.8 Hz, 1H, C8), 2.26 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.05 (s, 6H, C3Me), 0.85 (d, *J* = 6.7 Hz, 3H, C8Me).

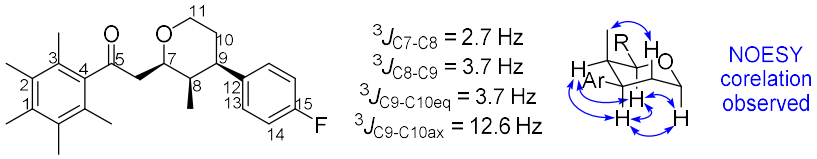
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.8 (C5), 200.6 (C11), 161.9 (d, *J* = 245.8 Hz, C15), 154.3 (C7), 137.8 (C4), 136.9 (d, *J* = 3.4 Hz, C12), 135.7 (C1), 133.5 (C6), 133.0 (C2/C3), 129.7 (d, *J* = 7.9 Hz, C13), 128.8 (C2/C3), 115.7 (d, *J* = 21.2 Hz, C14), 48.3 (C10), 44.0 (C9), 43.0 (C8), 17.7 (C8Me), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_f: -115.46 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 381.2232, $C_{25}H_{30}FO_2$ calculated 381.2224, Δ = 2.00 ppm.

FTIR(film)= 2926, 2360, 2341, 1772, 1684, 1509, 662 cm.$^{-1}$

$[\alpha]^{24}$= 62.4 (c= 0.5, CHCl3).



2-((2S,3S,4S)-4-(4-fluorophenyl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-132**)

Enantioenriched

aldehyde **4-127** (160 mg, 0.42 mmol, >25:1 d.r.) was subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-132** as a waxy solid (137 mg, 0.358 mmol, 85%, >25:1 d.r., 99% e.e.).

Racemic

aldehyde **4-127** (100 mg, 0.261 mmol, 1 eq, >25:1 d.r.) was subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-132** as a waxy solid (75 mg, 0.20 mmol, 77%, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.17 – 7.11 (m, 2H, C13), 7.01 (t, *J* = 8.7 Hz, 2H, C14), 4.30 (ddd, *J* = 8.3, 3.7, 2.1 Hz, 1H, C7), 4.14 (ddd, *J* = 11.4, 4.9, 1.4 Hz, $C11H_1$), 3.71 – 3.62 (m, 1H, $C11H_2$), 3.13 (dt, *J* = 12.6, 3.7 Hz, 1H, C9), 3.00 (dd, *J* = 17.7, 8.3 Hz, 1H, $C6H_1$), 2.63 (dd, *J* = 17.7, 3.8 Hz, 1H, $C6H_2$), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.13 (s, 6H, C3Me), 2.13-2.06 (m, 1H, $C10H_1$), 1.99 – 1.92 (m, 1H, C8), 1.57 – 1.52 (m, 1H, $C10H_2$), 0.63 (d, *J* = 7.0 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.7 (C5), 161.5 (d, *J* = 244.1 Hz, C15), 140.6 (C4), 139.6 (d, *J* = 3.1 Hz, C12), 135.7 (C1), 133.3 (br, C2), 128.8 (d, *J* = 7.7 Hz, C13), 127.7 (C3), 115.1 (d, *J* = 21.1 Hz, C14), 76.4 (C7), 68.7 (C11), 49.8 (C6), 44.7 (C9), 38.6 (C8), 24.5 (C10), 17.3 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 6.6 (C8Me) ppm.

^{19}F NMR (565 MHz, $CDCl_3$) δ_F: -117.3 ppm.

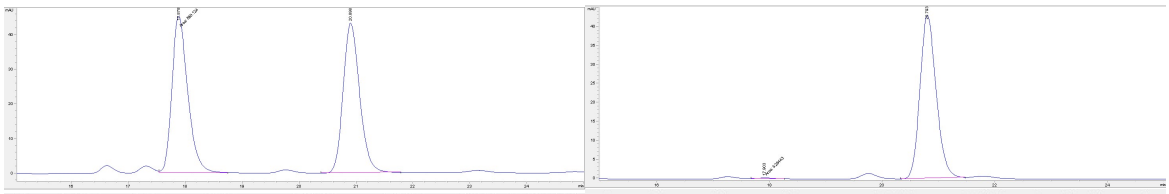
NOESY between C7, C8 and C9 supports assignment of the diastereomer and confirmer. Both J couplings and Noesy couplings to C10 further support this

HRMS: ESI^+ found $[M+H]^+$ = 383.2387, $C_{25}H_{32}O_2F$ calculated 383.2381, Δ = 1.60 ppm.

FTIR(film)= 2981, 2888, 2360, 2341, 1699, 1541, 1386, 954 cm^{-1}.

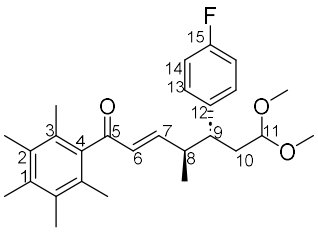
$[\alpha]_D^{25}$ = 41.1 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IB with Guard then IA with Guard with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.878	MM	880.1	45.3	0.3235	50.073	0.707
2	20.898	BB	877.6	43.4	0.312	49.927	0.792

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.903	MM	5.3	2.5E-1	0.3492	0.607	0.69
2	20.793	BB	861.7	43	0.3098	99.393	0.809



(4S,5S,E)-5-(4-fluorophenyl)-7,7-dimethoxy-4-methyl-1-(pentamethylphenyl)hept-2-en-1-one (**4-133)**

aldehyde **4-127** (381 mg, 1.00 mmol, >25:1 d.r.) was subjected to General Procedure 4B and quenched after 20 mins. Purification by FCC (Pentane:Et_2O, 99:1) gave the THP **4132** (245 mg, 0.640 mmol, 64%, >25:1 d.r.) and acetal **4-133** (74 mg, 0.17 mmol, 17% >1:25 d.r.).

THP data in agreement with that reported above.

Acetal

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.00 – 6.86 (m, 4H, C13+C14), 6.17 (dd, *J* = 15.9, 7.5 Hz, 1H, C7), 6.09 (d, *J* = 15.9 Hz, 1H, C6), 3.92 (dd, *J* = 8.7, 3.1 Hz, 1H, C11), 3.20 (s, 3H, OMe), 3.19 (s, 3H, OMe), 2.68 – 2.52 (m, 2H, C8+C9), 2.23 (s, 3H, C1Me), 2.15 (s, 6H, C2Me), 1.94 (brs, 3H, C3Me), 1.82 (brs, 3H, C3Me), 1.73 (ddd, *J* = 14.1, 11.0, 3.1 Hz, 1H, C10), 1.06 (d, *J* = 6.3 Hz, 3H, C8Me). ppm.

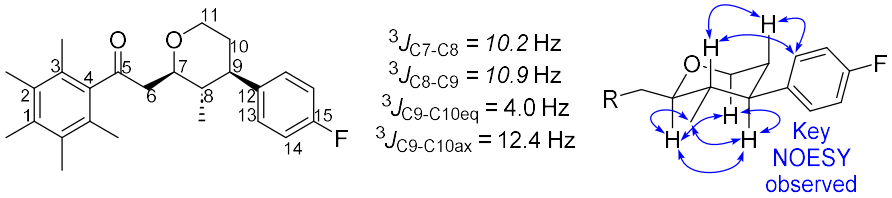
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.0 (C5), 161.6 (d, *J* = 245.0 Hz, C15), 155.2 (C7), 137.9 (C4), 137.7 (d, *J* = 3.3 Hz, C12), 135.3 (C1), 132.7 (C2), 132.6 (C6), 129.7 (d, *J* = 7.9 Hz, C13), 128.7 (C3), 115.2 (d, *J* = 21.1 Hz, C14), 102.7 (C11), 53.0 (OMe), 52.8 (OMe), 46.2 (C9), 42.5 (C8), 36.2 (C10), 17.7 (C8Me), 17.2 (br, C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

^{19}F NMR (565 MHz, $CDCl_3$) δ_F: -116.3 ppm.

HRMS: ESI$^+$ found $[M\text{-}OMe]^+$ =395.2373, $C_{26}H_{32}O_2F$ calculated 395.2381, Δ = 1.99 ppm.

FTIR(film)= 2981, 2889, 2360, 2341, 1653, 1386, 1251, 1157, 954 cm^{-1}.

$[\alpha]_D^{25}$ = 3.6 (C=0.5, $CHCl_3$)



2-((2R,3S,4R)-4-(4-fluorophenyl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (**4-132**)

Enantioenriched

aldehyde **4-127** (68 mg, 0.18 mmol, >1:25 d.r.) was subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-132** as a waxy solid (43 mg, 0.11 mmol, >1:25 d.r., 63%, 92% e.e.).

Racemic

THP **4-127** (30 mg, 0.079 mmol, 1 eq, >25:1 d.r.) was subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-132** as a waxy solid (21 mg, 0.055 mmol, 70%, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.13 (dd, *J* = 8.6, 5.5 Hz, 2H, C13), 6.99 (t, *J* = 8.7 Hz, 2H, C14), 4.06 – 4.00 (ddd, *J*= 11.5, 4.7, 1.5 Hz, 1H, $C11H_1$) , 3.79 (ddd, *J* = 10.2, 6.9, 4.2 Hz, 1H, C7), 3.61 (td, *J* = 12.0, 2.2 Hz, 1H, $C11H_2$), 2.95 – 2.88 (m, 2H, C6), 2.40 (ddd, *J* = 12.3, 10.8, 4.0 Hz, 1H, C9), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.15 (s, 6H, C3Me), 1.83 (qd, *J*= 12.9, 4.7 Hz, 1H, $C10H_1$), 1.68 (dm, *J* = 13.5 Hz, 1H, $C10H_2$), 1.71-1.66 (m, 1H, C8), 0.65 (d, *J* = 6.5 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.0 (C5), 161.6 (d, J = 244.1 Hz, C15), 140.7 (C4), 140.5 (d, J = 3.2 Hz, C12), 135.6 (C1), 133.2 (br, C2), 129.1 (d, J = 7.7 Hz, C13), 127.8 (br, C3) 115.4 (d, J = 20.9 Hz, C14) , 78.9 (C7), 68.1 (C11), 49.6 (C6), 49.2 (C9), 40.4 (C8), 35.3 (C10), 17.3 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 15.2 (C8Me) ppm.

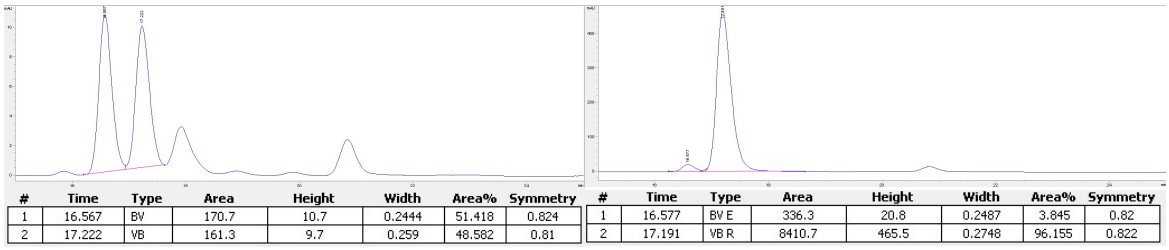
^{19}F NMR (565 MHz, $CDCl_3$) δ_F: -116.9 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 383.2385, $C_{25}H_{32}O_2F$ calculated 383.2381, Δ = 1.07 ppm.

FTIR(Film)= 2980, 1705, 1510, 1382, 1096, 834, 669 cm^{-1}.

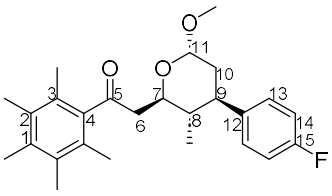
$[\alpha]_D^{25}$ = 31.1 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IB with guard, then IA with guard 5% IPA, 95% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.567	BV	170.7	10.7	0.2444	51.418	0.824
2	17.222	VB	161.3	9.7	0.259	48.582	0.81

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	16.577	BV E	336.3	20.8	0.2487	3.845	0.82
2	17.191	VB R	8410.7	465.5	0.2748	96.155	0.822



$^3J_{C10ax\text{-}C11eq}$ = 2.5 Hz
$^3J_{C10ax\text{-}C11eq}$ = 2.5 Hz
$^3J_{C7ax\text{-}C8ax}$ = 10.8 Hz

2-(4-(4-fluorophenyl)-6-methoxy-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-134**)

To the aldehyde **4-127** (110 mg, 0.289 mmol, 1 eq) was added MeOH (2 mL), followed by dropwise addition of DCM under rapid stirring until the solution was homogeneous. The solution was cooled to 0 °C, and $CeCl_3{\cdot}7H_2O$ (35 mg, 0.094 mmol, 0.33 eq) was added, followed by $NaBH_4$ (11 mg, 0.029 mmol, 1 eq).[a] After 20 mins, HCl (1.5 mL, 2M in Et_2O) was added dropwise, and the solution was warmed to rt. After 16 h, the solution was diluted with Et_2O (30 mL) and H_2O (15 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. Purification by FCC (Pentane: Et_2O, 90:10) gave the hemiacetal THP **4-134** as a waxy solid (35 mg, 0.084 mmol, 29%, >25:1 d.r.).

[a] $NaBH_4$ was believed to have decomposed resulting in the lack of reduction observed.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.15 (dd, *J* = 8.5, 5.6 Hz, 2H, C13), 6.98 (t, *J* = 8.7 Hz, 2H, C14), 4.79 (t, *J* = 2.5 Hz, 1H, C11), 4.38 (ddd, *J* = 10.8, 9.0, 2.5 Hz, 1H, C7), 3.54 (s, 3H, OMe), 2.96 (dd, *J* = 18.5, 9.1 Hz, 1H, $C6H_1$), 2.91 – 2.85 (m, 2H, $C6H_2$+C9), 2.24 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.17 (brs, 6H, C3Me), 1.90 – 1.84 (m, 2H, C10), 1.64 (m, 1H, C8), 0.67 (d, *J* = 6.5 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.5 (C5), 161.6 (d, *J* = 244.1 Hz, C15) , 140.8 (C4), 140.2 (d, *J* = 3.2 Hz, C12), 135.6 (C1), 133.2 (C2), 129.1 (d, *J* = 7.8 Hz, C13), 127.7 (br, C3) 115.4 (d, *J* = 21.1 Hz, C14), 98.0 (C11), 69.1 (C7), 55.1 (OMe), 49.0 (C6), 42.8 (C9), 39.7 (C8), 38.7 (C10), 17.1 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 15.1 (C8Me) ppm.

^{19}F NMR (565 MHz, $CDCl_3$) δ_F: -116.8 ppm.

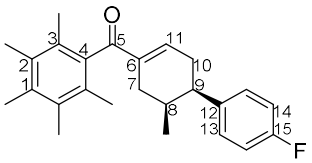
HRMS: ESI$^+$ found $[M+Na]^+$ = 435.2311 $C_{26}H_{33}O_3FNa$ calculated 435.2306, Δ = 1.15 ppm.

ESI$^+$ found $[M-OMe]^+$ = 381.2233 $C_{25}H_{30}O_2F$ calculated 381.2224, Δ = 2.26 ppm.

FTIR(Film)= 2981, 2889, 1382, 1251, 1153, 1131, 1008, 954 cm^{-1}.

$[\alpha]_D^{25}$ =61.6 (C=1.0, $CHCl_3$)

6.5.10. Optimisation of Stereo Divergent 1,5-Hydride Transfer.



((1R,2S)-4'-fluoro-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-138)**

THP **4-132** (27 mg, >25:1 d.r. 0.071 mmol, 1 eq) was subjected to General Procedure 4F. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-138** as a waxy solid (23 mg, 0.063 mmol, 89%, 10:1 d.r.).

^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 7.12 (dd, *J* = 8.6, 5.5 Hz, 2H, C13), 6.97 (t, *J* = 8.7 Hz, 2H, C14), 6.62 – 6.58 (m, 1H, C11), 3.04 (td, *J* = 6.7, 3.1 Hz, 1H, C9), 2.72 – 2.59 (m, 1H, $C7H_1$), 2.55-2.48 (m, 2H, C10), 2.27 –2.16 (m, 2H, $C7H_2$+C8) 2.25 (s, 3H, C1Me), 2.20 (d, *J* = 2.5 Hz, 6H, C2Me), 2.06 (s, 6H, C3Me), 0.80 (d, *J* = 6.6 Hz, 3H, C8Me) ppm.

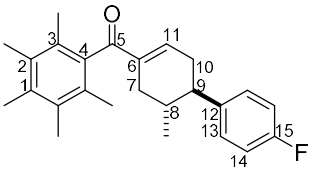
^{13}C NMR (151 MHz, $CDCl_3$) δ_C: 203.4 (C5), 161.6 (d, *J* = 244.3 Hz, C15),144.0 (C11), 140.0 (C6), 138.70 (d, *J* = 3.2 Hz, C12), 138.2 (C4), 135.3 (C1), 132.9 ($C2_1$), 132.8 ($C2_2$), 129.39 (d, *J* = 7.6 Hz, C13), 129.3 ($C3_1$), 129.1 ($C3_2$), 115.01 (d, *J* = 21.1 Hz, C14), 41.7 (C9), 32.1 (C8), 29.6 (C10), 29.1 (C7), 17.7 ($C3Me_1$), 17.6 ($C3Me_2$), 16.8 (C1Me), 16.1 (C2Me), 15.6 (C8Me) ppm.

^{19}F NMR (565 MHz, $CDCl_3$) δ_F: 117.1 ppm

HRMS: ESI$^+$ found $[M+Na]^+$ = 387.2110, $C_{25}H_{29}OFNa$ calculated 387.2095, Δ = 3.96 ppm.

FTIR(Film)= 2981, 1654, 1510, 1458, 1382, 1234, 1159, 1072, 9541, 762 cm^{-1}.

$[\alpha]_D^{25}$ = -47.1 (C=0.5, $CHCl_3$)



(4'-fluoro-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-138**)

The THP **4-132** (57 mg, 0.15 mmol, 1 eq) and Al_2O_3 (76 mg, 0.75 mmol, 5 eq) was added to a microwave vial and flushed with N_2 four times. Toluene (150 µL) was added *via* syringe, and the suspension was heated to 80 °C and stirred at 450 rpm. After 16 h, the temp was increased to 110 °C. After 24 h, the reaction was cooled to rt and diluted with EtOAc (2 mL). The suspension was filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4-138** as an inseparable mixture of isomers (45 mg, 0.12 mmol, 83%, 6.6:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.12 (dd, *J* = 8.5, 5.5 Hz, 2H, C13), 7.00 (t, *J* = 8.7 Hz, 2H, C14), 6.61 (dq, *J* = 4.2, 2.3 Hz, 0.1H, min), 6.53 – 6.50 (m, 1H, C11), 3.04 (td, *J* = 6.6, 3.0 Hz, 0.1H, min), 2.90 – 2.82 (m, 1H, $C7_{eq}$), 2.70 – 2.63 (m, 0.1H, min), 2.52 (tt, *J* = 6.7, 2.7 Hz, 0.1H, min), 2.49 – 2.41 (m, 2H, $C10H^1$+C9), 2.37 – 2.28 (m, 1H, $C10H^2$), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.05 (s, 6H, C3Me), 2.11-2.03 (m, 1H, $C7_{ax}$) 1.98-1.873 (m, 1H, C8), 0.82 (d, *J* = 6.5 Hz, 3H, C8Me), 0.80 (d, *J* = 6.7 Hz, 0.3H, min) ppm.

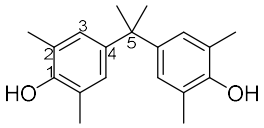
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 161.9 (d, *J*= 244.2 Hz, C15), 144.2, 140.6, 140.6 (d, *J*= 3.2 Hz, C12), 138.1, 135.3, 132.8, 132.8, 129.0 (d, *J*= 7.7 Hz, C13), 115.5 (d, *J*= 115.5 Hz, C14), 46.5 (C9), 35.8 (C10), 33.7 (C8), 31.8 (C7), 20.1 (C8Me), 17.7 (C3Me), 16.8 (C1Me), 16.1(C2Me) ppm.

^{19}F NMR (565 MHz, $CDCl_3$) δ_F: -116.9 ppm.

HRMS: ESI^+ found $[M+Na]^+$ = 387.2104, $C_{25}H_{29}OFNa$ calculated 387.2095, Δ = 2.41 ppm.

FTIR(Film)= 2981, 1653, 1510, 1383,1224,1159, 1071,762 cm^{-1}.

$[\alpha]_D^{25}$ = -37.0 (C=0.5, $CHCl_3$)



4,4'-(propane-2,2-diyl)bis(2,6-dimethylphenol) (**4-152**)

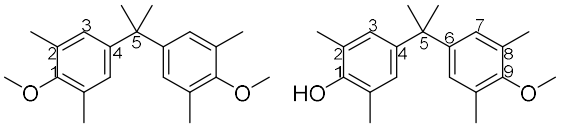
Based on literature procedure[266]

To a solution of 2,6-Me_2Phenol **4-151** (4.6 g, 37 mmol, 2 eq) in acetone (2.1 mL, 28 mmol, 1.5 eq) at 0 °C was added conc. sulfuric acid (4 mL) and acetic acid (4 mL) dropwise over 25 mins, such that the internal temperature remained below 10 °C, then the solution was allowed to warm to rt. After 18 h, the reaction was diluted in DCM (50 mL) and water (50 mL), the layers were separated, and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 95:5) to give the diphenol **4-152** (2.46 mg, 8.66 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.83 (s, 4H, C3), 2.20 (s, 12H, C2Me), 1.59 (s, 6H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 150.0 (C1), 142.9 (C4), 127.1 (C3), 122.3 (C2), 41.5 (C5), 31.4 (C5Me), 16.3 (C2Me) ppm.

Data in agreement with literature.[266]



4-(2-(4-methoxy-3,5-dimethylphenyl)propan-2-yl)-2,6-dimethylphenol (**4-154**) and 5,5'-(propane-2,2-diyl)bis(2-methoxy-1,3-dimethylbenzene) (**4-153**)

Based on literature procedure.[267]

To a solution of the diphenol **4-152** (730 mg, 2.57 mmol, 1 eq) and NaOH (205 mg, 5.12 mmol, 2 eq) in MeCN (25 mL) was added iodomethane (360 µL, 5.7 mmol, 2.2 eq) dropwise at rt. After 15 mins, the reaction was heated to 60 °C. After 2 h, upon consumption of the SM by TLC, the reaction was cooled to rt, quenched with water (50 mL) and diluted with Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (4 x 20 mL), the combined organic extracts were dried with Na_2SO_4 and concentrated in *vacuo* to give the crude products. The crude was purified by FCC (Pentane:Et_2O 98:2) to give the dimethylated product **4-154** (652 mg, 2.09 mmol, 81%) and methylated product **4-153**(118 mg, 0.39 mmol, 15%).

Dimethylated product

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.84 (s, 4H, C3), 3.71 (s, 6H, OMe), 2.24 (s, 12H, C2Me), 1.60 (s, 6H, C5Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 154.7 (C1), 145.9 (C4), 129.8 (C2), 127.1 (C3), 59.6 (OMe), 41.9 (C5), 31.1 (C5Me), 16.3 (C2Me) ppm.

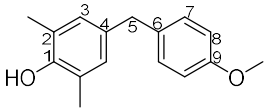
Data in agreement with literature.[267]

Methylated product

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.85 (s, 2H, C7), 6.83 (s, 2H, C3), 3.71 (s, 3H, OMe), 2.24 (s, 6H, C8Me), 2.21 (s, 6H, C2Me), 1.60 (s, 6H, C5Me) ppm.[a]

13C NMR (101 MHz, CDCl3) δ_C: 154.8 (C9), 150.1 (C1), 146.3 (C4), 142.6 (C6), 129.9 (C8), 127.3 (C7), 127.1 (C3), 122.3 (C2), 59.8 (OMe), 41.7 (C5), 31.3 (C5Me), 16.5 (C7Me), 16.3 (C2Me) ppm.

Data in agreement with literature.[267]



4-(4-methoxybenzyl)-2,6-dimethylphenol (**4-156**)

To a solution of 2,6-dimethylphenol **4-151** (366 mg, 3.00 mmol, 1 eq) and *p*-Methoxy benzyl alcohol (750 µL, 6.0 mmol, 2 eq) in DCM (9 mL) was added TFA (690 µL, 9.0 mmol, 3 eq) dropwise at 0 °C. After 10 mins, upon consumption of the SM by TLC, the reaction was quenched with water (25 mL) and warmed to rt. The layers were separated, the aqueous layer was extracted with DCM (4 x 20 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated in *vacuo* to give the crude products. The crude was purified by FCC (Pentane:Et_2O 95:5) to give the product **4-156** (439 mg, 1.80 mmol, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.12 (d, J = 8.6 Hz, 2H, C7), 6.84 (d, J = 8.7 Hz, 2H, C8), 6.81 (s, 2H, C3), 3.81 (s, 3H, C5), 3.80 (s, 3H, OMe), 2.22 (s, 6H, C2Me) ppm.

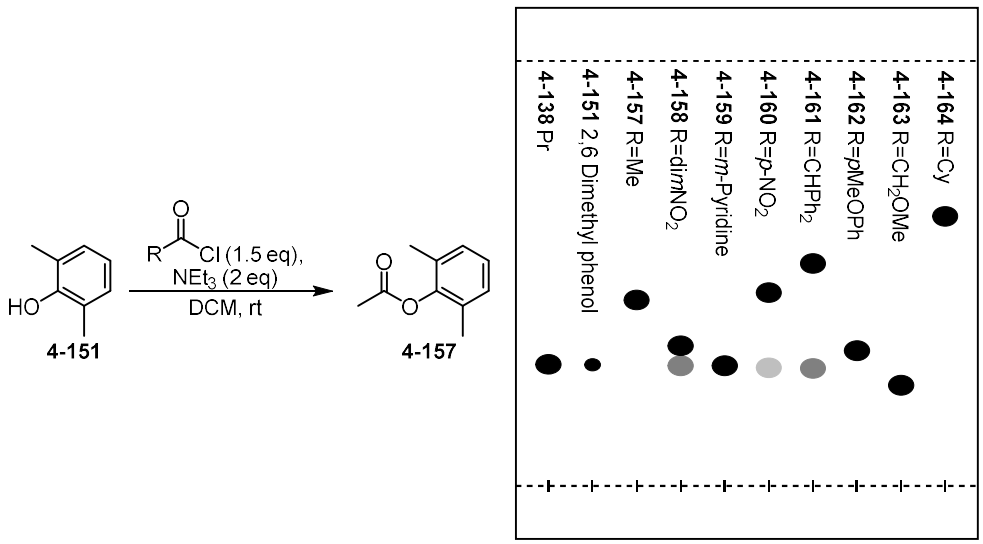
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 158.0 (C9), 150.5 (C1), 134.1 (C4/C6), 133.3 (C4/C6), 129.8 (C3/C7), 129.0 (C3/C7), 123.1 (C2), 113.9 (C8), 55.4 (OMe), 40.3 (C5), 16.0 (C2Me) ppm.

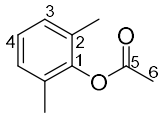
Data in agreement with literature.[268]

TLC plate of the acylated phenol species. See procedures and characterisation below.

Acylation of 2,6-methyl phenol was acylated using a variety of commercial acid chlorides.

[a] Assignment of NMR along the pseudosymmetric axis based on shift comparison of the dihydroxy and dimethyl species.





