

Hydrogen Borrowing Methods for the Synthesis of Quaternary Stereocentres



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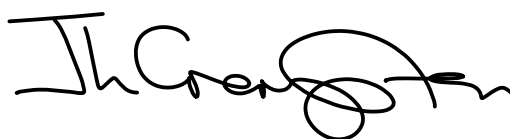
*A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment
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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from February 2021 until December 2024. 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.

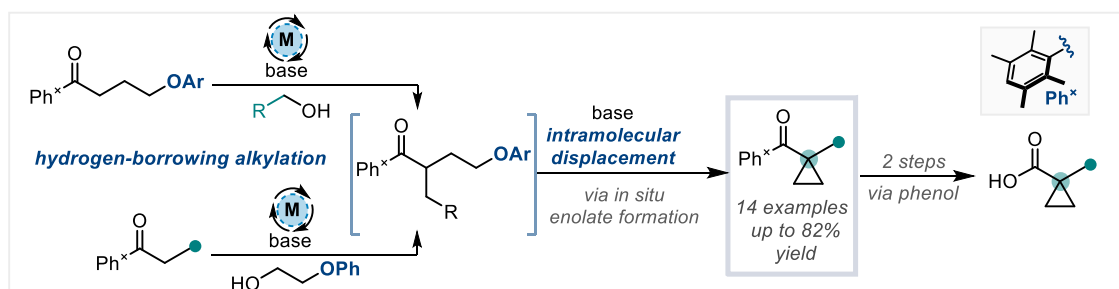
A handwritten signature in black ink, appearing to read 'Jh Crompton', with a large, stylized loop at the end.

Jessica L. Crompton

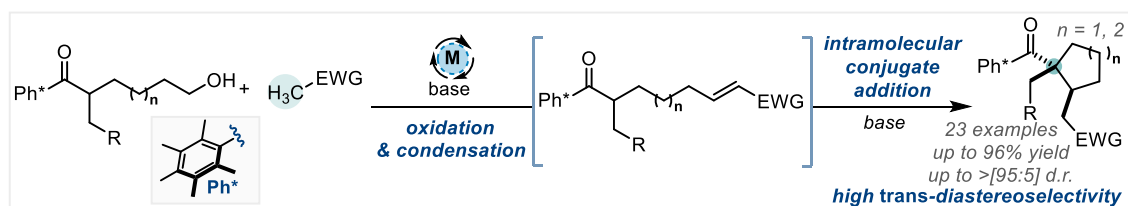
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Abstract

Hydrogen borrowing catalysis has recently been introduced as a powerful and sustainable method for the formation of C–C sp^3 bonds using reversible oxidation state changes to enable the use of alcohols as alkylating agents. While this method has been widely used for the formation of α - and β -branched ketones, the hydrogen borrowing catalytic cycle precludes the direct synthesis of quaternary stereocentres. As such, the formation of quaternary stereocentres within the hydrogen borrowing manifold is comparatively underexplored. In this thesis, the investigation of multiple hydrogen borrowing methods for the synthesis of this useful motif is described. In **Chapter 2**, two complementary approaches are reported to enable the formation of α -cyclopropyl ketones *via* hydrogen borrowing alkylation and subsequent intramolecular displacement of a leaving group (**Scheme I**). The α -cyclopropyl ketone products could be converted to the corresponding carboxylic acids in a two-step sequence.

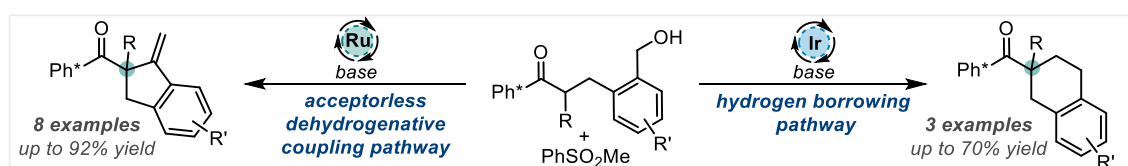


Chapter 3 describes the use of an acceptorless dehydrogenation–intramolecular conjugate addition cascade to enable the formation of quaternary stereocentres (**Scheme II**). The oxidation and condensation steps of the hydrogen borrowing method were exploited to enable the formation of a Michael acceptor, which could be intercepted by the pendant enolate to form a range of cyclic products containing an α -quaternary ketone with high diastereoselectivity. The key Ph^* protecting group could be removed in a single step to give a range of carboxylic acid derivatives in high yield, with retention of relative stereochemistry.



Scheme II Quaternary stereocentres via intramolecular conjugate addition

Substrates containing pendant benzylic alcohols behaved anomalously in this reaction, displaying divergent reactivity depending on the nature of the catalyst employed. **Chapter 4** of this thesis details the development of both sets of reaction conditions and a mechanistic study to elucidate the cause of the observed divergent behaviour (**Scheme III**).



Scheme III Divergent reactivity of benzylic alcohol substrates to give α -quaternary ketones

This thesis presents a variety of approaches which expand the chemical space accessible using hydrogen borrowing methods. Key to all three strategies is a single underlying approach: using hydrogen borrowing catalysis to access an α -branched ketone which can cyclise *in situ* via the enolate to give a product containing a quaternary centre. This strategy could be further expanded to enable the synthesis of related quaternary products and applied to the synthesis of natural products. Such potential future directions are discussed in **Chapter 5**.

Acknowledgements

Firstly, I would like to thank Prof. Tim Donohoe for welcoming me into the Donohoe group for my DPhil studies, despite the fact that my name is not Tim (there have been so many ‘Tims’ we are running out of nicknames to distinguish you all!) Your guidance and support during the past four years has been invaluable. Thank you for your willingness to embark upon yet another project when I got unexpected results.

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Huge thanks to those who have proof-read this thesis: Teddy, Andrew, Tim Jenkins, Lydia, Dani, Diana, Ana and Hannah. It really does “take a village” to help someone pull a thesis together, so thank you all for giving up your time to read it, make suggestions, and having the courage to tell me if you thought my schemes were “ugly” (looking at nobody in particular...Andrew!)

Thank you to all members of the Donohoe group past and present who had a huge impact on my DPhil and were a pleasure to work with. Special thanks go to Roly and Ciaran for helping me

learn the ropes of hydrogen borrowing in the early days, also for the endless impressions and conspiracy theories that made every day truly entertaining! I am grateful to Lydia for showing me how to run a lab with just the right amount of fear to keep it all running smoothly, and for your support at challenging times! Thanks to Bruno for always being up for a glass of white wine, for all of the Slovenian wine recommendations and for generally being iconic – the cries of “hallo, hallo, hallo” and “it’s happening” never failed to make me smile! Thank you to Francisco for providing so much humour and support in both parts of your Donohoe adventure, I was so pleased to have you back in the group last year! Hannah, thank you for allowing “savage Hannah” out every now and again, always with hilarious results, our time at ACS was truly special and I very much appreciated all of your food recommendations! Karan, you will likely never see this, but thank you for being such a great Part II student, being hydrogen borrowing’s biggest cheerleader and for your dedication to such a challenging project, you made supervising you very enjoyable. Matt, your time in the group was brief but thank you for always being so optimistic in my “big summer of synthesis” this year. Oskar, or should I say “Mercury Man”, you have made the last few months writing up much more bearable, thank you for always being up to some kind of mischief and betraying yourself with your facial expressions! Tim Jenkins, thank you for running all of my crystals without complaint, for always having a great anecdote (not always at the most opportune moment) and for being a great co-tutor for our Biochemistry kids! To Andrew, thank you for being so distractable and for listening to all of my crazy ideas, you’ll get there with your devilishly difficult project, you’ve got this!

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Finally, I would like to thank my family for all of their support, especially when most of them don’t really understand what a molecule is! I hope that my writing a thesis on Organic Chemistry will be enough to convince you that I study Chemistry, not Maths, and therefore should not (actually cannot) be relied upon to as a human calculator! Most of all, I would like to thank my parents for their never-ending support, spending hours on the road to come and visit, and even more hours on the phone listening to me talk about my day, I love you both so much! Thank you for always believing in me, and encouraging me to believe in myself.

