Controlling Absolute Stereochemistry in Hydrogen Borrowing Catalysed Alkylation

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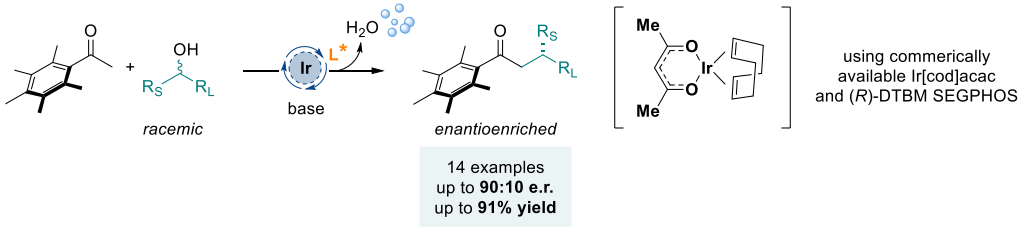
Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from May 2019 until May 2023. All of the work is entirely my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Daniella Cheang
May 2023

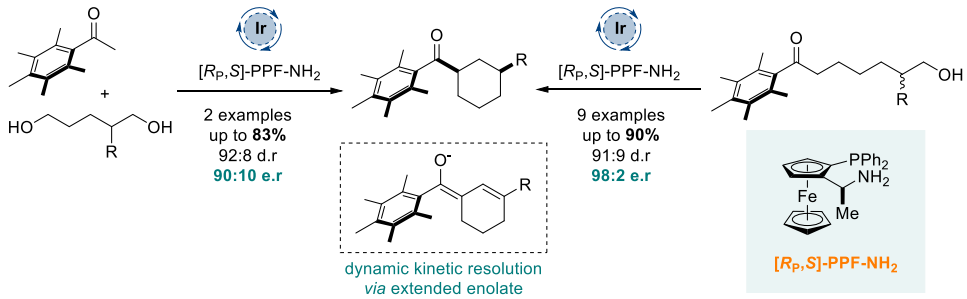
Abstract

Hydrogen borrowing catalysis has recently emerged as a powerful alternative strategy for C–C bond formation and represents a green alternative to typical alkylation methodologies. Described in this thesis are novel strategies for controlling the absolute stereochemistry in hydrogen borrowing catalysed alkylations. Chapter two details the enantioselective synthesis of β,β-disubstituted ketones, efficiently forming sterically hindered C(sp^3)–C(sp^3) carbon bonds. The key enantiodetermining step, controlling the β-stereogenic centre, is an asymmetric reduction of a tri-substituted enone. The β,β-disubstituted ketone products were further derivatised *via* Ph* cleavage to the corresponding amides, esters and alcohols showing no racemization of the newly installed stereogenic centre.



Scheme I. Enantioselective synthesis of β,β-disubstituted ketones *via* hydrogen borrowing catalysis.

Chapters three and four describe the development of methods controlling the γ-centre *via* dynamic kinetic resolution. Acyclic systems were explored, namely the alkylation of Ph* methyl ketone with racemic 1,2-amino alcohols demonstrating proof-of-concept reactivity *via* DKR (chapter 3). Subsequently, two complementary syntheses of enantioenriched γ-substituted cyclohexanes were developed (chapter 4). Mechanistic experiments revealed that alkylation with 1,5-diols led to a regioisomeric mixture of enone intermediates resulting in reduced enantioselectivity. By employing linear alcohols, a single enone intermediate was formed that could be racemised efficiently at the γ-centre *via* formation of an extended enolate, resulting in a highly enantioselective DKR process.



Scheme II. Enantioselective hydrogen borrowing annulation controlling the γ-stereogenic centre *via* DKR.

Acknowledgments

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Table of Contents

Abbreviations

Å	Ångström
Ac	acetyl
acac	acetylacetone
Ar	aryl
aq.	aqueous
B	base
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
°C	degree(s) Celsius
CBz	carboxybenzyl
cm^{-1}	wavenumber(s), inverse centimetre(s)
cod	1,5-cyclooctadiene
coe	Cyclooctadiene
conc.	Concentrated
COSY	COrrelation SpectroscopY
Cp*	pentamethylcyclopentadienyl
CPA	chiral phosphoric acid
Cy	cyclohexyl
d	days
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppBz	1,2-bis(diphenylphosphino)benzene
d.r.	diastereomeric ratio
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
ent-	enantiomeric-

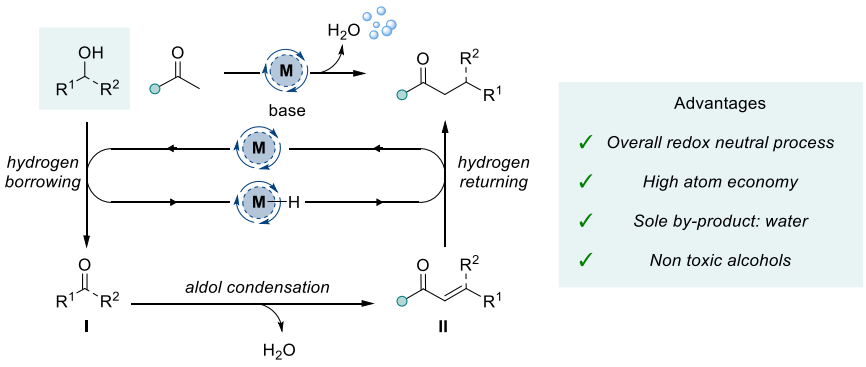
epi-	epimeric-
eq.	equivalent(s)
e.r.	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
[H]	hydride
HFIP	hexafluoroisopropanol
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQY	Heteronuclear Single Quantum coherence Spectroscopy
i	*iso*
IR	infrared spectroscopy
J	coupling constant (Hz)
L	ligand
L*	chiral ligand
LA	lewis acid
LDA	lithium diisopropylamide
M	molarity, mol dm^{-3}
*m*CPBA	*meta*-chloroperoxybenzoic acid
m.p.	melting point
Me	methyl
Mes	mesityl
min	minute(s)
mL	millilitre(s)
mol	mole(s)
MPV	Meerwein-Pondorf-Verley
MS	molecular sieves
n	normal, unbranched alkyl chain
NMR	Nuclear Magnetic Resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect SpectroscopY

Nu	nucleophile
o	*ortho*
[ox]	oxidation
p	*para*
PG	protecting group
Ph	phenyl
Ph*	pentamethylphenyl
PMP	4-methoxyphenyl
ppm	parts per million
Pr	propyl
q	quartet
Quant.	quantitative
R	generic substituent, Rest/Radical
recryst.	Recrystallisation
[red]	reduction
r.t.	room temperature
sat.	saturated
SET	single electron transfer
t	tertiary alkyl group, *tert*-alkyl
TBAF	tetra-*n*-butylammonium fluoride
Temp	Temperature
TFA	trifluoroaceticacid
THF	tetrahydrofuran
TLC	thin-layer chromatography
Tol	4-methylphenyl
Tr	trityl
Ts	toluenesulfonyl
UV	ultraviolet
ν_{max}	infrared absorption maximum
vs.	*versus*
X	generic halide
Xyl	3,5-di-methylphenyl

Chapter 1: Introduction

1.1. Hydrogen Borrowing Catalysis

Alkylation is a fundamental process in organic synthesis, typically achieved by deprotonation of the α-position of a carbonyl using a strong base. The resulting enolate is captured with a halide or pseudohalide electrophile. Despite this being a widely used strategy for carbon-carbon bond formation, in practice it suffers from significant drawbacks. For example, the electrophiles employed are typically highly toxic and the reactions produce stoichiometric quantities of waste. In addition, although good reactivity is observed with primary electrophiles, reactions with secondary electrophiles are often less efficient and can be hampered by competing elimination processes. Hydrogen borrowing catalysis has emerged as a powerful alternative alkylation strategy using transition metal catalysis, overcoming many of these disadvantages (Scheme 1.1).[1,2] A hydrogen borrowing reaction is initiated by dehydrogenation of an alcohol to form the corresponding carbonyl compound (**I**) and metal hydride *in situ*. Following aldol condensation with an enolate, the intermediate enone (**II**) is reduced by the metal hydride affording the saturated product and regenerating the active catalyst. This is therefore an overall redox neutral reaction and enables non-activated alcohols to serve as electrophiles, thereby negating the requirement for toxic alkyl halide electrophiles and producing water as the sole by-product of the alkylation.

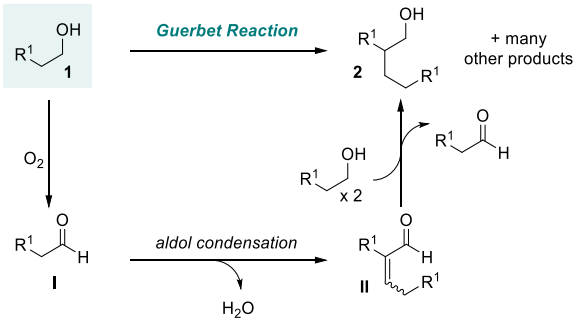


Scheme 1.1. An overview of hydrogen borrowing catalysis.

The majority of literature processes integrate an aldol condensation as the key C–C bond forming process. However, other transformations of the *in situ* formed carbonyl have been incorporated into the hydrogen borrowing pathway, including: Wittig,[3–5] Friedel-Crafts alkylation[6,7] or conjugate addition reactions.[8]

1.2. Early Developments in Hydrogen Borrowing Catalysis

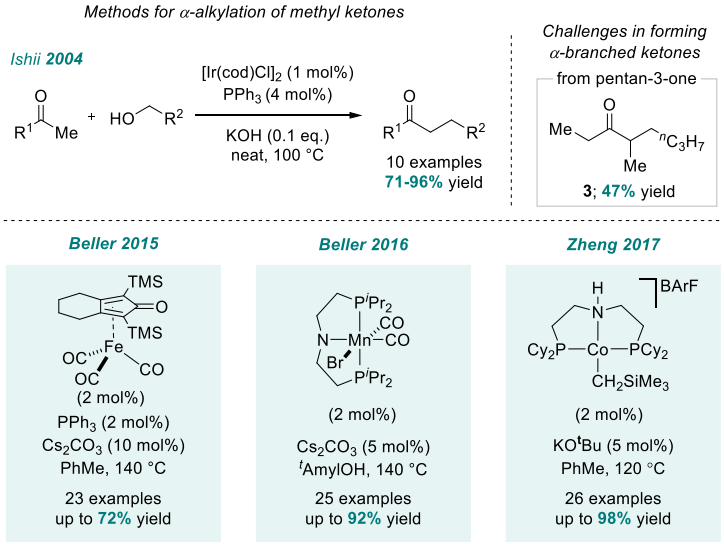
One of the earliest examples of a hydrogen borrowing-type reaction was developed by Guerbet in 1899.[9] Guerbet reported the homocoupling of linear alcohols at significantly elevated temperatures (typically 200 °C) to give branched mono-alcohols (Scheme 1.2). The reaction is initiated through spontaneous oxidation by oxygen (**I**), followed by self-aldol condensation (**II**) and two subsequent Meerwein-Pondorf-Verley (MPV) type reductions of the α,β-unsaturated aldehyde (by two additional equivalents of the alcohol) to give the saturated product (**2**). Alongside the product, two equivalents of aldehyde are generated, which propagates the reaction. The key limitation to this discovery is the tendency of side product and oligomer formation as well as competing processes such as Cannizzaro and Tishchenko reactions.[10]



Scheme 1.2. General mechanism of the Guerbet reaction.

Since then, development of a multitude of modern metal-catalysed processes forming C–C bonds *via* hydrogen borrowing catalysis have addressed the initial limitations of the Guerbet reaction, primarily focussing on the alkylation of ketones with primary alcohols.[1] A key breakthrough was reported by Ishii and co-workers in 2004, in which a range of methyl ketones

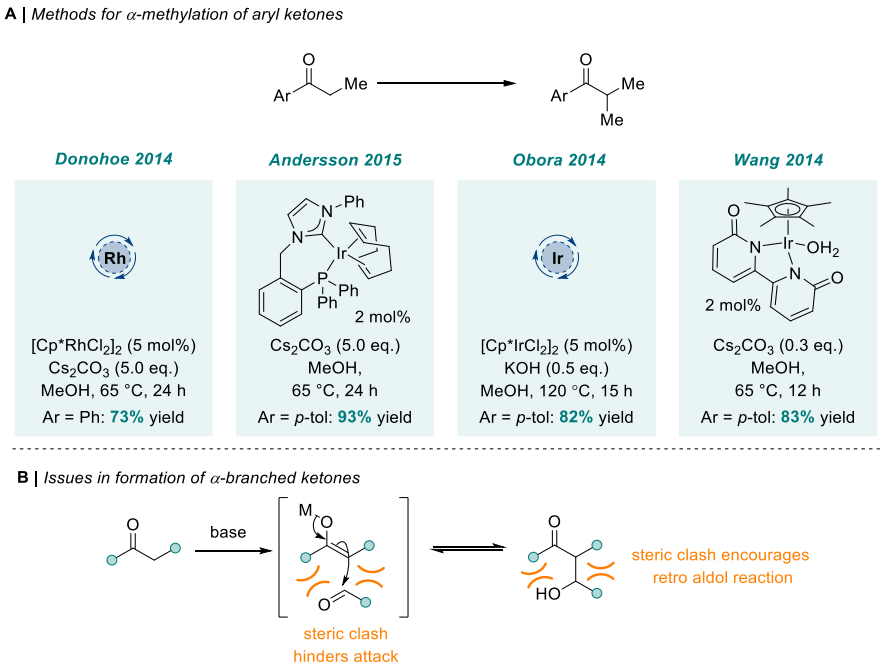
were α-alkylated with primary alcohols using [Ir(cod)Cl_2], PPh_3 and KOH in high yields (Scheme 1.3).[11] Although this was not the first report of transition metal catalysed hydrogen borrowing alkylation (previous methods typically used Ru catalysts and more dilute conditions),[12,13] Ishii's method removed the need for a sacrificial hydride acceptor, which earlier methods had employed to prevent over-reduction of the carbonyl. However, the authors reported that alkylation was less efficient for non-methyl ketones, affording α-branched ketone **3** in 47% yield (Scheme 1.3). Methods for α-alkylation of methyl ketones have since been developed for use with a wide range of earth-abundant metals, such as iron,[14] manganese[15] and cobalt (Scheme 1.3).[16]



Scheme 1.3. Iridium-catalysed ketone alkylation with primary alcohols.

While the synthesis of simple ketones in high yields was easily achieved using the method described above, the challenge of synthesising branched ketones remained. An alternative approach towards this, using a secondary alcohol substrate with a methyl ketone, was plagued by competing self-condensation of the ketone substrate and ketone intermediate derived from the secondary alcohol, resulting in a complex mixture of products. The problem of α-alkylation of higher order ketones (non-methyl) was first addressed through use of methanol as the electrophile in key contributions reported by Donohoe,[17] Andersson,[18] Obora,[19] and Wang[20]

groups (Scheme 1.4.A). Use of iridium or rhodium catalysts in combination with $CsCO_3$ or KOH in MeOH at elevated temperatures afforded a series of methylated aryl and hetereoaryl ketones in excellent yields. However, in the case of non-aryl ketones, double methylation and lower yields were generally observed. The success of using methanol as an electrophile is ascribed to three main factors: (i) its small size minimises the steric hindrance in the initial attack as well as in the aldol addition intermediate (Scheme 1.4.B); (ii) the high electrophilicity of formaldehyde facilitates the initial attack; (iii) formaldehyde cannot undergo competing self-condensation, which is often observed with aldehyde electrophiles.



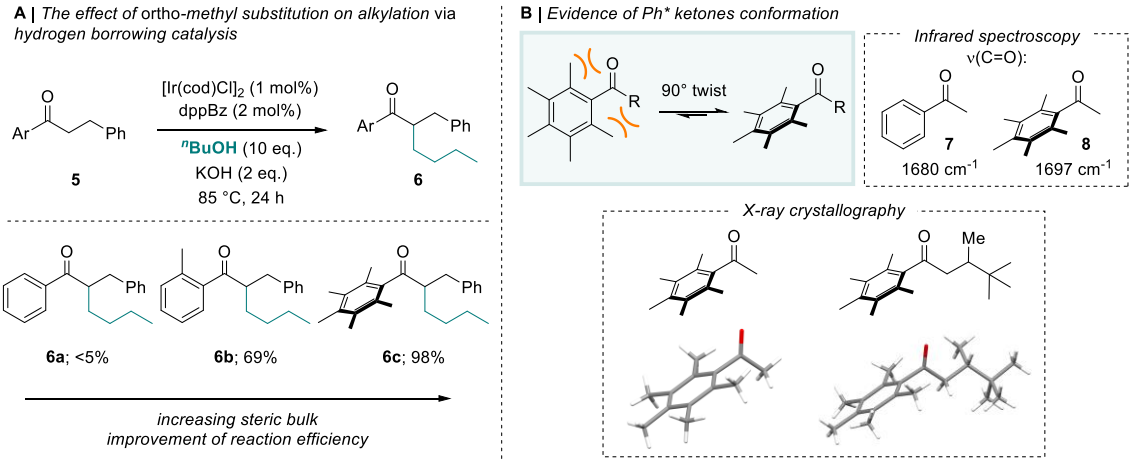
Scheme 1.4. Methods for α-methylation of ketones *via* hydrogen borrowing catalysis and issues facing the formation of branched ketones.

Although several methods for introducing α-methyl branched ketones had been established, a general transformation enabling the use of more complex alcohols to form branched ketones still remained unanswered. The additional steric bulk of 2° alcohols (or alkylation of non-methyl ketones) was detrimental on two accounts: increased hindrance (i) disfavoured initial enolate attack and (ii) destabilised the intermediate aldol adduct, likely favouring the retro-aldol reaction over elimination to the enone (Scheme 1.4.B).

1.3. Use of Ph Methyl Ketone in Hydrogen Borrowing Catalysis*

1.3.1 Acyclic Systems

To address the challenges in the synthesis of branched ketones, Donohoe and co-workers investigated a series of aryl ketones in hydrogen borrowing catalysis with *n*-butanol (Scheme 1.5.A).[21] Perhaps counterintuitively, they reported that increasing the steric bulk around the phenyl ring drastically improved the efficiency of α-alkylation. The pentamethyl phenyl (Ph*) group (**5c**) outperformed all other aryl ketones, and notably alkylation of acetophenone derived ketone (**5a**) only yielded trace product (**6a**). Using infrared (IR) spectroscopy and X-ray crystallographic analysis, the authors showed that due to steric clash of the di-*ortho* methyl groups of Ph* ketones, the aromatic ring is twisted out of conjugation with the carbonyl, resulting in an orthogonal structure (Scheme 1.5.B).[22]



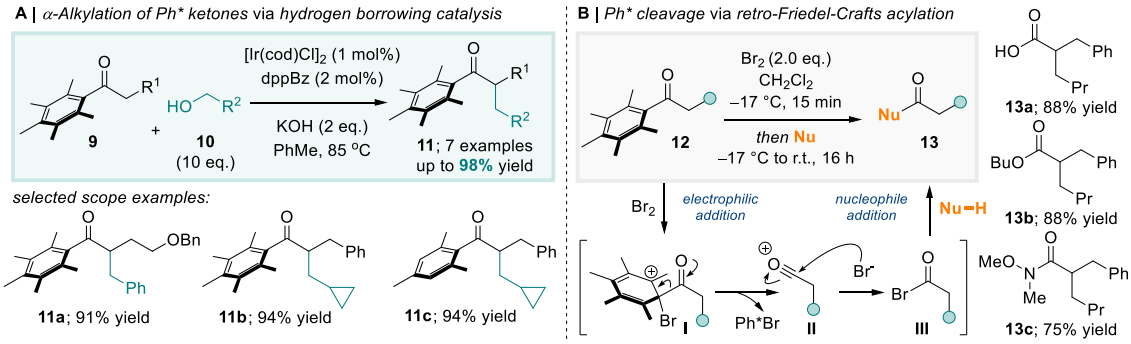
Scheme 1.5. Discovery of the Ph* group and its conformation.

Two key advantages were identified from this twisted conformation. Firstly, the di-*ortho* methyl groups project above and below the plane of the carbonyl and shield it from nucleophilic attack, ensuring no homo-dimerisation processes or over reduction at the carbonyl can occur.*

*Alcohol side products resulting from over reduction of the carbonyl are commonly observed in previous methodologies.[11,12,14]

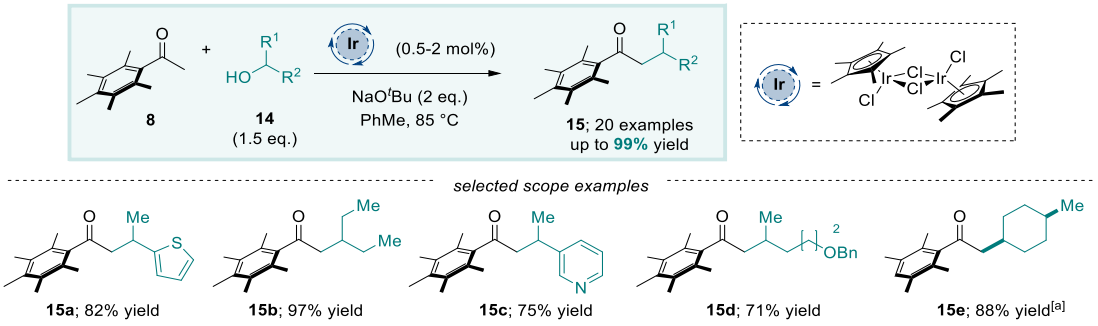
Secondly, the orthogonality between the aromatic ring and carbonyl may relieve steric hindrance at the α-position of the ketone, allowing favourable aldol reaction.

The discovery of the Ph* group represented an important advance in this area, as its employment addresses many of the previous limitations of hydrogen borrowing catalysis. This has enabled the development of a range of general processes – a brief overview follows. The first use of Ph* ketones was reported by Donohoe and co-workers in a series of α-alkylation processes (Scheme 1.6.A).[21] Initially, both Ph* and related mesityl ketones were alkylated using primary alcohol substrates in combination with $[Ir(cod)Cl]_2$ and dppBz ligand to give a range of α-branched ketones. However, a clear advantage of the Ph* group (*cf*. mesityl counterparts) was the ability to efficiently cleave it and simultaneously introduce functionality. The most versatile cleavage method involved treatment of the ketones with bromine in a retro-Friedel-Crafts acylation (Scheme 1.6.B).[23] The origins of this chemistry were first reported by Kitajima and co-workers, employing bromine in the presence of $AlBr_3$ to afford bromopentamethylbenzene and presumably the corresponding acid bromide.[24] Donohoe and co-workers utilised this by-product to develop Ph* cleavage conditions. The aromatic ring can be considered as relatively electron rich both due to the five methyl substituents and also as a result of the carbonyl being twisted out of conjugation. This allows *ipso*-addition to electrophiles such as bromine. The resulting Wheland intermediate (**I**) can then undergo fragmentation, forming an acylium ion (**II**) which can then be captured by a bromide ion. The resulting acid bromide (**III**) is a versatile intermediate, which can be directly converted in situ to a variety of functional groups, such as acids, esters and amides (**13a-c**, Scheme 1.6.B).



Scheme 1.6. α-Alkylation of Ph* ketones *via* hydrogen borrowing catalysis and Ph* cleavage.

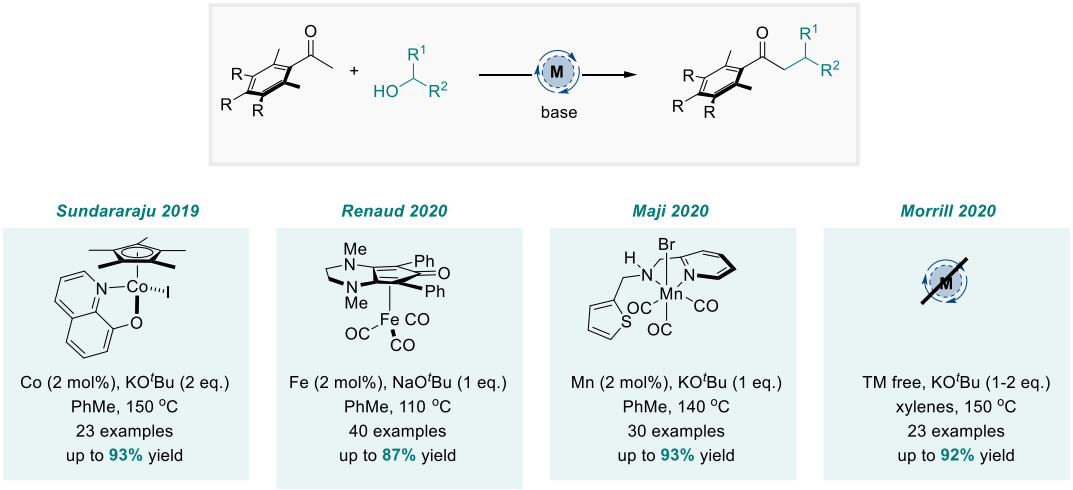
After this initial report, Donohoe and co-workers developed this methodology to enable the alkylation of Ph* methyl ketone (**8**) with secondary alcohols to afford β,β-branched ketones (Scheme 1.7).[25] The use of secondary alcohols in these transformations is more challenging as the *in situ* formed carbonyl is less electrophilic than the corresponding primary alcohol-derived aldehydes. Using commercially available $[IrCp^*Cl_2]_2$, a series of β,β-branched ketones were afforded in high yields. The authors attributed the success of this method to both the Ph* group, which prevents self-condensation and the slow oxidation of the secondary alcohol partner, ensuring formation of the desired cross-coupled aldol product. Notably, the equivalents of alcohol were reduced from the large excess that was needed in the initial work forming α-branched ketones, allowing more complex coupling partners to be used.



Scheme 1.7. Iridium catalysed alkylation of Ph* ketones with secondary alcohols. [a] KO^{t}Bu (3 eq.) and ROH (2 eq.) used.

Since the initial report of this work, it has been demonstrated that this transformation is possible using earth-abundant catalyst systems such as cobalt,[26] iron,[27] and manganese (Scheme

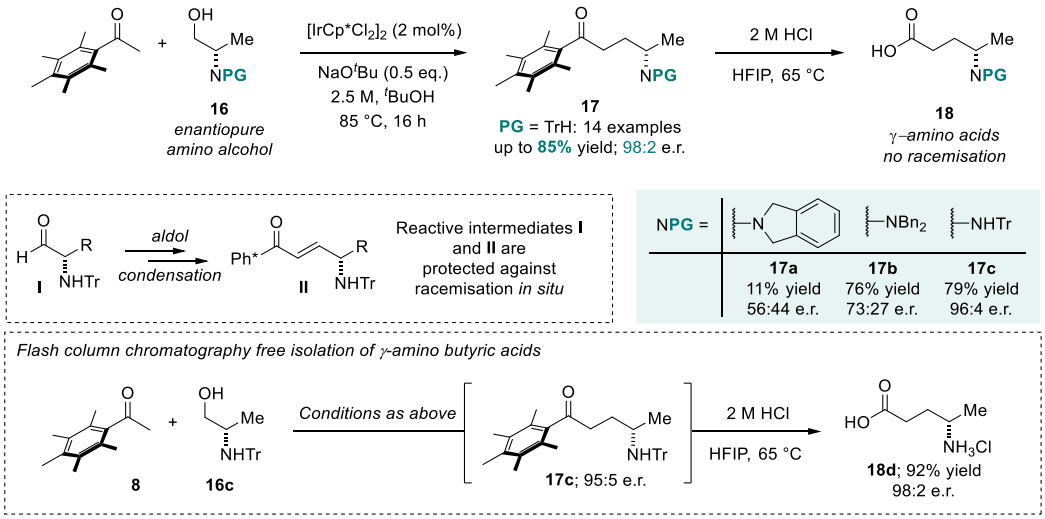
1.8).[28] Recently, Morrill and co-workers have reported a transition-metal-free alkylation of di-*ortho* substituted aryl ketones.[29] In this case elevated temperatures (150 °C) and a large excess of alcohol were needed to achieve efficient alkylation, with the metal-catalysed hydrogen borrowing and returning processes likely being replaced by Oppenauer oxidation and MPV reduction, respectively.



Scheme 1.8. Methods using earth-abundant catalysts or metal-free conditions in the alkylation of *ortho*-disubstituted aromatic ketones.

Generally, the scope of hydrogen borrowing alkylation reported in the literature has been limited to aliphatic and aromatic alcohols, with the use of nitrogen-containing alcohols in C–C bond formation processes underrepresented.[30,31] In light of this, Donohoe and co-workers developed an enantioretentive alkylation of Ph* methyl ketone (**8**) with 1,2-amino alcohols (Scheme 1.9).[32] Of note is the one-step access of the latter from the corresponding amino acids. The authors reported that the key to upholding stereochemical integrity in the presence of base was the careful choice of nitrogen protecting group. Increasing the steric hindrance of the substituents on nitrogen, for example triphenylmethane (trityl, Tr), resulted in a highly enantioretentive process with alanine-derived product accessed in 79% yield and 96:4 e.r. (**17c**, Scheme 1.9). This can be ascribed to reduction in the degree of deprotonation at the stereogenic centre in intermediates **I** and **II**, resulting in reduced racemisation *via* the enolate or extended

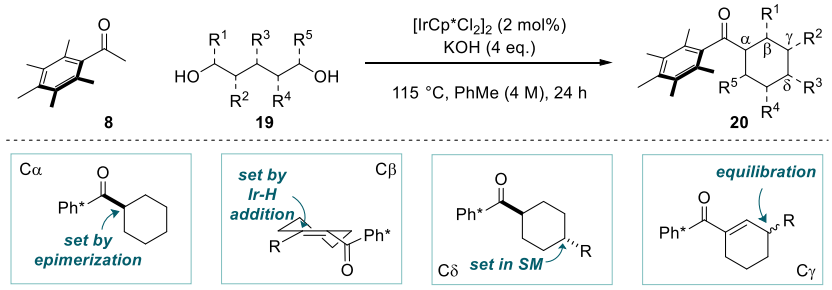
enolate respectively. The amino ketone products could easily be cleaved to γ-amino butyric acids using HCl, with no racemisation observed. Of note, the authors showed that the γ-amino butyric acid **18d** could be isolated by recrystallisation without isolation of the intermediate hydrogen borrowing product; this simultaneously increased the enantiomeric purity (98:2 e.r.).



Scheme 1.9. Enantioretentive synthesis of γ-amino Ph* ketones.

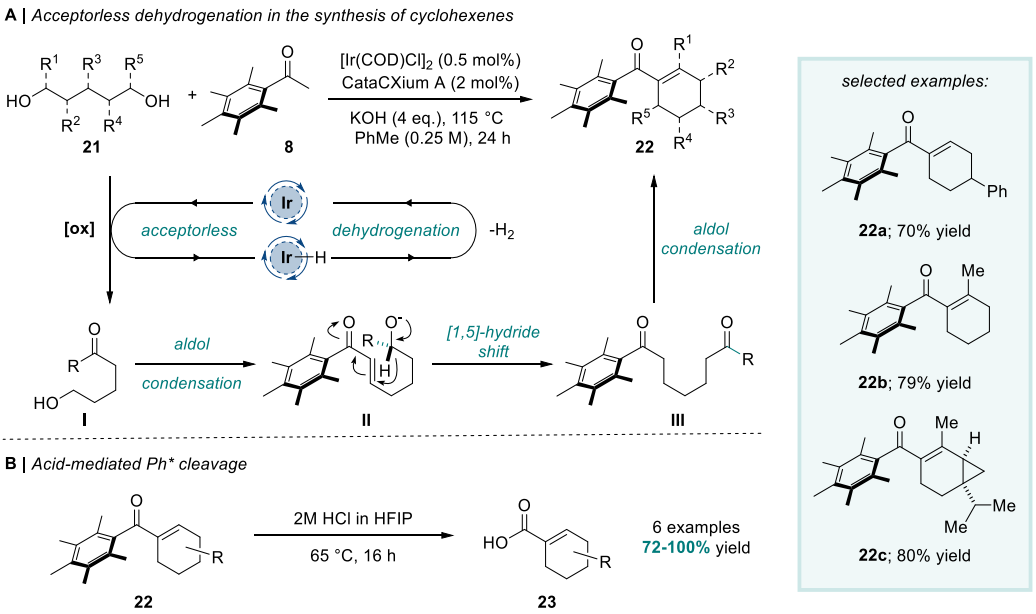
1.3.2 Carbocyclic Systems

After investigating the use of a range of mono-alcohol coupling partners, Donohoe and co-workers reported a "double" hydrogen borrowing alkylation in which 1,5-diols were employed to synthesise cyclohexanes (Scheme 1.10).[33] A number of different substituents were tolerated on the backbone and in many cases the desired cyclohexanes were isolated in excellent diastereoselectivity. The authors rationalised the stereochemical outcome at each position around the ring as follows: (i) C-α is under thermodynamic control and set by epimerisation under the basic reaction conditions; (ii) C-β is set by the facial selectivity of iridium hydride reduction (iii) the stereochemistry at C-γ can racemise *via* enolate or extended enolate formation; (iv) C-δ is set in the diol starting material and does not racemise in the reaction. The asymmetric synthesis of β-branched cyclohexanes was subsequently pursued by Donohoe and co-workers and will be discussed in Chapter 1.4.3.[34]



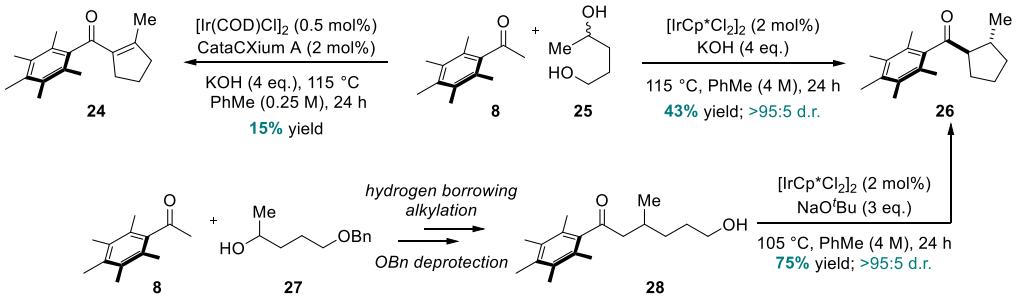
Scheme 1.10. Hydrogen borrowing catalysis in the synthesis of cyclohexanes.

In a mechanistically related approach to the synthesis of cyclohexanes, Donohoe and co-workers also developed an interrupted hydrogen borrowing method to provide access to the valuable cyclohexene intermediates from 1,5-diols (Scheme 1.11.A).[35] The authors found that under dilute conditions and use of sterically hindered ligand CataCXium® A, acceptorless dehydrogenation was favoured, thereby preventing the final reduction step and releasing H_2 gas. More than 30 examples of cyclohexenes bearing various substitution patterns were successfully isolated. Through extensive mechanistic experiments, including deuterium labelling studies, the reaction was shown not to proceed *via* the previously proposed double hydrogen borrowing sequence. Instead, once the diol undergoes iridium-mediated oxidation and aldol condensation to give intermediate **II**, a key [1,5]-hydride shift takes place to afford 1,7-dicarbonyl intermediate **III**. A second aldol condensation affords the cyclohexene and under concentrated conditions, is reduced to the cyclohexane. Furthermore, due to the reactive nature of the enone products, the Br_2 cleavage conditions were not suitable for these substrates and acidic conditions using 2 M HCl in HFIP were developed to efficiently cleave the Ph* group (Scheme 1.11.B).



Scheme 1.11. Acceptorless dehydrogenation in the synthesis of cyclohexenes and acid-mediated Ph* cleavage.

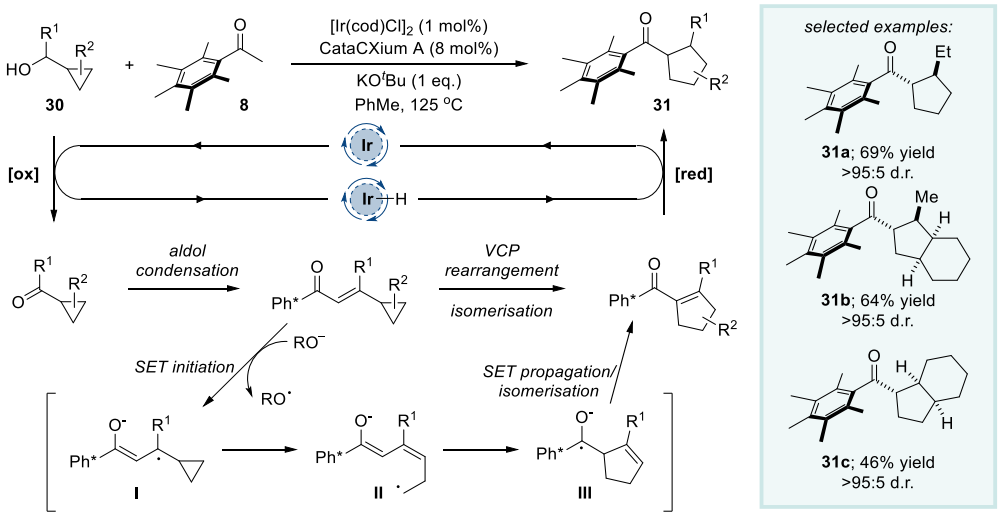
Although 1,4-diols could be employed in this process to make carbocycles, synthesis of 5-membered rings was generally less efficient (*cf*. 6-membered rings), typically formed in less than 50% yield for cyclopentanes and even lower yields were obtained in the synthesis of cyclopentenes (Scheme 1.12).[36] However, an alternative intramolecular stepwise approach to the cyclopentanes from linear alcohol precursors, was subsequently reported by Donohoe and co-workers, which substantially improved the yield of **26** to 75% in the hydrogen borrowing step.[37]



Scheme 1.12. Synthesis of 5-membered carbocycles.

A more complex application of hydrogen borrowing catalysis, which also afforded cyclopentanes was reported by Donohoe and co-workers in 2020 (Scheme 1.13).[38] Alkylation of Ph* methyl

ketone (**8**) with secondary cyclopropanols, gave the desired cyclopentanes in good yields, *via* an intermediate vinyl cyclopropane (VCP) rearrangement. Mechanistic experiments revealed that after the typical oxidation and aldol condensation, single electron transfer (SET) from an alkoxide or enolate to the enone results in formation of a radical-anion (**I**), which undergoes rearrangement to give a cyclopentyl radical-anion **III**. Intermediate **III** can presumably then propagate the reaction by electron donation to another enone molecule. Isomerisation of **III** followed by reduction affords the desired cyclopentanes. A range of complex diastereomerically pure cyclic and bicylic ketones were synthesised using this method. The authors noted that higher temperatures (125 °C) were typically needed to favour formation of the cyclopentane over the direct cyclopropane hydrogen borrowing product.



Scheme 1.13. Ph* methyl ketone alkylation with cyclopropyl-substituted secondary alcohols.

1.4. Asymmetric Hydrogen Borrowing Catalysis

Asymmetric hydrogen borrowing catalysis presents a powerful opportunity to convert racemic material into prochiral intermediates that can subsequently be reduced to give enantioenriched products. Two general methods could be employed to direct this process: (i) use of chiral auxiliaries to effect diastereoselective reduction or (ii) addition of a chiral ligand to mediate an asymmetric reduction. Despite the vast advances in the field of hydrogen borrowing catalysis, asymmetric methods are relatively underexplored, in particular C–C bond formation.[39,40] Two important challenges have contributed to the slow development of this field:

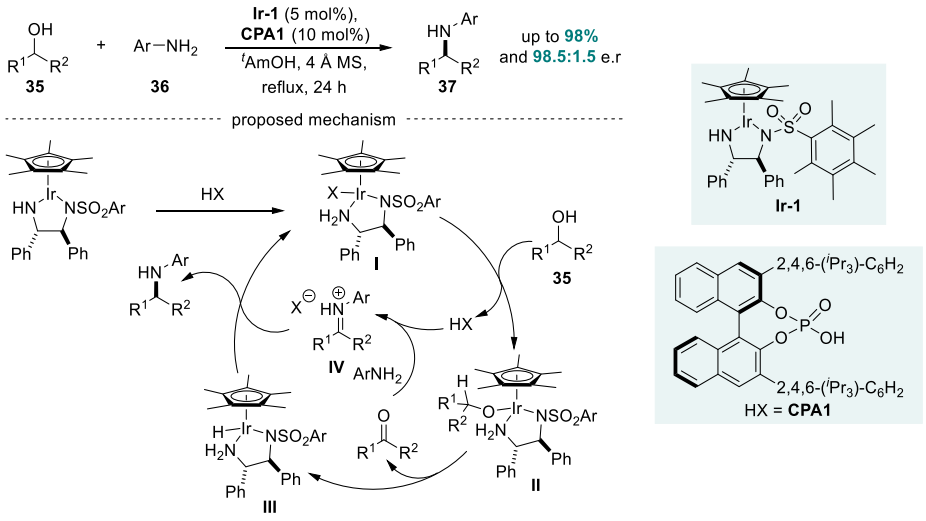
1. A catalytic system must facilitate oxidation and reduction (hydrogen borrowing) as well as inducing chirality in a complex multi-reaction process.

2. Although progress has been made in developing reaction conditions that facilitate hydrogen borrowing at lower temperatures, the requirement for high temperatures in many methodologies presents an additional challenge for achieving high enantioselective control.

In the area of C–C bond formation, three main strategies for enantioselective transition metal hydrogen borrowing catalysis exist: (i) asymmetric carbonyl reduction; (ii) conjugate addition reactions; (iii) asymmetric reduction of intermediate unsaturated systems. It should be noted that several strategies employing biocatalysis have also been developed for use in hydrogen borrowing alkylation.[41–44]

Although the focus of this thesis is on C–C bond formation, the use of amine nucleophiles has been widely explored and proceeds *via* an analogous mechanism, following condensation of an amine with a carbonyl, reduction of an intermediate imine (or iminium ion) by the metal catalyst yields the corresponding substituted amine.[39,45] In a representative example by Zhao and co-workers, an asymmetric alkylation of anilines with secondary alcohols is reported (Scheme

1.14).[46] A dual-catalytic system employing a chiral iridium catalyst in combination with a chiral Brønsted acid enabled the synthesis of substituted anilines in high yields and enantioselectivities. The authors propose that the phosphoric acid (**CPA1**) first protonates the iridium complex, followed by ligand exchange with the alcohol. Subsequent oxidation and condensation of the amine, facilitated by the acid affords the protonated iminium intermediate, which is reduced in an enantioselective manner in the final step to the corresponding amine. The authors demonstrated that both the chiral Brønsted acid and chiral iridium catalyst were essential for both yield and enantioselectivity, with high enantioselectivities only observed when the chirality of the phosphoric acid and iridium catalyst were correctly matched.[46] Remarkably high enantioselectivity (up to 98.5:1.5 e.r.) was observed in the corresponding functionalised amine products considering the elevated temperatures of this process (100 °C).

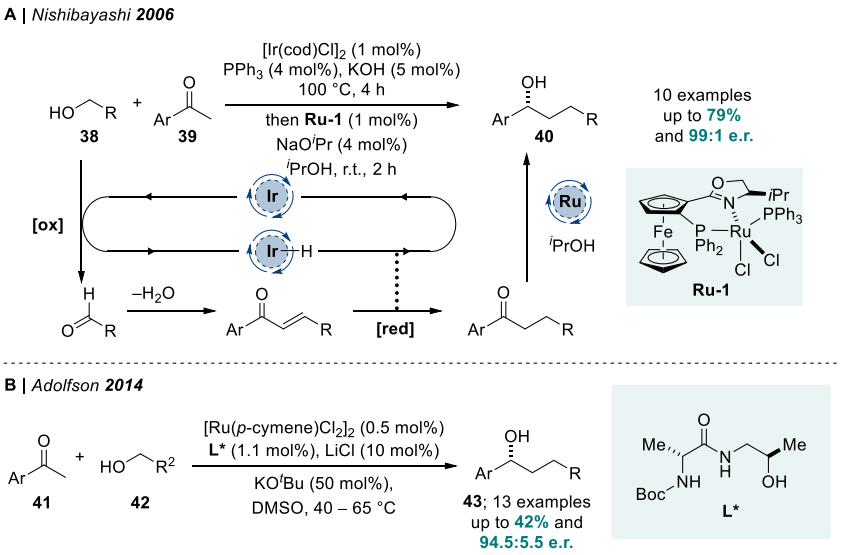


Scheme 1.14. Enantioselective amination of racemic alcohols *via* cooperative catalysis.

1.4.1 Asymmetric Carbonyl Reduction

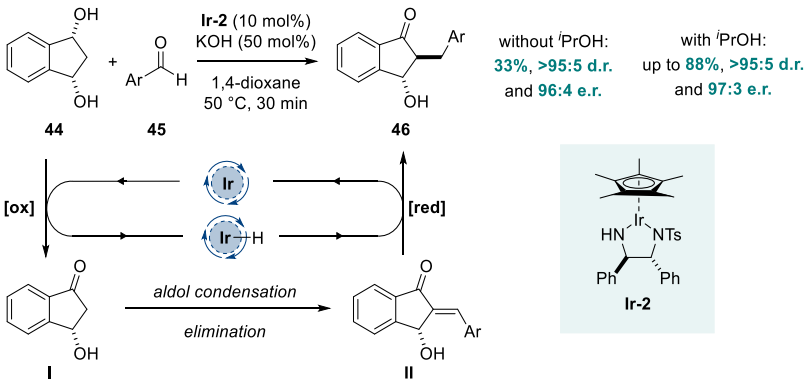
Considering the multitude of methods for asymmetric carbonyl reduction, it is not surprising that this area has been widely explored in the context of asymmetric hydrogen borrowing catalysis. In 2006, Nishibayashi and co-workers reported a dual-catalytic system for the sequential one-pot alkylation of acetophenones with primary alcohols, followed by an

asymmetric reduction of the ketone to afford the corresponding enantioenriched alcohols in up to 99:1 e.r. (Scheme 1.15.A).[47] An achiral iridium complex was used to catalysed the hydrogen borrowing pathway, while a second chiral ferrocenyl ruthenium catalyst was used for the subsequent asymmetric ketone reduction. The enantiodetermining reduction step employed isopropanol as a sacrificial hydride source. This method was later developed by Adolfsson and co-workers to use a single ruthenium catalyst with an amino acid derived ligand for the same transformation (Scheme 1.15.B).[48] In contrast to Nishibayashi's method, an excess of the alcohol reagent was used to serve as the terminal reductant for the asymmetric reduction instead of an additional hydride source. Despite reducing the complexity of the reaction conditions, the yields and enantioselectivity remained moderate.



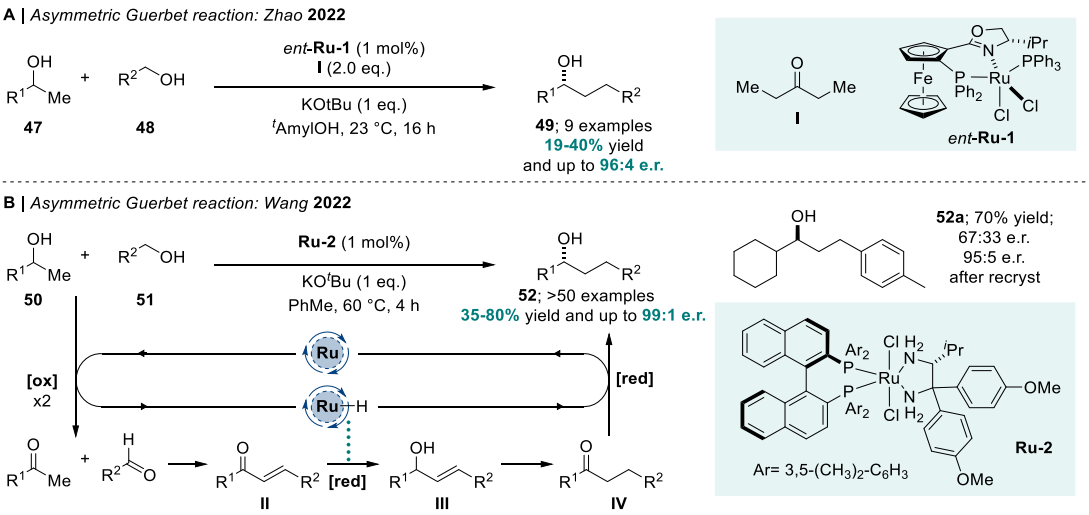
Scheme 1.15. Asymmetric hydrogen borrowing alkylation *via* carbonyl reduction.

In a mechanistically distinct strategy, Suzuki and co-workers reported the alkylation of a cyclic diol **44** with a variety of benzaldehydes using chiral iridium catalyst **Ir-2** (Scheme 1.16).[49] The authors proposed that the enantiodetermining step is an oxidative desymmetrisation of the diol, which is then followed by a typical hydrogen borrowing pathway. In a similar manner to the initial report by Nishibayashi and co-workers, isopropanol was needed as a sacrificial hydride source to ensure high yields.



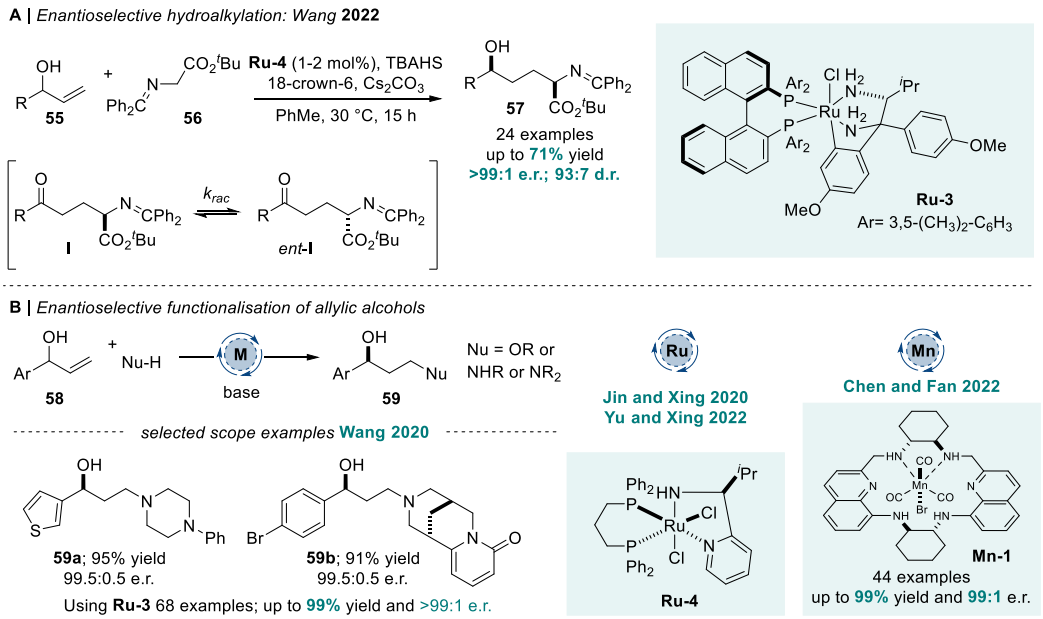
Scheme 1.16. Asymmetric hydrogen borrowing alkylation *via* a desymmetrisation of a diol.

The first example of an asymmetric Guerbet reaction was reported independently by Wang[50] and Zhao (Scheme 1.17).[51] Both methods used a chiral ruthenium catalyst to alkylate secondary alcohols with primary benzylic (and hetero-benzylic) alcohols. Zhao and co-workers reported a room temperature process, which required the use of a ketone promoter (**I**) to ensure high yields (Scheme 1.17.A). The authors propose that the ketone promoter acts as a hydrogen acceptor to allow build-up of the aldehyde and ketone intermediate, which facilitates the cross-aldol reaction. Wang and co-workers demonstrated the utility of this transformation showcasing a large variety in benzylic alcohols with products formed in up to 99:1 e.r. (Scheme 1.17.B). While this process required higher temperatures (60 °C), no ketone promoter was required. The authors reported a single non-benzylic example, albeit **52a** was isolated in significantly lower e.r. (67:33 e.r.), suggesting high efficiency of this method is limited to benzylic alcohols. Extensive mechanistic experiments and computational studies suggest that following initial ruthenium mediated dehydrogenation of both starting alcohols, the corresponding carbonyls undergo a cross aldol reaction to give an α,β-unsaturated ketone intermediate (**II**). They found that initial reduction to the allylic alcohol (**III**) is preferential, followed by base mediated isomerisation to afford the ketone (**IV**). In the final step, the chiral ruthenium hydride is delivered to the ketone to afford the enantioenriched alcohols (**52**).



Scheme 1.17. Asymmetric Guerbet reaction.

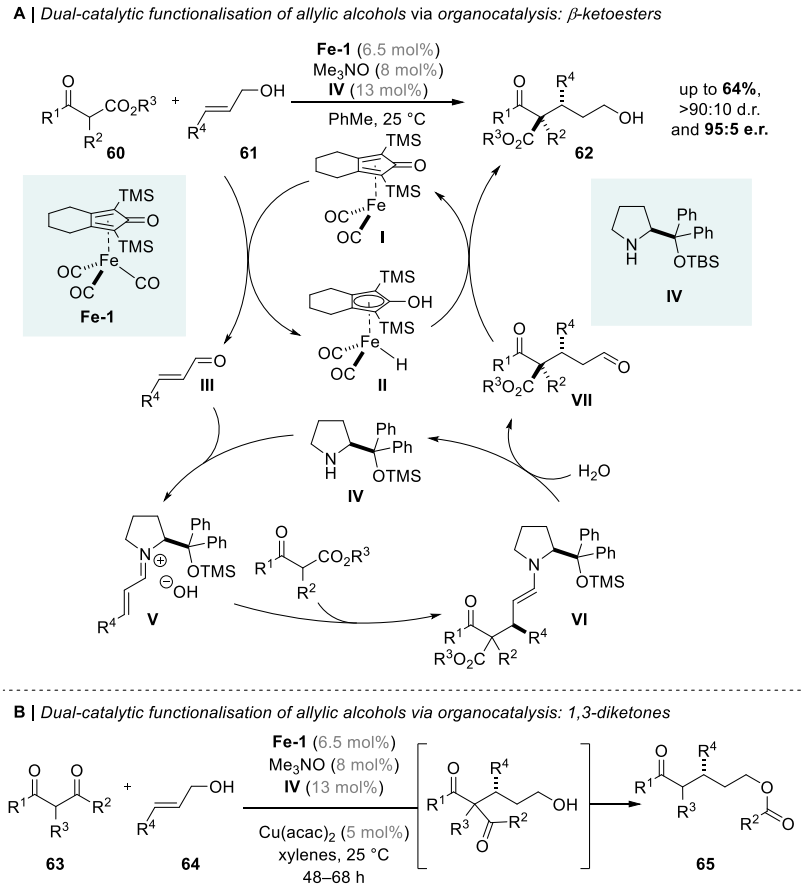
Recently, Wang and co-workers have developed the hydroalkylation of racemic allylic alcohols (**55**) with a glycine-derived Schiff base (**56**) *via* a dynamic kinetic resolution (DKR) process (Scheme 1.18.A).[52] Chiral α-amino acid derivatives were accessed in moderate yields, good diastereoselectivity and excellent enantioselectivity. Asymmetric reduction of the intermediate ketone **I** was enantiodetermining and racemisation at the α-position to the ester group facilitated the DKR (see chapter 3.2 for a more detailed discussion). Addition of other nucleophiles to allylic alcohols have been reported forming C–N and C–O bonds *via* hydrogen borrowing catalysis (Scheme 1.18.B).[53–55] Although in these cases no dynamic process occurs (or C–C bond formation), the enantiodetermining step remains a typical example of asymmetric reduction of a ketone intermediate. Several groups have realised this hydroamination with typical ruthenium hydrogenation catalysts. However, recently Chen, Fan and co-workers have developed the first asymmetric hydroamination of allylic alcohols using an earth-abundant manganese catalyst.[56]



Scheme 1.18. Functionalisation of allylic alcohols with carbon, nitrogen and oxygen nucleophiles.

1.4.2 Conjugate Addition

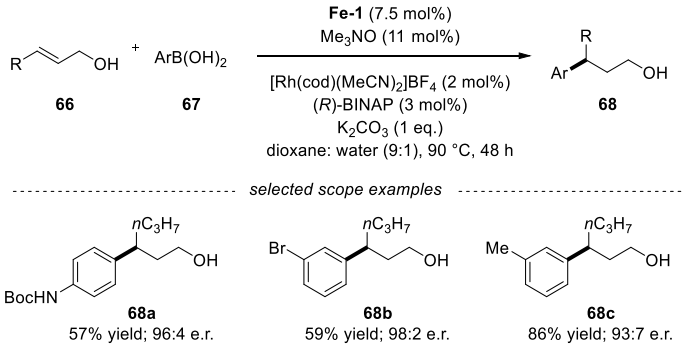
The use of allylic alcohols as substrates results in the formation of an α,β-unsaturated intermediate, which presents an opportunity to consider conjugate additions as the enantiodetermining step. Quintard, Rodriquez and co-workers have pioneered a dual-catalytic approach combining hydrogen borrowing catalysis with organocatalysis to facilitate asymmetric conjugate additions (Scheme 1.19).[57] By employing an achiral iron complex (Knölker complex, **Fe-1**) along with a Jørgensen-Hayashi type amine organocatalyst, β-ketoesters could be alkylated with primary allylic alcohols to afford γ-functionalised alcohols with high levels of diastereo- and enantioselectivity. The comparably low temperatures required for this process (10–25 °C) likely aid in accessing high enantioselectivities. Furthermore, the authors demonstrated that upon treatment with DBU, the alcohol products could undergo lactonization to afford enantioenriched spiro-δ-lactones.[58]



Scheme 1.19. Dual-catalytic functionalisation of allylic alcohols *via* organocatalysis.

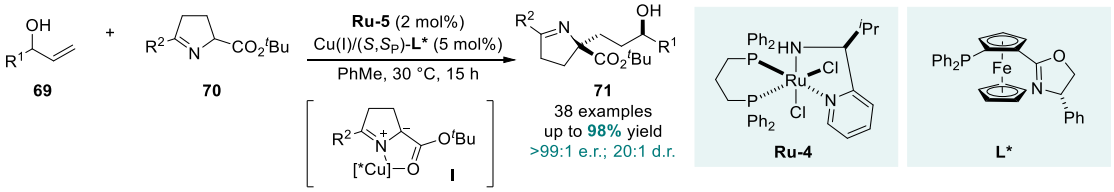
Mechanistically, the dual-catalytic cycle begins with activation of the Knölker complex (**Fe-1**) with Me_3NO to give the active catalytic species **I**, which is able to oxidise the allylic alcohol to form an α,β-unsaturated aldehyde intermediate (**III**). In the second catalytic cycle, condensation of the organocatalyst (**IV**) with the aldehyde forms an iminium species (**V**), which undergoes an asymmetric conjugate addition with the β-ketoester nucleophile. The resulting enamine (**VI**) is hydrolysed and the corresponding aldehyde (**VII**) is reduced by an achiral iron-hydride species, affording the enantioenriched product (**62**) and regenerating the active iron-complex. Subsequently, the authors reported that use of $Cu(acac)_2$ as an additive enhanced the enantioselectivity of this method and that 1,3-diketones could be employed as nucleophiles under these conditions (Scheme 1.19.B).[59,60] In this process, the formed alcohol products undergo spontaneous intramolecular acyl transfer to afford highly enantioenriched esters.

Metal-catalysed asymmetric conjugate additions have also been employed in dual-catalytic systems by Dydio and co-workers (Scheme 1.20).[61] Primary allylic alcohols were transiently activated by oxidation with Knölker's complex (**Fe-1**) and the resulting α,β-unsaturated aldehyde underwent Rh-BINAP catalysed conjugate addition with a variety of aryl boronic acids. The γ-functionalised alcohols were accessed in good yields and enantioselectivities. The authors reported that $RuH_2(PPh_3)$ could also promote the hydrogen borrowing process and, in some cases, gave higher selectivity, albeit at the expense of functional group tolerance.



Scheme 1.20. Dual-catalytic functionalistion of allylic alcohols with boronic acids.

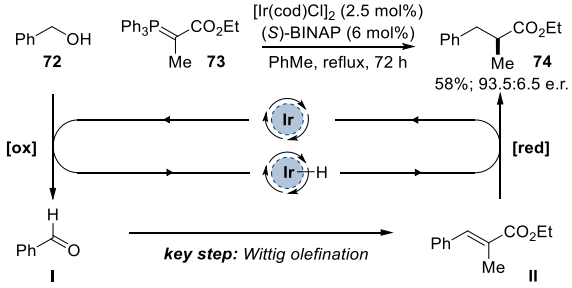
Recently, Wang and co-workers reported a stereodivergent hydroalkylation of allylic alcohols which afforded enantioenriched esters bearing 1,4-non adjacent stereocentres (Scheme 1.21).[62] This strategy combines two of the asymmetric methods discussed, namely a copper-mediated asymmetric conjugate addition followed by a ruthenium catalysed asymmetric ketone reduction. The authors propose that the allylic alcohol is oxidised with **Ru-4** to give the corresponding α,β-unsaturated ketone which undergoes an asymmetric copper-mediated conjugate addition with (**I**). Finally, an asymmetric reduction of the corresponding ketone by the chiral ruthenium hydride affords the enantioenriched product. By employing specific combinations of the enantiomers of the two catalysts, all four stereoisomers could be isolated in excellent yield and enantioselectivity, although in the cases of the (*R*,*R*) and (*S*,*S*) diastereomers, reduced diasteroselectivity was observed suggesting there was a slight mismatched effect.



Scheme 1.21. Hydroalkylation of allylic alcohols with ketimine esters.

1.4.3 Reduction of Unsaturated Systems

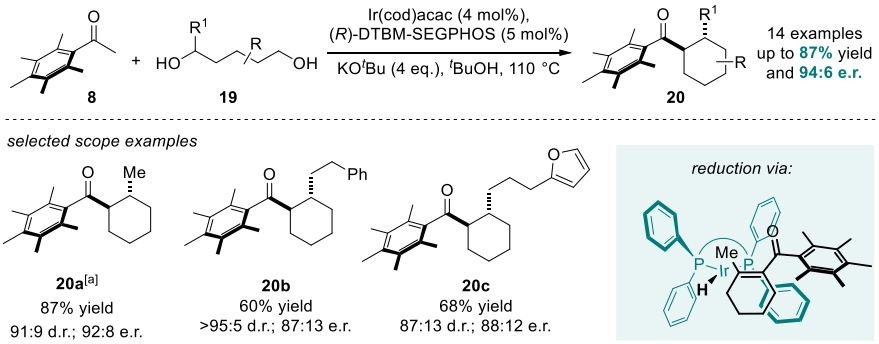
A powerful and direct strategy for controlling absolute stereochemistry within hydrogen borrowing catalysis is to control the facial selectivity of the final reduction of the unsaturated intermediate (typically an enone). Seminal work in this area of enantioselective hydrogen borrowing reactions was reported by Williams and co-workers in 2007.[3] In this case, the C–C forming step is a Wittig reaction, rather than a more typical aldol condensation (Scheme 1.22). Following a general hydrogen borrowing sequence, benzyl alcohol (**72**) is oxidised and subsequently reacts with stabilised ylide **73** in a Wittig olefination. The resulting alkene (**II**) then undergoes an asymmetric reduction to give **74**, which was isolated in 58% yield and 93.5:6.5 e.r. Integration of a Wittg olefination in this case ensured control of the enone geometry and negated the use of strong base, limiting the possibility of racemisation of the newly formed α-stereogenic centre.



Scheme 1.22. Wittig olefination embedded within an asymmetric hydrogen borrowing process.

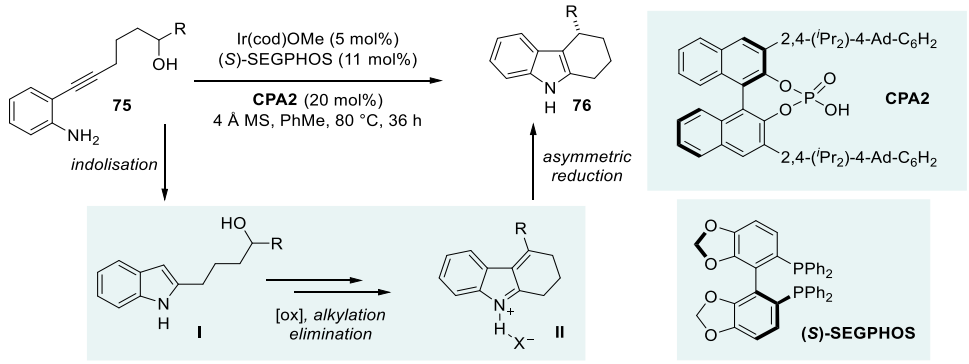
Donohoe and co-workers extended their work on the synthesis of cyclohexanes (see chapter 1.3.2) to enable the enantioselective synthesis of β-substituted cyclohexanes from functionalised 1,5-diols (Scheme 1.23).[34] This transformation proceeds *via* an

enantiodetermining reduction of the cyclic enone intermediate by a chiral iridium-hydride.[34] Due to the cyclic nature of the enone intermediate, a single geometric enone isomer is formed enabling a highly stereoselective reduction. The authors identified (*R*)-DTBM-SEGPHOS and Ir(cod)acac as an efficient catalytic system to afford 14 examples of highly enantioenriched β-branched cyclohexanes.



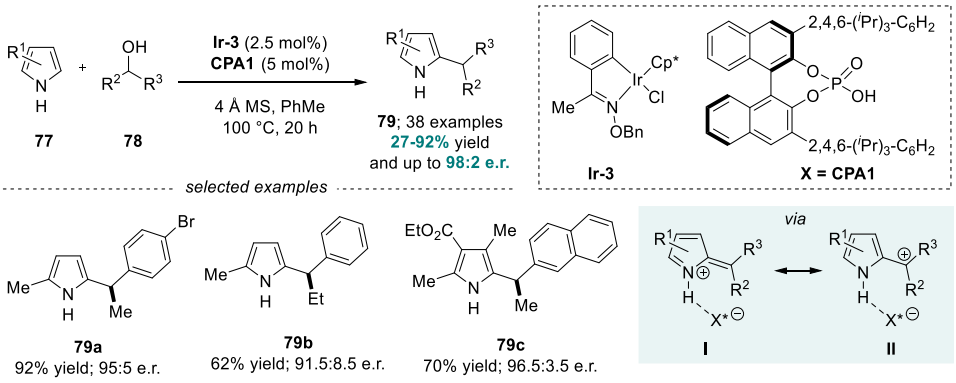
Scheme 1.23. Enantioselective synthesis of cyclohexanes from 1,5-diols *via* hydrogen borrowing catalysis.

More recently, Zhao and co-workers have developed an iridium and chiral phosphoric acid dual-catalysis strategy for C–C bond formation. Such dual catalytic systems have been highly effective in the asymmetric synthesis of C–N bonds and are less commonly used in C–C bond formation.[63–68] In their synthesis of tricyclic indoles, the first step involves an iridium mediated indolisation of alcohol-containing alkynyl anilines (**75**) to afford indole **I** (Scheme 1.24).[6] Subsequent, oxidation of the alcohol, followed by an acid-catalysed Friedel-Crafts addition and elimination results in α,β-unsaturated ketiminium **II**. This intermediate is then enantioselectively reduced by an iridium-hydride to afford a tricyclic indole (**76**). In a similar manner to the work by Donohoe and co-workers, restriction of the ketimine intermediate in a cyclic system prevented formation of stereoisomers, enabling an effective asymmetric reduction.



Scheme 1.24. Enantioconvergent synthesis of tricyclic indoles.

In a related method, Zhao and co-workers reported an enantioconvergent intermolecular pyrrole C2-substitution with secondary alcohols (Scheme 1.25).[69] Initially, chiral iridium catalysts were screened in combination with chiral phosphoric acids. However, the authors found that in contrast to previous methods, the chiral phosphoric acid was the sole determining factor in the asymmetric induction and use of achiral **Ir-3** with **CPA1** gave the desired pyrroles in high yields and enantioselectivity. Mechanistically, the authors propose that the alcohol undergoes an iridium-mediated oxidation to give the corresponding ketone electrophile. This is followed by an acid-mediated nucleophilic addition of pyrrole and subsequent elimination resulting in conjugated iminium intermediate **I/II**. The cationic intermediate enables ion pairing with the chiral phosphoric acid allowing for enantioselective reduction with iridium-hydride, to deliver the product and regenerate the catalyst. A range of pyrroles could be alkylated with both benzylic and aliphatic alcohols using this method. Generally, alcohols bearing an α-methyl group (R^2) were employed to ensure steric differentiation, however the authors showed an ethyl group was also tolerated (**79b**).

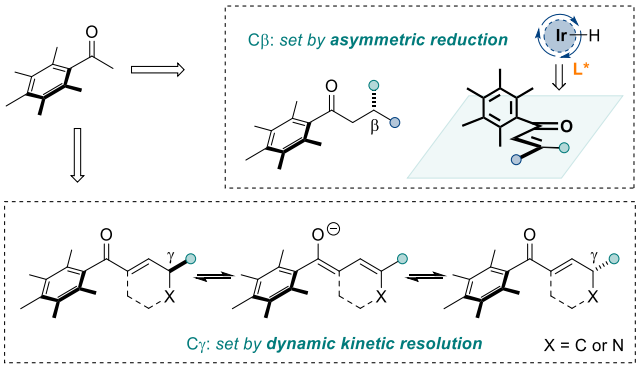


Scheme 1.25. Pyrrole alkylation *via* hydrogen borrowing catalysis.

1.5. Research Aims

Although various strategies have been explored for enantioselective hydrogen borrowing catalysis, it is clear that there are significant challenges associated with the development of such processes. Some innovative solutions to the challenges posed by this class of transformation have been presented, however, this area remains underexplored. The most direct approach for inducing asymmetry is asymmetric reduction of the unsaturated intermediate formed, although only four reported methods utilise this strategy to date.

The objective of the research described in this thesis, was to design and develop enantioselective hydrogen borrowing methods to afford enantioenriched ketones in both acyclic and cyclic systems (Scheme 1.26). Through utilisation of the Ph* group, deleterious reduction at the carbonyl is attenuated and therefore direct asymmetric reduction of the unsaturated intermediate could be pursued. The initial focus of this research was achieving stereochemical control at the β-centre in acyclic systems, wherein the enantiodetermining step was envisioned to be an asymmetric reduction of a tri-substituted enone. Building on this work, controlling the stereochemistry at the γ-centre was explored in acyclic and cyclic systems as well as the introduction of heteroatoms.



Scheme 1.26. Key research aims.

Chapter 2: Enantioconvergent Alkylation of Ketones with Racemic Secondary Alcohols via *Hydrogen Borrowing Catalysis*

2.1. Introduction

As discussed in Chapter 1.4, several strategies for induction of asymmetry in C-C bond forming hydrogen borrowing reactions exist.[39] Efforts in this field have mainly focused on carbonyl reduction and conjugate addition approaches. A powerful and direct method of controlling absolute stereochemistry within hydrogen borrowing enolate alkylation reactions would be to control the facial selectivity of the final enone reduction step. However, the development of such strategies has thus far been limited due to three main issues:

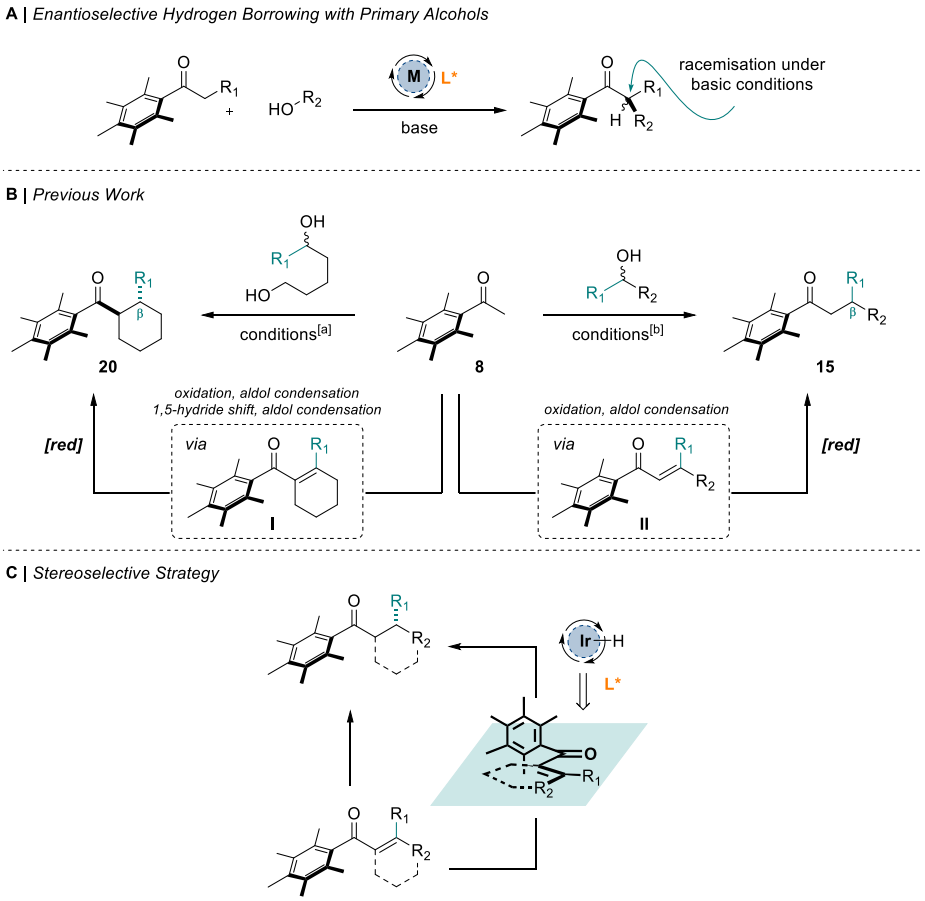
1. In classic aldol-condensation hydrogen borrowing reactions, the carbonyl is susceptible to reduction; therefore, many methods have utilised this and focused on asymmetric carbonyl reduction rather than the more challenging direct reduction of the enone intermediate.

2. Under the strongly basic conditions needed to facilitate the aldol condensation, racemisation at the α-stereogenic centre is typically observed, making it difficult to control.

3. For an asymmetric enone reduction, it is necessary to control the intermediate enone geometry to observe high levels of selectivity.

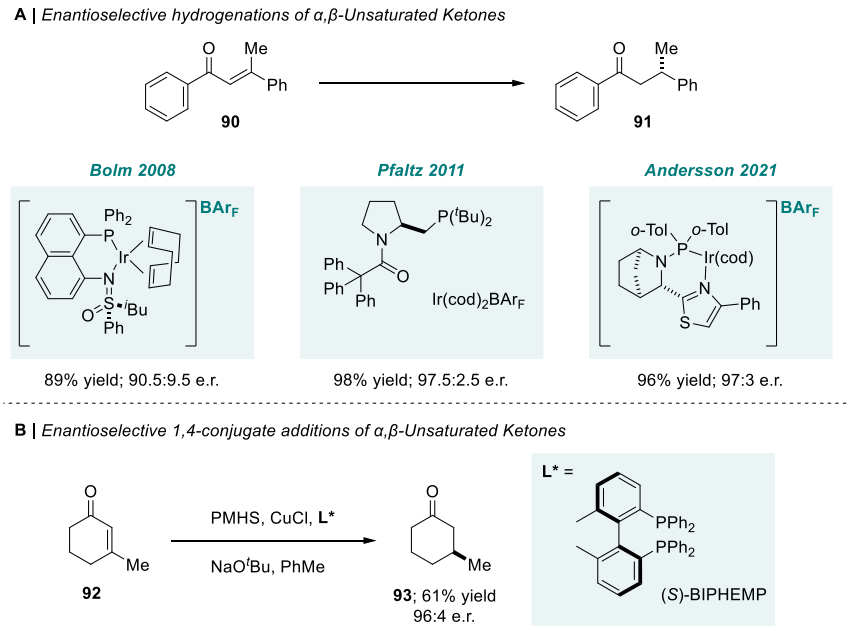
In order to develop a general enantioselective hydrogen borrowing enolate alkylation method, it was necessary to consider solutions to these problems. Firstly, the use of Ph* methyl ketone (**8**), pioneered by Donohoe and co-workers, protects the carbonyl from reduction and would allow reduction of the enone to the ketone product.[25] Secondly, while synthesis of enantioenriched α-branched ketones, using primary alcohols, would be desirable, control of the α-stereogenic centre would be difficult due to racemisation under the strongly basic conditions (Scheme 2.1.A). In contrast, synthesis of β-branched ketones would lead to non-enolisable

products and thus becomes a suitable target for an enantioselective hydrogen borrowing method. As discussed in Chapter 1.3, methods for achiral synthesis of β-branched ketones have been reported by Donohoe and co-workers[25,33]: alkylation of Ph* methyl ketone (**8**) with secondary alcohols or 1,5-diols afforded the corresponding acyclic and cyclic β-branched ketones (Scheme 2.1.B). The formation of achiral enone intermediates (**I** and **II**) provides a unique opportunity to induce asymmetry in various ways. Our proposed strategy for enantioselective control at C-β uses a chiral metal hydride to mediate an asymmetric enone reduction (Scheme 2.1.C).



Scheme 2.1. A: Enantioselective hydrogen borrowing with primary alcohols. **B:** Previous work by Donohoe and co-workers in the synthesis of β-branched cyclic and acyclic ketones.[25,33] **C:** Envisaged stereoselective strategy. [a] **8** (1 eq.), diol (2 eq.), Ir(cod)acac (4 mol%), (*R*)-DTBM-SEGPHOS (5 mol%), KO^{t}Bu (4 eq.), ^{t}BuOH (3 M), 110 °C, 24 h. [b] $[Cp^*IrCl_2]_2$ (0.5 mol%), alcohol (1.5 eq.), NaO^{t}Bu (2 eq.), PhMe (4 M), 85 °C, 24 h.

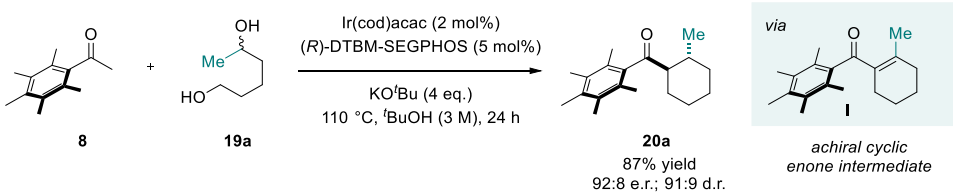
This key enantiodetermining step in the synthesis of the β-branched ketones is analogous to many transition metal-catalysed reductions. This is a well-established field in which a variety of chiral ligand metal complexes have been employed to reduce α,β-unsaturated ketones through three main strategies: hydrogenations, 1,4-conjugate additions and organocatalysis.[70] For example, various chiral iridium complexes have been employed in the enantioselective hydrogenation of α,β-unsaturated ketones **90** affording the corresponding ketone **91** with high enantioselectivites (Scheme 2.2.A).[71–73] Methods using organic hydride sources have also been developed: Buchwald and co-workers reported the use of silanes to generate a chiral copper hydride source using (*S*)-BIPHEMP to access cyclic enantioenriched ketones (**93**, Scheme 2.2.B). While these methods provide access to similar β-branched ketones, it would be advantageous to access these products directly through an enantioselective hydrogen borrowing method using simple ketone and alcohol starting materials.



Scheme 2.2. Selected examples of iridium-catalysed hydrogenations of trisubstituted α,β-unsaturated ketones.[71–73]

A final challenge that would need addressing in order to allow asymmetric hydrogen borrowing alkylation would be control of the enone geometry. This problem was addressed in part in the development of the enantioselective hydrogen borrowing annulation by Donohoe and

co-workers as discussed in Chapter 1.4.3. Alkylation of Ph* methyl ketone with 1,5-diols led to formation of achiral *cyclic* enone intermediate **I**, which inherently controls the enone geometry. After extensive screening of chiral ligands, alongside other reaction parameters, the optimal reaction conditions for the synthesis of the β-branched cyclohexanes were identified as: 4 mol% Ir(cod)acac, 5 mol% (*R*)-DTBM-SEGPHOS d, 4 equivalents of KO^{t}Bu, and ^{t}BuOH. When ketone **8** was alkylated with hexane-1,5-diol (**19a**) under these conditions at 110 °C for 24 h, the desired product was afforded in 87% yield and 92:8 e.r. (**20a**, Scheme 2.3).



Scheme 2.3. Enantioselective synthesis of cyclohexanes from 1,5-diols *via* hydrogen borrowing catalysis.[34]

The absolute stereochemistry was shown to be (*S*) by comparison of a derivatised cyclohexane to a known literature compound and this stereochemical outcome was supported by computational studies (Figure 2.1). *Si*-face coordination of the *s-cis* enone was favoured by 0.8 kcal mol^{-1} and thought to be due to the clash of the Ph* group with the P-Ar groups in the disfavoured *Re*-transition state.

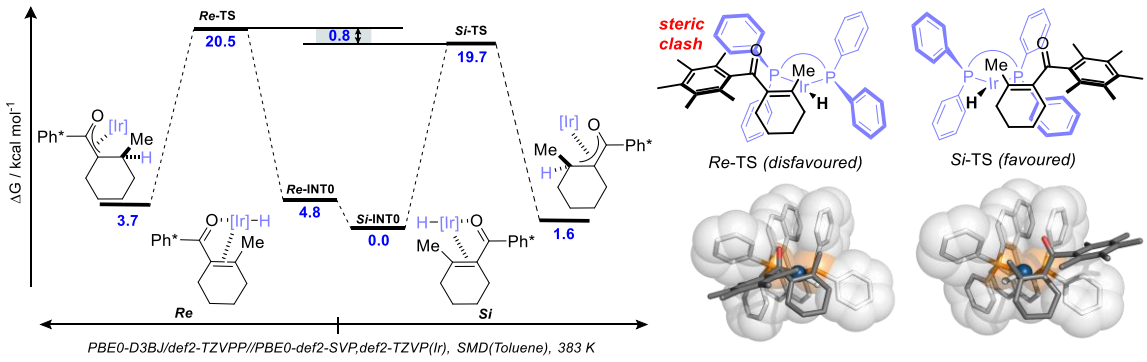


Figure 2.1. Computational studies to rationalise the stereochemical outcome for the enantioselective synthesis of cyclohexanes. Figure adapted from original paper.[34]

2.2. Project Aims

Our aim at the outset of this project was to develop an enantioconvergent synthesis of β-branched acyclic ketones using racemic alcohols *via* hydrogen borrowing catalysis.[74] Our proposed strategy for this process is outlined in Figure 2.2. The reaction would be initiated by dehydrogenation of a racemic alcohol, ablating the stereochemistry and forming the corresponding ketone *in situ*. Subsequent aldol condensation with Ph* methyl ketone (**8**) would generate the key achiral enone intermediate. The enantiodetermining step would then involve asymmetric reduction by the metal hydride to afford the enantioenriched ketone product and close the catalytic cycle. Importantly, the key challenge and difference in developing this method for the acyclic synthesis would be control of the intermediate enone geometry. Even if high facial selectivity is observed by the chiral ligand, formation of an isomerically pure enone intermediate is necessary in order to observe high enantioselectivity.

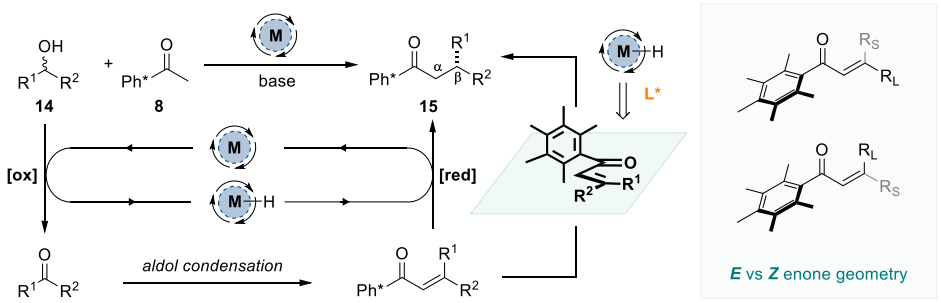


Figure 2.2. This work – enantioselective synthesis of acyclic β-branched ketones.

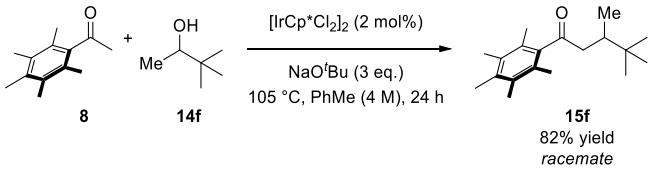
2.3. Note On Collaboration

This project was initiated by Dr Wasim Akhtar and Dr Roly Armstrong, both postdoctoral researchers in the Donohoe Group, at the time. They identified the initial substrate for optimisation and began the initial optimisation reactions. My involvement in the project commenced by collaborating on the optimisation and taking the project to completion. The section which follows on preliminary studies is the work of Dr Wasim Akhtar and Dr Roly

Armstrong. The section on optimisation represents our combined findings and thereafter is my work unless specifically indicated.