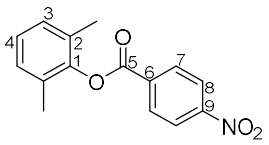
2,6-dimethylphenyl acetate (**4-157**)

To a solution of 2,6-Dimethylphenol (73 mg, 0.60 mmol, 1 eq) in DCM (5 mL) was added NEt_3 (120 µL, 0.90 mmol, 1.5 eq) and acetyl chloride (65 µL, 0.91 mmol, 1.5 eq) sequentially at rt. After 3 h, the reaction was quenched with aq. HCl (5 mL, 1 M). The layers were separated, and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude was purified by FCC (Pentane:Et_2O 99:1) to give an analytical sample of the ester **4-157**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.08 (s, 3H, C3+C4), 2.36 (s, 3H, C6), 2.19 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 168.8 (C5), 148.3 (C1), 130.1 (C2Me), 128.6 (C3), 125.9 (C4), 20.5 (C6), 16.3 (C2Me) ppm.

Data in agreement with literature.[269]



2,6-dimethylphenyl 4-nitrobenzoate (**4-160**)

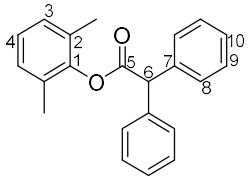
To a solution of 2,6-Dimethylphenol (73 mg, 0.60 mmol, 1 eq) in DCM (5 mL) was added NEt_3 (120 µL, 0.90 mmol, 1.5 eq) and 4-nitrobenzoyl chloride (167 mg, 0.90 mmol, 1.5 eq) sequentially at rt. After 3 h, the reaction was quenched with aq. HCl (5 mL, 1 M). The layers were separated, and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the crude product. The crude was purified by FCC (Pentane:Et_2O 99:1) to give an analytical sample of the ester **4-160**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.33 (d, J = 9.0 Hz, 2H, C7), 8.28 (d, J = 9.0 Hz, 2H, C8), 7.04 (s, 3H, C3+C4), 2.11 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 162.7 (C5), 151.1 (C9), 148.1 (C1), 134.7 (C6), 131.4 (C7), 130.1 (C2), 128.9 (C3), 126.5 (C4), 123.9 (C8), 16.5 (C2Me) ppm.

Product could not be observed by ESI mass spectrometry.

FTIR(Film)= 2361, 1737, 1529, 1267, 1163, 718 cm^{-1}.



2,6-dimethylphenyl 2,2-diphenylacetate (**4-161**)

To a solution of 2,6-Dimethylphenol (73 mg, 0.60 mmol, 1 eq) in DCM (5 mL) was added NEt_3 (125 µL, 0.90 mmol, 1.5 eq) and 2,2-diphenylacetyl chloride (210 mg, 0.90 mmol, 1.5 eq) sequentially at rt. After 3 h, the reaction was quenched with aq. HCl (5 mL, 1 M). The layers were separated, and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 99:1) to give an analytical sample of the ester **4-161**.

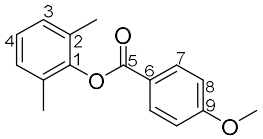
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.54 – 7.47 (m, 4H, C8), 7.42 – 7.37 (m, 4H, C9), 7.36 – 7.30 (m, 2H, C10), 7.03 (s, 3H, C3+C4), 5.36 (s, 1H, C6), 1.99 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 170.3 (C5), 148.2 (C1), 138.2 (C7), 130.4 (C2Me), 128.9 (C8+C9), 128.8 (C8+C9), 128.7 (C3), 127.7 (C10), 126.0 (C4), 57.0 (C6), 16.4 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+Na]^+$ = 339.1355, $C_{22}H_{22}O_2Na$ calculated 339.1356, Δ = 0.16 ppm.

FTIR(Film)= 2981, 2361, 2341, 1657, 1592, 1185cm^{-1}.

FTIR(Film)= 2981, 2361,1382, 1262, 1160, 1073, 954 cm^{-1}.



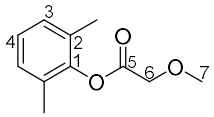
(4-hydroxy-3,5-dimethylphenyl)(4-methoxyphenyl)methanone (**4162**)

To a solution of 2,6-Dimethylphenol (488 mg, 4.00 mmol, 1 eq) in DCM (10 mL) was added pyridine (680 µL, 8.42 mmol, 2.1 eq) and 4-methoxybenzoyl chloride (790 µL, 5.8 mmol, 1.45 eq) sequentially at rt. After 3 h, the reaction was quenched with aq. HCl (10 mL, 1 M). The layers were separated, and the aqueous layer was extracted with DCM (3 x 7 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4162** (558 mg, 2.2 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.21 (d, *J* = 8.8 Hz, 2H, C7), 7.10 (s, 3H, C3+C4), 7.01 (d, *J* = 8.9 Hz, 1H, C8), 3.91 (s, 3H, OMe), 2.20 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 164.2 (C5/C9), 164.0 (C5/C9), 148.6 (C1), 132.4 (C7), 130.6 (C2), 128.7 (C3), 125.9 (C4), 121.8 (C6), 114.0 (C8), 55.7 (C10), 16.5 (C2Me) ppm.

Data in agreement with literature.[268]



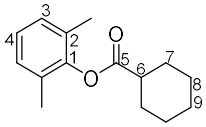
2,6-dimethylphenyl 2-methoxyacetate (**4163**)

To a solution of 2,6-Dimethylphenol (488 mg, 4.00 mmol, 1 eq) in DCM (10 mL) was added pyridine (680 µL, 8.42 mmol, 2.1 eq) and 2-methoxyacetyl chloride (540 µL, 5.9 mmol, 1.5 eq) sequentially at rt. After 3 h, the reaction was quenched with aq. HCl (10 mL, 1 M). The layers were separated, and the aqueous layer was extracted with DCM (3 x 7 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4163** (118 mg, 0.6 mmol, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.09 (s, 3H, C3+C4), 4.38 (s, 2H, C6), 3.58 (s, 3H, C7), 2.19 (s, 6H, C2Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 168.2 (C5), 147.8 (C1), 130.1 (C2), 128.8 (C3), 126.2 (C4), 69.6 (C6), 59.7 (C7), 16.4 (C2Me) ppm.

Data in agreement with literature.[270]



cyclohexyl(4-hydroxy-3,5-dimethylphenyl)methanone (**4-164**)

To a solution of 2,6-Dimethylphenol (488 mg, 4.00 mmol, 1 eq) in DCM (10 mL) was added pyridine (680 µL, 8.42 mmol, 2.1 eq) and cyclohexanecarbonyl chloride (809 µL, 6.04 mmol, 1.5 eq) sequentially at rt. After 3 h, the reaction was quenched with aq. HCl (10 mL, 1 M). The layers were separated, and the aqueous layer was extracted with DCM (3 x 7 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 98.5:1.5) to give the product **4-164** (118 mg, 0.510 mmol, 13%).

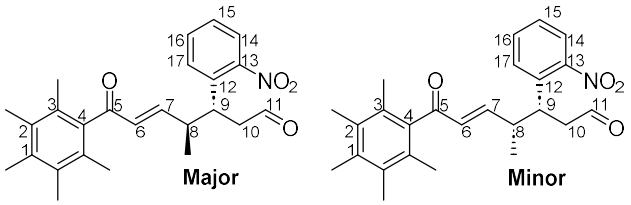
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.10 – 6.99 (m, 3H, C2+C3), 2.63 (tt, J = 11.4, 3.6 Hz, 1H, C6), 2.14 (s, 8H, C2Me +C7H$_1$), 1.95 – 1.80 (m, 2H, C8H$_1$), 1.79 – 1.54 (m, 4H, C7H$_2$+C9H$_1$), 1.47 – 1.24 (m, 3H, C8H$_2$+C9H$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 173.8 (C5), 148.3 (C1), 130.2 (C2), 128.7 (C3), 125.8 (C4), 43.5 (C6), 29.4 (C7), 25.9 (C9), 25.6 (C8), 16.5 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 233.1533, $C_{15}H_{21}O_2$ calculated 233.1536, Δ = 1.33 ppm

FTIR(Film)= 2981, 2361, 1657, 1593, 1185, 745 cm^{-1}.

6.5.11. 4,5-Substituted Aldehydes.



(3S,E)-4-methyl-3-(2-nitrophenyl)-7-oxo-7-(pentamethylphenyl)hept-5-enal (*anti*:syn) (**4-166**)

Enantioenriched

Silyl enol ether **4-114** (302 mg, 1.00 mmol, 2 eq, 17:1 *E*:*Z*), *o*-NO_2-cinnamaldehyde (89 mg, 0.50 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-166** as a waxy oil (134 mg, 0.329 mmol, 66%, 75:25 d.r. 94% e.e. (94% e.e.)). The major and minor isomers could be isolated as a single diastereomer (95 mg, 0.23 mmol, 46%, >25:1 d.r.) and (25 mg, 0.061 mmol, 12%, >1:25 d.r.), respectively. Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-114** (453 mg, 1.5 mmol, 2 eq, 2:1 *E*:*Z*) and *o*-NO_2-cinnamaldehyde (133 mg, 0.751 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-166** as a waxy oil (204 mg, 0.501 mmol, 67%, 56:44 d.r.). The major and minor isomers could be isolated as a single diastereomer (86 mg, 0.21 mmol, 28%) and (68 mg, 0.17 mmol, 22%), respectively.

Major-(*anti*)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.61 (dd, *J* = 2.1, 1.3 Hz, 1H, C11), 7.72 (dd, *J* = 8.1, 1.4 Hz, 1H, C14), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H, C16), 7.34 (ddd, *J* = 8.2, 7.4, 1.4 Hz, 1H, C15), 7.30 (dd, *J* = 7.9, 1.4 Hz, 1H, C17), 6.15 (dd, *J* = 15.8, 8.2 Hz, 1H, C7), 6.07 (d, *J* = 15.9 Hz, 1H, C6), 3.74 (td, *J* = 8.9, 4.9 Hz, 1H, C9), 2.91 (ddd, *J* = 17.4, 4.9, 1.3 Hz, 1H, C10H_1), 2.85 – 2.72 (m, 2H, C8+C10H_2), 2.22 (s, 3H, C1Me), 2.14 (s, 6H, C2Me), 1.92 (brs, 3H, C3Me_1), 1.65 (brs, 3H, C3Me_2), 1.11 (d, *J* = 6.6 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.9 (C5), 199.8 (C11), 153.4 (C7), 150.5 (C13), 137.4 (C4), 136.3 (C1/C12), 135.6 (C1/C12), 133.5 (C6), 132.9 (C2), 132.8 (C16), 129.3 (C17), 128.6 (C3), 127.9 (C15), 124.6 (C14), 47.4 (C10), 42.0 (C8), 38.5 (C9), 17.7 (C8Me), 17.2 (br, C3Me), 16.8 (C1Me), 16.0 (C2Me) ppm.

FTIR(Film)= 2981, 2889, 2360, 1652, 1527, 1383, 1151 cm.$^{-1}$

HRMS: ESI$^+$ found $[M+H]^+$ = 408.2182, $C_{25}H_{30}NO_4$ calculated 408.2169, Δ = 3.09 ppm.

$[\alpha]_D^{25}$ = 3.6 (C=0.5, $CHCl_3$)

Minor-(*syn*)

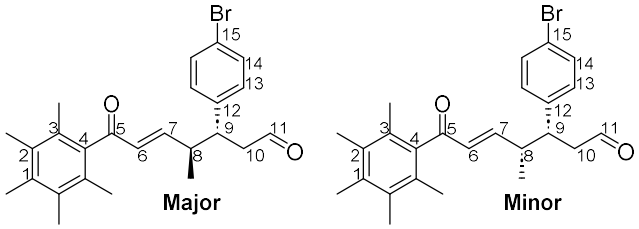
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.52 (dd, *J* = 2.0, 1.2 Hz, 1H, C11), 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H, C14), 7.54 (td, *J* = 7.7, 1.4 Hz, 1H, C16), 7.37 – 7.34 (m, 1H, C15), 7.32 (dd, *J* = 7.9, 1.4 Hz, 1H, C17), 6.37 (d, *J* = 15.8 Hz, 1H, C6), 6.28 (dd, *J* = 15.8, 8.8 Hz, 1H, C7), 3.69 (td, *J* = 9.3, 5.2 Hz, 1H, C9), 2.81 – 2.65 (m, 3H, C8+C10), 2.27 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.05 (s, 6H, C3Me), 0.90 (d, *J* = 6.7 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.8 (C5), 199.6 (C11), 153.2 (C7), 151.2 (C13), 137.6 (C4), 136.1 (C1/C12), 135.9 (C1/C12), 134.2 (C6), 133.2 (C2), 132.9 (C16), 128.7 (C17), 128.5 (C3), 128.0 (C15), 124.5 (C14), 48.4 (C10), 43.0 (C8), 38.2 (C9), 18.4 (C8Me), 17.6 (C3Me), 16.9 (C1Me), 16.1 (C2Me) ppm.

FTIR(Film)= 2981, 2889, 2360, 2341, 1722, 1527, 1383 cm.$^{-1}$

HRMS: ESI$^+$ found $[M+H]^+$ = 408.2175, $C_{25}H_{30}NO_4$ calculated 408.2169, Δ = 1.37 ppm.

$[\alpha]_D^{25}$ = 98.1 (C=0.5, $CHCl_3$).



(3S,E)-3-(4-bromophenyl)-4-methyl-7-oxo-7-(pentamethylphenyl)hept-5-enal (*syn*:*anti*) (**4-167**)

Enantioenriched

Silyl enol ether **4-114** (302 mg, 1.00 mmol, 2 eq, 17:1 *E*:*Z*) and *p*-Br-cinnamaldehyde (106 mg, 0.502 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-167** as a waxy oil (162 mg, 0.367 mmol, 73%, 9:1 d.r.). The major and minor isomers could be isolated as single diastereomers (141 mg, 0.32 mmol, 64%, 99% e.e.) and (21 mg, 0.048 mmol, 10%, 88% e.e.), respectively. Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-114** (453 mg, 2:1 d.r., 1.50 mmol, 2 eq, 2:1 *E*:*Z*) and p-Br-cinnamaldehyde (158 mg, 0.750 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-167** as a waxy oil (216 mg, 0.490 mmol, 65%, 2:1 d.r.). The major and minor isomers could be isolated as single diastereomers (53 mg, 0.12 mmol, 16%) and (80 mg, 0.18 mmol, 24%), respectively.

Major-(*anti*)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.54 (t, *J* = 1.6 Hz, 1H, C11), 7.30 – 7.24 (m, 2H, C13), 6.87 – 6.78 (m, 2H, C14), 6.07 (d, *J* = 4.0 Hz, 1H, C7), 6.07 (s, 1H, C6), 3.11 – 3.04 (m, 1H, C9), 2.77 – 2.70 (m, 2H, C10), 2.60 – 2.49 (m, 1H, C8), 2.17 (s, 3H, C1Me), 2.10 (s, 6H, C2Me), 1.83 (brs, 6H, C3Me), 0.98 (d, *J* = 6.8 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.6 (C5), 200.2 (C11), 153.9 (C7), 140.2 (C14), 137.7 (C1), 135.6 (C4), 133.4 (C6), 132.9 (C2/C3), 131.8 (C14), 129.8 (C13), 128.6 (C2/C3), 120.9 (C12), 48.0 (C10), 44.0 (C9), 42.6 (C8), 17.6 (C8Me), 17.4 (C3Me), 16.7 (C1Me), 16.0 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 441.1424, $C_{25}H_{30}BrO_2$ calculated 441.1424, Δ = 0.39 ppm.

FTIR(Film)= 2979, 2889, 2360, 1724, 1652, 1381, 954 cm^{-1}.

Minor-(*syn*)

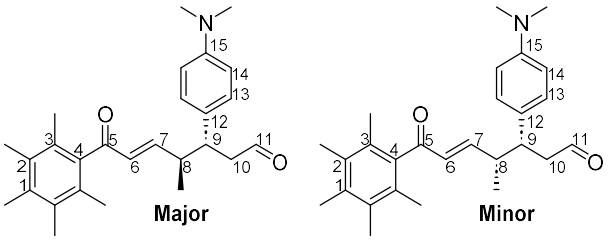
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.54 (t, *J* = 1.5 Hz, 1H, C11), 7.40 (d, *J* = 8.4 Hz, 2H, C13), 7.02 – 6.96 (m, 2H, C14), 6.31 (s, 1H, C6), 6.30 (d, *J* = 3.4 Hz, 1H, C7), 3.05 (td, *J* = 8.9, 5.5 Hz, 1H, C9), 2.79 – 2.64 (m, 2H, C10), 2.56 (ddt, *J* = 12.3, 6.6, 2.3 Hz, 1H, C8), 2.26 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.04 (s, 6H, C3Me), 0.85 (d, *J* = 6.7 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.7 (C5), 200.4 (C11), 153.4 (C7), 140.1 (C4), 137.8 (C1), 135.6 (C2), 133.2 (C6), 132.9 (C3), 131.8 (C13), 130.0 (C14), 128.7 (C12), 121.0 (C15), 47.2 (C10), 44.3 (C9), 41.9 (C8), 17.7 (C8Me), 17.3 (C3Me), 16.9 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 441.1422, $C_{25}H_{30}BrO_2$ calculated 441.1424, Δ = 0.39 ppm.

FTIR(Film)= 2980, 2360, 1724, 1652, 1605,, 1510, 1192, 834 cm^{-1}.

$[\alpha]_D^{25}$ = 7.62 (C=0.5, $CHCl_3$)



(3S,E)-3-(4-Dimethylaminophenyl)-4-methyl-7-oxo-7-(pentamethylphenyl)hept-5-enal (*syn*:*anti*) (**4-168**)

Enantioenriched

Silyl enol ether **4-114** (393 mg, 1.30 mmol, 2 eq, 17:1 *E*:*Z*) and cinnamaldehyde (113 mg, 0.650 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-168** as a waxy oil (198 mg, 0.488 mmol, 75%, 10:1 d.r., 95% e.e.). The major isomer could be isolated as a single diastereomer (102 mg, 0.251 mmol, 39%). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-114** (970 mg, 3.00 mmol, 2 eq, 2:1 *E*:*Z*) and cinnamaldehyde (262 mg, 1.50 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the major isomer **4-168** as a waxy oil (180 mg, 0.44 mmol, 30%).

Major-(*anti*)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.50 (t, *J* = 1.9 Hz, 1H, C11), 6.82 (d, *J* = 8.8 Hz, 2H, C13), 6.61 (d, *J* = 8.8 Hz, 2H, C14), 6.15 (dd, *J* = 15.9, 7.8 Hz, 1H, C7), 6.07 (d, *J* = 15.9 Hz, 1H, C6), 3.03 (dt, *J* = 8.6, 6.6 Hz, 1H, C9), 2.86 (s, 6H, NMe), 2.71 – 2.59 (m, 2H, C10), 2.59 – 2.49 (m, 1H, C8), 2.15 (s, 3H, C1Me), 2.09 (s, 6H, C2Me), 1.85 (brs, 6H, C3Me), 0.94 (d, *J* = 6.7 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.9 (C5), 201.6 (C11), 154.6 (C7), 148.6 (C15), 137.8 (C4), 135.2 (C1), 132.8 (C6), 132.7 (C2/C3), 129.9 (br, C12), 129.1 (C13), 128.6 (C2/C3), 113.5 (C14), 47.1 (C10), 44.0 (C9), 42.3 (C8), 41.3 (NMe), 17.4 (C8Me), 17.3 (C3Me), 16.7 (C1Me), 15.9 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 406.2745, $C_{27}H_{36}NO_2$ calculated 406.2471, Δ = 1.08 ppm.

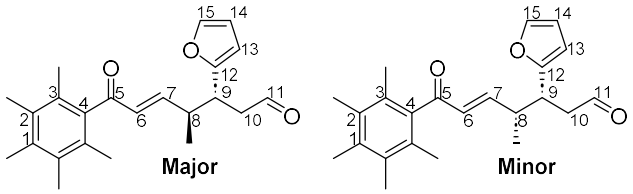
FTIR(Film)= 2923, 2360, 1652, 1191, 669 cm^{-1}.

$[\alpha]_D^{25}$ =6.4 (C=0.5, $CHCl_3$)

Minor-(*syn*)

Due to the high selectivity and difficulty to isolate the starting material characterisation of the minor isomer was done using. Only diagnostic peaks of the minor isomer could be reported

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.51 (dd, *J* = 2.4, 1.6 Hz, 1H, C11), 6.95 (d, *J* = 8.7 Hz, 2H, C13), 6.63 (d, *J* = 8.7 Hz, 1H, 14), 6.41 – 6.28 (m, 2H, C6+C7), 2.91 (s, 6H, NMe), 2.25 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.06 (s, 6H, C3Me), 0.86 (d, *J* = 6.6 Hz, 3H, C3Me) ppm.



(3S,E)-3-(furan-2-yl)-4-methyl-7-oxo-7-(pentamethylphenyl)hept-5-enal (*anti*:*syn*) (**4-169**)

Enantioenriched

silyl enol ether **4-114** (908 mg, 3.00 mmol, 1.5 eq, 17:1 *E:*Z) and trans-3-(2-Furyl)acrolein (244 mg, 2.00 mmol, 1 eq) was subjected to General Procedure 4B. Purification by FCC (Pentane: Et_2O, 80:20) gave the desired aldehyde **4-168** as a clear oil (638 mg, 1.81 mmol, 90 %, 4.8:1 d.r., 95% e.e., (81% e.e.)). Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

silyl enol ether **4-114** (453 mg, 1.50 mmol, 2 eq, 2:1 *E:*Z) and trans-3-(2-Furyl)acrolein (92 mg, 0.75 mmol, 1 eq) was subjected to General Procedure 4B. Purification by FCC (Pentane: Et_2O, 80:20) gave the desired aldehyde **4-168** as a clear oil (171 mg, 0.485 mmol, 65 %, 2.6:1 d.r).

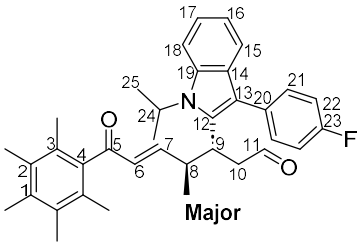
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.65 (t, *J* = 1.7 Hz, 1H, C11), 9.62 (t, *J* = 1.7 Hz, 0.2H, C11m), 7.28 (dd, *J* = 1.9, 0.8 Hz, 0.2H, C15m), 7.23 (dd, *J* = 1.9, 0.8 Hz, 1H, C15), 6.33 – 6.19 (m, 3.6H, C6+C7+C14+C6m+C7m+C14m) 6.00 (d, *J* = 3.2 Hz, 0.2H, C13m), 5.96 (d, *J* = 3.2 Hz, 1H, C13), 3.35 (dt, *J* = 9.2, 5.5 Hz, 1H, C9), 3.29 (ddd, *J* = 9.8, 7.4, 4.8 Hz, 0.2H, C9m), 2.78 (ddd, *J* = 17.1, 9.2, 1.9 Hz, 1H, $C10H_1$), 2.82-2.67 (m, 1.4H, C8+C8m+$C10H_1$m) 2.62 (ddd, *J* = 17.2, 5.2, 1.4 Hz, 1.2H, C10H2+C10H2m), 2.24 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.01 (s, 6H, C3Me), 1.03 (d, *J* = 6.8 Hz, 3H, C8Me), 0.95 (d, *J* = 6.8 Hz, 0.6H, C8Mem) ppm.

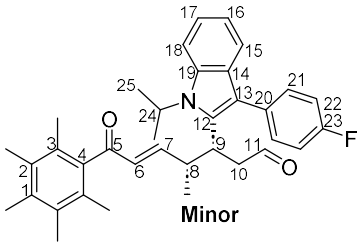
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.0 (C5M), 202.9 (C5m), 200.5 (C11M), 200.5 (C11m), 154.2 (C12m), 154.1 (C12M), 154.0 (C7m), 153.5 (C7M), 141.8 (C15m), 141.7 (C15M), 137.9 (C4M+C4m), 135.5 (C4M+C4m), 133.2 (C6m), 133.1 (C6M), 133.0 (C2m), 132.9 (C2M), 128.8 (C3M+C3m), 110.2 (C14m), 110.2 (C14M), 107.3 (C13m), 107.3 (C13M), 45.3 (C10m), 44.8 (C10M), 40.9 (C8m), 40.5 (C8M), 38.0 (C9M+C9m), 17.5 (C3m), 17.5 (C3M), 17.1 (C1M+C1m), 16.8 (C8M), 16.8 (C8m), 16.1 (C2m), 16.1 (C2M) ppm.

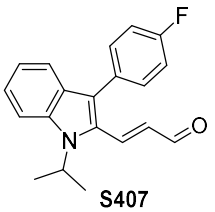
HRMS: ESI^+ found $[M+H]^+$ =353.2116, $C_{23}H_{29}O_3$ calculated 353.2111, Δ = 1.3 ppm.

FTIR(Film)= 2981, 2888, 2360, 2341, 1652, 1382, 1151, 954 cm^{-1}.

$[\alpha]_D^{25}$ = 14.9 (C=0.5, $CHCl_3$)







(3S,E)-3-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)-4-methyl-7-oxo-7-(pentamethylphenyl)hept-5-enal (*anti-syn*) (**4-170**)

Enantioenriched

Silyl enol ether **4-114** (604 mg, 2.00 mmol, 2 eq) and aldehyde **S4-07** (307 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→65:35) gave the product **4-170** as a waxy oil (377 mg, 0.702 mmol, 70%, 1.9:1 d.r.). The major and minor isomers could be isolated as a single diastereomer (168 mg, 0.312 mmol, 31%, 98% e.e.) and (104 mg, 0.19 mmol, 19%, 97% e.e.), respectively. Enantioselectivity was determined by HPLC analysis of the subsequent THP.

Racemic

Silyl enol ether **4-114** (604 mg, 2.00 mmol, 2 eq) and aldehyde **S4-07** (307 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→65:35) gave the major product **4-170** (337 mg, 0.62 mmol, 62%) and minor product (96 mg, 0.18 mmol, 18%), respectively.

Major

^{1}H NMR (400 MHz, C_6D_6, 333K) δ_H: 9.17 (t, *J* = 1.4 Hz, 1H, C11), 7.40 (d, *J* = 8.3 Hz, 1H, C18), 7.39 – 7.30 (m, 1H, C15), 7.21 – 7.12 (m, 1H, C17), 7.11 – 7.04 (m, 3H, C16+C21), 6.87 (t, *J* = 8.5 Hz, 2H, C22), 6.32 – 6.17 (m, 2H, C6+C7), 4.34 (hept, *J* = 7.4 Hz, 1H, C24), 3.38 (vbrs, 1H, C9), 2.49 – 2.39 (m, 2H, C8+C10H_1), 2.37 – 2.30 (m, 1H, C10H_2), 2.07 (s, 6H, C2Me), 1.97 (s, 3H, C1Me), 1.97 (s, 6H, C3Me), 1.40 (d, *J* = 6.9 Hz, 3H, C25$_1$), 1.33 (d, *J* = 7.0 Hz, 3H, C25$_2$), 0.63 (d, *J* = 6.7 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, C_6D_6, 333K) δ_C: 200.9 (C11), 198.5 (C5), 162.5 (d, *J* = 246.0 Hz, C23), 152.5 (C7), 139.0 (C4), 135.7 (vbr, quat), 135.5 (C1), 134.7 (vbr, quat), 134.3 (C6), 133.1 (C2), 132.9 (d, *J* = 7.8 Hz, C21), 132.1 (vbr, quat), 130.4 (vbr, quat), 129.1 (C3), 128.3 (quat), 122.0 (C17), 120.1 (C15+C16), 115.7 (d, *J* = 21.2 Hz, C23), 112.5 (C18), 48.3 (vbr, C24), 47.7 (vbr, C10), 43.0 (C8), 35.8 (C9), 21.2 (C25$_1$+C25$_2$), 18.9 (C8Me), 17.5 (C3Me), 16.5 (C1Me), 15.9 (C2Me) ppm.