“You’re braver than you believe, and stronger than you seem, and smarter than you think.”

- A. A. Milne, *“Winnie the Pooh”*

Table of Contents

Declaration	iii
Abstract	v
Acknowledgements	vii
Table of Contents	xi
Abbreviations	xv
Chapter 1: Introduction	1
1.1 Ketone Alkylation	1
1.2 Early Hydrogen Borrowing Reactions	2
1.2.1 Discovery of indirect aldol reactions	2
1.2.2 Alkylation of methyl ketones	4
1.2.3 Formation of α -branched ketones	6
1.3 Use of Ph* Ketones in Hydrogen Borrowing	7
1.3.1 Design of Ph* protecting group	7
1.3.2 Formation of β -branched ketones	10
1.3.3 Synthesis of carbocycles from acyclic precursors	12
1.4 Quaternary Stereocentres	16
1.4.1 Importance of Quaternary Stereocentres	16
1.4.2 Quaternary Stereocentres <i>via</i> alkylation	17
1.4.3 Quaternary Stereocentres <i>via</i> Hydrogen Borrowing Methods	19
1.5 Project Aims and General Strategy	24
Chapter 2: Intramolecular Displacement Strategies	27
2.1 Introduction	27
2.2 Project Aims	28
2.3 Preliminary Work	29
2.4 Starting Material Synthesis I	30
2.5 Optimisation	31
2.5.1 Ketone pre-functionalisation approach	31
2.5.2 Alcohol pre-functionalisation approach	37
2.6 Strategies for Derivatisation	41
2.7 Starting Material Synthesis II	46
2.8 Reaction Scope	47
2.8.1 Ketone pre-functionalisation approach	47
2.8.2 Alcohol pre-functionalisation approach	50
2.9 Derivatisation	52
2.10 Extension of the Method to Larger Carbocycle Synthesis	52
2.11 Conclusion	56

Chapter 3: Intramolecular Conjugate Addition	57
3.1 Introduction and Preliminary Work	57
3.1.1 Introduction: intramolecular aldol reaction	57
3.1.2 Preliminary work	58
3.1.3 Mechanistic considerations	59
3.2 Project Aims	61
3.3 Synthesis of Linear Hydroxy Ketones	61
3.4 Optimisation I	63
3.5 Preliminary Substrate Scope	66
3.6 Optimisation II	71
3.6.1 Optimisation of cyclohexane synthesis	71
3.6.2 Reproducibility issues in cyclopentane synthesis	74
3.6.3 Optimisation using sulfone nucleophiles	75
3.7 Substrate Scope	79
3.8 Mechanistic Experiments	84
3.8.1 Cause of diastereoselectivity	84
3.8.2 Gas evolution experiments	85
3.9 Product Derivatisation	87
3.10 Conclusions	89
Chapter 4: Quaternary Centres using Benzylic Alcohol Substrates	91
4.1 Introduction and Preliminary Results	91
4.2 Project Aims	92
4.3 Reaction Optimisation	92
4.3.1 Optimisation for formation of 6-membered ring product 225	93
4.3.2 Optimisation for formation of 5-membered ring product 224	96
4.4 Mechanistic Studies	99
4.5 Starting Material Synthesis	104
4.5.1 Diol mono-protection route	104
4.5.2 <i>ortho</i> -Lithiation route	105
4.5.3 Lithium-halogen exchange route	106
4.6 Substrate Scope	108
4.7 Product Derivatisation	110
4.8 Conclusion	112
Chapter 5: Conclusions and Future Work	115

Chapter 6: Experimental	119
6.1 General Experimental	119
6.2 Experimental for Chapter 2	123
6.2.1 General Procedures	123
6.2.2 Preparation and Characterisation of Compounds	125
6.2.3 Mechanistic Experiments	201
6.3 Experimental for Chapter 3	202
6.3.1 General Procedures	202
6.3.2 Preparation and Characterisation of Compounds	204
6.3.3 Mechanistic Experiments	319
6.4 Experimental for Chapter 4	320
6.4.1 General Procedures	320
6.4.2 Preparation and Characterisation of Compounds	323
6.4.3 Mechanistic Experiments	384
References	385
Appendices	390
Appendix I: Full Optimisation Table for Cyclopentane Reproducibility Issues	390
Appendix II: Data for Hydrogen Evolution Experiment	391
Appendix III: Single Crystal X-Ray Structure Data	392

Abbreviations

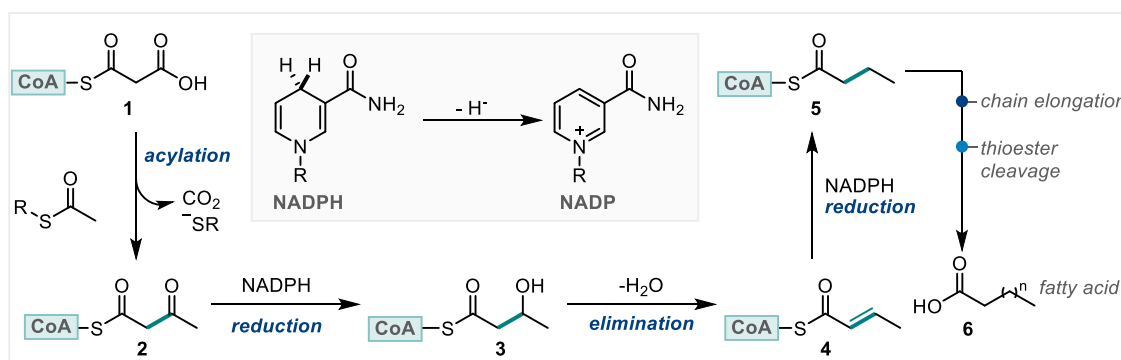
δ	chemical shift	EWG	electron-withdrawing group
Δ	heat	FG	functional group
ν	IR stretching frequency	g	gram(s)
acac	acetylacetonate	h	hour(s)
Ad	adamantyl	hex	hexyl
aq.	aqueous	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
Ar	aryl or denotes reaction under argon	HRMS	High Resolution Mass Spectrometry
Bn	benzyl	Hz	Hertz
br.	broad	ⁱPr	<i>iso</i> -propyl
Bu	butyl	IR	Infra-red spectroscopy
°C	degree(s) Celcius	J	coupling constant (Hz)
CAN	ceric ammonium nitrate	LG	leaving group
cataCXium® A	di(1-adamantyl)- <i>n</i> -butylphosphine	m	multiplet or milli (10 ⁻³)
Cp*	pentamethylcyclopentadienyl	M	molar (mol dm ⁻³)
cod	1,5-cyclooctadiene	[M]	metal species
Cy	cyclohexyl	m.p.	melting point
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	m/z	mass to charge ratio
DCAD	di-(4-chlorobenzyl)azodicarboxylate	Me	methyl
DIPEA	<i>N,N</i> -diisopropylethylamine	min	minute(s)
DMF	<i>N,N</i> -dimethylformamide	mol	mole(s)
dppBz	1,2-bis(diphenylphosphino)benzene	morph	morpholino
d.r.	diastereomeric ratio	MTBE	methyl <i>tert</i> -butyl ether
E⁺	generic electrophile	Nu	generic nucleophile
eq.	equivalent(s)	NMR	Nuclear Magnetic Resonance
e.r.	enantiomeric ratio	nOe	nuclear Overhauser effect
ESI	electrospray Ionisation	PG	protecting group
Et	ethyl	Ph	phenyl

Ph*	pentamethylphenyl	T	temperature
Ph^x	2,3,5,6-tetramethylphenyl	^tBu	tertiary butyl
Phth	phthalimide	THF	tetrahydrofuran
PMB	<i>para</i> -methoxybenzyl	THP	tetrahydropyran
PMP	<i>para</i> -methoxyphenyl	TLC	thin layer chromatography
PPTS	pyridinium <i>p</i> -toluenesulfonate	TMS	trimethylsilyl
<i>p</i>Tol	<i>para</i> -tolyl	Ts	tosyl
py	pyridyl	w/v%	weight for volume percent
R	generic substituent	wt%	weight for weight percent
RT	room temperature	X	generic halide
s	second(s)		
sat.	saturated		
SET	single electron transfer		