2.4. Preliminary Studies

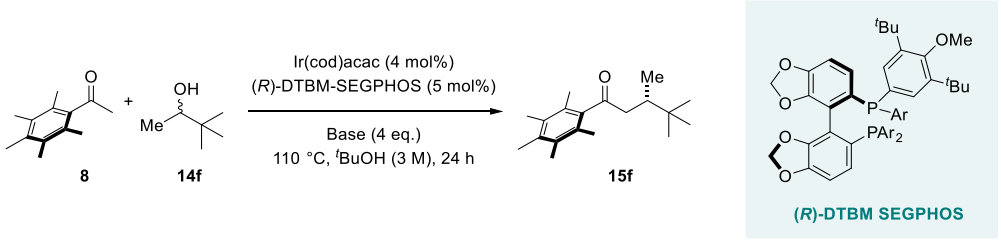
Initial investigation into the enantioselective α-alkylation of Ph* methyl ketone (**8**) was commenced using pinacolyl alcohol (**14f**). In line with previous studies in the Donohoe group,[25] in the presence of an achiral Ir(III) catalyst, 3 equivalents of NaO^{t}Bu in toluene at 105 °C, the racemic β-branched ketone (**15f**) was obtained in 82% yield (Scheme 2.4).



Scheme 2.4. Racemic synthesis of ketone **15f**.

Initially these conditions were used as a basis to investigate a range of chiral ligands (modified by using [Ir(cod)Cl]$_2$ to allow coordination of a chiral ligand), however, no hits were identified. In parallel to this initial investigation, Dr Roly Armstrong and Dr Wasim Akhtar developed the enantioselective hydrogen borrowing annulation (Scheme 2.3)[34] and, therefore, at this point the optimised annulation conditions were evaluated in the acyclic system. In the presence of these conditions: Ir(cod)acac (4 mol%), (*R*)-DTBM-SEGPHOS (5 mol%), KO^{t}Bu (4 eq.) in ^{t}BuOH (3 M) at 110 °C the desired product was isolated in 19% yield and, promisingly, 90:10 e.r. (Table 2.1, Entry 1). Using NaO^{t}Bu instead of KO^{t}Bu increased the yield to 91% while maintaining 90:10 e.r. (Table 2.1, Entry 2). With this very promising hit in hand, we set out to further optimise the system.

Table 2.1. Preliminary studies seeing the effect of using different bases.



Entry	Base	Yield 3a[a] / %	e.r.[b]
1	KO^{t}Bu	19	90:10
2	NaO^{t}Bu	91	90:10

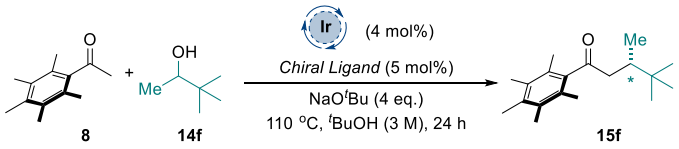
[a]Determined by reverse phase HPLC analysis *vs* durene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. For the determination of absolute stereochemistry see Chapter 2.7.

2.5. Optimisation

Given the success of the chiral ligand (*R*)-DTBM-SEGPHOS, we began investigation of a range of diphosphine ligands (Table 2.2). Changing the biaryl backbone to MeO-BIPHEP (**L3**) gave a similar yield to the optimal conditions, albeit with a slight reduction in enantioselectivity (Entry 2). Similarly, using (*R*)-DTBM-GARPHOS resulted in a slight loss of both yield and enantioselectivity (Entry 3). To probe the effect of the P-Ar group more thoroughly, we decided to evaluate a series of ligands with the MeO-BIPHEP backbone. This was due to the commercial availability of range of P-Ar derivatives. Removing the methoxy group from (*R*)-DTBM-MeO-BIPHEP ligand resulted in a significant loss in enantioselectivity (68:32 e.r.), albeit with no loss in yield (Entry 4). Replacing the *tert*-butyl substituents with methoxy groups also showed a reduction in enantioselectivity (79:21 e.r., Entry 5), however, the yield also decreased to 64%. Replacing the methoxy group with NMe_2 similarly resulted in a reduction in yield and enantioselectivity (Entry 6). Non-phenyl-based phosphine substituents had a detrimental effect on the reaction (Entries 7-8) and similarly, the simplified ligands (*R*)-MeO-BIPHEP, (*R*)-SEGPHOS and (*R*)-BINAP gave little enantioselectivity (Entries 9-11). Overall, these results suggest that the P-Ar group of the ligand must be both suitably sterically bulky and electron rich to ensure both high yields and enantioselectivities. Other classes of ligand were explored (Entries 12-14), however, no

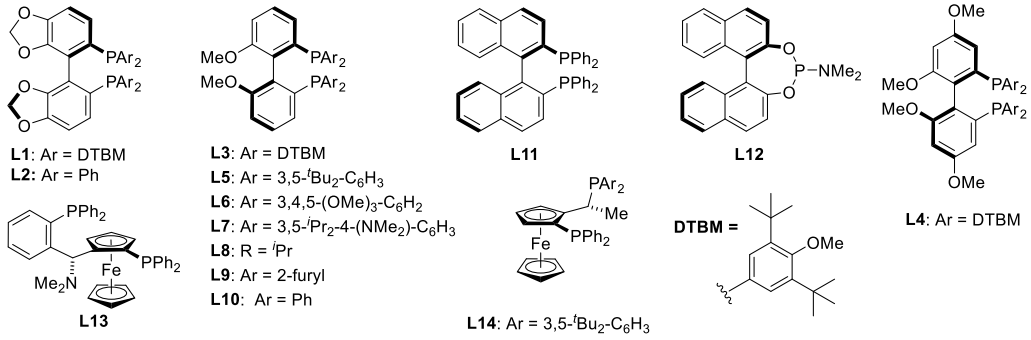
promising results were observed. Having identified (*R*)-DTBM-SEGPHOS to be the optimal ligand, we next turned our attention to other reaction parameters.

Table 2.2. Chiral Ligand Optimisation.



Entry	L*	Ligand	Yield 15f[a] / %	e.r.[b]
1	**L1**	(*R*)-DTBM-SEGPHOS	91	90:10
2	**L3**	(*R*)-DTBM-MeOBIPHEP	88	81:19
3	**L4**	(*R*)-DTBM-GARPHOS	90	83:17
4	**L5**	(*R*)-3,5-^{t}Bu-MeOBIPHEP	93	68:32
5	**L6**	(*R*)-3,4,5-OMe-MeOBIPHEP	64	79:21
6	**L7**	(*R*)-amino-MeOBIPHEP	62	61:39
7	**L8**	(*R*)-^{i}Pr-MeOBIPHEP	5	50:50
8	**L9**	(*R*)-furyl-MeOBIPHEP	8	52:48
9	**L10**	(*R*)-MeO-BIPHEP	45	50:50
10	**L2**	(*R*)-SEGPHOS	16	59:41
11	**L11**	(*R*)-BINAP	16	56:44
12	**L12**	(*R*)-MonoPhos	13	58:42
13	**L13**	(*R*$_P$,*R*)-TANIAPHOS	27	77:23
14	**L14**	Josiphos SL-J005-1	32	55:45

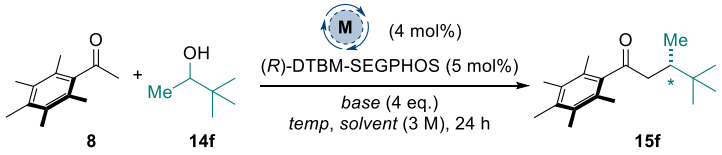
[a]Determined by reverse phase HPLC analysis *vs* durene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.



Alternative iridium precatalysts gave the desired product in good yield but led to reduced enantioselectivity (Table 2.3, Entries 2-3). Complete loss of enantioselectivity was observed using $[Rh(cod)Cl]_2$ (Entry 4). Ruthenium precatalysts also led to a reduction in both yield and enantioselectivity (Entries 5-6). We had previously seen that the reaction is highly sensitive to

the nature of the base (Table 2.1): KO^{t}Bu has a detrimental effect on the yield, however, still proceeds with excellent enantioselectivity. Similarly, replacing NaO^{t}Bu with KOH afforded the product in low yield and enantioselectivity (Entry 8). No conversion to the desired product was observed with NaOH or KHMDS (Entries 9-10).

Table 2.3. Optimisation of reaction parameters.



Entry	[M][a]	Base	Solvent	T/°C	Yield 15f[a] / %	e.r.[b]
1	Ir(cod)acac	NaO^{t}Bu	^{t}BuOH	110	91	90:10
2	[Ir(cod)Cl]$_2$	NaO^{t}Bu	^{t}BuOH	110	89	84:16
3	[Ir(coe)Cl]$_2$	NaO^{t}Bu	^{t}BuOH	110	75	83:17
4	[Rh(cod)Cl]$_2$	NaO^{t}Bu	^{t}BuOH	110	44	50:50
5	[Ru(cod)Cl]$_n$	NaO^{t}Bu	^{t}BuOH	110	62	77:23
6	Ru(acac)$_3$	NaO^{t}Bu	^{t}BuOH	110	70	65:35
7	Ir(cod)acac	KO^{t}Bu	^{t}BuOH	110	19	90:10
8	Ir(cod)acac	KOH	^{t}BuOH	110	16	78:22
9	Ir(cod)acac	NaOH	^{t}BuOH	110	0	-
10	Ir(cod)acac	KHMDS	^{t}BuOH	110	0	-
11	Ir(cod)acac	NaO^{t}Bu (2 eq.)	^{t}BuOH	110	81	86:14
12	Ir(cod)acac	NaO^{t}Bu	^{t}BuOH	90	73	75:25
13	Ir(cod)acac	NaO^{t}Bu	PhMe	110	86	87:13
14	Ir(cod)acac	NaO^{t}Bu	^{t}BuOH (1 M)	110	0	-

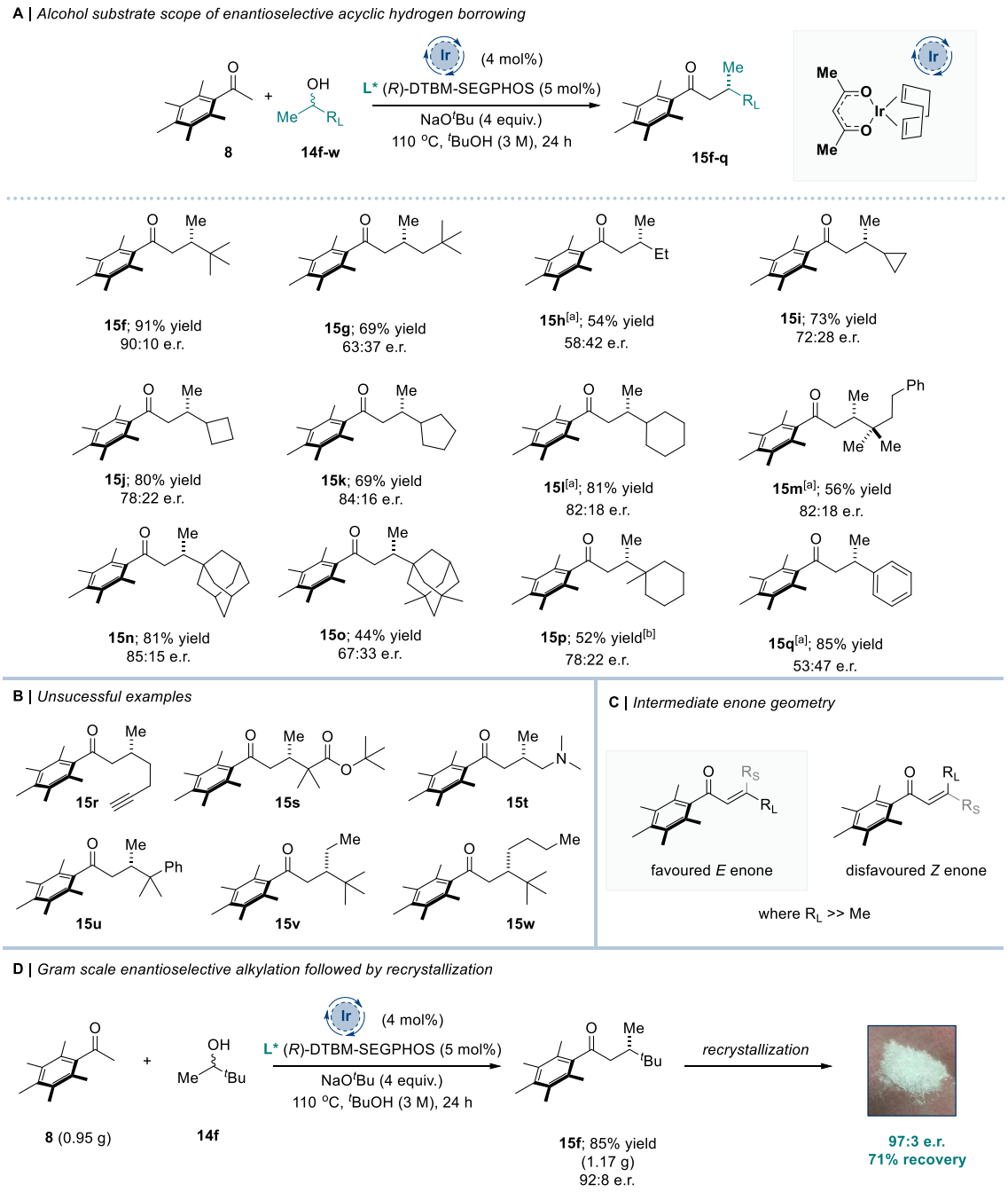
[a]Determined by reverse phase HPLC analysis *vs* durene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

Halving the equivalents of base led to a slight drop in efficiency (Entry 11). We proposed lowering the temperature to 90 °C would increase the energy difference between the diastereomeric transition states; surprisingly, this decreased the enantioselectivity significantly (75:25 e.r., Entry 12). While use of toluene as the solvent still gave good reactivity, it did not perform better than ^{t}BuOH (Entry 13). Furthermore, the reaction did not proceed at diluted concentrations (Entry 14). Ultimately the initial conditions were found to be optimal and gave the desired product in 91% yield and 90:10 e.r.

2.6. Reaction Scope: Alcohols

Having identified the optimised conditions, we set out to investigate the generality of the asymmetric hydrogen borrowing (Scheme 2.5). It quickly became evident that the size of R_L had a significant effect on the enantioselectivity of the reaction. For example, replacing the *tert*-butyl group with a less sterically encumbered neopentyl group gave ketone **15g** in good yield, however only 63:37 e.r. Decreasing the size of the *tert*-butyl group even further resulted in synthesis of ethyl substituted ketone **15h** in 58:42 e.r. We hypothesised that a bulky substituent would favour the formation of the key enone intermediate exclusively as the (*E*)-isomer (Scheme 2.5.C). Reducing the size of R_L leads to a mixture of enone isomers, therefore, reducing the enantioselectivity. This effect was seen in the systematic investigation of a series of cycloalkane substituents with increasing ring size. Cyclopropyl, cyclobutyl and cyclopentyl substituted ketones (**15i**-**k)** were isolated in 72:28, 78:22 and 84:16 e.r. respectively. Similarly high enantioselectivity was observed with cyclohexyl substituted ketone **15l** (82:18 e.r.). Ketone **15m** was isolated in 82:18 e.r. suggesting that introduction of a geminal dimethyl group also led to high geometric control. Furthermore, other carbon quaternary groups were tolerated well affording ketones **15n**-**o** with high levels of selectivity. Interestingly, there appeared to be a limit to the size increase of R_L that could be tolerated. Further increasing the size of R_L in the case of **15o** and **15p** gave lower enantioselectivities (*cf*. **15l** and **15p** to **15n** and **15o**, respectively) possibly due to increased steric repulsion with the metal-catalyst complex. Furthermore, these reactions were more sluggish as seen in the lower yields (56 and 44% yield, respectively). This suggests that in addition to the proposed steric repulsion with the catalyst, low enantioselectivity may be due to increased background metal-free reduction by the alcohol of a longer-lived enone intermediate. This could take place in a MPV type reduction whereby the secondary alcohol is able to directly reduce the enone intermediate. Catalyst-free autocatalyzed hydrogen borrowing alkylations are known in the literature[75,76] and recently Morrill and co-workers have reported a transition metal-free method employing similar substrates, albeit

at significantly higher temperature and excess alcohol.[29] Replacing the *tert*-butyl group with a phenyl, surprisingly gave the desired product (**15q**) in 85% yield and 53:47 e.r. While the reason for this decrease in enantioselectivity is unclear, it is possible that the phenyl group may be able to π-stack with the ligand and reduce the energy difference between the two transition states. Alternatively, benzylic alcohols are well suited to undergo MPV-type reductions, as they undergo facile oxidation when compared to their alkyl counterparts, so it is possible that this metal-free pathway is favoured in the presence of benzylic alcohols, leading to low enantioselectivity. Unfortunately, not all the investigated alcohols underwent the desired alkylation with Ph* methyl ketone (Scheme 2.5.B). Alcohols with alkynes, esters or amines were not tolerated (**15r**-**t**), in all cases consumption of starting materials was observed and resulted in a complex mixture of products. Perhaps unsurprisingly, in the case of **15r**, ^{1}H NMR spectra likely corresponded to reduction of the alkyne in alcohol type compounds as well as Ph*-containing products. With a highly sterically encumbered phenyl substituted alcohol, only unreacted starting materials were observed after 24 h (**15u**). When replacing the methyl group (R_S) with an ethyl (**15v**) or butyl (**15w**) group no reaction was observed. Increasing the reaction temperature to 125 °C still did not allow for the formation of **15v** and only starting materials were observed. Pleasingly, this method could readily be performed on gram scale with no reduction in efficiency, enabling the synthesis of **15f** in 85% yield and 92:8 e.r. (Scheme 2.5.D). Furthermore, stereoselective crystallization of the product was possible due to the highly crystalline nature of Ph*-containing compounds, leading to an increase in enantiomeric purity to 97:3 e.r. with 71% recovery.

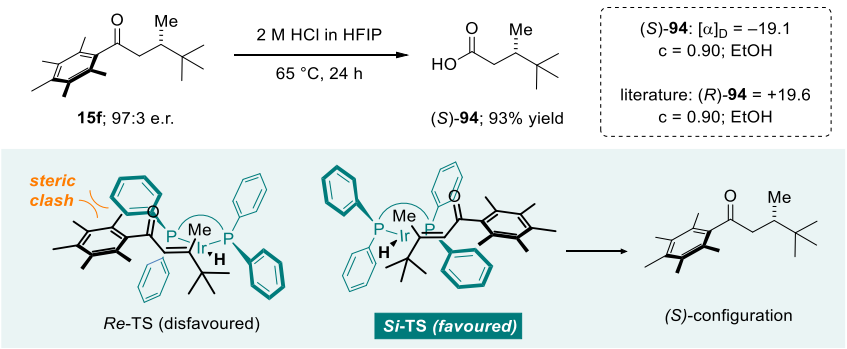


Scheme 2.5. A: Substrate scope of enantioselective synthesis of acyclic β-branched ketones *via* hydrogen borrowing catalysis. **B:** Unsuccessful examples. **C:** Intermediate enone geometry. **D:** Gram scale reaction. [a] Compounds were synthesised by Dr Roly Armstrong and Dr Wasim Akhtar. [b] Reaction time of 48 h. The absolute stereochemistry was proven for **15f** (see below) and the remaining compounds are assigned by analogy.

2.7. Determination of Absolute Stereochemistry

In order to determine the absolute stereochemistry of the β-branched ketones, **15f** was derivatised into known enantioenriched compound **94**. We have recently shown that under

acidic conditions the Ph* group can be efficiently cleaved to the corresponding carboxylic acid *via* a retro-Friedel-Crafts acylation.[35] Treating **15f** with 2 M HCl in HFIP at 65 °C afforded the corresponding acid in 93% yield (Scheme 2.6). Correlation of the specific rotation value of **94** with that previously reported in the literature allowed determination that the absolute configuration of **94**, and therefore by extension **15f**, as (*S*). The remaining examples in Scheme 2.5 are assigned by analogy. This can be rationalised through *Si*-face coordination of the *s-cis* enone intermediate to the chiral catalyst complex, placing the Ph* groups in the unhindered quadrant (Scheme 2.6). The disfavoured *Re*-transition state places the Ph* clashing with the P-Ar group of the ligand. This mode of induction is analogous to the enantioselective hydrogen borrowing annulation reaction, which, as discussed in Chapter 2.1, was supported by computational studies.



Scheme 2.6. Determination and rationalisation of the absolute stereochemical outcome.

2.8. Reaction Scope: Ketone

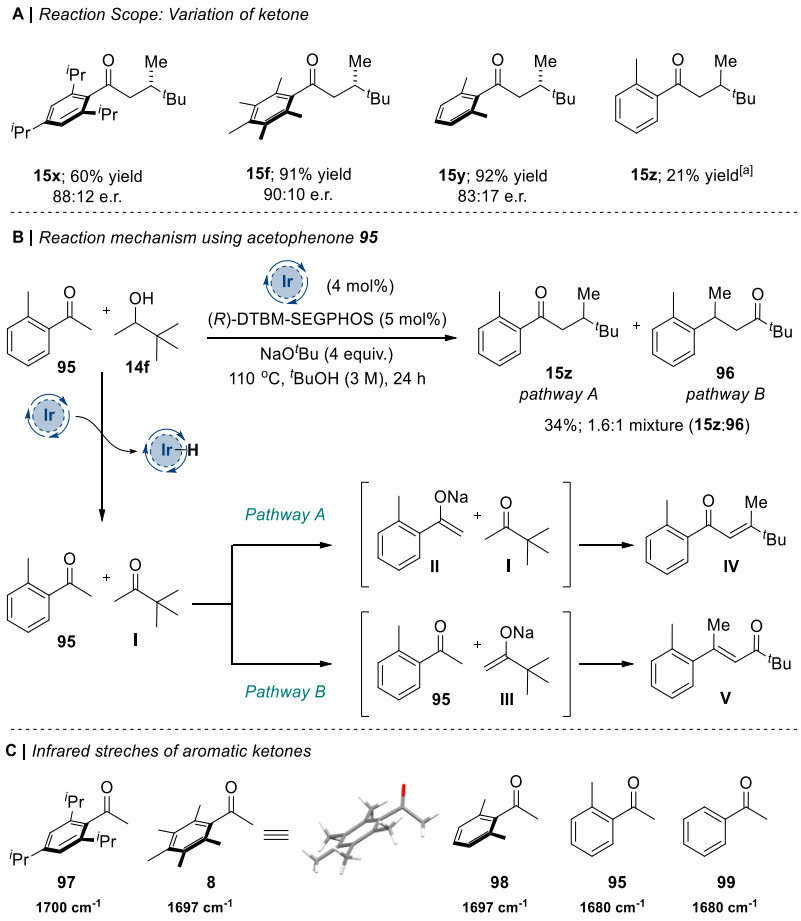
As discussed in Chapter 1.3, the Ph* group is key to the success of this methodology. The carbonyl is forced into the orthogonal plane due to the steric bulk of the Ph* group, preventing formation of any undesired by-products. Nevertheless, variations of similarly hindered aromatics were well tolerated in the enantioconvergent alkylation (Scheme 2.7.A). Decreasing the steric bulk (*cf*. Ph* methyl ketone) e.g. using 2,6-dimethylacetophenone affords the desired product (**15y**) in analogous yield but reduced enantioselectivity (92% yield; 83:17 e.r.). This is in

line with the proposed stereochemical model, as reducing the steric clash with the P-Ar group by removing the additional methyl groups would reduce the energy difference between the two transition states. In contrast, increasing the size of the aromatic group should disfavour the *Re*-transition state further, increasing the energy difference between the transition states affording a higher enantiomeric ratio. Unfortunately using 2,4,6-isopropyl substituted ketone afforded the desired ketone (**15x**) in slightly reduced e.r. in comparison to Ph* methyl ketone (88:12 e.r.). This is perhaps due to the substrate not efficiently coordinating to the catalyst-ligand complex due to the excessive steric bulk of the aromatic group, suggesting that Ph* group provides a good balance between allowing effective coordination of the enone substrate to the ligand whilst providing enough steric bulk to disfavour the *Re*-transition state.

Curious if a single *ortho*-methyl group would provide sufficient steric bulk to facilitate a selective reaction, we subjected *o*-methylacetophenone **95** to our optimised reaction conditions with pinacolyl alcohol (Scheme 2.7.B). This afforded **15z**[*] in 21% yield as an inseparable mixture with **96** (13% yield). For *o*-methylacetophenone **95**, the cross-aldol reaction with pinacolone (**I**) (generated *in situ* from **14f**) is no longer selective and gave a 1.6:1 mixture of regiomeric isomers **15z** and **96**. This loss in selectivity can attributed to the aryl ring in **95** no longer sitting orthogonal to the carbonyl and "blocking" nucleophilic attack at this position *(cf.* Ph* methyl ketone). As discussed in Chapter 1.3, this orthogonality has been previously shown for Ph* methyl ketone through X-Ray crystallography and IR stretches of the carbonyl group. This analysis was extended to **97** and **98** through analysis of the C=O bond IR stretch (Scheme 2.7.C). The IR stretches for the carbonyl group in both cases were ~10 cm^{-1} higher than acetophenone and in line with the C=O stretch in Ph* methyl ketone, implying an analogous lack of conjugation between the aromatic ring and the C=O group. In contrast, the IR stretch for the C=O bond in **95** matches

[*]It was not possible to determine an e.r. as **15z** could not be isolated with sufficient purity.

acetophenone implying adoption of a planar conformation and, therefore, **95** is unable to facilitate a selective reaction.



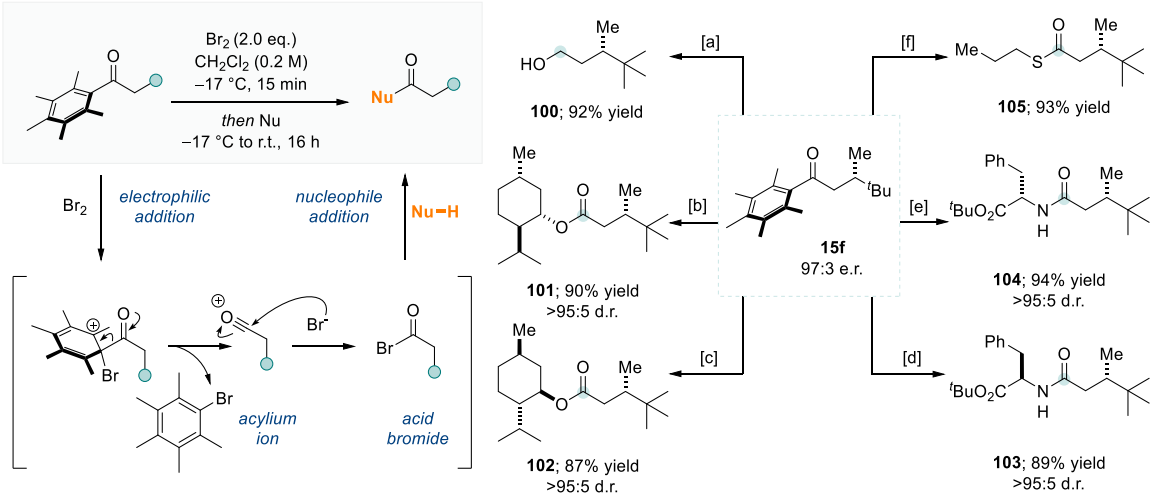
Scheme 2.7. Effect of changing the aromatic ketone. [a] Yield calculated based on quantitative ^{1}H NMR of a mixture of **15z** and **96**.

2.9. Derivatisation of Ph β-Branched Ketones*

To demonstrate the utility of the β-branched ketones, we aimed to carry out a series of derivatisation reactions to introduce a range of functionality. As discussed, the Ph* group is key to this methodology for multiple reasons – a final advantage is the that Ph* is a precursor for a highly versatile carbonyl intermediate, which facilitates incorporation of functionality that may not be tolerated in the hydrogen borrowing reaction. Donohoe and co-workers have previously reported a bromine-mediated Ph* cleavage procedure in which cleavage of the Ph* group can be readily achieved *via* a retro-Friedel–Crafts acylation reaction as discussed in Chapter 1.3

(Scheme 2.8).[25] Treatment of the Ph* ketones with Br_2 affords the corresponding acid bromide is a versatile intermediate, which can be directly converted in situ into a variety of other useful functional groups.

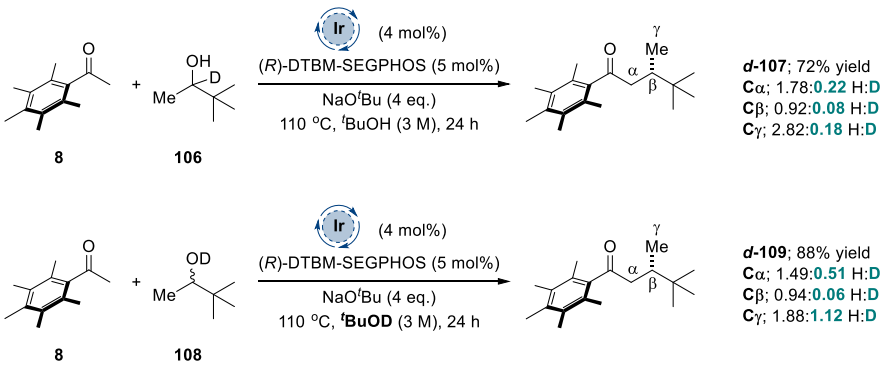
For example, treatment of **15** with Br_2 followed by $LiAlH_4$ gives the primary alcohol, **100** in 92% yield (Scheme 2.8). Addition of either enantiomer of menthol to the acid bromide gave the corresponding diastereomeric menthol esters. Both **101** and **102** were isolated as single diastereomers, confirming (as expected) that the Ph* cleavage proceeds with no epimerisation at the β-stereogenic centre. Amine nucleophiles were well tolerated, forming the corresponding amides in excellent yield (**103** and **104**). In a similar manner to the menthol esters, using enantiomeric chiral amine nucleophiles gave the amides as single diastereomers. Finally, addition of propane-1-thiol to the acid bromide gave thioester **105** in 93% yield.



Scheme 2.8. Mechanism and scope of pentamethylphenyl ketone cleavage. [a] Br_2 (2 eq.), CH_2Cl_2, –17 °C then $LiAlH_4$ (5 eq.), THF, r.t. [b] Br_2 (2 eq.), CH_2Cl_2, –17 °C then D-menthol (3 eq.), r.t. [c] Br_2 (2 eq.), CH_2Cl_2, –17 °C then L-menthol (3 eq.), r.t. [d] Br_2 (2 eq.), CH_2Cl_2, –17 °C then H-D-Phe-O^{t}Bu.HCl (2 eq.), ^{i}PrEt$_2$N (4 eq.), r.t. [e] Br_2 (2 eq.), CH_2Cl_2, –17 °C then H-L-Phe-O^{t}Bu.HCl (2 eq.), ^{i}PrEt$_2$N (4 eq.), r.t. [f] Br_2 (2 eq.), CH_2Cl_2, –17 °C then propane-1-thiol (3 eq.), r.t.

2.10. Mechanistic Probes

In order to probe the mechanism, deuterated alcohols **106** and **108*** were used to alkylate ketone **8** (Scheme 2.9). We hypothesised that **106** would be oxidised to form Ir-D and deliver a single deuterium atom to the C-β position. In contrast, **108** would oxidise to Ir-H and deliver a hydrogen atom to the C-β position. Subjecting **106** to the reaction conditions afforded ***d*-107** in 72% yield. On ^{1}H NMR analysis only 8% of deuterium incorporation was observed. Additionally, 16% and 9% of deuterium was seen at C-α (CH_2) and C-γ (CH_3), respectively. We hypothesise that the initial Ir-D species can undergo H/D exchange in the basic reaction mixture and thus only low levels of deuterium are observed at C-β.[77,78] Deuterium is likely incorporated at C-α and C-γ through reversible enolate and extended enolate formation, respectively.



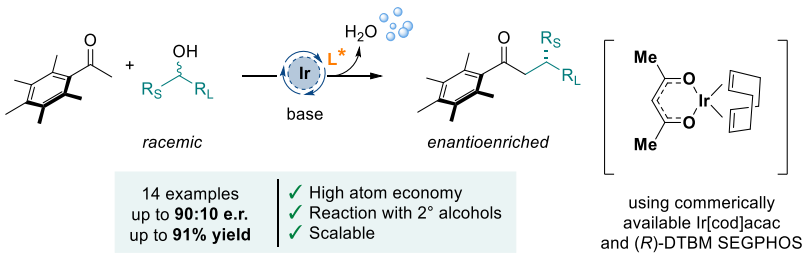
Scheme 2.9. Mechanistic probes using deuterated pinacolyl alcohol.

Using deuterated alcohol **108**, we observed a similar level of deuterium incorporation at the C-β position, whereas at C-α and C-γ, significantly higher levels of D are seen. This is presumably due to the use of ^{t}BuOD as solvent. The addition of deuterium at C-γ gives direct evidence for the formation of the extended enolate under the reaction conditions and prompted us to consider a dynamic kinetic resolution (DKR) strategy to control the absolute stereochemical outcome of C-γ, which will be explored further in Chapters 3 and 4.

*For the synthesis of **106** and **108** see Chapter 6.2.1.4.

2.11. Conclusion

This chapter describes the development of an enantioselective alkylation of Ph* methyl ketone with secondary alcohols to afford enantioenriched β,β-disubstituted ketones *via* hydrogen borrowing catalysis (Scheme 2.10). Using commercially available [Ir(cod)acac] and (*R*)-DTBM-SEGPHOS, this process is able to efficiently form sterically hindered C(sp^3)–C(sp^3) bonds in good yields. Particularly of note is that a range of β,β-disubstituted ketones were synthesised using neopentylic alcohols (or other quaternary centres) and it would be difficult to synthesise these compounds using traditional alkylation methods employing neopentyl halides. While facial addition of the metal hydride to the key enone intermediate is controlled by the chiral ligand, the outcome of the reaction is equally dependent on the formation of an isomerically pure enone intermediate. The enantioselectivity has therefore been shown to strongly correlate with the size of steric bulk of R_L, which influences the geometry of the enone. We have shown that this chemistry is efficient on gram scale and the e.r. of the ketones can be enriched through stereoselective crystallisation. Furthermore, it has been demonstrated that the Ph* group is a useful precursor to a wide range of functional groups. The β,β-disubstituted ketone products were readily cleaved *via* retro-Friedel-Crafts acylation to the corresponding acid bromide, which could be further derivatised *in situ* through reaction with a number of nucleophiles, without any epimerisation of the newly installed stereogenic centre.

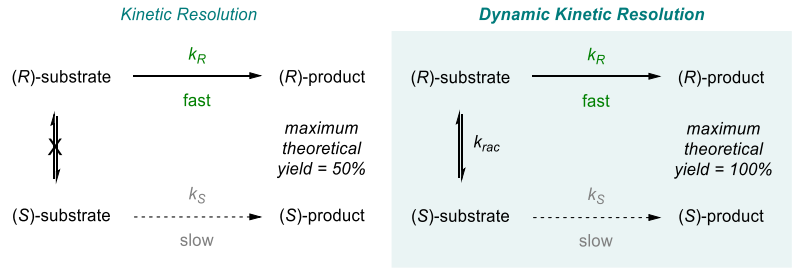


Scheme 2.10. Summary of the enantioselective synthesis of β,β-disubstituted ketones *via* hydrogen borrowing catalysis.

Chapter 3: Dynamic Kinetic Resolution via *Hydrogen Borrowing Catalysis: Acyclic Systems*

3.1. Dynamic Kinetic Resolution

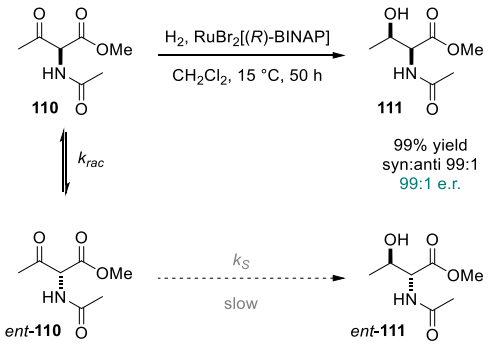
Resolution of racemic mixtures of enantiomers has long been employed as a strategy for accessing enantioenriched products.[79] In a kinetic resolution, preferential reaction with a single enantiomer leads to highly enantioenriched products. However, access to a maximum theoretical yield of 50% of a single enantiomer is a major practical limitation. To overcome this, *in situ* racemisation of the starting material would lead to a dynamic kinetic resolution (DKR). This represents a powerful alternative strategy; one in which a racemic starting material can converge to form a single enantiomer of product in up to 100% yield, overcoming the inherent inefficiency of kinetic resolution (Scheme 3.1). The efficiency of DKR generally relies on three major factors: (i) the kinetic resolution must proceed with high enantioselectivity ($k_R >> k_S$); (ii) racemisation must occur at a higher rate than the kinetic resolution ($k_{rac} > k_R$); and (iii) the product itself must not undergo racemisation.



Scheme 3.1. Kinetic Resolution and Dynamic Kinetic Resolution.

Asymmetric hydrogenation (and transfer hydrogenation) has become the most widely studied class of DKR following the pioneering work by Noyori and co-workers in the ruthenium catalysed asymmetric hydrogenation of β-ketoesters *via* DKR (Scheme 3.2).[80] This concept has been widely and routinely used both in research laboratories and large-scale industrial settings.[81,82]

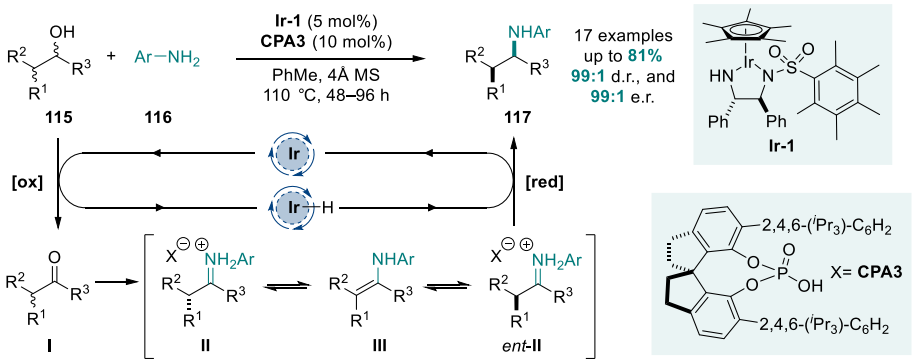
Since then, a significant number of reports utilising DKR have been disclosed such as enolate alkylation, C–H activation and acylation.[79]



Scheme 3.2. Asymmetric hydrogenation of β-ketoesters *via* DKR.

3.2. Dynamic Kinetic Resolution in the Context of Hydrogen Borrowing Catalysis

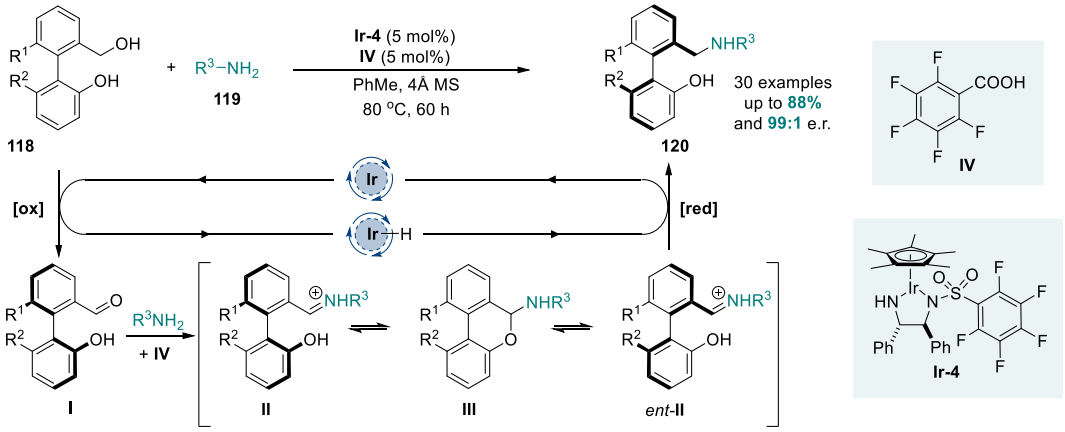
Whilst dynamic kinetic resolution strategies have frequently been incorporated into C–N bond forming hydrogen borrowing catalysis, there has been far more limited attention toward DKR in C–C bond forming reactions.[39]



Scheme 3.3. Asymmetric amination of alcohols *via* DKR.

Zhao and co-workers have developed a general dynamic kinetic resolution method which relies on interconversion of iminium intermediates *via* enamine formation; the utility of which has been demonstrated by application to several different systems.[63,65,66,83,84] A representative example is the enantioselective amination of alcohols to form α,β-branched amines using a dual-catalytic system employing chiral iridium catalyst **Ir-1** in conjunction with chiral Brønsted acid

CPA3 (Scheme 3.3).[63] As previously discussed, that both the chiral Brønsted acid *and* chiral iridium catalyst were essential for both yield and enantioselectivity. Mechanistically, the authors proposed a pathway involving catalyst mediated oxidation of the alcohol, followed by condensation of the amine. The resulting iminium intermediate **II** is able to rapidly epimerise *via* enamine **III**, followed by selective asymmetric reduction, controlling both the β-stereogenic centre as well as the facial selectivity of the iminium reduction. This method is able to control multiple stereogenic centres through stereoconvergence towards a single product which is both highly diastereomerically and enantiomerically enriched. More recently this concept has been applied to mono- and double-amination of 1,2-diols as well as amination of tetralin- and indane-derived alcohols.[65,66,83,84]

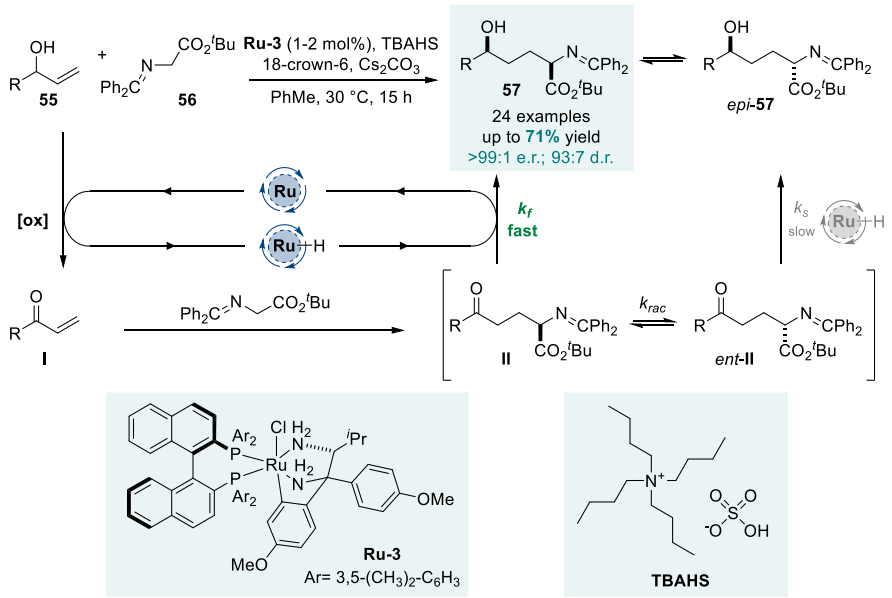


Scheme 3.4. Atroposelective amination of biaryls *via* DKR.

Enantioselective hydrogen borrowing catalysis has also been used to control axial chirality using a dynamic system (Scheme 3.4). Zhang and Wang have demonstrated that biaryl alcohols undergo highly atroposelective amination by employing cooperative catalysis with a chiral iridium catalyst and an achiral Brønsted acid.[85] The authors proposed that the reaction is initiated by catalyst-mediated oxidation of the biaryl, followed by condensation of the amine to the form iminium **II**. Interconversion between enantiomers **II** and *ent*-**II** is thought to proceed *via* hemiaminal **III**. Due to the "bridged biaryl" effect[86] it is expected that the hemiaminal

intermediate has a lower barrier to rotation and allows racemisation, thereby enabling an effective dynamic kinetic resolution wherein one iminium is preferentially reduced to afford the saturated product in very high enantioselectivities.

As briefly discussed in Chapter 1.4.1, Wang and co-workers have reported a C–C bond forming hydrogen borrowing DKR reaction, which involves a hydroalkylation of racemic allylic alcohols with a glycine-derived Schiff base (Scheme 3.5).[52] Chiral amino acid derivatives were accessed in moderate yields, good diastereoselectivity and excellent enantioselectivity. Mechanistically, the authors proposed a pathway involving oxidation of allylic alcohol **55**, followed by 1,4-addition of **56** to enone **I**.

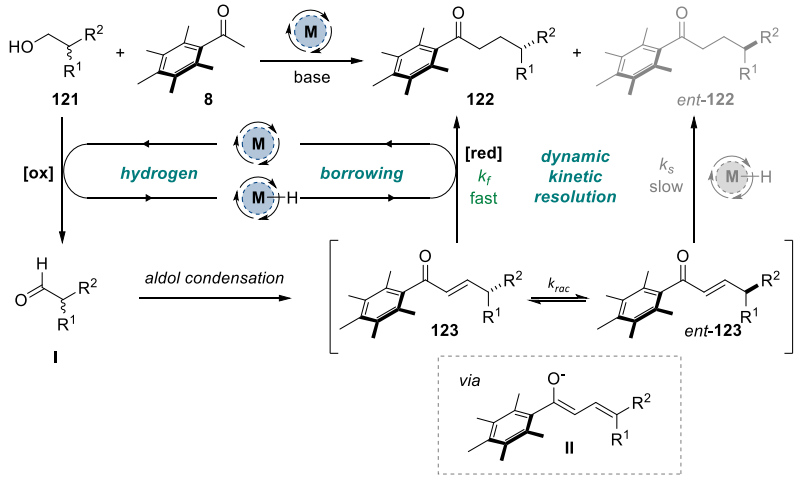


Scheme 3.5. Enantioselective hydroalkylation of allylic alcohols.

The resulting enantiomeric ketone intermediates were able to rapidly interconvert by reversible deprotonation/re-protonation and **II** was selectively reduced by the chiral ruthenium hydride leading to an efficient dynamic kinetic asymmetric hydroalkylation. Unusually, the alcohol product is able to epimerise through the same mechanism as the ketone intermediates and authors noted an amplification of diastereoselectivity of the product through deprotonation/re-protonation of the acidic proton alpha to the ester group.

3.3. Project Aims

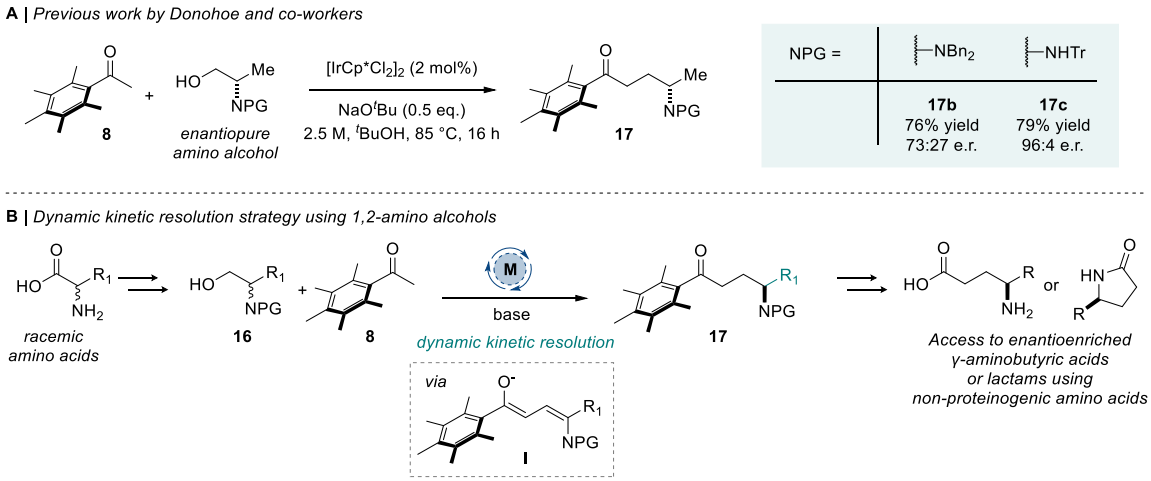
The aim at the outset of this project was to provide a general strategy for stereochemical control at the γ-stereogenic centre in acyclic systems by incorporating a dynamic kinetic resolution with enolate C–C hydrogen borrowing catalysis (Scheme 3.6). Alkylation of Ph* methyl ketone with β,β-branched primary alcohols (**121**) would lead to enone intermediate **II** following a standard hydrogen borrowing pathway. This enone intermediate would be able to interconvert by reversible deprotonation/re-protonation *via* an extended enolate. The chiral metal-hydride would then selectively reduce one enone intermediate to afford the saturated, enantioenriched ketone **122**. This process relies on rapid interconversion of the two enantiomeric enone intermediates (**123** and *ent*-**123**) coupled with selective reduction of one enantiomer by a chiral catalyst complex.



Scheme 3.6. Proposed hydrogen borrowing catalysed alkylation using β,β-branched primary alcohols controlling the γ-stereogenic centre *via* DKR.

We also envisaged alkylating Ph* methyl ketone with racemic 1,2-amino alcohols. As discussed in Chapter 1.3, Donohoe and co-workers have demonstrated that either racemisation or preservation of the γ-stereogenic centre can be achieved through variation of the *N*-protecting group (Scheme 3.7).[32] If an appropriate protecting group was selected to allow rapid racemisation of the γ-stereogenic centre, a DKR could be integrated into this system. This would

provide a complementary method for accessing enantioenriched γ-aminobutyric acid products from *racemic* non-proteinogenic amino acids. Furthermore, this would provide access to either enantiomer of the amino ketone by using the appropriate catalyst or ligand enantiomer.

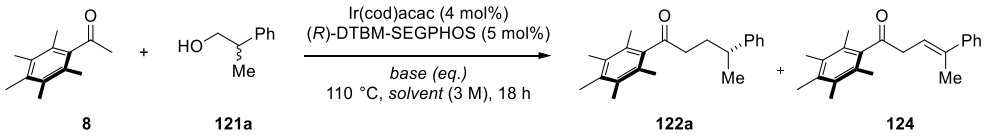


Scheme 3.7. Proposed hydrogen borrowing catalysed alkylation using 1,2-amino alcohols controlling the γ-stereogenic centre *via* DKR.

3.4. Preliminary Studies Using β,β*-Branched Primary Alcohols*

We began by investigating the alkylation of ketone **8** with commercially available 2-phenylpropan-1-ol **121a** using the reaction conditions developed for the enantioselective synthesis of acyclic β-branched ketones discussed in Chapter 2 (Table 3.1). Under these conditions, the desired product (**122a**) was afforded in 64:36 e.r., but was isolated in a 41:59 ratio (as an inseparable mixture) with skipped enone **124** (Entry 1). By reducing the equivalents of base, the formation of the skipped enone side product was suppressed, however this came at the expense of enantioselectivity (Entries 2-3). Changing the base to NaOH or KOH also supressed the formation of the skipped enone, and gave high yields of **122a**, but no enantioselectivity was observed (Entries 4-5). Replacing ^{t}BuOH with toluene led to 52% yield of the skipped enone and minimal enantioselectivity was observed for the formation of **122a** (Entry 6).

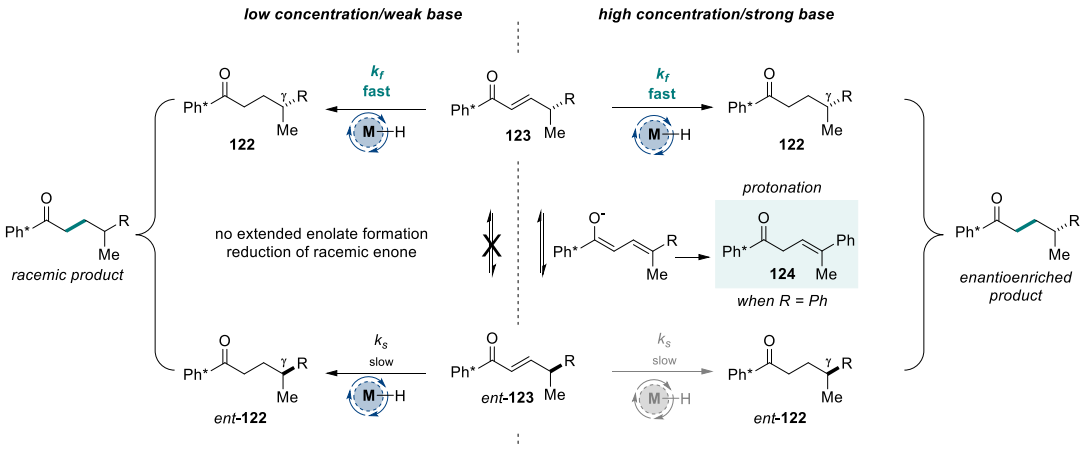
Table 3.1. Preliminary studies on the alkylation of ketone **8** with alcohol **121a**.



Entry	Base (eq.)	Solvent	Yield[a] 122a / %	e.r.[a]	Yield 124 / %
1	NaO^{t}Bu (4)	^{t}BuOH	[21]	64:36	[31]
2	NaO^{t}Bu (2)	^{t}BuOH	52	50:50	5
3	NaO^{t}Bu (1)	^{t}BuOH	89	50:50	-
4	NaOH (4)	^{t}BuOH	74	50:50	5
5	KOH (4)	^{t}BuOH	89	50:50	10
6	NaO^{t}Bu (4)	PhMe	17	54:46	52

[a] Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The absolute stereochemistry was not determined for **123a** and the enantiomer which has been depicted is arbitrary.

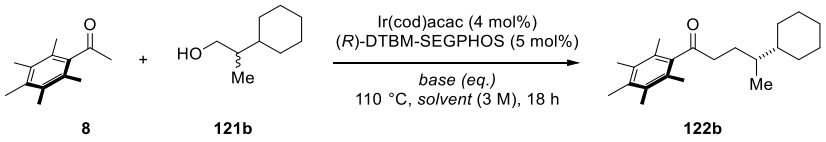
The low enantioselectivity observed when using higher equivalents of base, or stronger *tert*-butoxide bases, could be explained by the presence of a DKR in the system. We reasoned that at higher concentrations of base (or stronger bases), there is a sufficient rate of racemisation *via* the extended enolate, enabling a DKR (Entry 1 and 6). The formation of skipped enone **124** may support this mechanism of racemisation as it is likely formed by protonation of the intermediate extended enolate **I** (Scheme 3.8); in this particular skipped enone (R=Ph), the double bond is in conjugation with the phenyl ring, favouring its formation for this substrate. However, at lower concentrations of base, minimal skipped enone is observed, tentatively suggesting that the extended enolate is not able to form in sufficient quantities. The lack of efficient racemisation ensures a DKR is not possible, and therefore this may be a possible reason for formation of racemic ketone **122**, albeit in high yields (Scheme 3.8).



Scheme 3.8. Different pathways in the alkylation of Ph* methyl ketone with β,β-branched alcohols.

We reasoned that changing the alcohol substrate for alkylation to 2-cyclohexylpropan-1-ol (**121b**) would remove the additional stabilisation of the skipped enone, disfavouring the side product. With this unproductive pathway eliminated, we proposed that rapid interconversion of the enone intermediates could occur *via* the extended enolate, leading to a DKR. Pleasingly, the standard conditions gave the desired product (**122b**) in 90% yield and 57:43 e.r. and no formation of skipped enone was observed (Table 3.2, Entry 1). Due to the higher pKa of the enone intermediate at the γ-stereogenic center of **122b** (*cf*. to benzylic proton in **122a**), we suspected that the discrepancy in enantioselectivity between the two substrates may be a result of the enone intermediate in this system requiring stronger, or more equivalents of, base to racemise at a sufficient rate. Increasing the amount of NaO^{t}Bu to 6 or 8 equivalents gave a slight increase in e.r. (Entries 2-3). In order to use stronger bases and not form the *tert*-butoxide anion from the solvent, ^{t}BuOH was replaced with toluene – another typical solvent for hydrogen borrowing reactions. This led to a reduction in yield but had no effect on the enantioselectivity (Entry 4). Pleasingly, using an even stronger base (NaHMDS) gave an increase in e.r. (67:33 e.r., Entry 5). At this point, we wondered whether the conformational flexibility was an issue and if conformational restriction of the enone intermediate could lead to improved stereocontrol.

Table 3.2. Preliminary studies on the alkylation of ketone **8** with alcohol **121b**.

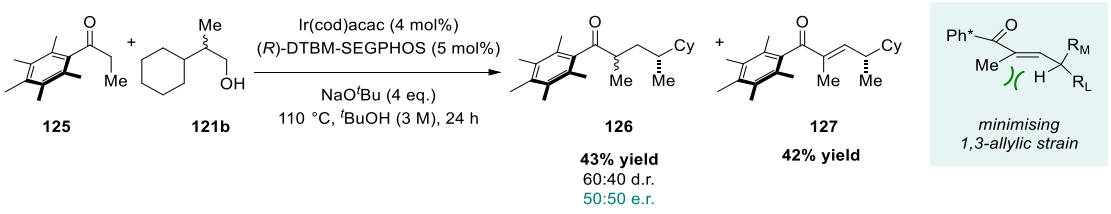


8 **121b** **122b**

Entry	Base (eq.)	Solvent	Yield[a] / %	e.r.[b]
1	NaO^{t}Bu (4)	^{t}BuOH	Quant. [90]	57:43
2	NaO^{t}Bu (6)	^{t}BuOH	68	61:39
3	NaO^{t}Bu (8)	^{t}BuOH	70	61:39
4	NaO^{t}Bu (4)	PhMe	62	57:44
5	NaHMDS (4)	PhMe	70	67:33

[a] Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [Isolated yields are given in parentheses].
[b] Determined by normal phase HPLC analysis using a chiral stationary phase. The absolute stereochemistry was not determined for **122b** and the enantiomer which has been depicted is arbitrary.

Accordingly, we explored introduction of a substituent at the α-position. We hoped that this would restrict the conformation of the intermediate enone through 1,3-allylic strain and thus improve the facial selectivity of the enantiodetermining reduction. This hypothesis was investigated through the alkylation of Ph* ethyl ketone (**125**) with 2-cyclohexylpropan-1-ol (**121b**) (Scheme 3.9). However, the desired product was isolated in 43% yield, and disappointingly as a racemate.* Additionally enone intermediate **127** was isolated in 42% yield, suggesting that the trisubstituted enone was too sterically hindered to reduce.



125 **121b** **126** **127**

43% yield
60:40 d.r.
50:50 e.r.

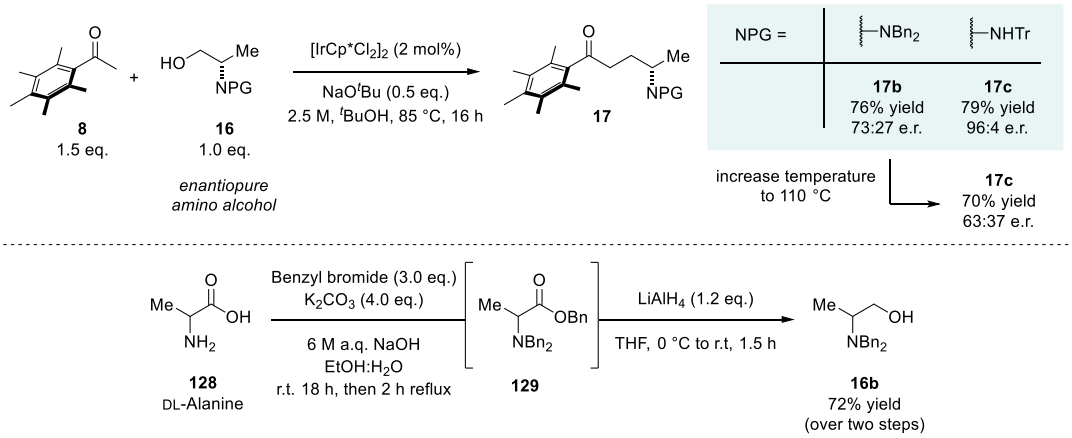
42% yield

Scheme 3.9. Alkylation of Ph* ethyl ketone with 2-cyclohexylpropan-1-ol.

N.B. **126** enantiomer and diastereomer HPLC separation was extremely challenging and baseline separation was not achieved. So, while this enantiomeric ratio must be interpreted with slight caution, it is evident from the HPLC trace that there was little to no enantioenrichment.

3.5. Preliminary Studies Using 1,2-Amino Alcohols

Next, we turned our attention to hydrogen borrowing alkylation with 1,2-amino alcohols. As discussed, racemisation of the γ-stereocentre has been observed in hydrogen borrowing alkylations with *N*,*N*-dibenzyl-L-alaninol and this substrate was therefore promising for a DKR strategy. The Donohoe group have shown that the desired amino ketone may be isolated in 76% yield and 73:23 e.r.[87] Enantioretention was achieved through use of *N*-Trityl protecting group, affording the amino ketone **17c** in 79% yield and 96:4 e.r. (Scheme 3.10). We wondered if we could increase the level of racemisation in the *N,N*-dibenzyl derivative by increasing the temperature. Pleasingly, an increase in racemisation was observed at 110 °C affording **17b** in 70% yield and 63:37 e.r.

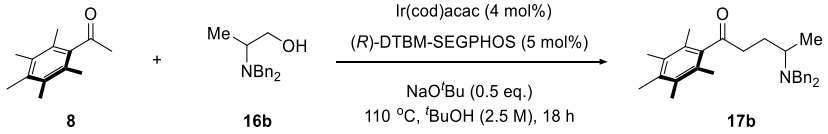


Scheme 3.10. Hydrogen borrowing alkylation of 1,2-amino alcohols and synthesis of *N*,*N*-dibenzyl-1,2-alaninol.

Significant racemisation of the γ-stereocentre under these conditions was promising for a DKR and the alkylation was attempted using the chiral catalytic system used in previous enantioselective hydrogen borrowing alkylations. Racemic amino alcohol **16b** was synthesised in two steps in 72% yield from DL-alanine (**128**, Scheme 3.10). Replacing the iridium(III) source for an iridium(I) source (Ir(cod)acac) and (*R*)-DTBM-SEGPHOS) unfortunately, gave the desired product in 32% yield as a racemate. The stoichiometry of the starting materials was inverted,

such that Ph* methyl ketone was used as the limiting reagent with an excess of amino alcohol and, interestingly, no product formation was observed.

Table 3.3. Preliminary studies investigating the enantioselective hydrogen borrowing alkylation with 1,2-amino alcohols.



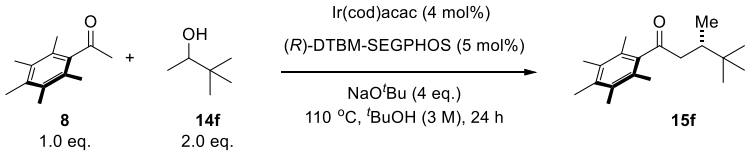
8 **16b** **17b**

Entry	Eq. of Ph*COMe	Eq. of amino alcohol	Yield / %	e.r.[a]
1	1.5	1.0	32	50:50
2	1.0	2.0	0	-

Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [a] Determined by normal phase HPLC analysis using a chiral stationary phase.

We hypothesised that the amino alcohol is able to coordinate to the iridium catalyst, displacing the chiral ligand. This would be unsurprising as 1,2-amino alcohols have been widely used as ligands in asymmetric reactions with a range of metals.[88] To probe this, our previously reported enantioselective hydrogen borrowing alkylation (using the same catalytic system; Chapter 2) was spiked with 10 mol% of amino alcohol (Table 3.4). Under standard conditions, the desired ketone **15f** is isolated in 90% yield and 90:10 e.r. However, when spiked with 10 mol% of amino alcohol **16b**, **15f** was obtained in 80% yield and 54:46 e.r. These results suggests that when present in sub-stoichiometric quantities, the amino alcohol can bind to the iridium and replace the chiral ligand. However, the catalyst is still able to facilitate the hydrogen borrowing alkylation, albeit with no enantioselectivity. Excess amino alcohol, presumably, is able to sequester the catalyst completely, rendering it inactive and no product formation is observed (Entry 2, Table 3.3). To address this problem, two approaches were considered: (i) alter the properties of the amino alcohol to prevent outcompeting of the chiral ligand, or (ii) identify a catalytic system which disfavours strong coordination of the amino alcohol.

Table 3.4. Effect of 1,2-amino alcohols on known enantioselective hydrogen borrowing alkylations.

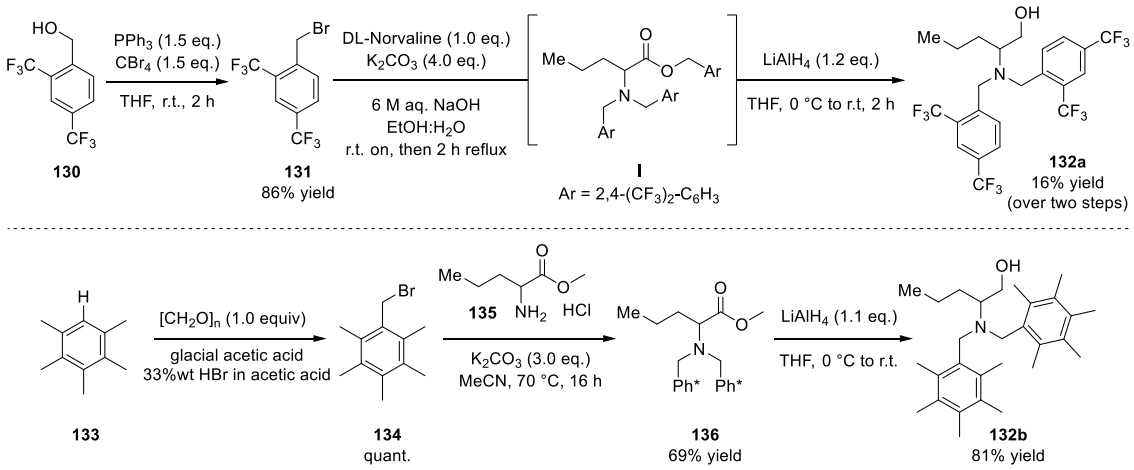


Entry	Deviation	Yield[a] / %	e.r.[b]
1	None	91 [91]	90:10
2	10 mol% of *N*,*N*-dibenzyl alaninol (**16b**)	80	54:46

[a]Determined by reverse phase HPLC analysis *vs* durene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. [Isolated yields are given in parentheses].

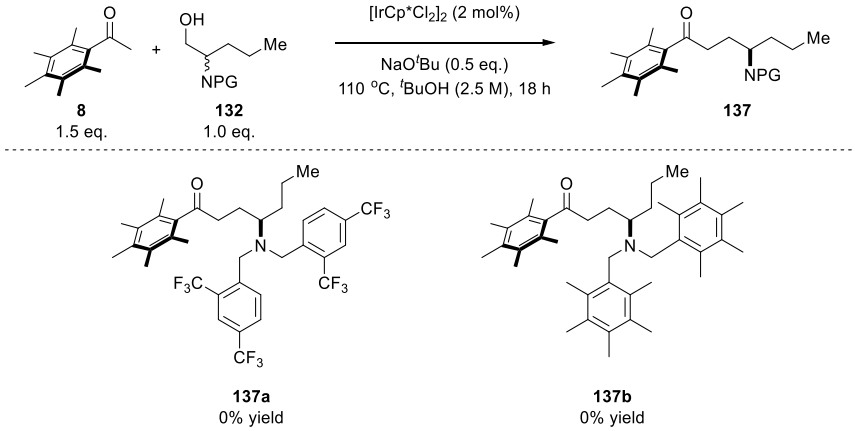
3.6. Selection of Protecting Group

To disfavour coordination of the amino alcohol to the metal catalyst, different nitrogen protecting groups were explored looking at both the electronics (–CF_3) and sterics (Ph*). Accordingly, *N*,*N*-diprotected derivatives of amino alcohols based on DL-norvaline, as an non-proteinogenic amino acid example, were synthesised. Bromide **131** was synthesised from the primary alcohol in an Appel reaction affording **131** in 86% yield (Scheme 3.11). Next, DL-norvaline was alkylated and the intermediate ester **I** was reduced to afford amino alcohol **132a** in 16% yield over two steps. To synthesise sterically hindered **132b**, pentamethylbenzene was bromomethylated to afford **134** in quantitative yield (Scheme 3.11). To reduce the equivalents of the aryl bromide needed, DL-norvaline was methylated to afford the corresponding methyl ester, **135**. Furthermore, due to the low yield obtained for **132**, the protected ester was isolated, instead of telescoping the reaction, and **136** was isolated 69% yield. Subsequent reduction afforded the 1,2-amino alcohol **132b** in 81% yield.



Scheme 3.11. Synthesis of *N*,*N*-protected 1,2-amino alcohols.

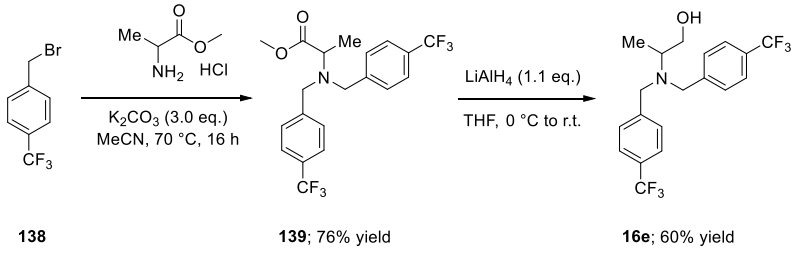
With these 1,2-amino alcohols in hand, they were first subjected to the racemic reaction conditions. Disappointingly, alkylation with bis-trifluoromethyl amino alcohol **132a** did not afford the desired product – presumably the oxidation is prevented due to the electron withdrawing nature of the protecting group. Similarly, alkylation with Ph* amino alcohol **132b** was not successful, leaving unreacted starting materials. This disappointing result was likely due to the steric hinderance of the Ph* groups preventing oxidation.



Scheme 3.12. Attempted hydrogen borrowing alkylation of *N*,*N*-protected 1,2-amino alcohols.

To try to find a suitable balance of preventing coordination of the amino alcohol to the metal whilst also allowing oxidation of the amino alcohol, mono-trifluromethyl amino alcohol was synthesised based on DL-alanine. The corresponding amino alcohol was synthesised in an

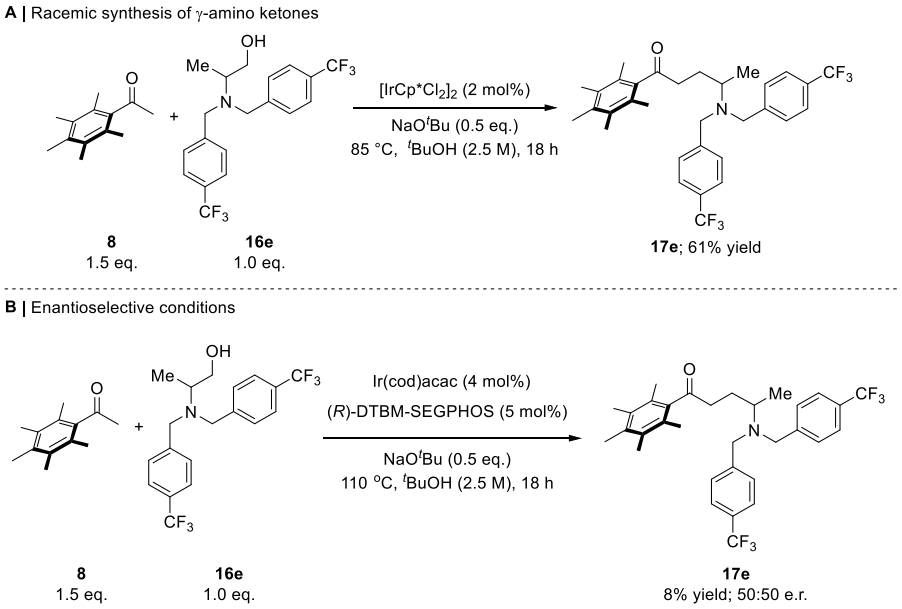
analogous procedure as previously described and afforded 1,2-amino alcohols **16e** in 46% overall yield (Scheme 3.13).



138 **139**; 76% yield **16e**; 60% yield

Scheme 3.13. Synthesis of *N*,*N*-protected 1,2-amino alcohol.

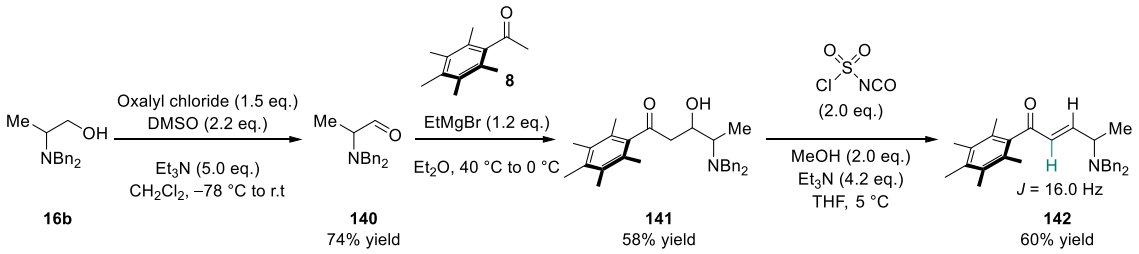
Pleasingly, when subjected to the (racemic) hydrogen borrowing alkylation conditions, the desired amino ketone (**17e**) was isolated in 61% yield (Scheme 3.14.A). DL-alaninol derivative **16e** was then exposed to the chiral catalyst system; however, under these conditions using an iridium(I) source and chiral catalyst, the desired amino ketone was isolated in only 8% yield and as a racemate (Scheme 3.14.B). This result suggests that even with the additional electron withdrawing nature of the $-CF_3$, it did not prevent the strong binding to the iridium catalyst.



Scheme 3.14. Hydrogen borrowing alkylation of *N*,*N*-protected 1,2-amino alcohols.

3.7. Transfer Hydrogenation

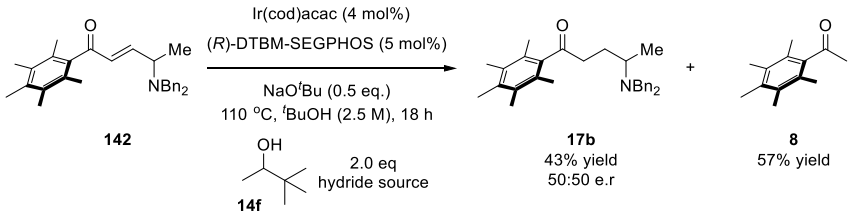
To interrogate the DKR step, we set out to investigate the enantioselective transfer hydrogenation of the intermediate enone. We hoped that transfer hydrogenation of the enone with a chiral catalyst would provide us with information about the effectiveness of the DKR since the asymmetric reduction would take place with no amino alcohol present to sequester the metal catalyst. Aldehyde **140** was accessed by Swern oxidation of alaninol **16b** in 74% yield. Subsequently, Ph* methyl ketone was added to EtMgBr to form the corresponding bromomagnesium enolate, which was captured by aldehyde **140** to afford β-hydroxyketone **141** in 58% yield and as a single diastereomer. Treatment of **141** with chlorosufonyl isocyanate, triethylamine and methanol formed the Burgess reagent which led to elimination affording enone (*E*)-**142** in 60% yield. The stereochemistry of enone **142** was determined through the large *J*-coupling constants indicative of a *trans* relationship of the alkenyl protons.



Scheme 3.15. Synthesis of enone **142**.

With enone **142** in hand, it was subjected to the standard hydrogen borrowing conditions with Ir(cod)acac and (*R*)-DTBM-SEGPHOS and alcohol **14f** as a hydride source. Disappointingly the desired amino ketone was isolated in 43% yield and as a racemate. Additionally, 57% of Ph* methyl ketone was isolated, presumably due to a retro aldol reaction of the enone. Transfer hydrogenation of cyclic enones had been shown to successfully replicate enantioselective hydrogen borrowing alkylations with no evidence of any retro aldol products.[36] Presumably the tri- or tetra-substituted enones are more stable to this pathway. Although no amino alcohol was isolated, we have shown that only 10% of their presence is detrimental to the enantioselectivity.

As such, we concluded that it was not possible to investigate the DKR by transfer hydrogenation of the intermediate enone.



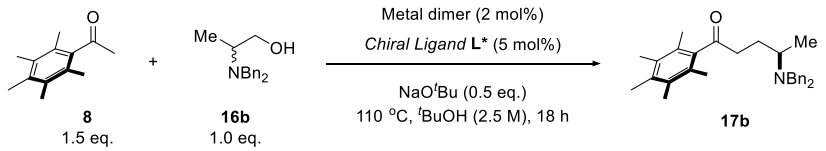
Scheme 3.16. Transfer hydrogenation of enone **142**.

3.8. Ligand Screening I

The next approach was to identify an effective catalytic system for the DKR which would outcompete coordination of the amino alcohol to the metal catalyst. Using DL-norvaline based amino alcohol**,** a small range of chiral ligands were screened using $[Ir(cod)Cl]_2$, however no hits were identified (See Appendix A). Initially DL-norvaline had been selected as a representative non-proteinogenic amino acid derivative, but it was quickly discovered that the crystalline nature of alaninol derivative **16b** was more practical to use when screening a large number of reactions. As such, the ligand screening was continued with this substrate. Furthermore, due to very low reactivity and enantioselectivity observed with iridium, different metal catalysts were also investigated.

Across a range of ligand classes low yields and enantioselectivity was observed with use of a rhodium pre-catalyst (Table 3.5). Use of ruthenium as the pre-catalyst gave similar, but slightly more promising, results – for example use of (*S*)-^{i}Pr-PHOX ligand with $[Ru(p\text{-cymene})Cl_2]_2$ gave the desired amino ketone in 23% yield and 64:36 e.r. compared to 50:50 e.r. with use of $[Rh(cod)Cl]_2$ (Entry 7 vs 8). Diphosphine ligands gave mixed results: some selectivity was seen in use of (*R*)-BINAP (Entries 9-10), however use of **L17** and **L18** gave the desired product as a racemate (Entries 11-12).

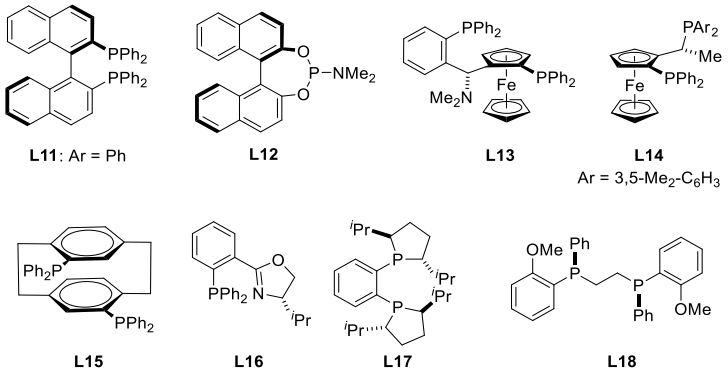
Table 3.5. Ligand screen for the enantioselective hydrogen borrowing alkylation with 1,2-amino alcohols.



8 1.5 eq. + **16b** 1.0 eq. → **17b**

Entry	L*	Ligand	[M]	Yield[a] / %	e.r.[b]
1	**L14**	Josiphos SL-J005-1	[Ru(*p*-cymene)Cl$_2$]$_2$	8	50:50
2	**L14**	Josiphos SL-J005-1	[Rh(cod)Cl]$_2$	0	-
3	**L13**	(R_P,*R*)-Taniaphos	[Ru(*p*-cymene)Cl$_2$]$_2$	8	56:44
4	**L13**	(R_P,*R*)-Taniaphos	[Rh(cod)Cl]$_2$	10	58:42
5	**L15**	(*S*)-PHANEPHOS	[Ru(*p*-cymene)Cl$_2$]$_2$	15	50:50
6	**L12**	(*R*)-MonoPhos	[Ru(*p*-cymene)Cl$_2$]$_2$	14	50:50
7	**L16**	(*S*)-^{i}Pr-PHOX	[Ru(*p*-cymene)Cl$_2$]$_2$	23	64:36
8	**L16**	(*S*)-^{i}Pr-PHOX	[Rh(cod)Cl]$_2$	10	50:50
9	**L11**	(*R*)-BINAP	[Ru(*p*-cymene)Cl$_2$]$_2$	10	57:43
10	**L11**	(*R*)-BINAP	[Rh(cod)Cl]$_2$	15	53:47
11	**L17**	(*R,R*)-^{i}Pr-DUPHOS	[Ru(*p*-cymene)Cl$_2$]$_2$	10	50:50
12	**L18**	(*R,R*) DIPAMP	[Ru(*p*-cymene)Cl$_2$]$_2$	40	50:50

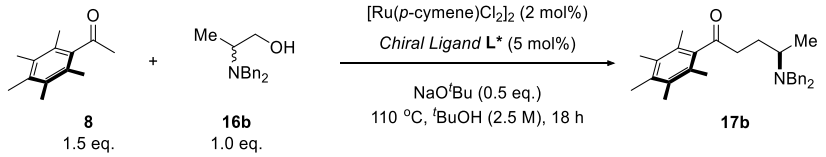
[a] Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. [Isolated yields are given in parentheses]. The absolute stereochemistry was determined to be (*R*) for **17b** (see below).



Given that (*R*)-BINAP showed some promising reactivity and selectivity, a range of biaryl diphosphine ligands were subsequently investigated (Table 3.6). Unfortunately, in varying the backbone of the ligands little enantioselectivity was observed, remaining around 60:40 e.r. and generally the yields of these reactions were poor (Entries 2-7). Replacing the phenyl group with Xyl or DTBM (**L1**, **L4** and **L24**) gave marginally higher yields but no enantioselectivity (Entries 8-10). Presumably, the bulkier the chiral ligand, then the easier it is for the amino alcohol to

outcompete in coordination to the metal. We wondered if using diamine ligands would be more successful in this reaction. Asymmetric hydrogenation catalysts **Ru-5** and **Ru-6** showed no improvement over biaryl diphosphine ligands. Significantly higher reactivity was observed using **Ru-7** and the desired ketone was isolated in 55% yield and 59:41 e.r. Encouragingly, Noyori hydrogenation catalyst (R_P,R_N)-**Ru-2** gave the desired product 39% yield and in 32:68 e.r. Interestingly, catalysts of the type $RuCl_2$(diphosphine)(diamine) are widely used in hydrogenations of ketones and have shown to selectively undergo 1,2-reduction of enones.[89,90] In this case, the selectivity is reversed to solely give 1,4-reduction; this is due to the Ph* group protecting the carbonyl from reduction. These catalysts have been effective in a range of hydrogen borrowing reactions forming both C-C bond and C-N bonds, however, in all cases the enantiodetermining step was hydrogenation of a carbonyl group.[50,52–55]

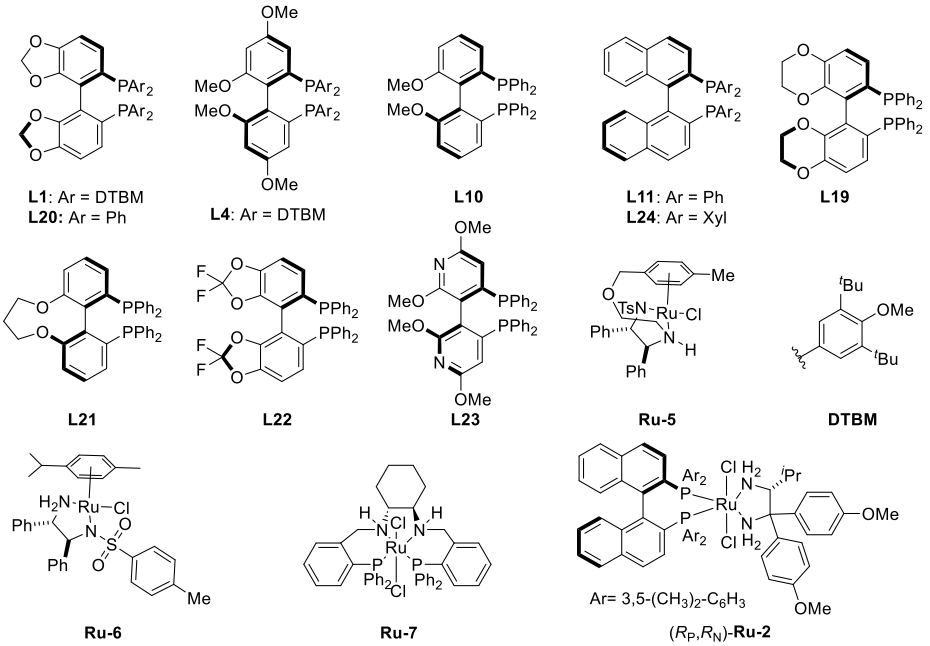
Table 3.6. Ligand screen for the enantioselective hydrogen borrowing alkylation with 1,2-amino alcohols.