^{19}F NMR (377 MHz, C_6D_6, {H}) δ_F: -115.6 ppm.

HRMS: ESI^+ found $[M+H]^+$ = 538.3103, $C_{36}H_{41}FNO_2$ calculated 538.3116, Δ = 2.39 ppm.

FTIR(Film)= 2980, 2888, 1381, 1252, 1161, 1131, 953, 817 cm^{-1}.

$[\alpha]_D^{25}$ = 10.5 (C=0.5, $CHCl_3$)

Minor

^{1}H NMR (600 MHz, C_6D_6, 338K) δ_H: 9.21 (t, *J* = 1.9 Hz, 1H, C11), 7.28 (d, *J* = 8.3 Hz, 1H, C18), 7.21 (d, *J* = 7.9 Hz, 1H, C15), 7.10 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H, C17), 7.02 (t, *J* = 7.5 Hz, 1H, C16), 6.89 – 6.81 (m, 2H, C22), 6.75 (brs, 2Hm C21), 6.14 (d, *J* = 16.0 Hz, 1H, C6), 6.06 (dd, *J* = 16.0, 8.2 Hz, 1H, C7), 4.18 (s, 1H, C24), 3.36 – 3.26 (m, 1H, C9), 2.37 – 2.29 (m, 1H, $C10H_1$), 2.28 – 2.22 (m, 1H, C8), 2.19 (ddd, *J* = 16.9, 5.7, 1.5 Hz, 1H, $C10H_2$), 2.03 (s, 3H, C1Me), 1.84 (s, 6H, C2Me), 1.36 (d, *J* = 6.9 Hz, 6H, C25), 1.26 (d, *J* = 6.4 Hz, 4H, C3Me), 0.64 (d, *J* = 6.6 Hz, 4H) ppm.

^{13}C NMR (151 MHz, C_6D_6, 333K) δ_C: 201.4 (C5), 198.5 (C11), 162.5 (d, *J* = 245.9 Hz, C23), 153.5, 138.6, 136.0 (br), 135.0, 134.7 (br), 133.4 (C6), 133.0 (d, *J* = 7.7 Hz, C21), 132.8 (br), 131.9 (br), 129.9 (br), 129.2 (br), 128.3, 122.0 (C17), 120.1 (br,C16), 120.0 (C15), 115.5 (d, *J* = 21.1 Hz, C22), 112.4 (C18), 48.4 (br,C24), 47.2 (br,C10), 41.5 (br,C8), 36.8 (C9), 21.1 (C25), 21.1 (C25), 19.7 (br,C8Me), 16.8 (br, C3Me), 16.6 (C1Me), 15.8 (C2Me) ppm.

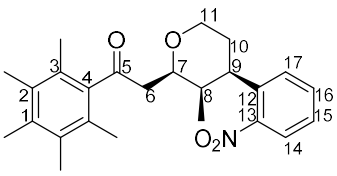
^{19}F NMR (377 MHz, C_6D_6, {H}) δ_F: -115.6 ppm.

HRMS: ESI^+ found $[M+H]^+$ = 538.3128, $C_{36}H_{41}FNO_2$ calculated 538.3116, Δ = 2.25 ppm.

FTIR(Film)= 2981, 2889, 2360, 2341, 1383, 1154, 954 cm^{-1}.

$[\alpha]_D^{25}$ = 44.2 (C=0.5, $CHCl_3$)

6.5.12. Synthesis of 2,3,4-Substituted THP Rings.



$^3J_{C7\text{-}C8}$ = 2.4 Hz
$^3J_{C8\text{-}C9}$ = 3.5 Hz
$^3J_{C9\text{-}C10eq}$ = 3.5 Hz
$^3J_{C9\text{-}C10ax}$ = 13.0 Hz
$^3J_{C10ax\text{-}C11eq}$ = 2.3 Hz
$^3J_{C10ax\text{-}C11ax}$ = 11.9 HZ

2-((cis)-3-methyl-4-(2-nitrophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-171**)

Enantioenriched

Aldehyde **4-166** (158 mg, 0.388 mmol, >25:1 d.r., 1 eq) was subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-171** as a waxy solid (124 mg, 0.303 mmol, 78%, 94% e.e.).

Racemic

Aldehyde **4-166** (60 mg, 0.15 mmol, 1 eq) was subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-171** as a waxy solid (34 mg, 0.083 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.79 (dd, *J* = 8.0, 1.4 Hz, 1H, C14), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H, C16), 7.40 – 7.33 (m, 2H, C15+C17), 4.31 (dt, *J* = 9.4, 2.4 Hz, 1H, C7), 4.13 (ddd, *J* = 11.4, 4.7, 1.5 Hz, 1H, $C11H_1$), 3.77 (dt, *J* = 12.9, 3.5 Hz, 1H, C9), 3.69 (td, *J* = 11.8, 2.3 Hz, 1H, $C11H_2$), 2.97 (dd, *J* = 17.4, 9.4 Hz, 1H, $C6H_1$), 2.53 (dd, *J* = 17.4, 2.5 Hz, 1H, $C6H_2$), 2.1-1.16 (m, 1H, $C10H_1$), 2.23 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.13 (s, 6H, C3Me), 2.01 – 1.92 (m, 1H, C8), 1.50 – 1.42 (m, 1H, $C10H_2$), 0.69 (d, *J* = 7.1 Hz, 3H, C8Me) ppm.

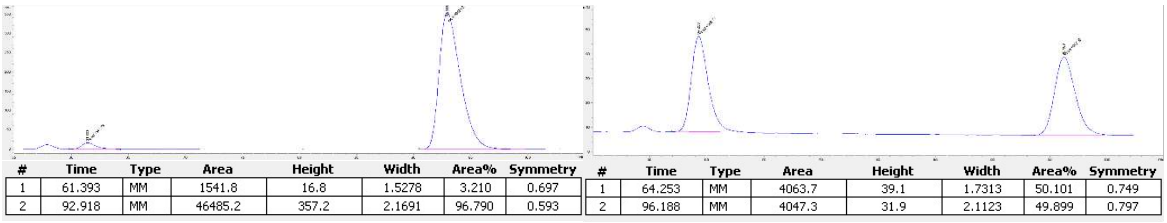
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.1 (C5), 150.1 (C13), 140.4 (C4), 137.4, 135.7, 133.2, 132.2 (C16), 129.6 (C15/C17), 127.8 (C3), 127.3 (C15/C17), 124.8 (C14), 76.2 (C7), 68.5 (C11), 49.7 (C6), 40.9 (C9), 36.7 (C8), 25.0 (C10), 17.3 (C2Me), 16.8 (C1Me), 16.1 (C3Me), 7.2 (C8Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 410.2340, $C_{25}H_{32}NO_4$ calculated 410.2326, Δ = 3.44 ppm.

FTIR(Film)= 2930, 1700,1527, 1218, 1100,764, 651 cm^{-1}.

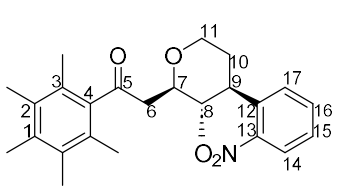
$[\alpha]_D^{25}$ = 54.5 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak ID with guard IC with guard, 13% IPA, 87% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

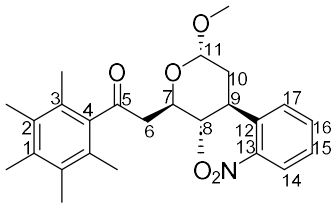


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	61.393	MM	1541.8	16.8	1.5278	3.210	0.697
2	92.918	MM	46485.2	357.2	2.1691	96.790	0.593

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	64.253	MM	4063.7	39.1	1.7313	50.101	0.749
2	96.188	MM	4047.3	31.9	2.1123	49.899	0.797



$^3J_{C7-C8}$ =
$^3J_{C8-C9}$ =
$^3J_{C9-C10eq}$ =
$^3J_{C9-C10ax}$ =
$^3J_{C10ax-C11eq}$ =
$^3J_{C10ax-C11ax}$ =



$^3J_{C7-C8}$ = *10.9 Hz*
$^3J_{C8-C9}$ = *12.0 Hz*
$^3J_{C9-C10eq}$ = 12.0 Hz
$^3J_{C9-C10ax}$ = 4.0 Hz
$^3J_{C10ax-C11eq}$ = br peak
$^3J_{C10eq-C11eq}$ = 2.9 Hz

2-((2R,3S,4R)-3-methyl-4-(2-nitrophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-171**) and 2-((2R,3S,4R,6S)-6-methoxy-3-methyl-4-(2-nitrophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-176**)

Enantioenriched

Aldehyde **4-166** (85 mg, 0.21 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave a mixture of the cyclic acetal **4-176** and THP **4-171** as a waxy solid (36 mg, 1.4:1, 0.036 mmol, 17%, >25:1 d.r. and 0.048 mmol, 23%, >25:1 d.r. respectively). The two products could be separated to give the acetal (13 mg, 0.030 mmol, 14%) and THP (17mg, 0.041 mmol, 20%, 94% e.e.).

Racemic

Aldehyde **4-166** (49 mg, 0.12 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave a mixture of THP **4-171** and cyclic acetal **4-176** as a waxy solid (23 mg, 4.7:1, 0.046 mmol, 38%, >25:1 d.r. and 0.0097 mmol, 8%, >25:1 d.r. respectively). For the purposes of HPLC analysis an analytical sample of the THP **4-171** was isolated.

THP

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.68 (dd, *J* = 8.1, 1.3 Hz, 1H, C14), 7.56 (ddd, *J* = 8.4, 7.4, 1.4 Hz, 1H, C16), 7.44 (dd, *J* = 7.9, 1.5 Hz, 1H, C17), 7.34 (ddd, *J* = 8.6, 7.4, 1.4 Hz, 1H, C15), 4.04 (ddd, *J* = 11.6, 4.4, 1.8 Hz, 1H, C11H_1), 3.75 (ddd, *J* = 9.7, 8.1, 3.1 Hz, 1H, C7), 3.62 (td, *J* = 11.6, 2.8 Hz, 1H, C11H_2), 3.03 – 2.95 (m, 1H, C9), 2.95 – 2.83 (m, 2H, C6), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.14 (s, 6H, C3Me), 1.91 – 1.75 (m, 3H, C8+C10), 0.63 (d, *J* = 6.5 Hz, 3H, C8Me).

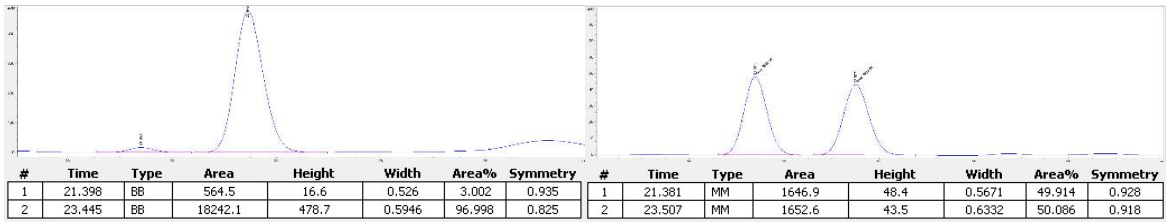
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.6 (C5), 151.2 (C13), 140.4 (C4), 138.4 (C1), 135.7 (C2), 133.3 (C3), 132.7 (C17), 128.3 (br, C16), 127.8 (C12), 127.2 (C15), 123.8 (C14), 78.9 (C7), 67.9 (C11), 49.3 (C6), 43.2 (C9), 39.8 (C8), 34.9 (C10), 17.3 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 15.1 (C8Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 432.2166, $C_{25}H_{31}NO_4Na$ calculated 432.2145, Δ = 4.78 ppm.

FTIR(Film)= 3447, 2980, 1702, 1527, 1460, 1260, 1128, 953, 784 cm^{-1}.

$[\alpha]_D^{25}$ = 127.4 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IG with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.398	BB	564.5	16.6	0.526	3.002	0.935
2	23.445	BB	18242.1	478.7	0.5946	96.998	0.825

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.381	MM	1646.9	48.4	0.5671	49.914	0.928
2	23.507	MM	1652.6	43.5	0.6332	50.086	0.918

Acetal

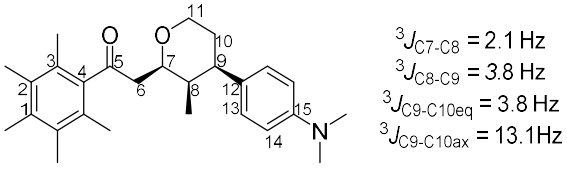
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.67 (dd, *J* = 8.1, 1.4 Hz, 1H, C14), 7.54 (td, *J* = 7.7, 1.4 Hz, 1H, C16), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H, C17), 7.33 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H, C15), 4.78 (d, *J* = 2.9 Hz, 1H, C11), 4.37 (ddd, *J* = 10.9, 8.6, 2.8 Hz, 1H, C7), 3.50 (s, 3H, OMe), 3.44 (td, *J* = 12.0, 4.0 Hz, 1H, C9), 2.94 (dd, *J* = 18.2, 8.5 Hz, 1H, C6H_1), 2.87 (dd, *J* = 18.2, 2.8 Hz, 1H, C6H=2), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.15 (s, 6H, C3Me), 2.03 (ddd, *J* = 13.2, 4.0, 0.9 Hz, 1H, C10H_1), 1.92 – 1.74 (m, 2H, C8+C10H_2), 0.66 (d, *J* = 6.6 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.1 (C5), 151.4 (C13), 140.7 (C4), 138.1 (C1), 135.6 (C2/C12), 133.2 (C2/C12), 132.6 (C16), 128.3 (br, C17), 127.7 (br, C3), 127.2 (C15), 123.8 (C14), 97.7 (C11), 69.0 (C7), 55.1 (OMe), 48.7 (C6), 39.2 (C8), 38.3 (C10), 37.2 (br, C9), 17.1 (br, C3Me), 16.9 (C1Me), 16.1 (C2Me), 15.1 (C8Me) ppm.

HRMS: ESI$^+$ not found.

FTIR(Film)= 2928, 1701, 1558, 1530, 1362, 1130, 1052, 770, 673 cm^{-1}.

$[\alpha]_D^{25}$ = 128.6 (C=0.5, $CHCl_3$)



2-((2R,3R,4R)-4-(4-(dimethylamino)phenyl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-173**)

Enantioenriched

Aldehyde **4-168** (138 mg, 0.340 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-173** as a waxy solid (66 mg, 0.162 mmol, 48%, 95% e.e.).

Racemic

Aldehyde **4-168** (145 mg, 0.357 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-173** as a waxy solid (102 mg, 0.250 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.07 (d, *J* = 8.5 Hz, 2H, C13), 6.73 (d, *J* = 8.8 Hz, 2H, C14), 4.28 (ddd, *J* = 8.3, 3.7, 2.1 Hz, 1H, C7), 4.13 (ddd, *J* = 11.3, 4.9, 1.4 Hz, 1H, $C11H_{eq}$), 3.66 (ddd, *J* = 12.3, 11.3, 2.4 Hz, 1H, $C11H_{ax}$), 3.07 (dt, *J* = 13.1, 3.8 Hz, 1H, C9), 3.00 (dd, *J* = 17.5, 8.3 Hz, 1H, $C7H_1$), 2.93 (s, 6H, NMe_2), 2.64 (dd, *J* = 17.5, 3.6 Hz, 1H, $C6H_2$), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.14 (s, 6H, C3Me), 2.18-2.03 (m, 1H, $C10H_1$)1.97 – 1.88 (m, 2H, C8H), 1.53 (dddt, *J* = 13.2, 3.8, 2.5, 1.2 Hz, 1H, $C10H_2$), 0.66 (d, *J* = 7.0 Hz, 3H, C8Me) ppm.

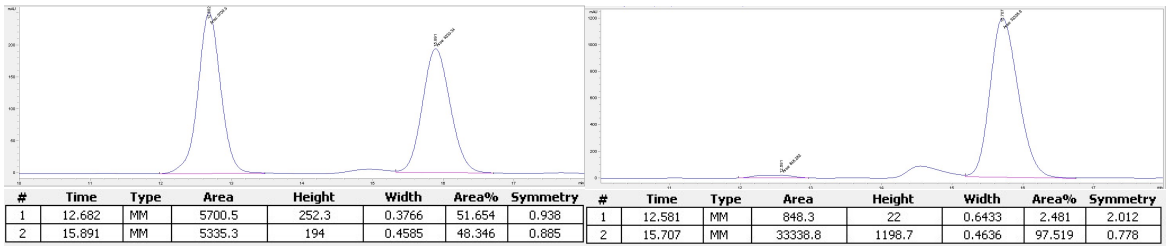
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.9 (C5), 149.2 (C15), 140.6 (C4), 135.6, 133.2, 132.2, 128.1 (C14), 127.7, 112.8 (C13), 76.5 (C7), 68.9 (C11), 50.0 (C6), 44.5 (C9), 40.9 (NME_2), 38.7 (C8), 24.5 (C10), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 6.7 (C8Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 430.2721, $C_{27}H_{37}NO_2$ calculated 430.2717, Δ = 1.04 ppm.

FTIR(Film) 2981, 2361, 2341, 1700, 1615, 1522, 1382, 1097, 1072, 732 =cm^{-1}

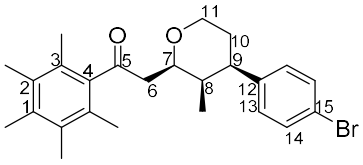
$[\alpha]_D^{25}$ = 43.2 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IG with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.682	MM	5700.5	252.3	0.3766	51.654	0.938
2	15.891	MM	5335.3	194	0.4585	48.346	0.885

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.581	MM	848.3	22	0.6433	2.481	2.012
2	15.707	MM	33338.8	1198.7	0.4636	97.519	0.778



$^3J_{C7\text{-}C8}$ = 2.1 Hz
$^3J_{C8\text{-}C9}$ = 3.8 Hz
$^3J_{C9\text{-}C10eq}$ = 3.8 Hz
$^3J_{C9\text{-}C10ax}$ = 13.1 Hz

2-((2R,3R,4R)-4-(4-bromophenyl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-172**)

Enantioenriched

Aldehyde **4-167** (149 mg, >25:1 d.r., 0.34 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-172** as a waxy solid (91 mg, 0.21 mmol, 61%, >25:1 d.r., 99% e.e.).

Racemic

Aldehyde **4-167** (39 mg, >25:1 d.r., 0.088 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-172** as a waxy solid (28 mg, 0.063 mmol, 70%, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 (d, *J* = 8.5 Hz, 2H, C14), 7.06 (d, *J* = 8.3 Hz, 2H, C13), 4.29 (ddd, *J* = 8.3, 3.7, 2.1 Hz, 1H, C7), 4.14 (ddd, *J* = 11.4, 4.9, 1.4 Hz, 1H, C11H_1), 3.65 (td, *J* = 12.0, 2.5 Hz, 1H, C11H_2), 3.11 (dt, *J* = 13.1, 3.8 Hz, 1H, C9), 2.99 (dd, *J* = 17.7, 8.2 Hz, 1H, C6H_1), 2.63 (dd, *J* = 17.7, 3.7 Hz, 1H, C6H_2), 2.23 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.13 (s, 6H, C3Me), 2.15 – 2.03 (m, 1H, C10H_1) 2.01 – 1.91 (m, 1H, C8), 1.58 – 1.50 (m, 1H, C10H_2), 0.62 (d, *J* = 7.0 Hz, 3H, C8Me). ppm.

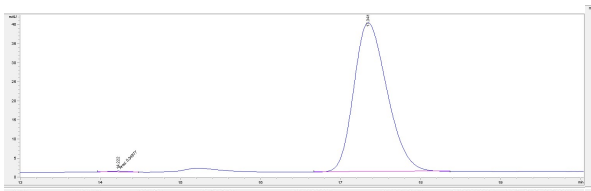
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.6 (C5), 143.0 (C15), 140.6 (C4), 135.7 (C1), 133.3 (C2), 131.5 (C14), 129.2 (C13), 127.7 (C3), 120.0 (C12), 76.4 (C7), 68.6 (C11), 49.7 (C6), 44.9 (C9), 38.3 (C8), 24.2 (C10), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 6.6 (C8Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 443.1580, $C_{25}H_{32}BrO$ calculated 443.1580, Δ = 0.05 ppm.

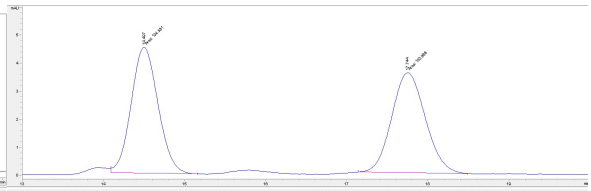
FTIR(Film)= 2856, 1704, 1682, 1098, 1008, 761 cm^{-1}.

$[\alpha]_D^{25}$ = 36.4 (C=1.0, $CHCl_3$)

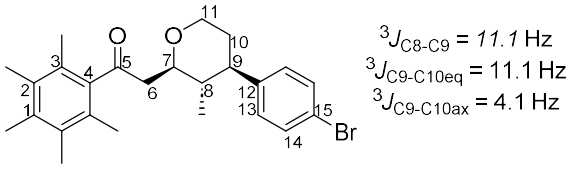
Chiral HPLC: (Chiralpak IG with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 o C, λ = 280 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.222	MM	5.3	2.9E-1	0.3095	0.471	1.05
2	17.341	BB	1129.5	39.1	0.4493	99.529	0.727



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.497	BB	290.7	12.9	0.3506	47.903	0.863
2	17.743	BB	316.1	10.6	0.453	52.097	0.917



2-((2R,3S,4R)-4-(4-bromophenyl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-172**)

Enantioenriched

Aldehyde **4-167** (22 mg, >25:1 d.r., 0.050 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-172** as a waxy solid (15 mg, 0.034 mmol, 68%, >25:1 d.r., 88% e.e.).

Racemic

Aldehyde **4-167** (64 mg, >25:1 d.r., 0.015 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-172** as a waxy solid (33 mg, 0.074 mmol, 51%, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43 (d, *J* = 8.4 Hz, 2H, C14), 7.06 (d, *J* = 8.4 Hz, 2H, C13), 4.04 (ddd, *J* = 11.5, 4.6, 1.6 Hz, 1H, C11H_1), 3.79 (ddd, *J* = 9.8, 6.3, 4.8 Hz, 1H, C7), 3.61 (td, *J* = 11.9, 2.3 Hz, 1H, C11H_2), 2.95 – 2.91 (m, 2H, C6), 2.38 (td, *J* = 11.1, 4.1 Hz, 1H, C9), 2.24 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.15 (s, 6H, C3Me), 1.82 (dtd, *J* = 13.5, 12.2, 4.6 Hz, 1H, C10H_1), 1.66 (m, 2H, C8+C10H_2), 0.94 –0.66 (d, *J* = 6.5 Hz, 3H, C8Me) ppm.

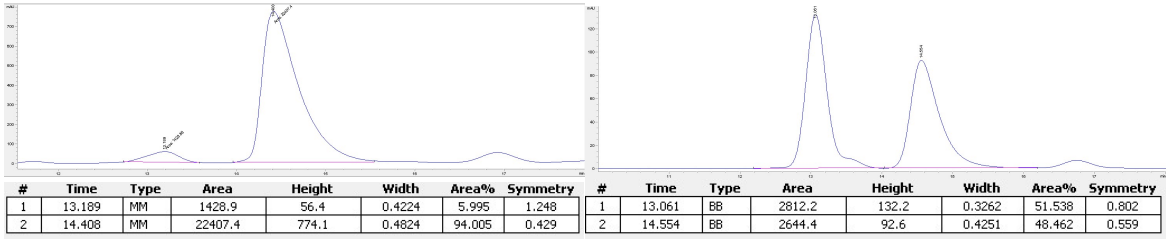
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.9 (C5), 143.8 (C4), 140.6 (C1), 135.6 (C2), 133.2 (C3), 131.8 (C14), 129.5 (C13), 127.8 (C12), 120.2 (C15), 78.8 (C7), 68.0 (C11), 49.6 (C6/C9), 49.4 (C6/C9), 40.1 (C8), 35.0 (C10), 17.3 (C3Me), 16.9 (C1Me), 16.1 (C2Me), 15.2 (C9Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 465.1417, $C_{25}H_{31}BrONa$ calculated 465.1400, Δ = 3.73 ppm.

FTIR(Film)= 2964, 1700, 1653, 1263, 1100 cm^{-1}.

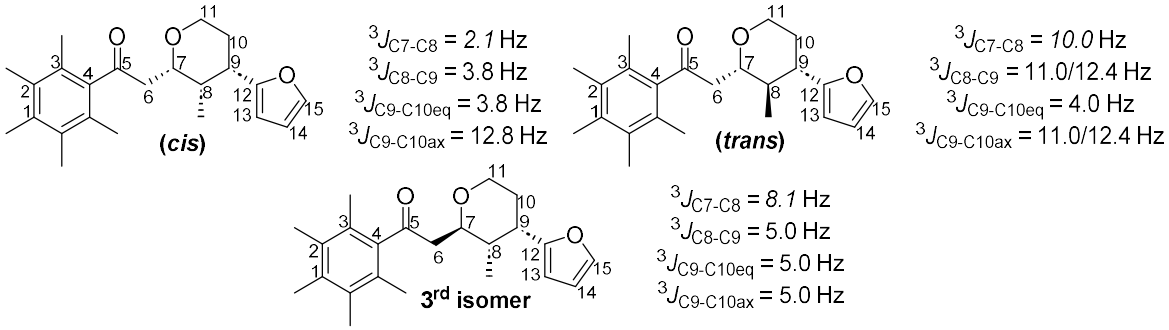
$[\alpha]_D^{25}$ =16.3 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IG with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.189	MM	1428.9	56.4	0.4224	5.995	1.248
2	14.408	MM	22407.4	774.1	0.4824	94.005	0.429

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.061	BB	2812.2	132.2	0.3262	51.538	0.802
2	14.554	BB	2644.4	92.6	0.4251	48.462	0.559



2-((2R,3R,4R)-4-(furan-2-yl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one **4-174-(*cis*)** and 2-((2R,3S,4R)-4-(furan-2-yl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one **4-174-(*trans*)** *and* 2-((2S,3R,4R)-4-(furan-2-yl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one **4-174**

Enantioenriched

Aldehyde **4-169** (350 mg, 4.8:1, d.r. 1.0 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-171** as a waxy solid (230 mg, 0.64 mmol, 64%, 9:2:1 d.r.).

Further purification by FCC gave the THP **4-171** (*cis*:*trans*) (190 mg, 0.53 mmol 5:1 d.r., 95% e.e., (81% e.e.)) and the 3rd diastereomer **4-171** (20 mg, 0.056 mmol, 6%, >1:0:10 d.r.).