1. Introduction

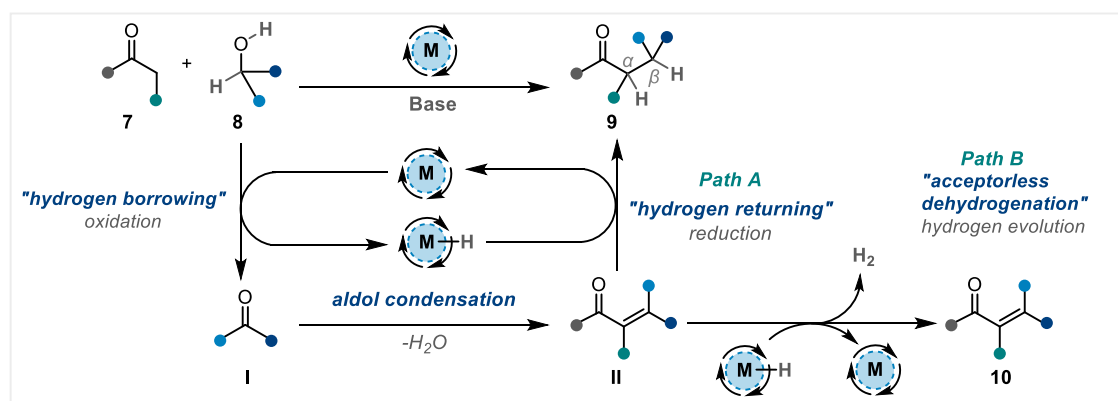
1.1 Ketone Alkylation

Ketone α -alkylation is a classical approach for the formation of C–C sp^3 bonds. This method usually involves the use of strong bases, such as lithium diisopropylamide (LDA), to form the corresponding enolate. This enolate can then be reacted with a range of halide or pseudohalide electrophiles to give the α -alkylated product. Despite widespread use in synthesis, this approach has a range of disadvantages. Firstly, the strong bases employed often require the use of cryogenic temperatures, can be pyrophoric, and therefore present safety concerns on large scale. The alkyl halide and pseudohalide electrophiles used are often highly toxic and generate stoichiometric amounts of waste. However, Nature has evolved an approach which effects ketone α -alkylation under much milder conditions (**Scheme 1. 1**).¹ In the biosynthesis of fatty acids, malonyl CoA (**1**) acts as the nucleophile in a decarboxylative Claisen-type condensation to give the corresponding 1,3-dicarbonyl, **2**. The ketone is then reduced by an enzyme using the cofactor NADPH to give the corresponding β -hydroxy ketone, **3**, which eliminates *via* E1cB to give an α,β -unsaturated thioester, **4**. Reduction of this unsaturated intermediate by NADPH forms the simple alkylated product, **5**. This can then undergo further reaction with more malonyl CoA subunits and thioester cleavage to form a long chain fatty acid, **6**. Inspired by this process, synthetic chemists have designed methods for ketone alkylation using reversible oxidation state changes.



Scheme 1. 1 Biosynthesis of fatty acids.

One such biomimetic method is hydrogen borrowing catalysis: a redox neutral method that employs reversible oxidation state changes to effect ketone alkylation using alcohols as alkylating agents.^{2, 3} The method usually employs a transition metal catalyst to oxidise an alcohol, **8**, to the corresponding carbonyl compound, **I**, which can then undergo aldol condensation with a ketone nucleophile, **7**, to form an enone, **II**, which can subsequently be reduced by the metal hydride to give the reduced product **9** and close the catalytic cycle (Path A, **Scheme 1. 2**). An alternative way to regenerate the transition metal catalyst and complete the catalytic cycle is *via* the evolution of hydrogen gas from the metal hydride; this gives the enone, **10**, as the final product in a net oxidative process (called an acceptorless dehydrogenative coupling, Path B, **Scheme 1. 2**). A variety of metal catalysts and nucleophiles have been employed in these processes to access a range of alkylated products while eliminating the hazardous reagents of the corresponding classical processes. It should be noted that amines can also be employed as nucleophiles in the hydrogen borrowing approach to access secondary and tertiary amines, however full discussion of these methods is beyond the scope of this thesis.



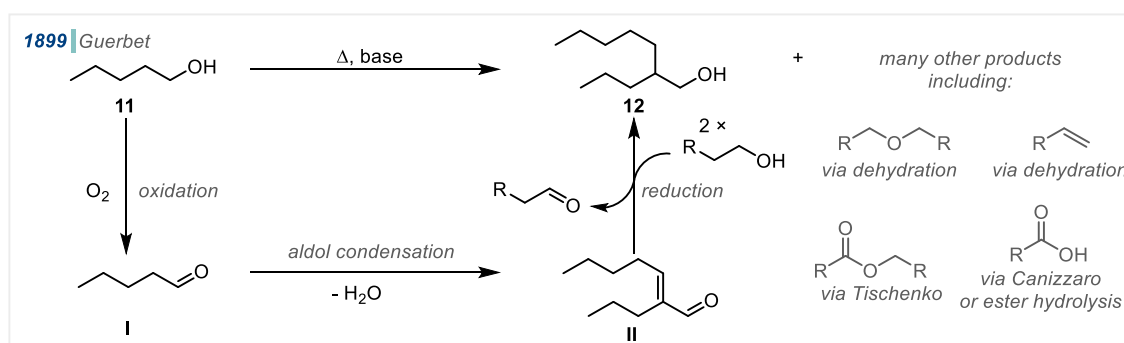
Scheme 1. 2 Typical hydrogen borrowing catalytic cycle and acceptorless dehydrogenative coupling process.

1.2 Early Hydrogen Borrowing Reactions

1.2.1 Discovery of indirect aldol reactions

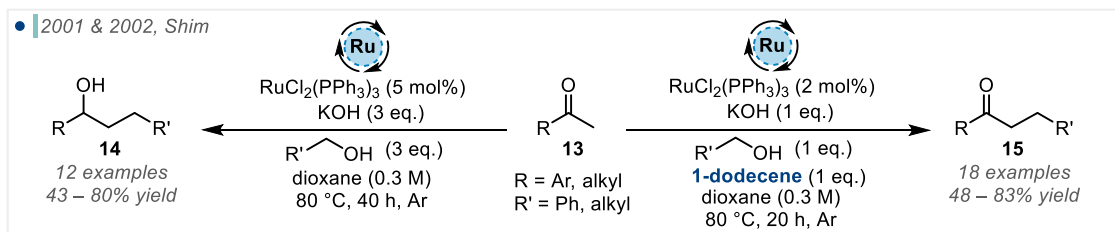
In 1899, Guerbet reported the homo-coupling of primary alcohols to form branched derivatives at elevated temperatures (**Scheme 1. 3**).⁴ Upon treating pentan-1-ol (**11**) with sodium and heating at reflux for 24 h, a variety of products were identified. The major product, 2-propylheptan-1-ol (**12**) was thought to have formed *via* the following sequence: initial

oxidation of the alcohol **11** using atmospheric oxygen to form the corresponding aldehyde, **I**, which enables aldol self-condensation to give a branched enone, **II**. This can then be reduced in a Meerwein-Ponndorf-Verley-type process with concomitant oxidation of an alcohol which can then undergo further aldol processes. This generates the branched alcohol product **12** alongside a complex mixture of side products, including products from dehydration (ethers and alkenes), from Tishchenko reactions (esters) and Cannizzaro reactions (carboxylic acids). The formation of these side products served to lower the process efficiency and therefore limited the use of this reaction directly. However, this reaction represents an early example of an indirect aldol reaction, which has been developed into the field of hydrogen borrowing catalysis.



Scheme 1. 3 Guerbet reaction and generalised side products.