8 1.5 eq. | **16b** 1.0 eq. | **17b**

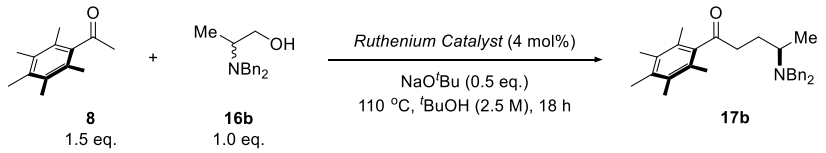
Entry	L*/M	Ligand/Catalyst	Yield[a] / %	e.r.[b]
1	**L11**	(*R*)-BINAP	10	57:43
2	**L19**	(*R*)-SYNPHOS	13	60:40
3	**L10**	(*R*)-MeO-BIPHEP	12	61:39
4	**L20**	(*R*)-SEGPHOS	13	60:40
5	**L21**	(*R*)-C3-Tunephos	14	62:38
6	**L22**	(*R*)-DIFLUOROPHOS	11	50:50
7	**L23**	(*R*)-P-Phos	<5	58:42
8	**L24**	(*R*)-Xyl-BINAP	17	50:50
9	**L1**	(*R*)-DTBM-SEGPHOS	11	50:50
10	**L4**	(*R*)-DTBM-GARPHOS	23	50:50
11	**Ru-5**	RuCl(S,S)-Ts-DENEB®	10	50:50
12	**Ru-6**	RuCl[(*S*,*S*)-Tspen](*p*-cymene)	19	50:50
13	**Ru-7**	**Ru-7**	55	59:41
14	**Ru-2**	$RuCl_2$[(*R*)-(Xyl-BINAP)][(*R*)-DAIPEN]	[39]	32:68

[a] Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The absolute stereochemistry was determined to be (*R*) for **17b** (see below).



Based on this hit, a range of $RuCl_2$(diphosphine)(diamine) catalysts were screened (Table 3.7). A systematic screening of backbone and diamine variation was challenging due to the limited commercial availability of these catalysts. Replacing the DAIPEN diamine ligand with DPEN (**Ru-2** vs. **Ru-8**) showed minimal selectivity (Entry 2). Probing the diphosphine backbone using the DPEN diamine ligand showed slight improvement in enantioselectivity ([(*R*)−Xyl−PhanePhos] or [(*R*)-P-Phos]) compared to Xyl-BINAP (Entries 3-4). Benzimidazole-based ligands were investigated on a range of diphosphine backbones (Entries 5-7). Increasing the steric bulk on the benzimidazole ligand did provide a slight increase in reactivity and selectivity (Me vs. ^{i}Pr; Entries 5 vs. 6), however overall this class of diamine ligands showed little promise. *N*-Methyl-*N*'-phenyl-ethylenediamine was screened with (*R*)-BINAP and (*R*)-Tol-BINAP backbones but showed little selectivity (Entries 8-9). Next, catalyst **Ru-3**, $RuCl_2$[(*S*)−Xyl−BINAP][(*S*)-RUCY] was screened. This catalyst, developed by Ohkuma and co-workers, has shown very high catalytic activity and in many cases was superior to the analogous $RuCl_2$[(*R*)-(Xyl-BINAP)][(*R*)-DAIPEN] in asymmetric hydrogenation.[91] We hoped the additional coordinate point of the diamine ligand would further disfavour any potential replacement by the amino alcohol substrate. Disappointingly, the desired ketone was obtained in 17% yield and 60:40 e.r. Both DIAPEN and DPEN diamines showed moderate reactivity when combined with (*R*)-SEGPHOS, however very low enantioselectivity was observed. We observed that replacing the DIAPEN ligand with DPEN favoured formation of opposite enantiomers of the product (Entries 11 vs. 12), revealing the strong influence that the diamine ligand had on the overall enantioselectivity. We wondered if the diastereomeric (*R*,*S*)-catalysts would perhaps improve the selectivity.

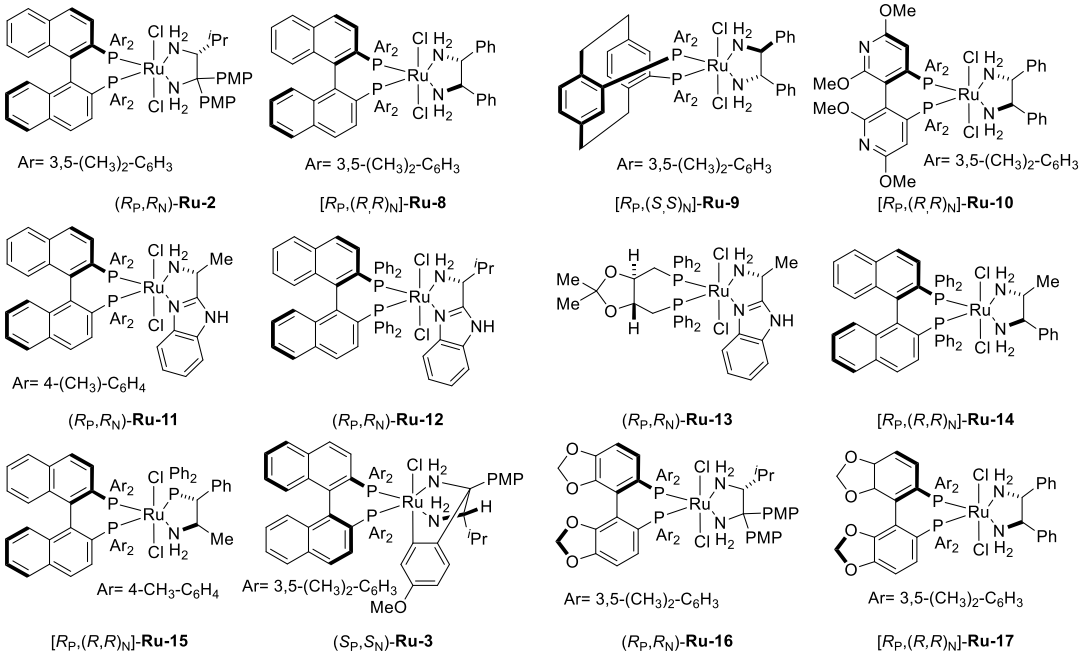
Table 3.7. Screening of Ru-diphosphine-diamine catalysts for the enantioselective hydrogen borrowing alkylation with 1,2-amino alcohols.



8 1.5 eq. **16b** 1.0 eq. **17b**

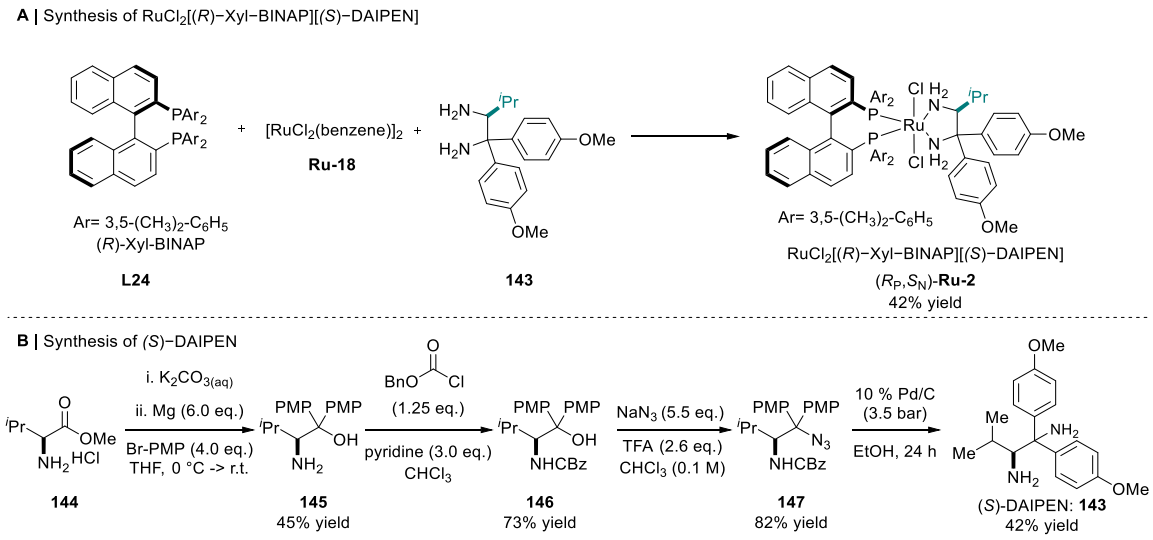
Entry	LX=L*	Catalyst	Yield[a] / %	e.r.[b]
1	**Ru-2**	$RuCl_2$[(*R*)-(Xyl-BINAP)][(*R*)-DAIPEN]	[39]	32:68
2	**Ru-8**	$RuCl_2$[(*R*)−Xyl−BINAP][(*R*,*R*)−DPEN]	24	51:49
3	**Ru-9**	$RuCl_2$[(*R*)−Xyl−PhanePhos][(*S*,*S*)−DPEN]	20	45:55
4	**Ru-10**	$RuCl_2$[(*R*)-P-Phos][(*R*,*R*)−DPEN]	35	57:43
5	**Ru-11**	$RuCl_2$[(*R*)-(Tol-BINAP)][(*R*)-**L25**]	<5	60:40
6	**Ru-12**	$RuCl_2$[(*R*)-(BINAP)][(*R*)-**L26**]	12	62:38
7	**Ru-13**	$RuCl_2$[(*R*)-**L27**][(*R*)-**L25**]	32	52:48
8	**Ru-14**	$RuCl_2$[(*R*)-BINAP][(*R*)-**L28**]	21	55:45
9	**Ru-15**	$RuCl_2$[(*R*)-(Tol-BINAP)][(*R*)-**L29**]	34	47:53
10	**Ru-3**	$RuCl_2$[(*S*)−Xyl−BINAP][(*S*)-RUCY]	17	60:40
11	**Ru-16**	$RuCl_2$[(*R*)−Xyl−SEGPHOS][(*R*)−DAIPEN]	33	52:48
12	**Ru-17**	$RuCl_2$[(*R*)−Xyl−SEGPHOS][(*R*,*R*)−DPEN]	44	47:53

[a] Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The absolute stereochemistry was determined to be (*R*) for **17b** (see below) and subsequent γ-amino ketones were assigned by analogy.



3.9. Investigation into $RuCl_2$(diphosphine)(diamine) Catalysts

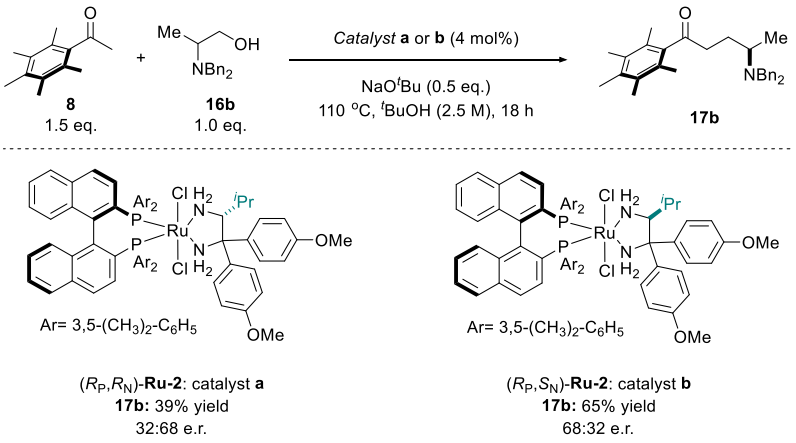
Generally, asymmetric hydrogenation utilizing $RuCl_2$(diphosphine)(diamine)-type catalysts combine an (*R*)-diphosphine with an (*R*)-1,2-diamine (or both *S*-enantiomers), although this is likely due to the non-mixed diastereomers being commercially available compared to their mixed analogues (i.e. *R,S or R,[S,S]*).* The utility of the non-mixed catalysts in asymmetric hydrogenations is vast,[90] however, early reports by Noyori showed the profound synergistic effects the diphosphine and diamine can have on the overall enantioselectivity.[92–94] There have been a few reports where mixed catalysts outperform non-mixed catalysts, so we were interested to see how these catalysts would perform in this reaction. Following a modified literature procedure, catalyst $RuCl_2$[(*R*)-(Xyl-BINAP)][(*S*)-DAIPEN] ((*R*$_P$,*R*$_N$)-**Ru-2**) was synthesised by complexation of (*R*)-Xyl-BINAP, $[RuCl_2(benzene)]_2$ and (*S*)-DAIPEN, which afforded (*R*$_P$,*S*$_N$)-**Ru-2** in 42% yield.[89] The (*S*)-DAIPEN ligand was synthesised following a literature procedure in 4 steps from L-valine (Scheme 3.17).[95]



Scheme 3.17. Synthesis of $RuCl_2$[(*R*)-(Xyl-BINAP)][(*S*)-DAIPEN] and (*S*)-DAIPEN.

*For catalysts such as $RuCl_2$[(*R*)-(Xyl-BINAP)][(*R*)-DAIPEN] or $RuCl_2$[(*R*)-(BINAP)][(*S,S*)-DPEN], mixed refers to opposite enanatiomeric sense of the diphosphine and diamine e.g. *R,S or R,[S,S]* whereas non-mixed refers to *R,R or R,[R,R]* or the *S*-enantiomers.

Pleasingly, subjecting this diastereomeric catalyst to the reaction afforded the desired product in 65% yield and 68:32 e.r. (Scheme 3.18). Although the enantioselectivity did not improve, the increase in reactivity was promising and we hoped that the enantioselectivity could be enhanced by varying the components of the mixed catalysts.

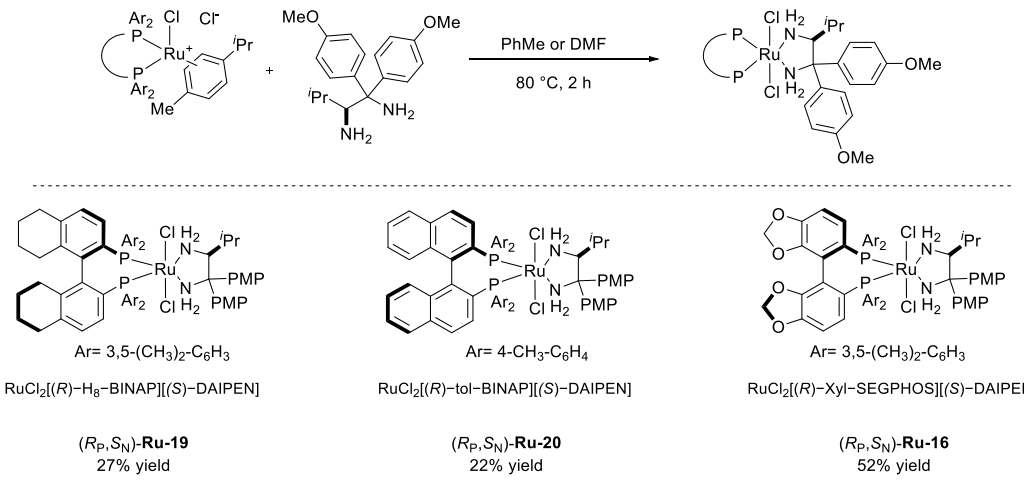


(R_P,R_N)-**Ru-2**: catalyst **a**
17b: 39% yield
32:68 e.r.

(R_P,S_N)-**Ru-2**: catalyst **b**
17b: 65% yield
68:32 e.r.

Scheme 3.18. Hydrogen borrowing alkylation of 1,2-amino alcohols with diastereomeric $RuCl_2$(diphosphine)(diamine) catalysts.

Various catalysts (**Ru-16**, **Ru-19** and **Ru-20**) replacing (*R*)-Xyl-BINAP with different diphosphine ligands were then synthesised by complexing the diamine ligand with a pre-complexed ruthenium-phosphine. The catalysts were isolated in moderate yields (Scheme 3.19) and subjected to the hydrogen borrowing alkylation (Table 3.8).



RuCl$_2$[(*R*)−H$_8$−BINAP][(*S*)−DAIPEN]

(R_P,S_N)-**Ru-19**
27% yield

RuCl$_2$[(*R*)−tol−BINAP][(*S*)−DAIPEN]

(R_P,S_N)-**Ru-20**
22% yield

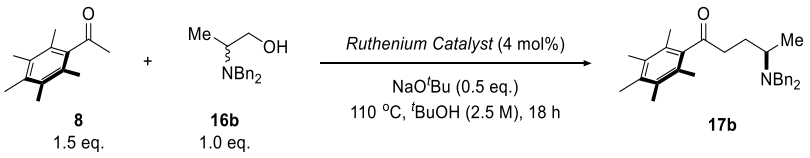
RuCl$_2$[(*R*)−Xyl−SEGPHOS][(*S*)−DAIPEN]

(R_P,S_N)-**Ru-16**
52% yield

Scheme 3.19. Synthesis of mixed Ru-diphosphine-diamine catalysts.

Ruthenium catalyst **Ru-19** was not beneficial to the hydrogen borrowing alkylation and showed moderate reactivity with low enantioselectivity (Entry 2; Table 3.8). Replacing Xyl-BINAP with Tol-BINAP had little effect and gave the desired ketone in similar yield and e.r. compared to $RuCl_2$[(*R*)-(Xyl-BINAP)][(*S*)-DAIPEN] (Entry 3). A slight decrease in both yield and enantioselectivty was observed on replacing Xyl-BINAP with Xyl-Segphos (Entry 4). Despite not outperforming **Ru-2**, this (R_P,S_N)-catalyst showed higher reactivity and enantioselectivity in comparison to the non-mixed catalyst (41% yield and 61:39 e.r. vs 33% yield and 52:48 e.r.; Table 3.7, Entry 11). Due to time constraints other catalysts were not synthesised, however, these results suggest that more efficient catalytic activity is observed for the mixed (R_P,S_N) catalysts and synthesis of more combinations of ruthenium catalysts provide a promising avenue for future work.

Table 3.8. Screening of mixed Ru-diphosphine-diamine catalysts.



8 1.5 eq. + **16b** 1.0 eq. → **17b**

Entry	Ru-cat	Ligand	Yield[a] / %	e.r.[b]
1	(R_P,S_N)-**Ru-2**	$RuCl_2$[(*R*)-(Xyl-BINAP)][(S)-DAIPEN]	65	68:32
2	(R_P,S_N)-**Ru-19**	$RuCl_2$[(*R*)−H_8−BINAP][(*S*)−DAIPEN]	31	58:41
3	(R_P,S_N)-**Ru-20**	$RuCl_2$[(*R*)−tol−BINAP][(*S*)−DAIPEN]	63	69:31
4	(R_P,S_N)-**Ru-16**	$RuCl_2$[(*R*)−Xyl−SEGPHOS][(*S*)−DAIPEN]	41	61:39

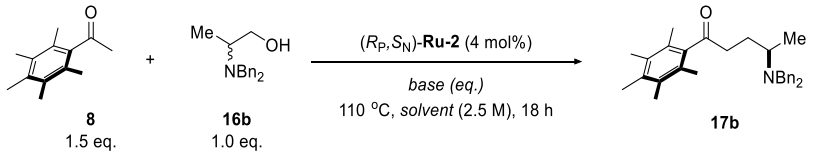
[a] Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The absolute stereochemistry was determined to be (*R*) for **17b** (see below). For catalysts structure see Scheme 3.19.

3.10. Ligand Screening II and Optimisation

Having identified a catalyst with moderate catalytic activity, other reaction parameters were investigated (Table 3.9). Reducing the equivalents of base (0.2 eq.) was detrimental to the yield but did show a slight increase in enantioselectivity (Entry 2). Increasing the base equivalents was beneficial, presumably as the rate of racemisation of the enone intermediates was increased,

providing ketone **17b** in 74% yield and 72:28 e.r. (Entry 3). A further increase in base was not advantageous (Entry 4). The solvent was switched to non protic toluene, which increased the enantioselectivity to give ketone **17b** in 80:20 e.r.; unfortunately, this was alongside a reduction in yield up to 49% (Entry 5). Other bases were investigated (KO^{t}Bu, NaOH and KOH) but unfortunately none outperformed NaO^{t}Bu in toluene. Pleasingly, when KOH was used in tBuOH, ketone **17b** was afforded in 62% yield and 81:19 e.r.

Table 3.9. Base and solvent optimisation.



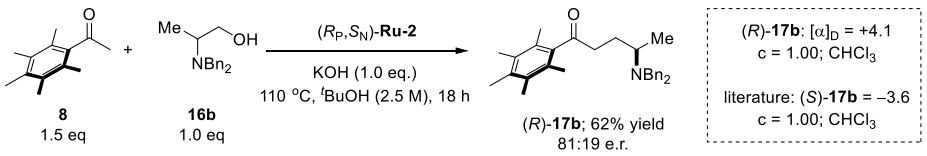
8 1.5 eq. + **16b** 1.0 eq. → **17b**

Entry	Base	Base eq.	Solvent	Yield[a] / %	e.r.[b]
1	NaO^{t}Bu	0.5	^{t}BuOH	69 [65]	68:32
2	NaO^{t}Bu	0.2	^{t}BuOH	25	72:28
3	NaO^{t}Bu	1.0	^{t}BuOH	74	72:28
4	NaO^{t}Bu	2.0	^{t}BuOH	74	69:31
5	NaO^{t}Bu	1.0	PhMe	49	80:20
6	KO^{t}Bu	1.0	PhMe	44	81:19
7	NaOH	1.0	PhMe	38	76:24
8	KOH	1.0	PhMe	41	80:20
9	KOH	1.0	^{t}BuOH	62	81:19

[a]Yields determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The absolute stereochemistry was determined to be (*R*) for **17b** (see below).

There were still many parameters to investigate thoroughly, namely different solvents, temperatures and a greater range of bases, all of which could provide the basis for future work.

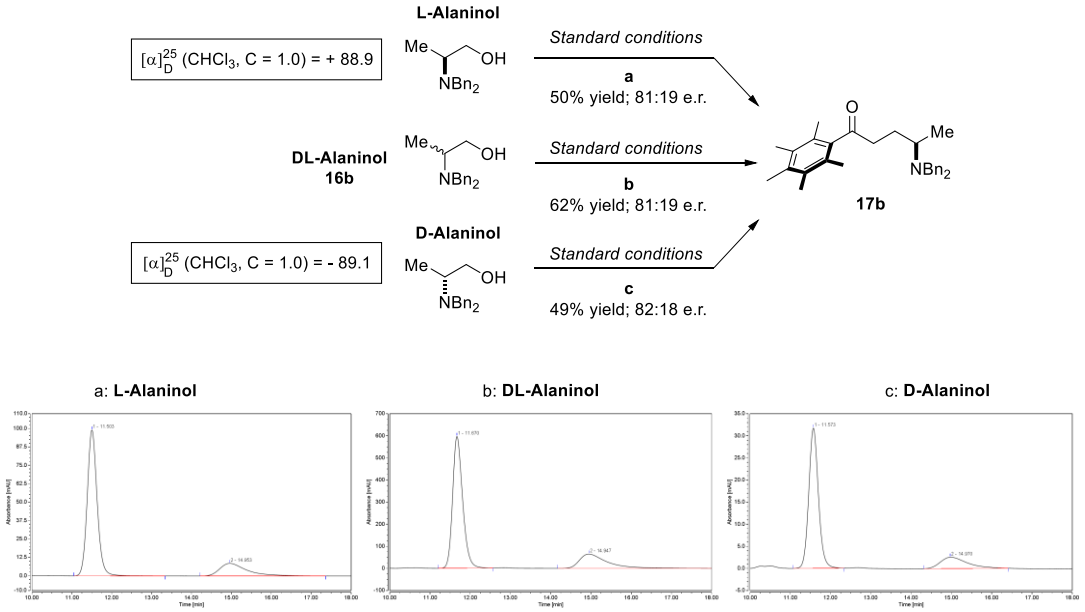
The absolute stereochemistry of the γ-amino ketone **17b** was determined by correlation of the specific rotation value of **17b** with that previously reported in the literature (Scheme 3.20).[87] This allowed determination of the absolute configuration of **17b** as (*R*).



Scheme 3.20. Determination of absolute stereochemistry.

3.11. Mechanistic Insight

To determine whether or not this was a dynamic kinetic resolution, rather than a kinetic resolution, the optimised conditions were employed in the alkylation of Ph* methyl ketone with either enantiomer of alaninol **16b** (Scheme 3.21). Pleasingly, both enantiopure amino alcohols as well as the racemic amino alcohol afforded the same major enantiomer of the desired ketone in analogous enantioselectivity and yield, confirming that the hydrogen borrowing alkylation proceeds *via* a DKR.



Scheme 3.21. Hydrogen borrowing alkylation with enantiopure and racemic 1,2-amino alcohols. Conditions: amino alcohol (1.0 eq.), ketone **8** (1.5 eq.), KOH (1.0 eq.), ^{t}BuOH (2.5 M), 110 °C.

3.12. Conclusion

In this chapter, asymmetric hydrogen borrowing alkylation affording γ-substituted acyclic ketones *via* DKR was explored. Alkylation with β,β-disubstituted primary alcohols was briefly

investigated and some evidence of racemisation was observed, although no promising hits were identified. An approach to restrict the conformation of the enone intermediate was unsuccessful, however other ways still remain to be investigated such as hydrogen borrowing alkylation *via* DKR in cyclic systems.

Next hydrogen borrowing alkylation with 1,2-amino alcohols was investigated due to the clear evidence of racemisation *via* an extended enolate. The effect of the *N*-protecting group was investigated and substantial ligand screenings were undertaken. Mixed enantiomer catalyst $RuCl_2$[(*R*)-Xyl-BINAP][(*S*)-DAIPEN] was identified to facilitate the alkylation with moderate enantioselectivity. Preliminary optimisation gave promising results, with it being found that by using KOH (1.0 eq.), the desired amino ketone could be obtained in 62% yield and 81:19 e.r. In addition, we were able to show that this reaction was proceeding *via* a DKR, however further investigation into optimisation of this system and synthesis of novel mixed enantiomer catalysts is required.

Chapter 4: Dynamic Kinetic Resolution via *Hydrogen Borrowing Catalysis: Carbocycles*

4.1. Introduction

Investigating DKR in acyclic systems was challenging for two main reasons: (i) a potential lack of conformational restriction of the enone intermediate; (ii) mechanistic experiments focussing on the transfer hydrogenation were unsuccessful due to the facile retro aldol in acyclic systems. Increasing conformational restriction of the enone intermediate was briefly explored in Chapter 3.4. We hoped addition of an α-methyl group would reduce free rotation of the γ-substituents to minimise 1,3-allylic strain.

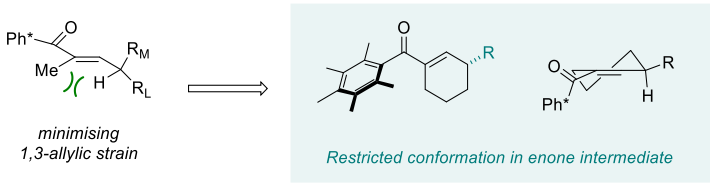
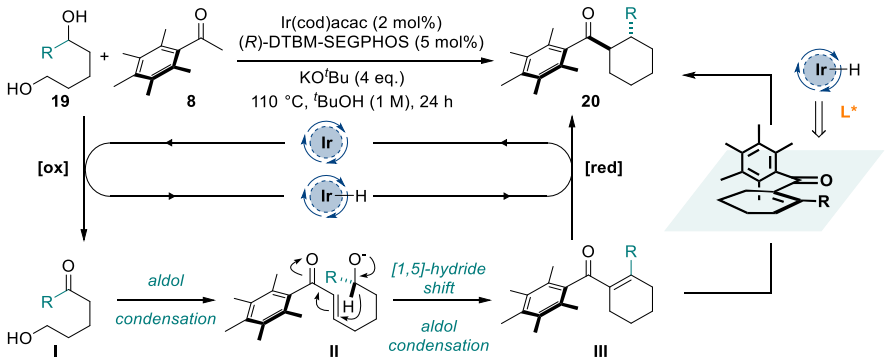


Figure 4.1. Proposed strategy for cyclic hydrogen borrowing DKR.

While this was not successful, an alternative strategy to restrict the enone conformation and configuration would be to explore the DKR in cyclic systems (Figure 4.1). As previously discussed, the synthesis of racemic substituted cyclohexanes as well as the enantioselective synthesis of β-branched cyclohexanes were both reported by Donohoe and co-workers in 2018 and 2019, respectively.[33,34] Alkylation of 1,5-diols with Ph* methyl ketone afforded a range of substituted cyclohexanes. Initially this reaction was thought to proceed *via* two consecutive hydrogen borrowing sequences, however, mechanistic investigations later revealed that this reaction proceeded through a key [1,5]-hydride shift (Scheme 4.1).[35] The reaction is initiated by an iridium-mediated oxidation of the diol **19** starting material to the corresponding hydroxyaldehyde (**I**), which then undergoes aldol condensation with Ph* methyl ketone to form

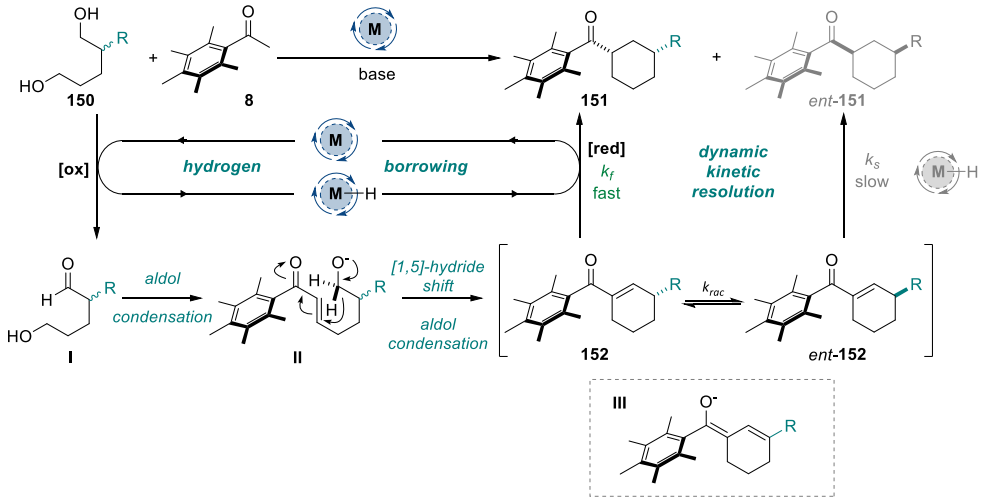
the key alkoxyenone (**II**). This intermediate then undergoes an intramolecular [1,5]-hydride shift, followed by a second aldol condensation. The cyclohexene is then reduced by iridium hydride to afford the corresponding saturated product. In the case of the enantioselective variant, this final reduction is an asymmetric hydrogenation.



Scheme 4.1. Enantioselective Hydrogen Borrowing Annulation.

4.2. Project Aims

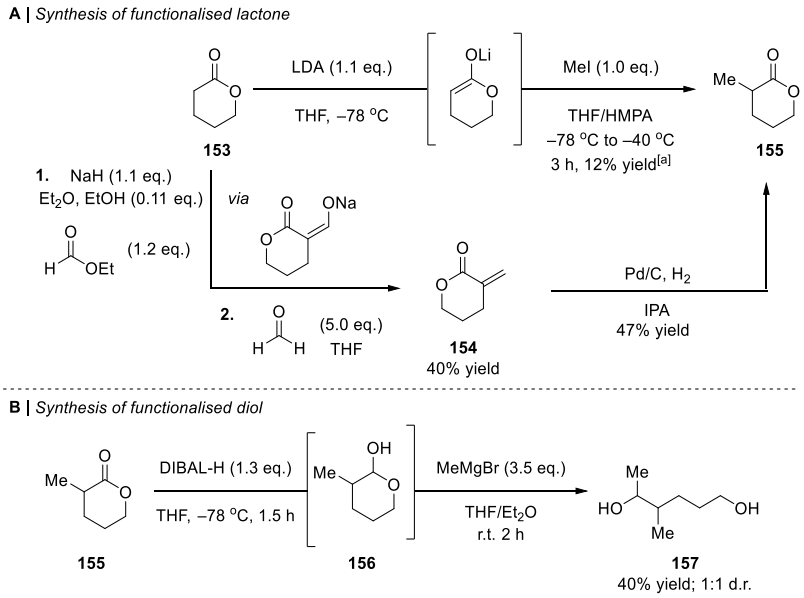
The aim at the outset of this project was to provide a general strategy for stereochemical control at the γ-stereogenic centre in cyclic systems by incorporating a dynamic kinetic resolution with C–C hydrogen borrowing catalysis. Alkylation of Ph* methyl ketone with 1,5-diols would lead to enone intermediate **152** following the mechanism described above (Scheme 4.1). The enone intermediates would be able to interconvert by reversible deprotonation/re-protonation *via* an extended enolate. The chiral metal-hydride could then selectively reduce one enone intermediate to afford the saturated, enantioenriched ketone. This process relies on rapid interconversion of the two enantiomeric enone intermediates (**152**), coupled with selective reduction of one enantiomer by a chiral catalyst complex. The key challenge would be the balancing the rates of all these processes with a single metal catalyst to ensure a successful DKR.



Scheme 4.2. Proposed hydrogen borrowing catalysed annulation controlling the γ-stereogenic centre *via* DKR.

4.3. Preliminary Studies: Cyclic System and Mechanistic Considerations

We began our investigation by alkylating Ph* methyl ketone with 4-methylhexane-1,5-diol (**157**), thus introducing a substituent at the γ-stereogenic center (*cf*. **20**, Scheme 4.1) and allowing us to evaluate the DKR within conformationally restricted cyclic systems.

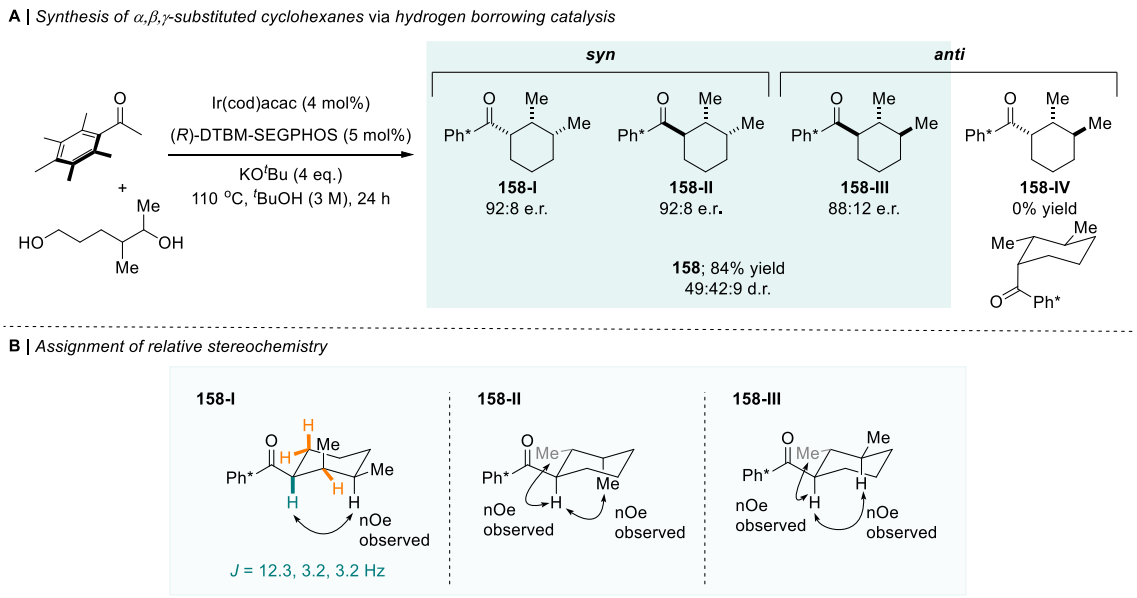


Scheme 4.3. Synthesis of substituted diol **157**. [a] Synthesised by Dr Roly Armstrong.

The most direct route to substituted diol **157** began with the α-alkylation of δ-valerolactone (**153**) with methyl iodide affording substituted lactone **155** in 12% yield (Scheme 4.3.A). This low

yield can be attributed to two main factors: (i) the enolate is highly insoluble and the reaction requires mechanical stirring; (ii) separation of the mono and di-substituted methyl lactones is non-trivial. To increase the yield of **155**, a different approach was taken. Deprotonation of δ-valerolactone (**153**) with sodium hydride, followed by Claisen condensation with ethyl formate, and addition of formaldehyde gave the desired α-methylene lactone **154** in 40% yield. Subsequent hydrogenation afforded lactone **155** in 47% yield. Overall, lactone **155** was afforded in 19% yield over two steps, and while no substantial increase in yield was observed compared to the first approach, the practical aspects and purification of these compounds was simpler. Subsequently, the functionalised lactone was reduced by DIBAL-H to lactol **156**, followed by the addition of MeMgBr to afford diol **157** in 40% yield over two steps (Scheme 4.3.B).

With diol **157** in hand, the standard conditions for enantioselective hydrogen borrowing annulation were employed and the desired α,β,γ-functionalised ketone was isolated in 84% yield as a mixture of three out of four possible diastereomers (49:42:9 d.r., Scheme 4.4.A). The major *syn*-product (**158-I/II**, *syn* w.r.t. C-β and C-γ) was obtained as two diastereomers since the stereochemical configuration at the α-stereogenic centre is under thermodynamic control due to reversible deprotonation *in situ.* In contrast, the minor *anti*-product (**158-III**) is exclusively formed as the all-equatorial diastereomer. The two *syn*-diastereomers were isolated in 92:8 e.r., while the minor, *anti*-diastereomer, was isolated in 88:12 e.r. A combination of *J*-coupling constants and 2D NOESY data was used to identify the relative stereochemistry of the diastereomers (Scheme 4.4.B). Furthermore trisubstituted cyclohexane **158** was previously synthesised racemically by the Donohoe group allowing further confirmation of the relative stereochemistry by comparison to literature data.[33]

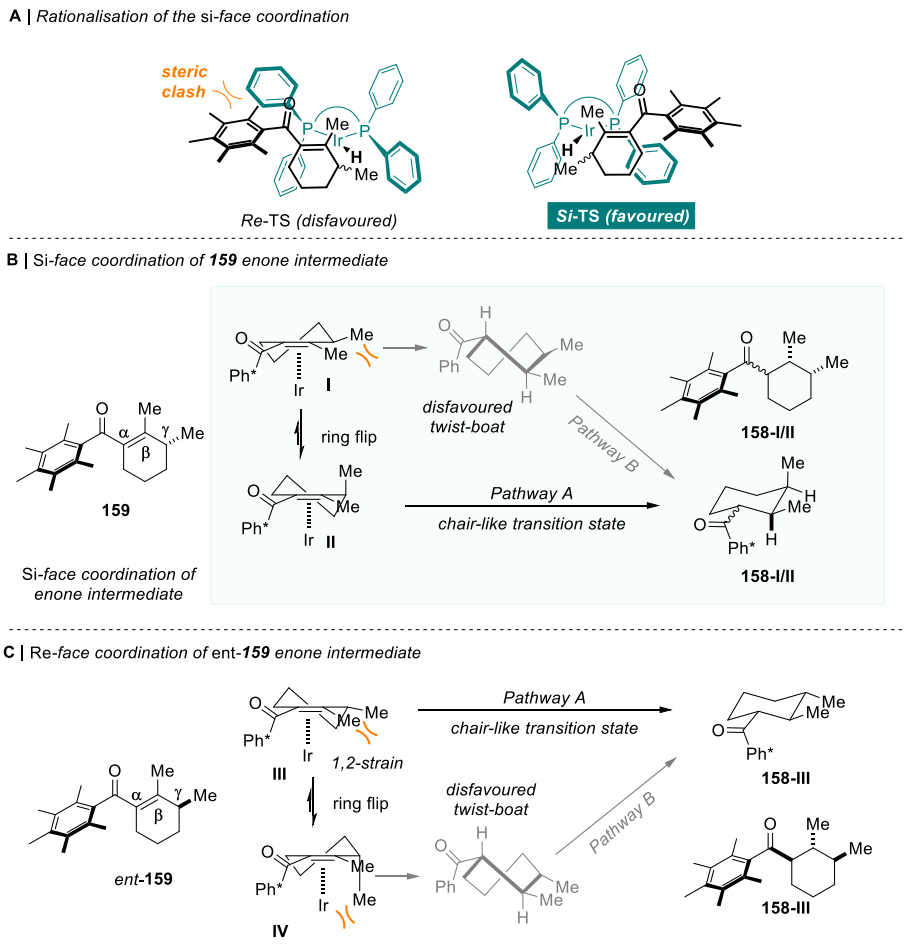


Scheme 4.4. Alkylation of Ph* methyl ketone with dimethyl substituted diol **158**. d.r. determined from crude ^{1}H NMR spectrum. **158-I** was isolated separately, **158-II** and **158-III** were isolated as an inseparable mixture. The absolute stereochemistry was not determined for **158-I-III**.

In order to rationalise the observed stereoselectivity we first considered the coordination of the enone intermediate to the iridium-ligand catalyst, as the facial selectivity is stereodetermining in the final reduction of the enone intermediate. We assumed it to be analogous to the previous hydrogen borrowing annulation for the synthesis of β-branched cyclohexanes as an identical catalyst-ligand complex is used under the same conditions (*cf*. Scheme 4.1). Computational studies on the β-branched cyclic system had shown that *Si*-face coordination was favoured due to the clash of the Ph* group with the P-Ar groups of the ligand. We extrapolated this to assume that addition of Ir-H to the α,β,γ-substituted enones also favours *Si*-face coordination (Scheme 4.5.A).

We speculated that the half chair conformation of the enone with a pseudoaxial C-γ methyl group is favoured to avoid the steric clash with the equatorial methyl group.[96] This is the case for both enone enantiomers; for **159** *Si*-face iridium hydride addition would proceed through the more favourable chair-like transition state and lead to **158-I** and **158-II** (Pathway A; Scheme 4.5.B). As discussed above, the ratio of **158-I** and **158-II** is purely a reflection of thermodynamics.

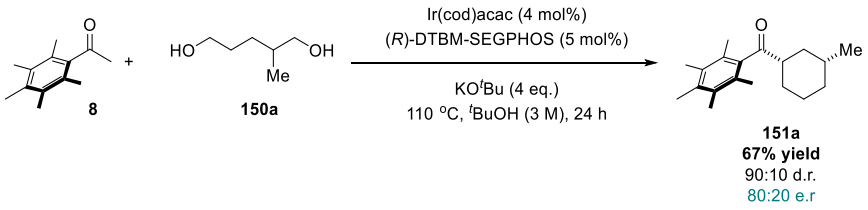
In contrast, to deliver *Si*-face iridium hyrdide to *ent*-**159** would lead to an unfavourable interaction between the pseudoaxial methyl group and Ir-H and this is reflected in *syn*:*anti* ratio (91:9). Although, as we have not determined the absolute configuration, this rationalisation must be interpreted cautiously, it is clear that this system demonstrates significant stereoselective control of the key γ-centre.



Scheme 4.5. Rationalisation of stereochemical outcome of **158**. *Si*- and *Re*-face assignment is relative to the carbonyl.

Given that the Donohoe group have previously shown that β-branched cyclohexanes can be accessed in excellent enantioselectivity, we wondered if the β-substituent was necessary for stereoselective control. Furthermore, removal of the β-substituent would simplify analysis as only two diastereomers could (possibly) be formed. Alkylation of Ph* methyl ketone with

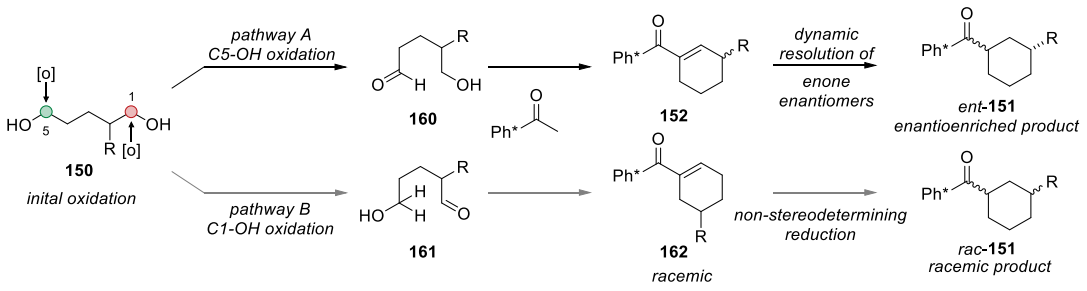
2-methylpentane-1,5-diol (**150a**)*, which lacks a β-substituent in the resulting product, gave the desired γ-substituted ketone in 67% yield and 80:20 e.r. (Scheme 4.6). Donohoe and co-workers have previously shown that the high *syn*-diastereoselectivity in this reaction is a result of reversible deprotonation of the product.[33]



Scheme 4.6. Hydrogen borrowing annulation to afford γ-substituted cyclohexane using hydrogen borrowing catalysis DKR. The absolute stereochemistry was determined to be (1*S*,3*R*) for **151a** (see below) and subsequent γ-substituted cyclohexanes were assigned by analogy.

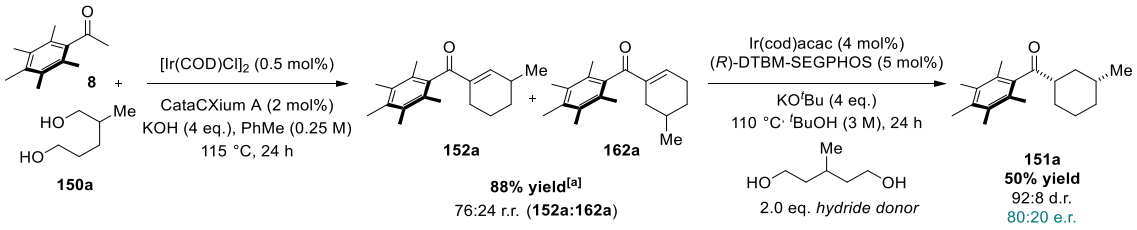
We postulated two explanations for this reduced enantioselectivity: (i) a β-substituent is necessary for facial selectivity during reduction; (ii) that there is a lack of regiocontrol in the aldol alkylation. Initial oxidation and aldol condensation of the less hindered C5-OH is expected to be the preferred pathway, leading to enone **152** (Pathway A, Scheme 4.7). However, competing oxidation of C1-OH could generate a small quantity of regioisomeric enone **162** (Pathway B), which is not able to racemise at the γ-stereogenic centre and is, therefore, unproductive in the DKR (Scheme 4.7). This intermediate will still afford the reduced product (albeit as a racemate) thereby not affecting the yield of the reaction but lowering the overall the e.r. of the product obtained.

*Synthesised by Dr Roly Armstrong by reduction of 2-methylpentanedioic acid.[33]



Scheme 4.7. Competing pathways *via* regioisomeric enone intermediates.

To investigate this hypothesis, the proposed enone intermediate **152a** was synthesised from 2-methylpentane-1,5-diol (**150a**), using an interrupted hydrogen borrowing method previously reported by Donohoe and co-workers (Scheme 4.8).[35] Enone **152a*** was isolated as regioisomeric mixture (with **162a**) as a result of an unselective aldol reaction at either end of the diol and then subjected to transfer hydrogenation using analogous conditions to the hydrogen borrowing reaction with an additional diol as a hydride source (Scheme 4.8).[34] This reduction afforded the desired product in 50% yield and 80:20 e.r. which is comparable to the direct alkylation of Ph* methyl ketone with diol **150a** (*cf*. Scheme 4.6).



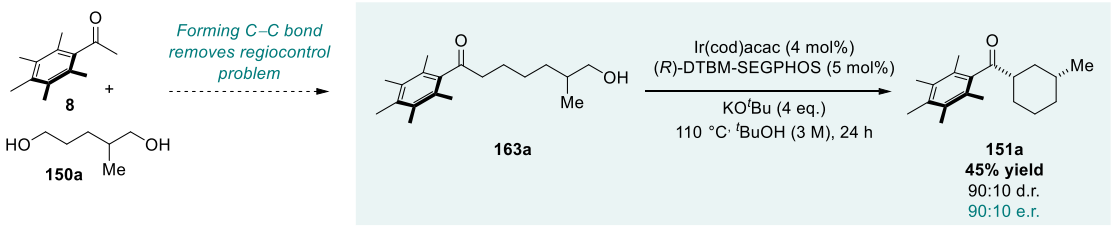
Scheme 4.8 Synthesis of enone intermediates and subsequent asymmetric transfer hydrogenation *via* DKR.
[a] Synthesised by Dr Lewis Smith.

This suggests that in the DKR (Scheme 4.6) the overall e.r. is lowered by the formation of the unproductive *regioisomer*. Given that we have subjected 24% of the minor enone regioisomer (**162a**) to the transfer hydrogenation, which is unproductive in the DKR, these results suggest that the expected e.r. resulting from reduction of the major enone intermediate would in fact

*Synthesised by Dr Lewis Smith.

be higher than 80:20 e.r. However, as the desired ketone is only isolated in 50% yield, it was necessary to seek further evidence for this hypothesis.

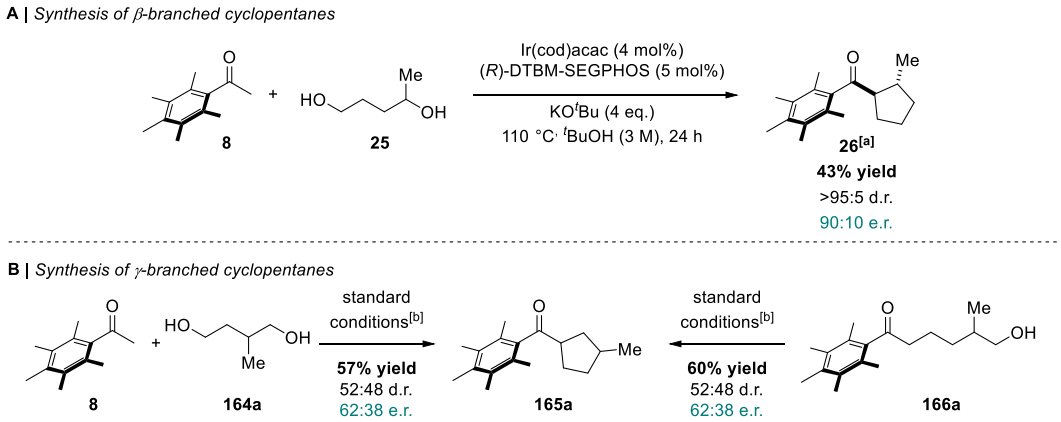
To this end, regiodefined linear substrate **163a** was synthesised* separately and subjected to the standard conditions (Scheme 4.9). With the first C–C bond already formed, this linear alcohol substrate removes the possibility of forming the unproductive enone intermediate upon exposure to our standard conditions. The desired product **151a** was isolated in 45% yield and 90:10 e.r. Pleasingly this result strongly supports the hypothesis that a lower e.r. is observed due to the presence of the unproductive enone intermediate **162a**. The low yield was attributed to the lack of hydride in the system (by definition only one equivalent of alcohol is present) and it was presumed addition of a hydride donor would increase the yield.



Scheme 4.9. Intramolecular hydrogen borrowing annulation *via* DKR.

We wondered if we would see a similar trend in the synthesis of γ-substituted cyclopentanes. Previously, Donohoe and co-workers had shown that β-substituted cyclopentanes were accessed with analogous enantioselectivity, however, the 5-membered ring formation suffered from poor reactivity (43% yield, 90:10 e.r., Scheme 4.10.A).[34]

*The synthesis of this substrate is discussed in Chapter 4.10.

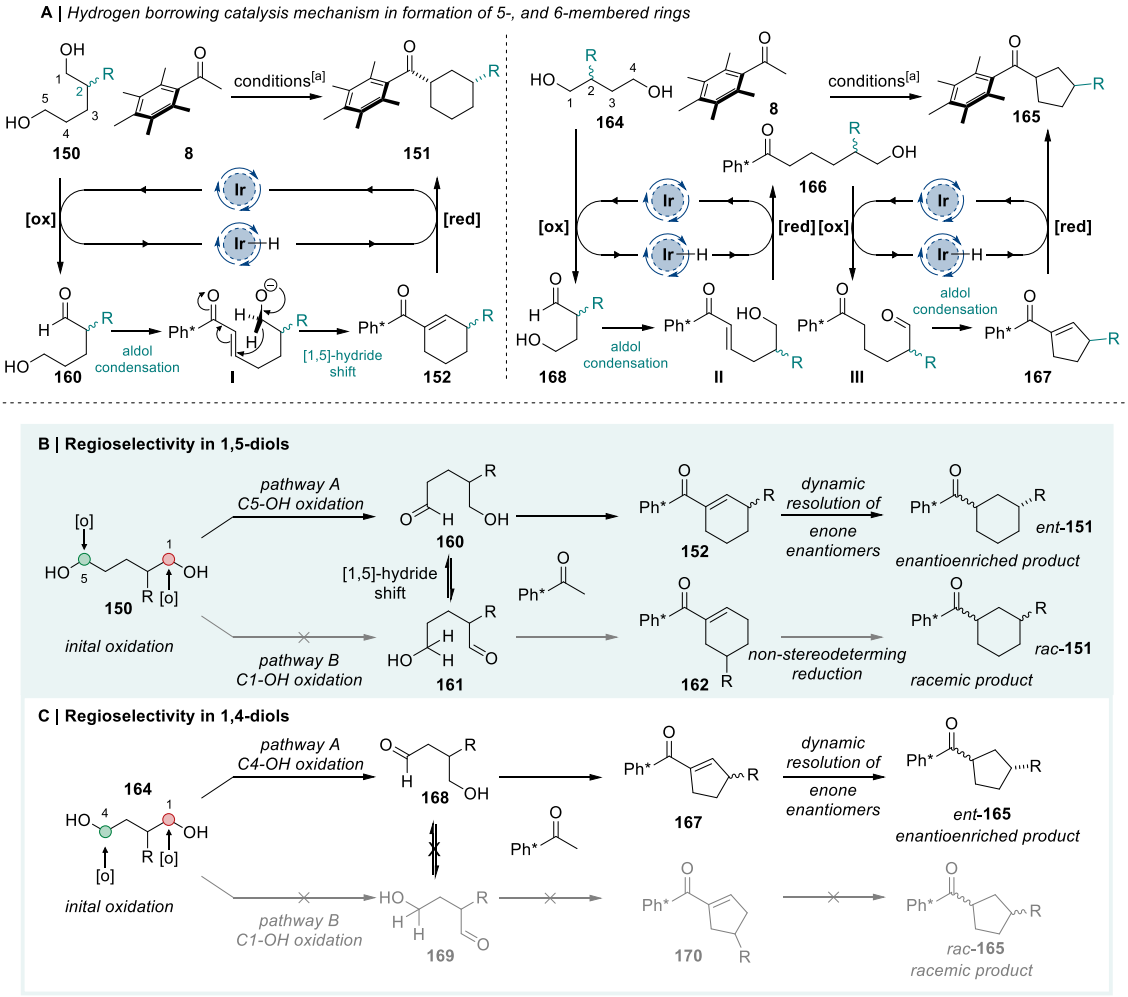


Scheme 4.10. Synthesis of β- and γ-substituted cyclopentanes *via* inter- and intramolecular hydrogen borrowing annulation. [a] Reported by Donohoe and co-workers.[34] [b] As stated in Scheme 4.10.A.

Employing 2-methylbutane-1,4-diol* (**25**) in the standard enantioselective hydrogen borrowing annulation, gave the desired γ-substituted cyclopentane (**165a**) in 57% yield but disappointingly only 62:38 e.r. (Scheme 4.10.B). Surprisingly, subjecting the regiodefined linear substrate (**166a**) gave the desired cyclopentane in analogous yield and identical enantioselectivity. Following our previous hypothesis, we had expected to observe a lower e.r. for the intermolecular reaction due to the lack of regioselectivity in the initial C–C bond formation. Based on this observation and previous observations that cyclopentanes are formed in much poorer yield (both as racemates[36] and asymmetrically[34]), we propose the following explanation. The mechanism for formation of the cyclohexanes has been shown to proceed *via* a [1,5]-hydride shift of the key alkoxyenone, instead of the initially proposed double hydrogen borrowing alkylation (Scheme 4.11). This is less likely to be the preferred pathway for the synthesis of the 5-membered rings due to the less favourable nature of [1,4]-hydride shifts.[97] In this case, the hydroxy enone **II** is reduced to the ketone **166** and subsequently oxidised to aldehyde **III**, which undergoes the second aldol condensation. Presumably this double hydrogen borrowing pathway is less efficient and is responsible for the poor reactivity observed in the formation of the 5-membered ring systems. However, even with this distinct mechanistic pathway, we would still expect to see

*Synthesised by Dr James Frost.

similar regioselectivity in the formation of the initial C-C bond. We postulated that initial oxidation is solely of less hindered C5-OH, forming hydroxyaldehyde **160**, which is able to form the desired allylic enone intermediate **152** (Scheme 4.11.B). However, competing [1,5]-hydride shift of hydroxyaldehyde **161** would allow formation of unproductive enone **162**, leading to racemic product.



Scheme 4.11. A: Hydrogen borrowing annulation mechanism for synthesis of 5- and 6-membered rings and regioselectivity in 1,4- and 1,5-diols. [a] Ir(cod)acac (4 mol%), (*R*)-DTBM-SEGPHOS (5 mol%), KO^{t}Bu (4 eq.), ^{t}BuOH (3 M), 110 °C, 24 h.

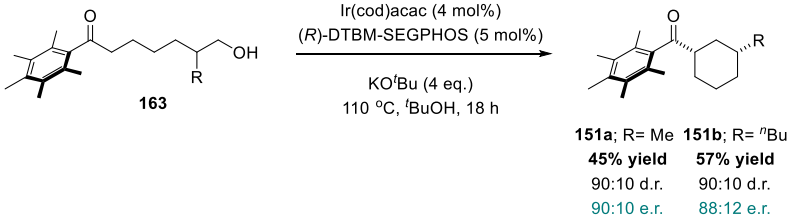
In the 1,4-diol system, no difference in selectivity between the regiodefined substrate and the diol is observed, which is tentatively thought to be due to the [1,4]-hydride shift not taking place for the 1,4-hydroxyaldehyde (**168**, Scheme 4.11.C). This suggests that the lower enantioselectivity observed in the synthesis of the 5-membered ring is not due to a lack of

regioselectivity, rather that the enantiodetermining step occurs with reduced selectivity. This may be due to less well-defined interactions of C-γ methyl group and the iridium catalyst in a 5-ring half chair.

Since we attributed the poor enantioselectivity in formation of cyclohexanes to the unproductive, and likely unavoidable, [1,5]-hydride shift in the hydroxyaldehyde, and we observed low selectivity in the enantiodetermining step in the synthesis of cyclopentanes, we chose to initially focus on the DKR step investigating the intramolecular hydrogen borrowing annulation synthesising γ-substituted cyclohexanes.

4.4. Preliminary Optimisation

We began our optimisation using the butyl-substituted linear alcohol **163b**[*]. Pleasingly, increasing the size of the R group from a methyl to a butyl gave an increased yield with only a slight decrease in enantioselectivity (Scheme 4.12). All corresponding racemic cyclohexanes were synthesised using the conditions from our previously reported method.[33]



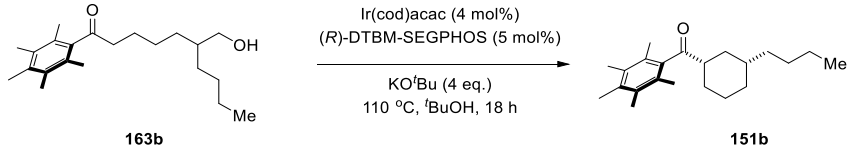
Scheme 4.12. Intramolecular hydrogen borrowing annulation *via* DKR. e.r. determined by normal phase HPLC using a chiral stationary phase. The absolute stereochemistry was determined for **151a** and **151b** and is discussed in chapter 4.13.

Our preliminary focus was on increasing the yield of reaction (Table 4.1). This was investigated in two ways: first, the effect of concentration on the reaction was evaluated. Intermolecular enolate hydrogen borrowing within the Donohoe group has been most efficient at high concentration (3-4 M) and often the reactivity is completely suppressed under more dilute

[*]The synthesis of this substrate is discussed in Chapter 4.10.

conditions (<2 M).[98] However, we wondered if reactivity in this intramolecular system could be enhanced at higher dilution. Dilution to 2 M, increased the yield by 10% but reduced the e.r. to 81:19 (Entry 2, Table 4.1). Further dilution to 1 M saw no increase to the yield, yet the e.r. was reduced further to 78:22 (Entry 3).

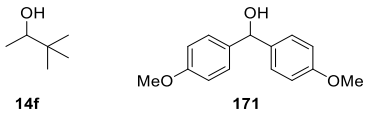
Table 4.1. Preliminary optimisation of the hydrogen borrowing annulation DKR.



163b **151b**

Entry	Hydride Donor	[^{t}BuOH] / M	Temp. / °C	Yield[a] / %	d.r.	e.r.[b]
1	none	3	110	57	90:10	88:12
2	none	2	110	67	90:10	81:19
3	none	1	110	64	92:8	78:22
4	IPA (1 eq.)	3	110	[86]	91:9	72:28
5	IPA (2 eq.)	3	110	Quant.	92:8	78:22
6	IPA (3 eq.)	3	110	Quant. [91]	92:8	80:20
7	IPA (6 eq.)	3	110	[75]	92:8	60:40
8	Cyclohexanol (3 eq.)	3	110	69	91:9	68:32
9	**14f** (3 eq.)	3	110	94	92:8	74:26
10	**171** (3 eq.)	3	110	65	93:7	68:32
11	none	3	95	69 [72]	91:9	71:29
12	none	3	85	-	-	-

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.



14f **171**

Secondly, the incorporation of additional hydride donors to increase the yield was investigated. Two equivalents of diol are used in the intermolecular hydrogen borrowing annulation system, leading to four possible equivalents of iridium hydride. In contrast only a single equivalent of iridium hydride can be formed in this intramolecular system. Addition of one equivalent of IPA increased the yield to 86% but reduced the e.r. to 72:28 (Entry 4). Increasing IPA to 3 eq. gave

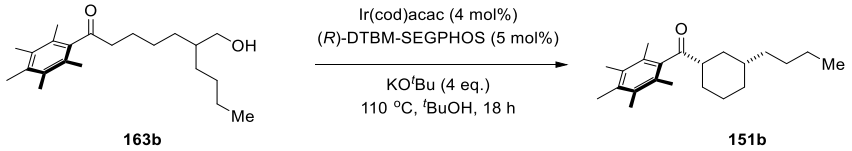
91% yield and 80:20 e.r. (Entry 6). Despite the slightly reduced enantioselectivity, we were pleased to see that the high yield (in combination with 80:20 e.r.) demonstrates that a dynamic kinetic resolution must be taking place rather than a simple kinetic resolution. A further increase of IPA (6 eq.) was detrimental to the enantioselectivity (Entry 7). All of the other hydride donors which were investigated were found to increase the yield, however the enantioselectivity was significantly reduced in all cases (Entries 8-10). The temperature dependence of enantioselective reactions is well documented. We aimed to increase the enantioselectivity by lowering the reaction temperature. Decreasing the temperature to 95 °C resulted in a slight increase in yield (72%) but surprisingly there was a significant reduction in e.r. (71:29 e.r.; *cf*. Entry 1 to 11). No reaction was observed upon further decreasing the temperature to 85 °C (Entry 12).

4.5. Reaction Reproducibility

Following these initial results, we started observing difficulty in reproducing the enantioselectivity of the reaction. In trying to reproduce the previous result (Table 4.1, Entry 6) using Ir(cod)acac (4 mol%), (*R*)-DTBM-SEGPHOS (5 mol%), KO^{t}Bu (4 eq.), IPA (3 eq.) in ^{t}BuOH (3 M) at 110 °C, the yield remained constant but a stark reduction in enantioselectivity from 80:20 to 62:38 was observed (Entries 1a-b, Table 4.2). To remove a variable, we attempted to reproduce the previous conditions without IPA as an additional hydride donor. Unfortunately, a similar trend was observed: similar yield with a reduction in e.r. (Entry 2a vs 2b). Multiple different sources of iridium and ^{t}BuOH were employed and ruled out as possible factors hindering the reaction, leaving KO^{t}Bu as the most likely source. It was been well documented that KO^{t}Bu is both moisture and air sensitive, so we suspected that our batch of KO^{t}Bu had, over time, been quenched to some degree.[99] Our group had previously noted the variability in the different grades of KO^{t}Bu available from Sigma Aldrich (95, 98 and 99.9%).[98] Up to this point, a single batch of 95% grade KO^{t}Bu had been used consistently. Two different batches of 95% grade

KO^{t}Bu (A and B, Entries 3 and 4) from other research groups were sourced. Both gave similar yields and enantioselectivity to our original batch of 95% grade KO^{t}Bu (*cf*. Entries 3-4 and 2b). Knowing that the 95% grade KO^{t}Bu from Sigma Aldrich was discontinued, we decided to use commercially available 99.9% grade KO^{t}Bu, which was also sold in smaller batches (5 g vs 100 g), and, therefore, easier to store under a strictly inert atmosphere. Using the 99.9% grade KO^{t}Bu gave a slight increase in enantioselectivity (90:10 e.r.) albeit with 19% yield (*cf*. Entries 2b to 5a).

Table 4.2. Reproducibility investigation.



163b **151b**

Entry	Base Grade	Conc. / M	Hydride Donor	Yield[a] / %	d.r.	e.r.[b]
1a	95% KO^{t}Bu	3	IPA 3 eq	Quant. [91]	92:8	80:20
1b	95% KO^{t}Bu	3	IPA 3 eq	92	92:8	62:38
2a	95% KO^{t}Bu	3	-	57	90:10	88:12
2b	95% KO^{t}Bu	3	-	62	90:10	75:25
3	A: 95% KO^{t}Bu	3	-	59	93:7	76:24
4	B: 95% KO^{t}Bu	3	-	54	93:7	76:24
5a	99.9% KO^{t}Bu	3	-	19	66:34	90:10
5b	99.9% KO^{t}Bu	3	-	19	66:34	90:10
5c				0	-	-
6a	99.9% KO^{t}Bu	1.5	-	38	86:14	90:10
6b				0	-	-
7a	99.9% KO^{t}Bu	0.6	-	42	91:9	90:10
7b				43 [44]	89:11	88:12
8	99.9% KO^{t}Bu	0.3	-	38	94:6	89:11
9	99.9% KO^{t}Bu	3	IPA 3 eq	50	86:14	88:12
10			IPA 6 eq	50	94:6	89:11

In grey = previous results that could not be reproduced. Sub-listing of entries a/b/c denotes the same conditions were used and different results were observed. [a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b]Determined by normal phase HPLC analysis using a chiral stationary phase.

At this point, it was decided that since these conditions had not been optimised, thorough investigation into KO^{t}Bu would be misplaced. Unfortunately, even with rigorous inert storage

and a new bottle of 99.9% grade KO^{t}Bu, it was not possible to reproduce the initial result (Entries 5a-c). We observed that some of the reactions were solidifying over the duration of the reaction. In these cases, full consumption of the starting material and formation of a complex mixture was observed. To prevent this, the dilution of the reactions was increased. Dilution to 1.5 M gave an increase in yield (38%) and maintained the enantioselectivity, however, on occasion, reactions would still solidify giving a complex mixture (Entries 6a vs 6b). Further increasing dilution to 0.6 M gave a further increase in yield (42-44%) with consistent enantioselectivity (Entries 7a-b). After repeating this reaction multiple times, it was found that the reaction did not solidify at 0.6 M (0.5 mL ^{t}BuOH at 0.3 mmol scale).* An additional increase in dilution to 0.3 M was not beneficial (Entry 8). Chisholm and co-workers have reported that KO^{t}Bu exists in two different structural forms, depending on the method of purification, each with different characteristics.[100] Addition of potassium metal to ^{t}BuOH with no further purification affords highly soluble KO^{t}Bu which adopts a ribbon-like chain structure in the solid state ([KO^{t}Bu·^{t}BuOH]$_\infty$), whereas the less soluble tetramer [KO^{t}Bu]$_4$ can be accessed upon sublimation. We reasoned that low solubility of the sublimed 99.9% grade KO^{t}Bu resulted in the reaction solidifying at high concentrations. Finally, we wondered if adding IPA as a hydride donor would increase the yield and simultaneously prevent the reaction from solidifying. Addition of three equivalents of IPA (0.07 mL at 0.3 mmol scale) at 3 M concentration increased the yield from 19% to 50% with only a marginal decrease in e.r. (Entry 9). Doubling the equivalents of IPA gave no improvement in the yield or e.r. (Entry 10). As no increase in enantioselectivity was observed upon the addition of IPA, it was decided to proceed without the addition of a hydride donor, at this stage, in order to limit the number of variables in the reaction optimisation.

*From this point any subsequent use or reference to KO^{t}Bu is specifically 99.9% grade purchased from Sigma Aldrich. Product code: 156671-5G.

4.6. Identification of Side Product

At increased dilution, we began to observe increased formation of a side product with nearly identical r.f. to the desired ketone product. It was not possible to isolate and analyse a sample using normal phase column chromatography as separation was challenging. Even when the desired ketone was >95% clean by ^{1}H NMR spectroscopy, a significant additional peak (10-20% by area) was observed by chiral normal phase HPLC (Figure 4.2).

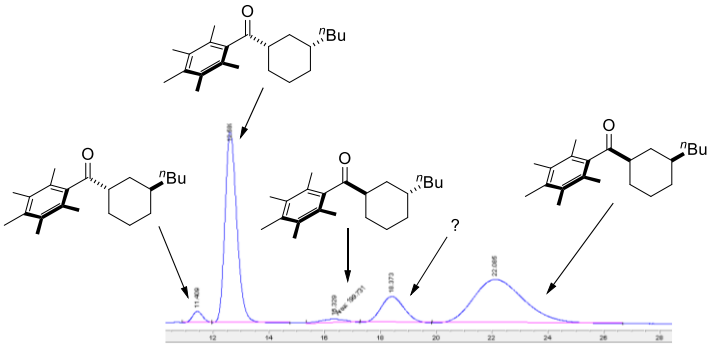


Figure 4.2. Analytical normal phase chiral HPLC spectra of **151b**.

Interestingly, despite difficulties with separation using normal phase methods, using reverse phase HPLC, we were able to observe a side product with a large difference in polarity (Figure 4.3.A). Multiple crude optimisation reactions were combined and the impurity was isolated, *via* preparative HPLC, and characterised as aromatic ketone **172**. The strongly UV active nature of this aromatic ketone explains its large peak area on HPLC even when only present in very small quantities.

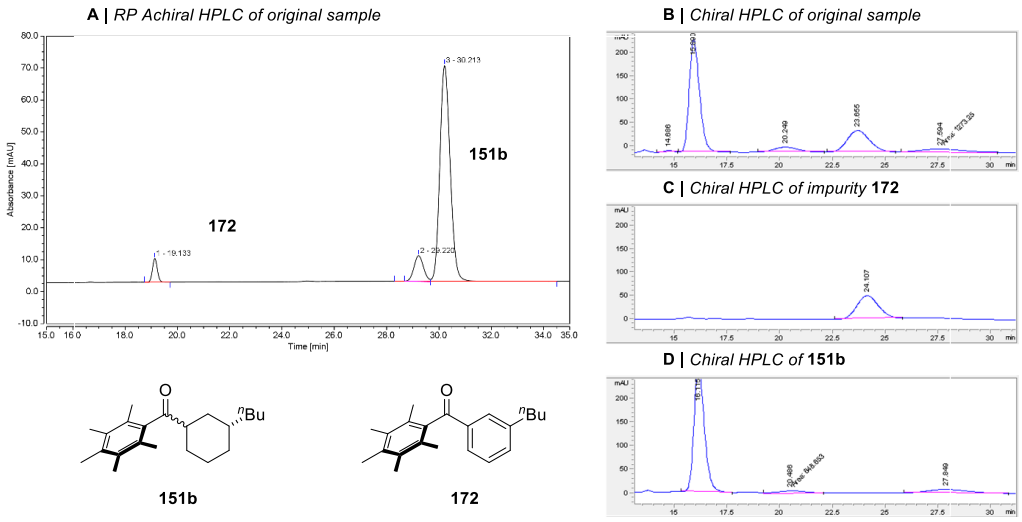
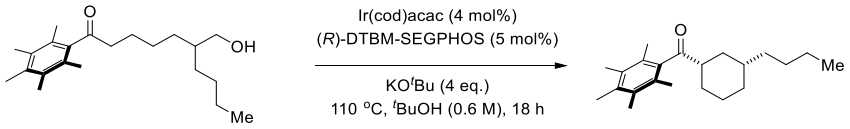


Figure 4.3. Reverse phase HPLC spectra and normal phase chiral HPLC spectra of **151b** and **172**.

Presumably, oxidation to the aromatic compound **172** is promoted by any oxygen in the system and increasing the volume of solvent, increases the amount of oxygen that can be dissolved in the reaction. As no precautions had previously been taken in running the reactions under an inert atmosphere, the solvent was thoroughly degassed with nitrogen and the reactions evacuated and backfilled with nitrogen. Gratifyingly this increased the yield of the desired cyclohexane to 66% yield and 90:10 e.r. and suppressed the aromatic side product to <1% by ^{1}H quantitative NMR (Table 4.3).*

Table 4.3. Investigation of inert reaction conditions.



Entry	Conditions	Yield[a] / %	d.r.	e.r.[b]
1	Under air	42	91:9	90:10
2	N_2 atmosphere	56 [66]	89:11	90:10

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

* It was not possible to isolate adequate quantities of aromatic ketone **172** for a calibration curve and therefore to determine yield by RP HPLC. Methods to independently synthesise **172** were unsuccessful.

Despite not being visible by ^{1}H NMR, due to the strong UV signal it was important to ensure separation of the aromatic ketone on chiral HPLC so accurate enantiomeric ratios were being determined. The distinct aromatic UV profile (peak at ~250 nm) allowed identification of **172** using chiral HPLC, even without an authentic reference sample (in the case of later substrates; Figure 4.4).

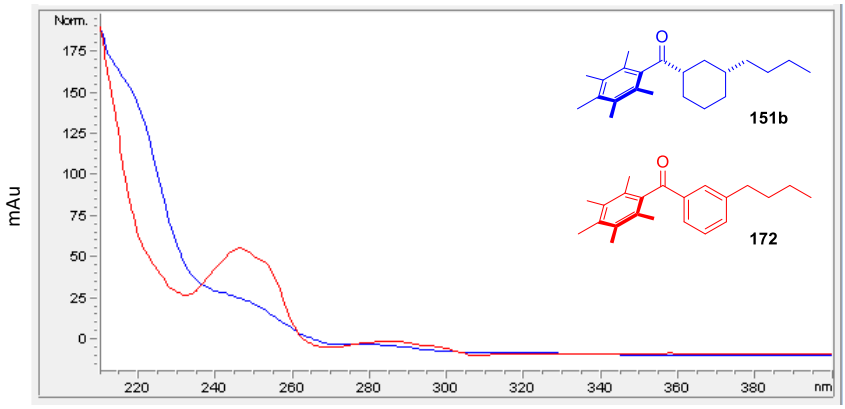
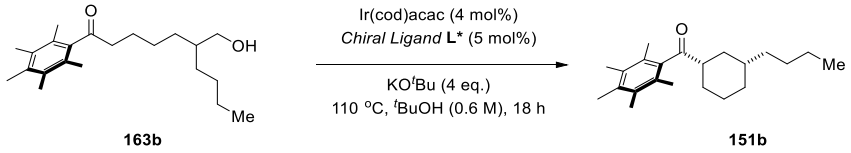


Figure 4.4. UV Spectra of **151b** and **172.**

4.7. Optimisation I

To improve the yield and enantioselectivity, we began our optimisation by screening a range of chiral diphosphine ligands (Table 4.4). Given the initial success with (*R*)-DTBM-SEGHOS, ligands with different P-Ar group were investigated. Using related (*R*)-Xyl-SEGPHOS resulted in an increase in yield (74%) but a significant reduction in e.r. (Entry 2). The simple (*R*)-SEGPHOS ligand gave a further reduction in enantioselectivity (Entry 3). Variation of the biaryl backbone (P-Ar = DTBM) gave a slight reduction in e.r. for MeOBIPHEP and was similar for GARPHOS, however, in both cases the yields were reduced (Entries 4-5). Variation of the P-Ar groups on the GARPHOS backbone showed that reducing the steric bulk could increase the yield, albeit with a reduced e.r. (Entry 6) and electron withdrawing groups were not tolerated ($-CF_3$, Entry 7). BINAP ligands gave moderate yields with little enantioselectivity (Entries 8-10). Other diphosphine ligands gave low yields (6-35%) with low levels of enantioselectivity (Entries 11-16).

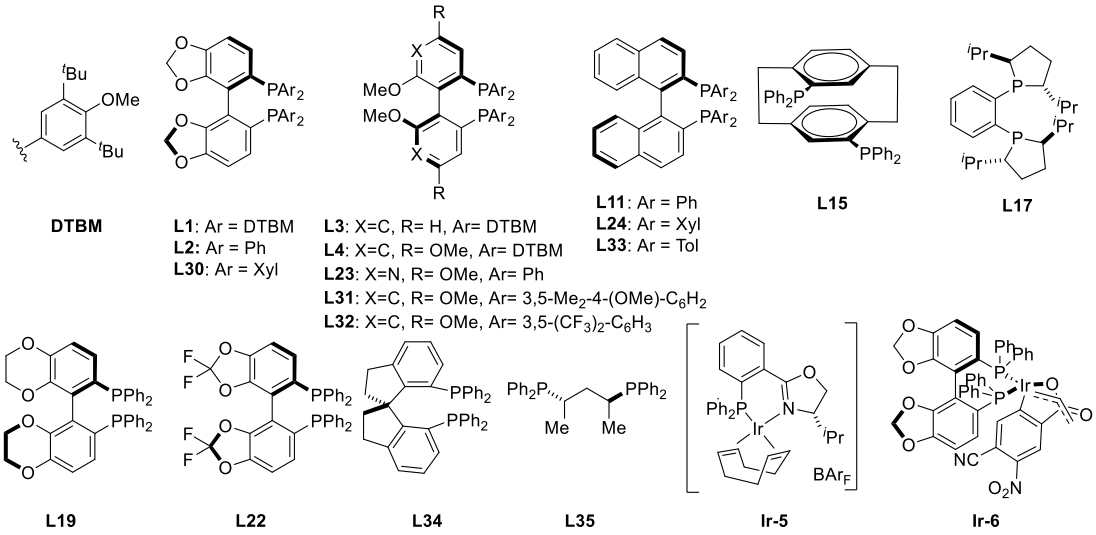
Table 4.4. Ligand screen for the intramolecular hydrogen borrowing annulation DKR.



163b 151b

Entry	L*	Ligand	Yield[a] / %	d.r.	e.r.[b]
1	**L1**	(*R*)-DTBM-SEGPHOS	66	89:11	90:10
2	**L30**	(*R*)-Xyl-SEGPHOS	74	84:16	65:35
3	**L2**	(*R*)-SEGPHOS	55	92:8	57:43
4	**L3**	(*R*)-DTBM-MeOBIPHEP	14	85:15	85:15
5	**L4**	(*R*)-DTBM-GARPHOS	18	87:13	89:11
6	**L31**	(*R*)-3,5-Me-4-OMe-GARPHOS	65	87:13	71:29
7	**L32**	(*R*)-3,5-CF_3-GARPHOS	5	85:15	63:36
8	**L11**	(*R*)-BINAP	43	88:12	56:44
9	**L33**	(*R*)-Tol-BINAP	59	82:18	41:59
10	**L24**	(*R*)-Xyl-BINAP	41	89:11	60:40
11	**L23**	(*R*)-P-Phos	31	89:11	29:71
12	**L22**	(*R*)-DIFLUOROPHOS	24	86:14	73:26
13	**L19**	(*R*)-SYNPHOS	35	84:16	54:46
14	**L17**	(*R,R*)-^{i}Pr-DUPHOS	11	88:12	45:55
15	**L15**	(*S*)-PHANEPHOS	25	91:9	48:52
16	**L34**	(*S*)-SDP	6	85:15	66:34
17	**L35**	(*S,S*)-BDPP	65	88:12	44:56
18	-	**Ir-5**	19	86:14	50:50
19	-	**Ir-6**	21	81:19	35:65

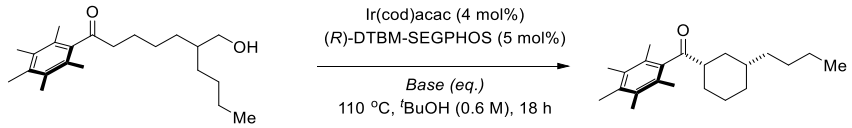
[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard.
[b] Determined by normal phase HPLC analysis using a chiral stationary phase.



Although a good yield (65%) of **151b** was obtained using acyclic diphosphine **L35**, the enantioenrichment was negligible (Entry 17). Complexation of (*S*)-^{i}Pr-PHOX ligand to iridium gave **Ir-5** which performed poorly. Similarly, **Ir-6** gave a disappointing yield and e.r. These results identified (*R*)-DTBM-SEGHOS as the optimum ligand in this screening.

The rate of racemisation of the enone intermediate, and by extension the efficiency of the DKR, is dependent on the nature and strength of the base so we expected to see a significant effect in changing the equivalents of base (Table 4.5). Pleasingly, halving the equivalents of base increased the yield by ~20% and resulted in only a slight difference in e.r. affording the desired product **151b** in 84% yield and 88:12 e.r. (Entry 3, Table 4.5). While further reduction in base still gave excellent yields, the enantioselectivities started to decrease (Entries 4-5). Increasing the stoichiometry of base to 8 equivalents caused the reaction to solidify and a complex mixture was obtained (Entry 6).

Table 4.5. Optimisation of the nature and equivalents of base.



163b **151b**

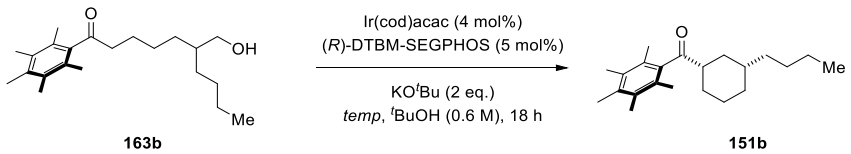
Entry	Base (Eq.)	Yield[a] / %	d.r.	e.r.[b]
1	KO^{t}Bu (4.0)	68	87:13	89:11
2	KO^{t}Bu (3.0)	82	89:11	88:12
3	KO^{t}Bu (2.0)	87 [84]	91:9	88:12
4	KO^{t}Bu (1.0)	87	92:8	83:17
5	KO^{t}Bu (0.5)	82	93:7	78:22
6	KO^{t}Bu (8.0)	0	-	-
7	LiO^{t}Bu (2.0)	<5% (85% SM)	94:6	-
8	KOH (2.0)	75	92:8	83:17
9	KOH (4.0)	87	91:9	85:15
10	NaOH (2.0)	73	91:9	60:40

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

Next, we expanded our optimisation to different bases. Use of LiO^{t}Bu was detrimental to the reaction; in this case 85% of starting material was isolated (Entry 7). A reduction in yield was seen for both KOH and NaOH (75 and 73%, respectively) but while KOH only gave a small reduction in enantioselectivity, NaOH gave a considerably lower e.r. (Entries 8 and 10). Due to the less basic nature of KOH (*cf*. KO^{t}Bu), we thought the lower e.r. could be due to slower racemisation of the enone intermediates, and therefore we investigated using 4 equivalents of KOH. Although a slight increase in yield and e.r. was observed compared to using 2 equivalents, this result did not outperform using 2 equivalents of KO^{t}Bu (Entry 9 vs Entry 3).

In the preliminary optimisation, using the 95% grade KO^{t}Bu and at high reaction concentrations, we had seen that decreasing the temperature was detrimental to the e.r. and that at 85 °C the reaction failed (Table 4.1). Under these new conditions a different trend was observed (Table 4.6).

Table 4.6. Optimisation of reaction temperature.



163b **151b**

Entry	Temperature / °C	Yield[a] / %	d.r.	e.r.[b]
1	110	87 [84]	91:9	88:12
2	100	84	93:7	89:11
3	90	83	92:8	88:12
4	80	80	92:8	89:11
5	70	41 (37% SM)	93:7	90:10
6	120	84	92:8	87:13

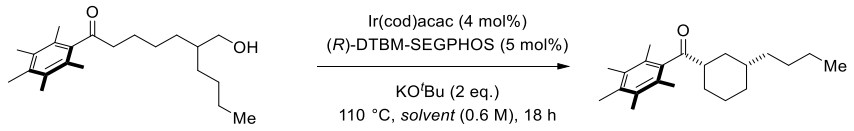
[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

At lower temperatures (80–100 °C) a slight reduction in yield was observed but the enantioselectivity was maintained (Entries 2-4). At 70 °C the reaction did not reach completion and 37% of starting material was observed by reverse phase HPLC (Entry 5). While the desired product was afforded in marginally higher enantioselectivity, the yield was significantly reduced.

Higher temperatures (120 °C) led to a slight decrease in both yield and enantioselectivity (Entry 6).

Next, the effect of different solvents was examined (Table 4.7). *tert*-Amyl alcohol facilitated the reaction in slightly decreased yield and enantioselectivity compared to ^{t}BuOH (Entry 2). Aromatic solvents such as *m*-xylene and toluene did not facilitate the reaction and led to starting material degradation (Entries 3-4). Similarly, heptane led to complete degradation of the starting materials (Entry 5). More polar solvents such as 1,4-dioxane and DMF were also unsuccessful (Entries 6-7).