Racemic

Aldehyde **4-169** (127 mg, xx:1 d.r. 0.36 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 90:10) gave the product **4-171** as a waxy solid (67 mg, 0.19 mmol, 53%, 4:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.33 (d, *J* = 1.5 Hz, 1H, C15M), 7.31 (dd, *J* = 1.8, 0.8 Hz, 0.2H, C15m), 6.32 – 6.27 (m, 1.2H, C14M+C14m), 6.03 (dd, *J* = 3.2, 0.8 Hz, 0.2H, C13m), 5.99 (dt, *J* = 3.2, 1.0 Hz, 1H, C13M), 4.23 (ddd, *J* = 8.5, 3.4, 2.1 Hz, 1H, C7M), 4.08 (ddd, *J* = 11.6, 5.0, 1.4 Hz, 1H, C11M), 4.03 (ddd, *J* = 11.5, 4.7, 1.6 Hz, 0.2H, C11m), 3.75 (ddd, *J* = 10.0, 6.6, 4.5 Hz, 0.2H, C7m), 3.65 (ddd, *J* = 12.6, 11.5, 2.6 Hz, 1H, C11M), 3.57 (ddd, *J* = 12.5, 11.6, 2.3 Hz, 0.2H, C11m), 3.18 (dt, *J* = 12.85, 3.8 Hz, 1H, C9M), 2.99 (dd, *J* = 17.7, 8.5 Hz, 1H, $C6H_1M$), 2.94 – 2.89 (m, 0.4H, $C6H_1m$+$C6H_2m$), 2.63 (dd, *J* = 17.7, 3.4 Hz, 1H, $C6H_2M$), 2.59 – 2.53 (m, 0.2H, C9m), 2.24 (s, 3.6H, C1MeM+C1Mem), 2.19 (s, 7.2H, C2MeM+C2Mem), 2.14 (s, 1.2H, C3Mem), 2.13 (s, 6H, C3MeM), 2.21-2.09 (m, C8MeM, C8Mem), 1.96 (qd, *J* = 13.0, 5.1 Hz, 2H, $C10H_1M$), 1.79 – 1.71 (m, 0.2H, $C10H_2m$), 1.67 – 1.58 (m, 1H, $C10H_2M$), 0.77 (d, *J* = 6.5 Hz, 0.6H, C8Mem), 0.69 (d, *J* = 7.0 Hz, 3H, C8MeM) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.9 (C5m), 209.5 (C5M), 158.0 (C12m), 157.8 (C12M), 141.1 (C15M), 141.0 (C15m), 140.7 (C4m), 140.6 (C4M), 135.7 (C1M), 135.6 (C1m), 133.3 (C2M), 133.2 (C2m), 127.8 (C3m), 127.7 (C3M), 110.1 (C14m), 110.0 (C14M), 105.1 (C13m), 104.9 (C13M), 78.7 (C7m), 75.5 (C7M), 68.3 (C11M), 67.7 (C11m), 49.7 (C6M), 49.6 (C6m), 42.6 (C9m), 39.8 (C9M), 39.1 (C8m), 35.6 (C8M), 32.5 (C10m), 23.5 (C10M), 17.2 (C3MeM+C3Mem), 16.8 (C1MeM+C1Mem), 16.1 (C2MeM+C2Mem), 15.5 (C8Mem), 7.4 (C8MeM) ppm.

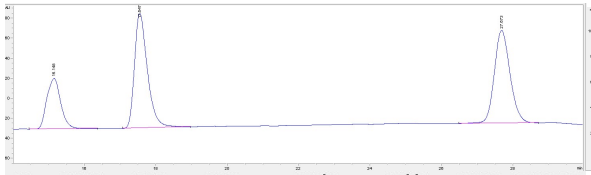
HRMS: ESI$^+$ found $[M+H]^+$ = 355.2277, $C_{23}H_{31}O_3$ calculated 355.2277, Δ = 2.60 ppm.

FTIR(Film)= 2981, 2361, 1700, 1615, 1522, 1097, 732 cm^{-1}.

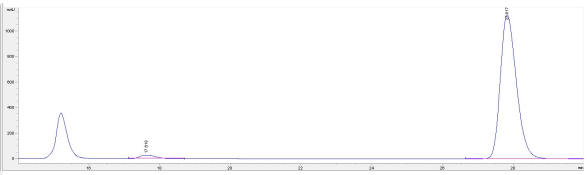
$[\alpha]_D^{25}$ = 35.6 (C=0.5, $CHCl_3$)

The two diastereomers required different HPLC conditions in order tor separate the peaks.

Chiral HPLC: (Chiralpak IA with guard then OD with guard, 5 % IPA, 95 % hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 µL injection).

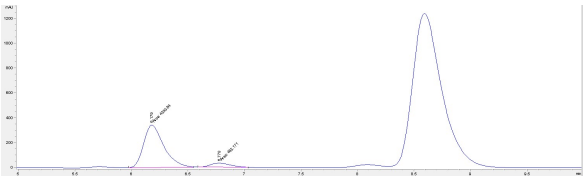


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	15.148	BB	1353	50.4	0.4314	19.153	1.009
2	17.547	BB	2878.8	114.5	0.3813	40.754	0.642
3	27.673	BB	2832.1	92.6	0.4729	40.093	0.839

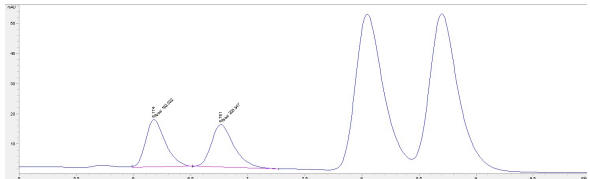


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	17.618	BB	831.7	27	0.4854	2.277	0.659
2	27.817	BB	35686	1127.1	0.4894	97.723	0.711

Chiral HPLC: (Chiralpak OD with guard, 5 % IPA, 95 % hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.179	MM	4355.6	347	0.2092	90.407	0.666
2	6.778	MM	462.2	34.8	0.2211	9.593	0.668



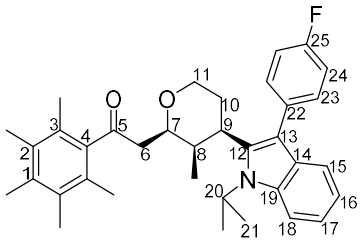
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.174	MM	192	15.9	0.2017	48.914	0.715
2	6.761	MM	200.5	14.3	0.2345	51.086	0.688

3rd isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 (d, *J* = 1.6 Hz, 1H, C15), 6.32 (dd, *J* = 3.2, 1.9 Hz, 1H, C14), 6.11 (d, *J* = 3.2 Hz, 1H, C13), 4.29 (td, *J* = 8.1, 3.8 Hz, 1H, C7), 3.97 (ddd, *J* = 11.7, 10.0, 3.1 Hz, 1H, C11), 3.80 (dt, *J* = 11.8, 4.5 Hz, 1H, C11), 3.17 (q, *J* = 5.0 Hz, 1H, C9), 2.96 (dd, *J* = 17.3, 8.1 Hz, 1H, $C6H_1$), 2.89 (dd, *J* = 17.2, 3.9 Hz, 1H, $C6H_2$), 2.23 (s, 3H, C1Me), 2.19 (s, 6H), 2.15 (s, 6H), 2.06 – 1.91 (m, 2H, C8+$C10H_1$), 1.82 (dtd, *J* = 13.2, 4.5, 3.1 Hz, 1H, $C10H_2$), 0.79 (d, *J* = 7.0 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 210.0 (C5), 157.1 (C12), 141.3 (C15), 140.8 (C4), 135.6 (C1), 133.2 (C2), 127.8 (C3), 110.0 (C14), 106.9 (C13), 74.1 (C7), 63.5 (C11), 48.8 (C6), 36.9 (C9), 36.5 (C8), 29.4 (C10), 17.3 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 15.3 (C8Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 337.2154, $C_{23}H_{29}O_2$ calculated 337.2162, Δ = 2.40 ppm.



$^3J_{C7\text{-}C8}$ = 5.0 Hz
$^3J_{C8\text{-}C9}$ = 3.2 Hz
$^3J_{C9\text{-}C10eq}$ = 3.2 Hz
$^3J_{C9\text{-}C10ax}$ = 12.9Hz

2-((2R,3R,4R)-4-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-175**)

Enantioenriched

Aldehyde **4-170** (153 mg, 0.400 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-175** as a waxy solid (134 mg, 0.247 mmol, 87%, >99% e.e.).

Racemic

Aldehyde **4-170** (70 mg, 0.13 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-175** as a waxy solid (39 mg, 0.072 mmol, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.50 (d, *J* = 8.3 Hz, 1H, C18), 7.25 – 7.16 (m, 2H. C21), 7.07 (td, *J* = 7.4, 1.3 Hz, 1H, C17), 7.03 – 6.86 (m, 4H,C15+C16+C22), 4.69 (p, *J* = 7.0 Hz, 1H, C24), 4.23 (td, *J* = 5.0, 1.8 Hz, 1H, C7), 3.80 (dd, *J* = 11.5, 4.4 Hz, 1H, C11H_1), 3.44 (t, *J* = 11.8 Hz, 1H, C11H_2), 3.35 (dt, *J* = 12.9, 3.2 Hz, 1H, C9), 2.91 (dd, *J* = 18.0, 7.7 Hz, 1H, C6H_1), 2.53 (dt, *J* = 17.8, 2.7 Hz, 1H, C6H_2), 2.15 (s, 3H, C1Me), 2.10 (s, 6H, C2Me), 2.03 (s, 6H, C3Me), 1.95 (d, *J* = 15.6 Hz, 1H, C8), 1.68 (d, *J* = 6.9 Hz, 3H, C25), 1.63 (d, *J* = 6.9 Hz, 4H, C10H_1+C25), 1.25 (d, *J* = 13.7 Hz, 1H, C10H_2), 0.73 (d, *J* = 6.9 Hz, 3H, C8Me).ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 208.7 (C5), 160.9 (d, *J* = 245.0 Hz, C23), 139.4, 134.7, 134.6, 132.4, 132.2, 131.4 (d, *J* = 3.5 Hz, C20), 129.8, 126.4, 120.0, 118.3, 117.8, 113.7, 113.5 (d, *J* = 21.1 Hz, C22), 110.7, 74.7 (C7), 68.2 (C11), 48.3 (C6), 45.7 (C24), 39.9 (C9), 35.9 (C8), 25.3 (C10), 20.7 (C25), 20.2 (C25), 16.0 (C3Me), 15.7 (C1Me), 14.9 (C2Me), 6.9 (C8Me) ppm.

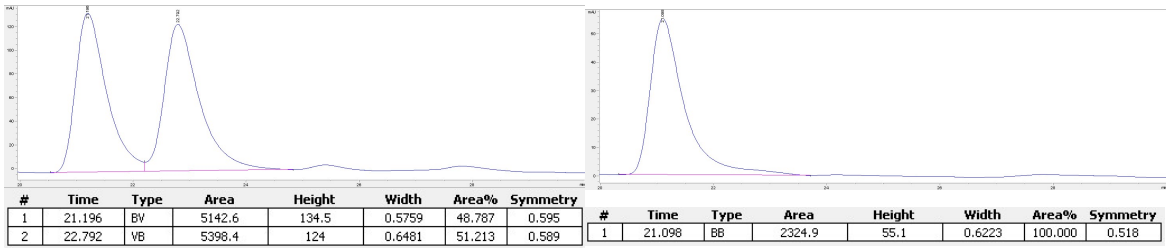
^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -116.4 ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 540.3287, $C_{36}H_{43}FNO_2$ calculated 540.3272, Δ = 1.46 ppm.

FTIR(Film)= 2980.2, 1700, 1501, 1461, 1223, 1099, 743 cm^{-1}.

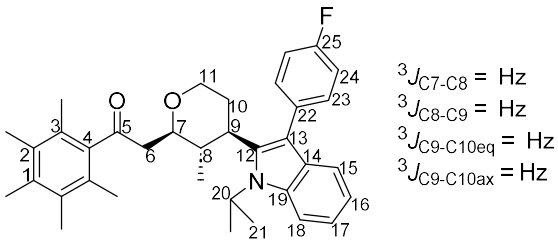
$[\alpha]_D^{25}$ = 43.3 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IC with guard then ID with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.196	BV	5142.6	134.5	0.5759	48.787	0.595
2	22.792	VB	5398.4	124	0.6481	51.213	0.589

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	21.098	BB	2324.9	55.1	0.6223	100.000	0.518



2-((2R,3S,4R)-4-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)-3-methyltetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-175**)

Enantioenriched

Aldehyde **4-170** (91 mg, 0.17 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-175** as a waxy solid (60 mg, 0.11 mmol, 64%, 3.4:1 d.r. 97% e.e.).

Racemic

Aldehyde **4-170** (70 mg, 0.13 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 95:5) gave the product **4-175** as a waxy solid (30 mg, 0.055 mmol, 43%, 4:1 d.r.).

Major isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.57 (d, *J* = 8.3 Hz, 1H, C18), 7.45 – 7.35 (m, 1H, C15), 7.29 (dd, *J* = 8.2, 5.5 Hz, 2H, C21), 7.21 – 7.12 (m, 3H, C17+C22), 7.11 – 6.98 (m, 1H, C16), 4.97 (p, *J* = 7.0 Hz, 1H, C24), 4.10 (dd, *J* = 11.8, 4.3 Hz, 1H, $C11H_1$), 3.67 – 3.48 (m, 2H, C7+$C11H_2$), 3.06 (ddd, *J* = 12.9, 11.5, 4.1 Hz, 1H, C9), 2.95 – 2.88 (m, 2H, C6), 2.37 – 2.25 (m, 1H, $C10H_1$), 2.23 (s, 3H, C1Me), 2.18 (s, 6H, C2Me), 2.12 (s, 6H, C3Me), 2.07 – 1.95 (m, 1H, $C8H_1$), 1.87 – 1.78 (m, 1H, $C10H_2$), 1.71 (d, *J* = 6.9 Hz, 3H, C25), 1.67 (d, *J* = 7.0 Hz, 3H, C25), 0.63 (d, *J* = 6.6 Hz, 3H, C8Me). ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.6, 161.8 (d, *J* = 245.2 Hz, C23),140.4, 136.9, 135.7, 134.4, 133.3, 132.1 (d, *J* = 7.9 Hz, C21), 131.8, 128.9, 127.7, 121.1, 119.5, 119.4, 115.7, 115.6 (d, *J* = 21.2 Hz, C22),112.4, 79.7, 68.2, 49.5, 48.5, 41.1, 38.3, 31.9, 21.1, 21.0, 17.3, 17.2, 16.9, 16.1, 15.5.ppm

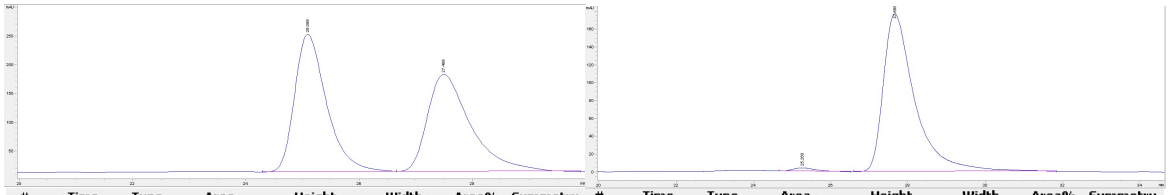
^{19}F NMR (377 MHz, $CDCl_3$) δ_F: 115.9 (m) -116.4 (M) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 562.3114, $C_{36}H_{42}FNO_2Na$ calculated 562.3092, Δ = 3.94ppm.

FTIR(Film)= 2925, 2361 1653, 1460, 1222, 744 cm^{-1}.

$[\alpha]_D^{25}$ = 4.7 (C=0.5, $CHCl_3$)

Chiral HPLC: (Chiralpak IC with guard then ID with guard, 5% IPA, 95% hexane, 1.0 mL/min, 25 o C, λ = 210 nm, 10 μL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.088	BV	9374.2	238.7	0.5963	51.178	0.655
2	27.489	VB	8942.6	168.7	0.7945	48.822	0.56

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.26	BB	148.8	3.7	0.5509	1.460	0.652
2	27.658	BB	10044.6	176.3	0.8407	98.540	0.518

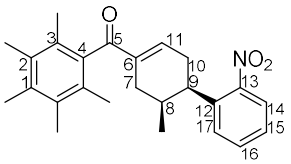
Minor Isomer

Minor isomer could not be fully characterised diagnostic peaks are reported below

^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 3.98 (ddd, *J* = 11.5, 4.5, 1.5 Hz, 1H, C11H_1), 3.73 (ddd, *J* = 10.7, 8.9, 2.1 Hz, 1H, C7), 0.69 (d, *J* = 6.5 Hz, 3H, C8Me) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ_C: 209.8, 162.9, 161.3, 140.5, 135.7, 119.2, 119.0, 115.3, 115.1, 79.3 (C7), 68.0 (C11), 46.5, 32.1, 30.5, 29.5, 22.8, 14.3 (C8Me) ppm.

6.5.13. Synthesis of 1,4,5-Cyclohexenes.



((1R,2S)-2-methyl-2'-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-177**)

THP **4-171** (28 mg, >25:1 d.r. 0.068 mmol, 1 eq) and Al(O-2,6-$Me_2C_6H_3$)$_3$ (1.6 mL, 0.043 M, 0.068 mmol, 1 eq) was subjected to General Procedure 4F. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-177** as a waxy solid (15 mg, 0.038 mmol, 55%, >25:1 d.r.).

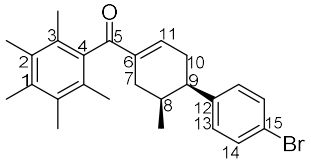
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.80 – 7.72 (m, 1H, C14), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H, C16), 7.41 – 7.34 (m, 2H, C15+C17), 6.57 (td, *J* = 3.5, 1.8 Hz, 1H, C11), 3.67 (ddd, *J* = 8.9, 5.6, 3.1 Hz, 1H, C9), 2.77 – 2.57 (m, 2H, C7H_1+C10H_2), 2.46 – 2.30 (m, 3H, C7H_2+C8+C10H_2), 2.25 (s, 3H, C1Me), 2.20 (s, 6H, C2Me), 2.06 (s, 6H, C3Me), 0.80 (d, *J* = 6.8 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 150.9 (C13), 143.1 (C11), 139.6 (C6), 138.1 (C4), 137.2 (C12), 135.3 (C1), 132.9 (C2_1), 132.8 (C2_2), 132.1 (C16), 129.4 (C3_1), 129.0 (C3_2), 128.7, 127.3, 124.7 (C14), 36.4 (C9), 31.1 (C8), 30.0 (C7), 28.2 (C10), 17.7 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 14.3 (C8Me) ppm.

HRMS: ESI^+ found $[M+Na]^+$ = 414.2040, $C_{25}H_{29}NO_3Na$ calculated 414.2040, Δ = 0.0 ppm.

FTIR(Film)= 2919, 2360, 2341, 1653, 1526, 738, 669, 656 cm^{-1}.

$[\alpha]_D^{25}$ = 35.0 (C=0.5, $CHCl_3$)



((1R,2S)-4'-bromo-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-178**)

THP **4-172** (25 mg, 0.056 mmol, 1 eq) was subjected to General Procedure 4F. After ligand acylation, Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-178** as a waxy solid (17 mg, 0.040 mmol, 71%, 10:1 d.r.).[a]

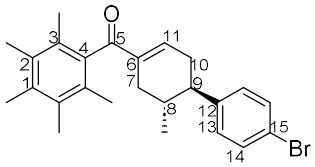
^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.41 (d, *J* = 8.4 Hz, 2H, C13), 7.04 (d, *J* = 8.5 Hz, 2H, C14), 6.60 (ddd, *J* = 5.5, 3.7, 1.5 Hz, 1H, C11), 3.01 (td, *J* = 6.5, 3.1 Hz, 1H, C9), 2.71 – 2.60 (m, 1H, $C7H_1$), 2.57 – 2.47 (m, 2H, C10), 2.25 (s, 3H, C1Me), 2.20 (d, *J* = 2.5 Hz, 6H, C2Me), 2.28-2.15 (m, 2H,$C7H_2$+C8) 2.06 (s, 6H, C3Me), 0.80 (d, *J* = 6.4 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.4 (C5), 143.9 (C11), 142.0, 140.0, 138.1 135.3, 132.8, 131.3 (C13), 129.8 (C14), 129.2 (C3), 129.1 (C3), 120.2, 41.9 (C9), 32.0 (C8), 29.3 (C10), 29.0 (C7), 17.7 (C3Me), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 15.6 (C8Me) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 447.1298, $C_{25}H_{29}BrO_2Na$ calculated 447.1294, Δ = 0.89 ppm.

FTIR(Film)= 2981, 2890, 2360, 1654, 1382, 955 cm^{-1}.

$[\alpha]_D^{25}$ = 37.4 (C=0.5, $CHCl_3$)



((1RS,2R)-4'-bromo-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-178**)

THP **4-172** (20 mg, 0.045 mmol, >1:25 d.r., 1 eq) was subjected to General Procedure 4G. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-178** as a waxy solid (19 mg, 0.045 mmol, 99%, 1:4.6 d.r.).

^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.36 (d, *J* = 8.4 Hz, 2H, C13), 6.98 (d, *J* = 8.4 Hz, 2H, C14), 6.44 (dt, *J* = 5.0, 1.7 Hz, 1H, C11), 2.79 (dd, *J* = 17.6, 4.1 Hz, 1H, $C7H_1$), 2.80 – 2.30 (m, 2H, C9+$C10H_1$), 2.31 – 2.18 (m, 1H, $C10H_2$), 2.17 (s, 3H, C1Me), 2.12 (s, 6H, C2Me), 2.05-1.95 (m, 1H, $C7H_2$), 1.98 (s, 6H, C3Me), 1.92 – 1.79 (m, 1H, C8), 0.75 (d, *J* = 6.4 Hz, 1H, C8Me) ppm.

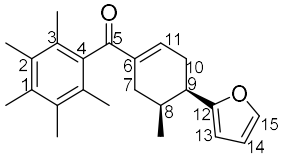
[a] d.r. determined based on the C10-position in the purified product due to the high ratio and slight overlap of the C11 position.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 144.1 (C11), 140.5, 138.0, 135.3, 132.8, 131.8 (C14), 131.3, 129.8, 129.4 (C13), 120.1 (C15), 46.7 (C9), 35.6 (C10), 33.4 (C8), 31.7 (C7), 20.1 (C8Me), 17.7 (C2Me), 16.8 (C1Me), 16.1 (C3Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 425.1473, $C_{25}H_{30}BrO$ calculated 425.1475, Δ = 0.4 ppm.

FTIR(Film)= 1700, 1558, 1506, 1459, 1218, 760 cm^{-1}.

$[\alpha]_D^{25}$ = -19.3 (C=0.5, $CHCl_3$)



((4R,5S)-4-(furan-2-yl)-5-methylcyclohex-1-en-1-yl)(pentamethylphenyl)methanone (**4-180**)

THP **4-174** (35 mg, 0.1 mmol, 1 eq) was subjected to General Procedure 4F. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-180** as a waxy solid (28 mg, 0.083 mmol, 83%, 5:1 d.r.).

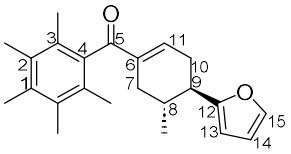
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.32 (d, *J* = 1.0 Hz, 1H, C15), 6.56 – 6.48 (m, 1H, C11), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H, C14), 5.97 (d, *J* = 3.1 Hz, 1H, C13), 3.10 (ddd, *J* = 8.4, 5.9, 2.9 Hz, 1H, C9), 2.68 – 2.53 (m, 1H, C7H1), 2.54 – 2.43 (m, 2H, $C10H_1$+$C10H_2$), 2.42 – 2.27 (m, 2H, $C7H_2$+C8), 2.25 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.05 (s, 3H, $C3Me_1$), 2.03 (s, 3H, $C3Me_2$), 0.87 (d, *J* = 6.7 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.6 (C5), 157.4 (C12), 143.2 (C11), 141.1 (C15), 139.6 (C4), 138.2 (C6), 135.2 (C1), 132.8 (C2), 132.8 (C2), 129.3 (C3), 129.2 (C3), 110.1 (C14), 105.3 (C13), 36.7 (C9), 30.3 (C8), 29.0 (C7), 28.3 (C10), 17.6 (C3Me), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me), 15.9 (C8Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 337.2174, $C_{23}H_{29}O_2$ calculated 337.2162, Δ = 3.53 ppm.

FTIR(Film)= 2957, 2920, 2360, 2341, 1654, 1190, 913, 738 cm^{-1}.

$[\alpha]_D^{25}$ = 6.5 (C=0.5, $CHCl_3$)



((4R,5R)-4-(furan-2-yl)-5-methylcyclohex-1-en-1-yl)(pentamethylphenyl)methanone (**4-180**)

THP **4-174** (35 mg, 0.1 mmol, 1 eq) was subjected to General Procedure 4G. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-180** as a waxy solid (33 mg, 0.098 mmol, 98%, 1:4 d.r.).

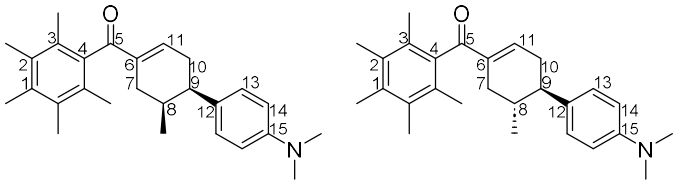
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.25 (dd, *J* = 1.8, 0.8 Hz, 1H, C15), 6.46 – 6.40 (m, 1H, C11), 6.21 (dd, *J* = 3.2, 1.9 Hz, 1H, C14), 5.95 (dd, *J* = 3.2, 0.8 Hz, 1H, C13), 2.76 – 2.65 (m, 1H, $C7H_1$), 2.56 (td, *J* = 9.4, 5.9 Hz, 1H, C9), 2.46 – 2.34 (m, 2H, $C10H_1C10H_2$), 2.17 (s, 3H, C1Me), 2.11 (s, 6H, C2Me), 1.95 (s, 6H, C3Me), 2.04-1.89, (m,2H, $C7H_2$+C8), 0.84 (d, *J* = 6.3 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 157.8 (C12), 143.8 (C11), 141.2 (C15), 140.1, 138.1, 135.2, 132.8, 132.7, 129.3, 129.2, 110.0 (C14), 105.4 (C13), 39.9 (C9), 32.5 (C8), 31.9 (C10), 31.0 (C7), 19.8 (C8Me), 17.6 (C3Me), 16.8 (C1Me), 16.1 (C2Me) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 337.2181, $C_{23}H_{29}O_2$ calculated 337.2162, Δ = 5 ppm.

FTIR(Film)= 2981, 2922, 2360, 1654, 1380, 1194, 1163, 1148, 736 cm^{-1}.

$[\alpha]_D^{25}$ = -25.9 (C=0.5, $CHCl_3$)



((1S)-4'-(dimethylamino)-2-methyl-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (cis:trans) (**4-179**)

Retentive

THP **4-173(*cis*)** (36.3 mg, 0.088 mmol, >25:1 d.r. 1 eq) was subjected to General Procedure 4F. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-179** as a waxy solid (20 mg, 0.051 mmol, 58%, 3.5:1 d.r.).

Inversion

THP **4-173(*cis*)** (15 mg, 0.037 mmol, >25:1 d.r. 1 eq) was subjected to General Procedure 4F. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-179** as a waxy solid (6 mg, 0.016 mmol, 44%, 1.3:1 d.r.).