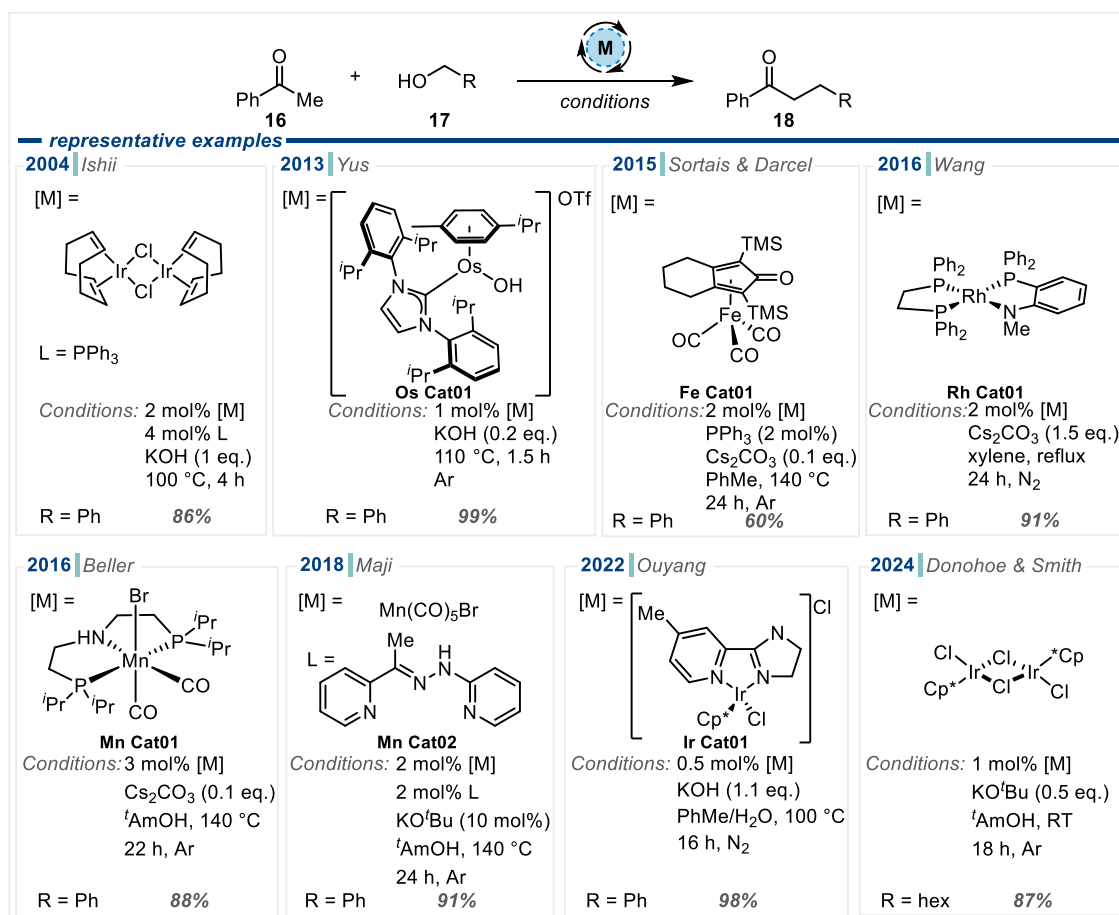
More recently, while investigating transfer hydrogenation of ketones, Shim and co-workers observed unexpected C–C (sp^3) formation (Scheme 1. 4).⁵ Using a ruthenium catalyst, alkylation of a number of methyl ketones, such as **13**, was achieved using primary alcohols, with subsequent reduction of the ketone *in situ* to access the corresponding secondary alcohol, **14**. Shim and co-workers later reduced the alcohol equivalents used and employed 1-dodecene as a sacrificial hydride acceptor to access the ketone product **15** without overreduction.⁶ Although the need for a hydride acceptor lowered the overall efficiency of the process, both aryl and alkyl methyl ketones could be employed in this method to selectively give the simple α -alkylation products in good yields. This work therefore represents one of the earliest examples of modern hydrogen borrowing involving the alkylation of ketones using a transition metal catalyst.



Scheme 1. 4 Hydrogen borrowing alkylation of methyl ketones to access secondary alcohol and ketone products.

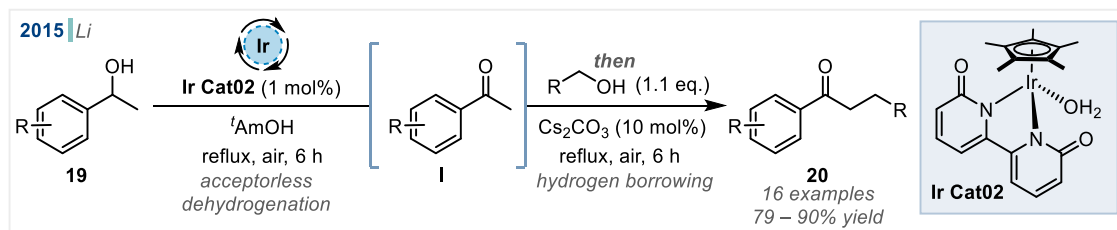
1.2.2 Alkylation of methyl ketones

Expanding on this discovery, Ishii and co-workers reported the use of $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ for the alkylation of ketones with primary alcohols in 2004. This method enabled the synthesis of the corresponding mono-substituted ketone products, such as **18**, with little over-reduction to the corresponding secondary alcohol side product, notably, the authors had no need for a sacrificial hydride acceptor to avoid this (**Scheme 1. 5**).⁷ Many other groups have since employed other transition metal catalysts for this process, including commercial catalysts and catalysts with bespoke ligands to increase activity.⁸⁻¹⁶ Beller and co-workers have delivered notable contributions in this area, pioneering the use of an iron-based Knölker-type complex, **Fe Cat01**, and manganese catalyst **Mn Cat01** for the hydrogen borrowing alkylation of ketones. This demonstrates that earth-abundant metals can be used in these processes, when activated with appropriate ligand (n.b. in these cases the ligands are non-innocent). It should be noted that the substrate scope for these examples was very similar as the alcohols employed were often limited to benzylic and simple alkyl alcohols; this is likely a result of the elevated temperatures required for reaction. However, Donohoe and Smith have recently reported a method which enables hydrogen borrowing alkylation of acetophenones with a range of alcohols at room temperature, offering a great improvement in functional group tolerance, although the scope of the ketone substrate was still limited to simple methyl ketones.¹⁶



Scheme 1. 5 Selected literature examples for hydrogen borrowing alkylation.

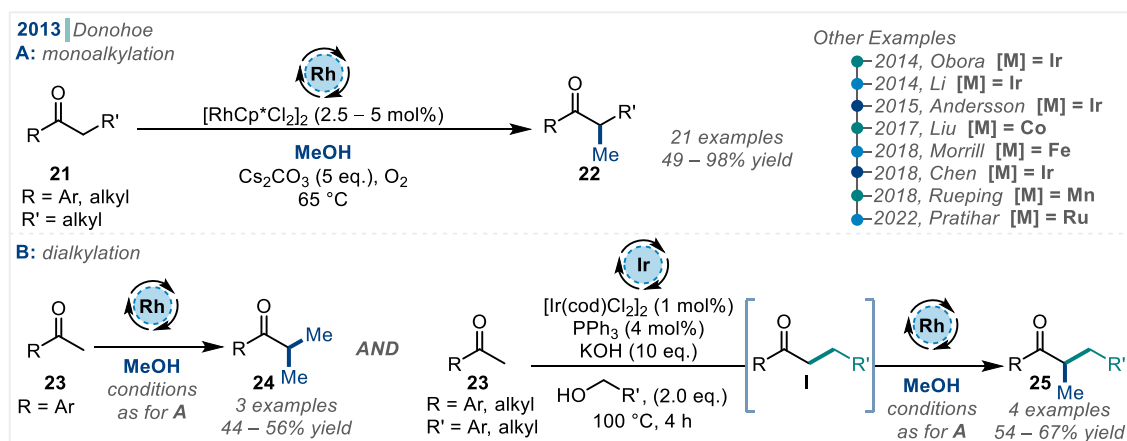
In a similar vein, Li and co-workers demonstrated that acceptorless dehydrogenation could be coupled with hydrogen borrowing alkylation to enable the synthesis of α -alkylated ketones from secondary and primary alcohols (Scheme 1. 6).¹⁷ Using a metal-ligand bifunctional iridium complex developed by Fujita and Yamaguchi, Ir Cat02,¹⁸ 1-arylethanol, **19**, could be oxidised to the corresponding aryl methyl ketones, **1**, which could then be directly employed in hydrogen borrowing alkylation with primary alcohols to furnish the alkylated ketone products, **20**. It was proposed that the nature of the bipyridonate ligand aids in the release of hydrogen gas from the catalyst in the acceptorless dehydrogenation step. By carrying out the initial acceptorless dehydrogenation in the absence of the primary alcohol substrate, Li and co-workers were able to prevent overreduction of the ketone products, maintaining high selectivity.