Table 4.7. Solvent screening.



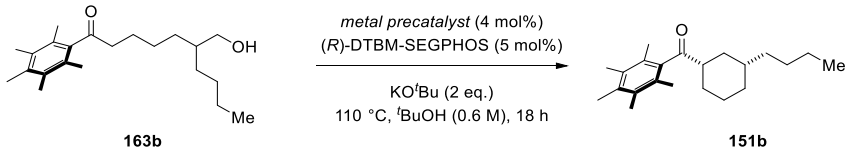
163b **151b**

Entry	Solvent	Yield[a] / %	d.r.	e.r.[b]
1	^{t}BuOH	87 [84]	91:9	88:12
2	^{t}AmOH	77	93:7	85:15
3	*m*-Xylene	0 (28% SM)	-	-
4	PhMe	0 (25% SM)	-	-
5	Heptane	0 (0% SM)	-	-
6	1,4-dioxane	0 (67% SM)	-	-
7	DMF	0 (0% SM)	-	-

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

Finally, a range of iridium precatalysts were investigated (Table 4.8). Iridium 1,5-cyclooctadiene based catalysts led to good yields and enantioselectivities, albeit slightly reduced compared to Ir(cod)acac (Entries 2-3). Switching to a cyclooctene ligand was detrimental to the yield of the reaction (Entry 4).

Table 4.8. Metal precatalyst screening.

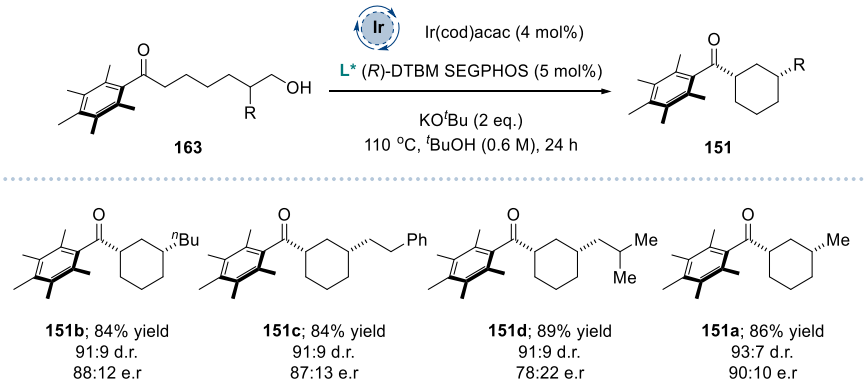


Entry	Precatalyst	Yield[a] / %	d.r.	e.r.[b]
1	Ir(cod)acac	87 [84]	91:9	88:12
2	$[Ir(cod)Cl]_2$	70	91:9	86:14
3	$[Ir(cod)OMe]_2$	79	91:9	87:13
4	$[Ir(coe)_2Cl]_2$	29	92:8	85:15

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The percentage of iridium refers to that of active iridium after dissociation of multimeric precursors.

4.8. Initial Reaction Scope

We set out to investigate the generality of this asymmetric cyclisation by varying the group in the γ-position for a small number of substrates (Scheme 4.13). For all three substrates investigated, excellent yields were obtained (**151a**-**d**). Phenethyl substituted product **151c** was obtained in similar enantioselectivity (87:13 e.r.) to **151b**. More sterically hindered isobutyl **151d** was obtained in excelled yield (89%) albeit in 78:22 e.r. Interestingly, replacing the butyl group with much smaller methyl group, afforded the desired product in 86% yield and 90:10 e.r. While these results were in line with the optimised substrate, we were disappointed by the overall level of enantioselectivity observed and decided to undertake further optimisation experiments in an effort to improve this.

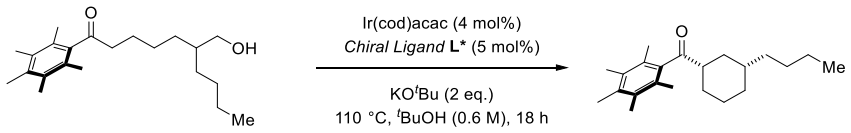


Scheme 4.13. Initial substrate scope of the intramolecular hydrogen borrowing annulation DKR. The absolute stereochemistry was determined to be (1*S*,3*R*) for **151a** (see chapter 4.13) and subsequent γ-substituted cyclohexanes were assigned by analogy.

4.9. Optimisation II

A second screening of chiral ligands was undertaken with the aim of increasing the enantioselectivity of the reaction (Table 4.9). Due to the commercial availability of range of P-Ar derivatives, a series of ligands with the MeOBIPHEP backbone were used to probe the effect of the P-Ar group more thoroughly. As seen previously, varying the DTBM ligand backbone from Segphos to MeOBIPHEP results in a moderate decrease in both yield and enantioselectivity (Entry 2). Removing the methoxy group of the P-Ar group led to an increase in e.r. (89:11) and a significant increase in yield (88%, Entry 3). Replacing the *tert*-butyl groups on the DTBM group with methoxy groups was detrimental to the enantioselectivity (69:31, Entry 4). Both tertiary amine group NMe_2 and replacement of the P-Ar group with isopropyl groups were not well tolerated (Entries 5-6). Replacing substituted phenyl groups with furyl groups gave the desired product in 70% yield but it was essentially racemic (Entry 7). Similarly, the simple MeOBIPHEP ligand (**L10**) led to a low enantioselectivity (Entry 8). Phosphoramidite ligands such as Monophos were not effective (Entry 9). Various other diphosphine ligands gave little or no enantioselectivity (Entries 10-12). Similarly, Taniaphos and Josiphos-type ligands gave essentially racemic products. Pleasingly, ferrocene ligand with a pendant amine [R_P,*S*]-PPF-NH_2 (**L37**) gave the desired product in 81% yield and 3:97 e.r.

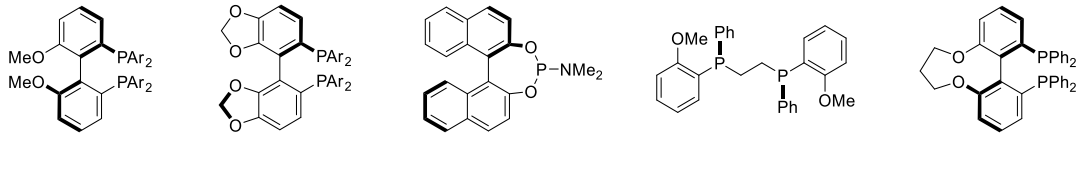
Table 4.9. Second ligand screening.



163b **151b**

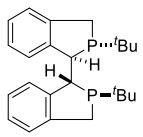
Entry	L*	Ligand	Yield[a] / %	d.r.	e.r.[b]
1	**L1**	(*R*)-DTBM-SEGPHOS	87 [84]	91:9	88:12
2	**L3**	(*R*)-DTBM-MeOBIPHEP	57	91:9	85:15
3	**L5**	(*R*)-3,5-^{t}Bu-MeOBIPHEP	88	91:9	89:11
4	**L6**	(*R*)-3,4,5-OMe-MeOBIPHEP	82	91:9	69:31
5	**L7**	(*R*)-amino-MeOBIPHEP	39	92:8	73:27
6	**L8**	(*R*)-^{i}Pr-MeOBIPHEP	17	93:7	38:62
7	**L9**	(*R*)-furyl-MeOBIPHEP	70	92:8	48:52
8	**L10**	(*R*)-MeO-BIPHEP	87	92:8	36:64
9	**L12**	(*R*)-MonoPhos	43	92:8	59:41
10	**L18**	(*R*,*R*)-DIPAMP	79	92:8	48:52
11	**L21**	(*R*)-C3-Tunephos	84	92:8	39:61
12	**L36**	Duanphos	12	92:8	55:45
13	**L13**	(R_P,*R*)-Taniaphos	33	93:7	50:50
14	**L14**	Josiphos SL-J005-1	87	90:10	48:52
15	**L37**	[R_P,*S*]-PPF-NH$_2$	82 [81]	91:9	3:97

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

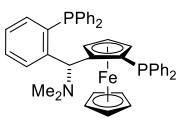


L3: Ar = DTBM
L5: Ar = 3,5-^{t}Bu$_2$-C$_6$H$_3$
L6: Ar = 3,4,5-(OMe)$_3$-C$_6$H$_2$
L7: Ar = 3,5-^{i}Pr$_2$-4-(NMe$_2$)-C$_6$H$_2$
L8: R = ^{i}Pr
L9: Ar = 2-furyl
L10: Ar = Ph

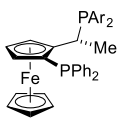
L1: Ar = DTBM **L12** **L18** **L21**



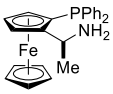
L36



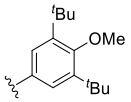
L13



L14
Ar = 3,5-Me$_2$-C$_6$H$_3$



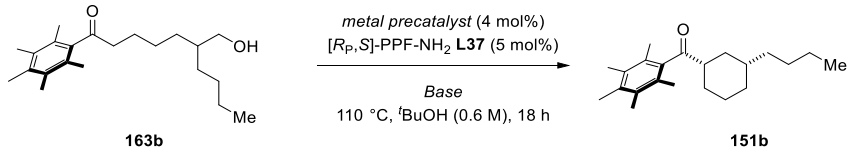
L37



DTBM

Following the identification of highly efficient ligand, [R_P,*S*]-PPF-NH_2 (**L37**), a small screen of other reaction parameters was conducted (Table 4.10). Similar trends were observed with [R_P,*S*]-PPF-NH_2 (**L37**) as with (*R*)-DTBM-SEGPHOS (**L1**): increasing the equivalents of base maintained the enantioselectivity (3:97 e.r.), albeit with a significant reduction in yield (59%, Entry 2). Reducing the equivalents of base (0.5 eq.) was detrimental to both yield and enantioselectivity (39%, 31:69 e.r., Entry 3). Various alternative metal precatalysts (Ir/Rh/Ru) did not give an improvement in yield or enantioselectivity (Entries 4-6). Replacing KO^{t}Bu with NaO^{t}Bu lowered both the yield and enantioselectivity (Entry 7). Similarly, KOH gave the desired product in reduced yield (51%) and 33:67 e.r. (Entry 8). Ultimately the optimised conditions were found to be Ir(cod)acac (4 mol%), [R_P,*S*]-PPF-NH_2 (5 mol%), KO^{t}Bu (2 eq.) in ^{t}BuOH (0.6 M) at 110 °C, which gave ketone **151b** in 82% yield and excellent enantioselectivity (3:97 e.r.).

Table 4.10. Final screening of optimisation parameters.

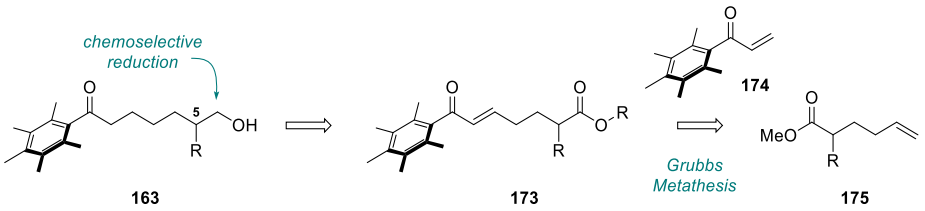


Entry	[M] 4 mol%	Base (eq.)	Yield[a] / %	d.r.	e.r.[b]
1	Ir(cod)acac	KO^{t}Bu (2.0)	82[81]	92:8	3:97
2	Ir(cod)acac	KO^{t}Bu (4.0)	59	88:12	3:97
3	Ir(cod)acac	KO^{t}Bu (0.5)	39	90:10	31:69
4	$[Ir(cod)Cl]_2$	KO^{t}Bu (2.0)	64	91:9	13:87
5	$[Rh(cod)Cl]_2$	KO^{t}Bu (2.0)	72	92:8	44:56
6	$[Ru(cod)Cl]_n$	KO^{t}Bu (2.0)	41	92:8	36:64
7	Ir(cod)acac	NaO^{t}Bu (2.0)	35	92:8	22:78
8	Ir(cod)acac	KOH (2.0)	51	92:8	33:67

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. The percentage of metal precatalyst refers to that of active iridium after dissociation of multimeric precursors.

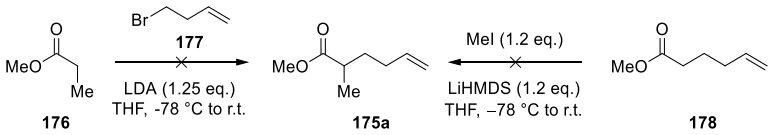
4.10. Substrate Synthesis

To evaluate the generality of the annulation, we set out to synthesise linear substrates with a range of substituents at C-5 (Scheme 4.14). We envisaged that the requisite precursors could be synthesised by cross metathesis of ester **175** with Ph* vinyl ketone **174**, followed by reduction to the hydroxyketone **163**.



Scheme 4.14. First generation retrosynthesis of linear alcohol substrates.

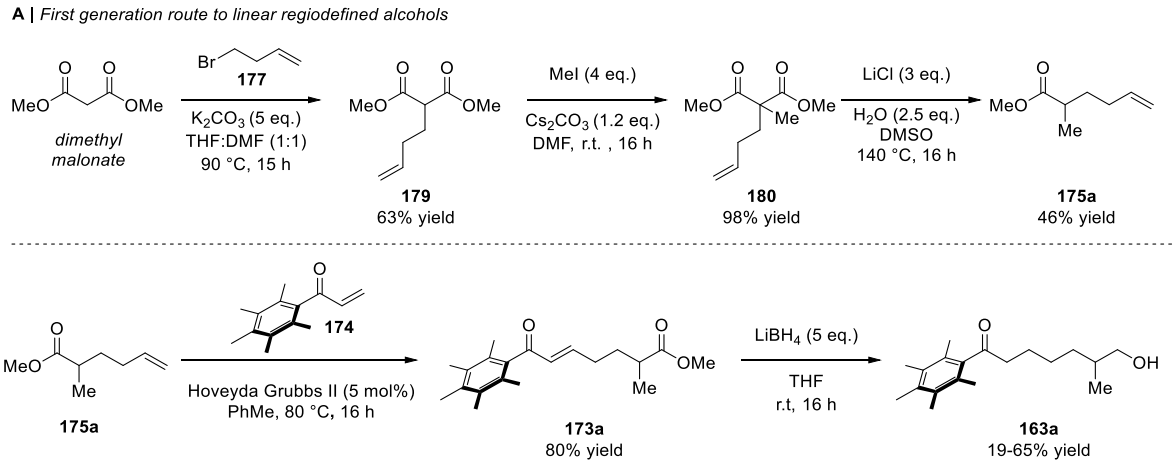
The most direct synthesis of ester coupling partner **175a** would be alkylation of methyl propionate (**176**) with 4-bromobut-1-ene (**177**, Scheme 4.15). Unfortunately, both this approach as well as alkylation of ester **178** with methyl iodide led to a complex mixture of products including over alkylation. To aid the alkylation, a more conservative approach was taken using dimethyl malonate as the starting material.



Scheme 4.15. Attempted synthesis of ester coupling partners.

Alkylation of dimethyl malonate with 4-bromobut-1-ene (**177**) afforded substituted malonate **179** in 63% yield. Subsequent alkylation of **179** with methyl iodide gave disubstituted malonate **180** in excellent yield (98%), followed by Krapcho decarboxylation affording the ester coupling partner **175a** in 46% yield. This moderate yield could likely be attributed to the volatility of the product at the high reaction temperatures. Alkene metathesis, using Hoveyda Grubbs second generation catalyst, with Ph* vinyl ketone **174** afforded linear substrate **173a** in 80% yield. Treatment of **173a** with $LiBH_4$ led to reduction of α,β-unsaturated ketone and ester to afford

desired linear alcohol starting material, albeit with variable levels of reproducibility (19-65% yield).



Scheme 4.16. First-generation synthesis of linear alcohol substrates.

Although this route gave access to enough material to pursue preliminary studies, clear disadvantages were the early-stage introduction of the R group and use of an expensive Grubbs catalyst, both of which needed addressing in a second-generation route.

We envisaged that Ph* ester **181** could be a key intermediate, which would be derivatised *via* chemoselective α-alkylation and subsequently only require a single reduction step to access the desired starting material. The Ph* ester **181** would be accessed from pimelic acid by esterification, followed by Friedel-Crafts acylation.

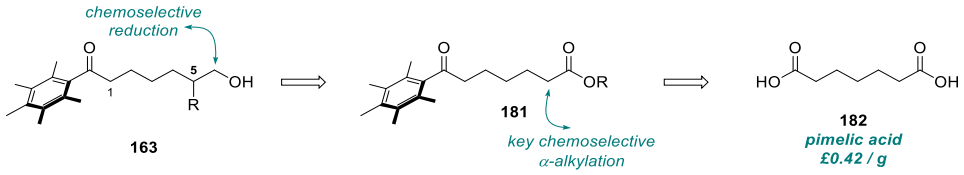
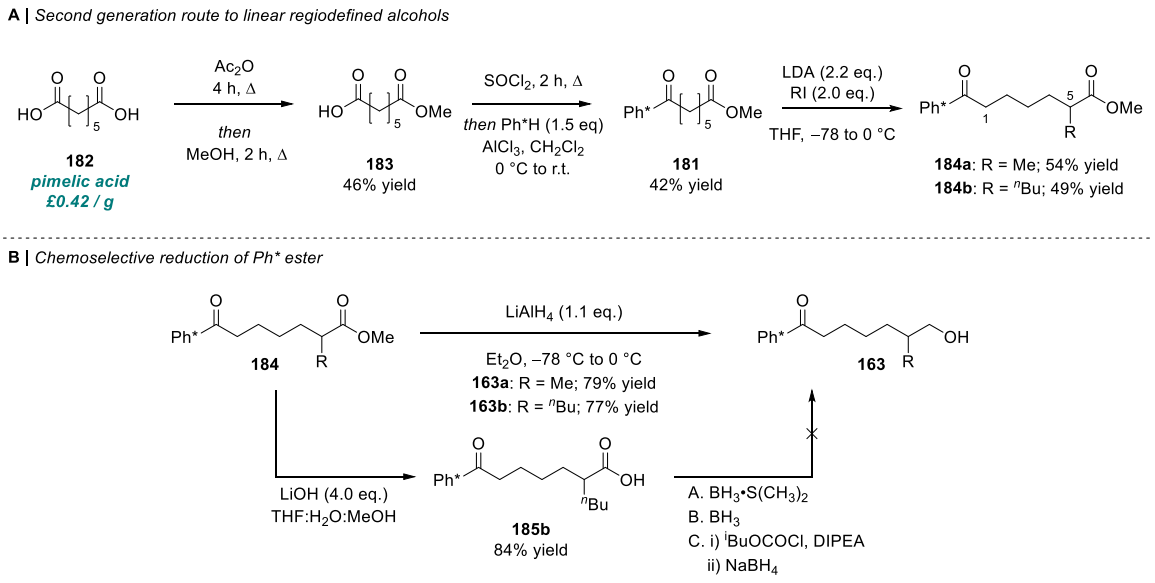


Figure 4.5. Second-generation retrosynthesis of linear alcohol substrates.

Pimelic acid was monoesterified to give **183** in 46% yield and subsequently, the corresponding acid chloride was formed *in situ*, which then was used in a Friedel-Crafts acylation with pentamethylbenzene to afford Ph* ester **181** in 42% yield (Scheme 4.17).



Scheme 4.17. Second-generation synthesis of linear alcohol substrates.

α-Alkylation of Ph* ester **181** was then possible with both methyl and butyl iodide, affording **184a** and **184b**, respectively in moderate yields. Use of excess base was necessary as enolate formation is possible with the Ph* ketone, although no alkylation was seen at C-1, presumably due to the steric hinderance of the Ph* group.

Reduction of the ester in **184** was sluggish using $LiBH_4$ at room temperature, however after heating to 40 °C for 1 hour, a complex mixture containing a diol derived from over reduction of the typically non-reactive Ph* ketone, the desired alcohol, as well as unreacted starting material were observed. Reduction of the corresponding acid (**185b**), using various reagents including borane, was also investigated without success. Pleasingly, a carefully controlled reduction[*] of **184a**-**b** was possible with $LiAlH_4$ and avoided further reduction of the Ph* methyl ketone on small scale.

Two other strategies were considered for the convergent synthesis of the linear precursors. Firstly, a hydrogen borrowing strategy was considered with a protected diol which could be accessed from a regioselective Baeyer-Villiger reaction. This route would also provide an

[*]Reaction conditions: 2 h at –78 °C and 10 min at 0 °C.

alternative strategy for accessing the desired 1,5-diols **150**. Secondly, a more direct route was envisaged in which linear alcohol **163** would be accessed by a final hydroboration. There are many possible reactions to access the required substituted terminal alkene from the corresponding alkyne.[101,102]

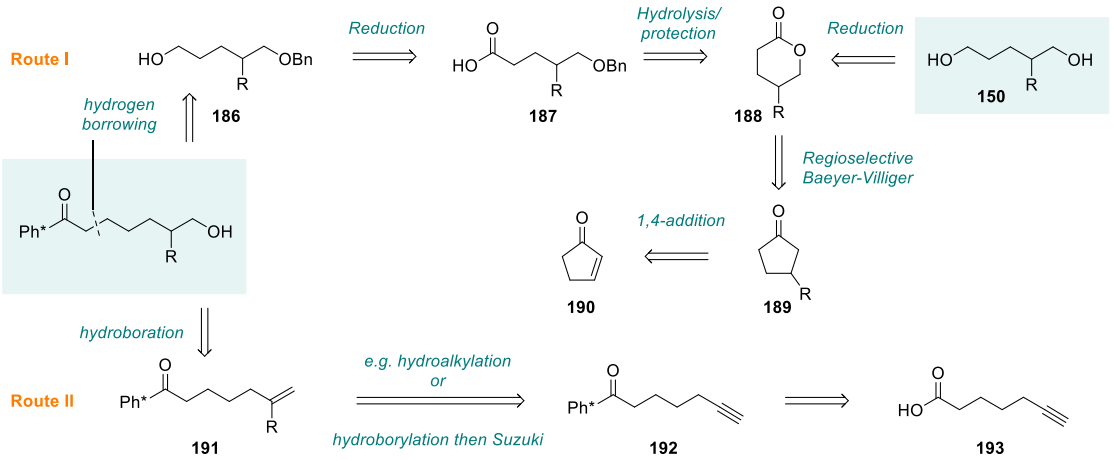
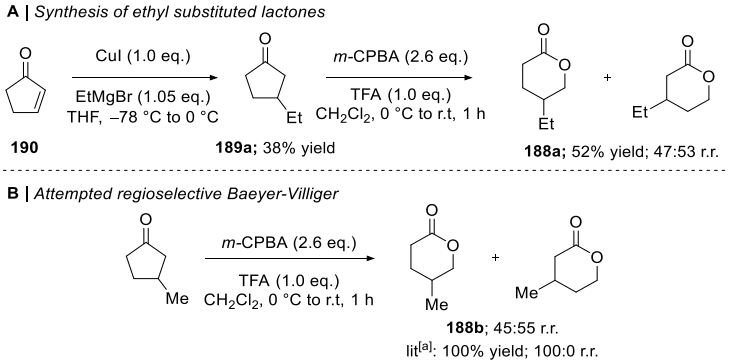


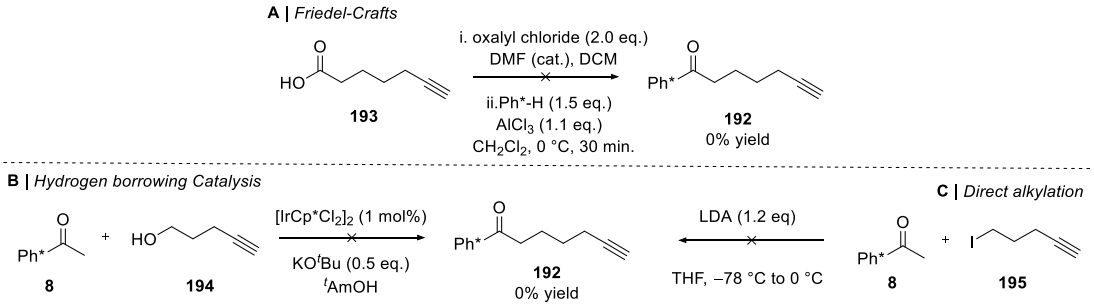
Figure 4.6. Route I and II retrosynthesis of linear alcohol substrates.

Investigation of route I was initiated by 1,4-addition to 2-cyclopentene-1-one using EtMgBr in the presence of copper iodide, affording **189a** in 38% yield.[103] With the substituted cyclopentanone in hand, the regioselective Baeyer-Villiger was attempted. Whilst the original report by Chamberlin and co-workers[104] showed complete regioselective Baeyer-Villiger reaction on multiple alkyl-substituted cyclopentanones, no rationale was given. However, this method was later used by Hatakeyama and co-workers in the total synthesis of (−)-englerin A.[105] In this synthesis a single regioisomer of the desired lactone was required. Unfortunately, in our hands we only observed a 1:1 regiomeric mixture of the lactones (**188a**, Scheme 4.18). Although we believed that the ethyl cyclopentanone would be a representative example, commercially available methyl cyclopentanone **189b** was subjected under these conditions as a direct repeat of the literature. Again, a mixture of regioisomers was observed by quantitative ^{1}H NMR (45:55 r.r.). The success of this step was crucial for synthesis of the desired regioisomer and as the diastereomers could not be separated, at this point route I was abandoned.



Scheme 4.18. Synthesis of substituted lactones. [a]Literature reference.[104]

Next, to investigate route II, synthesis of Ph* alkyne **192** was attempted (Scheme 4.19). First, the corresponding acid chloride was formed *in situ* from acid **193**. Unfortunately, Friedel-Crafts acylation with Ph* methyl ketone resulted in a complex mixture of products, with no indication that the desired alkyne was present. Next, a hydrogen borrowing strategy employing 4-pentyn-1-ol and Ph* methyl ketone was investigated. Modified conditions have been developed within the group to increase tolerance to various functional groups including *N*-heterocycles. Unfortunately, even under these milder conditions no product was formed; at room temperature no reaction was observed, and at 85 °C pent-4-yn-1-ol (**194**) decomposed. Since hydrogen borrowing alkylations have not previously shown to tolerate alkynes, we considered an alternative direct α-alkylation with iodo-alkyne **195**. Unfortunately, this also failed to produce any of the desired product (**192**).



Scheme 4.19. Attempted synthesis of Ph* alkyne **192**.

At this point, the second-generation route was revisited. Introduction of the side chain at a later stage was clearly beneficial, however, the modest yields of the alkylation, as well as practical aspects, such as need for cryogenic temperatures and over reliance on chromatography – which would prove difficult on a large scale were a bottleneck to accessing significant quantities of starting material. In a third-generation synthesis, development of a practically simple route, which would be successful on multigram scale was needed. By using Ph* malonate **196** as common intermediate we hoped this would facilitate the alkylation with various alkyl halides and subsequently only require decarboxylation and reduction to afford the desired linear Ph* alcohols (Figure 4.7). We envisaged that Ph* malonate **196** could be accessed in two steps from commercially available and inexpensive 5-bromovaleric acid.

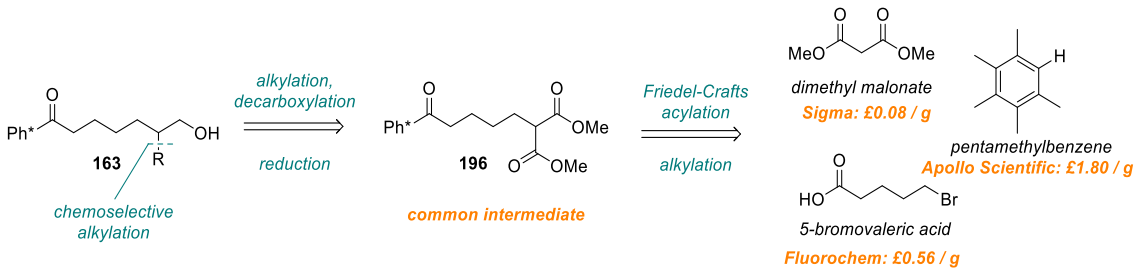
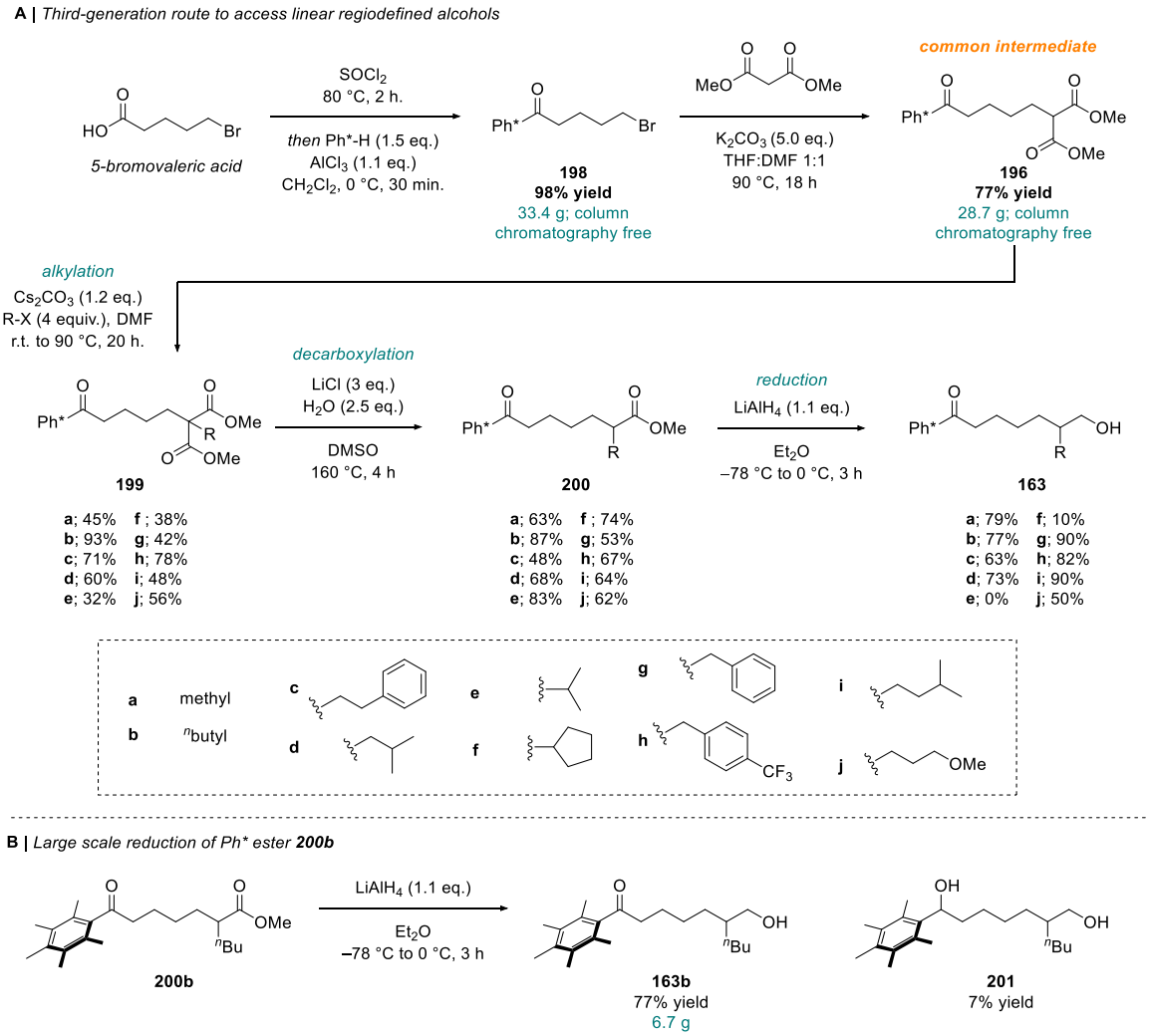


Figure 4.7. Third generation retrosynthesis of linear alcohol substrates.

Treatment of 5-bromovaleric acid with thionyl chloride resulted in *in situ* formation of the corresponding acid chloride (Scheme 4.20.A). Subsequent Friedels-Crafts acylation with pentamethylbenzene afforded Ph* bromide **198** in 98% yield. This could be scaled up to access >30 g as a single batch. Introduction of the Ph* group in the first step ensured that most intermediates were solids, and specifically **198** was a crystalline solid, only requiring trituration to afford clean product. Alkylation with dimethylmalonate using potassium carbonate afforded **196** in 77% yield. Again, this step avoided challenging large scale column chromatography as a purification method – solely requiring vacuum distillation of excess dimethyl malonate and subsequent trituration. This afforded ~30 g of common intermediate **196** in two facile steps in excellent yields.

Alkylation of **196** with alkyl halides and caesium carbonate gave variable yields (32 – 93%). For optimisation substrate **199b** the substituted malonate was accessed in 93% yield and, again, solely required trituration to afford analytically pure product.

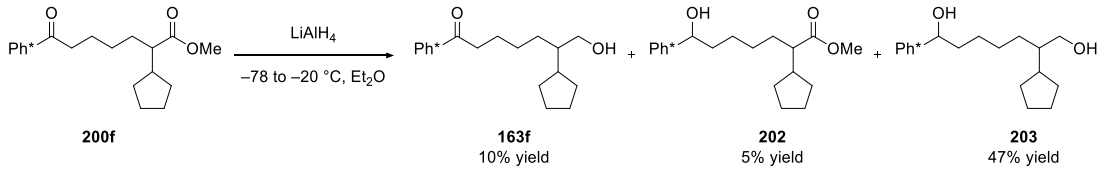


Scheme 4.20. Third-generation synthesis of linear alcohol substrates.

Other primary alkyl halides and benzyl halides gave moderate to good yields (45-78%); secondary halides, such as 2-bromopropane and bromocyclopentane, performed poorly (32-38% yield). Krapcho decarboxylation of the substituted Ph* malonates afforded esters **200a-j** in generally good yields and was more successful than in the first-generation route, likely due to the greater molecular mass reducing the volatility. Subsequently, using our previously developed reduction conditions, treatment of Ph* ester **200** with $LiAlH_4$ afforded **163a-d** and

163g-j substrates in moderate to excellent yields (50-90%). In the case of butyl Ph* alcohol **163b**, up to 6.7 g of material was accessed as a single batch. At larger scale, 5-10% formation of diol was observed but easily separated by column chromatography (Scheme 4.20.B).

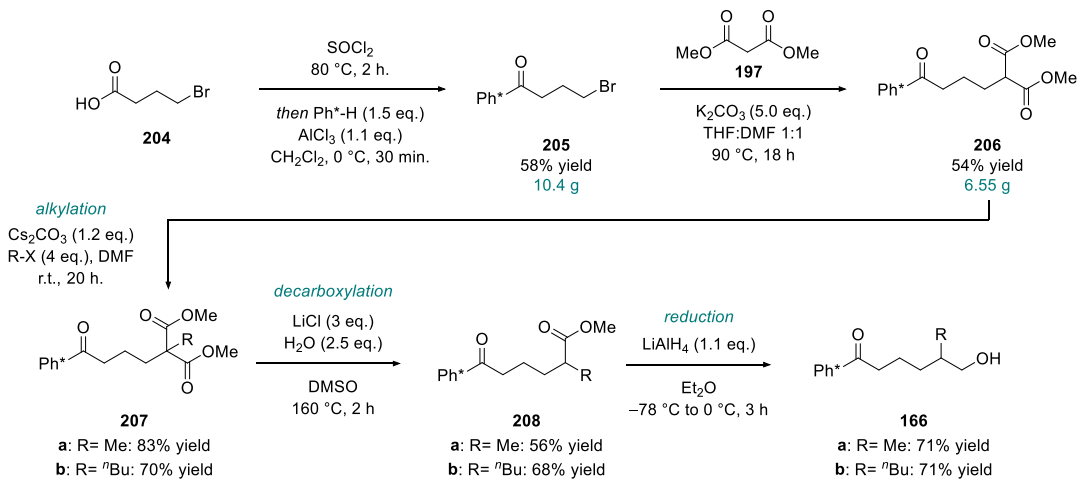
Not all of the esters underwent reduction to the desired alcohol successfully; esters bearing hindered secondary β-centres were problematic (**200e** and **200f**). For example, when treating cyclopentyl ester **200f** with $LiAlH_4$ at –78 °C, no reaction was observed (Scheme 4.21). Increasing the temperature to –20 °C afforded some of the desired product, however hydroxy ester **202** and significant quantities of diol **203** were also formed competitively (Scheme 4.21). While the Ph* ketone is susceptible to reduction with $LiAlH_4$, in all previous cases, the ester was more easily reduced and so formation of the diol could be prevented by carefully controlling the temperature. In this case, it is clear that the steric hindrance of the secondary centre slows down reduction of the ester so we observe little selectivity in the reduction. DIBAL-H and L-selectride were both investigated as alternative reductants, however, both of these reagents gave a distribution of products even when the reaction mixture was kept at –78 °C. For isopropyl ester **200e**, a similar distribution of the desired product, Ph* hydroxy ester and diol were also observed.



Scheme 4.21. Reduction of Ph* ester **200f**. It was not possible to determine diastereomeric ratios of **202** and **203** due to complete overlap of ^{1}H NMR signals.

Linear alcohols of different chain length were synthesised following the same "third-generation" route (Scheme 4.22). Friedel-Crafts acylation of *in situ* formed acid chloride afforded **205** in 58% yield, and subsequent alkylation with dimethylmalonate gave **206** in 54% yield. The lower yields (*cf*. to Scheme 4.20) may be due to the difference in scale; generally, these reactions are more

efficient on larger scale. Alkylation, decarboxylation and reduction all gave analogous yields to **199a**-**b**, **200a**-**b** and **163a**-**b** (Scheme 4.22).



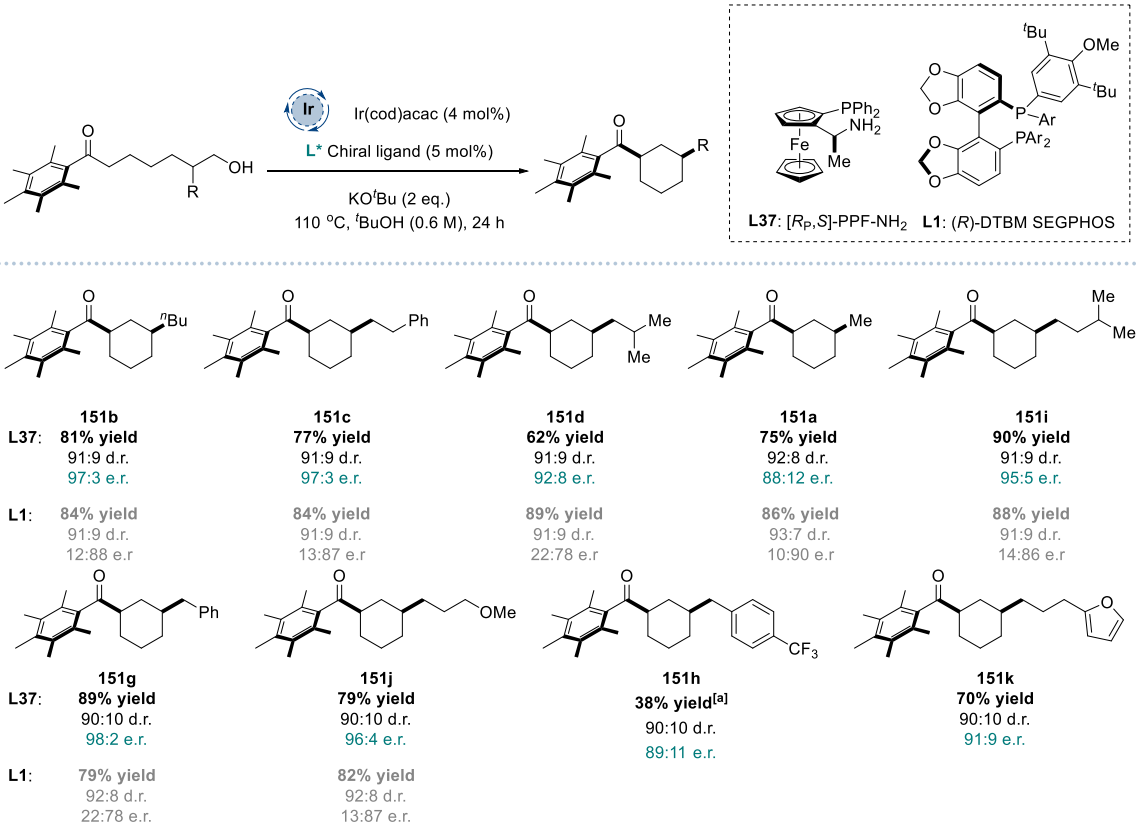
Scheme 4.22. Third-generation synthesis of linear alcohol substrates with differing chain length.

Ultimately, the third-generation route proved to be a divergent, efficient and scalable method to access the linear substrates and facilitated the preparation of grams of **163a-d** and **163h-j** which would be required to investigate the substrate scope of our enantioselective reaction. A limitation of this approach was a low tolerance to secondary centres at the β-position (e.g. **163e** and **163f**). However, with the eight substrates now in hand, we set out to investigate the generality of the asymmetric annulation reaction.

4.11. Reaction Scope

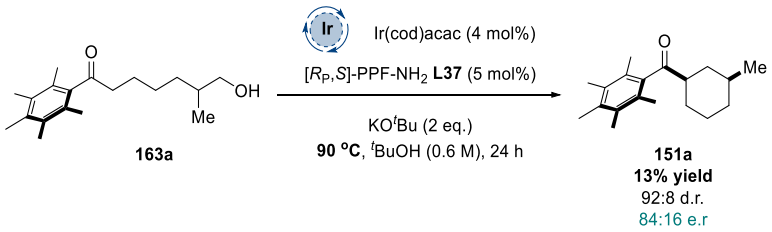
Having identified optimised conditions using [R_P,*S*]-PPF-NH_2 (**L37**), we set out to investigate the generality of the system (Scheme 4.23). Synthesis of phenethyl and isobutyl substrates followed a similar trend compared to using (*R*)-DTBM-SEGPHOS; phenethyl substrate **151c** was afforded in 77% yield and analogous enantioselectivity to **151b** (97:3 e.r.). Incorporation of an isobutyl group (**151d**) had previously led to a significant decrease in enantioselectivity (22:78 e.r.), but using [R_P,*S*]-PPF-NH_2 (**L37**) gave the desired ketone in 92:8 e.r. Interestingly, replacement of the butyl group with a methyl group (**151a**) led to reduced enantioselectivity using **L37** (88:12 e.r.),

whereas, this substrate gave the highest e.r. (10:90) with (*R*)-DTBM-SEGPHOS (**L1**). It is presumably more difficult for the ligand to differentiate between the enone enantiomers as the size of the γ-substituent decreases, resulting in lower enantioselectivities. Other branched alkyl groups were also well tolerated and **151i** was isolated in 90% yield and 95:5 e.r. Benzyl substituted ketone **151g** was isolated in excellent yield (89%) and 98:2 e.r.; notably this is significantly higher than with (*R*)-DTBM-SEGPHOS (22:78 e.r.). Similarly, methoxy groups were well tolerated and gave **151j** in 79% yield and 96:4 e.r. Unfortunately, incorporation of electron withdrawing $-CF_3$ on the benzyl group (**151h**) led to reduced yield, albeit still with good enantioselectivity (89:11 e.r.). Furyl ketone **151k** was well tolerated and isolated in 70% yield and 91:9 e.r. This sense of enantioselectivity was proven by single crystal X-ray diffraction for **151a**, **151b**, **151c**, and **151g** (see chapter 4.13) and the remaining compounds are assigned by analogy.



Scheme 4.23 Intramolecular hydrogen borrowing annulation controlling the γ-stereogenic centre via DKR. [a] **151h** was isolated in 92% purity; inseparable with the aromatised cyclohexane. For determination of absolute stereochemistry see chapter 4.13.

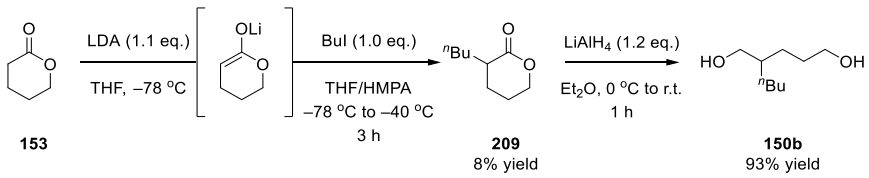
We wondered if we could increase the enantioenrichment of **151a** by lowering the temperature of the reaction (Scheme 4.24). Unfortunately, at 90 °C only 13% of the desired product was isolated and in lower e.r. (84:16).



Scheme 4.24. Synthesis of **151a** at reduced temperature.

4.12. Intermolecular Hydrogen Borrowing Annulation DKR

Having established an effective DKR method for synthesising γ-substituted cyclohexanes from linear regiodefined alcohols, the intermolecular hydrogen borrowing annulation was revisited and a small set of reaction parameters were screened. Butyl-substituted diol **150b** was synthesised by α-alkylation of δ-valerolactone (**153**) with butyl iodide affording lactone **209** in 8% yield (Scheme 4.25). As discussed previously, the low yield can be attributed to different multi-alkylation and polymerisation pathways and challenging separation of the mono- and disubstituted lactones. Subsequently the functionalised lactone **209** was reduced by $LiAlH_4$ to afford the desired diol in 93% yield.

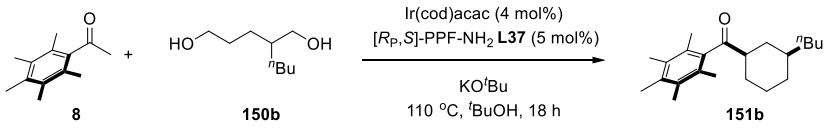


Scheme 4.25. Synthesis of butyl-substituted diol **150b**.

Diol **150b** was subjected to the optimised intramolecular hydrogen borrowing annulation conditions, affording **151b** in 53% and 70:30 e.r. (Entry 1, Table 4.11). The concentration was increased to 3 M to promote the intermolecular hydrogen borrowing. Pleasingly, an increase in yield (72%) and enantioselectivity (72:28 e.r.) was observed (Entry 2). As discussed previously,

the lower enantioselectivity in the intermolecular reaction is likely a result of a [1,5]-hydride shift of the oxidised diol (hydroxyaldehyde **160**). In order to promote the aldol condensation and outcompete the [1,5]-hydride shift, the stoichiometry of starting materials was inverted, providing an excess of Ph* methyl ketone **8**. Pleasingly, this gave a significant increase in both yield and enantioselectivity affording **151b** in 83% yield and 86:14 e.r. (Entry 3). A further increase in concentration was not beneficial (Entry 4). Halving the equivalents of base was detrimental to the enantioselectivity, presumably this is due to the rate of racemisation between the enone intermediates not being sufficiently high to ensure an effective DKR (Entry 5). Increasing the base stoichiometry to 4 equivalents led to a reduction in yield and a slight decrease in enantioselectivity (Entry 6). Having optimised the conditions for this process, benzyl diol **150g**[*] was subjected to the hydrogen borrowing DKR conditions.

Table 4.11. Optimisation of the intermolecular hydrogen borrowing annulation DKR.

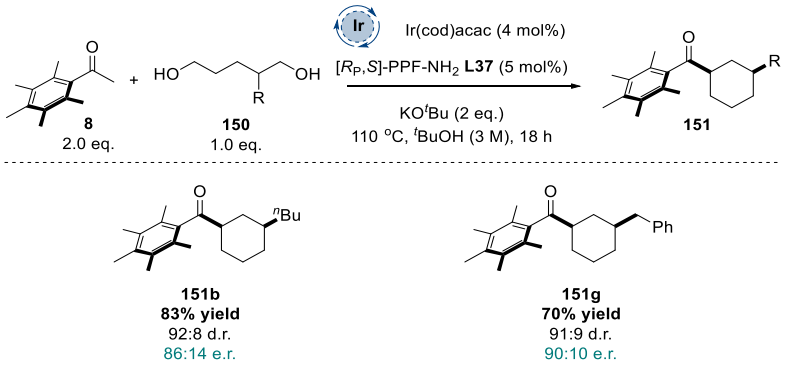


8 **150b** **151b**

Entry	Ph*COOMe eq.	Diol eq.	Conc. / M	Base Equiv.	Yield[a] / %	d.r.	e.r.[b]
1	1	2	0.6	2	53	91:9	70:30
2	1	2	3	2	72	92:8	72:28
3	2	1	3	2	86[83]	92:8	86:14
4	2	1	6	2	77	91:9	85:15
5	2	1	3	1	54	91:9	66:34
6	2	1	3	4	56	79:21	84:16

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. [Isolated yields are given in parentheses].

[*]This synthesis was carried out by Anna Chamberlain *via* an analogous method to that for **150g**.

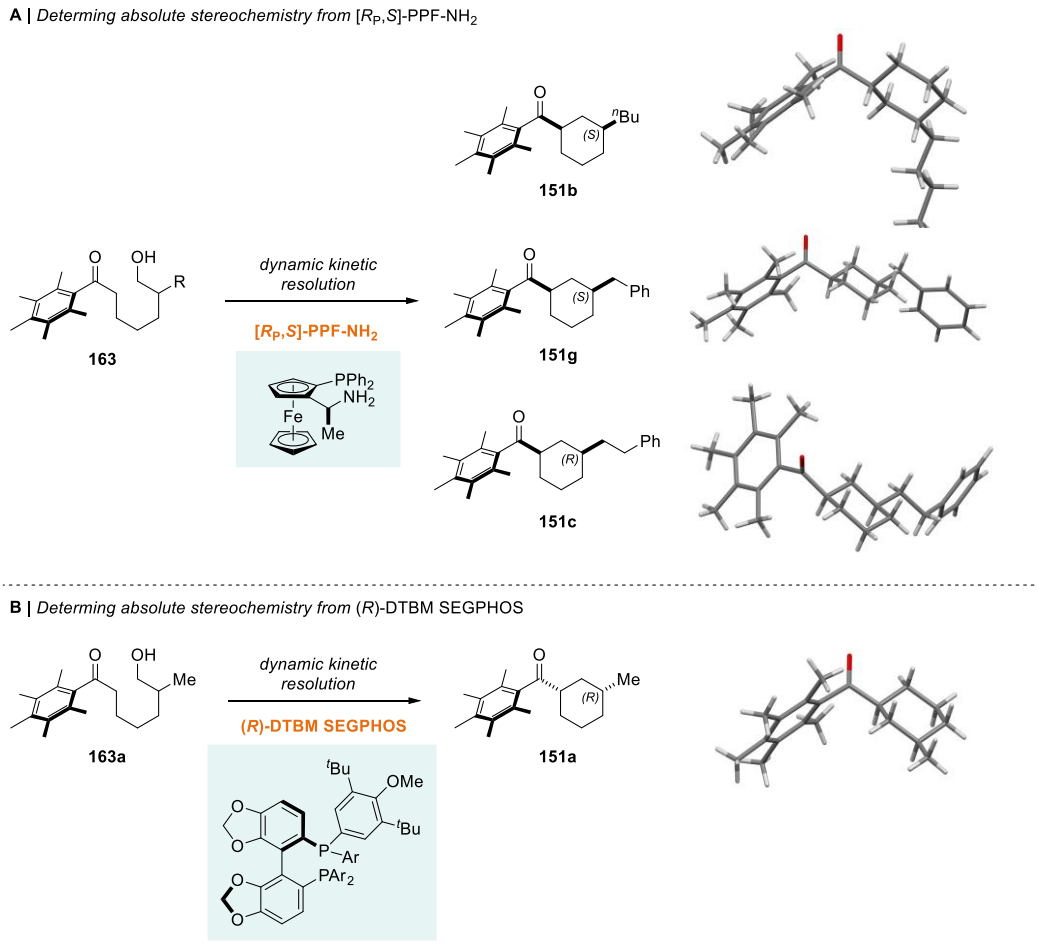


Scheme 4.26. Intermolecular hydrogen borrowing annulation controlling the γ-stereogenic centre via DKR.

Pleasingly, benzyl substituted ketone **151g** was isolated in 70% yield and 90:10 e.r. (*cf*. 98:2 e.r. from the linear system; Scheme 4.23). This intermolecular hydrogen borrowing annulation DKR is significantly more challenging than the intramolecular reaction and requires balancing of many different processes simultaneously. Even with some of the unproductive eneone isomer forming *via* [1,5]-hydride shift of the hydroxyaldehyde, we are still able to access the saturated cyclohexanes in good yields and enantioselectivity. Furthermore, the starting diols can be accessed in only two steps compared to the linear substrate synthesis.

4.13. Determination of Absolute Stereochemistry

Reactions using (*R*)-DTBM-SEGPHOS (**L1**) and [R_P,*S*]-PPF-NH_2 (**L37**) resulted in the formation of opposite enantiomers, as indicated by chiral HPLC. In order to determine the absolute stereochemistry, several cyclohexyl ketones were crystallised (Scheme 4.27).



Scheme 4.27. Determination of absolute stereochemistry by single crystal X-ray diffraction. X-ray crystallography data and analysis were provided by Dr Kirsten E. Christensen.

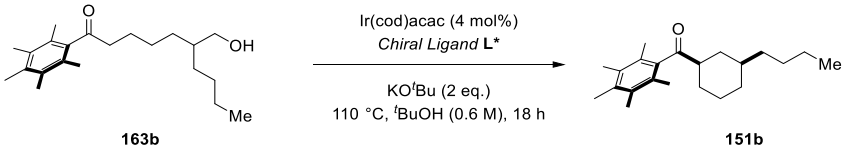
Single crystal X-ray diffraction of ketones **151b**, **151g** and **151c** (synthesised using [R_P,*S*]-PPF-NH_2) indicated the absolute stereochemistry to be of the same sense (**151b**, **151g** = (1*R*,3*S*) and **151c** = (1*R*,3*R*), (Scheme 4.27.A)). For ketone **151a** synthesised using (*R*)-DTBM-SEGPHOS, single crystal X-ray diffraction revealed the absolute stereochemistry to be (1*S*,3*R*) (Scheme 4.27.B). The configuration of all other substrates was assigned by analogy.

4.14. Stereochemical Rationale and Mechanistic Considerations

While there have been some literature reports of the use of [R_P,*S*]-PPF-NH_2 (**L37**) as an asymmetric ligand,[106,107] it is most commonly used as a precursor to more functionalised imine ligands.[108,109] Ligands of a similar type to [R_P,*S*]-PPF-NH_2 (**L37**) were screened in an effort to increase our understanding of the system (Table 4.12). Surprisingly replacing the methyl group

at the stereogenic centre with a phenyl (**L38**) led to a drastic reduction in e.r. (Entry 2). Interestingly, the opposite enantiomer was formed in slight excess when using this ligand compared to when [R_P,*S*]-PPF-NH_2 (**L37**) was employed. Introduction of a methyl group on the free –NH_2 (**L39**) was detrimental, affording the product in 14% yield and almost as a racemate (Entry 3). Interestingly, here the opposite enantiomer is also favoured compared to the results using **L37**,* albeit in very low enantioselectivity. This drastic change in enantioselectivity could be explained in a number of ways: replacing –NH_2 with –NHMe presumably either (i) alters the conformation significantly to hinder efficient binding to the catalyst or (ii) removes a hydrogen bond which could be involved in facilitating binding and ensuring conformational restriction of the substrate.

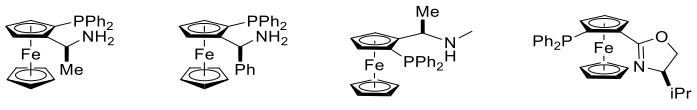
Table 4.12. Investigation of ferrocene-type ligands and ligand:metal ratio.



163b **151b**

Entry		Ligand	Ligand mol %	Yield[a] / %	d.r.	e.r.[b]
1	**L37**	[R_P,*S*]-PPF-NH_2	5	82 [81]	91:9	97:3
2	**L38**	[R_P,*S*]-**L38**	5	14	93:7	37:63
3	**L39**	[S_P,R]-PPF-NHMe	5	14	92:8	54:46
4	**L40**	[S_P,R]-**L40**	5	44	93:7	61:39
5	**L37**	[R_P,*S*]-PPF-NH_2	10	3	-	-
6	**L37**	[R_P,*S*]-PPF-NH_2	4	77	90:10	92:8
7	**L37**	[R_P,*S*]-PPF-NH_2	2.5[c]	78	91:9	96:4

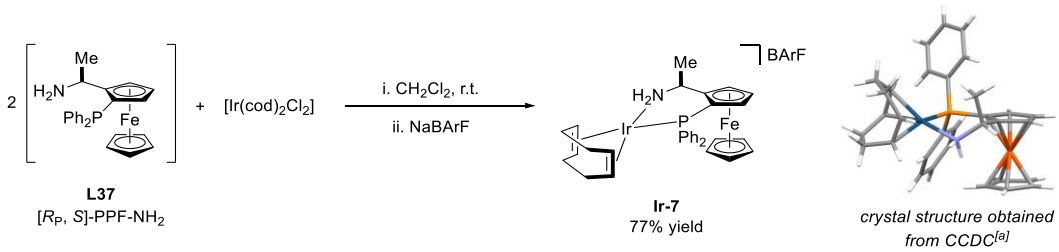
[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase. [c] 2 mol% Ir(cod)acac was used.



L37 **L38** **L39** **L40**

N.B. **L39** [S_P, *R*] is of opposite stereochemistry to **L37** [R_P, *S*].

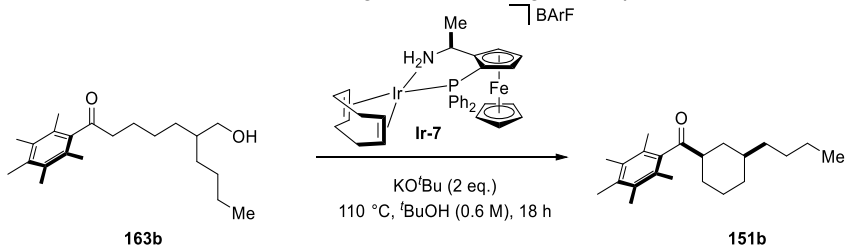
We observed that the reaction was highly sensitive to the ligand to metal ratio. The standard conditions use a slight excess of the chiral ligand (4 mol% iridium and 5 mol% ligand) to ensure no free iridium is present. Increasing the ligand loading to 10 mol % was detrimental to the reaction and only trace amounts of product were observed (Entry 5, Table 4.12). Presumably when the ligand is bound, it is not labile, and, therefore, one equivalent of ligand to metal is optimal in theory. However, two equivalents of the ligand completely sequester the catalyst, rendering it inactive. There was no further benefit in using a 1:1 ratio of ligand:metal, this is likely due to the difficulty of weighing very small amounts of catalyst and the accuracy limitation of the balance. Pleasingly, reducing the iridium loading to 2 mol% and the ligand loading to 2.5 mol% gave similar reaction efficacy (Entry 7).



Scheme 4.28. Synthesis of iridium-ligand complex. [a]CCDC no. 720880; *N.B.* the complex depicted in the crystal structure is the enantiomer of **Ir-7**.

Due to the sensitive nature of the ligand to metal ratio, the preformed complex (**Ir-7**) was synthesised in 77% yield as the BAr_F salt, following a literature procedure (Scheme 4.28).[110] To replicate the standard conditions, 4 mol% of **Ir-7** was used and the desired product was obtained in 72% yield and 8:92 e.r. While a slight reduction in efficiency was observed compared to the adding metal and ligand separately, it does suggest that bidentate iridium-ligand complex is being formed *in situ*. The reduced efficiency may be due to the presence of the of the complex as a BArF salt (*cf*. acetylacetone). Increasing the equivalents of **Ir-7** led to a reduction in enantioselectivity, albeit with analogous yields (Entries 2-3). Reducing the equivalents of **Ir-7** led to a slight reduction in yield, however it gave identical e.r. (Entry 4).

Table 4.13. Investigation of iridium-ligand complex.



163b 151b

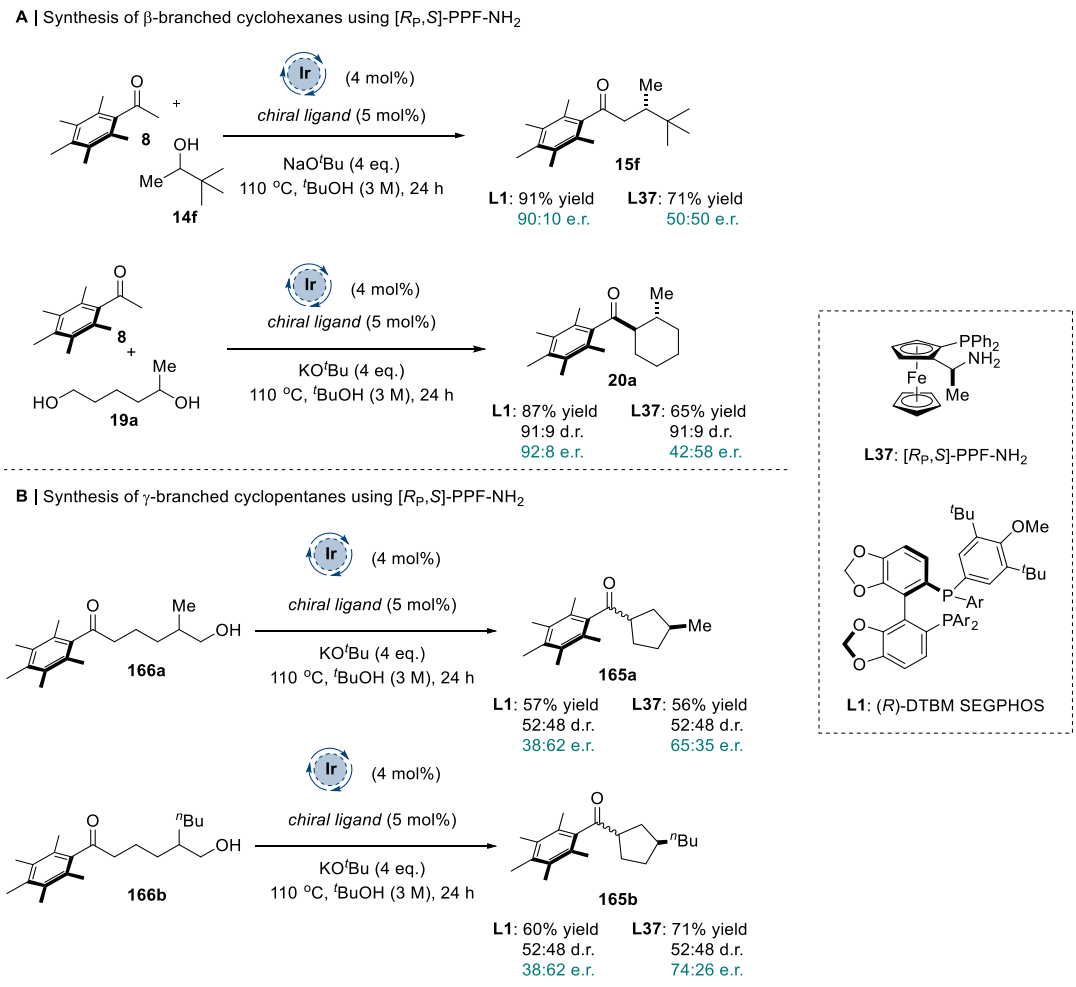
Entry	Ir-7 mol%	Yield[a] / %	d.r.	e.r.[b]
1	4	72	91:9	92:8
2	5	75	92:8	90:10
3	10	73	92:8	86:14
4	2	66	92:8	92:8

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

We reasoned that the reduction in enantioselectivity as the equivalents of **Ir-7** increases, is due to the increased the rate of enone reduction. By effectively slowing the rate of racemisation (relative to the rate of reduction), there will be a greater build-up of the disfavoured enone enantiomer and, therefore, more reduction of this disfavoured enone leading to an overall reduction in e.r. Decreasing the concentration iridium hydride, theoretically should increase the enantioselectivity as the rate of reduction is reduced. However, if the rate of racemisation is suitably high the e.r. will plateau. This will be the highest possible e.r. that the catalyst is able to achieve and presumably we see this effect as we reduce the iridium hydride complex to 2 mol% (Entry 4, Table 4.13).

We were interested in how ligand [R_P,*S*]-PPF-NH_2 (**L37**) would perform in other asymmetric hydrogen borrowing reactions. As previously discussed, synthesis of β-branched ketones **15f** and **20a** using (*R*)-DTBM-SEGPHOS (**L1**) gave high yields and enantioselectivity (Scheme 4.29.A). Using [R_P,*S*]-PPF-NH_2 (**L37**) afforded both ketones **15f** and **20a** in good yields but surprisingly, very low enantioselectivity, was observed. Clearly the iridium-ligand complex is able to effectively reduce the enone intermediate, although with limited stereocontrol. Next, we evaluated [R_P,*S*]-PPF-NH_2 (**L37**) in the formation of y-substituted cyclopentanes (Scheme 4.29.B). Reaction with (*R*)-DTBM-SEGPHOS gave ketones **165a** and **165b** in 57 and 60% yield respectively,

and both in 62:38 e.r. Ferrocene ligand **L37** afforded **165a** and **165b** in 56 and 71% yield, respectively and the enantioselectivity was slightly improved. In the synthesis of γ-cyclopentanes both (*R*)-DTBM-SEGPHOS (**L1**) and [R_P,*S*]-PPF-NH_2 (**L37**) in poor enantioselectivity, it is possible that the change in ring size impacts the selectivity in coordination to the catalyst to cause a significant difference in e.r.



Scheme 4.29. Comparison of **L1** and **L37** in the enantioselective synthesis of β- and γ-branched ketones. Absolute and relative stereochemistry of **165a** and **165b** was not determined and the enantiomer depicted is arbitrary.

Overall, these experiments suggest that: (i) a single [R_P,*S*]-PPF-NH_2 binds in a bidentate manner through the nitrogen and phosphorous;[106,107] (ii) the NH_2 group is imperative for achieving high enantioselectivity; (iii) the binding site is highly sensitive and is not able to accommodate β-substituted enones. Taken in conjunction, we tentatively propose the following stereochemical model (Figure 4.8): coordination of the Ph* enone is such that the Ph* group is

directed away for the PPh_2 to prevent steric clashes (**I**/**II** *vs.* **II**/**IV**). *Re*-face coordination of the enone to the iridium is facilitated by hydrogen bonding of the carbonyl to the NH_2. Unfavourable steric interactions with the PPh_2 group are minimised by preferential coordination of the enone intermediate in which the γ-R group is directed away from the catalyst (**III** vs **IV**). We also note that enone substrates with β-substituents gave low levels of enantioselectivity. We propose that in this case the orientation held by the hydrogen bond is disrupted by the steric hinderance of a β-substituent. Without the hydrogen bond dictating the conformational approach of the enone, the enone is reduced to the desired ketone, albeit in low enantioselectivity.

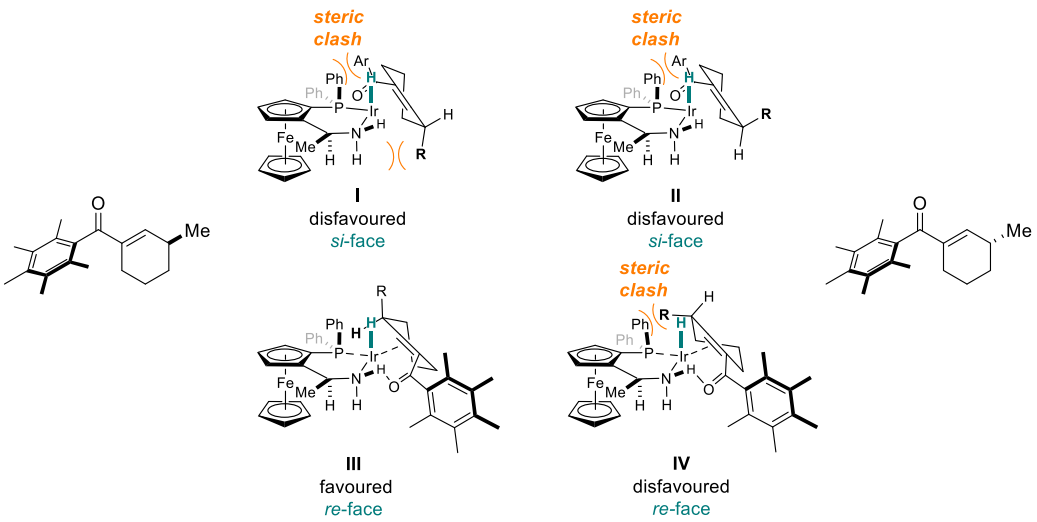
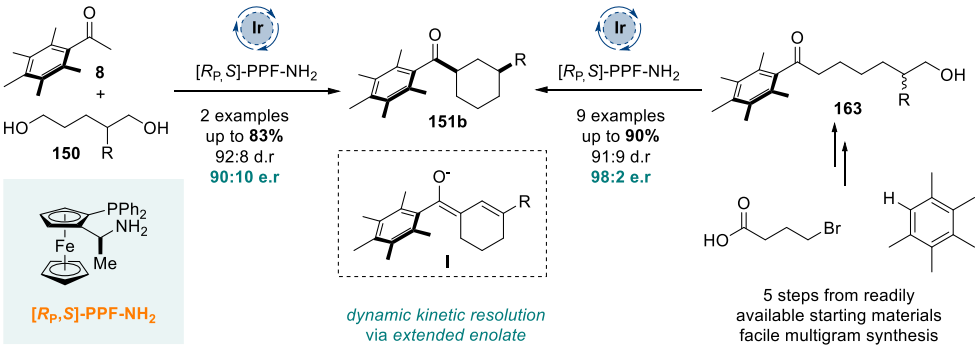


Figure 4.8. Proposed stereochemical model.

4.15. Conclusion

This chapter describes the development of an enantioselective hydrogen borrowing annulation to afford highly enantioenriched γ-substituted cyclohexanes *via* DKR (Scheme 4.30). Following extensive reaction optimisation, two strategies for accessing cyclohexanes were developed using commercially available [R_P,*S*]-PPF-NH_2 (**L37**) and Ir(cod)acac. Alkylation of Ph* methyl ketone with 1,5-diols in an intermolecular hydrogen borrowing annulation affords cyclohexane products in up to 83% yield and 90:10 e.r. Detailed mechanistic experiments were conducted to elucidate an undesired pathway in which the oxidised diol (hydroxyaldehyde) undergoes a

[1,5]-hydride shift to ultimately form a regioisomeric enone intermediate which is unproductive in the DKR, lowering the overall e.r. Alternatively, formation of the unproductive enone regioisomer can be prevented if the initial C–C bond is pre-formed. Using linear Ph* alcohol substrates in the intramolecular hydrogen borrowing annulation afforded a range of highly enantioenriched cyclohexanes in excellent yields (up to 90% yield and 98:2 e.r.). These starting materials can be accessed in 5 steps from readily available materials on multigram scale in a practically simple synthesis.



Scheme 4.30. Summary of the enantioselective hydrogen borrowing annulation controlling the γ-stereogenic centre via DKR.

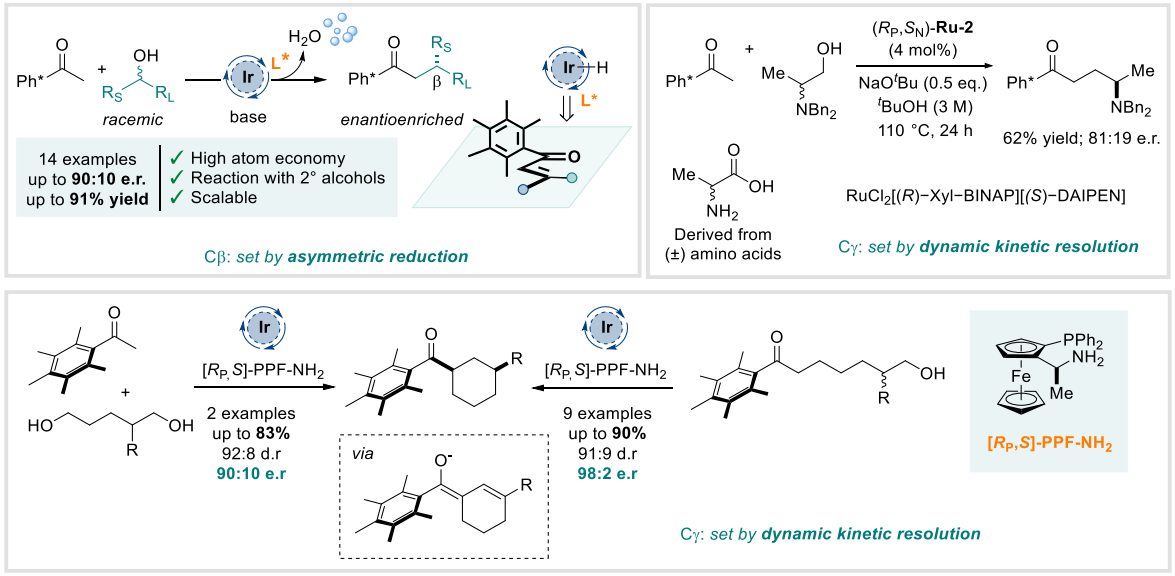
Chapter 5: Conclusion and Future Work

In this thesis, the successful development of asymmetric hydrogen borrowing transformations for carbon-carbon bonding forming processes have been described. This work contributes to the growing research area of enantioselective hydrogen borrowing strategies in which the enantiodetermining step is a direct reduction of an unsaturated intermediate.

To that effect, the enantioselective synthesis of β,β-branched Ph* ketones *via* hydrogen borrowing catalysis was developed (Scheme 5.1). The stereochemistry at the β-position was controlled in a key asymmetric reduction of an intermediate enone by a chiral iridium hydride complex. Using commercially available [Ir(cod)acac] and (*R*)-DTBM-SEGPHOS, this process is able to efficiently form sterically hindered $C(sp^3)$–$C(sp^3)$ bonds in good yields, including the use of neopentylic alcohols (or other quaternary centres). The β,β-disubstituted ketone products were further derivatised *via* Ph* cleavage to the corresponding amides, esters and acids showing no racemization of the newly installed stereogenic centre.

Subsequently, control of the γ-stereogenic centre was explored *via* hydrogen borrowing DKR. Previously in the group, an enantioretentive alkylation of Ph* methyl ketone with enantiopure 1,2-amino alcohols was developed. Access to enantioenriched γ-amino ketones from racemic 1,2-amino alcohols would be highly valuable, which led to the investigation of a complementary, enantioselective strategy relying on a dynamic kinetic resolution approach. A key benefit of this approach is that the alcohol starting materials are easily derived from racemic amino acids and the hydrogen borrowing products are readily cleaved to γ-amino butyric acids, therefore, providing a two-step enantioselective two-carbon homologation. $RuCl_2$(diphosphine)(diamine) type catalysts were found to be promising in this transformation afforded alanine-derived γ-amino ketone in up to 62% yield and 81:19 e.r. (Scheme 5.1). Future work should aim to improve the enantioselectivity of this process through further exploration of $RuCl_2$(diphosphine)(diamine) type catalysts.

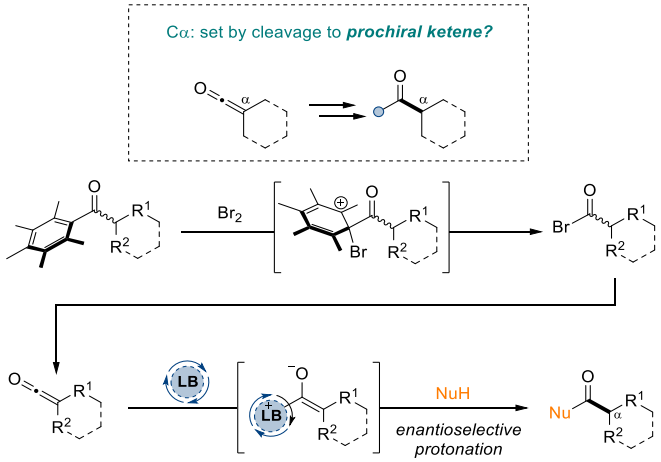
Secondly, the enantioselective synthesis of γ-branched cyclohexanes *via* a hydrogen borrowing DKR strategy was developed. By subjecting reaction intermediates to mechanistic studies concluded that alkylation of Ph* methyl ketone with 1,5-diols led to a regioisomeric mixture of enone intermediates, of which only one was productive in the DKR. Therefore, linear Ph* alcohol substrates were employed in an intramolecular hydrogen borrowing annulation, affording a range of γ-branched cyclohexanes in excellent yields and enantioselectivities (up to 90% yield and 98:2 e.r.). Employing the highly efficient catalytic system: Ir(cod)acac and [R_P,*S*]-PPF-NH_2, enabled direct access to the cyclohexane products from the corresponding 1,5-diols in good, albeit slightly reduced, enantioselectivity.



Scheme 5.1. Overview of the enantioselective strategies developed in this thesis.

The work in this thesis and previous work in the Donohoe group have has focused on the development of strategies controlling the β- and γ-stereogenic centres, whereas no processes have yet been developed to control the stereochemistry at the α-position in these systems. Due to the basic nature of hydrogen borrowing reactions, stereochemical information at the α-position is ablated *via* enolate formation. A potentially viable solution to this is controlling the stereochemistry at this position *via* derivatisation of the corresponding hydrogen borrowing product. It has been demonstrated that the Ph* group can be cleaved to the acid bromide by a

retro-Friedel-Crafts reaction with Br_2. Addition of a weak base to this intermediate would generate the corresponding ketene *in situ,* which could engage in enantioselective Lewis-base promoted cleavage reactions to form enantiopure esters and amides.



Scheme 5.2. α-Stereochemistry controlled by asymmetric Ph* release.

Chapter 6: Experimental Data and Procedures

6.1. General considerations

Materials: Diethyl ether, dichloromethane and tetrahydrofuran were purified by filtration through activated alumina columns employing the method of Grubbs et al.[111] All other solvents and reagents were used as supplied without prior purification. All other reagents were used directly as supplied by major chemical suppliers.

Conditions and Techniques: Room temperature (r.t.) refers to 20 – 25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of –17 °C were obtained using a salt/ice bath. Temperatures of –78 °C were obtained using a dry ice/acetone bath. Heating was achieved using an oil bath equipped with a contact thermometer. Thin layer chromatography was performed on Merck Kieselgel 60 F254 0.25 mm pre-coated aluminium plates. Product spots were visualized under UV light (λ = 254 nm) and/or by staining with potassium permanganate solution. Flash chromatography was performed using VWR silica gel 60 (40 – 63 or 15 – 40 µm particle size).

Analytical Techniques: NMR spectroscopy was carried out using a Bruker 400, 500 or 600 MHz spectrometer in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sext), septet (sept), octet (oct), nonet (non) and multiplet (m). The abbreviation br denotes broad. Coupling constants, J, are measured to the nearest 0.1 Hz and are presented as observed. Where necessary or appropriate, two-dimensional (COSY, HSQC, HMBC, H2BC or NOESY) NMR experiments were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra. Acidic protons, such as alcohols, are not reported, if not observed.

Infrared spectra were recorded neat on a Bruker Tensor 27 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (λmax) are quoted in wavenumbers (cm^{-1}). The abbreviation br denotes broad.

Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe for ESI+ and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most abundant isotopes, with each value rounded to 4 decimal places and within 5 ppm of the calculated mass. Electron impact ionisation (EI) HRMS were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass.

Optical rotations were recorded on a Schmidt Haensch Unipol L2000 polarimeter in a cell with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C. Chiral normal phase HPLC was performed on an Agilent 1260 Series HPLC unit equipped with UV-vis diodearray detector, fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm ø × 25 cm) along with the corresponding guard column (0.4 cm ø × 1 cm). Wavelengths (λ) are reported in nm, retention times (t_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}. Reverse phase HPLC was performed on a Dionex UltiMate 3000 system equipped with UV-vis variable wavelength detector, fitted with an Agilent InfinityLab Poroshell 120 EC-C18 column (0.46 cm ø × 150 mm, 4 μm pore size). Compounds that were purified by preparative liquid chromatography (Preparative HPLC) were

dissolved in the minimum amount of MeCN with some samples containing IPA, DMSO, or DMF to aid solubility. The solution was then filtered through a Fisherbrand PTFE syringe filter (30mm, 0.2µM) into an Agilent 5 mL vial with a pre-slit cap. Then the samples were purified using an Agilent 1260 Infinity II Semi Prep system with an Agilent prep C18 column [5µM, 50 × 21.2 mm], the flow rate was kept constant at 25 mL min-1 and the column was at room temperature. The mobile phases used unless otherwise stated were deionised water (mobile phase A) and HPLC grade MeCN (mobile phase B). After purification the fractions were collected and lyophilised. The injection volume was varied between purifications ranging from 50-1000 µL depending upon the level of resolution of the chromatograms.

6.2. Data for Chapter 2

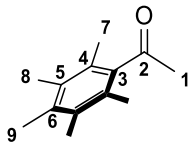
6.2.1 Experimental Procedures and Characterisation

General Procedure 2-A: Catalytic Asymmetric Hydrogen Borrowing of Acyclic Secondary Alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate alcohol (0.60 mmol, 2.0 equiv.), the appropriate ketone (0.30 mmol, 1.0 equiv.), (*R*)-DTBM-SEGPHOS (5.0 mol%), Ir(cod)acac (4.0 mol%), ^{t}BuOH (0.1 mL, 3M) and NaO^{t}Bu (1.2 mmol, 4.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and heated to 110 °C in a preheated oil bath for 24 h. The mixture was cooled, diluted with Et_2O (4 mL), quenched with 3M HCl (2 mL) and extracted with Et_2O (3 × 4 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. For ease of purification from residual (*R*)-DTBM-SEGPHOS, a solution of the crude product in Et_2O (~40 mL) was treated with *tert*-butyl hydroperoxide (5 – 6 M in decane, 50 µL, ~0.28 mmol), swirled and allowed to stand at r.t. for 10 min. The resulting solution was then concentrated and purified by column chromatography (see experimental methods section

for details). Racemic cyclohexane products were obtained using our previously reported procedure.[25]

1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one (pentamethylacetophenone), 8



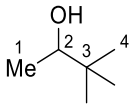
A solution of pentamethylbenzene (10.0 g, 67.4 mmol, 1.00 equiv.) and acetyl chloride (5.27 mL, 74.2 mmol, 1.10 equiv.) in CH_2Cl_2 (400 mL) was cooled to 0 °C. Aluminium chloride (11.2 g, 84.3 mmol, 1.25 equiv.) was added portionwise over 10 min. The resulting mixture was warmed to r.t. and stirred for 4 h and then poured onto crushed ice (ca. 500 g). After the ice had melted, the layers were separated and the aqueous layer was extracted CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5) afforded the title compound **8** as a white solid (11.5 g, 89%). The spectral data matched that previously reported in the literature.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.46 (3H, s, C1-H_3), 2.24 (3H, s, C9-H_3), 2.19 (6H, s, 2 × C8-H_3), 2.14 (6H, s, 2 × C7-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 210.2 (C2), 141.1 (C3), 135.5 (C6), 133.2 (2 × C5), 127.2 (2 × C4), 33.3 (C1), 17.2 (2 × C7), 16.8 (C9), 16.1 (2 × C8).

6.2.1.1 Synthesis of alcohols

3,3-Dimethyl-2-butanol, 14f

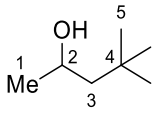


To a stirred solution of $LiAlH_4$ (4.16 g, 110 mmol, 1.10 equiv.) in Et_2O (500 mL) at 0 °C was added a solution of pinacolone (12.5 mL, 99.8 mmol, 1.00 equiv.) in Et_2O (100 mL) slowly. The reaction was warmed to r.t. and stirred for 1 h. After this time, the reaction was quenched by dropwise addition of H_2O (4.2 mL), aq. NaOH (15% w/v, 4.2 mL) and H_2O (12.6 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by atmospheric pressure distillation (b.p. 120 °C) afforded the title compound **14f** as a transparent oil (8.85 mg, 87%). The spectral data matched that previously reported in the literature.[112]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.46 (1H, q, *J*=6.4 Hz, C2-H), 1.43 (1H, s, O*H*), 1.11 (3H, d, *J*=6.4 Hz, C1-H_3), 0.88 (9H, s, 3 × C4-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.8 (C2), 35.0 (C3), 25.5 (3 × C4), 18.0 (C1).

4,4-Dimethylpentan-2-ol, 14g



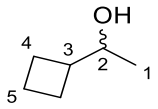
A solution of commercially available 3,3-dimethylbutanal (1.26 mL, 10.0 mmol, 1.00 equiv.) in Et_2O (30 mL) was cooled to –78 °C and MeMgBr (3 M in Et_2O, 6.7 mL, 20 mmol, 2.0 equiv.) was added dropwise. The resulting reaction mixture was stirred at –15 °C for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **14g**

as a transparent oil (550 mg, 48%). The spectral data matched that previously reported in the literature.[113]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.94 (1H, dqd, *J*=7.7, 6.2, 3.4 Hz, C2-H), 1.46 (1H, br s, O<u>H</u>), 1.39 (1H, dd, *J*=14.4, 7.7 Hz, C3-H_AH_B), 1.31 (1H, dd, *J*=14.4, 3.4 Hz, C3-H_AH_B), 1.17 (3H, d, *J*=6.2 Hz, C1-H_3), 0.93 (9H, s, 3 × C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 66.0 (C2), 53.2 (C3), 30.3 (C4), 30.2 (3 × C5), 26.1 (C1).