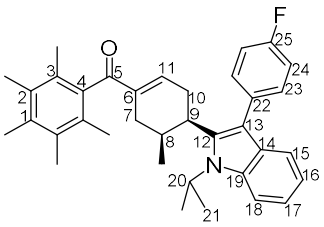
1H NMR (600 MHz, CDCl3) δH: 7.05 (d, *J* = 8.7 Hz, 2.5H, C13M+C13m), 6.71 (m, 2.5H, C14M+C14m), 6.62 (tt, *J* = 3.8, 1.6 Hz, 0.25H, C11m), 6.53 (ddd, *J* = 4.8, 2.4, 1.4 Hz, 1H, C11M), 2.93 (s, 7.5H, NMeM+m), 2.89 – 2.83 (m, 1H, $C7H_1M$), 2.66 – 2.61 (m, 0.25H, $C7H_1m$), 2.54 – 2.49 (m, 0.5H, C10m), 2.48 – 2.41 (m, 1H, $C10H_1M$), 2.41 – 2.34 (m, 2H, +C9M+$C10H_2M$), 2.34 – 2.29 (m, 0H), 2.26 (s, 0.75H, C1Mem), 2.24 (s, 3H, C1MeM), 2.21 (s, 1.5H, C2Mem), 2.19 (s, 3H, C2MeM), 2.08 (s, 0.75H, $C3Me_1m$), 2.07 (s, 0.75H, $C3Me_2m$), 2.07 (s, 3H, $C3Me_1M$), 2.06 (s, 3H, $C3Me_2M$), 0.84 (d, *J* = 6.5 Hz, 3H, C8MeM), 0.82 (d, *J* = 6.9 Hz, 0.75H, C8Mem) ppm.

13C NMR (151 MHz, CDCl3) δC: 203.6 (C5m), 203.4 (C5M), 150.5 (C15m), 149.4 (C15M), 145.1 (C11M), 144.9 (C11m), 140.4 (C6M), 139.9 (C6m), 138.4 (C4m), 138.3 (C4M), 135.1 (C1M+m), 133.1 (C12m), 133.0 (br,C12M), 132.8 ($C2Me_1m$), 132.7 ($C2Me_1M$), 132.7 ($C2Me_2m$), 132.7 ($C2Me_2M$), 129.3 ($C3Me_1M$), 129.3 ($C3Me_1m$), 129.2 ($C3Me_2M$), 129.2 ($C3Me_2m$), 128.7 (C13m), 128.3 (C13M), 113.0 (C14M), 112.6 (C14m), 46.2 (C9M), 41.4 (NMem), 40.9 (NMeM), 36.0 (C10M), 33.7 (C8M), 32.2 (m), 31.9 (C7M), 29.8 (m), 29.8 (m), 29.2 (C7m), 20.2 (C8MeM), 17.6 (C3MeM+m), 16.8 (C1MeM+m), 16.1 (C2MeM+m), 15.6 (C8Mem) ppm.

HRMS: ESI+ found [M+H]+ = 412.2624, C27H35NONa calculated 412.2611, Δ = 3.18 ppm.

FTIR(Film)= 2981, 2889, 1652, 1382, 1153, 1072, 953, 736 cm.$^{-1}$

$[\alpha]_D^{25}$ = 43.2 (C=0.5, $CHCl_3$)



((4S,5R)-4-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)-5-methylcyclohex-1-en-1-yl)(pentamethylphenyl)methanone (**4-181**)

THP **4-175** (25 mg, 0.046 mmol, 1 eq) was subjected to General Procedure 4F. Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-181** as a waxy solid (23 mg, 0.044 mmol, 96%, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.58 (d, *J* = 8.3 Hz, 1H, C18), 7.31-7.21 (m, 2H, C21), 7.16 (ddd, *J* = 8.3, 6.6, 1.7 Hz, 1H, C17), 7.11 – 6.95 (m, 4H, C15+C16+C22), 6.36 – 6.30 (m, 1H, C11), 4.63 (p, *J* = 7.0 Hz, 1H, C24), 3.30 (dt, *J* = 11.9, 4.1 Hz, 1H, C9), 2.76 – 2.63 (m, 1H, $C7H_1$), 2.56 (d, *J* = 17.7 Hz, 1H, $C7H_2$), 2.38 (s, 1H, C8), 2.22 (s, 3H, C1Me), 2.17 (s, 6H, C2Me), 2.04 (s, 3H, C3Me), 1.95 (s, 3H, C3Me), 1.82 (d, *J* = 6.9 Hz, 3H, C25), 1.67 (d, *J* = 6.9 Hz, 3H, C25), 0.80 (d, *J* = 6.9 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.7 (C5), 161.9 (d, *J* = 245.2 Hz, C25), 144.0 (C11), 137.9, 137.5, 135.8, 135.2, 133.6, 133.3 (d, *J* = 7.8 Hz, C21), 132.7, 132.6, 130.8, 129.0, 129.0, 121.1 (C17), 119.3 (C15/C16), 118.9 (C15/C16), 114.7 (d, *J* = 21.1 Hz, C22), 114.3, 111.7 (C18), 46.8 (C24), 37.0 (C9), 31.1 (C8), 30.5 (C7), 27.3 (C10), 21.8 (C25), 21.4 (C25), 17.6 (C3Me), 17.5 (C3Me), 16.7 (C1Me), 16.0 (C2Me), 13.4 (C8Me) ppm.

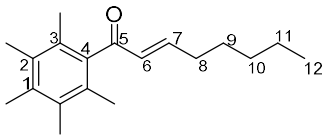
^{19}F NMR (565 MHz, $CDCl_3$) δ_F: -116.1 ppm

HRMS: ESI^+ found $[M+H]^+$ = 544.3167, $C_{36}H_{41}NOF$ calculated 544.2991, Δ = 0.89s ppm.

FTIR(Film)= 2925, 2361, 2341, 1653, 1460, 1222, 741, 668, 640 cm^{-1}.

$[\alpha]_D^{25}$ = -10.2 (C=0.3, $CHCl_3$)

6.5.14. *n*-Butyl Substrates.



(E)-1-(pentamethylphenyl)oct-2-en-1-one (**4-186**)

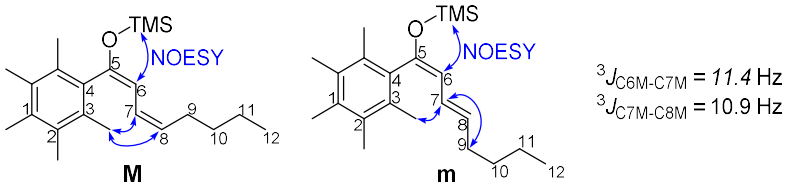
To a solution of Ph* methyl ketone (**4-116**) (1.52 g, 8.00 mmol, 1 eq) in THF (50 mL) was added LDA (4.2 mL, 8.4 mmol, 1.05 eq) dropwise at -78 °C and then the reaction was warmed to 0 °C. After 30 mins, the reaction was cooled to -78 °C and hexanal (1.0 mL, 8.4 mmol, 1.05 eq) was added dropwise and the reaction was warmed to rt. Upon consumption of the ketone by TLC, the reaction was quenched with aq. phosphate buffer (10 mL, pH=7), and THF was removed under reduced pressure. The reaction was diluted with Et_2O (30 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL), the combined organic extracts were dried with Na_2SO_4 and concentrated in *vacuo* to give the crude product. The crude was purified by FCC (Pentane:Et_2O 97:3) to give the enone **4-186** (922 mg, 3.39 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.48 (dt, J = 15.8, 6.8 Hz, 1H, C7), 6.31 (dt, J = 15.9, 1.4 Hz, 1H, C6), 2.25 (s, 3H, C1Me), 2.19 (s, 6H, C2Me), 2.26-2.07(m, 2H, C8), 2.06 (s, 6H, C3Me), 1.43 (p, J = 7.3 Hz, 2H, C9), 1.38 – 1.20 (m, 7H, C9-11), 0.88 (t, J = 7.0 Hz, 3H, C12) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.3 (C5), 153.0 (C7), 138.2 (C4), 135.3 (C1), 133.1 (C6), 132.8 (C2), 128.9 (C3), 32.6 (C8), 31.5 (C10/C11), 27.7 (C9), 22.5 (C10/C11), 17.5 (C2Me), 16.8 (C1Me), 16.1 (C3Me),14.1 (C12) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 273.2207, $C_{19}H_{29}O$ calculated 273.2213, Δ = 2.18 ppm.

FTIR(Film)= 2889, 1250,1654 1382, 1252, 1152, 954 cm^{-1}.



trimethyl(((1E,3Z)-1-(pentamethylphenyl)hepta-1,3-dien-1-yl)oxy)silane d.r. 2.5:1 (**4-187**)

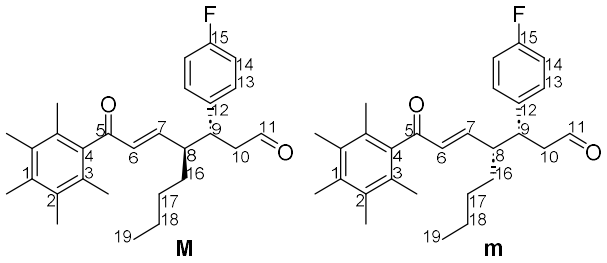
To a solution of enone **4-186** (855 mg, 3.14 mmol, 1 eq) in THF (100 mL) was added NaHMDS (3.8 mL, 1 M in THF, 3.8 mmol, 1.2 eq) over 10 mins at -78 °C. After 1 h TMSCl (520 µL, 4.1 mmol, 1.3 eq) was added over 30 mins, and the reaction was stirred for a further 1 h. The reaction was quenched with aq. NH_4Cl (10 mL, sat) and warmed to rt. The mixture was diluted with Et_2O (150 mL) and brine (100 mL), the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were partially concentrated by reduced pressure until water became immiscible, the mixture was diluted with Et_2O (50 mL) and the aqueous layer was separated. The organic extract was dried with Na_2SO_4. The crude was concentrated under reduced pressure and purified by FCC (Pentane) to give the product as a pale-yellow solid **4-187** (1.09 g, 2.92 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.97 (dd, *J* = 11.4, 1.3 Hz, 1H, C6M), 5.74 – 5.67 (m, 0.4H, C6m), 5.48 – 5.42 (m, 0.8H, C7m+C8m), 5.39 (tt, *J* = 11.2, 1.6 Hz, 1H, C7M), 5.04 (dt, *J* = 10.9, 7.5 Hz, 1H, C8M), 2.26 (s, 1.2H, C1Mem), 2.25 (s, 3H, C1MeM), 2.23 (s, 2.4H, C2Mem), 2.22 (s, 6H, C2MeM), 2.20 (s, 8.4H, C3MeM+C3Mem), 2.18 – 2.08 (m, 2H, C9M), 1.93 (qd, *J* = 5.8, 2.9 Hz, 1H, C9m), 1.41 – 1.23 (m, 5.6H, C10M+ C11M+ C10m +C11m), 0.93 (t, *J* = 7 Hz, 3H, C12M), 0.85 (t, *J*= 6.9 Hz, 1.2H, C12m), 0.19 (s, 3.6H, TMSm), 0.17 (s, 9H, TMSM) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 153.4 (C5M), 151.6 (C5m), 134.9 (C4M), 134.8 (C4m), 134.5 (C1M), 132.5 (C1m), 132.4 (C2/C3M), 132.2 (C2/C3m), 131.9 (C2/C3m), 131.8 (C2/C3M), 129.4 (C8m), 126.9 (C7m), 126.9 (C8M), 125.2 (C7M), 111.2 (C6m), 106.7 (C6M), 32.6 (C9m), 32.3 (C10/C11m), 32.2 (C10/C11M), 27.6 (C9M), 22.5 (C10/C11M), 22.3 (C10/C11m), 17.7 (C3Mem), 17.7 (C3MeM), 17.0 (C1Mem), 16.9 (C1MeM), 16.7 (C2Mem), 16.6 (C2MeM), 14.2 (C12M), 14.1 (C12m), 0.7 (TMSm), 0.7 (TMSM) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 245.2612, $C_{22}H_{37}OSi$ calculated 345.2608, Δ = 1.1 ppm.

FTIR(Film)= 2959, 2360, 2341, 1252, 1178, 871, 844cm^{-1}.



(3R)-3-(4-fluorophenyl)-4-((E)-3-oxo-3-(pentamethylphenyl)prop-1-en-1-yl)octanal (**4-188**) (*anti:syn*)

Enantioenriched

Silyl enol ether **4-187** (688 mg, 2.00 mmol, 1 eq) and cinnamaldehyde (155 mg, 1.00 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-188** as a waxy oil (241 mg, 0.571 mmol, 3.6:1 d.r., 94% e.e., (90% e.e.)). Enantioselectivity determined by HPLC analysis of the THP.

Racemic

Silyl enol ether **4-187** (160 mg, 0.465 mmol, 1 eq) and cinnamaldehyde (73 mg, 0.47 mmol, 1 eq) were subjected to General Procedure 4B. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-188** as a waxy oil (83 mg, 0.20 mmol, 43%).[a]

[a] d.r. not determined full characterisation not performed

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.64 (t, *J* = 1.6 Hz, 1H, C11M), 9.54 (t, *J* = 1.5 Hz, 0.3H, C11m), 7.10 (dd, *J* = 8.6, 5.4 Hz, 0.6H, C14m), 7.00 (t, *J* = 8.7 Hz, 0.6H, C13m), 6.96 (dd, *J* = 8.6, 5.5 Hz, 2H, C14M), 6.90 (t, *J* = 8.6 Hz, 2H, C13M), 6.36 (d, *J* = 15.8 Hz, 0.3H, C6m), 6.21 (dd, *J*= 15.9, 10.0 Hz, 0.3H, C7m) 6.17 (d, *J* = 15.8 Hz, 1H, C6M), 6.01 (dd, *J* = 15.8, 10.1 Hz, 1H, C7M), 3.26 (dt, *J* = 8.7, 6.2 Hz, 1H, C9M), 3.11 (td, *J* = 9.3, 5.1 Hz, 0.25H, C9m), 2.84 (ddd, *J* = 17.2, 5.7, 1.4 Hz, 1H, $C10H_1M$), 2.75 (ddd, *J* = 17.2, 8.8, 1.9 Hz, 1H, $C10H_2M$), 2.72 – 2.65 (m, 0.6H, C10m), 2.51 – 2.38 (m, 1.3H, C8M+C8m), 2.28 (s, 0.9H, C1Mem), 2.26 (s, 3H, C1MeM), 2.22 (s, 1.8H, C2MeM), 2.19 (brs, 6H, C2MeM), 2.09 (s, 1.8H, C3Mem), 1.96 (brs, 6H, C3MeM), 1.53 (m, 1H $C16MH_1$), 1.37 – 1.02 (m, 6.5H, C16MH2+C17M+C18M+C16m+C17m+C18m), 0.87 (t, *J* = 7.1 Hz, 3H, C19M), 0.78 (t, *J* = 7.0 Hz, 0.75H, C19m) ppm.

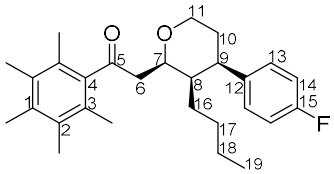
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 202.4 (C11m), 200.5 (C11M), 161.8 (d, *J* = 245.8 Hz, C15m), 161.7 (d, *J* = 245.7 Hz, C15M), 153.4 (C7m), 152.6 (C7M), 137.7 (C4M+C4m), 137.3 (d, *J* = 3.3 Hz, C12m), 136.5 (d, *J* = 3.3 Hz, C12M), 135.6 (C1m), 135.4 (C1M), 135.2 (C6m), 134.8 (C6M), 133.0 (C2Mem), 132.8 (br, C2MeM), 130.0 (d, *J* = 8.0 Hz, C13M), 129.5 (d, *J* = 7.7 Hz, C13m), 128.6 (C3m), 128.5 (br, C3M), 115.6 (d, *J* = 21.4 Hz, C14m), 115.4 (d, *J* = 21.2 Hz, C14M), 48.9 (C8m), 48.4 (C10m), 48.0 (C10M), 47.9 (C8M), 43.1 (C9m), 42.9 (C9M), 32.0 (C16M), 31.5 (C16m), 29.6 (C17M), 29.4 (C17m), 22.5 (C18M), 22.2 (C18m), 17.4 (C3Mem), 17.2 (C3MeM), 16.7 (C1Mem), 16.7 (C1MeM), 16.0 (C2Mem), 15.9 (C2MeM), 14.0 (C19M), 13.9 (C19m) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -115.5 (m), -115.6 (M) ppm.

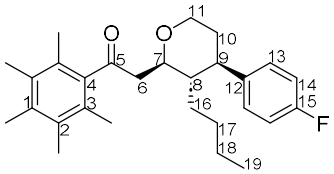
HRMS: ESI$^+$ found $[M+H]^+$ = 423.2694, $C_{28}H_{36}FO_2$ calculated, Δ = 0. ppm.

FTIR(Film)= 2931, 2360, 2341, 1724, 1653, 1510, 1225, 837, 735, 669 cm^{-1}.

$[\alpha]_D^{25}$ = 28.5 (C=1.0, $CHCl_3$)



$^3J_{C7\text{-}C8}$ = 2.5 Hz
$^3J_{C8\text{-}C9}$ = 3.7 Hz
$^3J_{C9\text{-}C10ax}$ = 12.7 Hz



$^3J_{C7\text{-}C8}$ = 10.6 Hz
$^3J_{C9\text{-}C10ax}$ = 12.3 Hz

2-((4R)-3-butyl-4-(4-fluorophenyl)tetrahydro-2H-pyran-2-yl)-1-(pentamethylphenyl)ethan-1-one (**4-189**) (*cis:trans*)

Enantioenriched

aldehyde **4-188** (200 mg, 0.473 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-189** as a waxy oil (78 mg, 0.8 mmol, 2.5:1 d.r., 94% e.e., (90% e.e.)).

Racemic

aldehyde **4-188** (76 mg, 0.18 mmol, 1 eq) was subjected to General Procedure 4C. Purification by FCC (Pentane:Et_2O, 80:20→77:23) gave the product **4-189** as a waxy oil (3.7 mg, 0.0087 mmol, 5%, 6.9:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.21 – 7.15 (m, 2.8H, C13M+C13m), 7.06 – 6.99 (m, 2.8H, C14M+C1m), 4.28 (dt, J = 9.0, 2.5 Hz, 1H, C7M), 4.13 (ddd, J = 11.4, 4.9, 1.4 Hz, 1H, $C11H_1M$), 4.03 (ddd, J = 11.6, 4.7, 1.5 Hz, 0.4H, $C11H_1m$), 3.98 (ddd, J = 10.6, 8.2, 2.9 Hz, 0.4H, C7m), 3.66 (td, J = 11.9, 2.4 Hz, 1H, $C11H_2M$), 3.61 (td, J = 12.0, 2.2 Hz, 0.4H, $C11H_2m$), 3.12 (dt, J = 13.1, 3.5 Hz, 1H, C9M), 3.08 (dd, J = 17.4, 9.0 Hz, 1H, $C6H_1M$), 2.96 (dd, J= 17.4, 3.0 Hz, 0.4H, $C6H_1m$), 2.91 (dd, J= 17.4, 8.1 Hz, 0.4H, $C6H_2m$), 2.70-2.66 (m, 0.4H, C9m), 2.66 (dd, J = 17.4, 2.8 Hz, 1H, $C6M_2$), 2.27 (s, 3H, C1MeM), 2.27 (s, 1.2H, C1Mem), 2.22 (s, 6H, C2MeM), 2.22 (s, 2.4H, C2Mem), 2.18 (s, 8.4H, C3MeM+C3Mem), 2.04 (qd, J = 12.7, 4.8 Hz, 1H, $C10H_1M$), 1.84 (qd, J = 12.3, 4.7 Hz, 0.4H, $C10H_1m$), 1.74 – 1.69 (m, 1.4H, C8M+$C10H_2m$), 1.62 – 1.57 (m, 1.4H, C8m+$C10H_2M$), 1.41 – 1.29 (m, 1H, $C16H_1M$), 1.21 – 1.12 (m, 0.4H, $C16H_1m$), 1.10 – 0.89 (m, 6H, $C16H_2M$+$C16H_2m$+$C17H_1M$+C17m+C18M+C18m), 0.74 (t, J = 7.2 Hz, 1.2H, C19m), 0.63 (t, J = 7.2 Hz, 3H, C19M), 0.61 – 0.55 (m, 1H, $C17H_2M$). ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 209.9 (C5m), 209.6 (C5M), 161.6 (d, J = 243.9 Hz, C15m), 161.5 (d, J = 244.1 Hz, C15M), 140.7 (C4M), 140.6 (C4m), 140.4 (d, J = 3.2 Hz, C12m), 139.5 (d, J = 3.3 Hz, C12M), 135.7 (C1M), 135.7 (C1m), 133.3 (C2MeM), 133.3 (br, C2Mem), 129.1 (d, J = 7.7 Hz, C13m), 128.8 (d, J = 7.7 Hz, C13M), 127.8 (br, C3MeM+C3Mem), 115.4 (d, J = 21.2 Hz, C14m), 115.1 (d, J = 20.9 Hz, C14M), 77.2 (C7M), 76.8 (C7m), 68.6 (C11M), 68.0 (C11m), 49.9 (C6M), 49.4 (C6m), 46.3 (C9m), 45.0 (C8M/C9M), 44.9 (C8m), 44.9 (C8M/C9M), 35.5 (C10m), 33.5 (C17M), 28.5 (C17m/C18m), 27.9 (C16m), 25.2 (C10M), 23.2 (C17m/C18m), 22.9 (C16M/C18M), 22.9 (C16M/C18M), 17.3 (C3MeM), 17.2 (C3Mem), 16.9 (C1MeM), 16.8 (C1Mem), 16.1 (C2MeM+C2Mem), 13.9 (C19m), 13.8 (C19M) ppm.

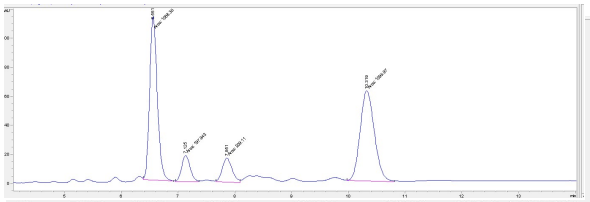
^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -116.8 (m) -117.2 (M) ppm.

HRMS: ESI^+ found $[M+Na]^+$ = 447.2671, $C_{28}H_{37}O_2FNa$ calculated 447.270, Δ = 0.26 ppm.

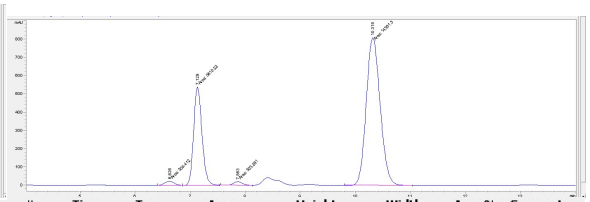
FTIR(Film)= 2981, 2360, 1704, 1511, 1382, 11600, 1094, 911, 736 cm^{-1}.

$[\alpha]_D^{25}$ = 45.2 (C=0.5, $CHCl_3$)

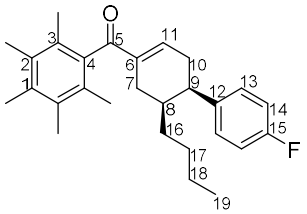
Chiral HPLC: (Chiralpak IG with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.551	MM	1068.3	112.7	0.1579	41.548	0.801
2	7.125	MM	197.9	18.5	0.1786	7.698	0.852
3	7.851	MM	209.1	16.8	0.2078	8.132	0.814
4	10.319	MM	1096	62.1	0.2939	42.622	0.846



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.626	MM	355.4	25	0.2368	1.706	1.051
2	7.129	MM	5810.2	540.9	0.179	27.893	0.831
3	7.863	MM	303.3	22	0.2295	1.456	0.866
4	10.318	MM	14361.3	809.2	0.2958	68.945	0.849



((1R,2S)-2-butyl-4'-fluoro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-190**)

THP **4-189** (25 mg, 0.059 mmol, 1 eq) was subjected to General Procedure 4F. After ligand acylation, purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-190** as a waxy solid (24 mg, 0.057 mmol, 97%, 2.5:1 d.r.).[a]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.14 – 7.08 (m, 2H, C14), 6.99 – 6.94 (m, 2H, C13), 6.67 – 6.61 (m, 1H, C11), 3.16 – 3.06 (m, 1H, C9), 2.70 – 2.63 (m, 1H, C7H$_1$), 2.63 – 2.51 (m, 1H, C10H$_1$), 2.51 – 2.41 (m, 1H, C10H$_2$), 2.34-2.15 (m, C7H$_2$) 2.26 (s, 3H, C1Me), 2.21 (s, 6H, C2Me), 2.07 (s, 6H, C3Me), 2.01 – 1.91 (m, 1H, C8), 1.44 – 1.34 (m, 1H, C17H$_1$), 1.34 – 1.11 (m, 4H, C16H$_1$+C17H$_2$+C18), 1.08 – 0.98 (m, 1H, C16H$_2$), 0.88 – 0.83 (m, 3H, C19) ppm.

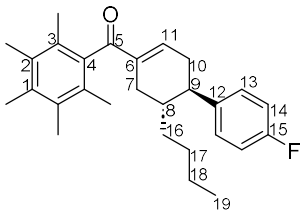
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 203.2 (C5), 161.5 (d, J = 244.2 Hz, C15), 144.5 (C11), 140.4 (C6), 138.5 (d, J = 3.3 Hz C12), 138.1 (C4), 135.2 (C1), 132.7 (C2), 129.3 (d, J = 7.6 Hz, C13), 129.1 (C3$_1$), 129.0 (C3$_2$), 114.8 (d, J = 20.8 Hz, C14), 40.8 (C9), 37.3 (C8), 30.9 (C10), 30.1 (C16), 29.7 (C17), 25.7 (C7), 22.8 (C18), 17.5 (C3Me), 16.7 (C1Me), 16.0 (C2Me), 14.0 (C19). ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -116.9 (m) -117.0 (M) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 407.2759, $C_{28}H_{36}FO$ calculated 407.2745, Δ = 3.50 ppm.

FTIR(Film)= 2929, 2360, 2341, 1655, 1510, 1224, 1188, 912, 738 cm^{-1}.

$[\alpha]_D^{25}$ = 43.9 (C=0.5, $CHCl_3$)



((1R,2R)-2-butyl-4'-fluoro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)(pentamethylphenyl)methanone (**4-190**)

THP **4-189** (20 mg, 0.047 mmol, 1 eq) was subjected to General Procedure 4G. After ligand acylation, Purification by FCC (Pentane:Et_2O, 99:1) gave the product **4-190** as a waxy solid (10 mg, 0.024 mmol, 50%, 1:3.2 d.r.) as well as recovered SM (10 mg, 0.023 mmol, 48%, 1:3 d.r.).

[a] 3 w/w% $HOMe_2C_6H_3$ observed in 1H NMR after purification by 3 x FCC mass accounted for in yield calculation.

1H NMR (400 MHz, CDCl3) δ_H: 7.15 – 7.11 (m, 2H, C14), 7.02 (t, J = 8.7 Hz, 2H, C13), 6.57 – 6.52 (m, 1H, C11), 2.91 (dd, J = 18.0, 4.5 Hz, 1H, C7H1), 2.58 (td, J = 10.2, 5.3 Hz, 1H, C9), 2.50 – 2.42 (m, 1H, C10H1), 2.37 – 2.29 (m, 1H, C10H2), 2.27 (s, 3H, C1Me) 2.22 (d, J = 1.4 Hz, 6H, C2Me), 2.08 (d, J = 4.6 Hz, 6H, C3Me), 1.85 (qdd, J = 9.8, 5.0, 3.3 Hz, 1H, C8), 1.45 – 1.36 (m, 1H, C17H1), 1.34 – 1.14 (m, 4H, C16H1+C17H2+C18), 1.07 – 1.01 (m, 1H, C16H2), 0.84 (t, J = 7.1 Hz, 3H, C19) ppm.