Scheme 1. 6 Tandem acceptorless dehydrogenation–hydrogen borrowing reaction.

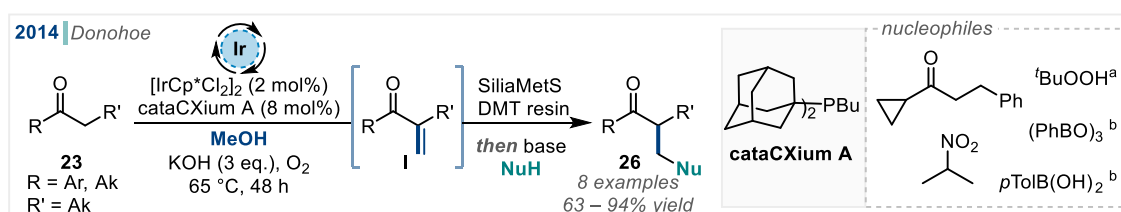
1.2.3 Formation of α -branched ketones

On the other hand, the alkylation of non-methyl ketones to form α -branched products has proven to be much more challenging: early examples were often limited to more activated nucleophiles, such as barbituric acids, nitriles and nitroalkanes as substrates,^{19–23} or employed cyclic ketones, such as tetralone,^{6, 7} to form α -branched products. In 2013, Donohoe and co-workers reported the use of a rhodium catalyst to carry out the methylation of unactivated ketones with methanol to form α -branched products, **22** (Scheme 1. 7A).²⁴ The process works by oxidation of methanol to give formaldehyde, which then undergoes aldol condensation to give an enone intermediate, which is reduced by the metal catalyst. Either mono- or di-methylation could be achieved using either non-methyl (**21**) or methyl ketones (**23**), respectively (Scheme 1. 7). Successive alkylation of methyl ketones could also be achieved: firstly, by α -alkylation with a primary alcohol to give **I**, using the method developed by Ishii and co-workers, and subsequent methylation using methanol to give the branched product **25** in a one-pot, two-step procedure (Scheme 1. 7B). A range of other metal catalysts have also been exploited in this process, as exemplified by the work of Obora, Li, Anderson and Morrill.^{25–32}



Scheme 1. 7 Hydrogen borrowing methylation of non-methyl ketones.

Donohoe and co-workers later investigated ways to intercept the enone intermediate in a formal acceptorless dehydrogenative approach.³³ Reduction of the enone intermediate was prevented by using a sterically hindered cataCXium® A ligand and by conducting the reaction under an oxygen atmosphere (**Scheme 1. 8**). After treatment of the crude reaction mixture with a SiliaMetS resin to scavenge the metal catalyst, enone **I** could be intercepted with a diverse range of nucleophiles in a conjugate addition process to give more complex products, **26**. This work demonstrated that it is possible to interrupt the hydrogen borrowing process and functionalise the enone intermediate to access a range of further substituted products.

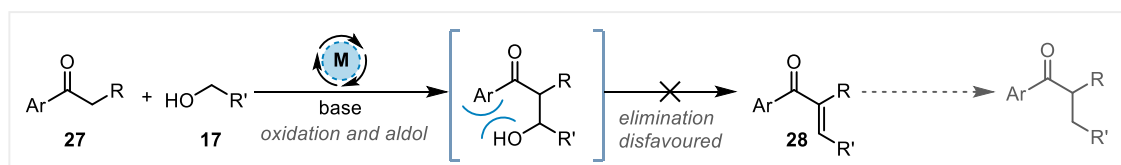


Scheme 1. 8 Acceptorless dehydrogenative coupling with nucleophilic interception of enone intermediate. ^a gives epoxide product. ^b SiliaMetS not employed, [RhCp*Cl₂]₂ (2.5 mol%) added with nucleophile.

1.3 Use of Ph* Ketones in Hydrogen Borrowing

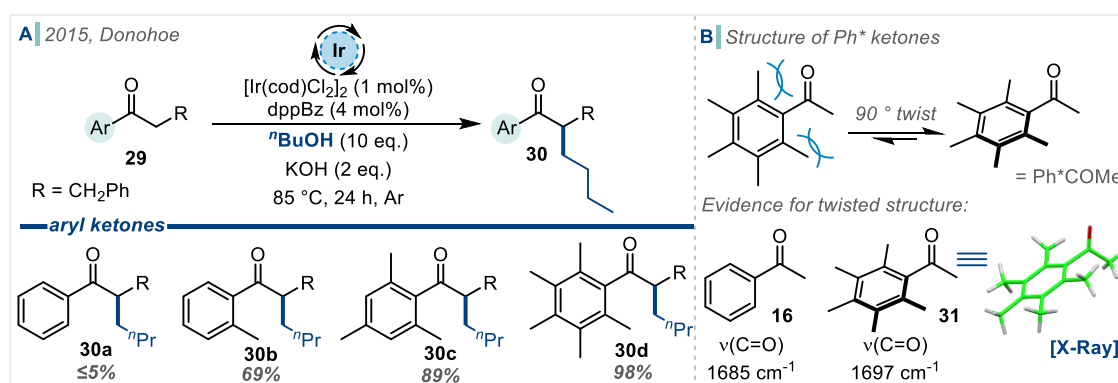
1.3.1 Design of Ph* protecting group

Thus far, the discussion has covered the preliminary literature in the field of hydrogen borrowing. However, a key limitation in the scope of the methodology persisted: methylation was the only option for the alkylation of unactivated non-methyl ketones to access α -branched ketones. A possible explanation for this, proposed by Donohoe and co-workers, is that the method could not be easily extended to other alcohols as the intermediate aldol adducts were unstable, with the desired elimination process to give enone **28** being disfavoured compared to the alternative retro-aldol process, which relieves strain (**Scheme 1. 9**).³⁴



Scheme 1. 9 Proposed unstable aldol adducts with primary alcohols other than MeOH.

In 2015, Donohoe and co-workers reported an investigation of alternative ketone substrates to address this problem, proposing that the ideal ketone substrate should be designed to reduce the steric hindrance within the aldol adduct to allow hydrogen borrowing alkylation to proceed with a range of primary alcohols. An additional benefit would be if the activating group could be easily removed to enable access to a range of derivatives. A range of aryl non-methyl ketones were investigated and it was observed that the yield of the α -alkylated product **30** increased with increasing *ortho*-substitution, with pentamethylphenyl (Ph*) ketones performing the best, allowing access to α -alkylated products, such as **30d**, in high yields (**Scheme 1. 10A**).