1-Cyclobutylethan-1-ol, 15j

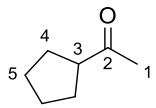


A solution of commercially available cyclobutanecarbaldehyde (841 mg, 10.0 mmol, 1.00 equiv.) in Et_2O (30 mL) was cooled to –78 °C and MeMgBr (6.70 mL, 3 M in Et_2O, 20.0 mmol, 2.00 equiv.) was added dropwise. The resulting reaction mixture was stirred at –15 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **15j** as a transparent oil (537 mg, 54%). The spectral data matched that previously reported in the literature.[114]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (1H, dq, *J*=7.7, 6.2 Hz, C2-H), 2.33 – 2.18 (1H, m, C3-H), 2.09 – 1.62 (6H, m, 2 × C4-H_2, C5-H_2), 1.50 (1H, br s, O<u>H</u>), 1.06 (3H, d, *J*=6.2 Hz, C1-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 72.2 (C2), 43.0 (C3), 24.4 (C4), 24.3 (C4'), 20.3 (C1), 17.8 (C5).

1-Cyclopentylethan-1-one, S1

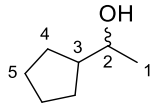


According to a modified literature procedure[115]: MeLi (1.6 M in Et_2O, 13.8 mL, 22 mmol, 2.2 equiv.) was added dropwise to a solution of cyclopentanecarboxylic acid (1.14 g, 10.0 mmol, 1.00 equiv.) in Et_2O (45 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was warmed up to r.t. and stirred for 2.5 h. The reaction was quenched by pouring the mixture onto a solution of conc. HCl (5 mL) and crushed ice (ca. 100 g) and then extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **S1** as a colourless oil (930 mg, 83%). The spectral data matched that previously reported in the literature.[116]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.92 – 2.77 (1H, m, C3-H), 2.15 (3H, s, C1-H_3), 1.90 – 1.69 (4H, m, 2 × C4-H_2), 1.69 – 1.51 (4H, m, 2 × C5-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.3 (C=O), 52.4 (C3), 28.9 (2 × C4), 28.9 (C1), 26.1 (2 × C5).

1-Cyclopentylethan-1-ol, 15k



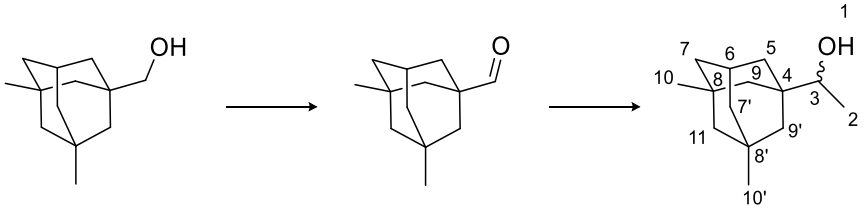
To a stirred solution of $LiAlH_4$ (266 mg, 7.00 mmol, 1.09 equiv.) in Et_2O (40 mL) at 0 °C, was added a solution of 1-cyclopentylethan-1-one **S1** (713 mg, 6.40 mmol, 1.00 equiv.) in Et_2O (10 mL) slowly. The reaction was slowly warmed to r.t. over 3 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.3 mL), aq. NaOH (15% w/v, 0.3 mL) and H_2O (0.9 mL) at 0 °C. The reaction mixture was diluted with Et_2O (10 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **15k** as a

transparent oil (327 mg, 45%). The spectral data matched that previously reported in the literature.[117]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 – 3.50 (1H, m, C2-H), 1.91 – 1.75 (2H, m, C3-H, C4-H_AH_B), 1.74 – 1.46 (5H, m, C4'-H_AH_B, 2 × C5-H_2), 1.46 – 1.27 (2H, m, C4-H_AH_B, O<u>H</u>), 1.20 – 1.13 (4H, m, C1-H_3, C4'-H_AH_B).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 72.5 (C2), 48.2 (C3), 29.3 (C4), 29.0 (C4'), 25.9 (C5), 25.8 (C5'), 22.4 (C1).

1-((1r,3*R*,5*S*,7r)-3,5-dimethyladamantan-1-yl)Ethan-1-ol, 14o



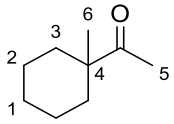
According to a literature procedure[115]: A solution of oxalyl chloride (1.06 mL, 12.5 mmol, 2.43 equiv.) in CH_2Cl_2 (20 mL) was cooled to –78 °C. DMSO (0.888 mL, 12.5 mmol, 2.5 equiv.) in CH_2Cl_2 (0.10 mL) was added dropwise and the reaction mixture was stirred for 5 min. Commercially available 3,5-dimehtyladamantane-1-methanol (1.00 g, 5.15 mmol, 1.00 equiv.) was added dropwise and stirred for 5 min, followed by addition of Et_3N (3.47 mL, 25.0 mmol, 4.85 equiv.). The reaction mixture was stirred for 15 min, warmed to r.t., diluted with CH_2Cl_2 (10 mL) and quenched with 0.5 M HCl (40 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford (1r,3*R*,5*S*,7r)-3,5-dimethyladamantane-1-carbaldehyde, which was immediately used in the next step without further purification. A solution of (1r,3*R*,5*S*,7r)-3,5-dimethyladamantane-1-carbaldehyde (0.990 g, 5.15 mmol, 1.00 equiv.) in Et_2O (15 mL) was cooled to –78 °C and MeMgBr (3.3 mL, 3 M in Et_2O, 2.0 equiv.) was added dropwise. The resulting reaction mixture was stirred at –15 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in*

vacuo. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **14o** as a transparent oil (0.620 g, 60% over two steps). The spectral data matched that previously reported in the literature.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.31 (1H, q, *J*=7.0 Hz, C3-H), 2.08 (1H, sept, *J*=3.2 Hz, C6-H), 1.47 – 1.03 (15H, m, C2-H_3, C5-H_2, 2 × C7-H_2, 2 × C9-H_2, C11-H_2), 0.81 (6H, s, 2 × C10-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.6 (C3), 51.5 (C11), 44.4 (C9), 44.3 (C9'), 43.7 (2 × C7), 38.8 (C4), 36.5 (C5), 31.2 (2 × C8), 30.9 (2 × C10), 29.6 (C6), 16.9 (C2).

1-(1-methylcyclohexyl)Ethan-1-one, S2

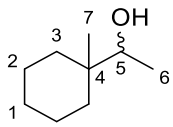


According to a literature procedure[115]: MeLi (9.0 mL, 1.6 M in Et_2O, 2.2 equiv.) was added dropwise to a solution of commercially available 1-methylcyclohexane-1-carboxylic acid (924 mg, 6.50 mmol, 1.00 equiv.) in Et_2O (30 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was warmed up to r.t. and stirred for 5 h. The reaction was quenched by pouring the mixture onto a solution of conc. HCl (3.2 mL) and crushed ice (ca. 50 g) and then extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5) afforded the title compound **S2** as a pale yellow oil (640 mg, 70%). The spectral data matched that previously reported in the literature.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.12 (3H, s, C5-H_3), 1.92 (2H, m, 2 × C3-H_{eq}), 1.20 – 1.57 (8H, m, C1-H_2, 2 × C2-H_2, 2 × C3-H_{ax}), 1.07 (3H, s, C6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 214.4 (C=O), 48.5 (C4), 34.9 (2 × C3), 26.0 (C1), 25.0 (br, C5,6), 23.1 (2 × C2).

1-(1-methylcyclohexyl)Ethan-1-ol, 14p

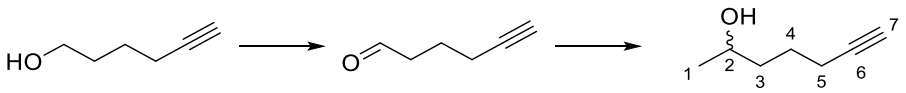


A solution of 1-(1-methylcyclohexyl)ethan-1-one **S2** (640 mg, 4.56 mmol, 1.00 equiv.) in Et_2O (10 mL) was slowly added to a stirred solution of $LiAlH_4$ (190 mg, 5.02 mmol, 1.10 equiv.) in Et_2O (30 mL) at 0 °C. The reaction mixture was slowly warmed to r.t. over 2 h. After this time, the reaction was quenched by sequential dropwise addition of water (0.19 mL), aq. NaOH (15% w/v, 0.19 mL) and water (0.57 mL). The reaction mixture was diluted with Et_2O (10 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **14p** as a pale yellow oil (499 mg, 76%). The spectral data matched that previously reported in the literature.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.51 (1H, q, *J*=6.4 Hz, C5-H), 1.63 – 1.12 (10H, m, C1-H_2, 2 × C2-H_2, 2 × C3-H_2), 1.10 (3H, d, *J*=6.5 Hz, C6-H_3), 0.84 (3H, s, C7-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.6 (C5), 37.3 (C4), 34.4 (C3), 33.8 (C3'), 26.5 (C1), 21.9 (C2), 21.9 (C2'), 17.7 (C7), 17.1 (C6).

Hept-6-yn-2-ol, 14r

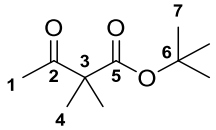


A solution of oxalyl chloride (1.1 mL, 13 mmol, 2.5 equiv.) in DCM (20 mL) was cooled to –78 °C. DMSO (0.92 mL, 13 mmol, 2.5 equiv.) in DCM (0.10 mL) was added dropwise and the reaction mixture was stirred for 5 min. 5-Hexyn-1-ol (0.57 mL, 5.2 mmol, 1.0 equiv.) was added dropwise and stirred for 5 min, followed by addition of Et_3N (3.6 mL, 26 mmol, 5.0 equiv.). The reaction mixture was stirred for 15 min, warmed to r.t., diluted with DCM (10 mL) and quenched with 0.5 M HCl (40 mL). The resulting mixture was extracted with DCM (2 × 30 mL) and the combined organic extracts were washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to afford hex-5-ynal, which was immediately used in the next step without further purification. A solution of hex-5-ynal (assumed quant., 5.2 mmol, 1.0 equiv.) in Et_2O (15 mL) was cooled to –78 °C and MeMgBr (3 M in Et_2O, 3.5 mL, 10 mmol, 2.0 equiv.) was added dropwise. The resulting reaction mixture was stirred at –15 °C for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **14r** (0.30 g, 52% over two steps) as a pale yellow oil. The spectral data matched that previously reported in the literature.[118]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.87 – 3.77 (1H, m, *J*= 6.0, C2-H), 2.22 (2H, td, *J*=6.8, 2.2 Hz, C5-H_2), 1.95 (1H, t, *J*=2.7 Hz, C7-H), 1.76 (1H, br s, O<u>H</u>), 1.46 – 1.72 (4H, m, C3-H_2, C4-H_2), 1.19 (3H, d, *J*=6.2 Hz, C1-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 84.5 (C5), 68.7 (C6), 67.8 (C1), 38.4 (C2), 24.8 (C3), 23.8 (C7), 18.5 (C4).

tert-Butyl 2,2-dimethyl-3-oxobutanoate, S3



According to a modified literature procedure[119]: K_2CO_3 (13.8 g, 100 mmol, 2.50 equiv.) was added to a solution of *tert*-butyl 3-oxobutanoate (6.70 mL, 40.0 mmol, 1.00 equiv.) in DMF (100 mL) at r.t. Methyl iodide (7.50 mL, 120 mmol, 3.00 equiv.) and $(n\text{Bu})_4\text{NI}$ (1.48 g, 4.00 mmol, 0.100 equiv.) were added to the mixture and heated to reflux for 20 h. The reaction mixture was cooled, quenched with water and extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with brine, dried (MgSO4), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 100:0 to 96:4) afforded the title compound **S3** as a transparent oil (2.60 g, 45%).

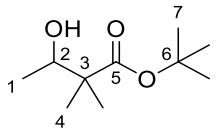
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.14 (3H, s, C1-H_3), 1.43 (9H, s, 3 × C7-H_3), 1.29 (6H, s, 2 × C4-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 206.3 (C2), 172.9 (C5), 81.7 (C6), 56.6 (2 × C4), 27.9 (3 × C7), 25.8 (C1), 21.9 (C4).

HRMS (ESI^+) m/z calcd. for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ 209.1154; found at 209.1150, Δ 0.76 ppm.

FTIR (neat) ν_{max}/cm^{-1} = 2981, 1711, 1460, 1387, 1369, 1274, 1148, 1116, 967, 874, 846, 736.

tert-Butyl 3-hydroxy-2,2-dimethylbutanoate, 14s



A solution of *tert*-butyl 2,2-dimethyl-3-oxobutanoate **S3** (1.86 g, 10.0 mmol, 1.00 equiv.) in MeOH (25 mL) was cooled to 0 °C and $NaBH_4$ (0.57 g, 10 mmol, 1.5 equiv.) was added portion wise. The reaction was slowly warmed to r.t. over 2 h. After this time, the reaction was quenched with saturated sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column

chromatography (Pentane:Et_2O, 80:20) afforded the title compound **14s** (1.35 g, 72%) as a transparent oil.

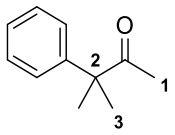
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.75 (1H, p, *J*=6.4 Hz, C2-H), 2.85 (1H, d, *J*=6.3 Hz, O*H*), 1.41 (9H, s, 3 × C7-H_3), 1.12 – 1.05 (9H, m, C1-H_3, 2 × C4-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.2 (C=O), 80.9 (C6), 72.6 (C2), 47.5 (C3), 28.1 (3 × C7), 22.3 (2 × C4), 20.2 (C4'), 17.9 (C1).

HRMS (ESI^+) m/z calcd. for $C_{10}H_{20}O_3Na$ $[M+Na]^+$ 211.1310; found at 211.1306, Δ 0.56 ppm.

FTIR (neat) ν/cm^{-1} = 3436, 2977, 1713, 1459, 1392, 1368, 1278, 1256, 1138, 1098, 1036, 909, 849.

3-Methyl-3-phenylbutan-2-one, S4

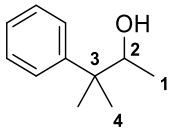


According to a modified literature procedure[115]: Methyl lithium (1.6 M in Et_2O, 13.8 mL, 22 mmol, 2.2 equiv.) was added dropwise to a solution of 2-methyl-2-phenylpropanoic acid (1.64 g, 10.0 mmol, 1.00 equiv.) in Et_2O (30 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was warmed up to r.t. and stirred for 1 h. The reaction was quenched by pouring the mixture onto a solution of conc. HCL (5 mL) and crushed ice (~ 50 g) and then extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried (MgSO4), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **S4** as a transparent oil (1.38 g, 85%). The spectral data matched that previously reported in the literature.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.31 (2H, m, 2 × Ar-H), 7.30 – 7.22 (3H, m, 3 × Ar-H), 1.91 (3H, s, C1-H_3), 1.49 (6H, s, 2 × C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 210.8 (C=O), 144.1 (Ar), 128.7 (2 × Ar), 126.8 (Ar), 125.9 (2 × Ar), 52.4 (C2), 25.4 (C1), 25.1 (2 × C3).

3-Methyl-3-phenylbutan-2-ol, 14u

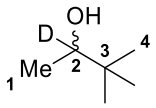


To a stirred solution $LiAlH_4$ (355 mg, 9.40 mmol, 1.10 equiv.) of in Et_2O (50 mL) at 0 °C was added slowly a solution of 3-methyl-3-phenylbutan-2-one **S4** (1.38 g, 8.50 mmol, 1.00 equiv.) in Et_2O (20 mL). The reaction was warmed to r.t. over 3 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (1.4 mL), aq. NaOH (15% w/v, 1.4 mL) and H_2O (4.2 mL) at 0 °C. The reaction mixture was diluted with Et_2O (10 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **14u** as a transparent oil (1.04 g, 75%). The spectral data matched that previously reported in the literature.[115]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.38 (2H, m, 2 × Ar-H), 7.38 – 7.31 (2H, m, 2 × Ar-H), 7.25 – 7.20 (1H, m, Ar-H), 3.87 (1H, qd, *J*=6.4, 2.5 Hz, C2-H), 1.43 (1H, d, *J*=2.5 Hz, O*H*), 1.35 (3H, s, C4-H_3), 1.33 (3H, s, C4'-H_3) 1.07 (3H, d, *J*=6.4 Hz, C1-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 147.1 (Ar), 128.3 (2 × Ar), 126.7 (2 × Ar), 126.2 (Ar), 75.5 (C2), 42.7 (C3), 24.5 (C4), 23.0 (C4'), 17.7 (C1).

3,3-Dimethylbutan-2-*d*-2-ol, 106



A solution of $NaBD_4$ (720 mg, 17.2 mmol, 0.430 equiv.) in MeOH (15 mL) was cooled to 0 °C and pinacolene (5.00 mL, 40.0 mmol, 1.00 equiv.) was added dropwise. The reaction was stirred at 0 °C for 15 min and subsequently warmed to r.t. and stirred for 3 h. A further portion of $NaBD_4$ (720 mg, 17.2 mmol, 0.430 equiv.) was added portionwise at 0 °C and then the reaction mixture was refluxed for 16 h. The mixture was cooled, the reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* Distillation at atmospheric pressure afforded the title

compound **106** (115 mg, 3%) as a transparent oil. (b.p 121-123 °C) The ^{1}H NMR spectrum of **106** was recorded with an extended relaxation delay (25 s) which was used to determine deuterium incorporation at 92%.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.03 (1H, s, O<u>H</u>), 1.10 – 1.06 (3H, m, C1-H_3), 0.86 (9H, s, 3 × C4-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.3 (1:1:1 t, $^{1}J_{CD}$=21.6 Hz, C2), 34.8 (C3), 25.4 (3 × C4), 17.7 (C1).

^{2}H NMR (77 MHz, $CDCl_3$) δ_C 3.45 (q, *J*=1.0 Hz).

FTIR (neat) ν_{max}/cm^{-1} = 3658, 2998, 2886, 1474, 1460, 1395, 1381, 1252, 1152, 1072, 954, 816.

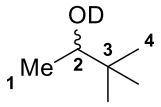
For reference NMR data of the protonated compound:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.43 (1H, q, *J*=6.4 Hz), 1.62 (1H, s, O<u>H</u>), 1.08 (3H, d, *J*=6.3 Hz, C1-H_3), 0.86 (9H, s, 3 × C4-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.7 (C2), 35.0 (C3), 25.5 (3 × C4), 18.0 (C1).

N.B. the absence of the peak at 3.43 ppm in the deuterated compound.

3,3-Dimethylbutan-2-ol-*d*, 108



A solution of 3,3-dimethylbutan-2-ol (0.640 mL, 51.0 mmol, 1.00 equiv.) in D_2O (20 mL, 1.1 mol, 22 equiv.) was stirred at r.t. for 5 h. After this time, the mixture was diluted with D_2O saturated Et_2O (5 mL) and, then extracted with D_2O saturated Et_2O (3 × 10 mL). Concentration of the combined organic extracts afforded the title compound **108** as a colourless oil (330 mg, 6.3%). The ^{1}H NMR spectrum of **108** was recorded with an extended relaxation delay (25 s) which was used to determine deuterium incorporation at >98%.

^{1}H NMR (400 MHz, C_6D_6) δ_H 3.21 (1H, q, *J*=6.5 Hz, C2-H), 0.92 (3H, d, *J*=6.5 Hz, C1-H_3), 0.82 (9H, s, 3 × C4-H_3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 75.1 (C2), 35.0 (C3), 25.6 (3 × C4), 18.2 (C1).

^{2}H NMR (77 MHz, C_6D_6) δ_H 0.88 (s, O*D*).

FTIR (neat) ν/cm^{-1} = 3324, 2936, 2855, 1447, 1338, 1364, 1200, 1081, 1049, 1007, 912.

For reference NMR data of the protonated compound:

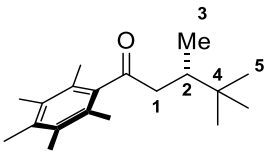
^{1}H NMR (400 MHz, C_6D_6) δ_H 3.42 (1H, qd, *J*=6.4, 4.9 Hz, C2), 2.33 (1H, d, *J*=4.9 Hz, O<u>H</u>), 1.10 (3H, d, *J*=6.4 Hz, C1-H_3), 0.95 (9H, s, 3 × C4-H_3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 75.3 (C2), 35.1 (C3), 25.7 (3 × C4), 18.2 (C1).

N.B. the absence of the peak at 2.33 ppm in the deuterated compound.

6.2.1.2 Enantioselective hydrogen borrowing alkylation with secondary alcohols

(*S*)-3,4,4-Trimethyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 15f



0.3 mmol scale reaction: Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 3,3-dimethyl-2-butanol **14f** (76 µL, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General procedure 2-A**. Purification by column chromatography (Penane:Et_2O, 98:2) afforded the title compound **14f** as a white solid (75 mg, 91%, 90:10 e.r.).

Gram scale hydrogen borrowing: To a 100 mL ACE pressure tube equipped with a stirrer bar was added 3,3-dimethyl-2-butanol **14f** (1.25 mL, 10.0 mmol, 2.0 equiv.), pentamethylacetophenone **8** (952 mg, 5.00 mmol, 1.0 equiv.), (*R*)-DTBM-SEGPHOS (295 mg, 5 mol%), Ir(cod)acac (80.0 mg, 4 mol%), ^{t}BuOH (1.70 mL, 3 M) and NaO^{t}Bu (1.92 g, 20.0 mmol, 4.0 equiv.) sequentially in an air atmosphere. The reaction vessel was sealed and stirred at 110 °C in a preheated oil bath for 24 h. The mixture was cooled to r.t., diluted with Et_2O (20 mL), quenched with 3 M HCl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. For ease of purification, residual (*R*)-DTBM-SEGPHOS was removed by treatment of the crude product in Et_2O (~80 mL) with *tert*-butyl hydroperoxide (5 – 6 M in decane, 0.50 mL, ~2.8 mmol), swirled and allowed to stand at r.t. for 10 min. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15f** as a white solid (1.17 g, 85%, 92:8 e.r.). Recrystallization from boiling methanol afforded the title compound **15f** as white needles (834 mg, 71% recovery, 97:3 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.85 (1H, dd, *J*=19.2, 0.7 Hz, C1-H_AH_B), 2.40 (1H, dd, *J*=19.2, 10.4 Hz, C1-H_AH_B), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (7H, m, 2 × Ar-CH_3, C2-H), 1.02 (3H, dd, *J*=6.7, 0.7 Hz, C3-H_3), 0.87 (9H, s, 3 × C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.7 (C=O), 141.1 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 48.9 (C1), 37.2 (C2), 32.6 (C4), 27.3 (3 × C5), 17.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 15.7 (C3).

HRMS (ESI^+) m/z calcd. for $C_{19}H_{31}O$ $[M+H]^+$ 275.2375; found at 275.2370, Δ 0.1 ppm.

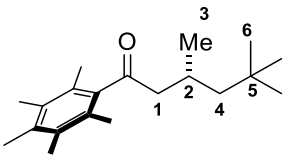
FTIR (neat) ν/cm^{-1} = 2959, 1703, 1467, 1404, 1365, 1308, 1119, 1054, 989, 912, 803, 676.

m.p. = 93 – 95 °C.

[α]$_D^{25}$ –29.1 (c = 0.43, $CHCl_3$).

Chiral HPLC: Chiralpak OD with guard, 0.3% IPA, 99.7% hexane, 0.5 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 14.5 min, τ_R (minor) = 13.8 min.

(*R*)-3,5,5-Trimethyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one, 15g



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 4,4-dimethylpentan-2-ol **14g** (70 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15g** as a white solid (60 mg, 69%, 63:37 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.73 (1H, dd, *J*=19.2, 3.9 Hz, C1-H_AH_B), 2.57 (1H, dd, *J*=19.2, 8.7 Hz, C1-H_AH_B), 2.42 – 2.27 (1H, m, C2-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 1.28 (1H, dd, *J*=14.0, 5.1 Hz, C4-H_AH_B), 1.16 (1H, dd, *J*=14.0, 5.6 Hz, C4-H_AH_B), 1.10 (3H, d, *J*=6.6 Hz, C3-H_3), 0.95 (9H, s, 3 × C6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.2 (C=O), 140.9 (Ar), 135.3 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 55.4 (C1), 51.2 (C4), 31.4 (C5), 30.1 (3 × C6), 24.6 (C2), 23.1 (C3), 17.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.0 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{20}H_{33}O$ $[M+H]^+$ 289.2531; found at 289.2526, Δ 0.11 ppm.

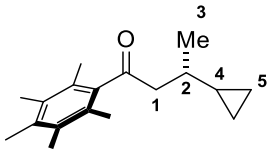
FTIR (neat) ν/cm^{-1} = 3658, 2980, 2956, 1702, 1464, 1381, 1251, 1150, 1113, 1072, 943.

m.p. = 85 – 86 °C.

[α]$_D^{25}$ –6.2 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IA with guard, 0.3% IPA, 99.7% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 12.8 min, τ_R (minor) = 14.7 min.

(*S*)-3-Cyclopropyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 15i



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), commercially available 1-cyclopropylethanol (59 µl, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15i** as a white solid (57 mg, 73%, 72:28 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.88 (1H, dd, *J*=19.0, 4.2 Hz, C1-*H*$_A$H$_B$), 2.64 (1H, dd, *J*=19.0, 8.3 Hz, C1-H$_A$*H*$_B$), 2.23 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 1.53 – 1.42 (1H, m, C2-H), 1.13 (3H, d, *J*=6.7 Hz, C3-H_3), 0.64 (1H, dtt, *J*=9.6, 8.0, 5.0 Hz, C4-H), 0.51 – 0.31 (2H, m, 2 × C5-*H*$_A$H$_B$), 0.24 – 0.10 (2H, m, 2 × C5-H$_A$*H*$_B$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.2 (C=O), 141.0 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 53.1 (C1), 33.5 (C2), 20.1 (C3), 18.3 (C4), 17.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 4.3 (C5), 4.1 (C5').

HRMS (ESI$^+$) m/z calcd. for $C_{18}H_{27}O$ $[M+H]^+$ 259.2062; found at 259.2058, Δ 0.41 ppm.

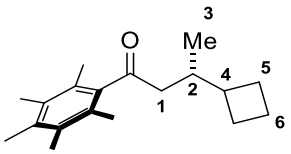
FTIR (neat) ν/cm^{-1} = 2927, 1701, 1457, 1401, 1351, 1313, 1129, 1016, 821.

m.p. = 43 – 44 °C.

[α]$_D^{25}$ –13.6 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 0.9% IPA, 99.1% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 17.3 min, τ_R (minor) = 20.0 min.

(*S*)-3-Cyclobutyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 15j



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 1-cyclobutylethan-1-ol **14j** (60 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15j** as a white solid (65 mg, 80%, 78:22 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.65 (1H, dd, *J*=18.8, 2.2 Hz, C1-H_AH_B), 2.40 – 2.29 (1H, m, C1-H_AH_B), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.15 – 1.89 (10H, m, 2 × Ar-CH_3, C2-H, C4-H, 2 × C5-H_AH_B) 1.89 – 1.55 (4H, m, C6-H_2, 2 × C5-H_AH_B), 0.97 (3H, d, *J*=6.1 Hz, C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.6 (C=O), 141.1 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 49.9 (C1), 41.9 (C4), 34.7 (C2), 26.8 (C5), 26.7 (C5'), 17.4 (C6), 17.2 (C3), 17.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{19}H_{29}O$ $[M+H]^+$ 273.2218; found at 273.2213, Δ 0.03 ppm.

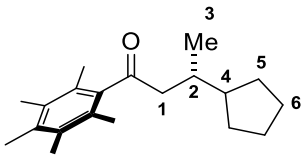
FTIR (neat) ν/cm^{-1} = 3657, 2980, 2923, 1703, 1462, 1380, 1252, 1153, 1072, 955.

m.p. = 69 – 70 °C.

[α]$_D^{25}$ –20.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 0.9% IPA, 99.1% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 14.9 min, τ_R (minor) = 21.6 min.

(*S*)-3-Cyclopentyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 15k



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 1-cyclopentylethan-1-ol **14k** (60 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15k** as a white solid (59 mg, 69%, 84:16 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.80 (1H, dd, *J*=19.0, 2.8 Hz, C1-H_AH_B), 2.51 (1H, dd, *J*=19.0, 9.5 Hz, C1-H_AH_B), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.15 – 2.04 (7H, m, 2 × Ar-CH_3, C2-H), 1.84 – 1.45 (7H, m, C4-H, 2 × C5-H_AH_B, 2 × C6-H_2), 1.30 – 1.10 (2H, m, 2 × C5-H_AH_B), 1.07 (3H, d, *J*=6.6 Hz, C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.5 (C=O), 141.1 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.9 (C1), 45.9 (C4), 33.0 (C2), 30.7 (C5), 30.2 (C5'), 25.8 (C6), 25.6 (C6'), 18.9 (C3), 17.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{20}H_{31}O$ $[M+H]^+$ 287.2369; found at 287.2370, Δ 0.12 ppm.

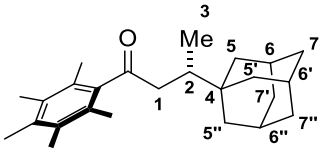
FTIR (neat) v/cm^{-1} = 2949, 2868, 1701, 1451, 1401, 1307, 1099, 934.

m.p. = 60 – 61 °C.

[α]$_D^{25}$ –21.1 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 0.9% IPA, 99.1% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 16.5 min, τ_R (minor) = 22.1 min.

(*S*)-3-(adamantan-1-yl)-1-(2,3,4,5,6-pentamethylphenyl)Butan-1-one, 15n



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 1-(adamantan-1-yl)ethan-1-ol[a] (108 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General procedure 2-A.** Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15n** as a white solid (85 mg, 81%, 85:15 e.r.). [a] Synthesised by Dr Roly Armstrong.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.90 (1H, dd, *J*=19.3, 1.4 Hz, C1-$H_A$$H_B$), 2.35 (1H, dd, *J*=19.3, 10.4 Hz, C1-$H_A$$H_B$), 2.24 (3H, s, Ar-$CH_3$), 2.19 (6H, s, 2 × Ar-$CH_3$), 2.11 (6H, s, 2 × Ar-$CH_3$), 1.96 (3H, m, 3 × C6-H), 1.87 (1H, dqd, *J*=10.4, 6.7, 1.4 Hz, C2-H), 1.79 – 1.41 (12H, m, 3 × C5-H_2, 3 × C7-H_2), 0.99 (3H, d, *J*=6.7 Hz, C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.1 (C=O), 141.2 (Ar), 135.3 (Ar), 133.2 (2 × Ar), 127.3 (2 × Ar), 47.3 (C1), 39.4 (3 × C5), 37.4 (3 × C7), 37.3 (C2), 34.2 (C4), 28.8 (3 × C6), 17.2 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.1 (C3).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{37}O$ $[M+H]^+$ 353.2844; found at 353.2840, Δ 0.17 ppm.

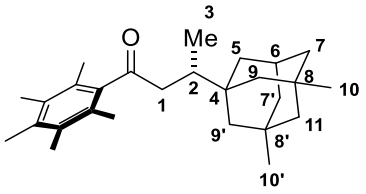
FTIR (neat) ν/cm^{-1} = 2901, 2847, 2360, 1703, 1447, 1403, 1379, 1356, 1308, 1123, 1102, 1021, 998, 914, 804, 732, 688, 647.

m.p. = 126 – 127 °C.

[α]$_D^{25}$ –23.2 (c = 0.43, $CHCl_3$).

Chiral HPLC: Chiralpak IA with guard, 0.3% IPA, 99.7% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 10.4 min, τ_R (minor) = 12.1 min.

(*S*)-3-((1r,3*R*,5*S*,7*S*)-3,5-Dimethyladamantan-1-yl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 15o



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 1-((1r,3*R*,5*S*,7r)-3,5-dimethyladamantan-1-yl)ethan-1-ol, **14o** (117 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 0.012 mmol) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.2 mmol) were subjected to **General procedure 2-A**. A combination of purification by column chromatography (Pentane:Et_2O, 98:2) and preparative TLC afforded the title compound **15o** as a transparent oil (50 mg, 44%, 67:33 e.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.89 (1H, dd, *J*=19.3, 1.6 Hz, C1-H_AH_B), 2.36 (1H, dd, *J*=19.3, 10.5 Hz, C1-H_AH_B), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.05 (1H, sext, *J*=3.2 Hz, C6-H), 1.92 (1H, dqd, *J*=10.9, 6.7, 1.6 Hz, C2-H), 1.39 – 0.97 (15H, m, C3-H_3, C5-H_2, 2 × C7-H_2, 2 × C9-H_2, C11-H_2), 0.82 – 0.77 (6H, m, 2 × C10-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9 (C=O), 141.3 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.3 (2 × Ar), 51.4 (C11), 47.6 (C1), 45.8 (C9), 45.7 (C9'), 43.6 (C7), 43.5 (C7'), 38.1 (C5), 36.7 (C2), 36.1 (C4), 31.2 (2 × C8), 31.0 (2 × C10), 29.8 (C6), 17.2 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.3 (C3).

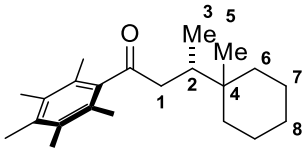
HRMS (ESI^+) m/z calcd. for $C_{27}H_{41}O$ $[M+H]^+$ 381.3157; found at 381.3152 Δ 0.11.

FTIR (neat) ν/cm^{-1} = 2941, 2899, 2840, 1703, 1454, 1403, 1376, 1356, 1310, 1279, 1116.

[α]$_D^{25}$ –9.9 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IC with guard, 0.3% IPA, 99.7% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 22.6 min, τ_R (minor) = 19.4 min.

(*S*)-3-(1-methylcyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)Butan-1-one, 15p



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 1-(1-methylcyclohexyl)ethan-1-ol **14p** (85 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A** with an extended reaction time (48 h). Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15p** as a white solid (55 mg, 52%, 78:22 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.85 (1H, dt, *J*=19.2, 1.2 Hz, C1-H_AH_B), 2.38 (1H, dd, *J*=19.2, 10.3 Hz, C1-H_AH_B), 2.21 (10H, s, 3 × Ar-CH_3, C2-H), 2.11 (6H, s, 2 × Ar-CH_3), 1.57 – 1.20 (10H, m, 2 × C6-H_2, 2 × C7-H_2, C8-H_2), 0.99 (3H, d, *J*=6.7, C3-H_3), 0.75 (3H, s, C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.9 (C=O), 141.2 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 48.1 (C1), 36.1 (C6), 35.2 (C6'), 35.9 (C2), 34.7(C4), 26.5 (C8), 22.0 (C7), 21.9 (C7'), 19.9 (C5), 17.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.7 (C3).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O$ $[M+H]^+$ 315.2688; found at 315.2682, Δ 0.01 ppm.

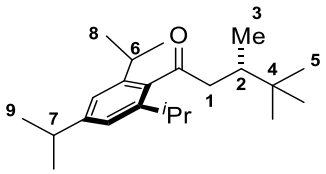
FTIR (neat) ν/cm^{-1} = 2923, 1702, 1459, 1381, 1309, 1114, 912.

m.p. = 90 – 91 °C.

[α]$_D^{25}$ –20.9 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IC with guard, 0.3% IPA, 99.7% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 32.8 min, τ_R (minor) = 30.0 min.

(*S*)-3,4,4-Trimethyl-1-(2,4,6-triisopropylphenyl)pentan-1-one, 15x



Commercially available 1-(2,4,6-triisopropylphenyl)ethan-1-one (74 mg, 0.30 mmol), 3,3-dimethyl-2-butanol **14f** (75 µL, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15x** as a light yellow oil (60 mg, 60%, 88:12 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (2H, s, 2 × Ar-H), 2.88 (1H, sept, *J*=6.9 Hz, C7-H) 2.85 (1H, d, *J*=19.3 Hz C1-H_AH_B), 2.78 – 2.54 (2H, m, 2 × C6-H), 2.44 (1H, dd, *J*=19.3, 10.4 Hz, C1-H_AH_B), 2.06 (1H, dqd, *J*=10.4, 6.7, 1.7 Hz, C2-H), 1.33 – 1.17 (18H, m, 4 × C8-H_3, 2 × C9-H_3), 1.00 (3H, d, *J*=6.7 Hz, C3-H_3), 0.87 (9H, s, 3 × C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 210.9 (C=O), 149.4 (Ar), 143.5, (2 × Ar) 138.5 (Ar), 121.2 (2 × Ar), 49.8 (C1), 37.3 (C2), 34.5 (C7), 32.5 (C4), 31.0 (br, 2 × C6), 27.3 (3xC5), 24.7 (br, 4 × C8), 24.1 (2 × C9), 15.6 (C3).

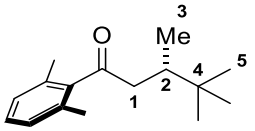
HRMS (ESI$^+$) m/z calcd. for $C_{23}H_{39}O$ $[M+H]^+$ 331.3001; found at 331.2995 Δ 0.22 ppm.

FTIR (neat) ν/cm^{-1} = 2960, 2871, 1703, 1607, 1461, 1404, 1364, 1293, 1245, 1215, 986, 877, 654.

[α]$_D^{25}$ –28.0 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IA with guard, 0.1% IPA, 99.9% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 6.7 min, τ_R (minor) = 6.1 min.

(*S*)-1-(2,6-dimethylphenyl)-3,4,4-Trimethylpentan-1-one, 15y



Commercially available 1-(2,6-Dimethylphenyl)ethan-1-one (45 mg, 0.30 mmol), 3,3-dimethyl-2-butanol **14f** (75 µL, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **15y** as a transparent oil (64 mg, 92%, 83:17 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18 – 7.15 (1H, m, Ar-H), 7.04 – 6.99 (2H, m, 2 × Ar-H), 2.86 (1H, dd, *J*=19.0, 1.5 Hz, C1-H_AH_B), 2.44 (1H, dd, *J*=19.0, 10.5 Hz, C1-H_AH_B), 2.23 (6H, s, 2 × Ar-CH_3), 2.06 (1H, dqd, *J*=10.5, 6.7, 1.5 Hz, C2-H), 1.00 (3H, d, *J*=6.8 Hz, C3-H_3), 0.88 (9H, s, 3 × C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 210.4 (C=O), 142.9 (Ar), 132.5 (2 × Ar), 128.5 (Ar), 127.9 (2 × Ar), 48.0 (C1), 37.3 (C2), 32.7 (C4), 27.3 (3 × C5), 19.2 (2 × Ar-$\underline{C}H_3$), 15.7 (C3).

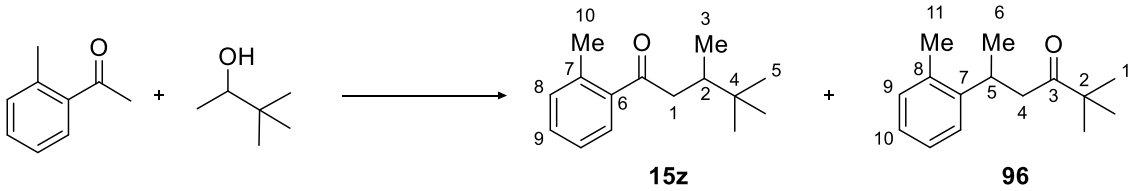
HRMS (ESI^+) m/z calcd. for $C_{16}H_{25}O$ $[M+H]^+$ 233.1905; found at 233.1903 Δ 1.09 ppm.

FTIR (neat) ν/cm^{-1} = 2959, 2871, 2361, 1703, 1596, 1464, 1403, 1365, 1295, 1247, 1212, 1113, 1034, 985, 920, 811, 770, 741, 686.

[α]$_D^{25}$ –21.3 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 0.3% IPA, 99.7% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 12.5 min, τ_R (minor) = 11.9 min.

Alkylation of 1-(o-tolyl)ethan-1-one with 3,3-dimethyl-2-butanol



15z **96**

Overall yield = 34%

Inseparable 1.6:1 mixture

1-(o-tolyl)Ethan-1-one (81 mg, 0.30 mmol), 3,3-dimethyl-2-butanol **14f** (76 µL, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure A**. Purification by column chromatography (Penane:Et_2O, 98:2) afforded **15z** and **96** as an inseparable mixture as a yellow oil (44.1 mg, 34%).

NMR Data for the mixture of **15z** and **96**:

3,4,4-Trimethyl-1-(o-tolyl)pentan-1-one, 15z

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 – 7.55 (1H, m, Ar-H), 7.36 (1H, td, *J*=7.3, 1.5 Hz, Ar-H), 7.29 – 7.21 (2H, m, 2 × Ar-H), 3.09 – 2.97 (1H, m, C1-H_AH_B), 2.56 (1H, dd, *J*=15.8, 10.4 Hz, C1-H_AH_B), 2.48 (3H, s, C10-H_3), 1.97 (1H, dtq, *J*=10.5, 6.9, 3.3 Hz, C2-H), 0.91 (9H, s, 3 × C5-H_3), 0.88 (3H, dd, *J*=6.8, 0.7 Hz, C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 205.7 (C=O), 139.0 (Ar), 137.7 (Ar), 132.0 (Ar), 131.0 (Ar), 128.2 (Ar), 125.7 (Ar), 44.9 (C1), 39.3 (C2), 33.0 (C4), 27.4 (C5), 21.1 (C10), 15.3 (C3).

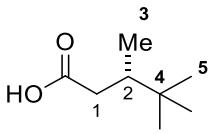
2,2-dimethyl-5-(o-tolyl)hexan-3-one, 96

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20 – 7.11 (3H, m, 3 × Ar-H), 7.08 (1H, ddd, *J*=7.6, 6.0, 2.4 Hz, Ar-H), 3.63 (1H, h, *J*=6.9 Hz, C5-H), 2.74 (2H, d, *J*=6.8 Hz, C4-H_2), 2.38 (3H, s, C11-H_3), 1.19 (3H, d, *J*=6.9 Hz, C6-H_3), 1.10 (9H, s, 3 × C1-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 214.6 (C=O), 145.1 (Ar), 135.5 (Ar), 130.6 (Ar), 126.2 (Ar), 125.9 (Ar), 125.2 (Ar), 44.6 (C4), 44.2 (C2), 29.9 (C5), 26.4 (C1), 21.3 (C6), 19.6 (C11).

6.2.1.3 Derivatisation of enantioenriched ketones

(*S*)-3,4,4-Trimethylpentanoic acid, 94



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added ketone **15f** (55 mg, 0.20 mmol, 97:3 e.r., 1.0 equiv.), hexafluoroisopropanol (1.8 mL) and 37% aq. HCl (0.26 mL, 12 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and stirred at 65 °C in a preheated oil bath for 24 h. The mixture was cooled to r.t., diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **94** as a light yellow oil (27 mg, 93%). The spectral data matched that previously reported in the literature.[120]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.97 (1H, br s, COO*H*), 2.55 (1H, dd, *J* = 15.0, 3.5 Hz, C1-H_AH_B), 1.99 (1H, dd, *J* = 15.0, 11.0 Hz, C1-H_AH_B), 1.84 – 1.75 (1H, m, C2-H), 0.92 (3H, d, *J* = 7.0 Hz, C3-H_3), 0.88 (9H, s, 3 × C5-H_3).

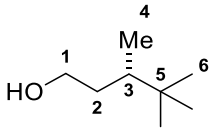
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 180.9 (C=O), 39.9 (C2), 37.4 (C1), 32.8 (C4), 27.2 (3 × C5), 15.1 (C3).

HRMS (ESI^-) m/z calcd. for $C_8H_{15}O_2$ $[M–H]^-$ 143.1078; found at 143.1075, Δ 1.89 ppm.

FTIR (neat) ν/cm^{-1} = 2962, 1707, 1468, 1413, 1367, 1304, 1220, 1179, 1109, 940, 669.

[α]$_D^{20}$ –19.1 (c = 0.9, EtOH); Lit. $[\alpha]_D^{20}$ +19.6 (c = 0.9, EtOH) for the (*R*)-enantiomer.[121]

(*S*)-3,4,4-Trimethylpentan-1-ol, 100



A stirred solution of ketone **15f** (110 mg, 0.40 mmol, 1.0 equiv., 97:3 e.r.) in CH_2Cl_2 (2 mL) was cooled to –17 °C (ice/NaCl bath). Br_2 (42 µL, 0.80 mmol, 2.0 equiv.) was added dropwise and the resulting solution was stirred at –17 °C for 15 min. The reaction mixture was then warmed to r.t. and the majority of the volatiles were removed under a stream of nitrogen and the resulting solid was dried *in vacuo* (0.2 mmHg) for 30 s. The residue was dissolved in THF (4 mL) and the resulting stirred solution was cooled to 0 °C. $LiAlH_4$ (76 mg, 2.00 mmol, 5.0 equiv.) was added in a single portion and the reaction mixture was warmed to r.t. and stirred for 1 h. The resulting mixture was diluted with Et_2O (4 mL) and quenched by sequential dropwise addition of H_2O (76 µL), aq. NaOH (15% w/v, 76 µL) and H_2O (228 µL). $MgSO_4$ was added and the resulting suspension was stirred vigorously for 15 min and then filtered and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 70:30) afforded the title compound **100** as a colourless oil (48 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.73 (1H, ddd, *J*=10.3, 8.2, 4.5 Hz, C1-H_AH_B), 3.60 (1H, ddd, *J*=10.3, 7.9, 7.1 Hz, C1-H_AH_B), 1.86 – 1.75 (1H, m, C2-H_AH_B), 1.42 (1H, s, O<u>H</u>), 1.31 – 1.12 (2H, m, C2-H_AH_B, C3-H), 0.96 – 0.75 (12H, m, C4-H_3, 3 × C6-H_3).

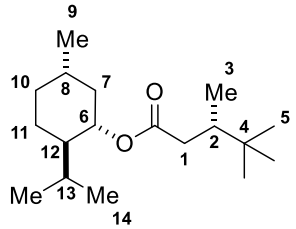
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 62.5 (C1), 39.5 (C3), 35.1 (C2), 33.0 (C5), 27.3 (3 × C6), 14.6 (C4).

HRMS (ESI^+) This compound could not be observed by ESI, APCI or EI analysis.

FTIR (neat) ν/cm^{-1} = 3319 (br), 2973, 2881, 1379, 1088, 1046, 880, 803.

[α]$_D^{20}$ –14.9 (c = 3.32, EtOH).

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (*S*)-3,4,4-trimethylpentanoate, 101



Br_2 (21 µL, 0.40 mmol, 2.0 equiv.) was added dropwise to a cooled (–17 °C ice/NaCl bath) solution of ketone **15f** (55 mg, 0.20 mmol, 1.0 equiv., 97:3 e.r.) in CH_2Cl_2 (1 mL). The resulting solution was stirred at –17 °C for 15 min followed by addition of D-Menthol (94 mg, 0.60 mmol, 3.0 equiv.). The reaction mixture was warmed to r.t. and stirred for 16 h. After this time, the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL), then extracted with Et_2O (3 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **101** as a colourless oil (51 mg, 90%, >95:5 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.68 (1H, td, *J*=10.9, 4.3 Hz, C6-H), 2.46 (1H, ddd, *J*=14.2, 3.4, 0.8 Hz, C1-H_AH_B), 2.04 – 1.74 (4H, m, C1-H_AH_B, C7-H_{eq}, C13-H, C2-H), 1.72 – 1.62 (2H, m, C10-H_{eq}, C11-H_{eq}), 1.55 – 1.32 (2H, m, C8-H, C12-H), 1.20 – 0.79 (21H, m, C7-H_{ax}, C10-H_{ax}, C11-H_{ax}, 2 × C14-H_3, C9-H_3, 3 × C5-H_3), 0.75 (3H, d, *J*=7.0 Hz, C3-H_3).

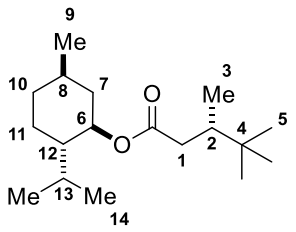
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.0 (C=O), 74.1 (C6), 47.2 (C12), 41.2 (C7), 40.3 (C2), 38.1 (C1), 34.5 (C11), 32.9 (C4), 31.6 (C8), 27.3 (3 × C5), 26.4 (C13), 23.6 (C10), 22.2 (C14), 20.9 (C14'), 16.4 (C9), 15.0 (C3).

HRMS (ESI^+) m/z calcd. for $C_{18}H_{35}O_2$ $[M+H]^+$ 283.2637; found at 283.2633, Δ 0.47 ppm.

FTIR (neat) ν/cm^{-1} = 2957, 2871, 1731, 1457, 1368, 1294, 1257, 1201, 1163, 1083, 1057, 1039, 1014, 987.

[α]$_D^{25}$ +38.5 (c = 1.00, $CHCl_3$).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*S*)-3,4,4-trimethylpentanoate, 102



Br_2 (21 µL, 0.40 mmol, 2.0 equiv.) was added dropwise to a cooled (–17 °C ice/NaCl bath) solution of ketone **15f** (55 mg, 0.20 mmol, 1.0 equiv., 97:3 e.r.) in CH_2Cl_2 (1 mL). The resulting solution was stirred at –17 °C for 15 min followed by addition of L-Menthol (94 mg, 0.60 mmol, 3.0 equiv.). The reaction mixture was warmed to r.t. and stirred for 16 h. After this time, the mixture was diluted with Et_2O (10 mL) and H_2O (10 mL), then extracted with Et_2O (3 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **102** as a colourless oil (49 mg, 87%, >95:5 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.68 (1H, td, *J*=10.9, 4.3 Hz, C6-H), 2.46 (1H, ddd, *J*=14.2, 3.4, 0.8 Hz, C1-H_AH_B), 2.09 – 1.73 (4H, m, C1-H_AH_B, C7-H_{eq}, C13-H, C2-H), 1.73 – 1.63 (2H, m, C10-H_{eq}, C11-H_{eq}), 1.56 – 1.31 (2H, m, C8-H, C12-H), 1.18 – 0.79 (21H, m, C7-H_{ax}, C10-H_{ax}, C11-H_{ax}, 2 × C14-H_3, C9-H_3, 3 × C5-H_3), 0.75 (3H, d, *J*=7.0 Hz, C3-H_3).

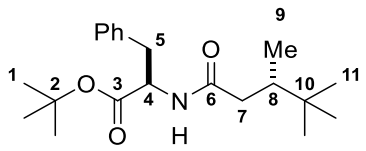
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 173.9 (C=O), 74.0 (C6), 47.2 (C12), 41.0 (C7), 40.0 (C2), 38.1 (C1), 34.5 (C11), 32.8 (C4), 31.5 (C8), 27.3 (3 × C5), 26.5 (C13), 23.7 (C10), 22.2 (C14), 20.9 (C14'), 16.5 (C9), 15.0 (C3).

HRMS (ESI^+) m/z calcd. for $C_{18}H_{34}NaO_2$ $[M+Na]^+$ 305.2457; found at 305.2452, Δ 0.31 ppm.

FTIR (neat) ν/cm^{-1} = 2956, 2870, 1731, 1457, 1368, 1294, 1256, 1201, 1163, 1082, 1057, 1039, 1013, 987.

[α]$_D^{25}$ –63.8 (c = 1.00, $CHCl_3$).

***tert*-Butyl ((*S*)-3,4,4-trimethylpentanoyl)-D-phenylalaninate, 103**



Br_2 (21 µL, 0.40 mmol, 2.0 equiv.) was added dropwise to a cooled (–17 °C ice/NaCl bath) solution of ketone **15f** (55 mg, 0.20 mmol, 1.0 equiv., 97:3 e.r.) in CH_2Cl_2 (1 mL). The resulting solution was stirred at –17 °C for 15 min followed by addition of H-D-Phe-O^{t}Bu·HCl (103 mg, 0.40 mmol, 2.0 equiv.) and ^{i}Pr$_2$EtN (140 µL, 0.80 mmol, 4.0 equiv.). The reaction mixture was warmed to r.t. and stirred for 16 h. After this time, the mixture was diluted with Et_2O (10 mL) and washed successively with 1 M HCl (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **103** as a pale yellow solid and a single diastereomer (62 mg, 89%, >95:5 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) 7.26 – 7.12 (3H, m, 3 × Ar-H), 7.12 – 7.05 (2H, m, 2 × Ar-H), 5.78 (1H, d, *J*=7.8 Hz, N*H*), 4.72 (1H, dt, *J*=7.8, 6.1 Hz, C4-H), 3.01 (2H, d, *J*=6.1 Hz, C5-H$_2$), 2.39 – 2.26 (1H, m, C7-*H$_A$*H$_B$), 1.73 – 1.59 (2H, m, C7-H$_A$*H$_B$*, C8-H), 1.34 (9H, s, 3 × C1-H$_3$), 0.80 – 0.76 (12H, m, C9-H$_3$, 3 × C11-H$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) 173.0 (C=O), 171.1 (C=O), 136.5 (Ar), 129.6 (2 × Ar), 128.5 (2 × Ar), 127.0 (Ar), 82.4 (C2), 53.5 (C4), 40.5 (C8), 39.8 (C7), 38.3 (C5), 32.8 (C10), 28.1 (3 × C1), 27.3 (3 × C11), 14.9 (C9).

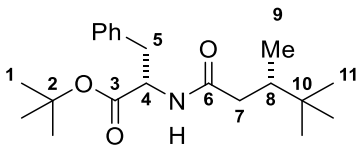
HRMS (ESI$^+$) m/z calcd. for $C_{21}H_{33}O_3NNa$ $[M+Na]^+$ 370.2353; found at 370.2355 Δ 0.01 ppm.

FTIR (neat) ν_{max}/cm^{-1} = 3291, 2964, 1732, 1644, 1546, 1498, 1456, 1367, 1255, 1155, 1104, 848, 740, 699.

m.p. = 105 – 106 °C.

[α]$_D^{25}$ –59.7 (c = 1.00, $CHCl_3$).

tert-Butyl ((*S*)-3,4,4-trimethylpentanoyl)-L-phenylalaninate, 104



Br_2 (21 µL, 0.40 mmol, 2.0 equiv.) was added dropwise to a cooled (–17 °C ice/NaCl bath) solution of ketone **15f** (55 mg, 0.20 mmol, 1.0 equiv., 97:3 e.r.) in CH_2Cl_2 (1 mL). The resulting solution was stirred at –17 °C for 15 min followed by addition of H-L-Phe-O^{t}Bu·HCl (103 mg, 0.40 mmol, 2.0 equiv.) and ^{i}Pr$_2$EtN (140 µL, 0.80 mmol, 4.0 equiv.). The reaction mixture was warmed to r.t. and stirred for 16 h. After this time, the mixture was diluted with Et_2O (10 mL) and washed successively with 1 M HCl (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **104** as a pale yellow solid and a single diastereomer (65 mg, 94%, >95:5 d.r.).

^{1}H NMR (400 MHz, $CDCl_3$) 7.34 – 7.02 (5H, m, 5 × Ar-H), 5.80 (1H, d, *J*=7.8 Hz, N*H*), 4.73 (1H, dt, *J*=7.8, 6.1 Hz, C4-H), 3.01 (2H, d, *J*=6.1 Hz, C5-H$_2$), 2.35 (1H, dd, *J*=13.6, 2.7 Hz, C7-*H*$_A$H$_B$), 1.77 – 1.58 (2H, m, C7-H$_A$*H*$_B$, C8-H), 1.33 (9H, s, 3 × C1-H$_3$), 0.78 (9H, s, 3 × C11-H$_3$), 0.75 – 0.70 (3H, m, C9-H$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) 172.9 (C=O), 171.1 (C=O), 136.5 (Ar), 129.6 (2 × Ar), 128.5 (2 × Ar), 127.0 (Ar), 82.4 (C2), 53.6 (C4), 40.2 (C8), 39.8 (C7), 38.5 (C5), 32.8 (C10), 28.1 (3 × C1), 27.3 (3 × C11), 14.9 (C9).

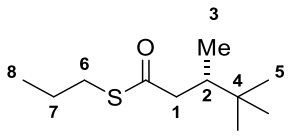
HRMS (ESI$^+$) m/z calcd. for $C_{21}H_{33}O_3NNa$ $[M+Na]^+$ 370.2353; found at 370.2353 Δ 0.01 ppm.

FTIR (neat) ν_{max}/cm^{-1} = 3292, 2965, 1735, 1646, 1543, 1498, 1456, 1367, 1226, 1155, 1102, 847, 740, 699.

m.p. = 89 – 91 °C.

[α]$_D^{25}$ +40.7 (c = 1.00, $CHCl_3$).

_S_-Propyl (_S_)-3,4,4-trimethylpentanethioate, 105



Br_2 (21 µL, 0.40 mmol, 2.0 equiv.) was added dropwise to a cooled (–17 °C ice/NaCl bath) solution of ketone **15f** (55 mg, 0.20 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL). The resulting solution was stirred at –17 °C for 15 min followed by addition of 1-propanethiol (56 µL, 0.60 mmol, 3.0 equiv.). The reaction mixture was warmed to r.t. and stirred for 16 h. After this time, the mixture was diluted with CH_2Cl_2 (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL), then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **105** as a pale yellow oil (37 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) 2.85 (2H, t, *J*=7.2 Hz, C6-H_2), 2.69 (1H, dd, *J*=14.4, 3.2 Hz, C1-H_AH_B), 2.23 (1H, dd, *J*=14.4, 10.8 Hz, C1-H_AH_B), 1.85 (1H, dqd, *J*=10.8, 6.8, 3.2 Hz, C2-H), 1.59 (2H, sext, *J*=7.3 Hz, C7-H_2), 0.97 (3H, t, *J*=7.3 Hz, C8-H_3), 0.91 – 0.82 (12H, m, 3 × C5-H_3, C3-H_3).

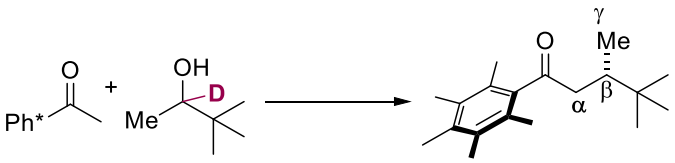
^{13}C NMR (101 MHz, $CDCl_3$) 200.4 (C=O), 47.4 (C1), 40.8 (C2), 33.0 (C4), 31.0 (C6), 27.3 (3 × C5), 23.2 (C7), 14.7 (C3), 13.5 (C8).

HRMS (APCI$^+$) m/z calcd. for $C_{11}H_{23}O_2S$ $[M+H]^+$ 203.1470; found at 203.1467, Δ 1.39 ppm.

FTIR (neat) ν_{max}/cm^{-1} = 2963, 2873, 2360, 2341, 1693, 1463, 1378, 1366, 1286, 1221, 1113, 1017, 986, 776, 692, 669.

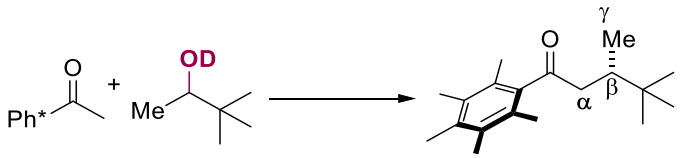
[α]$_D^{25}$ –22.1 (c = 1.00, $CHCl_3$).

6.2.1.4 Deuterium labelling experiments



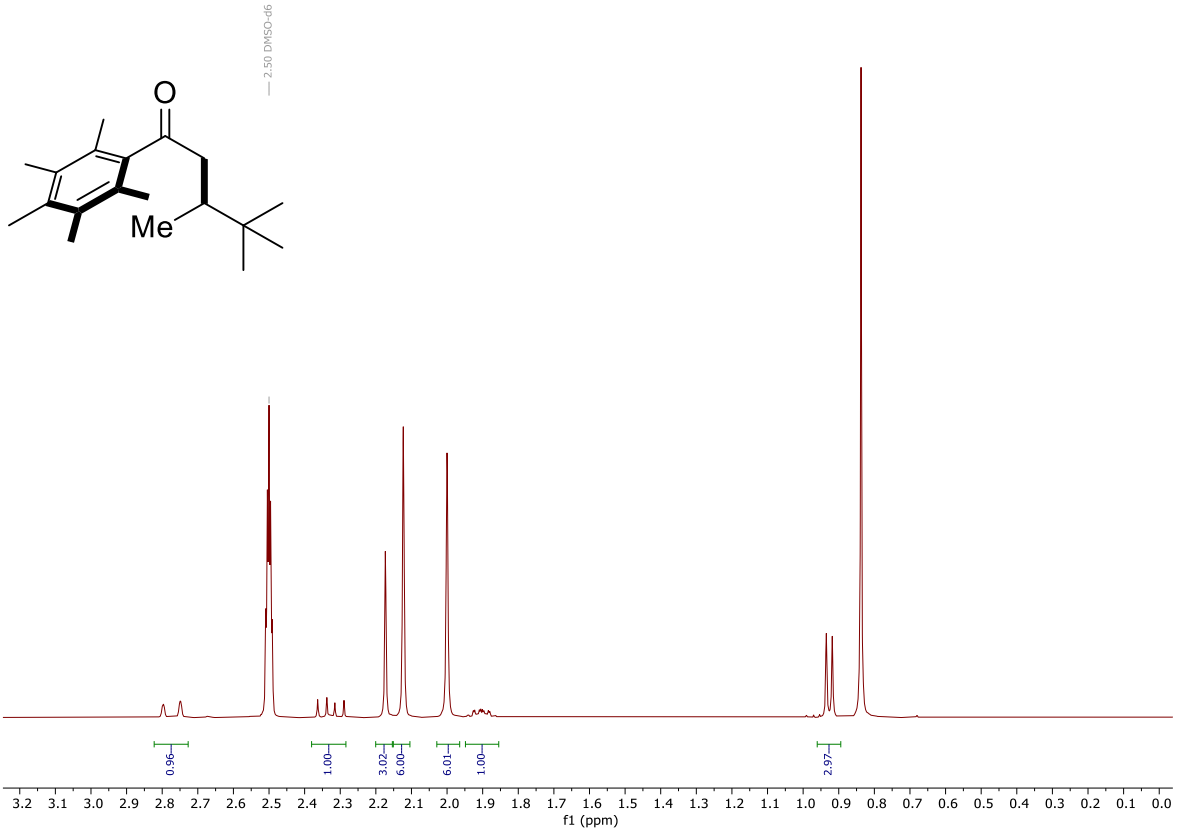
***d*-106**; 72% yield
Cα; 1.68:**0.32** H:**D**
Cβ; 0.92:**0.08** H:**D**
Cγ; 2.72:**0.28** H:**D**

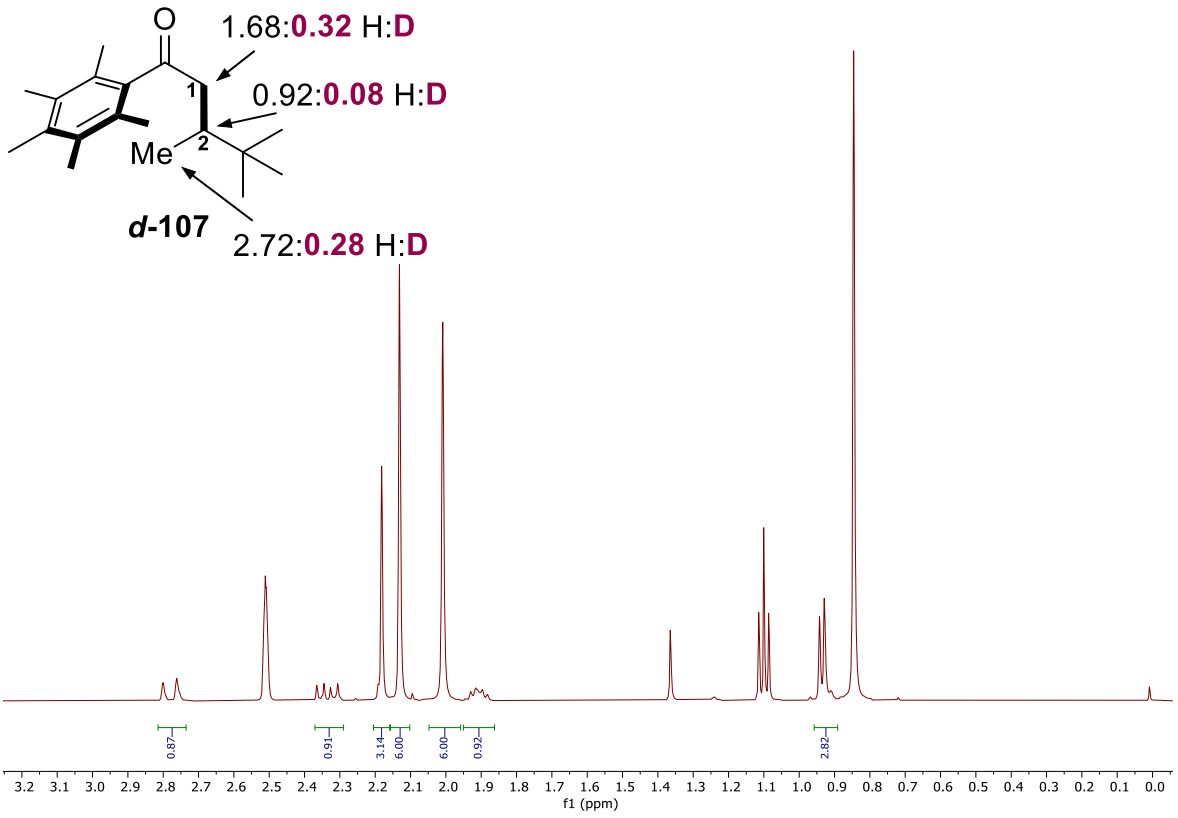
Pentamethylacetophenone **8** (57 mg, 0.30 mmol), deuterated alcohol **106** (62 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A.** Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound ***d*-107** as a white solid (59.1 mg, 72%). The ^{1}H NMR spectrum of ***d*-107** was recorded at 500 MHz with an extended relaxation delay (30 s) which was used to determine the level of deuterium incorporation (see spectra below).

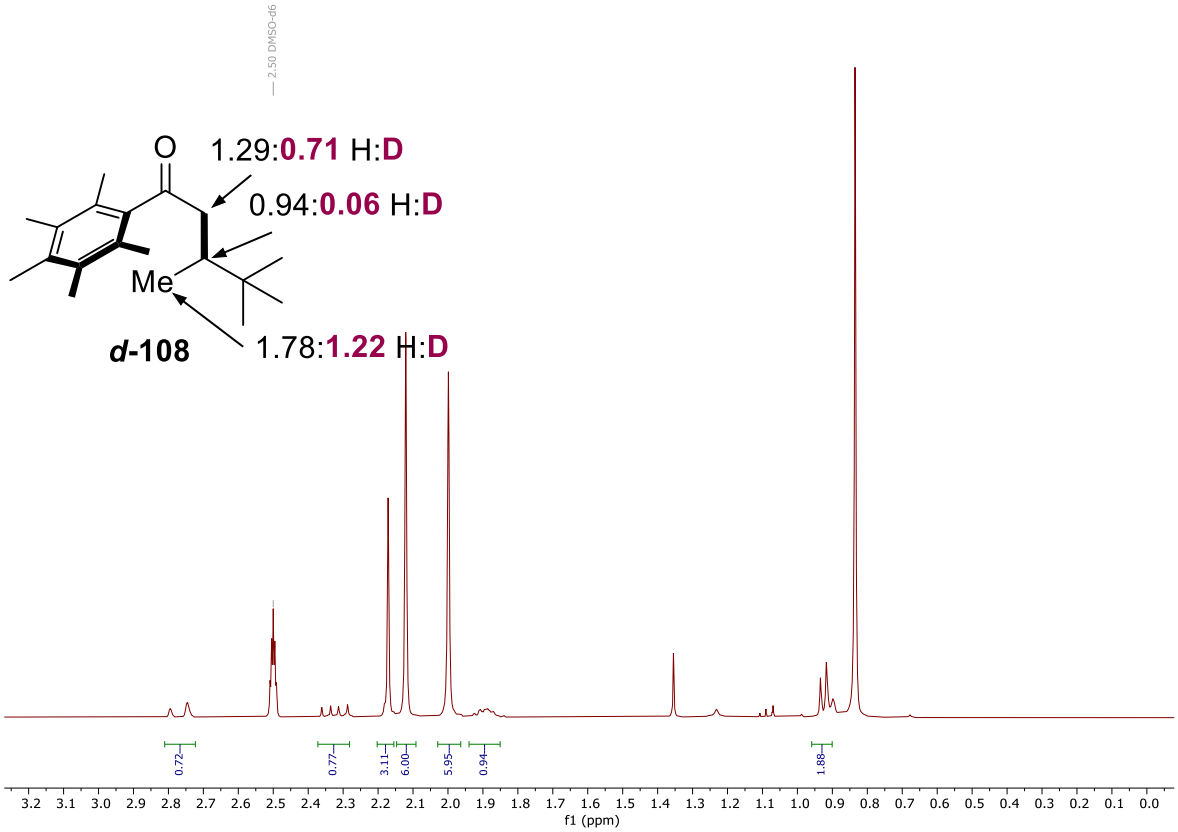


***d*-108**; 88% yield
Cα; 1.29:**0.71** H:**D**
Cβ; 0.94:**0.06** H:**D**
Cγ; 1.78:**1.22** H:**D**

Pentamethylacetophenone **8** (57 mg, 0.30 mmol), deuterated alcohol **107** (62 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A.** Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound ***d*-108** as a white solid (72.7 mg, 88%). The ^{1}H NMR spectrum of ***d*-108** was recorded at 400 MHz with an extended relaxation delay (25 s) which was used to determine the level of deuterium incorporation (see spectra below).


O
Me
2.50 DMSO-d6
0.96
1.00
3.02
6.00
6.01
1.00
2.97
3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
f1 (ppm)


O
1
2
Me
1.68:0.32 H:D
0.92:0.08 H:D
2.72:0.28 H:D
d-107
0.87
0.91
3.14
6.00
6.00
0.92
2.82
3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
f1 (ppm)


2.50 DMSO-d6
O
1.29:0.71 H:D
0.94:0.06 H:D
Me
1.78:1.22 H:D
d-108
0.72
0.77
3.11
6.00
5.95
0.94
1.88
3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
f1 (ppm)

6.3. Data for Chapter 3

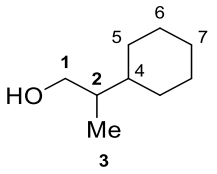
6.3.1 Experimental procedures and characterization

General Procedure 3-A: Hydrogen borrowing alkylation of 1,2-amino alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added amino alcohol (0.30 mmol, 1.0 equiv.), catalyst (4 mol%), chiral ligand (5 mol%), Ph* methyl ketone (0.45 mmol, 1.5 equiv.), base (0.30 mmol, 1.0 equiv.) and ^{t}BuOH (2.5 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), a nitrogen balloon fitted and heated to 110 °C in a preheated oil bath for 18 h. The mixture was cooled to r.t., diluted with Et_2O, filtered through a SiO_2 plug (eluting with ca. 50 mL Et_2O), concentrated and purified by column chromatography (see experimental methods section for details). Racemic products were obtained using our previously reported procedure using racemic amino alcohols.[32]

6.3.1.1 Carbon acyclic alcohols synthesis

2-Cyclohexylpropan-1-ol 121b



To a stirred solution of $LiAlH_4$ (0.645 g, 17.0 mmol, 1.11 equiv.) in Et_2O (80 mL) at 0 °C, was added a solution of commercially available ethyl 2-cyclohexylpropanoate (2.80 g, 15.3 mmol, 1.00 equiv.) in Et_2O (20 mL) dropwise. The reaction was warmed to r.t. and stirred for 2 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.65 mL), aq. NaOH (15% w/v, 0.65 mL) and H_2O (2.00 mL) at 0 °C. The reaction mixture was diluted with Et_2O (50 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 75:25) afforded

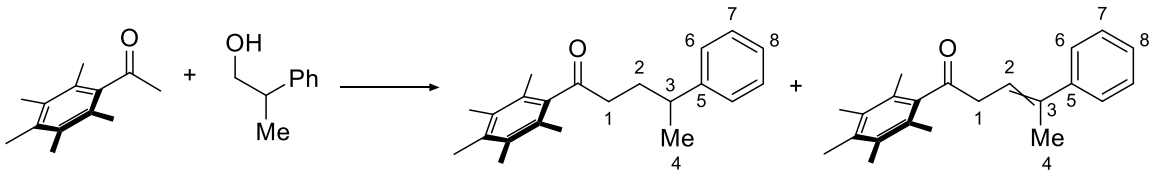
the title compound **121b** as a colourless oil (1.83 g, 84%). The spectral data matched that previously reported in the literature.[122]

^{1}H NMR (400 MHz, $CDCl_3$) 3.60 (1H, dd, *J*=10.5, 5.5 Hz, C1-H_AH_B), 3.45 (1H, dd, *J*=10.5, 7.0 Hz, C1-H_AH_B), 1.79 – 1.68 (2H, m, 2 x C6-H_{eq}), 1.68 – 1.58 (3H, m, 2 × C5-H_{eq}, C7-H_{eq}), 1.48 (1H, dqd, *J*=12.3, 7.0, 5.4 Hz, C2-H), 1.41 (1H, s, OH), 1.39 – 0.92 (6H, m, C4-H, 2 × C6-H_{ax}, C7-H_{ax}, 2 × C5-H_{ax}), 0.88 (3H, d, *J*=6.9 Hz, C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) 66.5 (C1), 41.1 (C2), 39.6 (C4), 31.1 (C5), 29.0 (C5'), 26.9 (C6/6'/7), 26.9 (C6'/6/7), 26.8 (C7/6/6'), 13.5 (C3).

6.3.1.2 Carbon acyclic hydrogen borrowing alkylation

1-(2,3,4,5,6-pentamethylphenyl)-4-Phenylpentan-1-one,1221 and **1-(2,3,4,5,6-pentamethylphenyl)-4-phenylpent-3-en-1-one, 124**



122a **124**

Pentamethylacetophenone **8** (57 mg, 0.30 mmol), commercially available 2-phenylpropan-1-ol (84 µL, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 99:1 to 99:2) afforded **122a** and **124** as an inseparable mixture, as a yellow oil (47 mg, 41:59 **122a**:**124**, 64:36 e.r. 21% yield of **122a**, 30% yield of **124**). Analytical data for **122a** is given from a reaction that afforded **122a** cleanly. Yields are calculated based on quantitative ^{1}H NMR integrations of the isolated mixture.

Data for 122a

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.22 (2H, m, 2 × C6-H), 7.21 – 7.13 (3H, m, 2 × C7-H, C8-H), 2.78 (1H, dt, *J*=9.0, 7.0 Hz, C3-H), 2.64 – 2.44 (2H, m, C1-H_2), 2.20 (3H, s, Ar-CH_3), 2.14 (6H, s, 2 × Ar-CH_3), 2.12 – 1.92 (8H, m, C2-H_2, 2 × Ar-CH_3), 1.29 (3H, d, *J*=7.0 Hz, C4-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.1 (C=O), 146.6 (C5), 140.9 (Ar), 135.4 (Ar), 133.1 (2 × Ar), 128.6 (2 × Ar), 127.4 (2 × Ar), 127.2 (2 × Ar), 126.3 (C8), 43.8 (C1), 39.5 (C3), 31.4 (C2), 22.8 (C4), 17.2 (2 × Ar-$\underline{C}H_3$), 16.7 (Ar-$\underline{C}H_3$), 16.0 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{28}ONa$ $[M+Na]^+$ 331.2032; found at 331.2033 Δ 0.12 ppm.

FTIR (neat) ν_{max}/cm^{-1} = 3027, 2958, 2921, 1700, 1603, 1494, 1406, 1324, 1205, 1152, 1093, 888, 735.

Chiral HPLC: Chiralpak IG with guard, 1% IPA, 99% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 26.3 min, τ_R (minor) = 22.1 min.

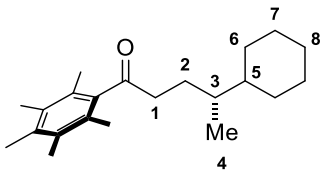
Data for 124: The *E*/*Z* ratio was determined by ^{1}H NMR analysis of the crude product through comparison of the C1-H signals: δ 6.12 (tq, *J*=7.0, 1.4 Hz, C2-H major), 5.81 (tq, *J*=7.0, 1.5 Hz, C2-H minor) as 86:14, however it was not determined if the major isomer was *E* or *Z*. The minor isomer could not be fully distinguished in the ^{1}H NMR, so only the data for the major isomer is reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.27 (5H, m, 2 × C6-H, 2 × C7-H, C8-H), 6.12 (1H, tq, *J*=7.0, 1.4 Hz, C2-H), 3.62 (2H, d, *J*=7.0 Hz, C1-H_2), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.14 (6H, s, 2 × Ar-CH_3), 2.02 (3H, d, *J*=1.4 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 209.40 (C=O), 143.3 (Ar), 140.7 (Ar), 138.2 (Ar), 135.7 (Ar), 133.3 (2 × Ar), 128.3 (2 × Ar), 127.8 (2 × Ar), 125.9 (2 × Ar), 119.1 (C2), 45.7 (C1), 17.5 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.5 (C4), 16.1 (2 × Ar-$\underline{C}H_3$). [*N.B*. A signal corresponding to C3 was not observed].

LRMS (ESI^+) m/z 329.2 (**124**, $[M+Na]^+$).

(*R*)-4-Cyclohexyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 122b



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 2-cyclohexylpropan-1-ol **121b** (85 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 99:1 to 99:2) afforded the title compound **122b** as a yellow solid (85 mg, 90%, 57:43 e.r.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.71 (1H, ddd, *J*=18.0, 10.5, 5.5 Hz, C1-H_AH_B), 2.61 (1H, ddd, *J*=18.0, 10.0, 5.5 Hz, C1-H_AH_B), 2.23 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.84 (1H, ddt, *J*=14.0, 10.5, 5.0 Hz, C2-H_AH_B) 1.78 – 1.45 (6H, m, C2-H_AH_B, 2 × C6-H_{eq}, 2 × C7-H_{eq}, C8-H_{eq}), 1.34 (1H, dqt, *J*=9.5, 7.0, 5.0 Hz, C3-H), 1.27 – 0.77 (9H, m, C5-H, 2 × C6-H_{ax}, 2 × C7-H_{ax}, C8-H_{ax}, C4-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.6 (C=O), 141.2 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 44.0 (C1), 42.8 (C5), 37.7 (C3), 30.9 (C6), 28.8 (C6'), 27.5 (C2), 27.1 (C7/7'/8), 27.0 (C7'/7/8), 26.9 (C8/7/7'), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.2 (C4), 16.1 (2 × Ar-$\underline{C}H_3$).

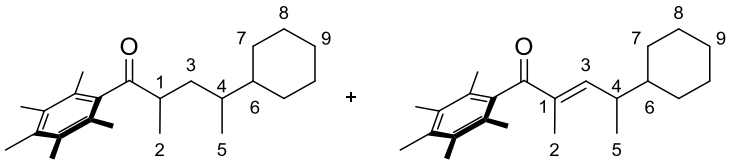
HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O$ $[M+H]^+$ 315.2682; found at 315.2682 Δ 0.17 ppm.

FTIR (neat) ν/cm^{-1} = 2922, 2851, 1701, 1448, 1406, 1380, 1307, 1266, 1115, 1070, 996, 930, 890, 840, 795.

m.p. = 75 – 76 °C.

Chiral HPLC: Chiralpak ID with guard, 0.3% IPA, 99.7% hexane, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection; τ_R (major) = 18.5 min, τ_R (minor) = 16.8 min.

4-Cyclohexyl-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one 126 and **(*E*)-4-cyclohexyl-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pent-2-en-1-one, 127.**



126 **127**

1-(2,3,4,5,6-pentamethylphenyl)Propan-1-one[a] (74 mg, 0.30 mmol), 2-cyclohexylpropan-1-ol **121b** (85.2 mg, 0.60 mmol), (*R*)-DTBM-SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General Procedure 2-A**. Purification by column chromatography (Pentane:Et_2O, 99:1 to 99:2) afforded **127** (41.2 mg, 42%) cleanly and **126** (42.0 mg, 43%, 60:40 d.r.) as an inseparable mixture of diastereoisomers, both (**126** and **127**) as yellow solids. Assignment of the major diastereomer as **126'** and minor as **126''** was arbitrary. [a]Synthesised by Dr Roly Armstrong.

Data for 126' and 126''

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.89 – 2.78 (1H', 1H'', m, C1'-H, C1''-H), 2.23 (3H', 3H'', s, 2 × Ar-CH_3), 2.18 (6H', 6H'', s, 4 × Ar-CH_3), 2.09 (6H', 6H'', s, 4 × Ar-CH_3), 1.90 (1H'', ddd, *J*=14.0, 7.8, 5.1 Hz, C3''-H_AH_B), 1.80 – 1.67 (2H', 2H'' m, 2 × Cy'-H, 2 × Cy''-H), 1.67 – 1.57 (2H', 3H'', m, 2 × Cy'-H, 3 × Cy''-H), 1.57 – 1.49 (1H', m, C3'-H_AH_B), 1.49 – 1.33 (2H', 3H'', m, C3'-H_AH_B, C6'-H, C6''-H, 2 × Cy''-H), 1.28 – 1.06 (8H', 7H'', m, C4'-H, 4 × Cy'-H, C2'-H_3, C4''-H, C3''-H_AH_B, 2 × Cy''-H, C2''-H_3,), 1.05 – 0.96 (2H', m, 2 × Cy'-H), 0.95 – 0.86 (1H'', m, Cy''-H), 0.82 (3H'', d, *J*=6.9 Hz, C5''-H_3), 0.77 (3H', d, *J*=6.7 Hz, C5'-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 216.1 (C'=O), 215.3 (C''=O), 140.4 (Ar'), 140.1 (Ar''), 135.5 (Ar'), 135.4 (Ar''), 133.1 (2 × Ar', 2 × Ar''), 128.3 (2 × Ar', 2 × Ar''), 46.3(C1''), 46.2 (C1'), 43.9 (C4'), 41.2 (C4''), 36.4(C3''), 35.9 (C3'), 35.5 (C6''), 35.1 (C6'), 31.4 (Cy''), 30.5 (Cy'), 29.4 (Cy'), 27.2 (Cy''), 27.0 (Cy'/Cy''), 27.0 (2 × Cy'/Cy''), 27.0 (Cy'/Cy''), 26.9 (Cy'/Cy''), 26.9 (Cy'/Cy''), 18.1 (2 × Ar-$\underline{C}H_3$',

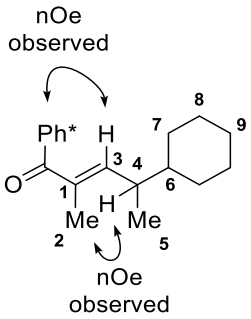
2 × Ar-$\underline{C}H_3$''), 16.9 (Ar-$\underline{C}H_3$', Ar-$\underline{C}H_3$''), 16.6 (C5''), 16.4 (C2''), 16.2 (2 × Ar-$\underline{C}H_3$', 2 × Ar-$\underline{C}H_3$''), 15.7 (C5'), 15.0 (C2').

HRMS (ESI$^+$) m/z calcd. for $C_{23}H_{37}O$ $[M+H]^+$ 329.2839; found at 329.2838, Δ 0.33 ppm.

FTIR (neat) ν/cm^{-1} = 2922, 2851, 1694, 1449, 1380, 1305, 1262, 1126, 1086, 989, 924, 890, 688.

m.p. = 56-58 °C.

Data for 127



^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.13 (1H, dq, *J*=10.5, 1.5 Hz, C3-H), 2.44 – 2.30 (1H, m, C4-H), 2.24 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.01 (3H, s, Ar-CH_3), 1.98 (3H, s, Ar-CH_3) 1.94 (3H, d, *J*=1.5 Hz, C2-H_3), 1.79 – 1.49 (5H, m, 2 × C7-H_AH_B, 2 × C8-H_AH_B, C9-H_AH_B), 1.24 – 0.99 (4H, m, C6-H, 2 × C8-H_AH_B, C9-H_AH_B), 0.96 – 0.70 (5H, m, C5-H_3, 2 × C7-H_AH_B).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 204.6 (C=O), 153.9 (C3), 138.6 (Ar), 137.4 (C1), 134.9 (Ar), 132.7 (2 × Ar), 129.2 (2 × Ar), 43.3 (C6), 39.5 (C4), 31.0 (C7), 30.8 (C7'), 26.7 (C8), 26.5 (C8', C9), 17.6 (Ar-$\underline{C}H_3$), 17.4 (Ar-$\underline{C}H_3$), 17.1 (C5), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 11.0 (C2).

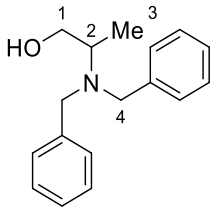
HRMS (ESI$^+$) m/z calcd. for $C_{23}H_{35}O$ $[M+H]^+$ 327.2682; found at 327.2682, Δ 0.26 ppm.