13C NMR (101 MHz, CDCl3) δ_C: 203.3 (C5), 161.4 (d, J = 244.1 Hz, C15), 144.0 (C11), 140.6 (d, J = 3.2 Hz, C12), 140.3 (C6), 138.0 (C4), 135.1 (C1), 132.7 (C21), 132.6 (C22), 129.2 (C31), 129.1 (C32), 128.9 (d, J = 7.9 Hz, C13), 115.3 (d, J = 21.1 Hz, C14) 44.8 (C9), 38.0 (C8), 35.5 (C10), 33.5 (C16), 28.5 (C17), 28.3 (C7), 22.8 (C18), 17.5 (C1Me), 16.7 (C2Me), 16.0 (C3Me), 14.0 (C19) ppm.

19F NMR (377 MHz, CDCl3) δ_F: -116.9 (M) -117.1 (m) ppm.

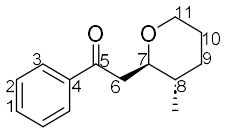
HRMS: ESI+ found [M+H]+ = 429.2564, C28H35OFNa calculated 429.2564, Δ = 0.04 ppm.

FTIR(Film)= 2929, 2360, 2341, 1655, 1510, 1224, 1188, 912, 738 cm-1.

$[\alpha]_D^{25}$ = -14 (C=0.5, $CHCl_3$)

6.5.15. Enantioenrichment.

Synthesis of the THP **4-135** and racemic enone **4-136** was performed by Roland Armstrong, characterisation of the compounds is included here for clarity.



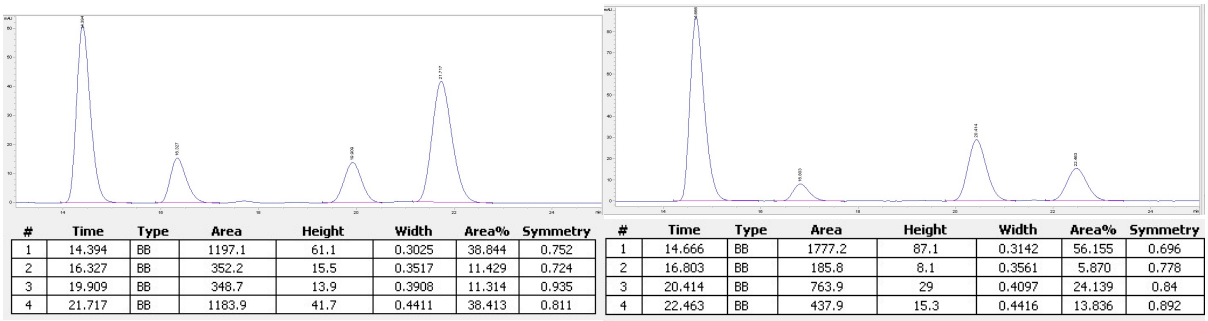
2-((2R,3S)-3-methyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (**4-135**)

69:31 d.r. 61% e.e.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.99 – 7.94 (m, 2.8H, C3M+C3m), 7.58 – 7.51 (m, 1.4H, C1M+C1m), 7.50 – 7.40 (m, 2.8H, C2M+C2m), 4.12 (ddd, *J* = 7.6, 5.0, 2.3 Hz, 0.4H, C7m), 3.94 – 3.85 (m, 1.4H, $C11M_1$+$C11m_1$), 3.63 (ddd, *J* = 9.8, 8.4, 3.4 Hz, 1H, C7M), 3.52 – 3.44 (m, 0.4H, $C11m_2$), 3.37 (ddd, *J* = 12.3, 11.3, 2.5 Hz, 1H, $C11M_2$), 3.26 (dd, *J* = 16.0, 7.8 Hz, 0.4H $C6m_1$), 3.17 (dd, *J* = 15.6, 8.4 Hz, 1H, $C6M_1$), 3.05 (dd, *J* = 15.6, 3.4 Hz, 1H, $C6M_2$), 2.82 (dd, *J* = 16.1, 5.0 Hz, 0.4H, $C6m_2$), 1.90 – 1.74 (m, 2.2H, $C9M_1$+$C9m_1$+$C10m_1$+C8m), 1.72 – 1.59 (m, 1.4H, $C10M_1$+$C9m_2$), 1.58 – 1.45 (m, 2H, $C10M_2$+C8M), 1.34-1.27 (m, 0.4H, $C10m_2$) 1.23 (tdd, *J* = 13.0, 11.6, 4.1 Hz, 1H, $C9M_2$), 1.04 (d, *J* = 7.0 Hz, 1.2H, C8Mem), 0.89 (d, *J* = 6.7 Hz, 3H, C8MeM) ppm.

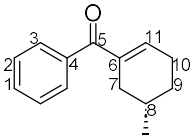
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 199.3 (C5M), 198.8 (C5m), 137.7 (C4M), 137.5 (C4m), 133.1 (C1m), 133.0 (C1M), 128.7 (C2/C3m), 128.6 (C2/C3M), 128.5 (C2/C3M), 128.4 (C2/C3m), 80.5 (C7M), 76.5 (C7m), 68.9 (C11m), 68.5 (C11M), 43.1 (C6M), 42.2 (C6m), 36.1 (C8M), 32.8 (C9M), 31.2 (C8m), 30.8 (C9m), 26.6 (C10M), 21.0 (C10m), 18.3 (C8MeM), 12.3 (C8Mem) ppm.

Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 o C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.394	BB	1197.1	61.1	0.3025	38.844	0.752
2	16.327	BB	352.2	15.5	0.3517	11.429	0.724
3	19.909	BB	348.7	13.9	0.3908	11.314	0.935
4	21.717	BB	1183.9	41.7	0.4411	38.413	0.811

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.666	BB	1777.2	87.1	0.3142	56.155	0.696
2	16.803	BB	185.8	8.1	0.3561	5.870	0.778
3	20.414	BB	763.9	29	0.4097	24.139	0.84
4	22.463	BB	437.9	15.3	0.4416	13.836	0.892



(S)-(5-methylcyclohex-1-en-1-yl)(phenyl)methanone (**4-136**)

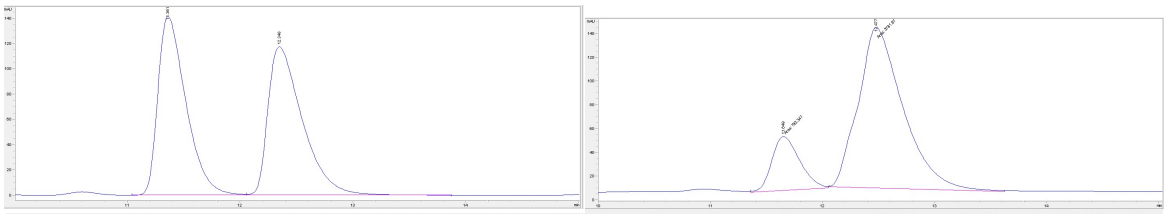
The enantioenriched THP **4-135** (5.1 mg, 0.025 mmol, 61% e.e., 1 eq) was subjected to General Procedure 4F. Purification by prep TLC (Pentane:Et_2O, 99:5) gave the enone **4-136** as a waxy solid (2.5 mg, 0.013 mmol, 51%, 65% e.e.).

^{1}H and ^{13}C-NMR characterisation of the racemic product isolated by Roland Armstrong.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.65 – 7.59 (m, 2H, C3), 7.52 – 7.45 (m, 1H, C1), 7.43 – 7.38 (m, 2H, 2C), 6.59 – 6.53 (m, 1H, C11), 2.63 (dddd, J = 17.4, 5.1, 2.0, 1.0 Hz, 1H, C7H_1), 2.36 – 2.25 (m, 2H, C10H_1+C10H_2), 1.98 – 1.86 (m, 1H, C7H_2), 1.82 – 1.67 (m, 2H, C8+C9H_1), 1.32 – 1.20 (m, 1H, C9H_2), 1.06 (d, J = 6.4 Hz, 3H, C8Me) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 198.3 (C5), 143.8 (C11), 139.0 (C4/C6), 138.5 (C4/C6), 131.4 (C1), 129.2 (C3), 128.1 (C2), 32.4 (C7), 30.0 (C9), 28.3 (C8), 26.4 (C10), 21.8 (C8Me) ppm.

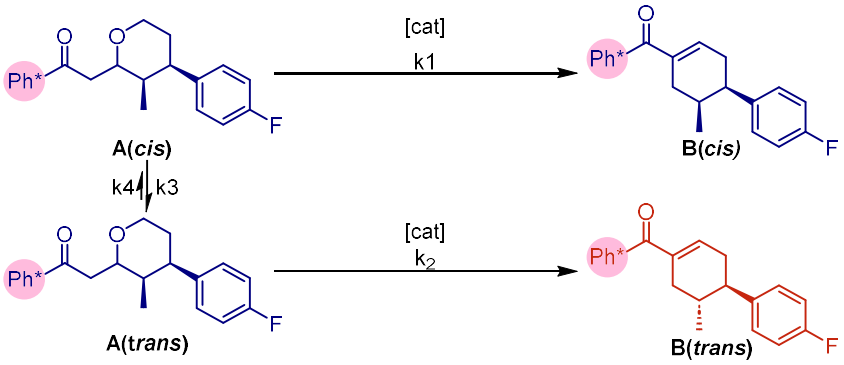
Chiral HPLC: (Chiralpak IB-N with guard, 0.5% IPA, 99.5% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.361	BV	2453.3	141.5	0.2642	49.602	0.529
2	12.348	VB	2492.7	117.6	0.3212	50.398	0.462

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.649	MM	793.3	45.6	0.2902	17.341	0.709
2	12.477	MM	3781.7	135.1	0.4667	82.659	0.652

6.5.16. Computational Calculations.



The numerical integration was performed using quadrature rules methodology, a computationally simple way of solving the multi-variable equations. The equations used in the four-component formula sheet is shown below.

The Tables are split into 3 sections. The first four rows calculate the rate of each transformation in the system. Each compound diastereomer is described in two columns; dX(*x*), the sum of the relevant terms in the first four rows and X(x), the quantity at that time step. The third section turns the abundance of all compounds into yields and d.e, which can then be plotted. Each cell refers only to other cells in the row and the starting values except for the current quantities, which refer to the row above. After the first line, all formulas are the same within each column.

All rate terms are divided by a constant value labelled the time step corresponding to the inverse of the quadratic width. Physically this corresponds to the length of time between each measurement. Mathematically the error will decrease as the number increases but requires more rows to model a reaction to completion. Catastrophic failure of the model was observed if Equation 6-1 is met; increasing the time step prevents this from occurring. No additional techniques were used in the six-component system.

$$\frac{-d[x]}{dt} > [x]$$

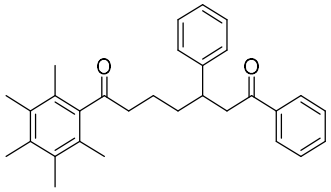
Equation 6-1) violating this equation results in negative mass formation.

	W	X	Y	Z	dA (cis)	A(cis)	dA(trans)	A(trans)	dB(cis)	B(Cis)	dB(trans)	B(trans)	A yield
1	Cat*k1* A(cis,t=1) /ts	Cat*k2* A(trans,t=1) /ts	k3* A(cis,t=1) /ts	Cat*k4* A(trans,t=1) /ts	Z(t=1) - Y(t=1)- W(t=1)	A(cis,t=1)[a]	Y(t=1)- X(t=1)- Z(t=1)	A(trans,t=1)[a]	W(t=1)	0[a]	X(t=1)	0[a]	A(cis,t=1) +A(trans,t=1)
2	Cat*k1* A(cis,t=1)/ts	Cat*k2* A(trans,t=2) /ts	k3* A(cis,t=2) /ts	Cat*k4* A(trans,t=2) /ts	Z(t=2)- Y(t=2)- W(t=2)	dA(cis,t=1) +A(cis,t=1)	Y(t=2)- X(t=2)- Z(t=2)	dA(trans,t=1) +A(trans,t=1)	W(t=2)	dB(cis,t=1) +B(cis,t=1)	X(t=2)	dB(trans,t=1) +B(trans,t=1)	A(cis,t=2) +A(trans,t=2)
n	Cat*k1* A(cis,t=n) /ts	Cat*k2* A(trans,t=n) /ts	k3* A(cis,t=n) /ts	Cat*k4* A(trans,t=n) /ts	Z(t=n)- Y(t=n)- W(t=n)	dA(cis,t=n-1) +A(cis,t=n-1)	Y(t=n)- X(t=n)- Z(t=n)"	dA(trans,t=n-1) +A(trans,t=n-1)	W(t=n)	dB(cis,t=n-1) +B(cis,t=n-11)	X(t=n)	dB(trans,t=n-1) +B(trans,t=n-1)	A(cis,t=n) +A(trans,t=n)

Sample of Table for the four-component system. Collums for A d.e, B yield and B d.e. are omitted. [a] These inputs have separate calculations for the other calculations in the column.

6.6. SI for Chapter 5.

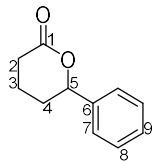
6.6.1. Catalytic 1,5-Hydride Transfer.



7-(pentamethylphenyl)-1,3-diphenylheptane-1,7-dione (**5-32**)

THP **5-31** (42 mg, 0.099 mmol, 1 eq) and Al(O*t*-Bu)$_3$ (5 mg, 0.02 mmol, 20 mol%) were added to a microwave vial. The sealed vial was evacuated and flushed with N_2 four times, dry toluene (0.5 mL) was added, and the solution was heated to 110 °C. After 36 h, the reaction was cooled to rt and diluted with EtOAc (2 mL) and the suspension was filtered through a Silica plug with EtOAc. The solution was concentrated under reduced pressure to give the crude product. The crude was purified by FCC (Pentane:Et_2O 95:5) to give the product **5-32** (35 mg, 0.081 mmol, 81%).

Data in agreement with that reported above.



6-phenyltetrahydro-2H-pyran-2-one (**5-40**)

Based on a procedure by Lehmann and co-workers[220]

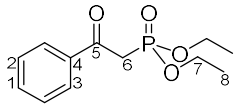
To a solution of carboxylic acid **5-39** (2.00 g, 10.4 mmol, 1 eq) in aq. NaOH (20 mL, 0.5 M) was added $NaBH_4$ (720 mg, 19.0 mmol, 1.8 eq) portion-wise at 0 °C, and the reaction was allowed to warm to rt. After 2 h, upon consumption of the starting material by TLC, the mixture was cooled to 0 °C and slowly quenched using aq. HCl (3 M) until the solution reached pH=2.[a] After 18 h, the solution was diluted with DCM (80 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 40 mL), and the combined organic layers were dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane:Et_2O, 80:20) gave the desired lactone **5-40** as a white waxy solid (1.45 g, 8.27 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.40 – 7.23 (m, 5H, C7+C8+C9), 5.29 (dd, *J* = 10.4, 3.3 Hz, 1H, C5), 2.65 (dtd, *J* = 17.9, 6.4, 1.1 Hz, 1H, C2H$_1$), 2.51 (dt, *J* = 17.8, 7.8 Hz, 1H, C2H$_2$), 2.15 – 2.06 (m, 1H, C3H$_1$), 1.98 – 1.89 (m, 2H, C4H$_1$+C4H$_2$), 1.87 – 1.74 (m, 1H, C3H$_2$) ppm.

[a]After an initially slow and decreasing release of H_2 upon quenching, the rate of H_2 gas formation increases rapidly part-way through the quench. The reaction should be performed with a large gas outlet and addition of acid should be done with caution.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 171.5 (C1), 139.9 (C6), 128.7 (C7/8), 128.4 (C9), 125.8 (C7/C8), 81.8 (C5), 30.7 (C3), 29.7 (C2), 18.7 (C4) ppm.

Data in agreement with literature.[220]



diethyl (2-oxo-2-phenylethyl)phosphonate (**5-42**)

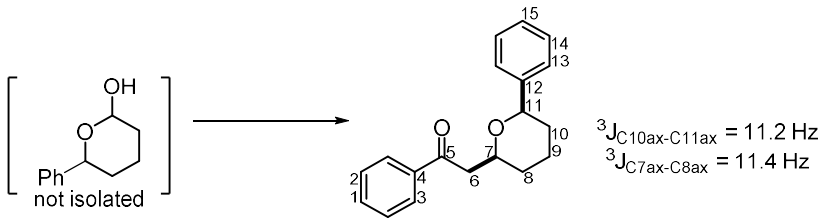
Based on a procedure by Donohoe and co-workers[94]

To a stirred solution of methyl benzoate (3.0 mL, 24 mmol, 1 eq) and diethyl methylphosphonate (3.8 mL, 26 mmol, 1.1 eq) in THF (120 mL) was added LDA (35 mL, 1 M in THF, 35 mmol, 1.5 eq) dropwise at 0 °C. After 5 mins, the reaction was warmed to rt. After 3 h, upon consumption of the ester by TLC, the reaction was quenched by slow addition of aq. HCl (20 mL, 3 M) and diluted with Et_2O (50 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 40 mL), the combined organic layers were dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product. Purification by FCC gave the desired product **5-42** as a yellow oil (4.93 g, 19.2 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.08 – 7.92 (m, 2H, C3), 7.57 (ddq, J = 8.6, 5.2, 1.4 Hz, 1H, C1), 7.50 – 7.43 (m, 2H, C2), 4.20 – 4.05 (m, 4H, C7), 3.62 (d, J= 23.2 Hz, 2H, C6), 1.26 (ddt, J = 8.0, 6.4, 0.9 Hz, 6H, C8) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 192.1 (d, J = 6.7 Hz, C5), 136.6 (d, J = 2.0 Hz, C4), 133.8 (C1), 129.2 (C3), 128.7 (C2), 62.8 (d, J = 6.4 Hz, C7), 38.6 (d, J = 130.0 Hz, C6), 16.4 (d, J = 6.4 Hz, C8) ppm.

Data in agreement with previous literature.[94]



1-phenyl-2-(6-phenyltetrahydro-2H-pyran-2-yl)ethan-1-one (**5-34**)

Based on a modified procedure by Maegawa and co-workers[271]

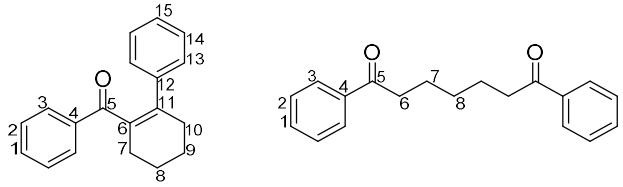
To a stirred solution of lactone **4-106** (800 mg, 4.54 mmol, 1 eq) in DCM (10 mL), was added DIBAL-H (6.3 mL, 1 M in hexane, 6.3 mmol, 1.4 eq) dropwise at -78 °C. After 2 h, upon completion by TLC, the solution was quenched with aq. Rochelle salt (9 mL, sat) and allowed to stir at rt for 30 mins. The product was diluted with DCM (20 mL), the layers were separated, and the aqueous layer was extracted with DCM (6 x 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Aluminium salts were removed by FCC (Pentane: Et_2O, 50:50), and the product **5-43** was used without further purification.

To a solution of the crude lactol **5-43** and ketone **5-42** (1.24 g, 5.90 mmol, 1.3 eq) in MeOH (50 mL) was added LiOMe (860 mg, 21.7 mmol, 4.8 eq) at rt. After 18 h, the solution was diluted with Et_2O (200 mL) and water (150 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane: Et_2O, 80:20) gave the desired lactone as a white solid (307 mg, 1.10 mmol, 24%, >25:1 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.92 (dd, *J* = 8.4, 1.4 Hz, 2H, C3), 7.49 (tt, *J* = 7.5, 1.1 Hz, 1H, C1), 7.44 – 7.34 (m, 2H, C2), 7.22 (d, *J* = 4.3 Hz, 2H, C13), 7.24 – 7.06 (m, 3H, C14+C15), 4.36 (dd, *J* = 11.4, 2.3 Hz, 1H, C11), 4.11 (dtd, *J* = 11.2, 6.2, 2.0 Hz, 1H, C7), 3.35 (dd, *J* = 16.0, 5.9 Hz, 1H, $C6H_1$), 2.99 (dd, *J* = 15.9, 6.6 Hz, 1H, $C6H_2$), 1.94 – 1.85 (m, 1H, $C9H_1$), 1.83 – 1.76 (m, 2H, $C8H_1$+$C10H_1$), 1.69 (qt, *J* = 12.9, 3.8 Hz, 1H, $C9H_2$), 1.44 (tdd, *J* = 12.7, 11.6, 3.6 Hz, 1H, $C10H_2$), 1.32 (tdd, *J* = 12.6, 11.0, 4.0 Hz, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 198.6 (C5), 143.2 (C4), 137.5 (C12), 133.0 (C1), 128.5 (C3), 128.4 (C2), 128.2 (C13/C14), 127.2 (C15), 125.8 (C13/C14), 79.8 (C11), 75.0 (C7), 45.6 (C6), 33.3 (C10), 31.4 (C8), 23.9 (C9) ppm.

Data in agreement with literature.[30]

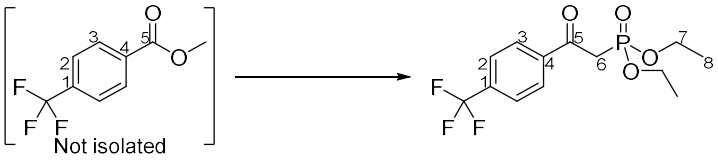


phenyl(3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (**5-35**) and 1,7-diphenylheptane-1,7-dione (**5-36**)

A freshly synthesised solution of Al(O*t*-Bu)$_3$ in toluene (0.1 M) was synthesised using General Method 4E.

A sealed microwave vial of THP **5-34** (28 mg, 0.10 mmol, 1 eq) was evacuated and flushed with N_2 four times. Al(O*t*-Bu)$_3$ (200 µL, 0.02 mmol, 20 mol%), dry toluene (50 µL) and dry *t*-BuOH (50 µL) were added *via* syringe. The solution was heated to 110 °C. After 20 h, the reaction was cooled to rt and diluted with EtOAc (2 mL). The suspension was filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The ^{1}H-NMR yield of the cyclohexene **5-35** (13%) and diketone **5-36** (38%) were determined using TMB as an internal standard.

Data in agreement with procedures described below.



diethyl (2-oxo-2-(4-(trifluoromethyl)phenyl)ethyl)phosphonate (**5-48**)

Based on the procedure by Taylor.[272]

To a stirred solution of MeOH (560 µL, 14 mmol, 1.2 eq) and NEt_3 (3.4 mL, 24 mmol, 2 eq) was added acid chloride **5-47** (1.8 mL, 12 mmol, 1 eq) dropwise to give a white suspension. After 1 h, the reaction was diluted with Et_2O (30 mL) and aq. HCl (30 mL, 1 M). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product **S5-01**, which was used without further purification.

The crude ester **S5-01** was analysed to confirm the structure, and key peaks are described below.

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 8.15 (br, d, *J* = 8.0 Hz, 2H, C3), 7.71 (br, d, *J* = 8.1 Hz, 2H, C2), 3.96 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 166.0 (C5), 130.1 (C3), 125.6 (q, *J* = 3.7 Hz, C2), 52.7 (OMe) ppm.[a]

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.1 ppm.

Data in agreement with literature.[272]

To a stirred solution of the crude ester **S5-01** and diethyl methylphosphonate (1.94 mL, 13.2 mmol, 1.1 eq) in THF (60 mL) was added LDA (27 mL, 1 M in THF, 27 mmol, 2.25 eq) dropwise at 0 °C. After 10 mins, upon consumption of the ester by TLC, the reaction was diluted with Et_2O (50 mL) and quenched by slow addition of aq. HCl (20 mL, 3 M) and water (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product. Purification by FCC gave the desired ketone **5-48** as a yellow oil (2.30 g, 7.00 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 8.11 (brd, *J* = 8.0 Hz, 2H, C3), 7.72 (brd, *J* = 7.6 Hz, 2H, C2), 4.20 – 4.05 (m, 4H, C7), 3.63 (dt, *J* = 22.9, 0.9 Hz, 2H, C6), 1.32 – 1.22 (m, 6H, C8) ppm.

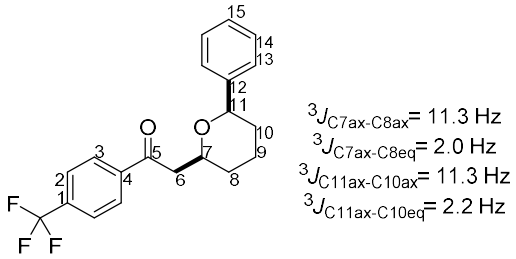
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 191.1 (d, *J* = 6.7 Hz, C5), 139.1 (C4), 134.8 (q, *J* = 33.0 Hz, C1), 129.4 (C3), 125.7 (q, *J* = 3.8 Hz, C2), 123.5 (q, *J* = 272.6 Hz, CF_3), 62.8 (d, *J* = 6.6 Hz, C7), 38.9 (d, *J* = 129.2 Hz, C6), 16.2 (d, *J* = 6.3 Hz, C8) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -63.2 ppm.

FTIR(film): 2981, 2360, 1689, 1329, 1130, 1067, 1026 cm^{-1}.

[a] The aliquot taken for analysis was insufficient to see the split quaternary carbons.

HRMS: ESI$^+$ found $[M+H]^+$ = 325.0809, $C_{13}H_{17}F_3O_4P$ calculated 325.0811, Δ = 0.65 ppm.



2-(6-phenyltetrahydro-2H-pyran-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one **(5-49**)

Based on a modified procedure by Maegawa and co-workers[271]

To a stirred solution of lactone **5-40** (792 mg, 4.50 mmol, 1 eq) in DCM (10 mL), was added DIBAL-H (6.3 mL, 1 M in hexane, 6.3 mmol, 1.4 eq) dropwise at -78 °C. After 2 h, upon completion by TLC, the solution was quenched with aq. Rochelle salt (9.0 mL, sat) and allowed to stir at rt for 30 mins. The product was diluted with DCM (20 mL), the layers were separated, and the aqueous layer was extracted with DCM (6 x 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Aluminium salts and diols were removed by FCC (Pentane: Et_2O, 50:50), and the product **5-43** was used without further purification.

To a solution of the crude lactol **5-43** and ketone **5-48** (1.88 g, 5.80 mmol, 1.4 eq) in MeOH (50 mL) was added LiOMe (854 mg, 22.5 mmol, 5 eq) at rt. After 18 h, the solution was diluted with Et_2O (200 mL) and water (150 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried with $NaSO_4$ and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane: Et_2O, 80:20) gave the desired lactone **5-49** as a yellow oil (328 mg, 0.94 mmol, 21%).

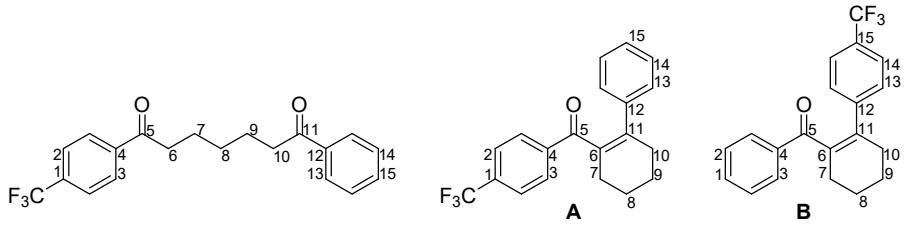
^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 8.10 (brd, *J* = 8.1 Hz, 2H, C3), 7.73 (brd, *J* = 8.2 Hz, 2H, C2), 7.32 – 7.20 (m, 5H, C13-C15), 4.43 (dd, *J* = 11.3, 2.2 Hz, 1H, C11), 4.18 (dtd, *J* = 11.3, 6.1, 2.0 Hz, 1H, C7), 3.44 (dd, *J* = 15.8, 6.4 Hz, 1H, $C6H_1$), 3.07 (dd, *J* = 15.7, 5.8 Hz, 1H, $C6H_2$), 2.03 – 1.95 (m, 1H, $C9H_1$), 1.93 – 1.82 (m, 2H, $C8H_1$+$C10H_1$), 1.76 (tt, *J* = 13.0, 3.8 Hz, 1H, $C9H_2$), 1.63 – 1.47 (m, 1H, $C10H_2$), 1.47 – 1.38 (m, 1H, $C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 198.1 (C5), 143.1 (C4), 140.3 (C12), 134.4 (C1), 128.9 (C3), 128.3 (C13/C14), 127.4 (C15), 125.8 (C13/C14), 125.7 (C2), 123.8 (CF_3), 80.0 (C11), 75.1 (C7), 45.9 (C6), 33.3 (C10), 31.5 (C8), 23.9 (C9) ppm. (^{19}F decoupled spectra)

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -63.1 ppm.