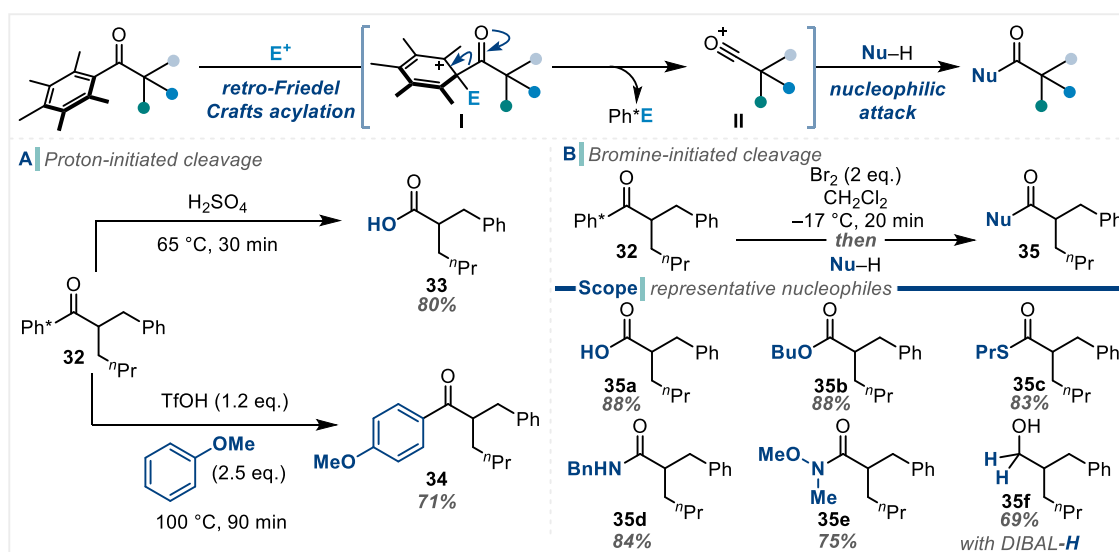


Scheme 1. 10 A) Use of *ortho*-di-substituted ketones for α -alkylation via hydrogen borrowing. B) Structure of Ph* ketones.

It was proposed that Ph* ketones were exceptionally effective substrates for hydrogen borrowing alkylation as a result of numerous characteristics of the Ph* group. Firstly, due to an unfavourable allylic interaction, the planar structure is highly disfavoured and instead the aryl ring is twisted out of conjugation (**Scheme 1. 10B**).³⁵ This is evidenced by a higher carbonyl stretch in the infrared spectrum of Ph* methyl ketone (**31**) compared to acetophenone (**16**), suggesting a lack of conjugation between the Ph* ring and the carbonyl; the twisted structure has been further confirmed in the solid state by X-ray crystallography. It was proposed that this twisted structure of Ph* ketones is key to the success of these substrates in hydrogen borrowing alkylation as it positions the *ortho*-methyl groups to shield the carbonyl group from nucleophilic attack, thus protecting the carbonyl from over-reduction and homo-dimerisation processes. However, the α -position remains comparatively sterically accessible for deprotonation to access the enolate, enabling ketones to undergo selective aldol reactions. The twisted structure also

reduces the steric hindrance in the aldol adduct, therefore allowing alcohols other than methanol to be employed in hydrogen borrowing alkylation. Finally, compounds containing the Ph* group are also highly crystalline, presenting opportunities for purification by recrystallisation.

Donohoe and co-workers also described how the structure of the key Ph* protecting group could facilitate its removal (**Scheme 1. 11**): since the carbonyl is twisted out of conjugation, the aromatic ring is highly electron-rich due to the electron-donating effect of its five methyl substituents. Upon treatment with an appropriate electrophile, the aromatic ketone undergoes reaction at the *ipso* position to form the Wheland intermediate, **I**. Collapse of this intermediate yields an acylium ion **II** which can be intercepted *in situ* with a nucleophile to give the corresponding carboxylic acid derivative. Donohoe and co-workers used ketone **32** to demonstrate that such Ph* cleavage could be achieved under acidic conditions to yield either the carboxylic acid **33**, or simple Friedel–Crafts product **34** (**Scheme 1. 11A**). Oxidative conditions could also be employed for Ph* cleavage using bromine as the electrophile to form the acid bromide *in situ* (**Scheme 1. 11B**). The acid bromide could then be intercepted with a range of nucleophiles to access a range of carboxylic acid derivatives, **35a – f**, in high yields.

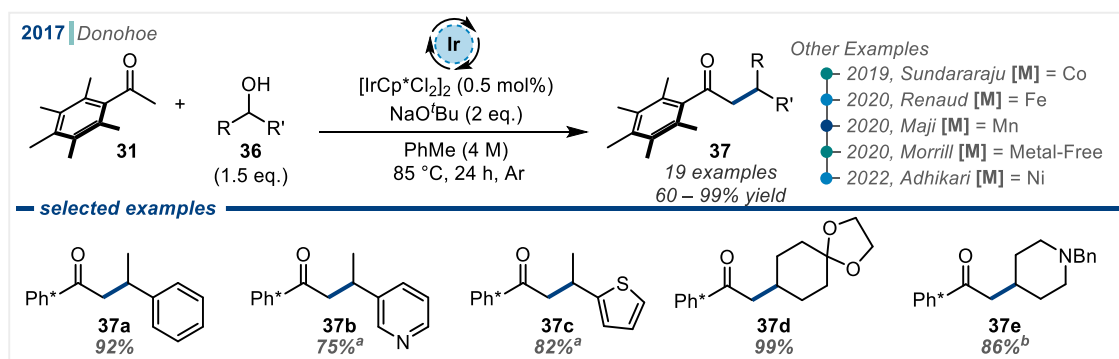


Scheme 1. 11 Ph* cleavage methods.

Overall, the use of the Ph* group in hydrogen borrowing reactions presented a huge breakthrough to enable the expansion of the scope of this methodology, aided by its ability to access a wide range of derivatives in a single step. Since the discovery of this protecting group within hydrogen borrowing catalysis, the Donohoe group has used Ph* ketones to enable the synthesis of a wide range motifs within the hydrogen borrowing manifold, which will now be discussed. Many other groups have employed similar approaches using the Ph* group in combination with alternative metal catalysts; while these contributions will be referenced, they will not be discussed in full unless they represent a novel application of the methodology.