FTIR (neat) ν/cm^{-1} = 2923, 2852, 1655, 1448, 1382, 1311, 1267, 1204, 1142, 1090, 1003, 868, 834, 733, 679.

m.p. = 95 – 97 °C.

6.3.1.3 1,2-Amino alcohol synthesis

2-(dibenzylamino)Propan-1-ol, 16b



To a stirred suspension of DL-alanine (4.46 g, 50.0 mmol, 1.00 equiv.) in EtOH (100 mL) and aq. NaOH (6M, 8.3 mL) was added benzyl bromide (20.8 mL, 150 mmol, 3.00 equiv.), K_2CO_3 (27.6 g, 200 mmol, 4.00 equiv.) and H_2O (100 mL). The resulting solution stirred at r.t. for 16 h, before being brought to reflux for a further 2 h. The ethanol was removed *in vacuo* and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The crude ester was carried through to the next step in the synthesis without further purification.

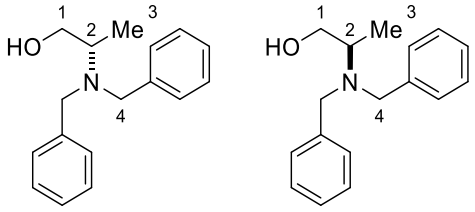
$LiAlH_4$ (2.28 g, 60.0 mmol, 1.20 equiv.) was added portionwise to a solution of crude ester (assumed quant., 50 mmol, 1.0 equiv.) in THF (50 mL) at 0 °C. The reaction was warmed to r.t. and the reaction stirred for 1.5 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (2.3 mL), aq. NaOH (15% w/v, 2.3 mL) and H_2O (6.9 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. The crude material was dissolved in THF (100 mL) and stirred vigorously with Rochelle's salt (150 mL) for 18 h, re-extracted with Et_2O and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **16b** as a colourless oil (9.19 g, 72% over two steps). The spectral data matched that previously reported in the literature.[32]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.36 – 7.28 (8H, m, 8 × Ar-H), 7.28 – 7.22 (2H, m, 2 × Ar-H), 3.83 (2H, d, *J*=13.3 Hz, 2 × C4-H_AH_B), 3.47 (1H, t, *J*=10.5 Hz, C1-H_AH_B), 3.41 – 3.29 (3H, m, C1-H_AH_B,

2 × C4-H_AH_B), 3.13 (1H, d, *J*=4.9 Hz, O*H*), 3.00 (1H, dqd, *J*=13.4, 6.7, 5.0 Hz, C2-H), 0.99 (3H, d, *J*=6.7 Hz, C3-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 139.4 (2 × Ar), 129.1 (4 × Ar), 128.6 (4 × Ar), 127.3 (2 × Ar), 62.9 (C1), 54.3 (C2), 53.1 (2 × C4), 8.8 (C3).

(*S*)-2-(dibenzylamino)Propan-1-ol, (*S*)-16b and (*R*)-2-(dibenzylamino)Propan-1-ol, (*R*)-16b



To a stirred suspension of L-alanine or D-alanine (891 g, 10.0 mmol, 1.00 equiv.) in EtOH (20 mL) and aq. NaOH (6M, 1.7 mL) was added benzyl bromide (4.16 mL, 35.0 mmol, 3.00 equiv.), K_2CO_3 (27.6 g, 30.0 mmol, 3.00 equiv.) and H_2O (20 mL). The resulting solution stirred at r.t. for 16 h, before being brought to reflux for a further 2 h. The ethanol was removed *in vacuo* and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The crude ester was carried through to the next step in the synthesis without further purification.

$LiAlH_4$ (455 g, 12.0 mmol, 1.20 equiv.) was added portionwise to a solution of crude ester (assumed quant., 10 mmol, 1.0 equiv.) in Et_2O (10 mL) at 0 °C. The reaction was warmed to r.t. and the reaction stirred for 1.5 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.5 mL), aq. NaOH (15% w/v, 0.5 mL) and H_2O (1.5 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. The crude material was dissolved in THF (20 mL) and stirred vigorously with Rochelle's salt (30 mL) for 18 h, re-extracted with Et_2O and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded (*S*)-2-(dibenzylamino)propan-1-ol **(*S*)-16b** as a colourless oil (1.77 g, 69% over two steps) or (*R*)-2-(dibenzylamino)propan-1-ol **(*R*)-16b** as a colourless oil (1.73 g, 68% over two

steps). The spectral data matched that previously reported in the literature and is given above.[32]

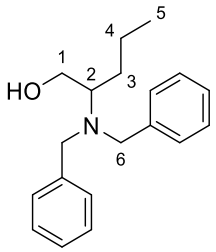
(*S*)-2-(dibenzylamino)propan-1-ol, (*S*)-16b

[α]$_D^{25}$ +88.9 (c = 1.00, $CHCl_3$); Lit. **[α]**$_D^{25}$ +109.0 (c = 1.00, $CHCl_3$).[123]

(*R*)-2-(dibenzylamino)propan-1-ol, (*R*)-16b

[α]$_D^{25}$ -89.1 (c = 1.00, $CHCl_3$) ; Lit. **[α]**$_D^{25}$ -86.4 (c = 1.00, $CHCl_3$).[123]

2-(dibenzylamino)Pentan-1-ol, 220



To a stirred suspension DL-Norvaline (996 mg, 8.50 mmol, 1.00 equiv.) in EtOH (10 mL) and aq. NaOH (6M, 1.42 mL) was added benzyl bromide (3.53 mL, 29.8 mmol, 3.50 equiv.), K_2CO_3 (4.69 g, 34.0 mmol, 3.00 equiv.) and H_2O (10 mL). The resulting solution stirred at r.t. for 16 h, before being brought to reflux for a further 2 h. The ethanol was removed *in vacuo* and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The crude ester was carried through to the next step in the synthesis without further purification.

$LiAlH_4$ (421 mg, 11.1 mmol, 1.30 equiv.) was added portionwise to a solution of crude ester (assumed quant., 8.5 mmol, 1.0 equiv.) in THF (50 mL) at 0 °C. The reaction was warmed to r.t. and the reaction stirred for 1.5 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.4 mL), aq. NaOH (15% w/v, 0.4 mL) and H_2O (1.2 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. The crude material was dissolved in THF (100 mL) and stirred vigorously with Rochelle's salt (150 mL) for 18 h, re-extracted with

Et_2O and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **220** as a pale yellow oil (1.99 g, 83% over two steps).

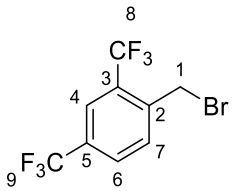
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.23 (10H, m, 10 × Ar-H), 3.84 (2H, d, *J*=13.3 Hz, 2 × C6-H_AH_B), 3.52 (1H, dd, *J*=10.6, 5.0 Hz, C1-H_AH_B), 3.48 – 3.39 (3H, m, C1-H_AH_B, 2 × C6-H_AH_B), 3.21 (1H, s, O*H*), 2.90 – 2.73 (1H, m, C2-H), 1.83 – 1.63 (1H, m, C3-H_AH_B), 1.51 – 1.12 (3H, m, C4-H_2, C3-H_AH_B), 0.96 (3H, t, *J*=7.1 Hz, C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 139.5 (2 × Ar), 129.1 (4 × Ar), 128.5 (4 × Ar), 127.3 (2 × Ar), 61.0 (C1), 58.9 (C2), 53.3 (2 × C6), 27.3 (C3), 20.5 (C4), 14.5 (C5).

HRMS (ESI^+) m/z calcd. for $C_{19}H_{26}ON$ $[M+H]^+$ 284.2009; found at 284.2009, Δ 0.09 ppm.

FTIR (neat) ν/cm^{-1} = 3426, 2958, 1494, 1453, 1377, 1046, 746, 728, 697.

1-(bromomethyl)-2,4-Bis(trifluoromethyl)benzene, 131



To a solution of (2,4-bis(trifluoromethyl)phenyl)methanol[a] (7.00 g, 28.7 mmol, 1.00 equiv.) and PPh_3 (11.3 g, 43.0 mmol, 1.50 equiv.) in THF (100 mL) was slowly added CBr_4 (14.3 g, 43.0 mmol, 1.50 equiv.) and stirred at r.t. for 2 h. After this time the mixture was concentrated, pentane (50 mL) was added and the resulting white ppt was removed by filtration. The filtrate was concentrated *in vacuo* and purified by column chromatography (Pentane) afforded the title compound **131** as a colourless oil (7.62 g, 86%). [a] Synthesised by Bruno Marinic

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.92 (1H, d, *J*=1.9 Hz, C4-H), 7.82 (1H, dd, *J*=8.2, 1.9 Hz, C6-H), 7.77 (1H, d, *J*=8.2 Hz, C7-H), 4.66 (2H, s, C1-H_2).

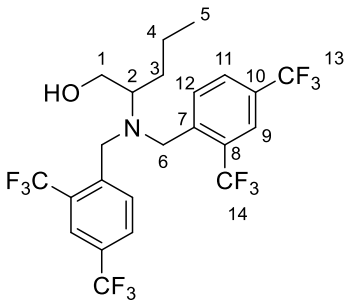
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 140.4 (C2), 133.6 (C7), 131.2 (q, *J*=33.7 Hz, C3/5), 29.4 (q, *J*=3 .7 Hz, C6), 129.3 (q, *J*=31.9 Hz, C5/3), 123.7 (dtt, *J*=9.6, 5.7, 3.8 Hz, C4), 123.5 (q, *J*=274.2 Hz, C8/9), 123.3 (q, *J*=272.3 Hz, C9/8), 27.0 (q, *J*=2.7 Hz, C1).

^{19}F NMR (470 MHz, $CDCl_3$) δ_F –60.0, –63.1.

HRMS (APCI$^-$) m/z calcd. for $C_9H_4BrF_6$ $[M-H]^-$ 304.9406; found at 304.9394, Δ 3.92 ppm.

FTIR (neat) v/cm^{-1} = 1345, 1274, 1121, 1083, 1056, 913, 846, 672, 621.

2-(bis(2,4-bis(trifluoromethyl)benzyl)amino)Pentan-1-ol, 132a



To a stirred suspension DL-Norvaline (497 mg, 4.25 mmol, 1.00 equiv.) in EtOH (5 mL) and aq. NaOH (6M, 0.71 mL) was added 1-(bromomethyl)-2,4-Bis(trifluoromethyl)benzene **131** (4.57 g, 14.9 mmol, 3.50 equiv.), K_2CO_3 (2.34 g, 17.0 mmol, 4.00 equiv.) and H_2O (5 mL). The resulting solution stirred at r.t. for 16 h, before being brought to reflux for a further 24 h. The ethanol was removed *in vacuo* and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The crude ester was carried through to the next step in the synthesis without further purification.

$LiAlH_4$ (358 mg, 9.40 mmol, 1.30 equiv.) was added portionwise to a solution of crude ester (assumed quant., 4.25 mmol, 1.00 equiv.) in Et_2O (40 mL) at 0 °C. The reaction was warmed to r.t. and the reaction stirred for 30 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.4 mL), aq. NaOH (15% w/v, 0.4 mL) and H_2O (1.2 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane: CH_2Cl_2, 80:20) afforded the title compound **132a** as a pale yellow solid (376 mg, 16% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99 (2H, d, *J*=8.2 Hz, 2 × C12-H), 7.94 – 7.85 (2H, m, 2 × C9-H), 7.79 (2H, dd, *J*=8.2, 2.0 Hz, 2 × C11-H), 3.98 (2H, d, *J*=15.5 Hz, 2 × C6-H_AH_B), 3.92 (2H, d, *J*=15.5 Hz, 2 × C6-H_AH_B), 3.79 – 3.58 (2H, m, C1-H_2), 2.71 (1H, tt, *J*=8.8, 4.2 Hz, C2-H), 2.20 (1H, d, *J*=4.8 Hz,

O*H*), 1.73 (1H, tq, *J*=10.3, 3.6 Hz, C3-H_AH_B), 1.48 – 1.17 (3H, m, C3-H_AH_B, C4-H_2), 0.93 (3H, t, *J*=7.1 Hz, C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 142.9 (2 × C7), 131.2 (2 × C12), 129.99 (q, *J*=33.4 Hz, 2 × C8/10), 129.71 (q, *J*=31.1 Hz, 2 × C10/8), 128.89 (q, *J*=3.8 Hz, 2 × C11), 123.74 (q, *J*=274.0 Hz, 2 × C13/14), 123.5 (q, *J*=272.2 Hz, 2 × C14/13), 123.5 – 123.1 (m, 2 × C9), 61.9 (C1), 61.2 (C2), 49.7 (2 × C6), 28.1 (C3), 20.6 (C4), 14.4 (C5).

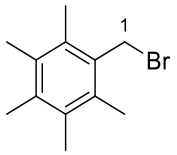
^{19}F NMR (377 MHz, $CDCl_3$) δ_F –59.7, –63.0.

HRMS (ESI^+) m/z calcd. for $C_{23}H_{22}ONF_{12}$ $[M+H]^+$ 556.1504; found at 556.1500, Δ 0.73 ppm.

FTIR (neat) v/cm^{-1} = 3395, 2937, 1345, 1299, 1275, 1168, 1122, 1084, 1055, 1021, 847, 675.

m.p. = 55 – 56 °C.

1-(bromomethyl)-2,3,4,5,6-Pentamethylbenzene, 134



According to a modified literature procedure[124]: To a mixture of pentamethylbenzene (1.85 g, 12.5 mmol, 1.00 equiv.), paraformaldehyde (375 mg, 12.5 mmol, 1.00 equiv.) and glacial acetic acid (5 mL) was added HBr in acetic acid (33% wt, 2.5 mL) and stirred at 50 °C for 2 h. After this time, the reaction mixture was poured into H_2O (50 mL) and the solid was filtered to afford the title compound **134** as a white solid (3.00 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.66 (2H, s, C1-H_2), 2.35 (6H, s, 2 × Ar-CH_3), 2.25 (3H, s, Ar-CH_3), 2.23 (6H, s, 2 × Ar-CH_3).

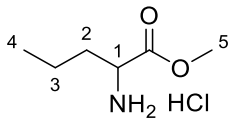
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.2 (Ar), 133.2 (2 × Ar), 133.2 (2 × Ar), 131.3 (Ar), 32.2 (C1), 17.3 (Ar-$\underline{C}H_3$), 16.9 (2 × Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{12}H_{17}$ $[M-Br]^+$ 161.1325; found at 161.1327, Δ 1.13 ppm.

FTIR (neat) v/cm^{-1} = 2918, 1438, 1204, 1068, 1011, 908, 805, 784, 734, 646.

m.p. = 87 – 88 °C.

Methyl 2-aminopentanoate hydrochloride, 135



To a stirred solution of MeOH (20 mL) at 0 °C was added $SOCl_2$ (4.38 mL, 60.0 mmol, 3.00 equiv.) dropwise and the reaction left to stir for 15 min. DL-Norvaline (2.34 g, 20.0 mmol, 1.00 equiv.) was added portionwise and the reaction warmed to r.t. and stirred for 16 h. The solvent was then removed *in vacuo*, pentane added and the solid was filtered to afford the title compound **135** as a white solid (3.35 g, 100%).

^{1}H NMR (400 MHz, MeOD) δ_H 4.04 (1H, t, *J*=6.5 Hz, C1-H), 3.84 (3H, s, C5-H_3), 1.97 – 1.78 (2H, m, C2-H_2), 1.57 – 1.33 (2H, m, C3-H_2), 1.00 (3H, t, *J*=7.3 Hz, C4-H_3).

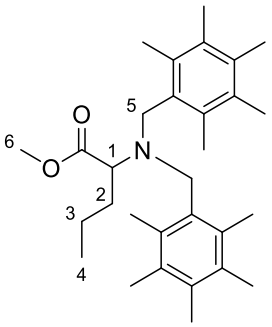
^{13}C NMR (101 MHz, MeOD) δ_C 171.1 (C=O), 53.8 (C1/5), 53.6 (C5/1), 33.5 (C2), 19.3 (C3), 13.8 (C4).

HRMS (ESI^+) m/z calcd. for $C_6H_{14}O_2N$ $[M+H]^+$ 132.1019; found at 132.1019, Δ 0.05 ppm.

FTIR (neat) ν/cm^{-1} = 3405, 2961, 2876, 1748, 1595, 1510, 1442, 1384, 1228, 1176.

m.p. = 117 – 119 °C.

Methyl 2-(bis(2,3,4,5,6-pentamethylbenzyl)amino)pentanoate, 136



To a stirred solution of methyl 2-aminopentanoate hydrochloride **135** (804 mg, 4.80 mmol, 1.00 equiv.), K_2CO_3 (1.99 g, 14.4 mmol, 3.00 equiv.) in MeCN (20 mL) was added 1-(bromomethyl)-2,3,4,5,6-pentamethylbenzene (2.89 g, 12.0 mmol, 2.50 equiv.) portionwise and stirred at 70 °C for 18 h. The reaction mixture was cooled diluted with H_2O (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$),

concentrated *in vacuo* and purified by column chromatography (Pentane: Et_2O, 97:3) afforded the title compound **136** as a white solid (1.50 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.96 (2H, d, *J*=12.7 Hz, 2 × C5-H_AH_B), 3.84 – 3.69 (5H, m, 2 × C5-H_AH_B, C6-H_3), 3.20 (1H, t, *J*=7.2 Hz, C1-H), 2.22 (6H, s, 2 × Ar-CH_3), 2.20 (12H, s, 4 × Ar-CH_3), 2.19 (12H, s, 4 × Ar-CH_3), 1.74 (2H, q, *J*=7.4 Hz, C2-H_2), 1.18 (1H, dp, *J*=14.7, 7.2 Hz, C3-H_AH_B), 0.99 (1H, ddd, *J*=15.6, 13.5, 7.4 Hz, C3-H_AH_B), 0.66 (3H, t, *J*=7.4 Hz, C4-H_3).

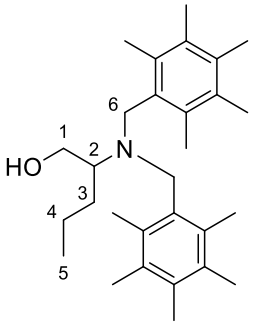
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.5 (C=O), 134.4 (4 × Ar), 133.7 (2 × Ar), 132.4 (4 × Ar), 131.9 (2 × Ar), 60.4 (C1), 51.0 (C6), 48.0 (2 × C5), 30.4 (C2), 19.8 (C3), 17.1 (2 × Ar-$\underline{C}H_3$), 16.9 (4 × Ar-$\underline{C}H_3$), 16.7 (4 × Ar-$\underline{C}H_3$), 13.7 (C4).

HRMS (ESI^+) m/z calcd. for $C_{30}H_{46}O_2N$ $[M+H]^+$ 452.3523; found at 452.3520, Δ 0.63 ppm.

FTIR (neat) ν/cm^{-1} = 2928, 1732, 1456, 1380, 1194, 1137, 1064, 909, 733.

m.p. = 173 °C.

2-(bis(2,3,4,5,6-pentamethylbenzyl)amino)Pentan-1-ol, 132b



To a solution of methyl 2-(bis(2,3,4,5,6-pentamethylbenzyl)amino)pentanoate **136** (1.47 g, 3.30 mmol, 1.00 equiv.) in THF (15 mL) at 0 °C was added $LiAlH_4$ (137 mg, 3.60 mmol, 1.10 equiv.) portionwise. The reaction was warmed to r.t. and the reaction stirred for 30 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.1 mL), aq. NaOH (15% w/v, 0.1 mL) and H_2O (0.3 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane: Et_2O, 95:5 to 93:7) afforded the title compound **132b** as a white solid (1.14 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.83 (2H, d, *J*=12.9 Hz, 2 × C6-H_AH_B), 3.68 (2H, d, *J*=12.8 Hz, C6-H_AH_B), 3.51 (1H, t, *J*=10.5 Hz, C1-H_AH_B), 3.42 (1H, td, *J*=10.1, 4.5 Hz, C1-H_AH_B), 2.87 (1H, d, *J*=9.6 Hz, O*H*), 2.64 (1H, tdt, *J*=11.0, 7.7, 3.4 Hz, C2-H), 2.22 (6H, s, 2 × Ar-CH_3), 2.18 (24H, br. s, 8 × Ar-CH_3), 1.91 (1H, tdd, *J*=12.4, 5.2, 3.0 Hz, C3-H_AH_B), 1.49 – 1.15 (3H, m, C3-H_AH_B, C4-H_2), 1.01 (3H, t, *J*=7.2 Hz, C5-H_3).

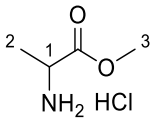
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 134.1 (2 × Ar), 133.8 (4 × Ar), 132.8 (br, 4 × Ar), 131.6 (2 × Ar), 60.2 (C1), 59.0 (C2), 46.3 (2 × C6), 27.8 (C3), 21.0 (C4), 17.1 (2 × Ar-$\underline{C}H_3$), 17.0 (4 × Ar-$\underline{C}H_3$), 16.7 (br, 4 × Ar-$\underline{C}H_3$), 15.0 (C5).

HRMS (ESI^+) m/z calcd. for $C_{29}H_{45N}O$ $[M+H]^+$ 424.3574; found at 424.3571, Δ 0.72 ppm.

FTIR (neat) ν/cm^{-1} = 3458, 2929, 2872, 1456, 1382, 1042, 909, 732.

m.p. = 198 – 199 °C.

Methyl alaninate hydrochloride, S5



To a stirred solution of MeOH (40 mL) at 0 °C was added $SOCl_2$ (8.76 mL, 120 mmol, 3.00 equiv.) dropwise and the reaction left to stir for 15 min. DL-Alanine (3.56 g, 40.0 mmol, 1.00 equiv.) was added portionwise and the reaction warmed to r.t. and stirred for 16 h. The solvent was then removed *in vacuo*, pentane added and the solid was filtered to afford the title compound **S5** as a white solid (5.56 g, 100%).

^{1}H NMR (400 MHz, MeOD) δ_H 4.12 (1H, q, *J*=7.2 Hz, C1-H), 3.84 (3H, s, C3-H_3), 1.54 (3H, d, *J*=7.2 Hz, C2-H_3).

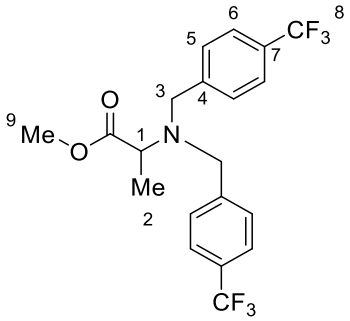
^{13}C NMR (101 MHz, MeOD) δ_C 171.4 (C=O), 53.7 (C3), 49.8 (C1), 16.2 (C2).

HRMS (ESI^+) m/z calcd. for $C_4H_{10}NO_2$ $[M+H]^+$ 104.0706; found at 104.0707, Δ 0.71 ppm.

FTIR (neat) ν/cm^{-1} = 2952, 2811, 2189, 1743, 1459, 1438, 1313, 1241, 1170, 1117, 906, 748.

m.p. = 94 – 95 °C.

Methyl bis(4-(trifluoromethyl)benzyl)alaninate, 139



To a stirred solution of methyl alaninate hydrochloride **S5** (670 mg, 4.80 mmol, 1.00 equiv.), K_2CO_3 (1.99 g, 14.4 mmol, 3.00 equiv.) in MeCN (20 mL) was added 1-(bromomethyl)-4-(trifluoromethyl)benzene (2.87 g, 12.0 mmol, 2.50 equiv.) portionwise and stirred at 70 °C for 18 h. The reaction mixture was cooled diluted with H_2O (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (Pentane: Et_2O, 95:5) to afford the title compound **139** as a colourless oil (1.52 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 – 7.53 (4H, m, 4 × C6-H), 7.48 (4H, d, *J*=7.9 Hz, 4 × C5-H), 3.86 (2H, d, *J*=14.4 Hz, 2 × C3-H_AH_B), 3.79 – 3.70 (5H, m, 2 × C3-H_AH_B, C9-H_3), 3.47 (1H, q, *J*=7.2 Hz, C1-H), 1.37 (3H, d, *J*=7.1 Hz, C2-H_3).

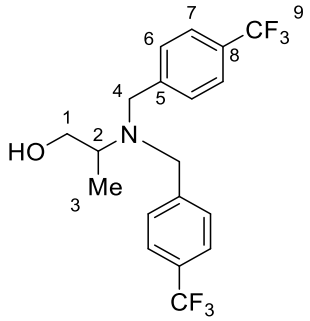
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 173.8 (C=O), 143.9 (2 × C4), 129.6 (q, *J*=32.3 Hz, 2 × C7), 128.9 (4 × C5), 125.4 (q, *J*=3.7 Hz, 4 × C6), 124.4 (q, *J*=271.9 Hz, 2 × C8) 56.8 (C1), 54.5 (2 × C3), 51.6 (C9), 15.2 (C2).

^{19}F NMR (377 MHz, $CDCl_3$) δ_F –62.5.

HRMS (ESI$^+$) m/z calcd. for $C_{20}H_{20}O_2NF_6$ $[M+H]^+$ 420.1393; found at 420.1389, Δ 0.93 ppm.

FTIR (neat) ν/cm^{-1} = 2981, 2360, 1738, 1620, 1327, 1162, 1125, 1107, 1067, 1019, 955, 826.

2-(bis(4-(trifluoromethyl)benzyl)amino)Propan-1-ol, 16e



To a solution of methyl bis(4-(trifluoromethyl)benzyl)alaninate **139** (1.52 g, 3.60 mmol, 1.00 equiv.) in THF (15 mL) at 0 °C was added $LiAlH_4$ (165 mg, 4.30 mmol, 1.20 equiv.) portionwise. The reaction was warmed to r.t. and the reaction stirred for 30 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.2 mL), aq. NaOH (15% w/v, 0.2 mL) and H_2O (0.6 mL) at 0 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. The crude material was dissolved in THF (30 mL) and stirred vigorously with Rochelle's salt (15 mL) for 18 h, re-extracted with Et_2O and concentrated *in vacuo*. Purification by column chromatography (Pentane: Et_2O, 75:25) afforded the title compound **139** as a colourless oil (843 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 (4H, d, *J*=8.0 Hz, 4 × C7-H), 7.40 (4H, d, *J*=7.9 Hz, 4 × C6-H), 3.84 (2H, d, *J*=13.7 Hz, 2 × C4-H_AH_B), 3.53 (1H, t, *J*=10.4 Hz, C1-H_AH_B), 3.49 (2H, d, *J*=13.8 Hz, 2 × C4-H_AH_B), 3.42 (1H, ddd, *J*=10.9, 8.7, 5.0 Hz, C1-H_AH_B), 2.96 (1H, dddd, *J*=11.6, 9.9, 6.6, 5.0 Hz, C2-H), 2.71 (1H, d, *J*=8.5 Hz, O*H*), 1.03 (3H, d, *J*=6.7 Hz, C3-H_3).

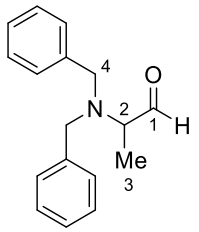
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.4 (2 × C5), 129.86 (q, *J*=32.6 Hz, 2 × C8), 129.2 (4 × C6), 125.7 (q, *J*=3.8 Hz. 4 × C7), 124.2 (q, *J*=272.0 Hz, 2 × C9), 63.2 (C1), 55.3 (C2), 53.2 (2 × C4), 9.2 (C3).

HRMS (ESI^+) m/z calcd. for $C_{19}H_{20}ONF_6$ $[M+H]^+$ 392.1444; found at 392.1442, Δ 0.42 ppm.

FTIR (neat) ν/cm^{-1} = 3435, 2936, 1322, 1159, 1118, 1065, 1042, 1017, 846, 825.

6.3.1.4 Enone synthesis and transfer hydrogenation

2-(dibenzylamino)Propanal, 140

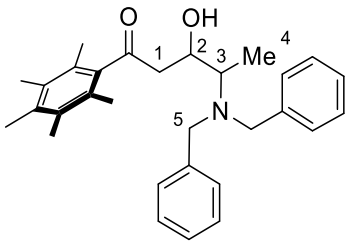


A solution of oxalyl chloride (0.50 mL, 5.9 mmol, 1.5 equiv.) in CH_2Cl_2 (5 mL) was cooled to –78 °C. DMSO (0.61 mL, 8.6 mmol, 2.2 equiv.) in CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was stirred for 5 min. 2-(dibenzylamino)Propan-1-ol **16b** (1.00 g, 3.92 mmol, 1.00 equiv.) in CH_2Cl_2 (5 mL) was added dropwise and stirred for 15 min, followed by addition of Et_3N (2.72 mL, 19.6 mmol, 5.00 equiv.). The reaction mixture was stirred for 30 min, warmed to r.t. and quenched with H_2O (20 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound **140** as a colourless oil (730 mg, 74%). The spectral data matched that previously reported in the literature.[125]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.74 (1H, s, C1-H), 7.46 – 7.37 (4H, m, 4 × Ar-H), 7.37 – 7.29 (4H, m, 4 × Ar-H), 7.26 (2H, ddt, *J*=8.2, 6.1, 1.5 Hz, 2 × Ar-H), 3.75 (2H, d, *J*=13.6 Hz, 2 × C4-H_AH_B), 3.58 (2H, d, *J*=13.7 Hz, 2 × C4-H_AH_B), 3.34 (1H, q, *J*=6.8 Hz, C2-H), 1.19 (3H, d, *J*=6.8 Hz, C3-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 204.6 (C=O), 139.2 (2 × Ar), 128.9 (4 × Ar), 128.6 (4 × Ar), 127.5 (2 × Ar), 63.0 (C2), 55.1 (2 × C4), 7.0 (C3).

4-(dibenzylamino)-3-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 141



To a stirred solution of EtMgBr (3M in Et_2O, 1.1 mL, 3.4 mmol, 1.2 equiv.) in a 2-neck round bottom flask fitted with a reflux condenser was added a solution of ketone **8** (540 mg, 2.84 mmol, 1.00 equiv.) in Et_2O (4 mL) dropwise. The mixture was heated at 40 °C for 30 mins, after which the reaction mixture was cooled to 0°C and a solution of aldehyde **140** (720 mg, 2.84 mmol, 1.00 equiv.) in Et_2O (4 mL) was added dropwise. The resulting mixture was stirred at 0 °C for a further 1 h, diluted with Et_2O (5 mL), poured onto an ice (ca. 2 g) and extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc:pentane 10:90) afforded the title compound **141** as a white solid (735 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 – 7.16 (10H, m, 10 × Ar-H), 4.33 (1H, t, *J*=9.3 Hz, C2-H), 3.76 (2H, d, *J*=13.8 Hz, 2 × C5-H_AH_B), 3.50 – 3.41 (3H, m, 2 × C5-H_AH_B, C1-H_AH_B), 3.21 (1H, d, *J*=3.3 Hz, O*H*), 2.69 (1H, dq, *J*=8.5, 6.6 Hz, C3-H), 2.54 (1H, dd, *J*=19.0, 10.1 Hz, C1-H_AH_B), 2.26 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.05 (6H, s, 2 × Ar-CH_3), 1.19 (3H, d, *J*=6.6 Hz, C4-H_3).

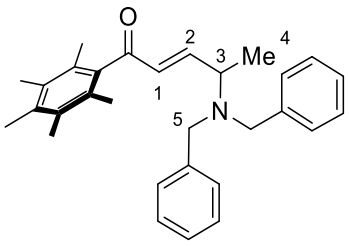
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 214.2 (C=O), 140.3 (Ar), 139.9 (2 × Ar), 135.8 (Ar), 133.3 (2 × Ar), 128.8 (4 × Ar), 128.4 (4 × Ar), 127.5 (2 × Ar), 127.1 (2 × Ar), 69.6 (C2), 56.6 (C3), 54.5 (2 × C5), 50.4 (C1), 17.2 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 8.5 (C4).

HRMS (ESI^+) m/z calcd. for $C_{30}H_{37}NO_2Na$ $[M+Na]^+$ 466.2717; found at 466.2716, Δ 0.05 ppm.

FTIR (neat) ν/cm^{-1} = 3340, 2970, 1379, 1128, 951, 817.

m.p. = 121 – 122 °C.

(*E*)-4-(dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)Pent-2-en-1-one, 142



To a solution of chlorosulfonyl isocyanate (0.19 mL, 2.2 mmol, 2.0 equiv.) in THF (10 mL) at 5 °C was added MeOH (0.09 mL, 2.2 mmol, 2.0 equiv.) and stirred for 15 min. After this time, Et_3N (0.62 mL, 4.5 mmol, 4.2 equiv.) was added and stirred for a further 30 min. A solution of **141** (476 mg, 1.10 mmol, 1.00 equiv.) in THF (10 mL) was added to the reaction mixture and subsequently heated to reflux for 30 min. The reaction mixture was cooled, quenched with H_2O and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 93:7) afforded the title compound **142** as a white solid (271 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.25 (8H, m, 8 × Ar-H), 7.22 (2H, ddd, J=9.6, 5.3, 1.8 Hz, 2 × Ar-H), 6.58 (1H, dd, J=16.1, 5.6 Hz, C2-H), 6.42 (1H, dd, J=16.0, 1.5 Hz, C1-H), 3.63 – 3.45 (5H, m, 2 × C5-H_2, C3-H), 2.27 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.05 (6H, br. s, 2 × Ar-CH_3), 1.21 (3H, d, J=6.7 Hz, C4-H_3)

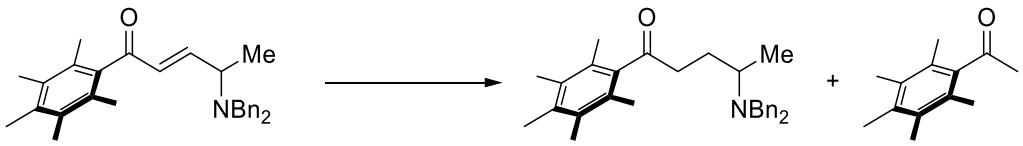
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 203.0 (C=O), 153.5 (C2), 139.8 (2 × Ar), 138.1 (Ar), 135.5 (Ar), 133.3 (C1), 133.0 (2 × Ar), 128.9 (2 × Ar), 128.7 (4 × Ar), 128.4 (4 × Ar), 127.1 (2 × Ar), 54.1 (C3), 54.0 (2 × C5), 17.7 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 13.7 (C4).

HRMS (ESI$^+$) m/z calcd. for $C_{30}H_{36}ON$ $[M+H]^+$ 426.2791; found at 426.2789, Δ 0.49 ppm.

FTIR (neat) v/cm^{-1} = 3335, 2970, 1655, 1379, 1129, 951, 817, 699.

m.p. = 107 – 108 °C.

Transfer Hydrogenation of enone 142

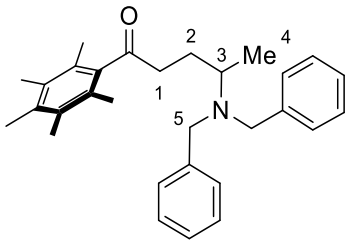


17b **8**

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added 3,3-dimethyl-2-butanol (31 mg, 0.30 mmol, 2.0 equiv.), the enone **142** (64 mg, 0.15 mmol, 1.0 equiv.), (*R*)-DTBM-SEGPHOS (8.9 mg, 5.0 mol%), Ir(cod)acac (2.4 mg, 4.0 mol%), ^{t}BuOH (0.06 mL, 3M) and NaO^{t}Bu (7.2 mg, 0.08 mmol, 0.50 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and heated to 110 °C in a preheated oil bath for 24 h. The mixture was cooled, diluted with Et_2O (4 mL), quenched with 3M HCl (2 mL) and extracted with Et_2O (3 × 4 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. For ease of purification from residual (*R*)-DTBM-SEGPHOS, a solution of the crude product in Et_2O (ca. 40 mL) was treated with *tert*-butyl hydroperoxide (5 – 6 M in decane, 50 µL, ~0.28 mmol), swirled and allowed to stand at r.t. for 10 min. The resulting solution was then concentrated and purification by column chromatography (Penane:Et_2O, 98:2) afforded the title compounds **17b** as a white solid (27.4 mg, 43%, 50:50 e.r.) and **8** as a white solid (16.2 mg, 57%). Characterisation data for **8** is reported in chapter 6.2 and data for **17b** is reported below.

6.3.1.5 Hydrogen borrowing alkylation with 1,2-amino alcohols

4-(dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)Pentan-1-one, 17b



Pentamethylacetophenone **8** (86 mg, 0.45 mmol, 1.5 equiv.), 2-(dibenzylamino)propan-1-ol **16b** (77 mg, 0.30 mmol, 1.0 equiv.), (R_P,S_N)-**Ru-2** (14.7 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and KOH (34 mg, 0.30 mmol) were subjected to **General Procedure 3-A**. Purification by column chromatography (Pentane:Et_2O, 95:5) afforded the title compound **17b** as a pale yellow solid (80 mg, 62%, 81:19 e.r.). The spectral data matched that previously reported in the literature.[32]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.38 – 7.34 (4H, m, 4 × Ar-H), 7.33 – 7.27 (4H, m, 4 × Ar-H), 7.25 – 7.20 (2H, m, 2 × Ar-H), 3.78 (2H, d, *J*=13.7 Hz, 2 × C5-H_AH_B), 3.42 (2H, d, *J*=13.8 Hz, 2 × C5-H_AH_B), 3.03 (1H, ddd, *J*=18.5, 10.6, 4.7 Hz, C1-H_AH_B), 2.78 (1H, ddt, *J*=12.0, 9.3, 6.4 Hz, C3-H), 2.59 (1H, ddd, *J*=18.6, 10.7, 5.0 Hz, C1-H_AH_B), 2.27 (3H, s, Ar-CH_3), 2.21 (6H, s, 2 × Ar-CH_3), 2.13 – 2.01 (7H, m, 2 × Ar-CH_3, C2-H_AH_B), 1.74 (1H, ddt, *J*=14.2, 10.6, 5.2 Hz, C2-H_AH_B), 1.09 (3H, d, *J*=6.6 Hz, C4-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.7 (C=O), 141.0 (Ar), 140.5 (2 × Ar), 135.4 (Ar), 133.1 (2 × Ar), 128.8 (4 × Ar), 128.3 (4 × Ar), 127.5 (2 × Ar), 126.8 (2 × Ar), 53.3 (2 × C5), 52.4 (C3), 43.3 (C1), 27.4 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 13.3 (C4).

HRMS (ESI$^+$) m/z calcd. for $C_{30}H_{38}ON$ $[M+H]^+$ 428.2948; found at 428.2947, Δ 0.19 ppm.

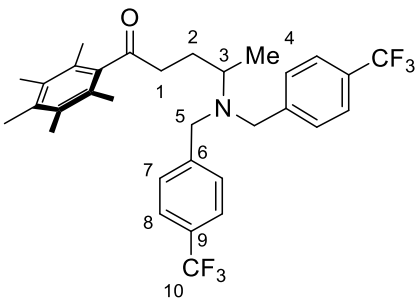
FTIR (neat) ν/cm^{-1} = 2960, 1698, 1453, 1381, 1155, 1071, 726, 699.

m.p. = 70 – 72 °C.

[α]$_D^{25}$ +4.1 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IA with guard, 1% IPA, 99% hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 11.6 min, τ_R (minor) = 14.9 min.

4-(bis(4-(trifluoromethyl)benzyl)amino)-1-(2,3,4,5,6-pentamethylphenyl)Pentan-1-one, 17e



Pentamethylacetophenone **8** (86 mg, 0.450 mmol, 1.50 equiv.), 2-(bis(4-(trifluoromethyl)benzyl)amino)propan-1-ol **16e** (117 mg, 0.300 mmol, 1.00 equiv.), Ir(cod)acac (4.8 mg, 4 mol%), (*R*)-DTBM-SEGPHOS (17.7 mg, 5 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (14.4 mg, 0.150 mmol, 0.5 equiv.) were subjected to **General Procedure 3-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **17e** as a pale yellow oil (13.8 mg, 8%, 50:50 e.r.).

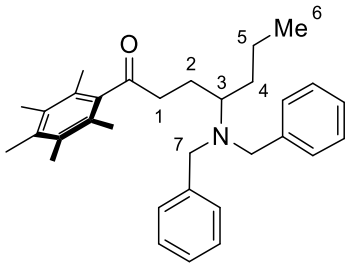
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.53 (4H, d, *J*=8.0 Hz, 4 × Ar-H), 7.43 (4H, d, *J*=7.9 Hz, 4 × Ar-H), 3.77 (2H, d, *J*=14.1 Hz, 2 × C5-H_AH_B), 3.52 (2H, d, *J*=14.2 Hz, 2 × C5-H_AH_B), 2.87 (1H, ddd, *J*=18.6, 10.0, 5.1 Hz, C1-H_AH_B), 2.73 (1H, dh, *J*=12.7, 6.4 Hz, C3-H), 2.59 (1H, ddd, *J*=18.5, 10.1, 5.2 Hz, C1-H_AH_B), 2.24 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.14 – 2.05 (1H, m, C2-H_AH_B), 2.00 (6H, s, 2 × Ar-CH_3), 1.75 (1H, ddt, *J*=15.2, 10.6, 5.6 Hz, C2-H_AH_B), 1.10 (3H, d, *J*=6.5 Hz, C4-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.1 (C=O), 144.4 (2 × Ar), 140.8 (Ar), 135.7 (Ar), 133.3 (2 × Ar), 129.4 (q, *J*=32.3 Hz, 2 × C9), 129.0 (4 × Ar), 127.4 (2 × Ar), 126.7 (q, *J*=286 Hz, 2 × C10), 125.4 (q, 3.7 Hz, 4 × C8), 53.4 (C3, 2 × C5), 43.1 (C1), 27.2 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 13.7 (C4).

HRMS (ESI^+) m/z calcd. for $C_{32}H_{36}ONF_6$ $[M+H]^+$ 564.2696; found at 564.2692, Δ 0.19 ppm.

FTIR (neat) ν/cm^{-1} = 2933, 1698, 1619, 1418, 1383, 1325, 1161, 1122, 1066, 1018, 825.

4-(dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)Heptan-1-one, 221



Pentamethylacetophenone **8** (86 mg, 0.45 mmol, 1.5 equiv.), 2-(dibenzylamino)pentan-1-ol **220** (85 mg, 0.30 mmol, 1.0 equiv.), $[Cp^*IrCl_2]_2$ (4.8 mg, 2 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (44 mg, 0.15 mmol, 0.50 equiv.) were subjected to **General Procedure 3-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **221** as a pale yellow oil (86 mg, 66%).

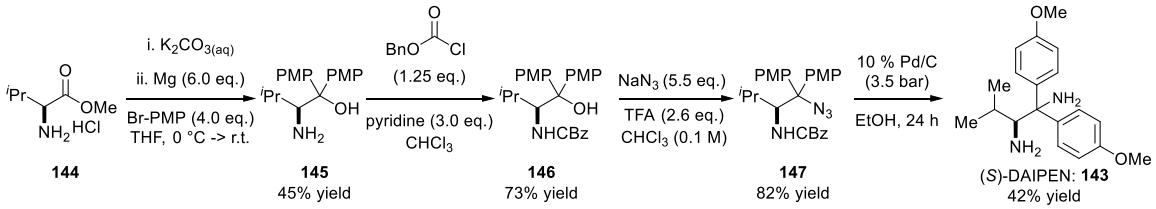
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.32 (4H, m, 4 × Ar-H), 7.32 – 7.25 (4H, m, 4 × Ar-H), 7.25 – 7.18 (2H, m, 2 × Ar-H), 3.70 (2H, d, *J*=13.6 Hz, 2 × C7-H_AH_B), 3.56 (2H, d, *J*=13.7 Hz, 2 × C7-H_AH_B), 2.94 (1H, ddd, *J*=18.5, 10.2, 5.0 Hz, C1-H_AH_B), 2.62 – 2.45 (2H, m, C1-H_AH_B, C3-H), 2.27 (3H, s, Ar-CH_3), 2.21 (6H, s, 2 × Ar-CH_3), 2.14 – 1.97 (7H, m, 2 × Ar-CH_3, C2-H_AH_B), 1.83 – 1.65 (2H, m, C2-H_AH_B, C4-H_AH_B), 1.38 (2H, h, *J*=7.3 Hz, C5-H_2), 1.31 – 1.15 (1H, m, C4-H_AH_B), 0.87 (3H, t, *J*=7.3 Hz, C6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.6 (C=O), 141.1 (Ar), 140.6 (2 × Ar), 135.4 (Ar), 133.1 (2 × Ar), 129.0 (4 × Ar), 128.3 (4 × Ar), 127.5 (2 × Ar), 126.8 (2 × Ar), 57.0 (C3), 53.5 (2 × C7), 43.6 (C1), 31.6 (C4), 23.7 (C3), 20.5 (C4), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.4 (C6).

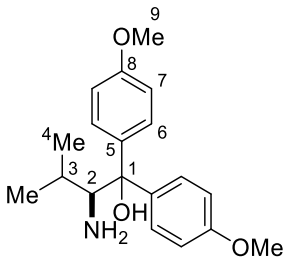
HRMS (ESI^+) m/z calcd. for $C_{32}H_{42}ON$ $[M+H]^+$ 456.3261; found at 456.3261, Δ 0.11 ppm.

FTIR (neat) v/cm^{-1} = 2929, 1698, 1453, 909, 730, 698.

6.3.1.6 Synthesis of (S)-DAIPEN



(*S*)-2-Amino-1,1-bis(4-methoxyphenyl)-3-methylbutan-1-ol, 145



According to a modified literature procedure[126]: Methyl L-valinate hydrochloride (6.00 g, 45.7 mmol, 1.00 equiv.) and aq. K_2CO_3 (6 M, 50 mL) were stirred for 1 h. After this time, methyl L-valinate was extracted with EtOAc (3 × 50 mL), the organic layers were combined, concentrated *in vacuo* and the crude product was carried through to the next step in the synthesis without further purification.

A suspension of magnesium turnings (6.66 g, 274 mmol, 6.00 equiv.) in THF (100 mL) was stirred at r.t. and a single crystal of iodine was added followed by addition of 1-bromo-4-methoxybenzene (22.9 mL, 183 mmol, 4.00 equiv.) at a rate which maintained a steady reflux. After the addition was complete the resulting suspension was cooled to r.t., THF (40 mL) added, transferred by cannulation to a round-bottomed flask and cooled to 0 °C. A solution of methyl L-valinate (assumed quant., 45.7 mmol, 1.00 equiv.) in THF (10 mL) was added dropwise to the grignard solution and the resulting mixture was warmed to r.t. and stirred for 18 h. After this time, the mixture was diluted with Et_2O, quenched by dropwise addition of sat. aq. NH_4Cl and then extracted with Et_2O (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by trituration with hexane afforded the title compound **145**

as a white solid (6.46 g, 45%). The spectral data matched that previously reported in the literature.[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 – 7.46 (2H, m, 2 × Ar-H), 7.41 – 7.35 (2H, m, 2 × Ar-H), 6.87 – 6.78 (4H, m, 4 × Ar-H), 3.77 (3H, s, C9-H_3), 3.76 (3H, s, C9'-H_3), 3.73 (1H, d, *J*=2.2 Hz, C2-H), 1.76 (1H, heptd, *J*=6.9, 2.1 Hz, C3-H), 0.92 (3H, d, *J*=7.1 Hz, C4-H_3), 0.87 (3H, d, *J*=6.8 Hz, C4'-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 158.3 (Ar), 158.0 (Ar), 140.5 (Ar), 137.6 (Ar), 127.1 (2 × Ar), 126.7 (2 × Ar), 113.8 (2 × Ar), 113.5 (2 × Ar), 79.3 (C1), 60.4 (C2), 55.4 (C9), 55.3 (C9'), 27.9 (C3), 23.2 (C4), 16.2 (C4').

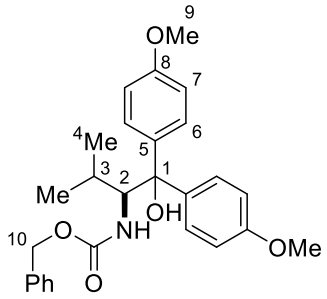
HRMS (ESI^+) m/z calcd. for $C_{19}H_{25}NO_3Na$ $[M+Na]^+$ 338.1727; found at 338.1728, Δ 0.39 ppm.

FTIR (neat) ν/cm^{-1} = 2956, 2836, 2361, 1608, 1509, 1464, 1247, 1173, 1035, 830.

m.p. = 133 – 134 °C.

[α]$_D^{25}$ -111.0 (c = 1.00, $CHCl_3$); Lit. $[\alpha]_D^{25}$ -109.0 (c = 1.00, $CHCl_3$).[127]

Benzyl (*S*)-(1-hydroxy-1,1-bis(4-methoxyphenyl)-3-methylbutan-2-yl)carbamate, 146



To a solution of (*S*)-2-amino-1,1-bis(4-methoxyphenyl)-3-methylbutan-1-ol **145** (4.38 g, 13.9 mmol, 1.00 equiv.) in $CHCl_3$ (70 mL) was added pyridine (3.36 mL, 41.6 mmol, 3.00 equiv.) and benzyl chloroformate (2.47 mL, 17.3 mmol, 1.25 equiv.) at 0 °C and stirred for 1.5 h. After this time, the reaction mixture was diluted with EtOAc (150 mL), washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 70:30 to 60:40) afforded the title compound **146** as a white solid (4.58 g, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.39 – 7.27 (7H, m, 7 × Ar-H), 7.24 – 7.18 (2H, m, 2 × Ar-H), 6.86 – 6.81 (2H, m, 2 × Ar-H), 6.79 – 6.74 (2H, m, 2 × Ar-H), 5.24 (1H, d, *J*=10.3 Hz, NH), 5.10 (1H,

d, *J*=12.4 Hz, C10-H_AH_B), 4.98 (1H, d, *J*=12.4 Hz, C10-H_AH_B), 4.57 (1H, dd, *J*=10.3, 2.1 Hz, C2-H), 3.78 (3H, s, C9-H_3), 3.75 (3H, s, C9'-H_3), 2.37 (1H, s, OH), 1.84 (1H, heptd, *J*=6.8, 2.1 Hz, C3-H), 0.92 (3H, d, *J*=6.8 Hz, C4-H_3), 0.85 (3H, d, *J*=6.7 Hz, C4'-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 158.4 (2 × Ar), 138.8 (Ar), 138.0 (Ar), 136.9 (Ar), 128.6 (2 × Ar), 128.0 (Ar), 127.9 (2 × Ar), 127.0 (2 × Ar), 126.7 (2 × Ar), 113.8 (2 × Ar), 113.7 (2 × Ar), 81.9 (C1), 66.7 (C10), 60.0 (C2), 55.3 (C9), 55.3 (C9'), 29.0 (C3), 22.8 (C4), 17.4 (C4'). [*N.B*. A signal corresponding to C=O was not observed].

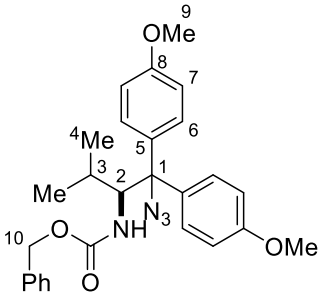
HRMS (ESI^+) m/z calcd. for $C_{27}H_{31}NO_5Na$ $[M+Na]^+$ 472.2094; found at 472.2098, Δ 0.74 ppm.

FTIR (neat) ν/cm^{-1} = 3440, 2958, 1681, 1510, 1249, 1179, 1035, 908, 776, 753, 625.

m.p. = 108 °C.

[α]$_D^{25}$ –38.3 (c = 1.00, $CHCl_3$).

Benzyl (S)-(1-azido-1,1-bis(4-methoxyphenyl)-3-methylbutan-2-yl)carbamate, 147



To a solution of benzyl (S)-(1-hydroxy-1,1-bis(4-methoxyphenyl)-3-methylbutan-2-yl)carbamate **146** (1.38 g, 3.07 mmol, 1.00 equiv.) in $CHCl_3$ (30 mL) was added TFA (0.61 mL, 8.0 mmol, 2.6 equiv.) and NaN_3 (1.10 g, 16.9 mmol, 5.50 equiv.) at 0 °C. The reaction mixture was stirred for 1 h and a further 4 h at r.t. The reaction mixture was quenched with sat. aq. $NaHCO_3$ until neutral and extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **147** as a colourless oil (1.19 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.20 (9H, m, 9 × Ar-H), 6.90 – 6.83 (4H, m, 4 × Ar-H), 5.13 (1H, d, *J*=12.3 Hz, C10-H_AH_B), 5.08 (1H, d, *J*=12.3 Hz, C10-H_AH_B), 4.86 (1H, d, *J*=11.0 Hz, N*H*), 4.65

(1H, dd, *J*=11.1, 1.7 Hz, C2-H), 3.81 (3H, s, C9-H_3), 3.80 (3H, s, C9'-H_3), 1.93 (1H, heptd, *J*=6.7, 1.7 Hz, C3-H), 0.98 (3H, d, *J*=6.9 Hz, C4-H_3), 0.52 (3H, d, *J*=6.7 Hz, C4'-H_3).

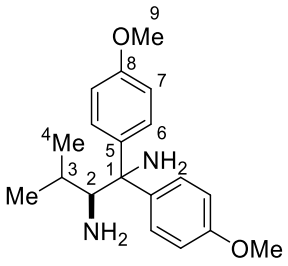
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 159.1 (Ar), 159.1 (Ar), 156.7 (Ar), 136.7 (Ar), 133.3 (Ar), 133.1 (Ar), 129.1 (2 × Ar), 129.0 (2 × Ar), 128.6 (2 × Ar), 128.2 (Ar), 128.1 (Ar), 113.8 (4 × Ar), 75.9 (C1), 67.0 (C10), 59.9 (C2), 55.4 (C9), 55.4 (C9), 28.9 (C3), 23.2 (C4), 16.7 (C4'). [*N.B*. A signal corresponding to C=O was not observed].

HRMS (ESI^+) m/z calcd. for $C_{27}H_{30}O_4N_4Na$ $[M+Na]^+$ 497.2159; found at 497.2171, Δ 2.35 ppm.

FTIR (neat) v/cm^{-1} = 3439, 2960, 2837, 2106, 1719, 1609, 1509, 1252, 1222, 1179, 910, 616.

[α]$_D^{25}$ –34.3 (c = 1.00, EtOH).

(*S*)-1-Azido-1,1-bis(4-methoxyphenyl)-3-methylbutan-2-amine [(*S*)-DAIPEN], 143



To a solution of benzyl (S)-(1-azido-1,1-bis(4-methoxyphenyl)-3-methylbutan-2-yl)carbamate **147** (1.00 g, 2.11 mmol, 1.00 equiv.) in EtOH (10 mL) was added Pd/C (10% w/w, 100 mg) in a single portion. The resulting suspension was sparged with a stream of H_2 for 5 min and then stirred under an atmosphere of H_2 (balloon pressure) for 24 h. After this time, the reaction mixture was filtered through a pad of Celite®, eluting with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification by trituration with hexane afforded the title compound **143** as a white solid (305 mg, 42%).

^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 – 7.29 (2H, m, 2 × Ar-H), 7.29 – 7.25 (2H, m, 2 × Ar-H), 6.78 – 6.72 (4H, m, 4 × Ar-H), 3.71 (3H, s, C9-H_3), 3.70 (3H, s, C9'-H_3), 3.50 (1H, d, *J*=1.7 Hz, C2-H), 1.81 (1H, pd, *J*=6.8, 1.7 Hz, C3-H), 0.92 (3H, d, *J*=7.0 Hz, C4-H_3), 0.66 (3H, d, *J*=6.8 Hz, C4'-H_3).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 158.0 (Ar), 158.0 (Ar), 140.3 (Ar), 139.7 (Ar), 127.9 (4 × Ar), 113.6 (2 × Ar), 113.5 (2 × Ar), 65.1 (C1), 61.1 (C2), 55.4 (C9), 55.3 (C9'), 28.0 (C3), 24.2 (C4), 17.1 (C4').

HRMS (ESI$^+$) m/z calcd. for $C_{19}H_{26}N_2O_2Na$ $[M+Na]^+$337.1887; found at 337.1891, Δ 1.32 ppm.

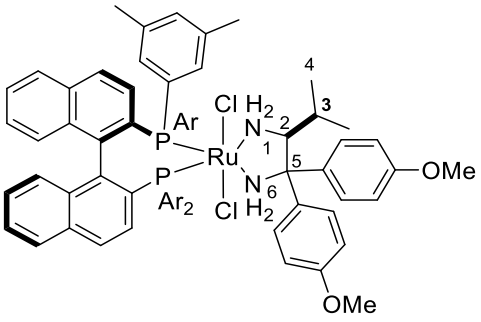
FTIR (neat) v/cm^{-1} = 3386, 2954, 2836, 1609, 1509, 1298, 1249, 1181, 1035, 913, 830, 737.

[α]$_D^{25}$ –4.4 (c = 1.00, $CHCl_3$).

m.p. = 58 – 59 °C.

6.3.1.7 Synthesis of $RuCl_2$(diphosphine)(diamine) Catalysts

trans-$RuCl_2$[(*R*)-Xyl-BINAP][(*S*)-DAIPEN], (R_P,S_N)-Ru-2



A schlenk flask was charged with $[RuCl_2(benzene)]_2$ (55.7 mg, 0.11 mmol, 1.00 equiv.) and (*S*)-Xyl-BINAP (81.6 mg, 0.22 mmol, 2.00 equiv.) and evacuated and backfilled with argon. Degassed DMF (1.6 mL) was added to the flask and the resulting mixture was evacuated and backfilled (3 × Ar) and stirred at 100 °C for 10 min to give a reddish brown solution. The reaction mixture was cooled to r.t. and (*S*)-DAIPEN **143** (70.0 mg, 0.22 mmol, 2.00 equiv.) was added and stirred at r.t. for 6 h. DMF was removed *in vacuo* and the residue was dissolved in ether (3 mL) and the resulting black turbidity was removed by filtration through a SiO_2 plug. The filtrate was concentrated to ~0.2 mL, and then hexane (0.2 mL) was added, precipitating a light brown solid. The supernatant was removed through a canula fitted with filter paper. The resulting powder was dried under reduced pressure to give the title compound **(R_P,S_N)-Ru-2** as a dark red/brown powder (54.5 mg, 41% yield).

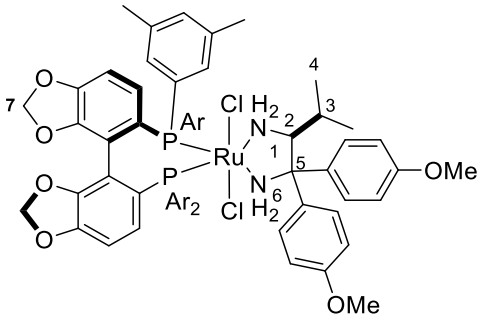
^{1}H NMR (500 MHz, C_6D_6) δ_H 9.02 (1H, dd, *J*=8.4, 6.2 Hz, Ar-H), 8.84 (1H, t, *J*=7.6 Hz, Ar-H), 8.32 (2H, d, *J*=6.9 Hz, 2 × Ar-H), 8.19 (2H, d, *J*=7.1 Hz, 2 × Ar-H), 7.90 (3H, br. s, 3 × Ar-H), 7.77 (1H, d, *J*=8.6 Hz, Ar-H), 7.69 (1H, d, *J*=8.6 Hz, Ar-H), 7.55 – 7.46 (2H, m, 2 × Ar-H), 7.43 (1H, d, *J*=8.1 Hz, Ar-H), 7.36 (1H, d, *J*=8.2 Hz, Ar-H), 7.10 – 7.03 (2H, m, 2 × Ar-H), 6.90 (2H, dddd, *J*=20.7, 8.0, 6.6, 1.2 Hz, 2 × Ar-H), 6.84 (1H, s, Ar-H), 6.81 (2H, d, *J*=8.6 Hz, 2 × Ar-H), 6.60 (1H, s, Ar-H), 6.54 – 6.48 (2H, m, 2 × Ar-H), 6.46 (1H, ddd, *J*=8.1, 6.6, 1.3 Hz, Ar-H), 6.41 (3H, ddd, *J*=8.6, 6.6, 1.3 Hz, 2 × Ar-H), 6.31 (1H, d, *J*=8.6 Hz, Ar-H), 5.96 (1H, s, Ar-H), 5.87 (1H, s, Ar-H), 4.77 (1H, dt, *J*=13.9, 3.0 Hz, C2-H), 4.69 (1H, dd, *J*=11.1, 2.7 Hz, N6-H_AH_B), 3.88 (1H, t, *J*=11.4 Hz, N1-H_AH_B), 3.36 – 3.30

(4H, m, OCH_3, N6-H_AH_B), 3.21 (3H, s, OCH_3), 2.75 (1H, d, *J*=9.5 Hz, N1-H_AH_B), 2.21 (6H, s, 2 × Ar-CH_3), 2.05 (6H, s, 2 × Ar-CH_3), 1.90 – 1.80 (1H, m, C3-H), 1.76 (6H, s, 2 × Ar-CH_3), 1.71 (6H, s, 2 × Ar-CH_3), 0.55 (3H, d, *J*=6.7 Hz, C4-H_3), 0.03 (3H, d, *J*=6.7 Hz, C4'-H_3).

^{31}P NMR (202 MHz, C_6D_6) δ_P 45.1 (d, *J*=37.2 Hz), 44.9 (d, *J*=37.4 Hz).

HRMS (ESI^+) m/z calcd. for $C_{71}H_{75}Cl_2N_2O_2P_2Ru$ $[M+H]^+$ 1220.3641; found at 1220.3614, Δ 2.1 ppm.

***trans*-RuCl$_2$[(*R*)-Xyl-SEGPHOS][(*S*)-DAIPEN], (R_P,S_N)-Ru-16**



According to a modified literature procedure: To a solution of [RuCl(p-cymene)((*R*)-Xyl-SEGPHOS)]Cl (100 mg, 0.10 mmol, 1.00 equiv.) in PhMe (1.0 mL) was added (*S*)-DAIPEN **143** (30.5 mg, 0.100 mmol, 1.00 equiv.). The reaction mixture was stirred at 80 °C for 2 h. After this time the solution was concentrated and purified by column chromatography (PhMe:EtOAc, 100:0 to 90:10) to afford the title compound **(R_P,S_N)-Ru-16** as a brown solid (61 mg, 52%).

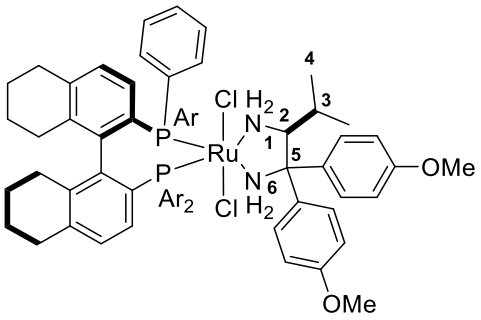
^{1}H NMR (400 MHz, C_6D_6) δ_H 8.24 (2H, d, *J*=9.3 Hz, 2 × Ar-H), 8.05 (2H, d, *J*=9.2 Hz, 2 × Ar-H), 7.91 (1H, t, *J*=8.5 Hz, Ar-H), 7.63 (2H, d, *J*=8.8 Hz, 2 × Ar-H), 7.38 – 7.32 (1H, m, Ar-H), 7.14 – 7.08 (2H, m, 2 × Ar-H), 7.07 – 6.99 (3H, m, 3 × Ar-H), 6.96 (1H, s, Ar-H), 6.86 (1H, s, Ar-H), 6.80 (2H, d, *J*=8.9 Hz, 2 × Ar-H), 6.68 (1H, d, *J*=1.7 Hz, Ar-H), 6.63 (1H, s, Ar-H), 6.58 (3H, dd, *J*=8.2, 6.5 Hz, 3 × Ar-H), 6.51 (1H, dd, *J*=8.1, 1.0 Hz, Ar-H), 6.40 (1H, dd, *J*=8.1, 1.0 Hz, Ar-H), 5.35 (1H, d, *J*=1.7 Hz, C7-H_AH_B), 5.29 (1H, d, *J*=2.0 Hz, C7'-H_AH_B), 5.17 (1H, d, *J*=1.8 Hz, C7-H_AH_B), 5.05 (1H, d, *J*=13.4 Hz, C2-H), 4.87 (1H, d, *J*=2.0 Hz, C7'-H_AH_B), 4.81 (1H, dd, *J*=10.8, 4.2 Hz, N6-H_AH_B), 4.10 – 3.97 (1H, m, N1-H_AH_B), 3.59 (1H, d, *J*=10.6 Hz, N6-H_AH_B), 3.46 (1H, d, *J*=9.2 Hz, N1-H_AH_B), 3.30 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 2.21 (6H, s, 2 × Ar-CH_3), 2.11 (3H, s, Ar-CH_3), 2.09 (6H, s,

2 × Ar-CH_3), 2.00 (6H, s, 2 × Ar-CH_3), 1.98 (3H, s, Ar-CH_3), 1.95 – 1.87 (1H, m, C3-H), 0.77 (3H, d, *J*=6.8 Hz, C4-H_3), 0.02 (3H, d, *J*=6.7 Hz, C4'-H_3).

^{31}P NMR (162 MHz, C_6D_6) δ_P 48.3 (d, *J*=37.6 Hz), 44.9 (d, *J*=37.4 Hz).

HRMS (ESI^+) m/z calcd. for $C_{65}H_{71}Cl_2N_2O_6P_2Ru$ $[M+H]^+$ 1208.3124; found at 1208.3130, Δ 0.5 ppm.

***trans*-RuCl$_2$[(*R*)-H$_8$BINAP][(*S*)-DAIPEN], (R_P,S_N)-Ru-19**



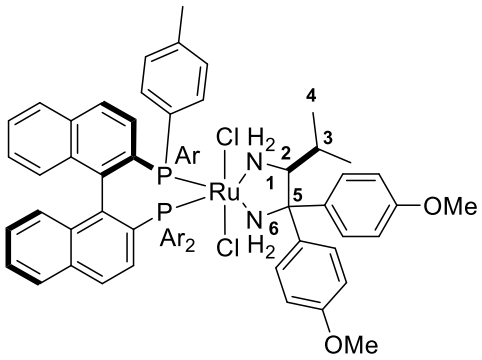
According to a modified literature procedure: To a solution of [RuCl(p-cymene)((*R*)-H_8-binap)]Cl (50.0 mg, 0.05 mmol, 1.00 equiv.) in PhMe (0.5 mL) was added (*S*)-DAIPEN **143** (16.8 mg, 0.05 mmol, 1.00 equiv.). The reaction mixture was stirred at 80 °C for 2 h. After this time the solution was concentrated and purified by column chromatography (PhMe:EtOAc, 100:0 to 90:10) to afford the title compound **(R_P,S_N)-Ru-16** as a brown solid (32 mg, 57%).

^{1}H NMR (500 MHz, C_6D_6) δ_H 8.46 (1H, t, *J*=8.1 Hz, Ar-H), 8.40 (2H, t, *J*=8.1 Hz, 2 × Ar-H), 8.27 (7H, ddt, *J*=33.8, 16.1, 8.3 Hz, 7 × Ar-H), 7.48 (2H, d, *J*=8.8 Hz, 2 × Ar-H), 7.27 – 7.19 (2H, m, 2 × Ar-H), 7.11 – 6.88 (11H, m, 11 × Ar-H), 6.85 (3H, t, *J*=7.4 Hz, 3 × Ar-H), 6.78 (2H, d, *J*=8.7 Hz, 2 × Ar-H), 6.57 – 6.49 (2H, m, 2 × Ar-H), 4.58 (1H, d, *J*=13.2 Hz, C2-H), 4.39 (1H, dd, *J*=10.9, 4.0 Hz, N6-H_AH_B), 3.71 (1H, t, *J*=11.5 Hz, N1-H_AH_B), 3.30 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 3.13 – 3.04 (1H, m, N6-H_AH_B), 2.55 – 2.32 (5H, m, 4 × Cy-H, N1-H_AH_B), 1.77 – 1.58 (3H, m, C3-H, 2 × Cy-H), 1.46 – 0.77 (10H, m, 10 × Cy-H), 0.43 (3H, d, *J*=6.8 Hz, C4-H_3), -0.11 (3H, d, *J*=6.7 Hz, C4'-H_3).

^{31}P NMR (202 MHz, C_6D_6) δ_P 45.54 (d, *J*=39.1 Hz), 44.88 (d, *J*=39.1 Hz).

HRMS (ESI^+) m/z calcd. for $C_{63}H_{67}Cl_2N_2O_2P_2Ru$ $[M+H]^+$ 1116.3015; found at 1116.2995, Δ 1.8 ppm.

***trans*-RuCl$_2$[(*R*)-tol-BINAP][(*S*)-DAIPEN], (R_P,S_N)-Ru-20**



According to a modified literature procedure: To a solution of [RuCl(p-cymene)((*R*)-tol-binap)]Cl (100 mg, 0.10 mmol, 1.00 equiv.) in PhMe (1.0 mL) was added (*S*)-DAIPEN **143** (31.9 mg, 0.10 mmol, 1.00 equiv.). The reaction mixture was stirred at 80 °C for 2 h. After this time the solution was concentrated and purified by column chromatography (PhMe:EtOAc, 100:0 to 90:10) to afford the title compound **(R_P,S_N)-Ru-20** as a brown solid (55.4 mg, 48%).

^{1}H NMR (500 MHz, C_6D_6) δ_H 8.73 (1H, t, *J*=8.0 Hz, Ar-H), 8.51 (2H, t, *J*=8.3 Hz, 2 × Ar-H), 8.40 (1H, t, *J*=8.4 Hz, Ar-H), 8.34 (2H, t, *J*=8.3 Hz. 2 × Ar-H), 8.05 – 7.92 (4H, m, 4 × Ar-H), 7.69 (1H, d, *J*=8.5 Hz, Ar-H), 7.61 (3H, dd, *J*=8.7, 3.8 Hz, 3 × Ar-H), 7.41 (1H, dd, *J*=8.2, 1.3 Hz, Ar-H), 7.32 (1H, d, *J*=8.1 Hz, Ar-H), 7.15 – 7.12 (4H, m, 4 × Ar-H), 7.04 – 6.87 (4H, m, 4 × Ar-H), 6.85 (2H, d, *J*=8.7 Hz, 2 × Ar-H), 6.63 (1H, d, *J*=8.6 Hz, Ar-H), 6.59 – 6.54 (2H, m, 2 × Ar-H), 6.52 (1H, ddd, *J*=8.4, 6.7, 1.4 Hz, Ar-H), 6.40 – 6.30 (4H, m, 4 × Ar-H), 6.25 – 6.19 (2H, m, 2 × Ar-H), 4.88 (1H, dt, *J*=14.0, 2.9 Hz, C2-H), 4.76 (1H, dd, *J*=10.9, 4.1 Hz, N6-H_AH_B), 3.92 (1H, ddd, *J*=13.8, 10.0, 3.6 Hz, N6-H_AH_B), 3.65 (1H, dd, *J*=10.8, 2.6 Hz, N1-H_AH_B), 3.33 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.14 (1H, d, *J*=9.6 Hz, N1-H_AH_B), 2.10 (3H, s, Ar-CH_3), 1.86 (4H, br. s, C3-H, Ar-CH_3), 1.70 (3H, s, Ar-CH_3), 1.64 (3H, s, Ar-CH_3), 0.63 (3H, d, *J*=6.8 Hz, C4-H_3), -0.02 (3H, d, *J*=6.7 Hz, C4'-H_3).

^{31}P NMR (162 MHz, C_6D_6) δ_P 48.7 (d, *J*=37.5 Hz), 45.7 (d, *J*=37.4 Hz).

HRMS (ESI$^+$) m/z calcd. for $C_{67}H_{67}Cl_2N_2O_2P_2Ru$ $[M+H]^+$ 1164.3015; found at 1164.2996, Δ 1.6 ppm.

6.4. Data for Chapter 4

6.4.1 Experimental procedures and characterization

General procedure 4-A: Hydrogen borrowing alkylation of linear alcohols.

To a 2 – 5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate linear alcohol (0.30 mmol, 1.0 equiv.), chiral ligand (5.0 mol%), Ir(cod)acac (4.0 mol%) and KO^{t}Bu (0.6 mmol, 2.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), then evacuated and backfilled with nitrogen. ^{t}BuOH (0.5 mL, 0.6 M) was purged with nitrogen for 15 min, added to the reaction vessel and stirred at 110 °C in a preheated oil bath for 18 h. [If the linear alcohols were oil instead of solids, and the reaction mixture was additionally sparged with Ar for 5 min after the addition of solvent and then heated to 110 °C.] The mixture was cooled to r.t., diluted with Et_2O, filtered through a SiO_2 plug (eluting with ca. 50 mL Et_2O), concentrated and purified by column chromatography (see experimental methods section for details). Purification generally required the use of Merck Silica gel 60 (15 – 40 μm). Racemic cyclohexane products were obtained using our previously reported procedure.[33]

General procedure 4-B: Hydrogen borrowing annulation using 1,5-diols.

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate diol (0.60 mmol, 2.0 equiv.), pentamethylacetophenone **8** (0.30 mmol, 1.0 equiv.), chiral ligand (5.0 mol%), Ir(cod)acac (4.0 mol%) and KO^{t}Bu (0.6 mmol, 2.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), then evacuated and backfilled with nitrogen. ^{t}BuOH (0.1 mL, 3 M) was purged with nitrogen for 15 min, added to the reaction vessel and stirred at 110 °C in a preheated oil bath for 18 h. The mixture was cooled to r.t., filtered through a SiO_2 plug (eluting with ca. 50 mL Et_2O). For ease of purification from residual (*R*)-DTBM-SEGPHOS, a solution of the crude product in

Et_2O (ca. 40 mL) was treated with *tert*-butyl hydroperoxide (5-6 M in decane, 50 µL, ~0.28 mmol), swirled and allowed to stand at r.t. for 10 min. The resulting solution was then concentrated and purified by column chromatography (see experimental methods section for details). Racemic cyclohexane products were obtained using a previously reported procedure.[33]

General procedure 4-C: Alkylation of Ph* malonates.

Cs_2CO_3 (13.2 mmol, 1.20 equiv.) was added to a solution of the appropriate malonate (11.0 mmol, 1.00 equiv.) in DMF (90 mL) and stirred for 15 min at r.t. The appropriate alkyl halide (44.0 mmol, 4.00 equiv.) was added and the resulting mixture was stirred overnight at r.t. to 80 °C (see experimental methods section for details). The reaction mixture was quenched with sat. aq. NH_4Cl (60 mL) and extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with aqueous LiCl (5 wt%, 3 × 50 mL), brine (3 × 50 mL), and dried ($MgSO_4$). The resulting solution was then concentrated and purified by column chromatography (see experimental methods section for details).

General procedure 4-D: Decarboxylation of Ph* malonates.

The appropriate malonate (1.00 equiv.) was added to a solution of LiCl (3.00 equiv.) in H_2O and DMSO. The resulting reaction mixture was stirred at 160 °C and monitored by TLC (see experimental methods section for details). The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (see experimental methods section for details).

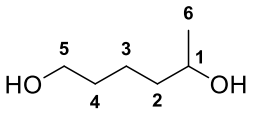
General procedure 4-E: Reduction of Ph* esters.

To a solution of the appropriate Ph* ester (1.00 equiv.) in Et_2O (0.2 M) at –78 °C was added $LiAlH_4$ (1.00 equiv.) in portions. The reaction was stirred at –78 °C for 2 h and then stirred at 0 °C for an additional 10 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O, aq. NaOH (15% w/v) and H_2O at 0 °C. The resulting mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered,

concentrated *in vacuo* and purified by column chromatography (see experimental methods section for details).

6.4.1.1 Synthesis of diols

Hexane-1,5-diol, 19a

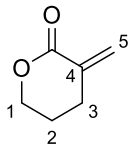


$LiAlH_4$ (2.00 g, 52.4 mmol, 1.2 equiv.) was added portionwise to a solution of commercially available δ-hexalactone (5.00 mL, 45.6 mmol, 1.0 equiv.) in Et_2O (250 mL) at 0 °C. The reaction was warmed to r.t. for 1 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (2 mL), aq. NaOH (15% w/v, 2 mL) and H_2O (6 mL) at 0 °C. The reaction mixture was diluted with Et_2O (100 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 96:4) afforded the title compound **19a** as a transparent oil (4.66 g, 86%). The spectral data matched that previously reported in the literature.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.83 – 3.70 (1H, m, C1-H), 3.59 (2H, t, *J*=6.3 Hz, C5-H_2), 2.77 (2H, s, 2 × O<u>H</u>), 1.66 – 1.28 (6H, m, C2-H_2, C3-H_2, C4-H_2), 1.15 (3H, d, *J*=6.2 Hz, C6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 67.9 (C1), 62.4 (C5), 38.8 (C2), 32.5 (C4), 23.5 (C6), 22.0 (C3).

3-Methylenetetrahydro-2H-pyran-2-one, 154



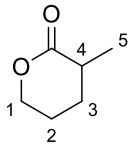
According to a literature procedure[128]: To a suspension of NaH (2.2 g, 55 mmol, 1.1 equiv., 60% dispersion in mineral oil) in Et_2O (90 mL) was added EtOH (0.32 mL, 5.5 mmol, 0.11 equiv.) dropwise. Followed by dropwise addition of a mixture of δ-valerolactone (5.0 g, 50 mmol, 1.0 equiv.) and ethyl formate (4.83 mL, 60 mmol, 1.2 equiv.) to give a steady reflux. After

completion of addition, the reaction mixture was stirred for 1 h. The resulting white solid was washed with Et_2O and filtered under nitrogen. To the white solid, THF (125 mL) and paraformaldehyde (7.5 g, 250 mmol, 5.0 equiv.) were added and heated to reflux for 1 h. Then the reaction mixture was cooled to 0 °C and quenched with aq. K_2CO_3 (30 mL, 6 M). The THF was evaporated and the resulting mixture was extracted with Et_2O (3× 60 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (CH_2Cl_2:pentane 80:20 to 100:0) afforded the title compound **154** as a transparent oil (2.25 g, 40%). The spectral data matched that previously reported in the literature.[128]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.42 (1H, q, *J*=1.8 Hz, C5-H_AH_B), 5.56 (1H, q, *J*=1.9 Hz, C5-H_AH_B), 4.41 – 4.33 (2H, m, C1-H_2), 2.66 (2H, tt, *J*=6.8, 2.0 Hz, C3-H_2), 2.00 – 1.90 (2H, m, C2-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.6 (C=O), 134.3 (C4), 128.4 (C5), 69.8 (C1), 28.3 (C3), 23.4 (C4).

3-Methyltetrahydro-2H-pyran-2-one, 155

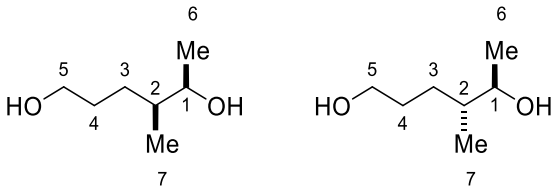


To a solution of lactone **154** (2.20 g, 19.6 mmol, 1.00 equiv.) in IPA (100 mL) was added Pd/C (10% w/w, 220 mg) in a single portion. The resulting suspension was sparged with a stream of H_2 for 5 min and then stirred under an atmosphere of H_2 (balloon pressure) for 1.5 h. After this time, the reaction mixture was filtered through a pad of Celite®, eluting with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification by column chromatography (Et_2O:pentane 40:60) afforded the title compound **155** as a transparent oil (1.04 g, 47%). The spectral data matched that previously reported in the literature.[129]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.39 – 4.22 (2H, m, C1-H_2), 2.62 – 2.49 (1H, m, C4-H), 2.14 – 2.02 (1H, m, C3-H_AH_B), 1.97 – 1.80 (2H, m, C2-H_2), 1.61 – 1.47 (1H, m, C3-H_AH_B), 1.25 (3H, dd, *J*=6.9, 1.0 Hz, C5-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 175.3 (C=O), 68.6 (C1), 34.7 (C4), 27.2 (C3), 22.1 (C2), 16.8 (C5).

4-Methylhexane-1,5-diol, 157



157a **157b**

To a stirred solution of 3-methyltetrahydro-2H-pyran-2-one **155** (1.02 g, 8.94 mmol, 1.00 equiv.) in CH_2Cl_2 (20 mL) at –78 °C was added DIBAL-H (1 M in hexanes, 11.6 mL, 11.6 mmol, 1.30 equiv.) dropwise over 5 min. The solution was stirred at –78 °C for 1.5 h. Rochelle's salt (55 mL) was added and the mixture was allowed to warm to r.t. over 16 h with vigorous stirring. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* The crude lactol was carried through to the next step in the synthesis without further purification.

To a stirred solution of MeMgBr (3 M in Et_2O, 10.4 mL, 31.3 mmol, 3.50 equiv.) at 0 °C was added a solution of the crude lactol (assumed quant., 8.94 mmol, 1.00 equiv.) in THF (10 mL) dropwise over 10 min. The reaction mixture was then warmed to r.t. and stirred for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried (MgSO4), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:EtOAc, 40:60) afforded the title compound **157** as an inseparable mixture of diastereoisomers as a colourless oil (473 mg, 40% over 2 steps, 50:50 d.r.). The spectral data matched that previously reported in the literature.[36]

157a

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.69 – 3.59 (3H, m, C1-H and C5-H_2), 1.81– 1.43 (6H, m, 2 × O*H*, C4-H_2, C3-H_AH_B, C2-H), 1.23–1.16 (1H, m, C3-H_AH_B), 1.14 (3H, d, *J*=6.3 Hz, C6-H_3), 0.88 (3H, d, *J*=6.8 Hz, C7-H_3).

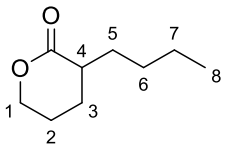
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 71.8 (C1), 63.2 (C5), 40.0 (C2), 30.3 (C4), 28.7 (C3), 19.9 (C6), 15.0 (C7).

157b

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.74 (1H, qd, *J*=6.3, 4.0 Hz, C1-H), 3.69 – 3.59 (2H, m, C5-H_2), 1.81 – 1.43 (6H, m, 2 × O*H*, C4-H_2, C3-H_AH_B, C2-H), 1.23 – 1.16 (1H, m, C3-H_AH_B), 1.15 (3H, d, *J*=6.4 Hz, C6-H_3), 0.89 (3H, d, *J*=6.8 Hz, C7-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 71.3 (C1), 63.2 (C5), 39.6 (C2), 30.6 (C4), 28.6 (C3), 20.2 (C6), 14.4 (C7).

3-Butyltetrahydro-2H-pyran-2-one, 209



A flame-dried Schlenk tube was charged with disopropylamine (7.73 mL, 54.8 mmol, 1.1 equiv.), dry THF (25 mL) and cooled to –78 °C under Argon. *n*BuLi in hexanes (35.0 mL, 1.6 M, 55.9 mmol, 1.1 equiv.) was added dropwise, and the resulting solution was stirred for 30 min at –78°C. A solution of commercially available δ-valerolactone (5.00 g, 49.9 mmol, 1.0 equiv.) in dry THF (30 mL) was added dropwise, and stirred for 20 min at –78 °C. A solution of 1-iodobutane (5.68 mL, 49.9 mmol, 1.0 equiv.) and HMPA (8.70 mL, 49.9 mmol, 1.0 equiv.) in dry THF (25 mL) was added dropwise, and the resulting solution was stirred for 10 minutes at –78 °C. The reaction mixture was then warmed to 0 °C and stirred for 4 h. The reaction was quenched by slow addition of sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (CH_2Cl_2:pentane 40:60 to 60:40) afforded the title compound **209** as a transparent oil (632 mg, 8%). The spectral data matched that previously reported in the literature.[130]

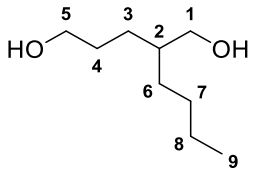
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.35 – 4.24 (2H, m, C1-H_2), 2.44 (1H, dtd, *J*=10.8, 7.7, 5.2 Hz, C4-H), 2.15 – 2.02 (1H, m, C3-H_{eq}), 1.98 – 1.80 (3H, m, C2-H_2, C5-H_AH_B), 1.60 – 1.43 (2H, m, C3-H_{ax}, C5-H_AH_B), 1.40 – 1.27 (4H, m, C6-H_2, C7-H_2), 0.94 – 0.85 (3H, m, C8-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 174.9 (C=O), 68.5 (C1), 39.7 (C4), 31.1 (C5), 29.1 (C6), 24.7 (C3), 22.8 (C7), 22.2 (C2), 14.1 (C8).

HRMS (ESI^+) m/z calcd. for $C_9H_{17}O_2$ $[M+H]^+$ 157.1223; found at 157.1223, Δ 0.25 ppm.

FTIR (neat) ν/cm^{-1} = 2957, 2931, 2873, 2860, 1743, 1730, 1464, 1390, 1345, 1258, 1248, 1154, 1094, 1065, 961.