HRMS: ESI$^+$ found $[M+Na]^+$=371.1231 $C_{20}H_{19}O_2F_3Na$ calculated, 371.1229 Δ = 0.43 ppm.

FTIR(film): 2939, 2360, 2341, 1641, 1325, 1112, 1066 cm^{-1}.



1-phenyl-7-(4-(trifluoromethyl)phenyl)heptane-1,7-dione (**5-50**) (3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)(4-(trifluoromethyl)phenyl)methanone (**5-51A**) phenyl(4'-(trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (**5-51B**)

A freshly synthesised Al(O*t*-Bu)$_3$ in dry toluene (0.3 M) was synthesised using General Method 4E.

A sealed microwave vial of THP **5-49** (35 mg, 0.10 mmol, 1 eq) was evacuated and flushed with N_2 four times. Al(O*t*-Bu)$_3$ (60 µL, 0.3 M, 0.02 mmol, 20 mol%) and dry toluene (240 µL) were added *via* syringe, and the solution was heated to 110 °C. After 36 h, the reaction was cooled to rt and diluted with EtOAc (2 mL); the suspension was filtered through a silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude products. The crude product was purified by FCC (Pentane: Et_2O 99:1→95:5) to give the cyclohexene **5-51A** (3.3 mg, 0.010 mmol, 10%), a mixture of the regioisomer **551B** and the starting material (6.1 mg, 36 w/w%, 0.067 mmol, 7%) and the diketone **5-50** (14 mg, 0.40 mmol, 40%).

For the purposes of characterisation, cyclohexene **A** was separated from the starting material by prep TLC in order to characterise the product.

Cyclohexene A

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.69 (d, *J* = 8.1 Hz, 2H, C3), 7.43 (d, *J* = 8.1 Hz, 2H, C2), 7.10 – 6.98 (m, 5H, C13+C14+C15), 2.56 – 2.52 (m, 2H, C10), 2.51 – 2.47 (m, 2H, C7), 1.94 – 1.87 (m, 2H, C9), 1.87 – 1.79 (m, 2H, C8) ppm.

^{13}C NMR {^{19}F} (101 MHz, $CDCl_3$) δ_C: 200.4 (C5), 142.4, 141.6, 140.3, 135.1, 133.4, 129.4 (C3), 128.2 (C13/C14), 128.1 (C13/C14), 127.8 (C15), 125.0 (C2), 123.7 (CF_3), 31.2 (C10), 28.0 (C7), 22.9 (C9), 22.2 (C8) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -63.1 ppm.

HRMS= ESI$^+$ found $[M+H]^+$ = 331.1304, $C_{20}H_{18}F_3O$ calculated 331.1304 Δ = 0.01 ppm.

FTIR 2932, 2361, 1661, 1326, 1257, 1170, 1133, 1068, 701 cm.$^{-1}$

Cyclohexene B

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.69 (dd, *J* = 8.2, 1.3 Hz, 2H, C3), 7.40 (tt, *J* = 7.5, 1.3 Hz, 1H, C1), 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.25 (m, 2H, C2), 7.22 (d, *J* = 7.8 Hz, 2H), 2.54 – 2.46 (m, 4H, C7+C10), 1.96 – 1.91 (m, 2H, C8/C9), 1.90 – 1.84 (m, 2H, C8/C9). ppm.

^{13}C NMR {^{19}F} (101 MHz, $CDCl_3$) δ_C: 200.9 (C5), 145.6, 141.1, 138.4, 137.2, 136.7, 133.0 (C1), 129.3 (C3), 128.4 (C2/C14), 128.3 (C2/C14), 125.0 (C13), 124.1 (CF_3), 30.9 (C7/C10), 28.2 (C7/C10), 22.8 (C8/C9), 22.0 (C8/C9) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -62.7 ppm.

HRMS= ESI$^+$ found $[M+H]^+$ = 331.1294, $C_{20}H_{18}F_3O$ calculated 331.1304 Δ = 3.11 ppm.

FTIR 2361, 2341, 1327, 1168, 1129, 1070, 649 cm.$^{-1}$

Diketone

^{13}C (151 MHz) used to elucidate the aryl region 150-115 ppm.

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 8.05 (dt, *J* = 7.9, 0.8 Hz, 2H, C3), 8.01 – 7.90 (m, 2H, C13), 7.73 (d, *J* = 7.9 Hz, 2H, C2), 7.60 – 7.52 (m, 1H, C15), 7.53 – 7.41 (m, 2H, C14), 3.01 (q, *J* = 7.1 Hz, 4H, C6+C10), 1.88 – 1.74 (m, 4H, C7+C9), 1.56 – 1.45 (m, 2H, C8)ppm.

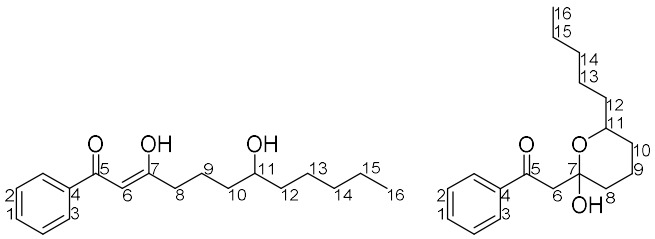
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 200.3 (C11), 199.3 (C5), 38.8 (C6/C10), 38.4 (C6/C10), 29.0 (C8), 24.1 (C7/C9), 24.0 (C7/C9) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ_C: 139.80 (q, *J* = 1.2 Hz, C4), 137.2 (C12), 134.3 (q, *J* = 32.7 Hz, C15), 128.7 (C14), 128.5 (C3), 128.2 (C13), 125.7 (q, *J* = 3.6 Hz, C2), 123.6 (q, *J* = 272.7 Hz, CF_3) ppm

^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -63.1 ppm.

HRMS= ESI$^+$ found $[M+H]^+$ = 371.1236, $C_{20}H_{19}F_3O_2Na$ calculated 371.1229, Δ = 1.78 ppm.

FTIR= 3650, 2981, 1682, 1379, 1335



7-hydroxy-1-phenyldodecane-1,3-dione (**S5-02**) and 2-(2-hydroxy-6-pentyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (**S5-03**)

Based on a modified procedure by VanDeusen.[174]

To a stirred solution of LiHMDS (8.0 mL, 0.25 M in THF, 2.0 mmol, 2 eq) was added a solution of acetophenone (390 µL, 2.0 mmol, 2 eq) in THF (2 mL) dropwise at -78 °C. After 30 mins, Lactone **5-40** (170 mg, 0.97 mmol, 1 eq) in THF (2.5 + 0.5 mL) was added dropwise. The reaction was allowed to stir at -78 °C for 1.5 h until the lactone was consumed by TLC. The reaction was quenched by dropwise addition of AcOH (10 mL). The product was diluted with Et_2O (10 mL), the layers were separated and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. In the crude material, diketone **S50-2** and hemiacetal **S5-03** were observed in an 8:1 ratio. The crude product was purified by FCC to give an isomeric mixture of the diketone **S5-02** and hemiacetal **S5-03** (112 mg, 0.39 mmol, 40%, 11:1, **S5-02**:**S5-03**).

1,3-dicarbonyl

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.85 – 7.76 (m, 2H, C3), 7.50 – 7.41 (m, 1H, C1), 7.42 – 7.34 (m, 2H, C2), 6.12 (s, 1H. C6), 3.56 (tt, *J* = 8.5, 4.4 Hz, 1H, C11), 2.41 (t, *J* = 7.5 Hz, 2H, C8), 1.89 – 1.61 (m, 2H, C9), 1.55 – 1.31 (m, 5H, C10+C12+C14H_1), 1.28 – 1.18 (m, 5H, C13+C14H_2+C15), 0.82 (t, *J* = 6.8 Hz, 3H, C16) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 197.0 (C5/C7), 183.2 (C5/C7), 134.9 (C4), 132.3 (C1), 128.6 (C2/C3), 127.0 (C2/C3), 96.2 (C6), 71.6 (C11), 39.2 (C8), 37.5 (C10/C12), 36.8 (C10/C12), 31.9 (C13), 25.3 (C14), 22.7 (C15), 21.8 (C9), 14.1 (C16) ppm.

HRMS and IR taken of the 1.6:1 isomeric mixture.

HRMS: ESI$^+$ found $[M\text{-}OH]^+$ = 273.1856, $C_{18}H_{25}O_2$ calculated 273.1849, Δ = 2.52 ppm.

FTIR(film)= 2930, 2857, 1616, 1418, 1075, 740, 651 cm^{-1}.

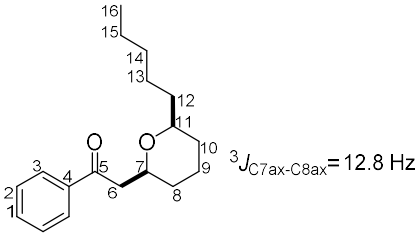
Hemiacetal

After 200 h, the isomers, in a solution of $CDCl_3$, was found to interconvert 1.6:1 r.r.
Only the ^{1}H peaks that could be distinguished are reported for clarity.

1H NMR (400 MHz, CDCl3) δH: 7.92 – 7.84 (m, 2H, C3), 7.53 – 7.48 (m, 1H, C1), 3.87 – 3.76 (m, 1H, C11), 3.48 (d, J = 15.7 Hz, 1H, C6H1), 2.78 (d, J = 15.7 Hz, 1H, C6H2), 0.76 – 0.64 (m, 3H, C16) ppm.

13C NMR (101 MHz, CDCl3) δC: 201.8 (C5), 137.9 (C4), 133.5 (C1), 128.6 (C2/C3), 128.5 (C2/C3), 96.5 (C7), 69.9 (C11), 47.7 (C6), 36.2, 35.4, 31.9, 31.1, 25.1, 22.7, 19.0, 14.1 (C16) ppm.

1D EXSY NMR taken at 6.12, 3.48 and 2.78 ppm did not show interconversion of the isomers.



2-(6-pentyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (**S5-04**)

To a rapidly stirred solution of 1,3 dicarbonyl **S50-2/S5-03** (101 mg, 0.33 mmol, 1 eq)[a] and $SiEt_3H$ (210 µL, 1.3 mmol, 3.5 eq) in DCM (5 mL) was added TFA (150 µL, 0.88 mmol, 2.5 eq) dropwise over 5 mins at -78 °C. After 2 min, the reaction was warmed to -30 °C. After 1 h, upon consumption of the 1,3-dicarbonyl by TLC, the reaction was quenched with water (10 mL), warmed to rt and diluted with DCM (5 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 x 7 mL). The combined organic layers were dried with $NaSO_4$ and concentrated *in vacuo* to give the crude product. Purification by FCC (Pentane: Et_2O, 90:10) gave the desired THP **S5-04** as a yellow oil (80 mg, 0.29 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.97 (d, *J* = 8.4 Hz, 2H, C3), 7.54 (td, *J* = 7.4, 1.1 Hz, 1H, C1), 7.44 (t, *J* = 7.6 Hz, 2H, C2), 3.93 (dtd, *J* = 12.8, 6.4, 2.0 Hz, 1H, C7), 3.30 (dd, *J* = 15.7, 6.5 Hz, 2H, $C6H_1$+C11), 2.93 (dd, *J* = 15.6, 6.2 Hz, 1H, $C6H_2$), 1.87 – 1.79 (m, 1H, $C9H_1$), 1.77 – 1.70 (m, 1H, $C8H_1$), 1.60 – 1.51 (m, 2H, $C9H_2$+$C13H_1$), 1.47 – 1.39 (m, 1H, $C10H_1$/$C12H_1$), 1.37 – 1.28 (m, 2H, $C10H_2$+$C12H_2$), 1.28 – 1.13 (m, 7H, $C8H_2$+$C13H_2$+C14+C15+$C10H_1$/$C12H_1$), 0.87 – 0.80 (m, 3H, C16) ppm.

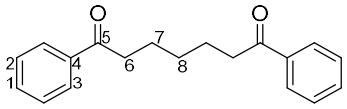
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 199.0 (C5), 137.6 (C4), 133.1 (C1), 128.6 (C3), 128.5 (C2), 78.2 (C11), 74.7 (C7), 45.8 (C6), 36.6 (C10/C12), 32.0 (C8+C14), 31.5 (C13), 25.3 (C10/C12), 23.7 (C9), 22.7 (C15), 14.2 (C16) ppm.

HRMS: ESI^+ found $[M+Na]^+$ = 297.1835, $C_{18}H_{26}O_2Na$ calculated 297.1825, Δ = 3.35 ppm.

FTIR(Film)= 2981, 1686, 1472, 1381, 1251, 1153, 1073, 955 $cm.^{-1}$

[a] The material was subjected 2 h after the initial 11:1 ratio was measured. The effect of the initial isomeric ratio on the reduction is not known

6.6.2. Ring Closing Reactions.



1,7-dipheone (**5-36**)

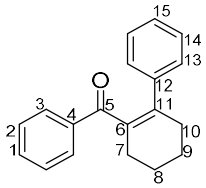
$SOCl_2$ (1.6 mL) was added dropwise to neat heptanedioic acid (1.28 g, 8.00 mmol) at rt under rapid stirring. After 30 min, once effervescence had stopped, the reaction was heated to reflux (80 °C). After 4h, the reaction was concentrated under reduced pressure with gaseous $SOCl_2$ filtered through a KOH trap. The acid chloride was used in the next step without further purification.

To a solution of the crude acid chloride in benzene: DCM (1:1, 8 mL) was added $AlCl_3$ (2.3 g, 17.6 mmol, 2.2 eq) portion-wise and the mixture was heated to 79 °C. After 90 mins, the reaction was cooled to rt; the solution was diluted with DCM (30 mL) and quenched by pouring the solution over ice (c.a. 100 g). The layers were separated, and the aqueous layer was extracted with DCM (3 x 40 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by FCC (Pentane:Et_2O, 99:1→98:2) gave the desired dicarbonyl **5--36** as a white solid (1.62 g, 5.77 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 8.00 – 7.92 (m, 4H, C3), 7.56 (tt, *J* = 7.6, 1.3 Hz, 2H, C1), 7.49 – 7.42 (m, 4H, C2), 3.00 (t, *J* = 7.3 Hz, 4H, C6), 1.81 (p, *J* = 7.4 Hz, 4H, C7), 1.56 – 1.44 (m, 2H, C8) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 200.5 (C5), 137.2 (C4), 133.1 (C1), 128.7 (C2), 128.2 (C3), 38.5 (C6), 29.1 (C8), 24.2 (C7) ppm.

Data in agreement with literature.[273]



phenyl(3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (**5-35**)

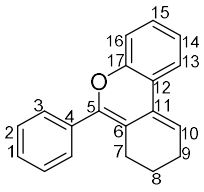
A freshly synthesised Al(O*t*-Bu)$_3$ in dry toluene (0.5 M) was made using General Method 4E.

To diketone **5-36** (83 mg, 0.30 mmol, 1 eq) was added Al(O*t*-Bu)$_3$ (1.5 mL, 0.5 M, 0.75 mmol, 2.5 eq). The solution was heated to 110 °C and stirred for 18 h. The solution was cooled to rt, filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude product was purified by FCC (Pentane:Et_2O 99:1) to give the product (42 mg, 0.16 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.64 – 7.58 (m, 2H, C3), 7.29 – 7.22 (m, 1H, C1), 7.18 – 7.10 (m, 2H, C2), 7.04 – 6.96 (m, 4H, C13+C14), 6.96 – 6.90 (m, 1H, C15), 2.48 – 2.42 (m, 2H, C7/C10), 2.42 – 2.36 (m, 2H, C7/C10), 1.86 – 1.71 (m, 4H, C8+C9) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 201.4 (C5), 141.8 (C11), 139.9 (C6), 136.9 (C4), 135.4 (C12), 132.4 (C1), 129.2 (C3), 128.0 (C2), 127.9 (C13+C14), 127.2 (C15), 30.9 (C10), 28.1 (C7), 22.9 (C9), 22.1 (C8) ppm.

Data in agreement with literature.[94]



6-phenyl-8,9-dihydro-7H-benzo[c]chromene (**5-53**)

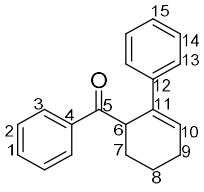
To a solution of diketone **5-36** (83 mg, 0.30 mmol, 1 eq) in toluene (1.5 mL) was added *p*TSA·H_2O (29 mg, 0.15 mmol, 0.15 mmol) dropwise and the reaction was heated to 80 °C. After 18 h, the suspension was cooled to rt, filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude product was purified by FCC (Pentane) to give the product **5-53** (49 mg, 0.19 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.59 (d, *J* = 6.7 Hz, 1H, C13/C16), 7.54 – 7.44 (m, 4H, C2+C3), 7.40 – 7.32 (m, 2H, C1+C13/C16), 7.22 (td, *J* = 7.5, 1.3 Hz, 1H, C14/C15), 7.16 (td, *J* = 7.3, 1.2 Hz, 1H, C14/C15), 6.98 (t, *J* = 4.5 Hz, 1H, C10), 2.79 (t, *J* = 6.5 Hz, 2H, C7), 2.53 (td, *J* = 5.9, 4.5 Hz, 2H, C9), 1.90 (p, *J* = 6.1 Hz, 2H, C8) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 143.3, 140.4, 135.4, 135.2, 134.9, 134.6, 129.9 (C10), 128.9 (C2/C3), 128.5 (C2/C3), 127.3, 127.2, 124.3, 119.2 (C13/16), 119.2 (C13/16), 26.4 (C9), 24.6 (C8), 24.1 (C7) ppm.

HRMS: ESI$^+$ found $[M+H]^+$ = 261.1274, $C_{19}H_{17}O^+$ calculated 261.1274, Δ = 0 ppm.

FTIR(film) = 2981, 2888, 2360, 2341, 1382, 1251, 1152, 1074, 700 cm^{-1}.



phenyl(2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)methanone (**5-35'**)

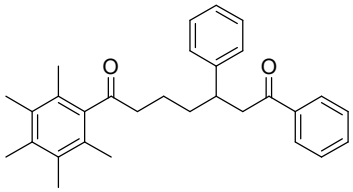
diketone **5-36** (83 mg, 0.30 mmol, 1 eq) and *p*TSA·H_2O (29 mg, 0.15 mmol, 0.15 mmol) were added to a microwave vial, and the flask was evacuated and backfilled with N_2 6 times. Argon-sparged toluene (1.5 mL) was added, and the solution was heated to 80 °C. After 8 h, the reaction was cooled to rt and the solution was filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude product was purified by FCC (Pentane) to give the product **5-35'** as an inseparable mixture of regioisomers (42 mg, 0.16 mmol, 53%, 3:1 r.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.05 – 7.99 (m, 2H, C3), 7.60 – 7.53 (m, 1H, C1), 7.52 – 7.41 (m, 2H, C2), 7.31 – 7.25 (m, 2H, C13), 7.24 – 7.18 (m, 2H, C14), 7.17 – 7.11 (m, 1H, C15), 6.39 (ddd, *J* = 4.5, 3.7, 1.1 Hz, 1H, C10), 4.73 (tt, *J* = 4.8, 1.6 Hz, 1H, C6), 2.42 – 2.33 (m, 1H, $C9H_1$), 2.32 – 2.20 (m, 1H, $C9H_2$), 2.18 – 2.07 (m, 1H, $C7H_1$), 2.02 (dq, *J* = 13.7, 4.5 Hz, 1H, $C7H_2$), 1.68 (dq, *J* = 7.3, 4.7 Hz, 2H, $C8H_1$+$C8H_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 201.2 (C5), 141.8 (C11), 136.2 (C4), 135.3 (C12), 133.1 (C1), 129.0 (C10), 128.8 (C2), 128.6 (C3), 128.5 (C14), 126.8 (C15), 125.5 (C13), 45.2 (C6), 27.4 (C7), 25.7 (C9), 18.8 (C8) ppm.

HRMS: ESI^+ found $[M+H]^+$ = 263.1430, C19H18NaO+ calculated 263.1430, Δ = 0.

FTIR: 2981, 2888, 2360,2341, 1382, 1252, 1152, 1073, 955 cm^{-1}.



7-(pentamethylphenyl)-1,3-diphenylheptane-1,7-dione (**5-32**)

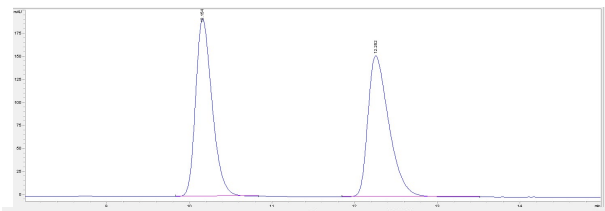
Enantioselective catalytic method

Al Binol complex **5-23** (0.05M in toluene) was prepared as described in General Procedure 4E.

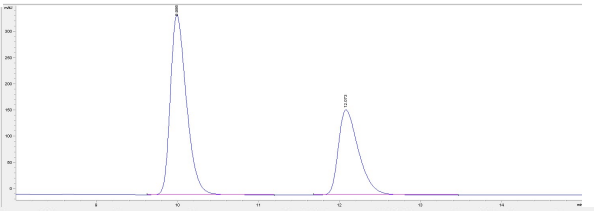
THP **5-31** (26 mg, 0.060 mmol, 1 eq) were added to a microwave vial, and the flask was evacuated and backfilled with N_2 four times. Al Binol complex **5-23** (180 µL, 0.05 M, 0.009 mmol, 15 mol%) and dry toluene (160 µL) were added *via* syringe, and the solution was heated to 110 °C. After 6 h, the reaction was cooled to rt; the suspension was filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. NMR Yield (12%) was determined using TMB as a standard. The crude was purified by prep TLC to allow the e.e. (26%) to be determined.

Data in agreement with structure previously reported.

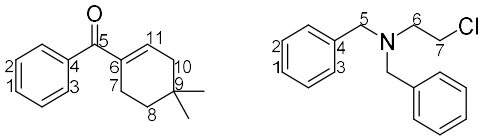
Chiral HPLC: (Chiralpak IA with guard, 10% IPA, 90% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.154	BB	2674.3	192.7	0.2139	49.711	0.689
2	12.252	BB	2705.3	153.1	0.2701	50.289	0.562



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.986	BB	4750.4	343.9	0.2112	62.680	0.639
2	12.073	BB	2828.4	162.7	0.2648	37.320	0.563



(4,4-dimethylcyclohex-1-en-1-yl)(phenyl)methanone (**5-61**) and N,N-dibenzyl-2-chloroethan-1-amine (**5-62**)

Dibenzylamine (288 µL, 1.5 mmol, 3eq) was subjected to General Method 4E to form $Al(NBn_2)_3$ in solution (0.19 M in DCE).

THP **5-60** (23 mg, 0.1 mmol, 1 eq) was added to a microwave vial, and the flask was evacuated and backfilled with N_2 four times. $Al(NBn_2)_3$ (1.10 mL, 0.19 M in DCE, 0.20 mmol, 2 eq) was added, and the solution was heated to 110 °C and stirred for 18 h. The solution was cooled to rt, filtered through a Silica plug (eluting with EtOAc) and concentrated under reduced pressure to give the crude product. The crude product was purified by FCC (Pentane:Et_2O 98:2→95:5) to give the amine **5-62** (14 mg, 0.054 mmol, 9% w.r.t. dibenzyl amine) and the cyclohexene **5-61** (10 mg, 0.046 mmol, 46%).

Tertiary amine

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.42 – 7.35 (m, 4H, C3), 7.35 – 7.29 (m, 4H, C2), 7.24 (tt, *J* = 6.1, 1.6 Hz, 2H, C1), 3.65 (s, 4H, C5), 3.49 (t, *J* = 7.2 Hz, 2H, C6), 2.83 (t, *J* = 7.1 Hz, 2H, C7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 139.3 (C4), 128.9 (C3), 128.4 (C2), 127.3 (C1), 58.9 (C5), 55.5 (C7), 42.0 (C6) ppm.

Data in agreement with previous literature.[274]

Cyclohexene

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.57 – 7.53 (m, 2H, C3), 7.46 – 7.39 (m, 1H, C1), 7.33 (ddt, *J* = 8.3, 6.6, 1.2 Hz, 2H, C2), 6.43 (tt, *J* = 4.0, 1.7 Hz, 1H, C11), 2.38 (ddq, *J* = 6.5, 4.3, 2.1 Hz, 2H, C7), 1.97 (dt, *J* = 4.5, 2.4 Hz, 2H, C10), 1.42 (t, *J* = 6.5 Hz, 2H, C8), 0.90 (s, 6H, C9Me) ppm.

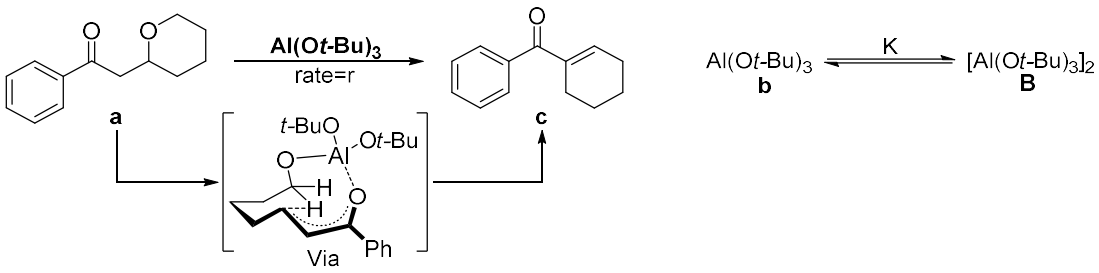
^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 198.2 (C5), 143.3 (C11), 138.9 (C4/C6), 137.6 (C4/C6), 131.4 (C1), 129.2 (C3), 128.1 (C2), 40.2 (C10), 35.0 (C8), 28.7 (C9), 28.3 (C9Me), 21.9 (C7) ppm.

Data in agreement with previous literature.[16]

6.7. Mathematics for Aluminium Rate Orders.

The derivation of the aluminium rate orders shown in (Table 7-1) are described below for reference. The assumptions made in the derivations are in bold

Assume One Aluminium is in the Bridge. Aluminium species are in equilibrium.



$Rate = r[a][b]$, $K = \frac{[B]}{[b]^2}$ and $[b]_0 = [b] + 2[B]$

Where $[b]_0$ is the initial input concentration.

Then $[b]_0 = 2K[b]^2 + [b]$

Using the quadratic formula.

$$[b] = \frac{(1 + 8K[b]_0)^{0.5} - 1}{4K}$$

If $1 >> 8K[b]_0$ *i.e.* The equilibrium heavily favours the aluminium dimer.

Then $(1 + 8K[b]_0)^{0.5} - 1 \approx 8K{[b]_0}^{0.5}$ inserting this back in the rate equation.