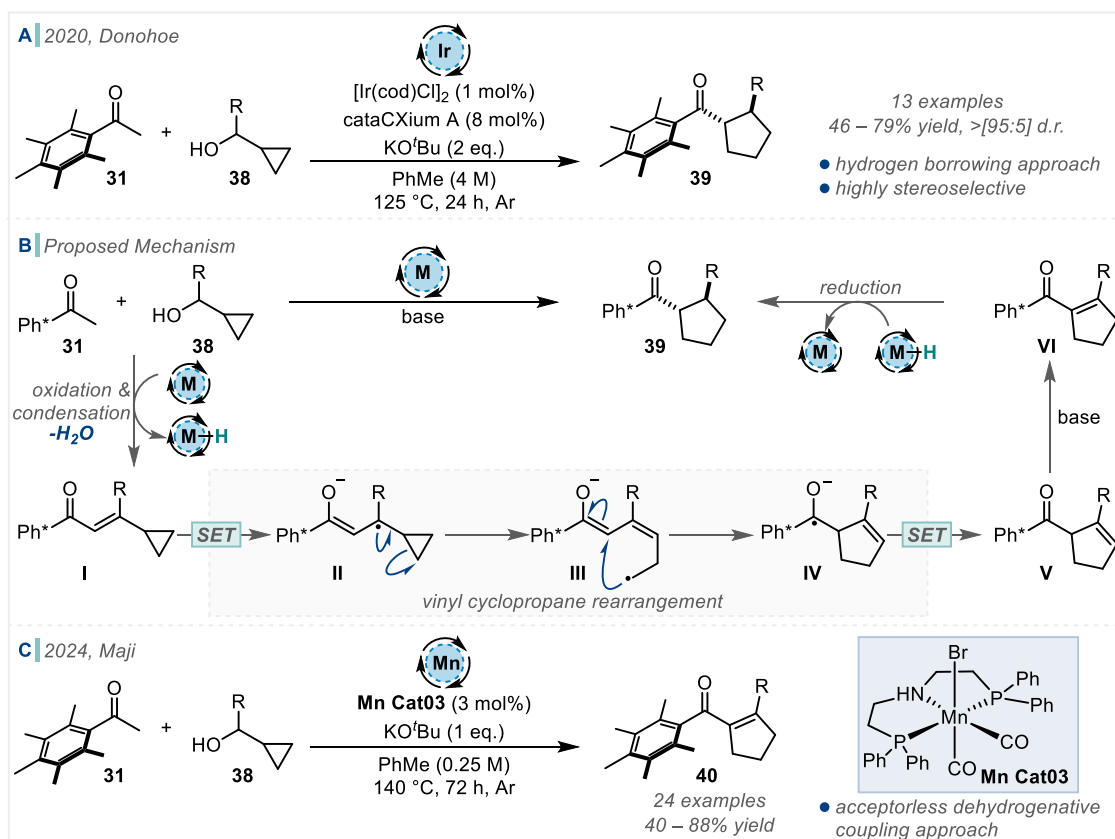
1.3.2 Formation of β -branched ketones

Next, Donohoe and co-workers investigated whether hydrogen borrowing methodology could be used to access products that would be more challenging to synthesise *via* the traditional method of ketone α -alkylation. The use of secondary alkyl halides as electrophiles in this classical process often results in less efficient reactions and can result in the formation of elimination side products. In 2017, Donohoe and co-workers reported a method using secondary alcohols for the alkylation of Ph* methyl ketone, **31**, resulting in the formation of β -branched ketone products, **37**, in high yields (**Scheme 1. 12**). The design of the hydrogen borrowing system results in the slow release of the intermediate ketone *via* oxidation of the secondary alcohol, minimising self-condensation reactions. As the Ph* ketone nucleophile is not susceptible to self-condensation due to the steric hindrance of the shielding *ortho* groups, this system can give high yields of the desired crossed-condensation products. A range of cyclic and acyclic secondary alcohols could be employed in this process to give the desired β -branched ketones. As previously mentioned, the key Ph* protecting group could be cleaved in a two-step process using bromine to give a range of carboxylic acid derivatives. This approach was subsequently employed by many others for the synthesis of β -branched ketones using earth-abundant metals, including Sundararaju, Renaud, Maji and Adhikari,³⁶⁻⁴⁰ and has also been extended to include the synthesis of enantioenriched β -branched ketones.⁴¹



Scheme 1. 12 Formation of β -branched products using secondary alcohols. ^a Reaction performed at 105°C . ^b $[\text{IrCp}^*\text{Cl}_2]_2$ (2 mol%) used as the catalyst and KO^tBu (3 eq.) employed as the base.

In 2020, Donohoe and co-workers reported the use of secondary alcohols to access cyclopentanes *via* a hydrogen borrowing–vinyl cyclopropane rearrangement cascade (**Scheme 1. 13A**).⁴² Under hydrogen borrowing conditions, a cyclopropyl-substituted alcohol, **38**, can undergo oxidation and condensation with Ph^* methyl ketone **31**, resulting in the formation of the intermediate enone, **I** (**Scheme 1. 13B**). It was demonstrated that enone reduction could be delayed by using the sterically hindered ligand, cataCXium® A. This allows time for rearrangement of the enone *via* single electron transfer from KO^tBu to **I**, to give a radical anion, **II**, which can fragment to generate radical anion **III**, which can cyclise to give **IV** and undergo SET to enable chain propagation. After base-promoted isomerisation, the resulting cyclopentene **VI** can then be reduced by the iridium-hydride species to yield the product cyclopentane **39** in high yield and with high diastereoselectivity. Although formally a hydrogen borrowing process, the development of a reaction involving a delayed reduction step was very promising for the development of acceptorless dehydrogenative coupling methods using similar strategies. Recently, Maji and co-workers reported an analogous process for the formation of cyclopentenes, from cyclopropyl-substituted alcohols, in a formal acceptorless dehydrogenative coupling approach (**Scheme 1. 13C**).⁴³ In this case, the selectivity for the cyclopentene product was attributed to the nature of the manganese catalyst employed, **Mn Cat03**, which was proposed to favour hydrogen evolution over enone reduction due to metal-ligand co-operation, giving the cyclopentene **40** as the final product.

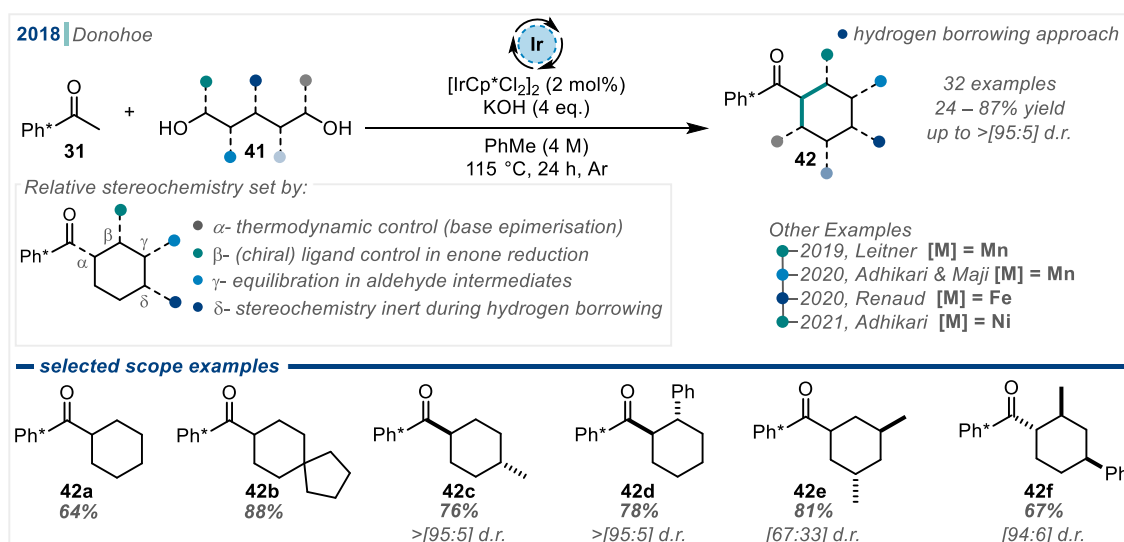


Scheme 1. 13 Synthesis of A) cyclopentanes and C) cyclopentenones via a vinyl cyclopropane rearrangement.

1.3.3 Synthesis of carbocycles from acyclic precursors

In contrast to the ring-expansion approach previously described, Donohoe and co-workers have also developed the synthesis of carbocycles *via* hydrogen borrowing alkylation of acyclic precursors in a single step. In 2018, Donohoe and co-workers reported their [5+1] approach for the synthesis of cyclohexanes, **42**, using Ph^* methyl ketone **31** and an acyclic diol **41** (**Scheme 1. 14**).^{44, 45} Initially believed to proceed *via* two consecutive hydrogen borrowing alkylations, this process enabled the stereoselective synthesis of a range of substituted cyclohexanes, such as **42a – f**. It should be noted that the yield of the cyclohexane products was significantly improved by the inclusion of substitution on the diol backbone, presumably as a result of the Thorpe–Ingold effect, however the formation of cyclopentanes and cycloheptanes was comparatively poor under the same reaction conditions. It was proposed that the relative stereochemistry observed in the cyclohexane products was governed by a number of factors: epimerisation under the basic reaction conditions governs the stereochemistry at the ketone