2-Butylpentane-1,5-diol, 150b



$LiAlH_4$ (172 mg, 4.53 mmol, 1.2 equiv.) was added portionwise to a solution of 3-butyltetrahydro-2H-pyran-2-one **209** (615 mg, 3.94 mmol, 1.0 equiv.) in Et_2O (25 mL) at 0 °C. The reaction was warmed to r.t. for 1 h. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.2 mL), aq. NaOH (15% w/v, 0.2 mL) and H_2O (0.6 mL) at 0 °C. The reaction mixture was diluted with Et_2O (10 mL) and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 95:5) afforded the title compound **150b** as a transparent oil (632 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.64 (2H, t, *J*=6.4 Hz, C5-H_2), 3.58 (1H, dd, *J*=10.7, 5.0 Hz, C1-H_AH_B), 3.51 (1H, dd, *J*=10.7, 5.9 Hz, C1-H_AH_B), 1.83 (2H, s, 2 × O<u>H</u>), 1.66 – 1.54 (2H, m, C4-H_2), 1.54 – 1.23 (9H, m, C2-H, C3-H_2, C6-H_2, C7-H_2, C8-H_2), 0.95 – 0.81 (3H, m, C9-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 65.6 (C1), 63.3 (C5), 40.3 (C2), 30.9 (C6/7/8), 29.9 (C4), 29.3 (C6/7/8), 27.1 (C3), 23.2 (C6/7/8), 14.2 (C9).

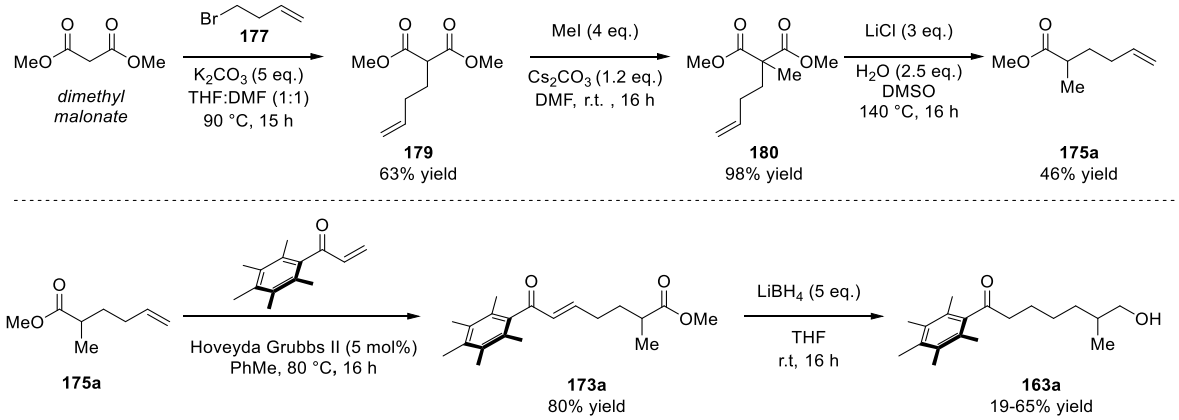
HRMS (ESI^+) m/z calcd. for $C_9H_{20}O_2Na$ $[M+Na]^+$ 183.1356; found at 183.1359, Δ 1.07 ppm.

FTIR (neat) ν/cm^{-1} = 3440, 2957, 2928, 2873, 2857, 1468, 1455, 1378, 1108, 1057, 1038, 895, 728.

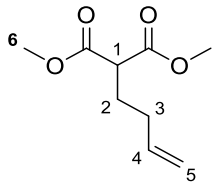
6.4.1.2 Synthesis of linear alcohols

6.4.1.2.1 First Generation Route

A | *First generation route to linear regiodefined alcohols*



Dimethyl 2-(but-3-en-1-yl)malonate, 179

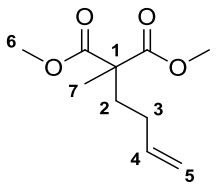


According to a modified literature procedure[131]: K_2CO_3 (13.8 g, 100 mmol, 5.00 equiv.) was added to a solution of dimethylmalonate (11.5 mL, 100 mmol, 5.00 equiv.) and 4-bromobut-1-ene (2.03 mL, 20.0 mmol, 1.00 equiv.) in THF/DMF (1:1, 75 mL). The mixture was stirred at 90 °C for 15 h. The reaction was cooled, diluted with H_2O (60 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 100:0 to 95:5) afforded the title compound **179** (2.33 g, 63%) as a clear oil. The spectral data matched that previously reported in the literature.[132]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.75 (1H, ddt, *J*=17.0, 10.0, 6.5 Hz, C4-H), 5.10 – 4.97 (2H, m, C5-H_2), 3.73 (6H, s, 2 × C6-H_3), 3.39 (1H, t, *J*=7.5 Hz, C1-H), 2.14 – 2.05 (2H, m, C3-H_2), 2.04 – 1.97 (2H, m, C2-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.9 (2 × C=O), 136.9 (C4), 116.2 (C5), 52.6 (2 × C6), 51.0 (C1), 31.4 (C3), 28.0 (C2).

Dimethyl 2-(but-3-en-1-yl)malonate, 180

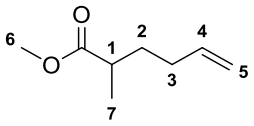


According to a literature procedure[133]: a solution of dimethyl 2-(but-3-en-1-yl)malonate **179** (1.13 g, 6.10 mmol, 1.00 equiv.) in DMF (5 mL) was added to a stirring suspension of Cs_2CO_3 (2.12 g, 6.50 mmol, 1.20 equiv.) in DMF (25 mL). MeI (1.52 mL, 24.4 mmol, 4.00 equiv.) was added and the resulting mixture was stirred for 21 h. The reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (3 × 25 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **180** (1.20 g, 98%) as a transparent oil. The spectral data matched that previously reported in the literature.[133]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.73 (1H, ddt, *J*=17.0, 10.0, 6.0 Hz, C4-H), 4.98 (1H, dq, *J*=17.0, 1.5 Hz, C5-H_AH_B), 4.91 (1H, ddt, *J*=10.0, 2.0, 1.0 Hz, C5-H_AH_B), 3.67 (6H, s, 2 × C6-H_3), 2.02 – 1.85 (4H, m, C2-H_2, C3-H_2), 1.38 (3H, s, C7-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.7 (2 × C=O), 137.6 (C4), 115.1 (C5), 53.5 (C1), 52.4 (2 × C6), 34.9 (C2/3), 28.7 (C3/2), 20.0 (C7).

Methyl 2-methylhex-5-enoate, 175a



Dimethyl 2-(but-3-en-1-yl)malonate **180** (1.20 g, 6.00 mmol, 1.00 equiv.) was added to a solution of LiCl (760 mg, 18.0 mmol, 3.00 equiv.) in H_2O (0.27 mL) and DMSO (10 mL) and the resulting reaction mixture was stirred at 140 °C for 1 h. The reaction mixture was cooled and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in*

vacuo. Purification by column chromatography (Pentane:Et_2O, 80:20) afforded the title compound **175a** (390 mg, 46%) as a transparent oil.

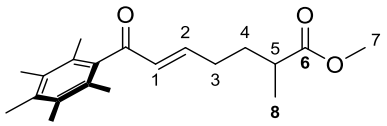
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.78 (1H, ddt, *J*=17.0, 10.0, 6.5 Hz, C4-H), 5.08 – 4.89 (2H, m, 2 × C5-H), 3.67 (3H, s, 3 × C6-H), 2.47 (1H, hex, *J*=7.0 Hz, C1-H), 2.06 (2H, dtt, *J*=8.0, 6.5, 1.5 Hz, 2 × C3-H), 1.86 – 1.68 (1H, m, C2-H), 1.55 – 1.44 (1H, m, C2-H'), 1.15 (3H, d, *J*=7.0 Hz, 3 × C7-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.3 (C=O), 138.0 (C4), 115.2 (C5), 51.6 (C6), 38.9 (C1), 33.0 (C2), 31.5 (C3), 17.1 (C7).

HRMS This compound could not be observed by ESI, APCI or EI analysis.

FTIR (neat) ν/cm^{-1} = 2955, 1731, 1642, 1435, 1380, 1238, 1203, 1153, 1113, 996, 914, 875 ,734.

Methyl (*E*)-2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)hept-5-enoate, 173a



1-(2,3,4,5,6-pentamethylphenyl)Prop-2-en-1-one[a] (101 mg, 0.50 mmol, 1.00 equiv.) and Hoveda Grubbs 2nd Generation Catalyst (15.7 mg, 5 mol%) were added sequentially to a solution of methyl 2-methylhex-5-enoate **175a** (85.3 mg, 0.60 mmol, 1.20 equiv.) in degassed PhMe (2 mL) and the resulting mixture was stirred at 80 °C for 21 h. After this time, the reaction mixture was cooled and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 90:10 to 85:15) afforded the title compound **173a** (127 mg, 80%) as a transparent oil. [a]Synthesised by Ciaran Lunt.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.43 (1H, dt, *J*=16.0, 6.5 Hz, C2-H), 6.31 (1H, dt, *J*=16.0, 1.0 Hz, C1-H), 3.66 (3H, s, C8-H_3), 2.48 – 2.37 (1H, m, C5-H), 2.28 – 2.15 (11H, m, 9 × Ar-C$\underline{H}_3$, C3-H_2), 2.05 (6H, s, 6 × Ar-C$\underline{H}_3$), 1.79 (1H, dq, *J*=14.0, 7.5 Hz, C4-H_AH_B), 1.53 (1H, dtd, *J*=14.0, 7.5, 6.5 Hz, C4-H_AH_B), 1.15 (3H, d, *J*=7.0 Hz, C8-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 203.0 (C=O), 176.7 (C6), 151.2 (C2), 138.0 (Ar), 135.5 (Ar), 133.5 (C1), 132.9 (2 × Ar), 128.9 (2 × Ar), 51.8 (C7), 39.0 (C5), 31.9 (C4), 30.3 (C3), 17.5 (2 × Ar-$\underline{C}H_3$), 17.2 (C8), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

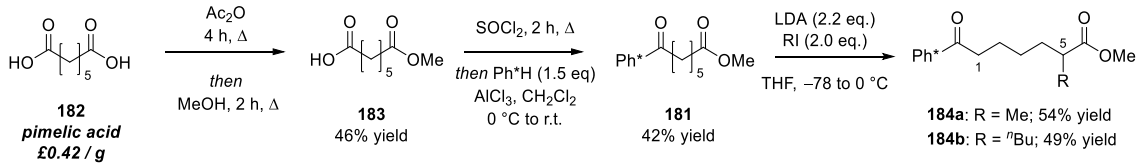
HRMS (ESI^+) m/z calcd. for $C_{20}H_{29}O_3$ $[M+H]^+$ 317.2111; found at 317.2112, Δ 0.38 ppm.

FTIR (neat) v/cm^{-1} = 2947, 1736, 1655, 1460, 1380, 1314, 1274, 1193, 1164, 985.

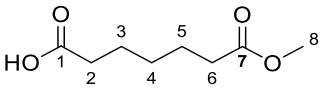
m.p. = 63 – 65 °C.

6.4.1.2.2 Second Generation Route

A | *Second generation route to linear regiodefined alcohols*



7-Methoxy-7-oxoheptanoic acid, 183

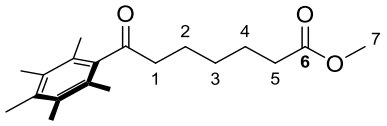


Pimelic acid (5.50 g, 41.6 mmol, 1.00 equiv.) was refluxed in acetic anhydride (80 mL) for 4 h. The reaction mixture was cooled, concentrated *in vacuo* and the resulting white solid was dried under high vacuum. The crude compound was then heated at reflux in methanol (20 mL) for 2 hr, before being concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10 to 60:40) afforded the title compound **183** as a colourless oil (3.31 g, 46%). The spectral data matched that previously reported in the literature.[134]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.66 (3H, s, C8-H_3), 2.39 – 2.28 (4H, m, 2 × C2-H, 2 × C6-H), 1.72 – 1.57 (4H, m, C3-H_2, C5-H_2), 1.47 – 1.30 (2H, m, C4-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 179.7 (C=O), 174.2 (C=O), 51.7 (C8), 33.9 (C2, C6), 28.6 (C4), 24.7 (C3/5), 24.4 (C5/3).

Methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 181



A solution of 7-methoxy-7-oxoheptanoic acid **183** (1.00 g, 5.74 mmol, 1.00 equiv.) in $SOCl_2$ (2.3 mL) was stirred at 80 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in CH_2Cl_2 (15 mL). Pentamethylbenzene (1.28 g, 8.61 mmol, 1.50 equiv.) was added, the reaction mixture was cooled to 0 °C and $AlCl_3$ (1.37 g, 10.3 mmol, 1.80 equiv.) was added portionwise over 10 min. The reaction was monitored by TLC and after

2 h, poured onto ice and conc. HCl (~15 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:CH_2Cl_2, 60:40) afforded the title compound **181** as a white solid (839 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (3H, s, C7-H_3), 2.67 (2H, t, *J*=7.3 Hz, C1-H_2), 2.33 (2H, t, *J*=7.5 Hz, C5-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.79 – 1.61 (4H, m, C2-H_2, C4-H_2), 1.42 (2H, ttd, *J*=10.0, 6.7, 3.4 Hz, C3-H_2).

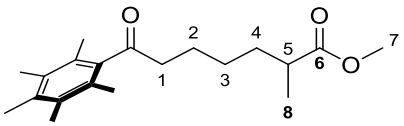
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.0 (C=O), 174.3 (C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.6 (C7), 45.5 (C1), 34.0 (C5), 28.8 (C3), 24.9 (C4), 23.0 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{19}H_{29}O_3$ $[M+H]^+$ 305.2111; found at 305.2110, Δ 0.33 ppm.

FTIR (neat) v/cm^{-1} = 2981, 2889, 1738, 1700, 1461, 1382, 1252, 1153, 1073, 954, 816.

m.p. = 60 – 61 °C.

Methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 184a

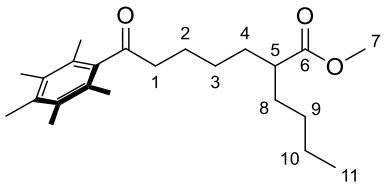


A flame-dried Schlenk tube was charged with disopropylamine (0.32 mL, 2.3 mmol, 2.3 equiv.), dry THF (5 mL) and cooled to –78 °C under Argon. *n*BuLi in hexanes (0.880 mL, 2.5 M, 2.20 mmol, 2.2 equiv.) was added dropwise, and the resulting solution was stirred for 30 minutes at –78 °C. A solution of methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **181** (304 mg, 1.00 mmol, 1.0 equiv.) in dry THF (5 mL) was added dropwise, and stirred for 20 min at –78 °C. Methyl iodide (0.120 mL, 2.00 mmol, 2.0 equiv.) was added dropwise, and the resulting solution was stirred at –78 °C for 1 h. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The reaction was quenched by slow addition of sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.*

Purification by column chromatography (Pentane:Et_2O, 99:1 to 95:5) afforded the title compound **184a** as a white solid (214 mg, 63%).

For data see chapter 6.4.1.2.4.

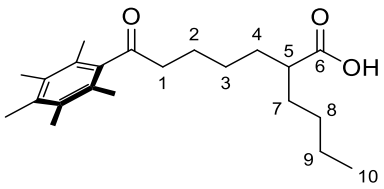
Methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 184b



A flame-dried Schlenk tube was charged with disopropylamine (0.64 mL, 4.6 mmol, 2.3 equiv.), dry THF (10 mL) and cooled to –78 °C under Argon. *n*BuLi in hexanes (1.76 mL, 2.5 M, 4.40 mmol, 2.20 equiv.) was added dropwise, and the resulting solution was stirred for 30 minutes at –78 °C. A solution of methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **181** (608 mg, 2.00 mmol, 1.00 equiv.) in dry THF (10 mL) was added dropwise, and stirred for 20 min at –78 °C. Butyl iodide (0.45 mL, 4.0 mmol, 2.0 equiv.) was added dropwise, and the resulting solution was stirred at –78 °C for 1 h. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The reaction was quenched by slow addition of sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 99:1 to 95:5) afforded the title compound **184b** as a white solid (350 mg, 49%).

For data see chapter 6.4.1.2.4.

2-Butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoic acid, 185b



To a solution of methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **184b** (422 mg, 1.20 mmol, 1.00 equiv.) in THF:H_2O:MeOH (7 mL, 1:1:4) was added LiOH (113 mg, 4.70 mmol, 4.00 equiv.). The reaction was stirred at 70 °C for 16 h. After cooling, the reaction mixture was cooled, diluted with Et_2O, acidified (3 M HCl) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O, 90:10 to Et_2O) afforded the title compound **185b** as a white solid (349 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.67 (2H, t, *J*=7.4 Hz, C1-H_2), 2.37 (1H, tt, *J*=8.5, 5.3 Hz, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.80 – 1.57 (4H, m, C2-H_2, C4-$H_A$$H_B$, C7-$H_A$$H_B$), 1.57 – 1.37 (4H, m, C4-$H_A$$H_B$, C8-$H_A$$H_B$, C3-$H_2$), 1.37 – 1.24 (4H, m, C8-H_2, C9-H_2), 0.92 – 0.83 (3H, m, C10-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.0 (C=O), 181.8 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 45.5 (C1), 45.4 (C5), 32.1 (C4/7), 32.0 (C7/4), 29.6 (C8), 27.1 (C3), 23.3 (C2), 22.7 (C9), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.0 (C10).

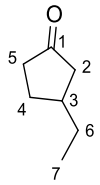
HRMS (ESI$^+$) m/z calcd. for $C_{22}H_{35}O_3$ $[M+H]^+$ 347.2581; found at 347.2581, Δ 0.12 ppm.

FTIR (neat) ν/cm^{-1} = 2936, 2161, 2009, 1977, 1694, 1466, 1406, 1225, 1116, 930.

m.p. = 89 – 91 °C.

6.4.1.2.3 Route I

3-Ethylcyclopentan-1-one, 189a

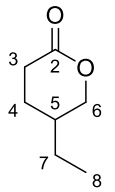


A suspension of magnesium turnings (425 mg, 17.5 mmol) in THF (4 mL) was stirred at r.t. and a single crystal of iodine was added followed by addition of bromoethane (0.75 mL, 10.1 mmol) at a rate which maintained a steady reflux. After the addition was complete the resulting suspension was cooled to r.t. and added dropwise by cannulation to a stirred solution of CuI (1.05 g, 5.50 mmol) in THF (40 mL) at –78 °C. The resulting solution was stirred for 5 min and cyclopentenone (0.42 mL, 5.00 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 3 h and then warmed to 0 °C for 30 min. After this time, the mixture was diluted with Et_2O, quenched by dropwise addition of sat. aq. NH_4Cl and then extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **189a** as colourless oil (212 mg, 38%). The spectral data matched that previously reported in the literature.[135]

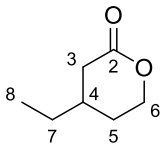
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.42 – 2.34 (1H, m, C2-H_AH_B), 2.34 – 2.23 (1H, m, C5-H_AH_B), 2.20 – 2.02 (3H, m, C5-H_AH_B, C4-H_AH_B, C3-H), 1.80 (1H, ddd, *J*=18.1, 10.1, 1.5 Hz, C2-H_AH_B), 1.55 – 1.40 (3H, m, C4-H_AH_B, C6-H_2), 0.95 (3H, t, *J*=7.4 Hz, C7-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 220.2 (C=O), 45.2 (C2), 39.1 (C3), 38.7 (C5), 29.3 (C4), 28.6 (C6), 12.4 (C7).

5-Ethyltetrahydro-2H-pyran-2-one, 188a



188a'



188a''

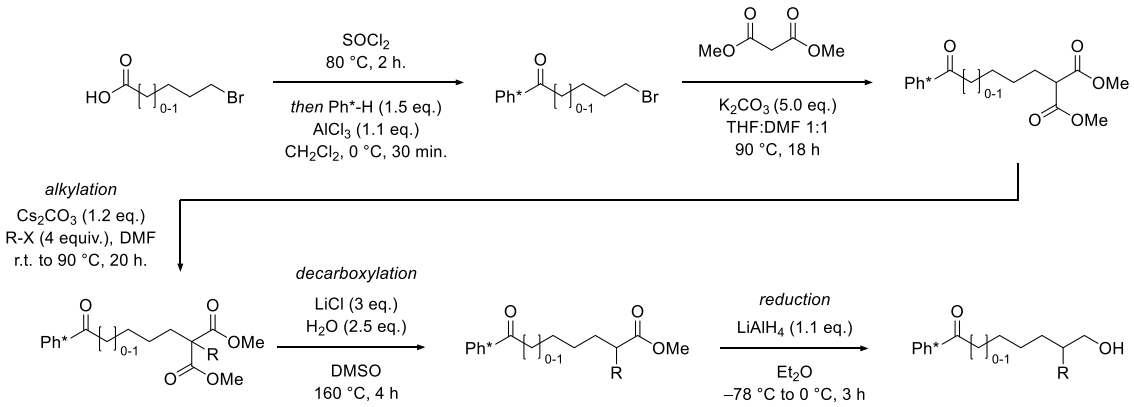
According to a literature procedure[104]: a stirred solution of 3-ethylcyclopentan-1-one (90 mg, 0.80 mmol) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C and *m*-CPBA (362 mg, 2.1 mmol) was added, followed by dropwise addition of trifluoroacetic acid (0.06 mL, 0.80 mmol) in the dark. The reaction mixture is warmed to r.t. and stirred for 1 h. After this time, the mixture was diluted with CH_2Cl_2 and quenched with 10% aqueous sodium sulphite solution, extracted with CH_2Cl_2 and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5) afforded the title compounds **188a'** and **188a''** as an inseparable mixture as a colourless oil (53 mg, 52%, 47:53 r.r.). The spectral data matched that previously reported in the literature.[136]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.40 (1H, ddd, *J*=11.3, 4.8, 4.0 Hz, C6''-H_{eq}), 4.33 (1H, ddd, *J*=11.1, 4.6, 1.9 Hz, C6'-H_{eq}), 4.24 (1H, ddd, *J*=11.3, 10.4, 3.7 Hz, C6''-H_{ax}), 3.94 (1H, dd, *J*=11.1, 9.8 Hz, C6'-H_{ax}), 2.68 (1H, ddd, *J*=17.3, 5.8, 1.5 Hz, C3''-H_{eq}), 2.64 – 2.56 (1H, m, C3'-H_{eq}), 2.48 (1H, ddd, *J*=17.8, 9.5, 7.3 Hz, C3'-H_{ax}), 2.12 (1H, dd, *J*=17.3, 10.1 Hz, C3''-H_{ax}), 2.06 – 1.73 (4H, m, C4'-H_AH_B, C5'-H, C5''-H_AH_B, C4''-H), 1.64 – 1.44 (2H, m, C4'-H_AH_B, C5''-H_AH_B), 1.44 – 1.24 (4H, m, C7'-H_2, C7''-H_2), 0.94 (3H, t, *J*=7.5 Hz, C8'-H_3), 0.92 (3H, t, *J*=7.5 Hz, C8''-H_3).

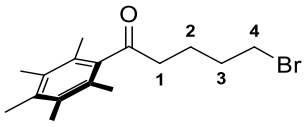
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.9 (2 × C=O), 73.6 (C6'), 68.7 (C6''), 36.4 (C3''), 34.5 (C5'), 33.2 (C4''), 29.1 (C3'), 29.0 (C7''), 28.6 (C5''), 25.2 (C4'), 24.6 (C7'), 11.4 (C8'), 11.0 (C8'').

6.4.1.2.4 Third Generation Route

A | *Third-generation route to access linear regiodefined alcohols*



5-Bromo-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 198



A solution of 5-bromopentanoic acid (20.0 g, 110 mmol, 1.00 equiv.) in $SOCl_2$ (44 mL) was stirred at 80 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in CH_2Cl_2 (250 mL). Pentamethylbenzene (21.2 g, 143 mmol, 1.30 equiv.) was added, the reaction mixture was cooled to 0 °C and $AlCl_3$ (16.1 g, 121 mmol, 1.10 equiv.) was added portionwise over 10 min. After 1 h the mixture was poured onto ice (ca. 200 g) and conc. HCl (ca. 15 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by trituration with hexane afforded the title compound **198** as a white solid (31.7 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.45 (2H, t, *J*=6.6 Hz, C4-H_2), 2.71 (2H, t, *J*=7.1 Hz, C1-H_2), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 2.05 – 1.92 (2H, m, C3-H_2), 1.92 – 1.80 (2H, m, C2-H_2).

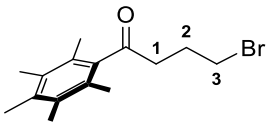
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.3 (C=O), 140.6 (Ar), 135.6 (Ar), 133.3 (2 × Ar), 127.4 (2 × Ar), 44.6 (C1), 33.4 (C4), 32.2 (C3), 22.1 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{16}H_{24}O_1Br$ $[M+H]^+$ 311.1005; found at 311.1006, Δ 0.36 ppm.

FTIR (neat) ν/cm^{-1} = 2944, 2925, 1699, 1576, 1457, 1404, 1382, 1350, 1303, 1267, 1251, 1226, 1110, 1069, 997, 918.

m.p. = 64 – 65 °C.

4-Bromo-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one, 204



A solution of 4-bromobutyric acid (10.0 g, 59.9 mmol, 1.00 equiv.) in $SOCl_2$ (24 mL) was stirred at 80 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in CH_2Cl_2 (150 mL). Pentamethylbenzene (11.5 g, 77.9 mmol, 1.30 equiv.) was added, the reaction mixture was cooled to 0 °C and $AlCl_3$ (8.72 g, 65.6 mmol, 1.10 equiv.) was added portionwise over 10 min. After 1 h the mixture was poured onto ice (ca. 100 g) and conc. HCl (ca. 8 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:pentane 20:80) followed by triturated with hexane afforded the title compound **204** as a white solid (10.4 g, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.57 (2H, t, *J*=6.4 Hz, C3-H_2), 2.88 (2H, t, *J*=6.9 Hz, C1-H_2), 2.33 – 2.25 (2H, m, C2-H_2), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3).

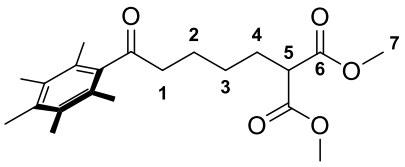
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 210.8 (C=O), 140.4 (Ar), 135.7 (Ar), 133.3 (2 × Ar), 127.4 (2 × Ar), 43.5 (C1), 33.5 (C3), 26.4 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{15}H_{21}O$ $[M\text{-}Br]^+$ 217.1587; found at 217.1589, Δ 1.08 ppm.

FTIR (neat) ν/cm^{-1} = 3025, 2922, 2360, 1699, 1437, 1352, 1313, 1242, 1109, 997, 909, 732.

m.p. = 72 – 73 °C.

Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 196



K_2CO_3 (62.1 g, 450 mmol, 5.00 equiv.) was added to a solution of dimethylmalonate (51.7 mL, 450 mmol, 5.00 equiv.) and 5-bromo-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one **199** (27.9 g, 90.0 mmol, 1.00 equiv.) in THF/DMF (1:1, 340 mL). The mixture was stirred at 90 °C for 16 h. The reaction was cooled, diluted with H_2O (300 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* For ease of purification, residual dimethylmalonate was removed by distillation and the remaining crude product was purified by trituration with hexane to afford the title compound **196** as a white solid (26.1 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.74 (6H, s, 2 × C7-H_3), 3.38 (1H, t, *J*=7.5 Hz, C5-H), 2.67 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.99 – 1.89 (2H, m, C4-H_2), 1.82 – 1.70 (2H, m, C2-H_2), 1.47 – 1.36 (2H, m, C3-H_2).

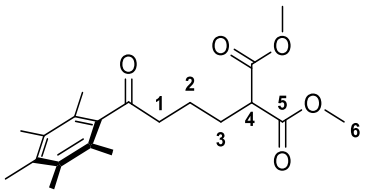
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.6 (C=O), 169.8 (2 × C6), 140.6 (Ar), 135.4 (Ar), 133.1 (2 × Ar), 127.3 (2 × Ar), 52.5 (2 × C7), 51.5 (C5), 45.1 (C1), 28.7 (C4), 26.9 (C3), 22.9 (C2), 17.2 (2 × Ar-$\underline{C}H_3$), 16.7 (Ar-$\underline{C}H_3$), 15.9 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{21}H_{30}O_5Na$ $[M+Na]^+$ 385.1985; found at 385.1987, Δ 0.32 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 2865, 1756, 1735, 1699, 1461, 1435, 1405, 1383, 1350, 1302, 1231, 1196, 1149.

m.p. = 56 – 58 °C.

Dimethyl 2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate, 206



K_2CO_3 (24.2 g, 175 mmol, 5.00 equiv.) was added to a solution of dimethylmalonate (20.1 mL, 175 mmol, 5.00 equiv.) and 4-bromo-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one **204** (10.4 g, 35.0 mmol, 1.00 equiv.) in THF/DMF (1:1, 130 mL). The mixture was stirred at 90 °C for 16 h. The reaction was cooled, diluted with H_2O (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo.* For ease of purification, residual dimethylmalonate was removed by distillation (< 0.1 mbar) and the remaining crude product was purified by column chromatography (CH_2Cl_2:pentane 70:30) to afford the title compound **206** as a white solid (6.55 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.75 (6H, s, 2 × C6-H_3), 3.42 (1H, t, *J*=7.5 Hz, C4-H), 2.70 (2H, t, *J*=7.3 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 2.05 – 1.93 (2H, m, C3-H_2), 1.82 – 1.69 (2H, m, C2-H_2).

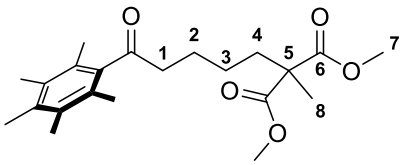
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.1 (C=O), 169.8 (2 × C5), 140.5 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 52.7 (2 × C6), 51.7 (C4), 45.1 (C1), 28.4 (C3), 21.2 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.0 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{20}H_{29}O_5$ $[M+H]^+$ 349.2010; found at 349.2019, Δ 2.71 ppm.

FTIR (neat) ν/cm^{-1} = 2954, 2360, 1736, 1701, 1437, 1350, 1241, 1155, 1121, 1064, 1004, 920.

m.p. = 64 – 65 °C.

Dimethyl 2-methyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199a



Methyl iodide (2.07 mL, 33.2 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (3.00 g, 8.3 mmol, 1.00 equiv.), Cs_2CO_3 (3.26 g, 10.0 mmol, 1.20 equiv.) and DMF (70 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **199a** as a white solid (1.40 g, 45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s, 2 × C7-H_3), 2.67 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.93 – 1.84 (2H, m, C4-H_2), 1.72 (2H, p, *J*=7.6 Hz, C2-H_2), 1.41 (3H, s, C8-H_3), 1.35 – 1.23 (3H, m, C3-H_2).

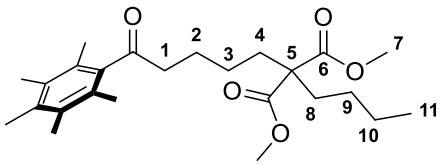
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9 (C=O), 172.9 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 53.8 (C5), 52.6 (2 × C7), 45.4 (C1), 35.7 (C4), 24.1 (C3), 23.6 (C2), 20.2 (C8), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.2142; found at 399.2147, Δ 1.25 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 1735, 1700, 1463, 1380, 1254, 1164, 1115, 987, 913, 873, 733.

m.p. = 81 – 82 °C.

Dimethyl 2-butyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199b



Cs_2CO_3 (21.6 g, 66.2 mmol, 1.20 equiv.) was added to a solution of dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (20.0 g, 55.2 mmol, 1.00 equiv.) in DMF (450 mL) and stirred for 15 min at r.t. Butyl iodide (25.0 mL, 221 mmol, 4.00 equiv.) was added and the resulting mixture was stirred for 21 h. The reaction mixture was quenched with sat. aq. NH_4Cl (300 mL) and extracted with Et_2O (3 × 350 mL). The combined organic extracts were washed with LiCl (5 wt%, 3 × 200 mL), brine (3 × 300 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by trituration with hexane afforded the title compound **199b** as a white solid (21.4 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.71 (6H, s, 2 × C7-H_3), 2.66 (2H, t, *J*=7.5 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.96 – 1.82 (4H, m, C4-H_2, C8-H_2), 1.72 (2H, qn, *J*=7.5 Hz, C2-H_2), 1.39 – 1.18 (4H, m, C10-H_2, C3-H_2), 1.18 – 1.05 (2H, m, C9-H_2), 0.89 (3H, t, *J*=7.3 Hz, C11-H_3).

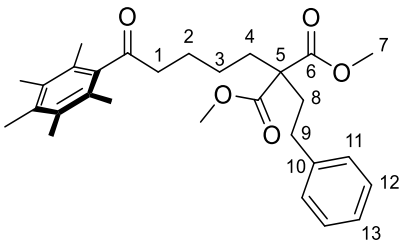
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.8 (C=O), 172.5 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 57.7 (C5), 52.4 (2 × C7), 45.4 (C1), 32.5 (C4/8), 32.5 (C8/4), 26.4 (C9), 23.9 (C3), 23.7 (C2), 23.0 (C10), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.0 (C11).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{39}O_5$ $[M+H]^+$ 419.2792; found at 419.2792, Δ 0.06 ppm.

FTIR (neat) ν/cm^{-1} = 2955, 1733, 1700, 1461, 1433, 1405, 1381, 1304, 1266, 1203, 1157, 1128, 1077.

m.p. = 92 – 93 °C.

Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)-2-phenethylmalonate, 199c



(2-bromoethyl)Benzene (4.52 mL, 33.2 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (3.00 g, 8.3 mmol, 1.00 equiv.), Cs_2CO_3 (3.26 g, 10.0 mmol, 1.20 equiv.) and DMF (70 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 48 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **199c** an oil which solidified on standing to a white solid (2.73 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31 – 7.24 (2H, m, 2 × Ar-H), 7.23 – 7.14 (3H, m, 3 × Ar-H), 3.72 (6H, s, C7-H_3), 2.67 (2H, t, *J*=7.4 Hz, C1-H_2), 2.55 – 2.46 (2H, m, C9-H_2), 2.23 (3H, s, Ar-CH_3), 2.22 – 2.19 (2H, m, C8-H_2), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 2.04 – 1.97 (2H, m, C4-H_2), 1.73 (2H, p, *J*=7.6 Hz, C2-H_2), 1.34 – 1.24 (2H, m, C3-H_2).

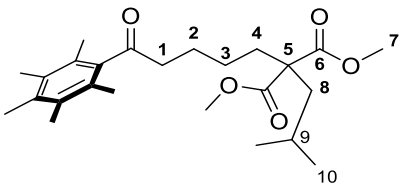
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8 (C=O), 172.1 (2 × C6), 141.4 (Ar), 140.7 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.6 (2 × Ar), 128.5 (2 × Ar), 127.4 (2 × Ar), 126.2 (Ar), 57.7 (C5), 52.6 (2 × C7), 45.4 (C1), 34.7 (C8), 32.9 (C4), 30.8 (C9), 23.9 (C3), 23.6 (C2), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{29}H_{39}O_5$ $[M+H]^+$ 467.2792; found at 467.2794, Δ 0.42 ppm.

FTIR (neat) ν/cm^{-1} = 2951, 2360, 1732, 1699, 1454, 1247, 1175, 1124, 910, 732, 700, 649.

m.p. = 141 – 142 °C.

Dimethyl 2-isobutyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199d



1-Bromo-2-methylpropane (3.61 mL, 33.2 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (3.00 g, 8.3 mmol, 1.00 equiv.), Cs_2CO_3 (3.26 g, 10.0 mmol, 1.20 equiv.) and DMF (70 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 48 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **199d** as a pale yellow solid (2.09 g, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.70 (6H, s, 2 × C7-H_3), 2.66 (2H, t, *J*=7.5 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.99 – 1.89 (2H, m, C4-H_2), 1.88 (2H, d, *J*=6.4 Hz, C8-H_2), 1.72 (2H, p, *J*=7.6 Hz, C2-H_2), 1.66 – 1.51 (1H, m, C9-H), 1.27 – 1.17 (2H, m, C3-H_2), 0.86 (6H, d, *J*=6.7 Hz, 2 × C10-H_3).

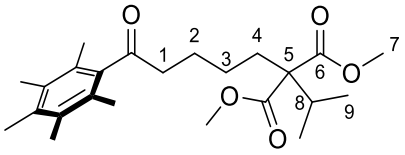
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8 (C=O), 172.7 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 57.0 (C5), 52.4 (2 × C7), 45.4 (C1), 41.0 (C8), 32.7 (C4), 24.2 (C9), 24.0 (C3), 23.7 (2 × C10), 23.7 (C2), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{39}O_5$ $[M+H]^+$ 419.2792; found at 419.2796, Δ 0.94 ppm.

FTIR (neat) ν/cm^{-1} = 2954, 1733, 1700, 1435, 1238, 1163, 1129, 1077, 1011, 911, 732, 648.

m.p. = 69 – 70 °C.

Dimethyl 2-isopropyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199e



2-Bromopropane (4.13 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h and then at 80 °C for a further 8 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **199e** as a white solid (1.41 g, 32%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.87 (6H, s, 2 × C7-H_3), 2.84 – 2.78 (2H, m, C1-H_2), 2.47 (1H, p, *J*=6.9 Hz, C8-H), 2.38 (3H, s, Ar-CH_3), 2.33 (6H, s, 2 × Ar-CH_3), 2.23 (6H, s, 2 × Ar-CH_3), 2.10 – 2.01 (2H, m, C4-H_2), 1.86 (2H, p, *J*=7.6 Hz, C2-H_2), 1.47 – 1.37 (2H, m, C3-H_2), 1.10 (6H, d, *J*=6.9 Hz, 2 × C9-H_3).

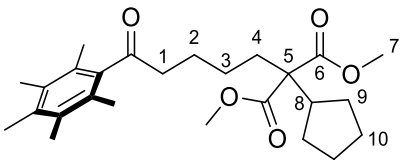
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9 (C=O), 171.8 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 62.1 (C5), 52.0 (2 × C7), 45.4 (C1), 34.0 (C4), 32.4 (C8), 24.5 (C3), 23.8 (C2), 18.7 (2 × C9), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{24}H_{37}O_5$ $[M+H]^+$ 405.2636; found at 405.2643, Δ 1.84 ppm.

FTIR (neat) ν/cm^{-1} = 2949, 1736, 1701, 1461, 1195, 1174, 1152, 1120, 1068, 1000, 915, 736.

m.p. = 70 – 71 °C.

Dimethyl 2-cyclopentyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199f



Bromocyclopentane (4.71 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h and then at 80 °C for a further 8 h. Purification by column chromatography (Pentane:Et_2O, 90:10 to 85:15) afforded the title compound **199f** as a white solid (1.78 g, 38%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s, 2 × C7-H_3), 2.66 (2H, t, *J*=7.5 Hz, C1-H_2), 2.50 – 2.38 (1H, m, C8-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.98 – 1.87 (2H, m, C4-H_2), 1.83 – 1.74 (2H, m, 2 × C9-H_AH_B), 1.71 (2H, p, *J*=7.6 Hz, C2-H_2), 1.57 – 1.46 (4H, m, 2 × C10-H_2), 1.42 – 1.34 (2H, m, 2 × C9-H_AH_B), 1.34 – 1.26 (2H, m, C3-H_2).

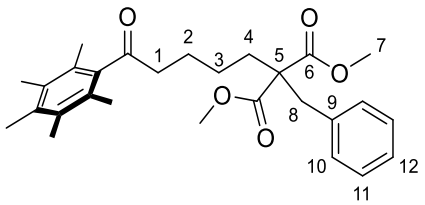
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9 (C=O), 172.1 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 60.8 (C5), 52.1 (2 × C7), 45.4 (C1), 43.5 (C8), 34.7 (C4), 28.2 (2 × C9), 25.4 (2 × C10), 24.5 (C3), 23.8 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{26}H_{39}O_5$ $[M+H]^+$ 431.2792; found at 431.2807, Δ 3.47 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 2872, 1730, 1701, 1453, 1382, 1357, 1240, 1161, 1128, 1076, 1013, 733.

m.p. = 72 – 73 °C.

Dimethyl 2-benzyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199g



Benzyl bromide (5.23 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h and then at 80 °C for a further 8 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **199g** as a white solid (2.07 g, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.32 – 7.20 (3H, m, 3 × Ar-H), 7.10 – 7.03 (2H, m, 2 × Ar-H), 3.71 (6H, d, *J*=1.5 Hz, C7-H_3), 3.24 (2H, s, C8-H_2), 2.67 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.88 – 1.78 (2H, m, C4-H_2), 1.72 (2H, p, *J*=7.5 Hz, C2-H_2), 1.37 (2H, dtd, *J*=12.3, 8.6, 6.5 Hz, C3-H_2).

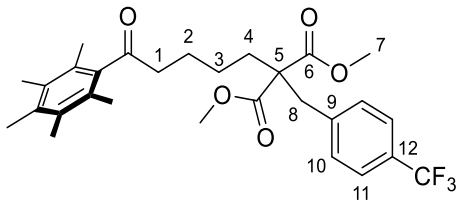
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8 (C=O), 171.8 (2 × C6), 140.7 (Ar), 136.1 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 129.9 (2 × Ar), 128.5 (2 × Ar), 127.4 (2 × Ar), 127.2 (Ar), 59.0 (C5), 52.5 (2 × C7), 45.3 (C1), 38.6 (C8), 32.1 (C4), 24.0 (C3), 23.6 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{28}H_{36}O_5Na$ $[M+Na]^+$ 475.2455; found at 475.2460, Δ 1.05 ppm.

FTIR (neat) ν/cm^{-1} = 2951, 1736, 1699, 1496, 1455, 1266, 1198, 1178, 1125, 1086, 1031, 915, 735.

m.p. = 92 – 93 °C.

Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)-2-(4-(trifluoromethyl)benzyl)malonate, 199h



1-(bromomethyl)-4-(trifluoromethyl)Benzene (5.23 mL, 22.0 mmol, 2.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **199h** as an oil which solidified on standing to a white solid (4.47 g, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.53 (2H, d, *J*=8.0 Hz, 2 × C11-H), 7.21 (2H, d, *J*=7.9 Hz, 2 × C10-H), 3.72 (6H, s, C7-H_3), 3.29 (2H, s, C8-H_2), 2.67 (2H, t, *J*=7.2 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.86 – 1.79 (2H, m, C4-H_2), 1.72 (2H, p, *J*=7.4 Hz, C2-H_2), 1.38 (2H, tt, *J*=9.5, 6.2 Hz, C3-H_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.7 (C=O), 171.4 (2 × C6), 140.7 (Ar), 140.4, 135.6 (Ar), 133.2 (2 × Ar), 130.3 (2 × C10), 129.5 (q, *J*=32.6 Hz, C12), 127.4 (2 × Ar), 125.4 (q, *J*=3.6 Hz, 2 × C11), 124.3 (q, *J*=272.0 Hz, C13-F_3), 58.9 (C5), 52.6 (2 × C7), 45.2 (C2), 38.5 (C8), 32.4 (C4), 24.0 (C3), 23.5 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

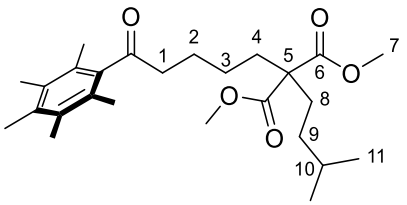
^{19}F NMR (470 MHz, $CDCl_3$) δ_F -62.5.

HRMS (ESI^+) m/z calcd. for $C_{29}H_{36}O_5F_3$ $[M+H]^+$ 521.2509; found at 521.2510, Δ 0.12 ppm.

FTIR (neat) ν/cm^{-1} = 2953, 2361, 1736, 1699, 1436, 1326, 1165, 1123, 1068, 1019, 914, 854, 736, 644.

m.p. = 79 – 80 °C.

Dimethyl 2-isopentyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199i



1-Bromo-3-methylbutane (5.27 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h and then at 80 °C for a further 8 h. Purification by column chromatography (Pentane:Et_2O, 85:15) afforded the title compound **199i** as a white solid (2.30 g, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s, 2 × C7-H_3), 2.66 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 2.01 – 1.83 (4H, m, C4-H_2, C8-H_2), 1.72 (2H, p, *J*=7.5 Hz, C2-H_2), 1.51 (1H, dp, *J*=13.2, 6.7 Hz, C10-H), 1.32 – 1.14 (2H, m, C3-H_2), 1.11 – 0.95 (2H, m, C9-H_2), 0.88 (6H, d, *J*=6.6 Hz, 2 × C11-H_3).

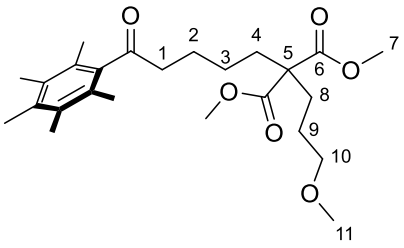
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8 (C=O), 172.5 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 57.7 (C5), 52.4 (2 × C7), 45.4 (C1), 33.1 (C9), 32.4 (C4), 30.5 (C8), 28.4 (C10), 23.9 (C3), 23.7 (C2), 22.6 (2 × C11), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{26}H_{41}O_5$ $[M+H]^+$ 433.2949; found at 433.2952, Δ 0.80 ppm.

FTIR (neat) ν/cm^{-1} = 2955, 1735, 1701, 1459, 1265, 1206, 1168, 1133, 1082, 1012, 918, 735.

m.p. = 82 – 83 °C.

Dimethyl 2-(3-methoxypropyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate, 199j



1-Bromo-3-methoxypropane (4.95 mL, 44.0 mmol, 4.00 equiv.), dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **196** (4.00 g, 11.0 mmol, 1.00 equiv.), Cs_2CO_3 (4.30 g, 13.2 mmol, 1.20 equiv.) and DMF (90 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **199j** as a white solid (2.65 g, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.71 (6H, s, 2 × C7-H_3), 3.36 (2H, t, *J*=6.4 Hz, C10-H_2), 3.31 (3H, s, C11-H_3), 2.66 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.98 – 1.85 (4H, m, C8-H_2, C4-H_2), 1.71 (2H, p, *J*=7.6 Hz, C2-H_2), 1.52 – 1.39 (2H, m, C9-H_2), 1.32 – 1.18 (2H, m, C3-H_2).

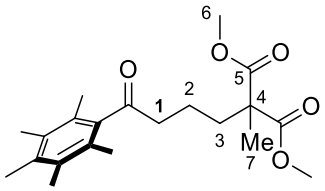
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8 (C=O), 172.2 (2 × C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 72.6 (C10), 58.7 (C11), 57.5 (C5), 52.5 (2 × C7), 45.4 (C1), 32.8 (C4), 29.6 (C8), 24.6 (C9), 23.9 (C3), 23.6 (C2), 17.4 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{39}O_6$ $[M+H]^+$ 435.2741; found at 435.2750, Δ 2.02 ppm.

FTIR (neat) v/cm^{-1} = 2952, 2360, 1734, 1700, 1456, 1387, 1210, 1120, 1002, 918, 865, 735, 647.

m.p. = 81 – 82 °C.

Dimethyl 2-methyl-2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate, 207a



Methyl iodide (0.72 mL, 11.5 mmol, 4.00 equiv.), dimethyl 2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate **206** (1.00 g, 2.87 mmol, 1.00 equiv.), Cs_2CO_3 (1.14 g, 3.44 mmol, 1.20 equiv.) and DMF (25 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **207a** as a white solid (867 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.74 (6H, s, 2 × C6-H_3), 2.68 (2H, t, *J*=7.2 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.99 – 1.89 (2H, m, C3-H_2), 1.74 – 1.63 (2H, m, C2-H_2), 1.48 (3H, s, C7-H_3).

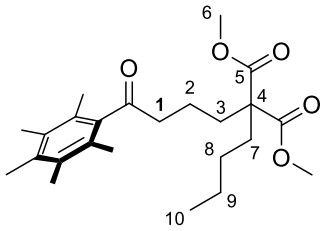
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.2 (C=O), 172.8 (2 × C5), 140.7 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 53.9 (C4), 52.7 (2 × C6), 45.6 (C1), 35.3 (C3), 20.1 (C7), 18.4 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{21}H_{31}O_5$ $[M+H]^+$ 363.2166; found at 363.2170, Δ 1.09 ppm.

FTIR (neat) ν/cm^{-1} = 2951, 1734, 1700, 1435, 1380, 1258, 1196, 1168, 1112, 985, 916, 886, 734.

m.p. = 95 – 96 °C.

Dimethyl 2-butyl-2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate, 207b



Butyl iodide (5.86 mL, 51.6 mmol, 4.00 equiv.), dimethyl 2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate **206** (4.50 g, 12.9 mmol, 1.00 equiv.), Cs_2CO_3 (5.05 g, 15.5 mmol, 1.20 equiv.) and DMF (110 mL) were subjected to **General Procedure 4-C** and stirred at r.t. for 24 h. Purification by column chromatography (Pentane:Et_2O, 85:15 to 80:20) afforded the title compound **207b** as a white solid (3.67 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.73 (6H, s, 2 × C6-H_3), 2.67 (2H, t, *J*=7.1 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 2.01 – 1.89 (4H, m, C3-H_2, C7-H_2), 1.65 – 1.57 (2H, m, C2-H_2), 1.39 – 1.21 (2H, m, C9-H_2), 1.21 – 1.06 (2H, m, C8-H_2), 0.91 (3H, t, *J*=7.3 Hz, C10-H_3).

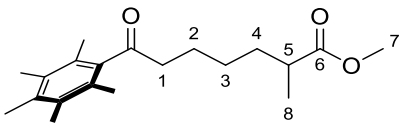
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.2 (C=O), 172.4 (2 × C5), 140.7 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 57.8 (C4), 52.5 (2 × C6), 45.5 (C1), 32.3 (C3/7), 32.2 (C7/3), 26.4 (C8), 23.1 (C9), 18.1 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.0 (C10).

HRMS (ESI^+) m/z calcd. for $C_{24}H_{36}O_5Na$ $[M+Na]^+$ 427.2455; found at 427.2454, Δ 0.31 ppm.

FTIR (neat) ν/cm^{-1} = 2957, 1734, 1700, 1457, 1382, 1257, 1205, 1126, 1071, 1019, 917, 731.

m.p. = 76 – 77 °C.

Methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200a



Dimethyl 2-methyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199a** (1.38 g, 3.67 mmol, 1.00 equiv.), LiCl (467 mg, 11.0 mmol, 3.00 equiv.), H_2O (0.17 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **200a** as a white solid (732 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (3H, s, C7-H_3), 2.73 – 2.60 (2H, m, C1-H_2), 2.54 – 2.41 (1H, m, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.77 – 1.64 (3H, m, C2-H_2, C4-H_AH_B), 1.53 – 1.31 (3H, m, C4-H_AH_B, C3-H_2), 1.15 (3H, d, J=7.0 Hz, C8-H_3).

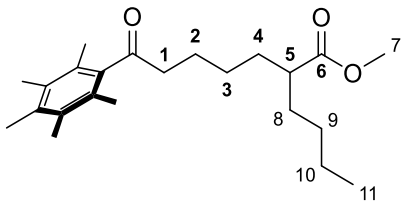
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 212.0 (C=O), 177.3 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.6 (C7), 45.5 (C1), 39.5 (C5), 33.7 (C4), 26.9 (C3), 23.3 (C2), 17.3(2 × Ar-$\underline{C}H_3$), 17.2 (C8), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{20}H_{30}NaO_3$ $[M+Na]^+$ 341.2087; found at 341.2088, Δ 0.38 ppm.

FTIR (neat) v/cm^{-1} = 3654, 2980, 2938, 1736, 1699, 1461, 1381, 1303, 1260, 1196, 1159, 1131, 1075, 991, 839.

m.p. = 52 – 54 °C.

Methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200b



Dimethyl 2-butyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199b** (20.4 g, 48.8 mmol, 1.00 equiv.) was added to a solution of LiCl (6.21 mg, 146 mmol, 3.00 equiv.) in H_2O (2.20 mL) and DMSO (90 mL) and the resulting reaction mixture was stirred at 140 °C for 3 h. The reaction mixture was cooled and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (Pentane:Et_2O 90:10) afforded the title compound **200b** as a white solid (15.4 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s, C7-H_3), 2.65 (2H, t, *J*=7.5 Hz, C1-H_2), 2.35 (1H, tt, *J*=8.9, 5.3 Hz, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.80 – 1.55 (4H, m, C2-H_2, C4-H_AH_B, C8-H_AH_B), 1.55 – 1.40 (2H, m, C4-H_AH_B, C8-H_AH_B), 1.40 – 1.17 (6H, m, C3-H_2, C9-H_2, C10-H_2), 0.88 (3H, t, *J*=7.1 Hz, C11-H_3).

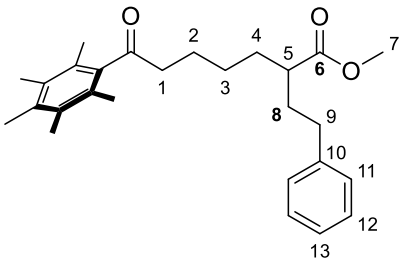
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 177.0 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.5 (C7), 45.7 (C5), 45.5(C1), 32.4 (C4, C8), 29.8 (C10), 27.2 (C3), 23.3 (C2), 22.7 (C9), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.1 (C11).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{37}O_3$ $[M+H]^+$ 361.2737; found at 361.2737, Δ 0.04 ppm.

FTIR (neat) v/cm^{-1} = 3018, 2935, 2860, 2012, 1736, 1701, 1456, 1379, 1303, 1264, 1193, 1168, 1113, 1000, 916, 730.

m.p. = 96 – 97 °C.

Methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)-2-phenethylheptanoate, 200c



Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)-2-phenethylmalonate **199c** (2.71 g, 5.80 mmol, 1.00 equiv.), LiCl (738 mg, 17.4 mmol, 3.00 equiv.), H_2O (0.26 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **200c** as a pale yellow oil (1.14 g, 48%).

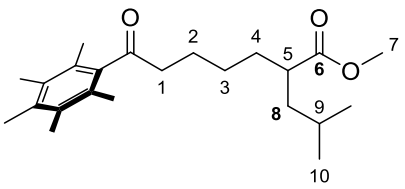
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31 – 7.24 (2H, m, 2 × Ar-H), 7.21 – 7.14 (3H, m, 3 × Ar-H), 3.68 (3H, s, C7-H_3), 2.65 (2H, t, *J*=7.4 Hz, C1-H_2), 2.63 – 2.53 (2H, m, C9-H_2), 2.42 (1H, tt, *J*=8.9, 5.2 Hz, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.97 (1H, dtd, *J*=13.5, 9.3, 5.9 Hz, C8-H_AH_B), 1.82 – 1.63 (4H, m, C8-H_AH_B, C2-H_2, C4-H_AH_B), 1.53 (1H, ddt, *J*=13.5, 10.9, 5.7 Hz, C4-H_AH_B), 1.40 – 1.28 (2H, m, C3-H_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.9 (C=O), 176.6 (C6), 141.7 (Ar), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.5 (2 × Ar), 128.5 (2 × Ar), 127.4 (2 × Ar), 126.1 (Ar), 51.6 (C7), 45.5 (C1), 45.1 (C5), 34.2 (C8), 33.8 (C9), 32.4 (C4), 27.1 (C3), 23.3 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{27}H_{37}O_3$ $[M+H]^+$ 409.2737; found at 409.2745, Δ 1.89 ppm.

FTIR (neat) ν/cm^{-1} = 2945, 2360, 1734, 1699, 1496, 1454, 1381, 1303, 1262, 1200, 1158, 1120, 1070, 1029, 912, 741, 700.

Methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200d



Dimethyl 2-isobutyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199d** (1.80 g, 4.30 mmol, 1.00 equiv.), LiCl (547 mg, 12.9 mmol, 3.00 equiv.), H_2O (0.19 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **200d** as a clear oil (1.22 g, 68%).

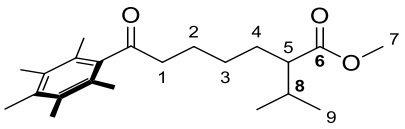
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.66 (3H, s, C7-H_3), 2.65 (2H, t, *J*=7.4 Hz, C1-H_2), 2.45 (1H, tt, *J*=9.3, 5.2 Hz, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.81 – 1.42 (6H, m, C2-H_2, C4-H_2, C9-H, C8-H_AH_B), 1.42 – 1.27 (2H, m, C3-H_2), 1.23 (1H, ddd, *J*=13.1, 8.0, 5.3 Hz, C8-H_AH_B), 0.89 (3H, d, *J*=6.5 Hz, C10-H_3), 0.87 (3H, d, *J*=6.5 Hz, C10-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 177.2 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.5 (C7), 45.5 (C1), 43.7 (C5), 41.9 (C8), 32.9 (C4), 27.2 (C3), 26.4 (C9), 23.3 (C2), 23.1 (C10), 22.3 (C10), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. For $C_{23}H_{37}O_3$ $[M+H]^+$ 361.2737; found at 361.2747, Δ= 2.70 ppm.

FTIR (neat) ν/cm^{-1} = 2950, 2869, 1736, 1701, 1461, 1405, 1383, 1265, 1194, 1167, 1123, 1069, 1000, 920, 732.

Methyl 2-isopropyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200e



Dimethyl 2-isopropyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199e** (1.80 g, 4.45 mmol, 1.00 equiv.), LiCl (566 mg, 13.3 mmol, 3.00 equiv.), H_2O (0.20 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **200e** as a clear oil (1.28 g, 83%).

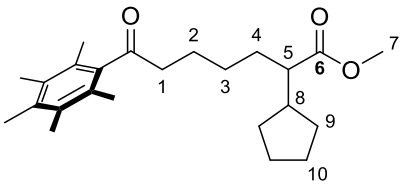
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.66 (3H, s, C7-H_3), 2.65 (2H, ddd, *J*=8.1, 6.6, 2.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.13 (1H, ddd, *J*=10.6, 7.5, 4.0 Hz, C5-H), 2.08 (6H, s, 2 × Ar-CH_3), 1.84 (1H, dq, *J*=13.8, 6.9 Hz, C8-H), 1.79 – 1.59 (3H, m, C2-H_2, C4-H_AH_B), 1.57 – 1.48 (1H, m, C4-H_AH_B), 1.35 – 1.25 (2H, m, C3-H_2), 0.93 (3H, d, *J*=6.8 Hz, C9-H_3), 0.90 (3H, d, *J*=6.7 Hz, C9-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 176.4 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 52.8 (C5), 51.3 (C7), 45.6 (C1), 30.8 (C8), 29.7 (C4), 27.6 (C3), 23.3 (C2), 20.7 (C9), 20.4 (C9), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O_3$ $[M+H]^+$ 347.2581; found at 347.2582, Δ 0.36 ppm.

FTIR (neat) ν/cm^{-1} = 2951, 2362, 1731, 1701, 1435, 1391, 1276, 1245, 1162, 1074, 1002, 914, 734.

Methyl 2-cyclopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200f



Dimethyl 2-cyclopentyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199f** (1.78 g, 4.13 mmol, 1.00 equiv.), LiCl (526 mg, 12.4 mmol, 3.00 equiv.), H_2O (0.19 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **200f** as a clear oil (774 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.66 (3H, s, C7-H_3), 2.68 – 2.60 (2H, m, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.20 – 2.14 (7H, m, 2 × Ar-CH_3, C5-H), 2.08 (6H, s, 2 × Ar-CH_3), 1.96 (1H, qt, *J*=9.5, 7.2 Hz, C8-H), 1.86 – 1.78 (1H, m, C9-H_AH_B), 1.78 – 1.70 (1H, m, C2-H_AH_B), 1.70 – 1.46 (8H, m, C2-H_AH_B, C4-H_2, C9-H_AH_B, 2 × C10-H_2), 1.36 – 1.27 (2H, m, C3-H_2), 1.23 – 1.06 (2H, m, C9'-H_2).

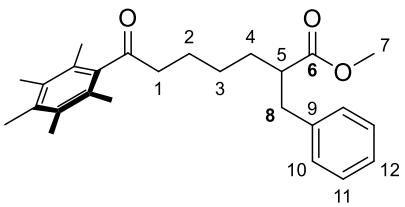
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 176.7 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.5 (C5), 51.4 (C7), 45.5 (C1), 43.0 (C8), 31.6 (C4), 31.0 (C9), 30.9 (C9'), 27.4 (C3), 25.1 (2 × C10), 23.3 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{24}H_{37}O_3$ $[M+H]^+$ 373.2737; found at 373.2737, Δ 0.07 ppm.

FTIR (neat) v/cm^{-1} = 2952, 2871, 2361, 2343, 1737, 1703, 1453, 1363, 1260, 1155, 914, 733, 649, 614.

m.p. = 73 – 74 °C.

Methyl 2-benzyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200g



Dimethyl 2-benzyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199g** (2.02 g, 4.46 mmol, 1.00 equiv.), LiCl (567 mg, 13.4 mmol, 3.00 equiv.), H_2O (0.20 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **200g** as a clear oil (936 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29 – 7.23 (2H, m, 2 × Ar-H), 7.23 – 7.17 (1H, m, Ar-H), 7.16 – 7.12 (2H, m, 2 × Ar-H), 3.60 (3H, s, C7-H_3), 2.94 (1H, dd, *J*=13.4, 8.0 Hz, C8-H_AH_B), 2.74 (1H, dd, *J*=13.4, 6.7 Hz, C8-H_AH_B), 2.71 – 2.65 (1H, m, C5-H), 2.63 (2H, t, *J*=7.2 Hz, C1-H_2), 2.22 (3H, s, Ar-CH_3), 2.17 (6H, s, 2 × Ar-CH_3), 2.07 (6H, s, 2 × Ar-CH_3), 1.80 – 1.61 (3H, m, C2-H_2, C4-H_AH_B), 1.57 – 1.47 (1H, m, C4-H_AH_B), 1.42 – 1.31 (2H, m, C3-H_2).

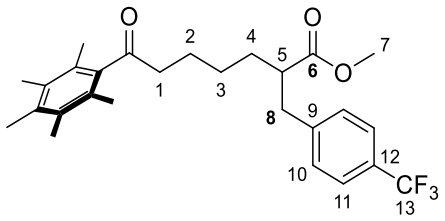
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 176.2 (C6), 140.8 (Ar), 139.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 129.0 (2 × Ar), 128.5 (2 × Ar), 127.4 (2 × Ar), 126.5 (Ar), 51.6 (C7), 47.6 (C5), 45.4 (C1), 38.7 (C8), 32.0 (C4), 27.1 (C3), 23.2 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{26}H_{35}O_3$ $[M+H]^+$ 395.2581; found at 395.2587, Δ 1.58 ppm.

FTIR (neat) v/cm^{-1} = 2947, 2360, 1736, 1700, 1496, 1455, 1380, 1201, 1163, 1119, 1071, 744, 701.

m.p. = 93 – 94 °C.

Methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)-2-(4-(trifluoromethyl)benzyl)heptanoate, 200h



Dimethyl 2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)-2-(4-(trifluoromethyl)benzyl)malonate **199h** (2.66 g, 5.11 mmol, 1.00 equiv.), LiCl (649 mg, 15.3 mmol, 3.00 equiv.), H_2O (0.23 mL) and DMSO (15 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 93:7 to 90:10) afforded the title compound **200h** an oil which solidified on standing to a white solid (1.58 g, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.53 (2H, d, *J*=8.0 Hz, 2 × C11-H), 7.27 (2H, d, *J*=8.3 Hz, 2 × C10-H), 3.60 (3H, s, C7-H_3), 3.00 (1H, dd, *J*=13.7, 8.6 Hz, C8-H_AH_B), 2.80 (1H, dd, *J*=13.7, 6.4 Hz, C8-H_AH_B), 2.70 (1H, tdd, *J*=9.0, 6.4, 5.2 Hz, C5-H), 2.64 (2H, t, *J*=7.3 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.07 (6H, s, 2 × Ar-CH_3), 1.70 (3H, tdd, *J*=14.4, 11.4, 6.6 Hz, C2-H_2, C4-H_AH_B), 1.54 (1H, td, *J*=8.6, 4.5 Hz, C4-H_AH_B), 1.40 (2H, h, *J*=7.2 Hz, C3-H_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.8 (C=O), 175.7 (2 × C6), 143.6 (C9), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 129.3 (2 × C10), 128.9 (q, *J*=32.3 Hz, C12), 127.4 (2 × Ar), 125.5 (q, *J*=3.7 Hz, 2 × C11), 124.4 (q, *J*=272.0, C13-F_3), 51.7 (C6), 47.3 (C5), 45.4 (C1), 38.3 (C8), 32.2 (C4), 27.0 (C3), 23.1 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

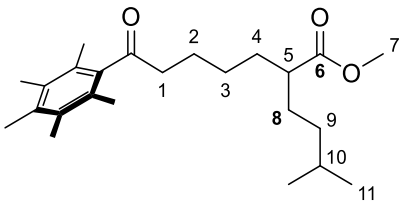
^{19}F NMR (470 MHz, $CDCl_3$) δ_F –62.4.

HRMS (ESI^+) m/z calcd. for $C_{27}H_{33}O_3F_3Na$ $[M+Na]^+$ 485.2274; found at 485.2292, Δ 3.70 ppm.

FTIR (neat) v/cm^{-1} = 2948, 1737, 1700, 1619, 1449, 1418, 1326, 1163, 1122, 1068, 735, 633.

m.p. = 94 – 95 °C.

Methyl 2-isopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200i



Dimethyl 2-isopentyl-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199i** (2.26 g, 5.22 mmol, 1.00 equiv.), LiCl (664 mg, 15.7 mmol, 3.00 equiv.), H_2O (0.23 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 4 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 95:5 to 93:7) afforded the title compound **200i** as a clear oil (1.26 g, 64%).

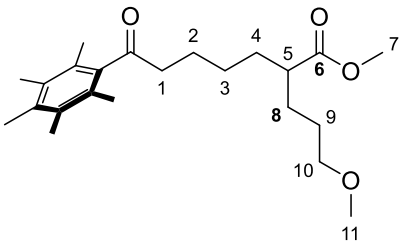
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s, C7-H_3), 2.66 (2H, t, *J*=7.5 Hz, C1-H_2), 2.32 (1H, tt, *J*=8.9, 5.3 Hz, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.79 – 1.55 (4H, m, C2-H_2, C4-H_AH$_B$, C8- H_AH$_B$), 1.55 – 1.40 (3H, m, C10-H, C4-H$_A$$H_B$, C8-H$_A$$H_B$), 1.40 – 1.28 (2H, m, C3-H_2), 1.21 – 1.06 (2H, m, C9-H_2), 0.87 (3H, d, *J*=6.6 Hz, C11-H_3), 0.86 (3H, d, *J*=6.6 Hz, C11-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 177.0 (C6), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.5 (C7), 45.9 (C5), 45.5 (C1), 36.7 (C9), 32.4 (C4), 30.5 (C8), 28.1 (C10), 27.2 (C3), 23.3 (C2), 22.7 (C11), 22.6 (C11), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{24}H_{39}O_3$ $[M+H]^+$ 375.2894; found at 375.2902, Δ= 2.20 ppm.

FTIR (neat) ν/cm^{-1} = 2952, 2869, 1737, 1702, 1459, 1405, 1384, 1366, 1303, 1258, 1193, 1169, 1069, 1001, 918, 852, 739, 634.

Methyl 2-(3-methoxypropyl)-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200j



Dimethyl 2-(3-methoxypropyl)-2-(5-oxo-5-(2,3,4,5,6-pentamethylphenyl)pentyl)malonate **199j** (2.65 g, 6.10 mmol, 1.00 equiv.), LiCl (776 mg, 18.0 mmol, 3.00 equiv.), H_2O (0.27 mL) and DMSO (12 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **200j** as a clear oil (1.42 g, 62%).

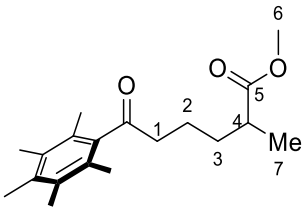
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (3H, s, C7-H_3), 3.35 (2H, td, *J*=5.6, 2.6 Hz, C10-H_2), 3.32 (3H, s, C11-H_3), 2.65 (2H, t, *J*=7.4 Hz, C1-H_2), 2.38 (1H, tt, *J*=9.1, 4.6 Hz, C5-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.79 – 1.61 (4H, m, C2-H_2, C4-H_AH_B, C8-H_AH_B), 1.59 – 1.45 (4H, m, C4-H_AH_B, C8-H_AH_B, C9-H_2), 1.35 (2H, tq, *J*=9.6, 6.0 Hz, C3-H_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.0 (C=O), 176.7 (C6), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 72.5 (C10), 58.7 (C11), 51.6 (C7), 45.5 (C1), 45.4 (C5), 32.4 (C4), 29.1 (C8), 27.6 (C9), 27.1 (C3), 23.3 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{37}O_4$ $[M+H]^+$ 377.2686; found at 377.2698, Δ 3.07 ppm.

FTIR (neat) v/cm^{-1} = 2989, 2865, 1736, 1701, 1454, 1383, 1197, 1165, 1121, 1001, 916, 842.

Methyl 2-methyl-6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexanoate, 208a



Dimethyl 2-methyl-2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate **207a** (850 mg, 2.34 mmol, 1.00 equiv.), LiCl (299 mg, 7.05 mmol, 3.00 equiv.), H_2O (0.11 mL) and DMSO (3.5 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **208a** as a clear oil (401 mg, 56%).

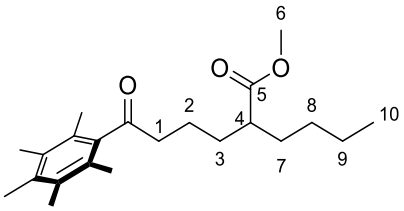
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.68 (3H, s, C6-H_3), 2.71 – 2.63 (2H, m, C1-H_2), 2.49 (1H, h, *J*=6.9 Hz, C4-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.77 – 1.62 (3H, m, C2-H_2, C3-H_AH_B), 1.54 – 1.46 (1H, m, C3-H_AH_B), 1.18 (3H, d, *J*=6.9 Hz, C7-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.7 (C=O), 177.2 (C5), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.7 (C6), 45.5 (C1), 39.6 (C4), 33.3 (C3), 21.1 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 17.2 (C7), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{19}H_{28}O_3Na$ $[M+Na]^+$ 327.1931; found at 327.1931, Δ 0.04 ppm.

FTIR (neat) v/cm^{-1} = 3023, 2938, 1736, 1700, 1457, 1406, 1359, 1304, 1260, 1128, 1069, 734, 645.

Methyl 2-butyl-6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexanoate, 208b



Dimethyl 2-butyl-2-(4-oxo-4-(2,3,4,5,6-pentamethylphenyl)butyl)malonate **207b** (2.94 g, 7.27 mmol, 1.00 equiv.), LiCl (924 mg, 21.8 mmol, 3.00 equiv.), H_2O (0.33 mL) and DMSO (10 mL) were subjected to **General Procedure 4-D** and stirred at 160 °C for 2 h. The reaction mixture was cooled and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 90:10) afforded the title compound **208b** as a white solid (1.72 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.68 (3H, s, C6-H_3), 2.67 (2H, ddd, *J*=9.5, 6.2, 2.6 Hz, C1-H_2), 2.39 (1H, tt, *J*=8.2, 5.1 Hz, C4-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.77 – 1.42 (6H, m, C2-H_2, C3-H_2, C7-H_2), 1.36 – 1.16 (4H, m, C9-H_2, C10-H_2), 0.88 (3H, t, *J*=7.1 Hz, C10-H_3).

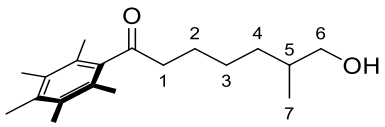
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 211.7 (C=O), 176.9 (C6), 140.7 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 51.6 (C6), 45.7 (C4), 45.4 (C1), 32.3 (C7), 32.0 (C3), 29.8 (C8), 22.7 (C9), 21.3 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.1 (C10).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O_3$ $[M+H]^+$ 347.2581; found at 347.2588, Δ 2.09 ppm.

FTIR (neat) v/cm^{-1} = 2933, 2861, 1735, 1700, 1456, 1380, 1262, 1193, 1163, 1122, 996, 909, 731, 648.

m.p. = 62 – 63 °C.

7-Hydroxy-6-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one, 163a



$LiAlH_4$ (73 mg, 1.92 mmol, 1.00 equiv.), methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200a** (610 mg, 1.92 mmol, 1.00 equiv.) and Et_2O (15 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.07 mL), aq. NaOH (15% w/v, 0.07 mL) and H_2O (0.21 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 65:35) afforded the title compound **163a** as a white solid (441 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.51 (1H, dd, *J*=10.5, 5.8 Hz, C6-H_AH_B), 3.43 (1H, dd, *J*=10.5, 6.4 Hz, C6-H_AH_B), 2.68 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.76 – 1.67 (2H, m, C2-H_2), 1.67 – 1.59 (1H, m, C5-H), 1.52 – 1.31 (3H, m, C3-H_2, C4-H_AH_B), 1.16 (1H, dt, *J*=10.5, 7.9 Hz, C4-H_AH_B), 0.92 (3H, d, *J*=6.7 Hz, C7-H_3).

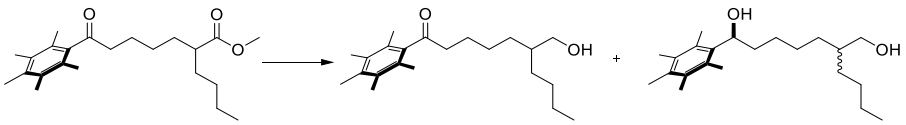
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2 (C=O), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 68.4 (C6), 45.7 (C1), 35.8 (C5), 33.1 (C4), 26.7 (C3), 23.6 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.7 (2 × Ar-$\underline{C}H_3$), 16.1 (C7).

HRMS (ESI^+) m/z calcd. for $C_{19}H_{29}O$ $[M\text{-}OH]^+$ 273.2213; found at 273.2212, Δ 0.37 ppm.

FTIR (neat) ν/cm^{-1} = 3423, 2929, 2870, 1698, 1575, 1461, 1403, 1382, 1304, 1263, 1127, 1096, 1045, 935, 729.

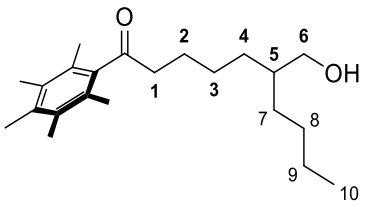
m.p. = 96 – 97 °C.

Reduction of Methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 200b



$LiAlH_4$ (994 mg, 26.2 mmol, 1.00 equiv.), methyl 2-butyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200b** (9.43 g, 26.2 mmol, 1.00 equiv.) and Et_2O (130 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.99 mL), aq. NaOH (15% w/v, 0.99 mL) and H_2O (2.97 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 80:20 to 60:40) afforded both title compounds as oils which solidified on standing to white solids (6.73 g, 77%, **163b**) and (701 mg, 7%, **201**).

6-(Hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)decan-1-one, 163b



^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.55 (2H, d, *J*=5.5 Hz, C6-H_2), 2.72 – 2.64 (2H, m, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.76 – 1.67 (2H, m, C2-H_2), 1.48 (1H, p, *J*=5.8 Hz, C5-H), 1.44 – 1.21 (10H, m, C3-H_2, C4-H_2, C7-H_2, C8-H_2, C9-H_2), 0.93 – 0.86 (3H, m, C10-H_3).

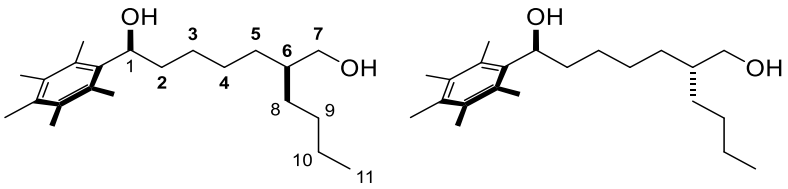
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2 (C=O), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 65.7 (C6), 45.7 (C1), 40.5 (C5), 30.9 (C4/7), 30.8 (C7/4), 29.3 (C8), 26.6 (C3), 23.7 (C2), 23.2 (C9), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.2 (C10).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{37}O_2$ $[M+H]^+$ 333.2788; found at 333.2788, Δ 0.09 ppm.

FTIR (neat) v/cm^{-1} = 3447, 2955, 2928, 2856, 1576, 1464, 1403, 1381, 1359, 1303, 1263, 1127, 1069, 1041, 996, 934, 919, 795, 729.

m.p. = 46 – 48 °C.

6-Butyl-1-(2,3,4,5,6-pentamethylphenyl)heptane-1,7-diol, 201



201 was isolated as an inseperable mixture of diasteromers in which the ratio could not be determined due to complete overlapping of all ^{1}H NMR peaks. The relative stereochemistry of the diastereoisomers could not be distinguished or attributed to a set of NMR signals, the data is reported accordingly.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.29 (1H, dd, *J*=8.9, 5.4 Hz, C1-H), 3.53 (2H, d, *J*=5.4 Hz, C7-H_2), 2.37 (6H, s, 2 × Ar-CH_3), 2.25 (3H, s, Ar-CH_3), 2.22 (6H, s, 2 × Ar-CH_3), 2.11 – 2.02 (1H, m, C2-H_AH_B), 1.84 – 1.70 (1H, m, C2-H_AH_B), 1.63 – 1.53 (1H, m, C3-H_AH_B), 1.51 – 1.42 (1H, m, C6-H), 1.43 – 1.21 (11H, m, C3-H_AH_B, C4-H_2, C5-H_2, C8-H_2, C9-H_2, C10-H_2), 0.93 – 0.85 (3H, m, C11-H_3).

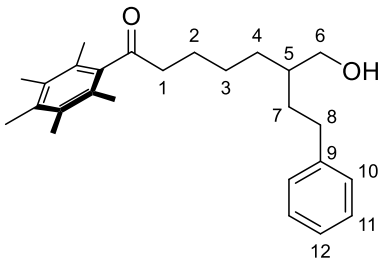
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 137.9 (Ar), 134.2 (Ar), 133.5 (br, 2 × Ar), 131.9 (br, 2 × Ar), 72.4 and 72.3 (C1), 65.8 and 65.8 (C7), 40.63 and 40.58 (C6), 36.33 and 36.31 (C2), 31.0 and 30.9 (C8), 30.82 and 30.78 (C5), 29.27 and 29.25 (C9), 27.42 and 27.39 (C3), 27.0 and 26.9 (C4), 23.2 (C10), 17.3 (2 × Ar-$\underline{C}H_3$), 17.2 (Ar-$\underline{C}H_3$), 16.8 (2 × Ar-$\underline{C}H_3$), 14.2 (C11).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{38}O_2Na$ $[M+Na]^+$ 357.2764; found at 357.2763, Δ 0.18 ppm.

FTIR (neat) ν/cm^{-1} = 3361, 2927, 2858, 1459, 1380, 1043, 909, 732, 649.

m.p. = 46 – 47 °C.

6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)-8-Phenyloctan-1-one, 163c



$LiAlH_4$ (103 mg, 2.72 mmol, 1.00 equiv.), methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)-2-phenethylheptanoate **200c** (1.11 g, 2.72 mmol, 1.00 equiv.) and Et_2O (20 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.1 mL), aq. NaOH (15% w/v, 0.1 mL) and H_2O (0.3 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 65:35) afforded the title compound **163c** as a clear oil (654 mg, 63%).

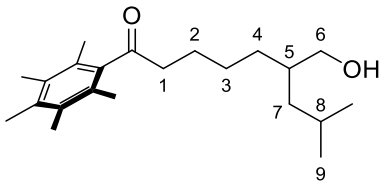
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34 – 7.23 (2H, m, 2 × Ar-H), 7.22 – 7.13 (3H, m, 3 × Ar-H), 3.60 (2H, br t, *J*=4.4 Hz, C6-H_2), 2.68 (2H, t, *J*=7.4 Hz, C1-H_2), 2.65 (2H, t, *J*=8.0 Hz, C8-H_2), 2.23 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.76 – 1.51 (5H, m, C2-H_2, C7-H_2, C5-H), 1.48 – 1.36 (4H, m, C3-H_2, C4-H_2), 1.27 (1H, br d, *J*=5.4 Hz, O*H*).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2 (C=O), 142.7 (Ar), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.5 (2 × Ar), 128.5 (2 × Ar), 127.4 (2 × Ar), 125.9 (Ar), 65.5 (C6), 45.7 (C1), 40.2 (C5), 33.4 (C8), 33.0 (C7), 30.9 (C4), 26.6 (C3), 23.7 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{26}H_{36}O_2Na$ $[M+Na]^+$ 403.2608; found at 403.2620, Δ 3.09 ppm.

FTIR (neat) ν/cm^{-1} = 3450, 3026, 2933, 2864, 2360, 1698, 1603, 1496, 1306, 1124, 1030, 913, 643.

6-(hydroxymethyl)-8-Methyl-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one, 163d



$LiAlH_4$ (71 mg, 1.86 mmol, 1.00 equiv.), methyl 2-methyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200d** (670 mg, 1.86 mmol, 1.00 equiv.) and Et_2O (15 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.07 mL), aq. NaOH (15% w/v, 0.07 mL) and H_2O (0.21 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 65:35) afforded the title compound **163d** as a white solid (453 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.55 (1H, dd, *J*=10.7, 5.1 Hz, C6-H_AH_B), 3.51 (1H, dd, *J*=10.7, 5.6 Hz, C6-H_AH_B), 2.69 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.77 – 1.68 (2H, m, C2-H_2), 1.68 – 1.60 (1H, m, C8-H), 1.55 (1H, hept, *J*=5.4 Hz, C5-H), 1.44 – 1.35 (3H, m, C3-H_2, C4-H_AH_B), 1.34 – 1.27 (1H, m, C4-H_AH_B), 1.19 (1H, dt, *J*=13.9, 7.0 Hz, C7-H_AH_B), 1.09 (1H, dt, *J*=13.9, 7.1 Hz, C7-H_AH_B), 0.89 (3H, d, *J*=6.6 Hz, C9-H_3), 0.88 (3H, d, *J*=6.6 Hz, C9-H_3).

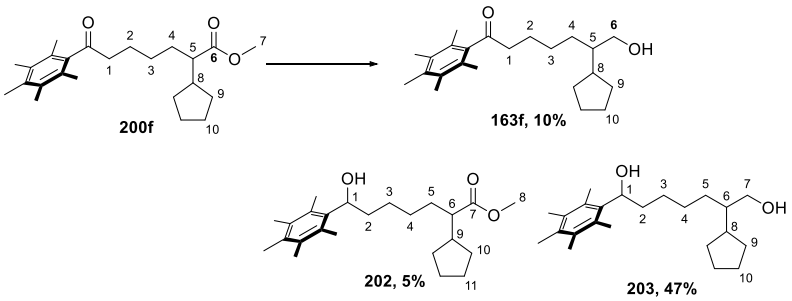
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.3 (C=O), 140.9 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 65.9 (C6), 45.7 (C1), 40.8 (C7), 38.1 (C5), 31.2 (C4), 26.5 (C3), 25.5 (C8), 23.7 (C2), 23.1 (C9), 23.0 (C9), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{37}O_2$ $[M+H]^+$ 333.2788; found at 333.2800, Δ 3.57 ppm.

FTIR (neat) ν/cm^{-1} = 3432, 2952, 1700, 1466, 1384, 1043, 918, 735.

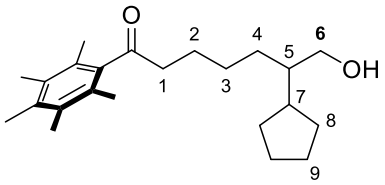
m.p. = 39 °C.

Reduction of methyl 2-cyclopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate 200f



$LiAlH_4$ (38 mg, 1.0 mmol, 1.0 equiv.) was added portionwise to a solution of methyl 2-cyclopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200f** (371 mg, 1.00 mmol, 1.00 equiv.) in Et_2O (5 mL) at –78 °C. The reaction was stirred at –78 °C for 2 h and then the reaction was warmed to –17 °C for 20 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.04 mL), aq. NaOH (15% w/v, 0.04 mL) and H_2O (0.12) at –17 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 75:25 to 70:30) afforded the title compounds **200f** (35 mg, 10%), **202** (18 mg, 5%) and **203** (164 mg, 47%) as clear oils.

6-Cyclopentyl-7-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one, **200f**:



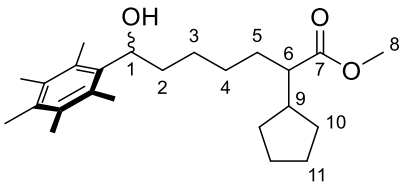
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.67 (1H, dd, *J*=10.9, 4.2 Hz, C6-H_AH_B), 3.59 (1H, dd, *J*=10.8, 5.3 Hz, C6-H_AH_B), 2.69 (1H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.81 – 1.66 (5H, m, C2-H_2, C7-H, 2 × C8-H_AH_B), 1.65 – 1.57 (2H, m, 2 × C9-H_AH_B), 1.57 – 1.29 (7H, m, 2 × C9-H_AH_B, C3-H_2, C4-H_2, C5-H), 1.20 – 1.07 (2H, m, 2 × C8-H_AH_B).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.3 (C=O), 140.9 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 64.3 (C6), 45.7 (C1, C5), 41.6 (C7), 30.9 (C8), 30.7 (C8'), 29.4 (C4), 26.6 (C3), 25.4 (C9), 25.2 (C9'), 23.8 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{23}H_{37}O_2$ $[M+H]^+$ 345.2788; found at 345.2782, Δ 1.77 ppm.