$Rate \approx \frac{2^{0.5} r[a][\boldsymbol{b}]_0^{\mathbf{0.5}}}{2K^{0.5}}$, **Order 0.5**

Physically this corresponds to formation of the dimer increasing inhibiting the reaction.

If $1 << 8K[b]_0$ *i.e.* The equilibrium heavily favours the aluminium monomer.

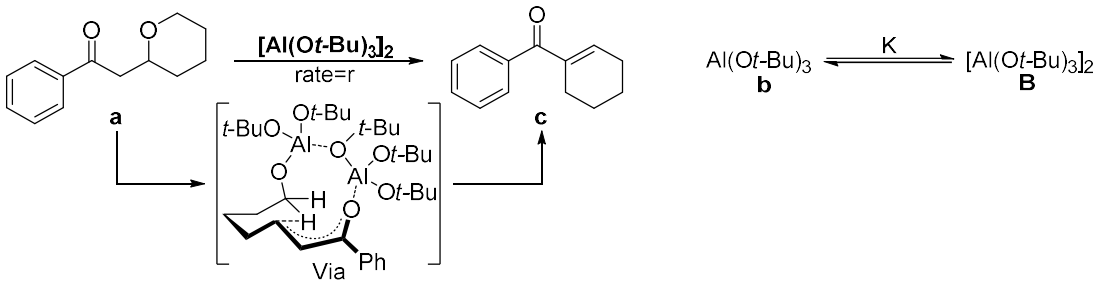
Then using a taylor expansion $(1 + 8K[b]_0)^{0.5} \approx 1 + 4k[b]_0 + \ldots$

$[b] \approx [b]_0$ inserting this back in the rate equation.

$Rate \approx r[a][\boldsymbol{b}]_0$, **Order 1**

Physically this intuitively says that if the dimer doesn't form these terms disappear.

Assume Two Aluminiums are in the Bridge. Aluminium species are in equilibrium.



$Rate = r[a][B]$, $K = \frac{[B]}{[b]^2}$ and $[b]_0 = [b] + 2[B]$

Then $[b]_0 = 2[B] + K^{-0.5}[B]^{0.5}$ or $K^{0.5}[b]_0 = 2K^{0.5}[B] + [B]^{0.5}$

Using the quadratic formula.

$$[B]^{0.5} = \frac{(1 + 8K[b]_0)^{0.5} - 1}{4K^{0.5}}$$

If $1 >> 8K[\boldsymbol{b}]_0$ *i.e.* The equilibrium heavily favours the aluminium dimer.

Then $(1 + 8K[b]_0)^{0.5} - 1 \approx 8K{[b]_0}^{0.5}$

$[B]^{0.5} \approx 2^{-0.5}{[b]_0}^{0.5}$ inserting this back in the rate equation.

$Rate \approx \frac{r[a][\boldsymbol{b}]_0}{2}$, **Order 1**

Physically this corresponds to the amount of dimer being equal to half the monomer added.

If $1 << 8K[\boldsymbol{b}]_0$ *i.e.* The equilibrium heavily favours the aluminium monomer.

Then using a taylor expansion $(1 + 8K[b]_0)^{0.5} \approx 1 + 4K[b]_0 + \ldots$

$[B]^{0.5} \approx K^{0.5}[b]_0$ inserting this back in the rate equation.

$Rate \approx rK[a][\boldsymbol{b}]_0^2$, **Order 2**

Physically this corresponds to an independent 3 component transition state.

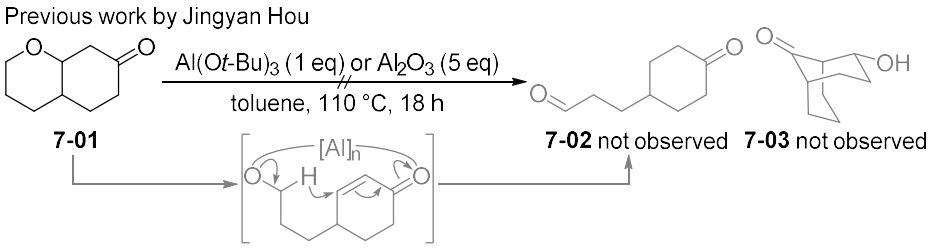
Chapter 7. Appendix

7.1. Kinetics of Aluminium Catalysis.

In Chapters 4 and 5, we have avoided discussing the exact aluminium complexes involved in each step of the reaction sequence. The following section collates the experimental data collected by Jingyan Hou and myself, which we believe gives insight into some of these mechanistic details and compares it to the conclusions of the computational work by Ming Kit Sze and co-workers[93,217]

7.1.1. Aluminium Coordination and Bridging.

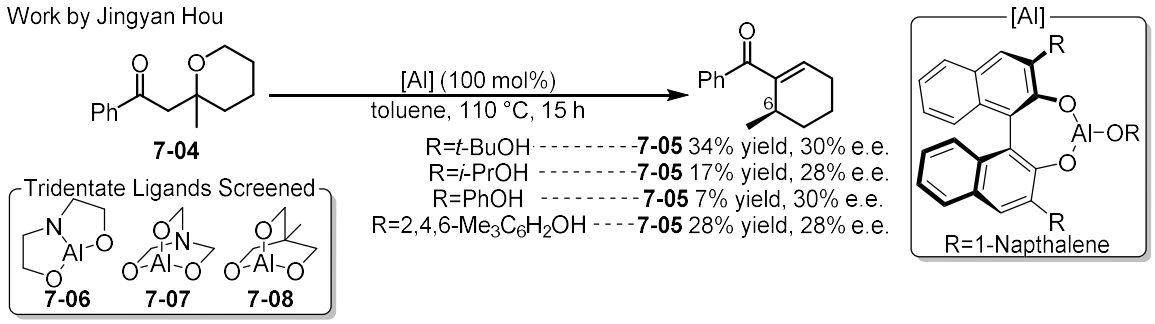
We previously showed in Section 4.13.2 that aluminium alkoxides didn't facilitate intermolecular hydride transfer into enones, suggesting the reaction occurs intramolecularly even when a large amount of free alcohol is available. Computational work by Ming Kit Sze suggests that aluminium bridges the two oxygen in the substrate; hence, the rigid structure of the cyclohexene **7-01** would be unable to react. This was validated experimentally by Jingyan Hou. Based on this, we believe the 1,5-hydride shift involves intramolecular bridging in the transition state (Scheme 7-1). The number of atoms in the bridge is discussed later in the Appendix.



Scheme 7-1) Reactions suggest hydride transfer is intramolecular and involves bridging of the oxygens.

7.1.2. Ligand Exchange.

During the reaction, formal ligand exchange may occur on the Al-complex, this makes intuitive sense and is supported by two experiments (Scheme 7-2). It was found that tridentate aluminium-complexes **7-06-7-08** did not facilitate hydride transfer suggesting the chelate effect stops the reaction from occurring. Jingyan Hou also found changing the third ligand of the aluminium reagent was found to have minimal effect on the e.e., which is consistent with the ligand not being present during the enantiodetermining hydride shift.

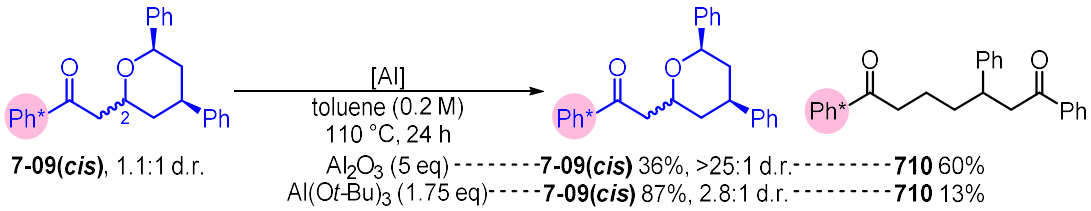


*Scheme 7-2) No effect was observed when Jingyan Hou changed the monodentate ligand on the Al-complex during the 1,5-hydride transfer reaction. Tridentate aluminium complexes **7-06**-**7-08** were screened by Ciaran Lunt.*

7.1.3. The Rate Limiting Step.

Experimental data suggest the rate-determining step dependends on the substrate and the Al-complex used. The diketone is selectively formed as the major product in the 2,6-substituted THP rings discussed throughout Chapter 5; hence, condensation is clearly rate-limiting in these examples.[a]

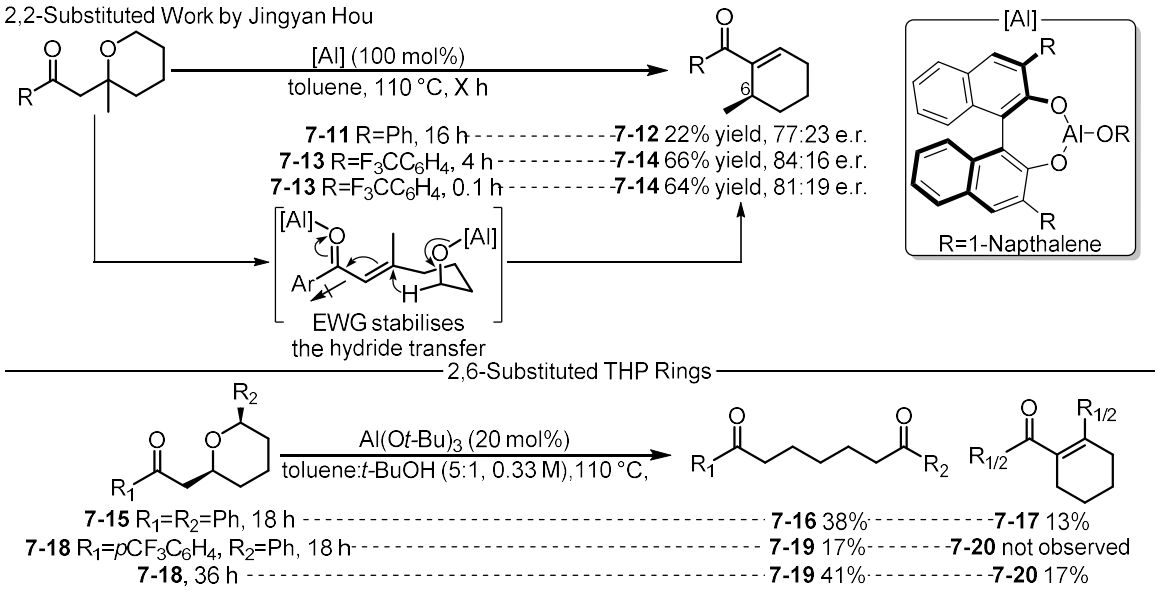
Our initial presumption was that the reaction proceeds with rapid, reversible ring opening of the THP **7-09** with the rate limiting hydride transfer. When the 2,4,6-substituted THP **7-09** was subjected to 1,5-hydride transfer using Al_2O_3, the C2-centre of the recovered SM was found to fully epimerise, consistent with our initial assumption (Scheme 7-3). However, under alkoxide conditions the THP **7-09** was recovered in 2.8:1 d.r., suggesting that using Al(O*t*-Bu)$_3$, ring opening was happening at a similar rate to the 1,5-hydride transfer.



*Scheme 7-3) 1,5-hydride transfer in 2,4,6-substituted THP rings **7-09**. The lack of C2-epimerisation under alkoxide conditions suggests rate-limiting THP ring opening.*

Jingyan Hou observed a significant increase in the reactivity with *p*-CF_3 substituted ketone **7-13** compared to the unsubstituted ketone **7-11**, allowing the reaction to run at lower temperatures and a shorter time periods than previously possible (Scheme 7-4). The rate increase would be consistent with the 1,5-hydride shift, where charge builds up as the enolate is formed, being the slow step. When the same group was incorporated into the 2,6-substrates **7-18**, the rate decreased, suggesting a significant change in the reaction profile.

[a] No evidence for the condensation being reversible has been observed.



Scheme 7-4) Relative Rates of hydride transfer when the ketone group is changed. Addition of the p-CF_3 group results in a rapid increase in the 1,5-hydride transfer rate.

7.1.4. Number of Aluminium Alkoxides Involved in the Reaction.

Whilst the computational and experimental data suggest the aluminium reagent bridges the two oxygen atoms, determining the bridge's length is a more complex question.

Computational work by Ming Kit Sze looked at whether a one or two aluminium bridges best facilitate the reaction.[217] Regardless of the alkene conformation, having two metals in the bridge appeared to be favoured (Figure 7-1). According to these calculations, a single aluminium transition state is disfavoured because of the high free energy cost of splitting the $[Al(O\textit{t}\text{-}Bu)_3]_2$ dimer.[a]

[a] Calculations suggest the monomer, dimer equilibrium value is not significantly changed between the OMe and O*t*-Bu substrates.

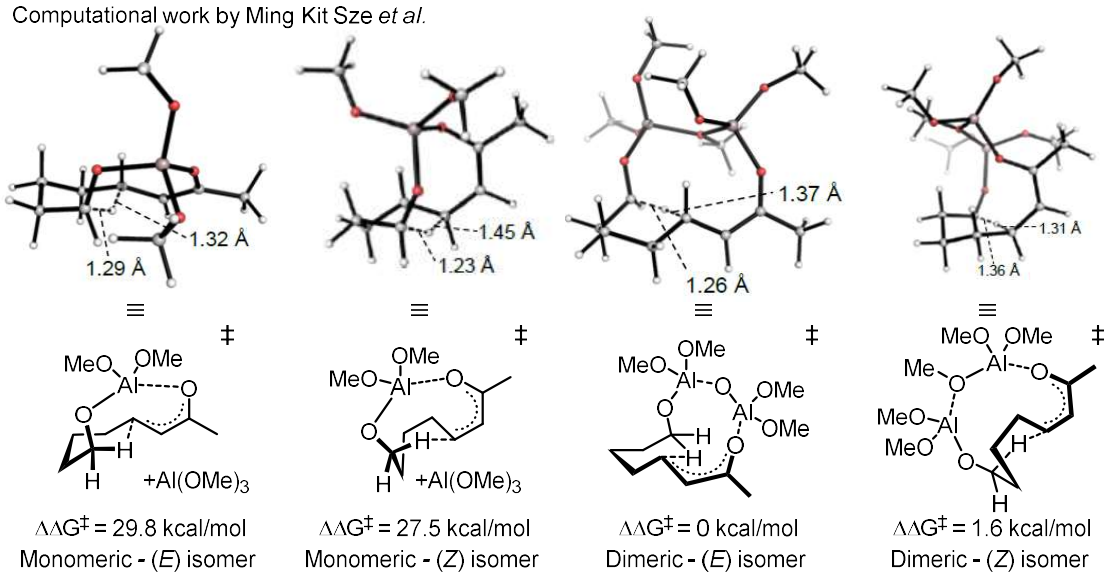
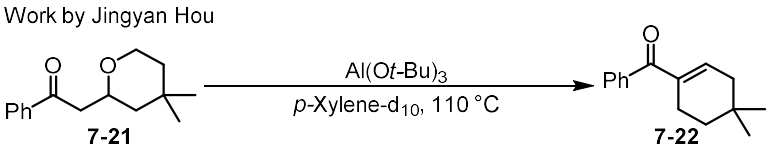


Figure 7-1) Free energy of the 1,5-hydride shift transition state with different mechanistic modes via s-cis-conformer of the E-enone with the unsubstituted system. Calculations and graphics were done by Ming Kit Sze.

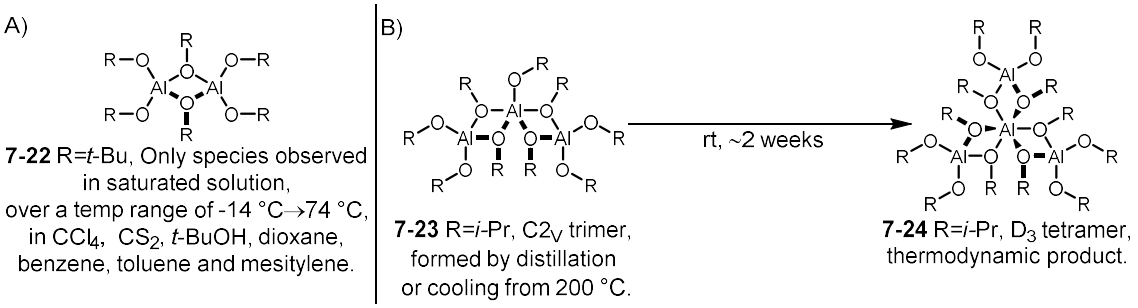
Jingyan Hou undertook kinetic studies to experimentally determine the order of reactivity w.r.t. Al(O*t*-Bu)$_3$ to try and corroborate the computational work (Scheme 7-5).



Scheme 7-5) Model system used by Jingyan Hou.

The first thing to consider is what aggregates of aluminium alkoxides exist in solution. Al(O*t*-Bu)$_3$ has been shown to sit as a dimer **7-22** in a saturated solution across a range of temperatures and solvents, including toluene at 85 °C (Scheme 7-6 A).[275,276] No higher aggregates have been observed with Al(O*t*-Bu)$_3$,[277] but smaller complexes such as Al(O*i*-Pr)$_3$ thermodynamically favour tetramer complex **7-24**, which can form a crystalline solid (Scheme 7-6 B).[278,279][a] If the complex is cooled rapidly from 200°C→rt or freshly distilled, the trimeric structure **7-23** can be isolated, which reverts to the tetramer **7-24** over approximately two weeks at rt.[280] To our knowledge, the dimer/monomer equilibrium has not been measured. The lower aggregation of Al(O*t*-Bu)$_3$ has previously been shown to increase the reaction rate of MPV reactions, which involve a single Al in the transition state.[277]

[a] Structures have been proven by X-ray Crystallisation, ^{27}Al-NMR spectroscopy and ^{1}H-NMR spectroscopy.



*Scheme 7-6) (A) The bulk of the t-butoxide group results in dimerisation without larger oligomers forming. (B) Al(Oi-Pr)$_3$ is known to exist as a trimeric complex **7-23** or tetrameric complex **7-24**.*

If the free reagent sits in a monomer/dimer equilibrium, then the expected rate orders can be summarised in a simple Table depending on the dimerisation equilibrium and the number of aluminium substrates in the transition state. This results in four possible orders (Table *7-1*).[281,282]a

		Behaviour of the free aluminium complex.	
		Monomeric	Dimeric
Transition state.	One aluminium	1	0.5
	Two aluminium	2	1

Table 7-1) The theoretical rate order of a catalytic reagent which undergoes partial dimerisation.

Jingyan Hou measured the rate order of the 1,5-hydride shift and observed an order of 0.50±0.04 w.r.t. to Al(O*t*-Bu)$_3$ across a concentration range of 0.05 M to 0.4 M consistent with only one aluminium alkoxide being involved in the transition state (Figure 7-2). The data however, appears to be nonlinear, changing from approximately 0.80→0.32 across the range.[b] These experiments were also complicated by partial insolubility and the formation of Al_2O_3, which may result in the order not being accurately measured. The higher order at low concentrations would be consistent with the free aluminium complex tending toward being monomeric at sufficiently low concentration. In order to prove this explanation, the aggregation constant needs to be measured quantitatively.[275]

The apparent decrease of the order to 0.3 is harder to explain. The most obvious explanation is the formation of higher-order inactive aluminium oligomers [Al(O*t*-Bu)$_3$]$_n$ (n>2), although there is no evidence of these forming in the literature. Ligand exchange with the substrate **7-21** may allow higher-order inactive aggregates to form that are not observed with the pure Al

[a] The derivation of these values are included in the SI for future reference.
[b] Each concentration was repeated three times. Errors reported based on linear regression of the unaveraged data points. Curvature based on linear regression of the first six and last six data points respectively.

reagent. However, if higher order aggregates are forming, than the initial assumptions used to generate Table 7-1 are invalid.[275]

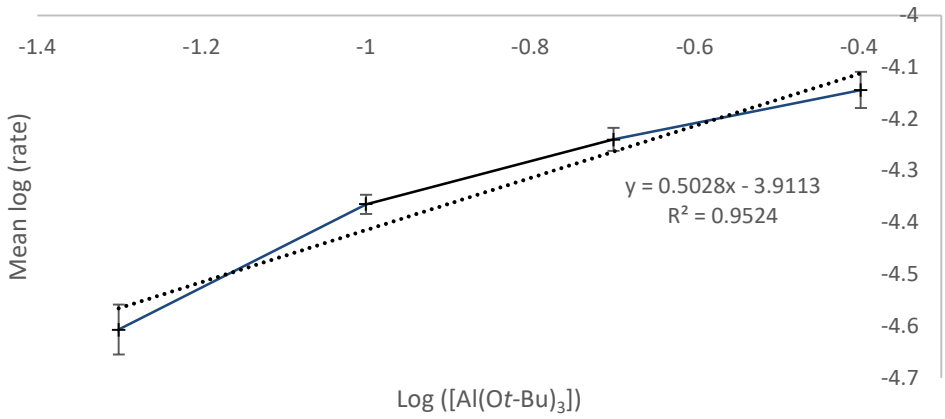
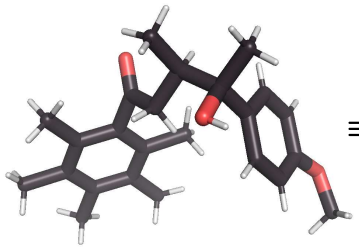


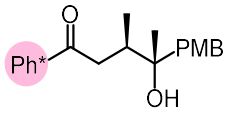
Figure 7-2) Reaction order of 1,5-hydride transfer to form the enone ***7-22*** *w.r.t. Al(Ot-Bu)3.*

An enantioselective version of the reaction allows non-linear effects of the reaction to be investigated.[283] However, non-linear effects are not generally measured for unstable chiral reagents meaning that a unique set of kinetics could cause any observed effect.

7.2. X-Ray Crystallographic Data and Structure Refinement for Compound **3-58**.



≡



Identification code 7320

Empirical formula $C_{24}H_{32}O_3$

Formula weight 368.52

Temperature 150 K

Wavelength 1.54184 Å

Crystal system Monoclinic

Space group P 21/c

Unit cell dimensions

a = 9.7446(3) Å, α= 90°.

b = 26.8775(8) Å, β= 98.057(3)°.

c = 7.9440(2) Å, γ = 90°.

Volume 2060.08(10) $Å^3$

Z^4

Density (calculated) 1.188 Mg/m^3

Absorption coefficient 0.600 mm^{-1}

F(000) 800

Crystal size 0.12 x 0.10 x 0.02 mm^3

Theta range for data collection 4.870 to 76.297°.

Index ranges -6<=h<=12, -33<=k<=32, -9<=l<=9

Reflections collected 10723

Independent reflections 4235 [R(int) = 0.033]

Completeness to theta = 72.848° 99.9%

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.99 and 0.97

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 4235 / 2 / 248

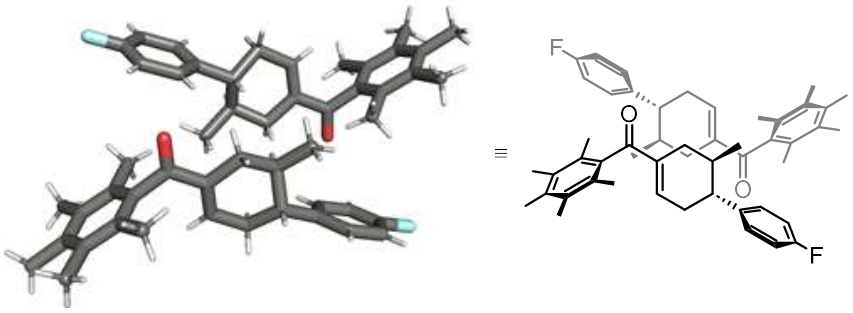
Goodness-of-fit on F2 0.9927

Final R indices [I>2sigma(I)] R1 = 0.0450, wR2 = 0.1127

R indices (all data) R1 = 0.0588, wR2 = 0.1253

Largest diff. peak and hole 0.30 and -0.28 $e.Å^{-3}$

7.3. X-Ray Crystallographic Data and Structure Refinement for Compound **4-138**.



Identification code 7674

Empirical formula $C_{25}H_{29}FO$

Formula weight 364.50

Temperature 150 K

Wavelength 1.54184 Å

Crystal system Triclinic

Space group P 1

Unit cell dimensions

a = 7.4929(2) Å α = 104.935(2)°.

b = 8.9245(2) Å β = 102.405(2)°.

c = 15.7499(4) Å γ = 91.067(2)°.

Volume 990.81(4) $Å_3$

Z^2

Density (calculated) 1.222 Mg/m^3

Absorption coefficient 0.619 mm^{-1}

F(000) 392

Crystal size 0.25 x 0.12 x 0.03 mm^3

Theta range for data collection 5.145 to 64.032°.

Index ranges -8<=h<=9, -11<=k<=11, -19<=l<=19

Reflections collected 27168

Independent reflections 7837 [R(int) = 0.037]

Completeness to theta = 73.960° 99.5%

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.98 and 0.89

Refinement method Full-matrix least-squares on F_2

Data / restraints / parameters 6433 / 3 / 488

Goodness-of-fit on F_2 0.9778

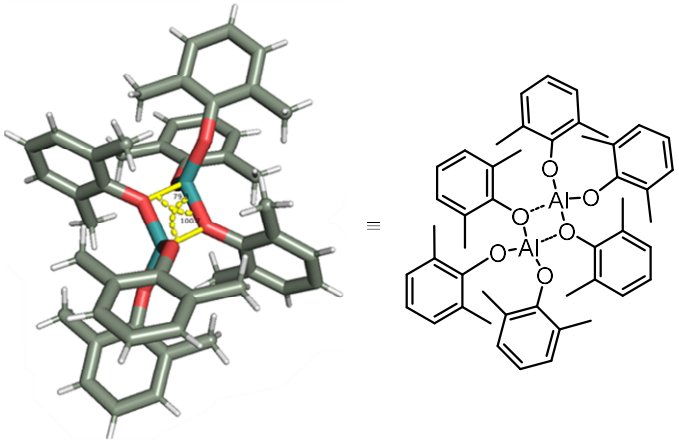
Final R indices [I>2σ(I)] R1 = 0.0813, wR2 = 0.2408

R indices (all data) R1 = 0.0819, wR2 = 0.2436

Absolute structure parameter 0.02(6)

Largest diff. peak and hole 0.49 and -0.44 $e.Å^{-3}$

7.4. X-Ray Crystallographic Data and Structure Refinement for Compound **4-165**.



Identification code 7668

Empirical formula $C_{49}H_{56}Al_2ClO_6$

Formula weight 830.40

Temperature 150 K

Wavelength 1.54180 Å

Crystal system Triclinic

Space group P -1

Unit cell dimensions

a = 12.1721(4) Å, α= 86.577(3)°.

b = 12.9178(4) Å, β= 73.261(3)°.

c = 15.5109(5) Å, γ = 70.764(3)°.

Volume 2203.48(13) $Å^3$

Z^2

Density (calculated) 1.251 Mg/m^3

Absorption coefficient 1.538 mm^{-1}

F(000) 882.000

Crystal size 0.22 x 0.17 x 0.15 mm^3

Theta range for data collection 3.627 to 76.182°.

Index ranges -12<=h<=15, -15<=k<=16, -19<=l<=19

Reflections collected 22088

Independent reflections 9093 [R(int) = 0.023]

Completeness to theta = 73.897° 99.6%

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.79 and 0.75

Refinement method Full-matrix least-squares on F_2

Data / restraints / parameters 9090 / 0 / 543

Goodness-of-fit on F_2 1.0033

Final R indices [I>2σ(I)] R1 = 0.0334, wR2 = 0.0880

R indices (all data) R1 = 0.0357, wR2 = 0.0908

Extinction coefficient 24(4)

Largest diff. peak and hole 0.33 and -0.25 $e.Å^{-3}$

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