FTIR (neat) ν/cm^{-1} = 3459, 2946, 2868, 1698, 1451, 1403, 1039, 919, 734.

Methyl 2-cyclopentyl-7-hydroxy-7-(2,3,4,5,6-pentamethylphenyl)heptanoate, 202



202 was isolated as an inseperable mixture of diasteromers in which the ratio could not be determined due to complete overlapping of all ^{1}H NMR peaks. The relative stereochemistry of the diastereoisomers could not be distinguished, and their overlapping spectra could not be deconvoluted. In the cases where only one signal is assigned to a carbon, this signal indicates an overlapping signal for both diastereomers.

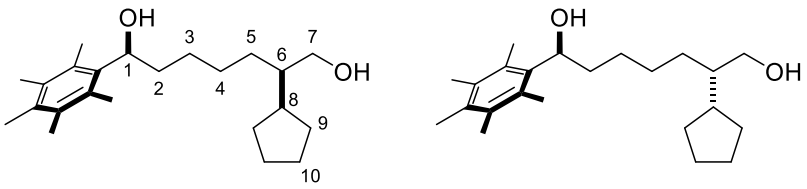
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.27 (1H, ddd, *J*=8.9, 5.3, 1.6 Hz, C1-H), 3.69 – 3.63 (3H, m, C8-H_3), 2.35 (6H, s, 2 × Ar-CH_3), 2.24 (3H, s, Ar-CH_3), 2.22 (6H, s, 2 × Ar-CH_3), 2.18 – 2.09 (1H, m, C6-H), 2.07 – 1.89 (2H, m, C2-H_AH_B, C9-H), 1.86 – 1.46 (10H, m, C10-H_2, C2-H_AH_B, C5-H_2, C3-H_AH_B, 2 × C11-H_2), 1.38 – 1.03 (5H, m, C3-H_AH_B, C4-H_2, C10'-H_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 176.7 (C7), 137.7 (Ar), 134.1 (Ar), 133.4 (br, 2 × Ar), 131.8 (br, 2 × Ar), 72.2 and 72.0 (C1), 51.5 (C6), 51.2 (C8), 42.8 (C9), 36.1 and 36.0 (C2), 31.6 (C5), 30.8 (2 × C10), 27.8 and 27.6 (C4), 26.9 and 26.7 (C3), 25.0 (2 × C11), 17.1 (3 × Ar-$\underline{C}H_3$), 16.7 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{24}H_{38}O_3Na$ $[M+Na]^+$ 397.2713; found at 397.2721, Δ 1.96 ppm.

FTIR (neat) ν/cm^{-1} = 2949, 1736, 1452, 1197, 1155, 1064, 735.

6-Cyclopentyl-1-(2,3,4,5,6-pentamethylphenyl)heptane-1,7-diol, 203



203 was isolated as an inseperable mixture of diasteromers in which the ratio could not be determined due to complete overlapping of all ^{1}H NMR peaks. The relative stereochemistry of the diastereoisomers could not be distinguished, and their overlapping spectra could not be deconvoluted. In the cases where only one signal is assigned to a carbon, this signal indicates an overlapping signal for both diastereomers.

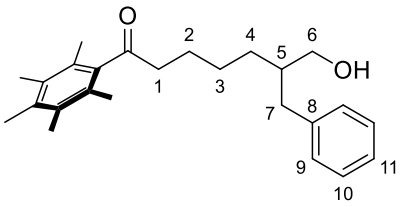
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.29 (1H, ddd, *J*=8.9, 5.3, 1.7 Hz, C1-H), 3.66 (1H, ddd, *J*=10.8, 4.2, 1.2 Hz, C7-H_AH_B), 3.58 (1H, dd, *J*=10.8, 5.2 Hz, C7-H_AH_B), 2.36 (6H, s, 2 × Ar-CH_3), 2.25 (3H, s, Ar-CH_3), 2.22 (6H, s, 2 × Ar-CH_3), 2.06 (1H, dddd, *J*=14.0, 9.3, 6.9, 4.7 Hz, C2-H_AH_B), 1.82 – 1.69 (4H, m, C2-H_AH_B, C8-H, 2 × C9-H_AH_B), 1.68 – 1.48 (6H, m, C3-H_2, 2 × C10-H_2), 1.48 – 1.26 (5H, m, C4-H_2, C5-H_2, C6-H), 1.19 – 1.08 (2H, m, 2 × C9-H_AH_B).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 137.9 (Ar), 134.2 (Ar), 133.5 (br, 2 × Ar), 131.9 (br, 2 × Ar), 72.4 and 72.3 (C1), 64.43 and 64.39 (C7), 45.9 and 45.8 (C6), 41.6 and 41.5 (C8), 36.3 (C2), 30.9 (C9), 30.7 (C9'), 29.4 (C5), 27.53 and 27.46 (C3), 27.1 and 26.8 (C4), 25.4 (C10), 25.19 and 25.17 (C10'), 17.3 (2 × Ar-$\underline{C}H_3$), 17.2 (Ar-$\underline{C}H_3$), 16.8 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{38}O_2Na$ $[M+Na]^+$ 369.2764; found at 369.2766, Δ 0.53 ppm.

FTIR (neat) ν/cm^{-1} = 3361, 2944, 1452, 1037, 909, 734.

6-Benzyl-7-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one, 163g



$LiAlH_4$ (89.2 mg, 2.35 mmol, 1.00 equiv.) was added portionwise to a solution of methyl 2-isopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200g** (928 mg, 2.35 mmol, 1.00 equiv.) in Et_2O:THF (3:1, 20 mL) at –78 °C. The reaction was stirred at –78 °C for 2 h and then due to insolubility, the reaction was warmed to –17 °C for 20 min. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.09 mL), aq. NaOH (15% w/v, 0.09 mL) and H_2O (0.27) at –17 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 75:25 to 70:30) afforded the title compound **163g** as a clear oil (774 mg, 90%).

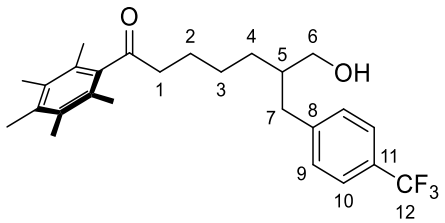
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31 – 7.24 (2H, m, 2 × Ar-H), 7.22 – 7.15 (3H, m, 3 × Ar-H), 3.54 (2H, br d, *J*=5.2 Hz, C6-H_2), 2.71 – 2.56 (4H, m, C7-H_2, C2-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.82 (1H, p, *J*=6.3 Hz, C5-H), 1.70 (2H, p, *J*=7.2 Hz, C2-H_2), 1.51 – 1.32 (4H, m, C3-H_2, C4-H_2), 1.28 (1H, s, O*H*).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2 (C=O), 140.9 (Ar), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 129.3 (2 × Ar), 128.5 (2 × Ar), 127.4 (2 × Ar), 126.0 (Ar), 64.9 (C6), 45.6 (C1), 42.6 (C5), 37.9 (C7), 30.8 (C4), 26.7 (C3), 23.6 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{35}O_2$ $[M+H]^+$ 367.2632; found at 367.2638, Δ 1.74 ppm.

FTIR (neat) ν/cm^{-1} = 3029, 2359, 1695, 1496, 1454, 1306, 1123, 1042, 911, 737, 701, 649, 621.

7-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)-6-(4-(trifluoromethyl)benzyl)heptan-1-one, 163h



$LiAlH_4$ (116 mg, 3.07 mmol, 1.00 equiv.) was added portionwise to a solution of methyl 7-oxo-7-(2,3,4,5,6-pentamethylphenyl)-2-(4-(trifluoromethyl)benzyl)heptanoate (1.42 mg, 3.07 mmol, 1.00 equiv.) in THF (18 mL) at –20 °C and stirred for 1 h at this temperature. After this time, the reaction was quenched by sequential dropwise addition of H_2O (0.1 mL), aq. NaOH (15% w/v, 0.1 mL) and H_2O (0.3 mL) at –20 °C. The reaction mixture was diluted with Et_2O and $MgSO_4$ was added. The mixture was stirred vigorously for 15 min then filtered and concentrated *in vacuo*. Purification by column chromatography (Pentane:Et_2O, 70:30 to 40:60) afforded the title compound **163h** as a clear oil (1.09 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.53 (2H, d, *J*=7.9 Hz, 2 × C10-H), 7.30 (2H, d, *J*=7.9 Hz, 2 × C9-H), 3.54 (2H, t, *J*=5.1 Hz, C6-H_2), 2.77 (1H, dd, *J*=13.6, 7.4 Hz, C7-H_AH_B), 2.69 – 2.60 (3H, m, C1-H_2, C7-H_AH_B), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.07 (6H, s, 2 × Ar-CH_3), 1.84 (1H, p, *J*=6.4 Hz, C5-H), 1.76 – 1.63 (2H, m, C2-H_2), 1.50 – 1.29 (5H, m, C3-H_2, C4-H_2, O*H*).

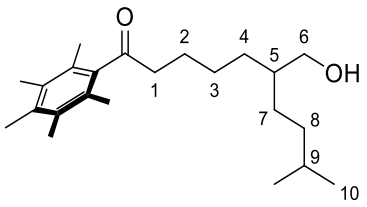
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.1 (C=O), 145.1 (C8), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 129.6 (2 × C9), 128.4 (q, *J*=32.3 Hz, C11), 127.4 (2 × Ar), 125.4 (q, *J*=3.8 Hz, 2 × C10), 124.5 (q, *J*=271.7 Hz, C12-F_3), 64.5 (C6), 45.5 (C1), 42.4 (C5), 37.6 (C7), 30.7 (C4), 26.6 (C3), 23.5 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

^{19}F NMR (470 MHz, $CDCl_3$) δ_F –62.3.

HRMS (ESI^+) m/z calcd. for $C_{26}H_{34}O_2F_3$ $[M+H]^+$ 435.2505; found at 435.2514, Δ 1.97 ppm.

FTIR (neat) ν/cm^{-1} = 3450, 2935, 1696, 1449, 1327, 1163, 1124, 1068, 1042, 1019, 911, 856, 809, 638.

6-(hydroxymethyl)-9-Methyl-1-(2,3,4,5,6-pentamethylphenyl)decan-1-one, 163i



$LiAlH_4$ (91.5 mg, 2.41 mmol, 1.00 equiv.), methyl 2-isopentyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200i** (904 mg, 2.41 mmol, 1.00 equiv.) and Et_2O (15 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.09 mL), aq. NaOH (15% w/v, 0.09 mL) and H_2O (0.27 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 75:25 to 70:30) afforded the title compound **163i** as a clear oil (669 mg, 80%).

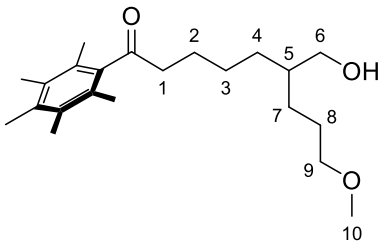
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.54 (2H, d, *J*=5.4 Hz, C6-H_2), 2.68 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.72 (2H, p, *J*=7.4 Hz, C2-H_2), 1.55 – 1.21 (8H, m, C9-H, C5-H, C3-H_2, C4-H_2, C7-H_2), 1.21 – 1.12 (2H, m, C8-H_2), 0.88 (6H, d, *J*=6.6 Hz, C10-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.3 (C=O), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 65.7 (C6), 45.7 (C1), 40.8 (C5), 36.2 (C8), 30.9 (C4), 28.8 (C7), 28.5 (C9), 26.6 (C3), 23.7 (C2), 22.8 (C10), 22.7 (C10), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{38}O_2$ $[M+H]^+$ 347.2945; found at 347.2955, Δ 2.99 ppm.

FTIR (neat) ν/cm^{-1} = 3431, 2928, 2868, 1696, 1466, 1403, 1384, 1365, 1043, 913, 736, 647, 632.

6-(hydroxymethyl)-9-Methoxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one, 163j



$LiAlH_4$ (139 mg, 3.67 mmol, 1.00 equiv.), methyl 2-(3-methoxypropyl)-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanoate **200j** (1.38 mg, 3.67 mmol, 1.00 equiv.) and Et_2O (20 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.14 mL), aq. NaOH (15% w/v, 0.14 mL) and H_2O (0.42 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 40:60) afforded the title compound **163j** as a clear oil (641 mg, 50%).

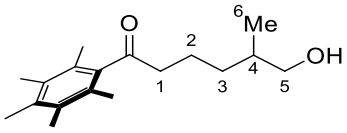
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.59 – 3.50 (2H, m, C6-H_2), 3.37 (2H, t, *J*=6.5 Hz, C9-H_2), 3.33 (3H, s, C10-H_3), 2.68 (2H, t, *J*=7.4 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.71 (2H, p, *J*=7.3 Hz, C2-H_2), 1.59 (2H, dt, *J*=8.4, 6.6 Hz, C8-H_2), 1.55 – 1.20 (7H, m, C5-H, C3-H_2, C4-H_2, C7-H_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2 (C=O), 140.9 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 73.3 (C9), 65.5 (C6), 58.7 (C10), 45.7 (C1), 40.4 (C5), 31.0 (C4), 27.6 (C7), 27.0 (C8), 26.6 (C3), 23.7 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{37}O_3$ $[M+H]^+$ 349.2737; found at 349.2752, Δ 4.22 ppm.

FTIR (neat) ν/cm^{-1} = 3463, 2933, 2868, 1700, 1577, 1459, 1386, 1306, 1189, 1118, 1042, 917, 871.

6-Hydroxy-5-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one, 166a



$LiAlH_4$ (49.0 mg, 1.29 mmol, 1.00 equiv.), methyl 2-methyl-6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexanoate **208a** (393 mg, 1.29 mmol, 1.00 equiv.) and Et_2O (10 mL) were subjected to **General Procedure 4-E**. The reaction was quenched by sequential dropwise addition of H_2O (0.05 mL), aq. NaOH (15% w/v, 0.05 mL) and H_2O (0.15 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 40:60) afforded the title compound **166a** as a white solid (253 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.53 (1H, dd, *J*=10.6, 6.0 Hz, C5-H_AH_B), 3.49 (1H, dd, *J*=10.6, 6.2 Hz, C5-H_AH_B), 2.77 – 2.60 (2H, m, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.85 – 1.75 (1H, m, C2-H_AH_B), 1.75 – 1.63 (2H, m, C2-H_AH_B, C4-H), 1.50 (1H, ddt, *J*=13.3, 11.1, 5.5 Hz, C3-H_AH_B), 1.23 (1H, dddd, *J*=13.1, 11.0, 7.8, 5.2 Hz, C3-H_AH_B), 0.96 (3H, d, *J*=6.8 Hz, C6-H_3).

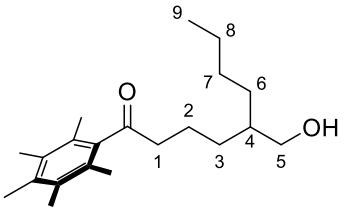
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.2 (C=O), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 68.1 (C5), 45.9 (C1), 35.8 (C4), 32.6 (C3), 20.6 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.6 (C6), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{18}H_{29}O_2$ $[M+H]^+$ 277.2162; found at 277.2171, Δ 3.21 ppm.

FTIR (neat) ν/cm^{-1} = 3438, 3015, 2944, 2875, 2360, 1698, 1576, 1458, 1403, 1127, 915, 736.

m.p. = 70 – 71 °C.

5-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Nonan-1-one, 166b



$LiAlH_4$ (188 mg, 4.96 mmol, 1.00 equiv.), methyl 2-butyl-6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexanoate **208b** (1.72 g, 4.96 mmol, 1.00 equiv.) and Et_2O (50 mL) were subjected to **General Procedure 4-E**. The increase dilution of the reaction was due to the insolubility of the starting material. The reaction was quenched by sequential dropwise addition of H_2O (0.2 mL), aq. NaOH (15% w/v, 0.2 mL) and H_2O (0.6 mL) at 0 °C. Purification by column chromatography (Pentane:Et_2O, 70:30 to 40:60) afforded the title compound **166b** as a white solid (253 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.59 (2H, dp, *J*=20.4, 5.3 Hz, C5-H_2), 2.69 (2H, t, *J*=7.2 Hz, C1-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.79 – 1.70 (2H, m, C2-H_2), 1.61 (1H, d, *J*=5.1 Hz, O*H*), 1.52 (1H, p, *J*=5.8 Hz, C4-H), 1.48 – 1.24 (8H, m, C3-H_2, C6-H_2, C7-H_2, C8-H_2) 0.94 – 0.87 (3H, m, C9-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 212.3 (C=O), 140.8 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 127.4 (2 × Ar), 65.4 (C5), 45.9 (C1), 40.6 (C4), 30.7 (C6), 30.4 (C3), 29.3 (C7), 23.2 (C8), 20.3 (C2), 17.3 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.2 (C9).

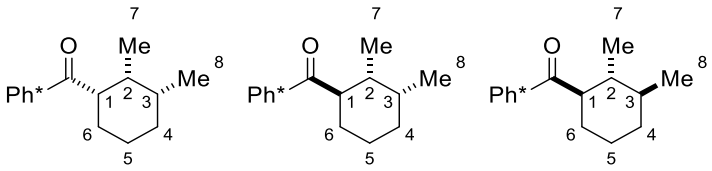
HRMS (ESI^+) m/z calcd. for $C_{21}H_{35}O_2$ $[M+H]^+$ 319.2632; found at 319.2631, Δ 0.30 ppm.

FTIR (neat) ν/cm^{-1} = 2928, 1697, 1458, 1382, 1304, 1265, 1127, 1039, 909, 732, 647.

m.p. = 63 – 64 °C.

6.4.1.3 Enantioselective synthesis of carbocycles via hydrogen borrowing catalysis

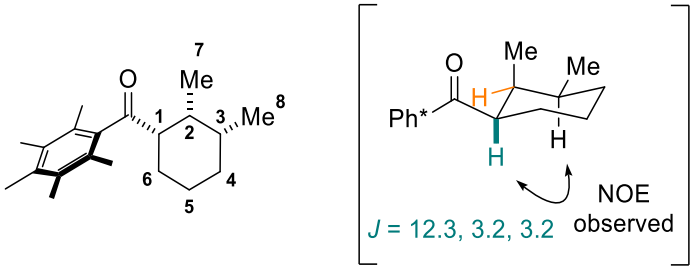
(2,3-dimethylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 158



158-I **158-II** **158-III**

Ketone **8** (57.0 mg, 0.3 mmol), 4-methylhexane-1,5-diol **157** (79.2 mg, 0.6 mmol), (*R*)-DTBM--SEGPHOS (18 mg, 5 mol%), Ir(cod)acac (4.8 mg, 0.012 mmol) and KO^{t}Bu (135 mg, 1.2 mmol) were subjected to **General Procedure 4-B**. Purification by column chromatography (Pentane:Et_2O, 100:0 to 99:1) afforded the **158-I** (35.0 mg, 41%) cleanly and **158-II** and **158-III** (36.9 mg, 43%, 81:18 d.r.) as an inseparable mixture of diastereoisomers, all as white solids. The overall d.r. (49:42:9, **158-I**: **158-II**: **158-III**) was determined by ^{1}H NMR analysis of the isolated mixture of **158-II** and **158-III** (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.77 (1H, td, *J*=8.5, 4.3 Hz, C1-H, major) and 2.59 – 2.50 (1H, m, C1-H, minor) and compared to the isolated mass of **158-I**. The relative stereochemistry of each diastereomer was determined through *J*-couping constant analysis and key nOe correlations from NOESY data. The racemic cyclohexane was obtained using our previously reported procedure.[33]

Data for 158-I



^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.74 (1H, dt, *J*=12.3, 3.2 Hz, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.18 – 2.12 (1H, m, C2-H), 2.10 (6H, s, 2 × Ar-CH_3), 1.84 – 1.48 (4H, m, C5-H_{eq}, C6-H_2,

C3-H), 1.41 – 1.15 (3H, m, C5-H_{ax}, C4-H_2), 0.91 (3H, d, *J*=7.0 Hz, C7-H_2), 0.86 (3H, d, *J*=7.0 Hz, C8-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 214.6 (C=O), 140.8 (Ar), 135.3 (Ar), 133.1 (2 × Ar), 58.6 (C1), 36.8 (C3), 33.8 (C2), 27.9 (C4), 26.2 (C5), 21.5 (C6), 20.0 (C8), 17.9 (br 2 × Ar-CH_3), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$), 7.5 (C7). [*N.B*. The signal for the *ortho*-quaternary aromatic carbon of the Ph* group was not observed, presumably due to restricted rotation about the Ar-CO axis].

HRMS (ESI^+) m/z calcd. for $C_{20}H_{31}O$ $[M+H]^+$ 287.2369; found at 287.2369, Δ 0.01 ppm.

FTIR (neat) ν/cm^{-1} = 2922, 1690, 1451, 1385, 1308, 1146, 1089, 1000, 892, 860, 705.

m.p. = 95 – 97 °C.

[α]$_D^{25}$ +3.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 0.8% IPA, 99.2% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 20.3 min, τ_R (minor) = 29.6 min.

Data for mixture of 158-II /158-III (81:19 d.r.):

HRMS (ESI^+) m/z calcd. for $C_{20}H_{31}O$ $[M+H]^+$ 287.2369; found at 287.2369, Δ 0.12 ppm.

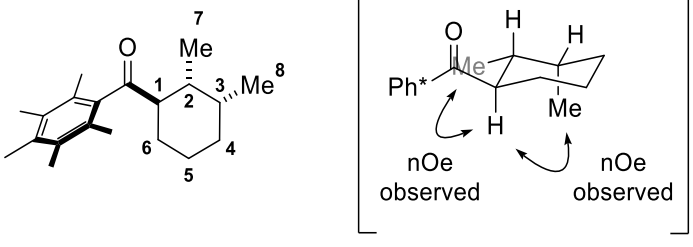
FTIR (neat) ν/cm^{-1} = 2927, 1691, 1461, 1381, 1300, 1270, 1149, 1102, 995, 889, 865, 694.

m.p. = 76 – 79 °C.

[α]$_D^{25}$ + 0.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 0.8% IPA, 99.2% hexane, 1 mL/min, 25 °C, λ = 254 nm, 10 µL injection; ***syn*-19bi**: τ_R (major) = 22.3 min, τ_R (minor) = 32.4 min; ***anti*-19b**: τ_R (major) = 14.4 min, τ_R (minor) = 12.6 min.

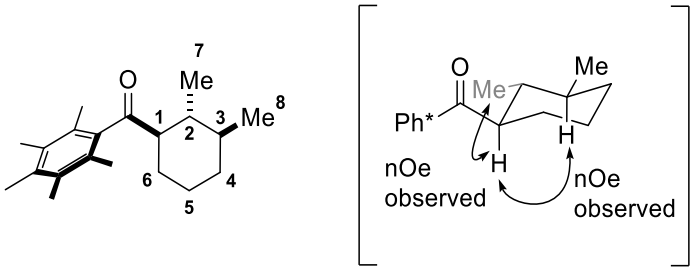
NMR data for 158-II reported from a mixture of 158-II /158-III



^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.77 (1H, td, *J*=8.5, 4.3 Hz, C1-H), 2.23 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.17 – 2.08 (7H, m, 2 × Ar-CH_3, C2-H), 2.00 – 1.93 (1H, m, C3-H), 1.77 – 1.69 (1H, m, C6-H_{eq}), 1.59 – 1.51 (2H, m, C5-H_{eq}), 1.50 – 1.41 (3H, m, C4-H_2, C5-H_{ax}), 1.40 – 1.32 (1H, m, C6-H_{ax}), 1.03 (3H, d, *J*=7.0 Hz, C7-H_3), 0.87 (3H, d, *J*=7.0 Hz, C8-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 213.9 (C=O), 140.2 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 128.8 (br, 2 × Ar), 53.8 (C1), 34.6 (C2), 32.7 (C3), 31.6 (C4), 27.5 (C6), 21.4 (C5), 18.0 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.6 (C7), 16.2 (2 × Ar-$\underline{C}H_3$), 15.2 (C8).

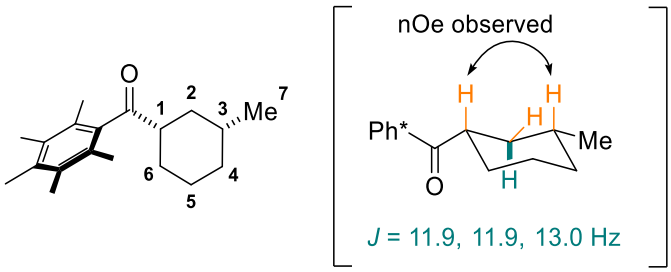
NMR data for 158-III reported from a mixture of 158-II /158-III



^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.59 – 2.50 (1H, m, C1-H), 2.24 (3H, s, Ar-CH_3), 2.18 (6H, s, Ar-CH_3), 2.13 (6H, s, Ar-CH_3), 1.85 – 1.78 (1H, m, C6-H_{eq}), 1.77 – 1.69 (1H, m, C5-H_{eq}), 1.68 – 1.59 (2H, m, C4-H_{eq}, C2-H), 1.25 – 1.13 (3H, m, C5-H_{ax}, C6-H_{ax}, C3-H), 1.12 (3H, d, *J*=6.4 Hz, C7-H_3), 1.04 – 1.00 (1H, m, C4-H_{ax}), 0.99 (3H, d, *J*=6.4 Hz, C8-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 213.1 (C=O), 139.8 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 128.8 (br, 2 × Ar), 59.3 (C1), 38.9 (C2), 38.2 (C3), 35.4 (C4), 30.2 (C6), 26.6 (C5), 20.5 (C8), 18.0 (2 × Ar-$\underline{C}H_3$, C7), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

((1*S*,3*R*)-3-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151a



7-Hydroxy-6-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one **163a** (87 mg, 0.3 mmol, 1.0 equiv.), (R)-DTBM-SEGPHOS (17.7 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **151a** as a white solid (70 mg, 86%, 90:10 e.r., 93:7 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the isolated product (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.66 (1H, tt, *J*=11.9, 3.2 Hz, C1-H, major diastereoisomer) and 2.85 (1H, tt, *J*=8.6, 4.3 Hz, C1-H, minor diastereoisomer). The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform (see Appendix B).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.66 (1H, tt, *J*=11.9, 3.3 Hz, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.94 – 1.87 (2H, m, C6-H_{eq}, C2-H_{eq}), 1.81 (1H, dp, *J*=13.1, 3.0 Hz, C5-H_{eq}), 1.67 (1H, dtt, *J*=12.7, 3.2, 1.7 Hz, C4-H_{eq}), 1.42 – 1.30 (2H, m, C3-H, C6-H_{ax}) 1.25 (1H, qt, *J*= 13.1, 3.2 Hz, C5-H_{ax}), 1.10 (1H, dt, *J*=13.0, 11.9 Hz, C2-H_{ax}), 0.96 – 0.81 (4H, m, 3x C7-H, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0 (C=O), 140.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 53.4 (C1), 36.6 (C2), 34.8 (C4), 32.6 (C3), 28.0 (C6), 26.0 (C5), 22.8 (C7), 18.1 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^{+}) m/z calcd. for $C_{19}H_{29}O$ $[M+H]^+$ 273.2213; found at 273.2212 Δ= 0.37.

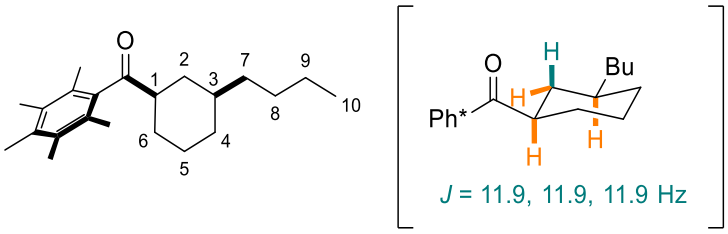
FTIR (neat) ν/cm^{-1} = 2923, 2854, 1691, 1456, 1381, 1305, 1265, 1162, 1142, 1110, 1084, 1002, 926, 857, 795, 701.

m.p. = 96 – 97 °C.

$[\alpha]_D^{25}$ +10.7 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IB-N5 coupled to IC with guard, 1% IPA, 99% hexane, 0.5 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 40.1 min, τ_R (minor) = 41.9 min [*N.B*. peaks at 38.5 and 38.9 min correspond to the minor diasteroisomer].

((1*R*,3*S*)-3-butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151b



From linear regiodefined alcohol: 6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Decan-1-one **163b** (100 mg, 0.3 mmol, 1.0 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **151b** as a white solid (76 mg, 81%, 97:3 e.r., 91:9 d.r.).

From the diol: Pentamethylacetophenone **8** (114 mg, 0.60 mmol, 2.0 equiv.), 2-butylpentane-1,5-diol **150b** (48 mg, 0.30 mmol, 1.0 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and KO^{t}Bu (67 mg, 0.60 mmol, 2.0 equiv.) were subjected to **General Procedure 4-B**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **151b** as a white solid (78 mg, 83%, 86:14 e.r., 92:8 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the isolated product (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H, major diastereoisomer) and 2.89 (1H, tt, *J*=8.4, 4.2 Hz, C1-H, minor diastereoisomer). The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform (see Appendix B).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.99 – 1.87 (2H, m, C2-H_{eq}, C6-H_{eq}), 1.82 (1H, dp, *J*=13.2, 3.3 Hz, C5-H_{eq}), 1.77 – 1.70 (1H, m, C4-H_{eq}), 1.35 (1H, qd, *J*=12.7, 3.5 Hz, C6-H_{ax}), 1.31 – 1.14 (8H, m,

C3-H, C5-H_{ax}, C7-H_2, C8-H_2, C9-H_2), 1.10 (1H, q, *J*=11.9 Hz, C2-H_{ax}), 0.92 – 0.79 (4H, m, C4-H_{ax}, C10-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.1 (C=O), 140.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 53.4 (C1), 37.4 (C3), 37.3 (C7), 34.9 (C2), 32.7 (C4), 29.2 (C8/9), 28.5 (C6), 26.0 (C5), 23.1 (C9/8), 18.1 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$), 14.3 (C10).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O$ $[M+H]^+$ 315.2682; found at 315.2682 Δ 0.17 ppm.

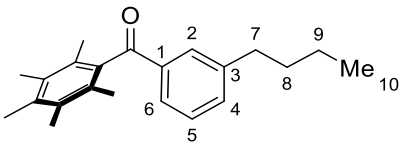
FTIR (neat) ν/cm^{-1} = 2956, 2926, 2854, 1692, 1574, 1464, 1445, 1381, 1307, 1263, 1155, 1113, 1070, 999, 925, 805, 701.

m.p. = 72 – 74 °C.

[α]$_D^{25}$ +12.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IG with guard, 1% IPA, 99% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 30.5 min, τ_R (minor) = 19.2 min. [*N.B*. peaks at 17.5 and 24.0 min correspond to the minor diasteroisomer].

(3-butylphenyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 172



A number of crude reactions from optimisation reactions for **151b** were combined and purification *via* Reverse Phase preparative HPLC afforded the title compound **172** as a clear oil that solidified on standing (11 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.74 (1H, s, C2-H), 7.54 (1H, d, *J*=7.6 Hz, C6-H), 7.38 (1H, dt, *J*=7.7, 1.6 Hz, C4-H), 7.31 (1H, t, *J*=7.6 Hz, C5-H), 2.69 – 2.59 (2H, m, C7-H_2), 2.28 (3H, s, Ar-CH_3), 2.21 (6H, s, 2 × Ar-CH_3), 2.01 (6H, s, 2 × Ar-CH_3), 1.68 – 1.56 (2H, m, C8-H_2), 1.35 (2H, h, *J*=7.3 Hz, C9-H_2), 0.92 (3H, t, *J*=7.3 Hz, C10-H_3).

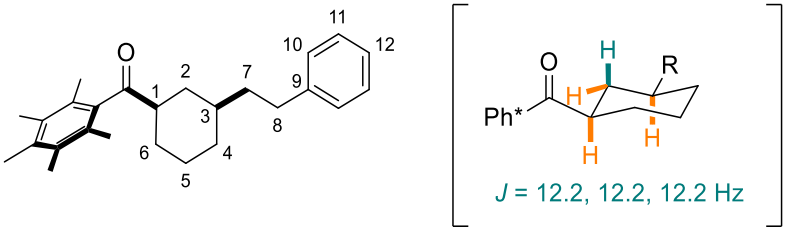
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 202.4 (C=O), 143.8 (Ar), 138.0 (Ar), 137.8 (Ar), 135.6 (Ar), 133.8 (Ar), 133.0 (2 × Ar), 129.2 (2 × Ar), 129.0 (Ar), 128.7 (Ar), 127.7 (Ar), 35.6 (C7), 33.7 (C8), 22.4 (C9), 17.7 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$), 14.1 (C10).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{28}ONa$ $[M+Na]^+$ 331.2032; found at 331.2039 Δ 1.99 ppm.

FTIR (neat) ν/cm^{-1} = 2928, 2858, 2359, 1672, 1600, 1440, 1311, 1273, 1231, 1163, 830, 734.

m.p. = 78 – 79 °C.

(2,3,4,5,6-pentamethylphenyl)((1*R*,3*R*)-3-phenethylcyclohexyl)Methanone, 151c



6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)-8-Phenyloctan-1-one **163c** (114 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **151c** as a white solid (84 mg, 77%, 97:3 e.r., 91:9 d.r.).

The d.r. was determined by analytical RP-HPLC of the crude mixture due to overlapping signals in ^{1}H NMR analysis of both the crude and isolated product. The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform (see Appendix B).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34 – 7.21 (2H, m, C10/11-H_2), 7.21 – 7.09 (3H, m, C11/10-H_2, C12-H), 2.71 – 2.51 (3H, m, C1-H, C8-H_2), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 2.06 – 1.98 (1H, m, C2-H_{eq}), 1.96 – 1.89 (1H, m, C6-H_{eq}), 1.88 – 1.79 (2H, m, C5-H_{eq}, C4-H_{eq}), 1.63 – 1.50 (2H, m, C7-H_2), 1.37 (1H, qd, *J*=12.8, 3.3 Hz, C6-H_{ax}), 1.32 – 1.20 (2H, m, C3-H, C5-H_{ax}), 1.17 (1H, q, *J*=12.2 Hz, C2-H_{ax}), 0.93 (1H, qd, *J*=13.0, 3.9 Hz, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0 (C=O), 142.9 (Ar), 140.3 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.5 (2 × Ar), 128.4 (2 × Ar), 128.3 (2 × Ar), 125.8 (Ar), 53.2 (C1), 39.3 (C7), 37.0 (C3), 34.6 (C2), 33.3 (C8), 32.6 (C4), 28.4 (C6), 25.9 (C5), 18.1 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{26}H_{35}O$ $[M+H]^+$ 363.2682; found at 363.2690 Δ 2.08 ppm.

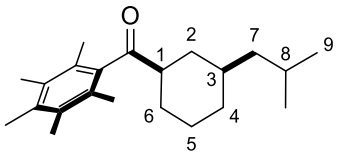
FTIR (neat) ν/cm^{-1} = 2929, 2855, 1692, 1497, 1454, 1383, 1308, 1263, 1135, 1071, 1001, 927, 749, 700, 637, 627.

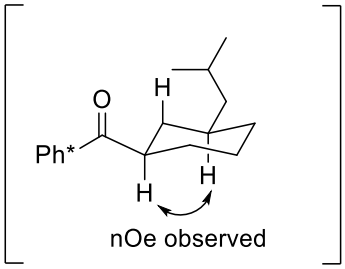
m.p. = 146 – 147 °C.

[α]$_D^{25}$ +19.0 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IA with guard, 1% IPA, 99% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 15.5 min, τ_R (minor) = 14.3 min. [*N.B*. peak at 12.8 min corresponds to the minor diasteroisomer].

((1*R*,3*R*)-3-isobutylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151d





6-(hydroxymethyl)-8-Methyl-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one **163d** (101 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 99:1) afforded the title compound **151d** as a white solid (58 mg, 62%, 92:8 e.r., 91:9 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the isolated product (due to overlapping signals in the crude mixture) through comparison of the C1-H signals: δ 2.66 (1H, tt, *J*=12.1, 3.3 Hz, C1-H, major diastereoisomer) and 2.89 (1H, td, *J*=8.8, 4.3 Hz, C1-H, minor diastereoisomer). The

relative stereochemistry of the major diastereomer was determined by nOe analysis. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.66 (1H, tt, *J*=12.1, 3.3 Hz, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 1.99 – 1.85 (2H, m, C2-H_{eq}, C6-H_{eq}), 1.82 (1H, dp, *J*=13.5, 3.4 Hz, C5-H_{eq}), 1.77 – 1.71 (1H, m, C4-H_{eq}), 1.70 – 1.62 (1H, m, C8-H), 1.36 (1H, qd, *J*=12.6, 3.5 Hz, C6-H_{ax}), 1.33 – 1.29 (1H, m, C3-H), 1.24 (1H, qt, *J*=13.1, 3.5 Hz, C5-H_{ax}), 1.12 – 1.03 (3H, m, C2-H_{ax}, C7-H_2), 0.89 – 0.75 (7H, m, 2 × C9-H_3, C4-H_{ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 215.1 (C=O), 140.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 53.4 (C1), 47.1 (C7), 35.1 (C2), 35.0 (C3), 32.8 (C4), 28.5 (C6), 26.0 (C5), 24.8 (C8), 23.3 (C9), 22.7 (C9), 18.1 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O$ $[M+H]^+$ 315.2682; found at 315.2691, Δ 2.71 ppm.

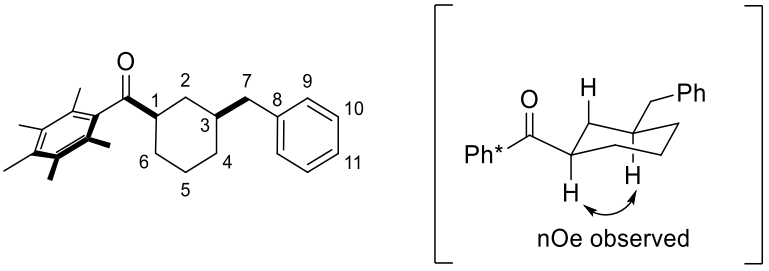
FTIR (neat) v/cm^{-1} = 3014, 2953, 2928, 2868, 1694, 1467, 1448, 1384, 1366, 1307, 1262, 1198.

m.p. = 82 – 83 °C.

[α]$_D^{25}$ +11.9 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak OD with guard, 0.3% IPA, 99.7% hexane, 0.5 mL/min, 25 °C, λ = 230 nm, 10 µL injection; τ_R (major) = 24.1 min, τ_R (minor) = 20.5 min. [*N.B*. peak at 18.4 min corresponds to the minor diasteroisomer].

((1*R*,3*S*)-3-benzylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151g



From linear regiodefined alcohol: 6-Benzyl-7-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one **163g** (110 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were

subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **151g** as a white solid (93 mg, 89%, 98:2 e.r., 91:9 d.r.).

From the diol: Pentamethylacetophenone **8** (114 mg, 0.60 mmol, 2.00 equiv.), 2-benzylpentane-1,5-diol[a] **150g** (48 mg, 0.30 mmol, 1.0 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and KO^{t}Bu (67 mg, 0.60 mmol, 2.0 equiv.) were subjected to **General Procedure 4-B**. Purification by preparative RP-HPLC (MeCN:H_2O, 60:40 to 100:0) to afford the title compound **151g** as a white solid (73 mg, 70%, 90:10 e.r., 91:9 d.r.). [a] Synthesised by Anna Chamberlain

The d.r. was determined by analytical RP-HPLC of the crude mixture due to overlapping signals in ^{1}H NMR analysis of both the crude and isolated product. The relative and absolute stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis after crystallization from deuterated chloroform (see Appendix B).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29 – 7.23 (2H, m, 2 × C9/10-H), 7.20 – 7.15 (1H, m, C11-H), 7.14 – 7.09 (2H, m, 2 × C10/9-H), 2.64 (1H, tt, *J*=12.5, 3.5 Hz, C2-H), 2.59 (1H, dd, *J*=13.4, 6.4 Hz, C7-H_2), 2.48 (1H, dd, *J*=13.3, 7.7 Hz, C7-H_2), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 2.04 – 1.95 (1H, m, C2-H_{eq}), 1.94 – 1.87 (1H, m, C6-H_{eq}) 1.80 (1H, dq, *J*=13.6, 3.4 Hz, C5-H_{eq}), 1.73 – 1.64 (1H, m, C4-H_{eq}), 1.61 – 1.49 (1H, m, C3-H), 1.38 (1H, qd, *J*=12.9, 3.7 Hz, C6-H_{ax}), 1.26 – 1.13 (2H, m, C2-Ha_x, C5-H_{ax}), 0.92 (1H, qd, *J*=12.9, 3.7 Hz, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 214.8 (C=O), 140.7 (Ar), 140.3 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 129.3 (2 × Ar), 128.3 (2 × Ar), 128.3 (2 × Ar), 125.9 (Ar), 53.2 (C1), 44.2 (C7), 39.5 (C3), 34.7 (C2), 32.3 (C4), 28.3 (C6), 25.8 (C5), 18.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{25}H_{33}O$ $[M+H]^+$ 349.2526; found at 349.2523, Δ 0.85 ppm.

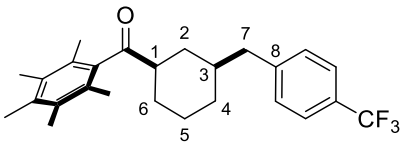
FTIR (neat) ν/cm^{-1} = 3026, 2928, 2855, 1692, 1496, 1448, 1383, 1309, 1263, 1218, 1174, 1102, 1000, 925, 844, 801, 748, 701, 638, 626, 606.

m.p. = 63 °C.

[α]$_D^{25}$ –13.7 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IH with guard coupled to OD with guard, 0.5% IPA, 99.5% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 41.2 min, τ_R (minor) = 38.9 min. [*N.B.* peaks at 32.7 and 35.6 min correspond to the minor diasteroisomer].

(2,3,4,5,6-pentamethylphenyl)((1*R*,3*S*)-3-(4-(trifluoromethyl)benzyl)cyclohexyl)Methanone, 151h



7-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)-6-(4-(trifluoromethyl)benzyl)heptan-1-one **163h** (130 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **151h** as a white solid (47 mg, 38%, 89:11 e.r., 90:10 d.r.).

The d.r. was determined by analytical RP-HPLC of the crude mixture due to overlapping signals in ^{1}H NMR analysis of both the crude and isolated product. The relative stereochemistry of the major diastereomer was determined by nOe analysis. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.52 (2H, d, *J*=7.9 Hz, 2 × C10), 7.24 (2H, d, *J*=7.9 Hz, 2 × C9), 2.71 – 2.60 (2H, m, C1-H, C7-H_AH_B), 2.56 (1H, dd, *J*=13.3, 7.6 Hz, C7-H_AH_B), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.08 (6H, s, 2 × Ar-CH_3), 1.99 – 1.87 (2H, m, C2-H_{eq}, C6-H_{eq}), 1.83 (1H, dt, *J*=13.4, 3.4 Hz, C5-H_{eq}), 1.70 – 1.62 (1H, m, C4-H_{eq}), 1.57 (1H, dddd, *J*=15.0, 11.5, 7.7, 5.4 Hz, C3-H), 1.38 (1H, qd, *J*=12.9, 3.6 Hz, C6-H_{ax}), 1.29 – 1.15 (2H, m, C2-H_{ax}, C5-H_{ax}), 0.94 (1H, qd, *J*=12.9, 3.7 Hz, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 214.5 (C=O), 144.9 (Ar), 140.2 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 129.6 (2 × Ar), 128.3 (q, *J*=32.2 Hz, C11), 128.2 (br. 2 × Ar), 125.2 (q, *J*=3.7 Hz, C10), 124.5 (q, *J*=271.7 Hz, C12), 53.1 (C1), 43.9 (C7), 39.3 (C3), 34.5 (C2), 32.2 (C4), 28.2 (C6), 25.7 (C5), 18.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

^{19}F NMR (470 MHz, $CDCl_3$) δ_F –62.3.

HRMS (ESI^+) m/z calcd. for $C_{26}H_{32}O_2F_3$ $[M+H]^+$ 417.2400; found at 417.2415, Δ 3.64 ppm.

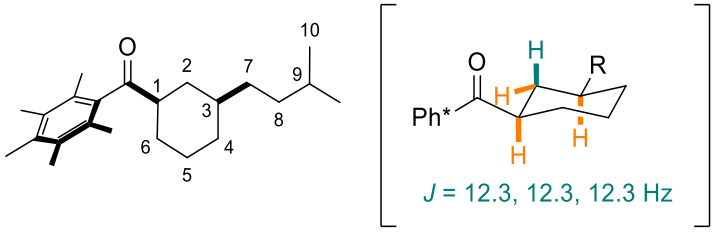
FTIR (neat) ν/cm^{-1} = 2931, 1691, 1448, 1325, 1163, 1123, 1019, 911, 843, 734, 635.

m.p. = 84 – 85 °C.

$[\alpha]_D^{25}$ –8.1. (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IC with guard coupled to OD with guard, 1% IPA, 99% hexane, 0.7 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 24.3 min, τ_R (minor) = 26.3 min. [*N.B.* peak at 22.4 corresponds to the minor diasteroisomer].

((1*R*,3*R*)-3-isopentylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151i



6-(hydroxymethyl)-9-methyl-1-(2,3,4,5,6-pentamethylphenyl)decan-1-one **163i** (104 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **163i** as a white solid (88 mg, 90%, 95:5 e.r., 91:9 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the crude product through comparison of the C1-H signals: δ 2.65 (1H, tt, *J*=11.8, 3.2 Hz, C1-H, major diastereoisomer) and 2.90 (1H, tt, *J*=8.7, 4.1 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer

was determined by J-coupling constants. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.96 (1H, dt, *J*=12.6, 2.6 Hz, C2-H_{eq}), 1.94 – 1.88 (1H, m, C6-H_{eq}), 1.82 (1H, dp, *J*=13.3, 3.3 Hz, C5-H_{eq}), 1.78 – 1.68 (1H, m, C4-H_{eq}), 1.52 – 1.42 (1H, m, C9-H), 1.35 (1H, qd, *J*=12.7, 3.5 Hz, C6-H_{ax}), 1.28 – 1.16 (6H, m, C3-H, C5-H_{ax}, C7-H_2, C8-H_2), 1.11 (1H, q, *J*=12.3 Hz, C2-H_{ax}), 1.88 – 1.84 (7H, m, 2 × C10-H_3, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.1 (C=O), 140.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 53.4 (C1), 37.8 (C3), 36.3 (C7/8), 35.3 (C8/7), 34.9 (C2), 32.7 (C4), 28.5 (C6), 28.4 (C9), 26.0 (C5), 22.8 (C10), 22.8 (C10), 18.1 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{23}H_{37}O$ $[M+H]^+$ 329.2839; found at 329.2848, Δ 2.75 ppm.

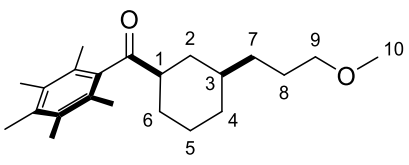
FTIR (neat) ν/cm^{-1} = 2927, 2853, 2363, 1693, 1449, 1384, 1366, 1309, 1264, 1157, 1089, 999, 926, 799, 760, 702, 652, 618.

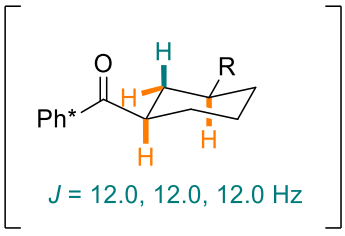
m.p. = 90 °C.

[α]$_D^{25}$ +11.5 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IBN-5 with guard, 0.1% IPA, 99.9% hexane, 0.5 mL/min, 25 °C, λ = 230 nm, 10 µL injection; τ_R (major) = 66.1 min, τ_R (minor) = 58.9 min. [*N.B*. peaks at 50.3 and 55.2 min correspond to the minor diasteroisomer].

((1*R*,3*R*)-3-(3-methoxypropyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151j





6-(hydroxymethyl)-9-Methoxy-1-(2,3,4,5,6-pentamethylphenyl)nonan-1-one **163j** (105 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General**

Procedure 4-A. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **151j** as a white solid (78 mg, 79%, 96:4 e.r., 90:10 d.r.).

The d.r. was determined by ^1H NMR analysis of the crude product through comparison of the C1-H signals: δ 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H, major diastereoisomer) and 2.91 (1H, td, *J*=8.5, 4.2 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer was determined by J-coupling constants. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.34 (2H, t, *J*=6.9 Hz, C9-H_2), 3.32 (3H, s, C10-H_3), 2.65 (1H, tt, *J*=12.0, 3.3 Hz, C1-H), 2.23 (3H, s, Ar-CH_3), 2.18 (6H, s, 2 × Ar-CH_3), 2.09 (6H, s, 2 × Ar-CH_3), 2.01 – 1.88 (2H, m, C2-H_{eq}, C6-H_{eq}), 1.83 (1H, dp, *J*=13.0, 3.1 Hz, C5-H_{eq}), 1.79 – 1.69 (1H, m, C4-H_{eq}), 1.64 – 1.49 (2H, m, C8-H_2), 1.36 (1H, qd, *J*=12.7, 3.4 Hz, C6-H_{ax}), 1.30 – 1.17 (4H, m, C7-H_2, C3-H, C5-H_{ax}), 1.10 (1H, q, *J*=12.0 Hz, C2-H_{ax}), 0.93 – 0.80 (1H, m, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0 (C=O), 140.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 73.3 (C9), 58.7 (C10), 53.3 (C1), 37.4 (C3), 34.8 (C2), 33.9 (C7), 32.6 (C4), 28.4 (C6), 27.1 (C8), 25.9 (C5), 18.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI^+) m/z calcd. for $C_{22}H_{35}O_2$ $[M+H]^+$ 331.2632; found at 331.2639, Δ 2.23 ppm.

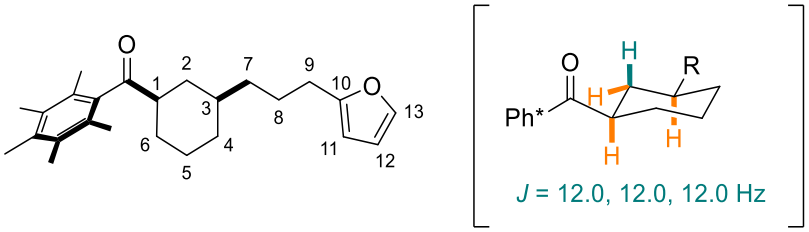
FTIR (neat) ν/cm^{-1} = 2930, 2855, 2362, 1693, 1449, 1308, 1263, 1118, 1001, 928, 802, 762, 703, 640.

m.p. = 59 °C.

[α]$_D^{25}$ +12.2 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IH with guard coupled to IG with guard, 3% IPA, 97% hexane, 0.5 mL/min, 25 °C, λ = 230 nm, 10 µL injection; τ_R (major) = 66.1 min, τ_R (minor) = 58.9 min. [*N.B*. peaks at 50.3 and 55.2 min correspond to the minor diasteroisomer].

((1*R*,3*R*)-3-(3-(furan-2-yl)propyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 151k



9-(furan-2-yl)-6-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Nonan-1-one **163k** (115 mg, 0.30 mmol, 1.00 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 93:7) afforded the title compound **151k** as a white solid (77 mg, 70%, 91:9 e.r., 90:10 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the crude product through comparison of the C1-H signals: δ 2.66 (1H, tt, *J*=12.1, 3.3 Hz, C1-H, major diastereoisomer) and 2.89 (1H, td, *J*=8.5, 4.3 Hz, C1-H, minor diastereoisomer). The relative stereochemistry of the major diastereomer was determined by J-coupling constants. The absolute stereochemistry of the major diastereoisomer was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29 (1H, dd, *J*=1.9, 0.8 Hz, C13-H), 6.28 (1H, dd, *J*=3.1, 1.9 Hz, C12-H), 5.98 – 5.94 (1H, m, C11-H), 2.66 (1H, tt, *J*=12.1, 3.3 Hz, C1-H), 2.59 (2H, t, *J*=7.5 Hz, C9-H_2), 2.25 (3H, s, Ar-CH_3), 2.20 (6H, s, 2 × Ar-CH_3), 2.10 (6H, s, 2 × Ar-CH_3), 1.97 (1H, dq, *J*=11.3, 2.7 Hz, C2-H_{eq}), 1.92 (1H, ddt, *J*=12.7, 3.4, 1.6 Hz, C6-H_{eq}), 1.84 (1H, dp, *J*=13.2, 3.3 Hz, C5-H_{eq}), 1.79 – 1.72 (1H, m, C4-H_{eq}), 1.71 – 1.53 (2H, m, C8-H_2), 1.41 – 1.33 (1H, m, C6-H_{ax}), 1.33 – 1.18 (4H, m, C7-H_2, C3-H, C5-H_{ax}), 1.12 (1H, q, *J*=12.0 Hz, C2-H_{ax}), 0.93 – 0.81 (1H, m, C4-H_{ax}).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 214.9 (C=O), 156.5 (C10), 140.8 (C13), 140.3 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 110.2 (C12), 104.7 (C11), 53.3 (C1), 37.3 (C3), 37.0 (C7), 34.7 (C2), 32.6 (C4), 28.4 (C6), 28.4 (C9), 25.9 (C5), 25.4 (C8), 18.1 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

HRMS (ESI$^+$) m/z calcd. for $C_{25}H_{34}O_2Na$ $[M+Na]^+$ 389.2451; found at 389.2465, Δ 3.58 ppm.

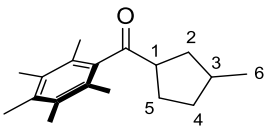
FTIR (neat) ν/cm^{-1} = 2930, 2855, 2360, 1692, 1508, 1448, 1384, 1261, 1074, 924, 800, 732.

m.p. = 55 – 56 °C.

[α]$_D^{25}$ +9.0 (c = 1.00, $CHCl_3$).

Chiral HPLC: Chiralpak IC with guard coupled to IG with guard, 1% IPA, 99% hexane, 0.5 mL/min, 25 °C, λ = 254 nm, 10 µL injection; τ_R (major) = 20.8 min, τ_R (minor) = 23.0 min. [*N.B.* peaks at 20.0 and 21.7 min correspond to the minor diasteroisomer].

(3-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)Methanone, **165a**



From linear regiodefined alcohol: 6-hydroxy-5-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one **166a** (83 mg, 0.3 mmol, 1.0 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **166a** as a white solid (44 mg, 56%, 35:65 e.r., 52:48 d.r.).

From the diol: Pentamethylacetophenone **8** (57 mg, 0.30 mmol, 1.0 equiv.), 2-methylbutane-1,4-diol (62 mg, 0.60 mmol, 2.0 equiv.), (*R*)-DTBM-SEGPHOS (18 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.1 mL, 3 M) and KO^{t}Bu (135 mg, 1.20 mmol) were subjected to **General Procedure 4-B**. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **165a** as an inseparable mixture of diastereomers and as a pale yellow oil (44 mg, 57%, 62:38 e.r., 52:48 d.r.).

The d.r. was determined by ^{1}H NMR analysis of the crude mixture by comparison of the following signals: δ 0.98 (3H, d, *J* = 6.5 Hz, C6-H_3, diastereoisomer **165a'**), 1.05 (3H, d, *J* = 6.3 Hz, C6-H_3, diastereoisomer **165a''**). The relative stereochemistry of the diastereoisomers could not be distinguished. The absolute stereochemistry was not determined. The spectral data matched that previously reported in the literature.[36]

NMR data: 165a'

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.36 – 3.27 (1H, m, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.17 – 2.13 (2H, m, C2-H_AH_B, C3-H), 2.11 (6H, s, 2 × Ar-CH_3), 1.96 – 1.88 (3H, m, C5-H_2, C4-H_AH_B), 1.45 – 1.37 (1H, m, C2-H_AH_B), 1.23 – 1.11 (1H, m, C4-H_AH_B), 0.98 (3H, d, *J*=6.5 Hz, C6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 215.2 (C=O), 141.3 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.9 (2 × Ar), 53.5 (C1), 37.6 (C2), 35.2 (C4), 34.2 (C3), 29.7 (C5), 20.8 (C6), 17.9 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

NMR data: 165a''

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.27 – 3.18 (1H, m, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.11 (6H, s, 2 × Ar-CH_3), 2.09 – 1.96 (3H, m, C2-H_AH_B, C3-H, C5-H_AH_B), 1.87 – 1.74 (2H, m, C5-H_AH_B, C4-H_AH_B), 1.52 – 1.42 (1H, m, C2-H_AH_B), 1.35 – 1.24 (1H, m, C4-H_AH_B), 1.05 (3H, d, *J*=6.3 Hz, C6-H_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 215.1 (C=O), 141.5 (Ar), 135.4 (Ar), 133.2 (2 × Ar), 127.8 (2 × Ar), 54.8 (C1), 39.1 (C2), 35.5 (C3), 34.2 (C4), 28.8 (C5), 20.2 (C6), 17.9 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

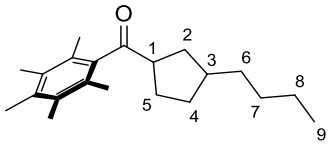
Data for 165:

FTIR (neat) ν/cm^{-1} = 2951, 2868, 1692, 1452, 1381, 1347, 1302, 1259, 1118, 1069, 1003, 908, 875, 831, 731, 649.

HRMS (ESI^+) m/z calcd. for $C_{18}H_{27}O$ $[M+H]^+$ 259.2056; found at 259.2061, Δ 1.75 ppm.

Chiral HPLC: Chiralpak IG with guard, 0.5% IPA, 99.5% hexane, 0.7 mL/min, 30 °C, λ = 210 nm, 10 µL injection; major diasteromer: τ_R (major) = 43.9 min, τ_R (minor) = 32.1 min, minor diasteromer: τ_R (major) = 30.1 min, τ_R (minor) = 35.6 min.

(3-butylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)Methanone, **165b**



5-(hydroxymethyl)-1-(2,3,4,5,6-pentamethylphenyl)Nonan-1-one **166b** (96 mg, 0.3 mmol, 1.0 equiv.), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4.0 mol%), ^{t}BuOH (0.5 mL, 0.6 M) and KO^{t}Bu (67 mg, 1.2 mmol, 2.0 equiv.) were subjected to **General Procedure 4-A**. Purification by column chromatography (Pentane:Et_2O, 92:8) afforded the title compound **165b** as a colourless oil (64 mg, 71%, 74:26 e.r., 52:48 d.r.). The d.r. was determined by Chiral-HPLC of the isolated product due to overlapping signals in ^{1}H NMR analysis of both the crude and

isolated product. The relative stereochemistry of the diastereoisomers could not be distinguished. The absolute stereochemistry was not determined.

NMR data: 165b'

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.30 – 3.24 (1H, m, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.18 – 2.14 (1H, m, C2-H_AH_B), 2.12 (6H, s, 2 × Ar-CH_3), 2.02 – 1.87 (4H, m, C3-H, C4-H_AH_B, C5-H_2), 1.41 – 1.35 (1H, m, C2-H_AH_B), 1.35 – 1.23 (6H, m, C6-H_2, C7-H_2, C8-H_2), 1.17 (1H, dq, *J*=10.7, 8.2 Hz, C4-H_AH_B), 0.89 (3H, t, *J*=7.0 Hz, C9-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.2 (C=O), 141.1 (Ar), 135.3 (Ar), 133.1 (2 × Ar), 127.8 (2 × Ar), 53.3 (C1), 39.6 (C3), 35.8 (C6), 35.5 (C2), 33.3 (C4), 30.8 (C8), 29.6 (C5), 22.9 (C7), 17.8 (2 × Ar-$\underline{C}H_3$), 16.7 (Ar-$\underline{C}H_3$), 16.0 (2 × Ar-$\underline{C}H_3$), 14.1 (C9).

NMR data: 165b''

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.24 – 3.16 (1H, m, C1-H), 2.24 (3H, s, Ar-CH_3), 2.19 (6H, s, 2 × Ar-CH_3), 2.12 (6H, s, 2 × Ar-CH_3), 2.07 – 1.98 (2H, m, C2-H_AH_B, C5-H_AH_B), 1.88 – 1.77 (3H, m, C5-H_AH_B, C4-H_AH_B, C3-H), 1.49 – 1.41 (1H, m, C2-H_AH_B), 1.35 – 1.23 (7H, m, C4-H_AH_B, C6-H_2, C7-H_2, C8-H_2), 0.89 (3H, t, *J*=7.0 Hz, C9-H_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 215.0 (C=O), 141.3 (Ar), 135.3 (Ar), 133.1 (2 × Ar), 127.7 (2 × Ar), 54.4 (C1), 40.8 (C3), 37.1 (C2), 35.4 (C6), 32.0 (C4), 30.9 (C8), 28.4 (C5), 22.9 (C7), 17.8 (2 × Ar-$\underline{C}H_3$), 16.7 (Ar-$\underline{C}H_3$), 16.0 (2 × Ar-$\underline{C}H_3$), 14.1 (C9).

Data for 165b:

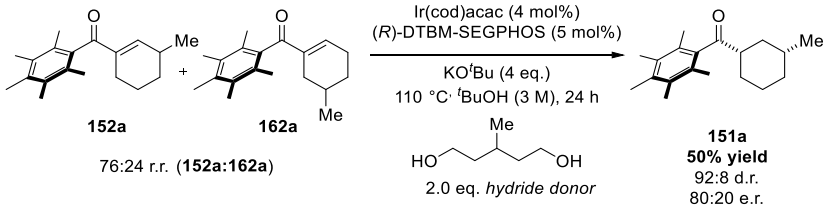
FTIR (neat) ν/cm^{-1} = 2926, 1692, 1455, 1381, 1303, 1119, 1001, 908, 732, 648.

HRMS (ESI^+) m/z calcd. for $C_{21}H_{33}O$ $[M+H]^+$ 301.2526; found at 301.2523, Δ 0.93 ppm.

Chiral HPLC: Chiralpak IG with guard, 1% IPA, 99% hexane, 0.7 mL/min, 30 °C, λ = 254 nm, 10 µL injection; major diasteromer: τ_R (major) = 23.4 min, τ_R (minor) = 16.4 min, minor diasteromer: τ_R (major) = 17.2 min, τ_R (minor) = 28.9 min.

6.4.1.4 Mechanistic experiments

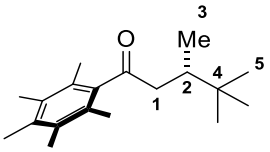
Transfer Hydrogenation of cyclic enone



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added a regiomeric mixture of (3-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone **152a** and (5-methylcyclohex-1-en-1-yl)(2,3,4,5,6-pentamethylphenyl)methanone **162a** (47 mg, 0.20 mmol, 1.0 equiv., 76:24 r.r.), commercially available 3-methylpentane-1,5-diol (47 mg, 0.40 mmol, 2.0 equiv.), (*R*)-DTBM-SEGPHOS (12 mg, 5 mol%), Ir(cod)acac (3.2 mg, 4 mol%), ^{t}BuOH (0.07 mL, 3 M) and KO^{t}Bu (90 mg, 0.80 mmol, 4.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and stirred at 110 °C in a preheated oil bath for 24 h. The mixture was cooled to r.t., filtered through a SiO_2 plug (eluting with ~50 mL Et_2O). For ease of purification, residual (*R*)-DTBM-SEGPHOS was removed by treatment of the crude ethereal solution with *tert*-butyl hydroperoxide (5-6 M in decane, 50 µL, ~0.28 mmol), swirled and allowed to stand at r.t. for 10 min. Purification by column chromatography (Pentane:Et_2O, 99:1 to 99:2) afforded the title compound **151a** as a white solid (22 mg, 50%, 80:20 e.r., 92:8 d.r.). For data see above.

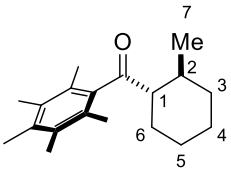
Using [R_P,*S*]-PPF-NH_2 in previously reported hydrogen borrowing alkylations.

(*S*)-3,4,4-Trimethyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one, 15f



Pentamethylacetophenone **8** (57 mg, 0.30 mmol), 3,3-dimethyl-2-butanol **14f** (76 μL, 0.60 mmol), [R_P,*S*]-PPF-NH_2 (6.2 mg, 5 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and NaO^{t}Bu (115 mg, 1.20 mmol) were subjected to **General procedure 2-A**. Purification by column chromatography (Penane:Et_2O, 98:2) afforded the title compound **15f** as a white solid (58 mg, 71%, 50:50 e.r.). For data see chapter 6.2.1.2.

((1*S*,2*S*)-2-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone, 20a



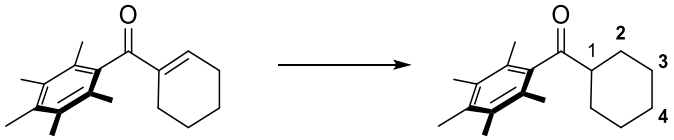
Pentamethylacetophenone **8** (57 mg, 0.30 mmol), hexane-1,5-diol **19a** (71 mg, 0.60 mmol), [R_p,*S*]-PPF-NH_2 (6.2 mg, 5.0 mol%), Ir(cod)acac (4.8 mg, 4 mol%), ^{t}BuOH (0.1 mL, 3 M) and KO*t*Bu (135 mg, 1.20 mmol) were subjected to **General Procedure 4-B**. Purification by column chromatography (Pentane:Et_2O, 98:2) afforded the title compound **20a** as a white solid (53 mg, 65%, 58:42 e.r., 91:9 d.r.). The spectral data matched that previously reported in the literature.[34]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.45 (1H, ddd, *J*=11.6, 10.3, 3.3 Hz, C1-H), 2.24 (3H, s, Ar-C$\underline{H}_3$), 2.19 (6H, s, 2 × Ar-C$\underline{H}_3$), 2.13 (6H, s, 2 × Ar-C$\underline{H}_3$), 1.95 (1H, dddd, *J*=11.8, 10.3, 6.5, 3.9 Hz, C2-H), 1.87 – 1.63 (4H, m, C6-H_{eq}, C3-H_{eq}, C5-H_{eq}, C4-H_{eq}), 1.33 – 1.11 (3H, m, C4-H_{ax}, C6-H_{ax}, C5-H_{ax}), 1.09 (3H, d, *J*=6.5 Hz, C7-H_3), 1.03 (1H, tdd, *J*=13.0, 11.8, 3.7 Hz, C3-H_{ax}). The minor diastereoisomer displays a diagnostic peak at δ = 2.77 (1H, dt, *J* = 11.6, 3.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 213.2 (C=O), 139.8 (Ar), 135.6 (Ar), 133.2 (2 × Ar), 59.4 (C1), 34.8 (C3), 32.6 (C2), 29.7 (C6), 26.7 (C5), 26.0 (C4), 21.1 (C7), 18.0 (2 × Ar-$\underline{C}H_3$), 16.9 (Ar-$\underline{C}H_3$), 16.2 (2 × Ar-$\underline{C}H_3$).

Investigating the background reaction

Cyclohexyl(2,3,4,5,6-pentamethylphenyl)methanone, S7



S6 **S7**

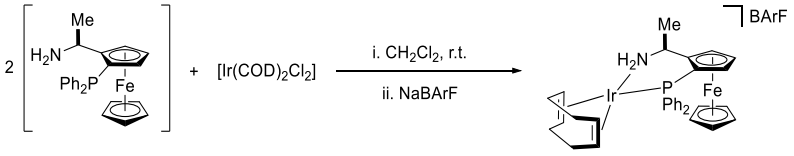
To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added cyclohex-1-en-1-yl(2,3,4,5,6-pentamethylphenyl)methanone[a] **S6** (76.1 mg, 0.3 mmol, 1.0 equiv.), commercially available 3-methylpentane-1,5-diol (46 mg, 0.39 mmol, 2.0 equiv.), ^{t}BuOH (0.1 mL, 3 M) and KO^{t}Bu (135 mg, 1.2 mmol, 4.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and stirred at 110 °C in a preheated oil bath for 24 h. The mixture was cooled to r.t., filtered through a SiO_2 plug (eluting with ~50 mL Et_2O). Purification by column chromatography (Pentane:Et_2O, 99:1 to 99:2) afforded the title compound **S7** as a white solid (13.4 mg, 17%). The spectral data matched that previously reported in the literature.[33] [a] Synthesised by Dr Roly Armstrong.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.61 (1H, tt, *J*=11.8, 3.3 Hz, C1-H), 2.24 (3H, s, Ar-C$\underline{H}_3$), 2.19 (6H, s, 2 × Ar-C$\underline{H}_3$), 2.09 (6H, s, 2 × Ar-C$\underline{H}_3$), 1.98 – 1.89 (2H, m, 2 × C2-H_{eq}), 1.89 – 1.76 (2H, m, 2 × C3-H_{eq}), 1.73 – 1.61 (1H, m, C4-H_{eq}), 1.50 – 1.35 (2H, m, 2 × C2-H_{ax}), 1.29 – 1.14 (3H, m, C4-H_{ax}, 2 × C3-H_{ax}).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 215.1 (C=O), 140.4 (Ar), 135.5 (Ar), 133.2 (2 × Ar), 128.3 (2 × Ar), 53.3 (C1), 28.4 (2 × C2), 26.1 (2 × C3), 26.1 (C4), 18.0 (2 × Ar-$\underline{C}H_3$), 16.8 (Ar-$\underline{C}H_3$), 16.1 (2 × Ar-$\underline{C}H_3$).

6.4.1.5 Catalyst Synthesis

[Ir(cod)([R_P,S]-PPF-NH_2)]BArF, Ir-7



[R_P, S]-PPF-NH_2

XX
77% yield

To a flame-dried Schlenk tube was charged with $[Ir_2(COD)_2Cl_2]$ (43.0 mg, 0.06 mmol) and [R_P,S]-PPF-NH_2 **L37** (53.0 mg, 0.13 mol, 2.0 eq.) and CH_2Cl_2 (0.6 mL) was stirred at r.t. for 3 h. After this time, NaBArF (114.3 mg, 0.13 mmol, 2.0 eq.) was added as a solid and the mixture was stirred for further 18 h. The cloudy red mixture was filtered through a millipor-filter and washed with 0.2 mL CH_2Cl_2 giving a red solution, which was overlaid with *n*-pentane. Cooling down to 4 °C overnight gave a red microcrystalline solid and the solvent evaporated. The solid was washed with *n*-pentane and dried *in vacuo* to afford the title compound **Ir-7** as a red solid (158 mg, 77%). The spectral data matched that previously reported in the literature.[110]

^{1}H NMR (400 MHz, CD_2Cl_2) δ_H 8.10 (2H, ddd, *J*=11.8, 7.6, 1.9 Hz, 2 × Ar-H), 7.72 (8H, m, 8 × Ar-H), 7.70 – 7.64 (3H, m, 3 × Ar-H), 7.56 (4H, br. s, 4 × Ar-H), 7.46 – 7.32 (3H, m, 3 × Ar-H), 6.99 – 6.92 (2H, m, 2 × Ar-H), 4.81 (1H, td, *J*=7.8, 4.1 Hz), 4.65 (1H, td, *J*=2.4, 1.3 Hz), 4.59 (1H, t, *J*=2.6 Hz), 4.53 (1H, d, *J*=5.9 Hz), 4.46 – 4.37 (2H, m), 4.34 – 4.23 (1H, m), 4.21 – 4.16 (1H, m), 3.83 (3H, s), 3.69 (1H, td, *J*=7.0, 3.5 Hz), 3.00 (1H, tt, *J*=7.5, 3.8 Hz), 2.52 – 2.18 (3H, m), 2.10 (2H, dd, *J*=18.1, 7.9 Hz), 2.04 – 1.85 (1H, m), 1.80 (3H, d, *J*=6.6 Hz), 1.76 – 1.63 (1H, m).

HRMS (ESI$^+$) m/z calcd. for $C_{32}H_{36}NFeIrP$ $[M+H]^+$ 714.1560; found at 714.1557, Δ 0.78 ppm.

m.p. = decomp.

[α]$_D^{25}$ +75.1 (c = 1.00, $CHCl_3$).

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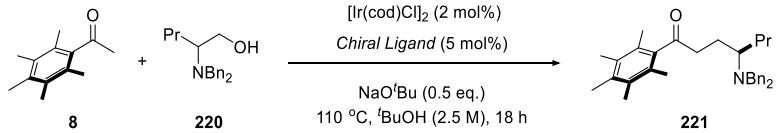
Appendix

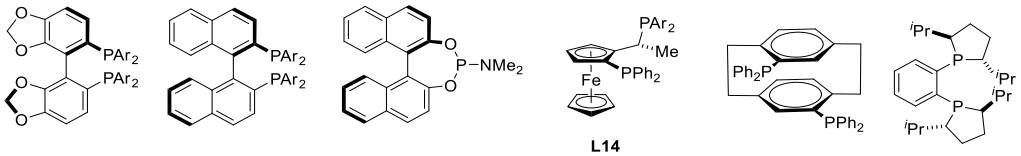
Appendix A – Initial ligand screening



8 **220** **221**

Entry	L*	Ligand	Yield[a] / %	e.r.[b]
1	**L1**	(*R*)-DTBM-SEGPHOS	11	50:50
2	**L11**	(*R*)-BINAP	12	50:50
3	**L17**	(*R,R*)-^{i}Pr-DUPHOS	<5	50:50
4	**L12**	(*R*)-MonoPhos	<5	50:50
5	**L14**	Josiphos SL-J005-1	<5	50:50
6	**L15**	(*S*)-PHANEPHOS	<5	50:50

[a]Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard. [Isolated yields are given in parentheses]. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.

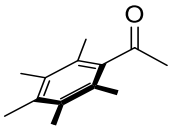


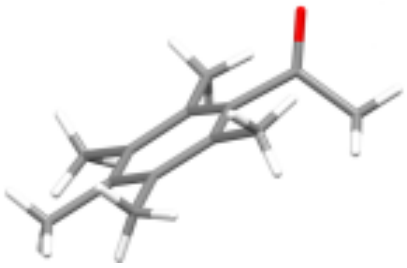
L1: Ar = DTBM **L11**: Ar = Ph **L12** **L14** Ar = 3,5-Me_2-C_6H_3 **L15** **L17**

Appendix B- X-ray Crystallography Data

X-ray Crystallographic data for **8**: 1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one

(pentamethylacetophenone)

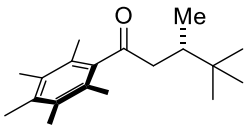


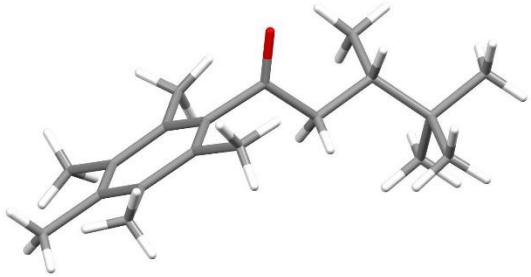


Identification code	7322	
Empirical formula	C13 H18 O	
Formula weight	190.29	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P c	
Unit cell dimensions	a = 12.5875(11) Å	α= 90°.
	b = 9.1237(5) Å	β= 94.032(8)°.
	c = 9.5455(7) Å	γ = 90°.
Volume	1093.54(14) $Å^3$	
Z	4	
Density (calculated)	1.156 Mg/m^3	
Absorption coefficient	0.543 mm^{-1}	
F(000)	416	
Crystal size	0.22 x 0.10 x 0.01 mm^3	
Theta range for data collection	3.520 to 68.093°.	
Index ranges	-14<=h<=14, -10<=k<=6, -11<=l<=11	
Reflections collected	4891	
Independent reflections	2838 [R(int) = 0.055]	
Completeness to theta = 63.327°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.69	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2838 / 2 / 254	
Goodness-of-fit on F^2	0.9958	
Final R indices [I>2sigma(I)]	R1 = 0.0721, wR2 = 0.1058	
R indices (all data)	R1 = 0.0937, wR2 = 0.1187	
Absolute structure parameter	-0.2(5)	
Largest diff. peak and hole	0.37 and -0.35 e.$Å^{-3}$	

X-ray Crystallographic data for **15f**: (*S*)-3,4,4-Trimethyl-1-(2,3,4,5,6-

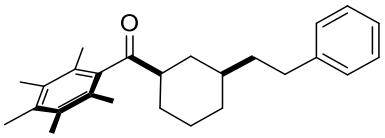
pentamethylphenyl)pentan-1-one

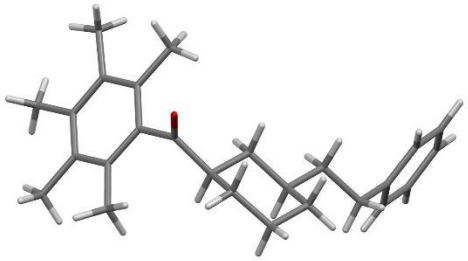




Identification code	7753	
Empirical formula	C19 H30 O	
Formula weight	274.45	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 2**1** 2**1** 2**1**	
Unit cell dimensions	a = 6.00580(10) Å	α= 90°.
	b = 10.7904(2) Å	β= 90°.
	c = 26.5548(7) Å	γ = 90°.
Volume	1720.88(6) $Å^3$	
Z	4	
Density (calculated)	1.059 Mg/m^3	
Absorption coefficient	0.472 mm^{-1}	
F(000)	608	
Crystal size	0.24 x 0.10 x 0.02 mm^3	
Theta range for data collection	4.423 to 76.241°.	
Index ranges	-7<=h<=7, -9<=k<=13, -33<=l<=33	
Reflections collected	18400	
Independent reflections	3606 [R(int) = 0.037]	
Completeness to theta = 76.241°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.80	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3606 / 0 / 182	
Goodness-of-fit on F^2	1.0140	
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.1026	
R indices (all data)	R1 = 0.0430, wR2 = 0.1081	
Absolute structure parameter	-0.09(13)	
Largest diff. peak and hole	0.08 and -0.08 $e.Å^{-3}$	

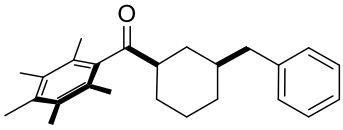
X-ray Crystallographic data for **151c**: (2,3,4,5,6-pentamethylphenyl)((1*R*,3*R*)-3-phenethylcyclohexyl)methanone

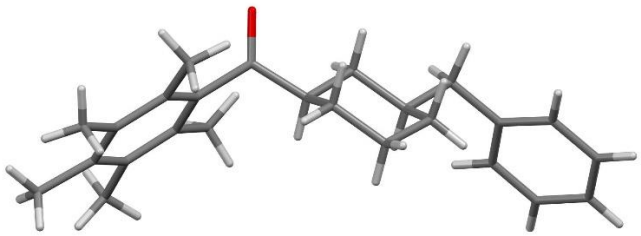




Identification code	7752	
Empirical formula	C26 H34 O	
Formula weight	362.56	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 2**1** 2**1** 2**1**	
Unit cell dimensions	a = 5.58060(10) Å	α = 90°.
	b = 11.9554(2) Å	β= 90°.
	c = 31.1944(4) Å	γ = 90°.
Volume	2081.24(6) $Å^3$	
Z	4	
Density (calculated)	1.157 Mg/m^3	
Absorption coefficient	0.512 mm^{-1}	
F(000)	792	
Crystal size	0.20 x 0.18 x 0.03 mm^3	
Theta range for data collection	3.960 to 76.165°.	
Index ranges	-6<=h<=6, -12<=k<=14, -38<=l<=39	
Reflections collected	48092	
Independent reflections	4317 [R(int) = 0.049]	
Completeness to theta = 74.642°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.84	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4317 / 0 / 245	
Goodness-of-fit on F^2	1.0029	
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0862	
R indices (all data)	R1 = 0.0350, wR2 = 0.0888	
Absolute structure parameter	0.04(9)	
Largest diff. peak and hole	0.09 and -0.07 e.Å-3	

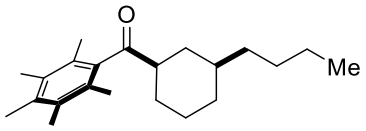
X-ray Crystallographic data for **151g**: ((1*R*,3*S*)-3-benzylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone

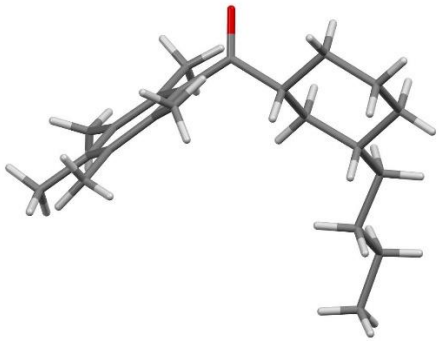




Identification code	7751	
Empirical formula	C25 H32 O	
Formula weight	348.53	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 2**1**	
Unit cell dimensions	a = 17.8980(4) Å	α= 90°.
	b = 10.75260(10) Å	β= 116.475(2)°.
	c = 17.9306(3) Å	γ = 90°.
Volume	3088.86(11) $Å^3$	
Z	6	
Density (calculated)	1.124 Mg/m^3	
Absorption coefficient	0.500 mm^{-1}	
F(000)	1140	
Crystal size	0.38 x 0.26 x 0.02 mm^3	
Theta range for data collection	4.689 to 76.287°.	
Index ranges	-22<=h<=22, -13<=k<=13, -22<=l<=21	
Reflections collected	66937	
Independent reflections	12801 [R(int) = 0.046]	
Completeness to theta = 76.287°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.68	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	12801 / 1 / 704	
Goodness-of-fit on F^2	1.0031	
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1018	
R indices (all data)	R1 = 0.0452, wR2 = 0.1082	
Absolute structure parameter	-0.07(9)	
Largest diff. peak and hole	0.26 and -0.16 e.Å-3	

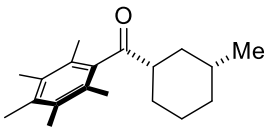
X-ray Crystallographic data for **151b**: ((1*R*,3*S*)-3-butylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone

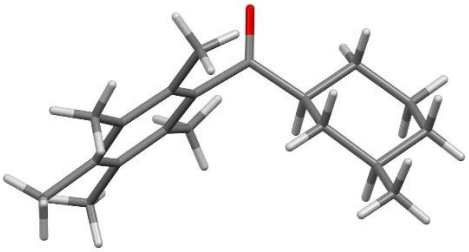




Identification code	7716	
Empirical formula	C22 H34 O	
Formula weight	314.51	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 2**1** 2**1** 2**1**	
Unit cell dimensions	a = 5.38770(10) Å	α= 90°.
	b = 16.7335(4) Å	β= 90°.
	c = 21.1766(5) Å	γ = 90°.
Volume	1909.18(7) $Å^3$	
Z	4	
Density (calculated)	1.094 Mg/m^3	
Absorption coefficient	0.483 mm^{-1}	
F(000)	696	
Crystal size	0.28 x 0.05 x 0.02 mm^3	
Theta range for data collection	4.175 to 76.254°.	
Index ranges	-6<=h<=6, -17<=k<=20, -26<=l<=24	
Reflections collected	20127	
Independent reflections	3971 [R(int) = 0.038]	
Completeness to theta = 76.254°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.83	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3971 / 0 / 209	
Goodness-of-fit on F^2	0.9979	
Final R indices [I>2sigma(I)]	R1 = 0.0350, wR2 = 0.0914	
R indices (all data)	R1 = 0.0398, wR2 = 0.0957	
Absolute structure parameter	0.11(12)	
Largest diff. peak and hole	0.23 and -0.20 $e.Å^{-3}$	

X-ray Crystallographic data for **151a**: ((1*S*,3*R*)-3-methylcyclohexyl)(2,3,4,5,6-pentamethylphenyl)Methanone





Identification code	7383	
Empirical formula	C19 H28 O	
Formula weight	272.43	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.4471(3) Å	α= 90°.
	b = 21.8813(8) Å	β= 102.958(4)°.
	c = 8.9494(4) Å	γ = 90°.
Volume	1612.03(11) Å3	
Z	4	
Density (calculated)	1.122 Mg/m^3	
Absorption coefficient	0.504 mm^{-1}	
F(000)	600	
Crystal size	0.19 x 0.18 x 0.05 mm3	
Theta range for data collection	4.041 to 76.270°.	
Index ranges	-10<=h<=10, -27<=k<=27, -11<=l<=8	
Reflections collected	15834	
Independent reflections	6614 [R(int) = 0.046]	
Completeness to theta = 73.982°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.49	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6612 / 1 / 362	
Goodness-of-fit on F^2	1.0038	
Final R indices [I>2sigma(I)]	R1 = 0.0657, wR2 = 0.1629	
R indices (all data)	R1 = 0.0742, wR2 = 0.1804	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.07 and -0.06 $e.Å^{-3}$	