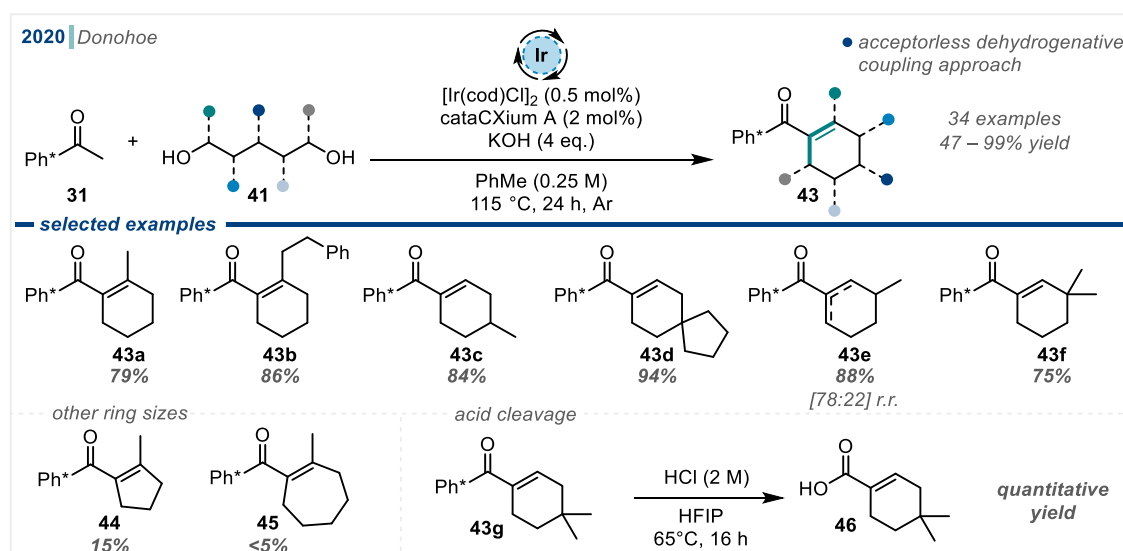
α -position. In addition, the γ -position is vulnerable to epimerisation as after oxidation of the diol to the corresponding carbonyl, protons at these positions are acidified. However, it was shown that the δ -position is configurationally stable under hydrogen borrowing reaction conditions, and can therefore act as a reporter group, influencing the stereochemistry at other positions around the ring. It was suggested that the relative stereochemistry at the β -position is set by the addition of the iridium-hydride in the reduction step, this was later exploited for the asymmetric synthesis of cyclohexanes by employing a chiral ligand in the process.⁴⁶ Earth-abundant metal catalysts have also been used for the racemic [5+1] synthesis of cyclohexanes, as demonstrated by Leitner, Maji, Renaud, and Adhikari.⁴⁷⁻⁵⁰



Scheme 1. 14 Synthesis of cyclohexanes via hydrogen borrowing catalysis.

Donohoe and co-workers have also developed a [5+1] approach for the synthesis of cyclohexenes using an acceptorless dehydrogenation strategy (**Scheme 1. 15**).⁵¹ By employing cataCXium® A as the ligand, reduction could be sufficiently outcompeted by the evolution of hydrogen gas, giving the product acyl cyclohexenes **43** in high yields. Using more dilute reaction conditions were also shown to suppress reduction and therefore favour the formation of the cyclohexene product. It should be noted that when non-symmetrical diols were employed, regioisomeric mixtures of products were formed; it was proposed that this could be a result of poor regioselectivity in the initial oxidation step or 1,5-hydride shift of the hydroxy-aldehyde intermediates. The reaction was also comparatively poor for the formation of other ring sizes,

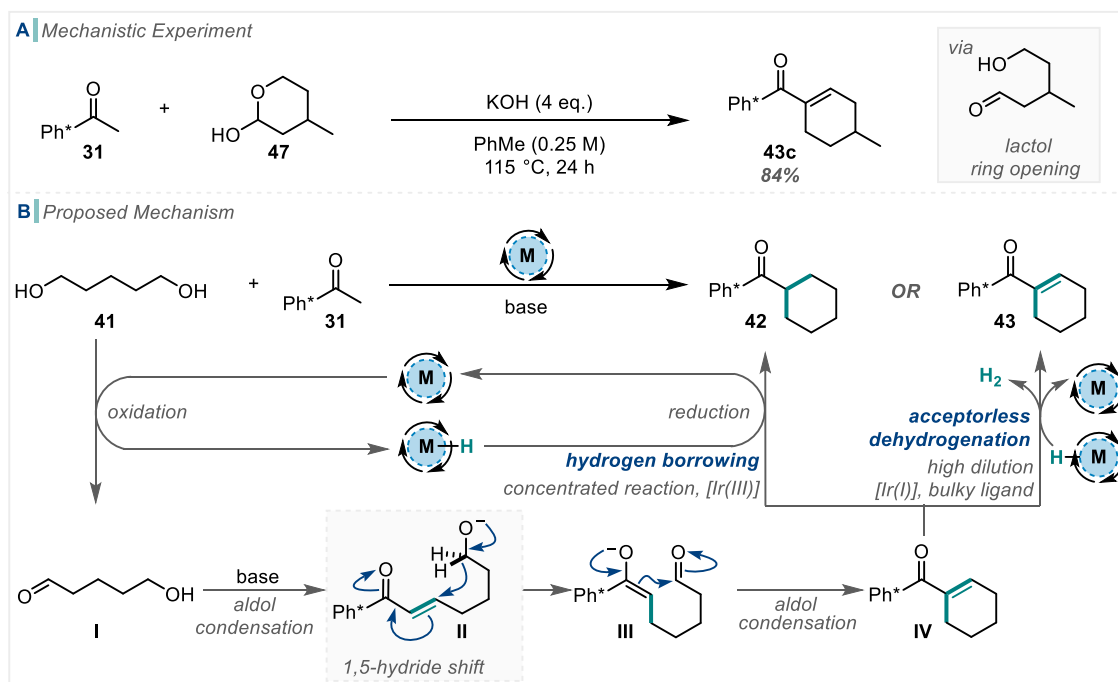
demonstrated by the synthesis of 5- and 7-membered enones **44** and **45**, which prompted a mechanistic investigation (*vide infra*). Since the key Ph* group could not be cleaved from the product cyclohexenes with retention of the enone using the previously developed bromine-mediated conditions, an alternative acidic cleavage was developed. By heating the α,β -unsaturated Ph* ketone products in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with hydrochloric acid, the corresponding carboxylic acids could be accessed in excellent yield. It should be noted that out of all solvents investigated for this process, HFIP was singularly effective, likely due to its unique ability to stabilise the intermediate acylium ion due to its high dielectric constant and non-nucleophilic properties.⁵²



Scheme 1.15 Synthesis of cyclohexenes via acceptorless dehydrogenation.

Although Donohoe and co-workers initially proposed that a double hydrogen borrowing and tandem hydrogen borrowing-acceptorless dehydrogenation mechanistic pathway was operative to access cyclohexanes and cyclohexenes, respectively, the observation that the analogous processes were much less effective for the synthesis for 5- and 7-membered rings was not consistent with this hypothesis. The authors also demonstrated that the metal catalyst is only involved in the initial oxidation step when forming cyclohexenes: when a partially oxidised diol, namely lactol **47**, was subjected to the reaction conditions in the absence of an iridium catalyst,

the desired acyl cyclohexene **43c** was formed in high yield, which was inconsistent with the initially proposed metal-catalysed mechanism for the ring closure (**Scheme 1. 16A**).



Scheme 1. 16 A) Mechanistic experiment disproving metal-catalysed mechanism for ring closure. B) Proposed mechanism for the formation of cyclohexanes and cyclohexenes in a [5+1] approach.

After a thorough mechanistic investigation, Donohoe and co-workers reconsidered their initial hypothesis and proposed the following mechanistic pathway (**Scheme 1. 16B**). After oxidation of the 1,5-diol and condensation with Ph* methyl ketone to form the hydroxy-enone **II**, an intramolecular 1,5-hydride shift occurs to generate intermediate **III**, which condenses to give the enone **IV**. The fate of this enone is then dictated by the reaction conditions. When using an iridium (III) catalyst at high reaction concentrations, enone **IV** is reduced to complete the hydrogen borrowing cycle, giving the cyclohexane **42** as the final product. However, when an iridium (I) catalyst is used in combination with a sterically hindered ligand under high dilution conditions, the evolution of hydrogen gas from the metal catalyst outcompetes the reduction of the enone, regenerating the metal catalyst to allow turnover and giving the acyl cyclohexene **43** as the final product. The authors also demonstrated that the reaction outcome in this acceptorless dehydrogenative coupling is affected by both the reaction concentration and the sterically encumbered nature of the catalyst, in accordance with the observations of Beller and

co-workers.⁵³ This mechanism aligns with the observation that the yields were lower for the formation of 5- and 7-membered rings in both processes, which is consistent with poorer orbital overlap for 1,4- and 1,6- hydride shifts: low-to-moderate yields were obtained for the hydrogen borrowing process, where a higher energy, double hydrogen borrowing alkylation pathway could still take place to access the products. However, the analogous acceptorless dehydrogenative coupling processes gave very low yields of product, as in this scenario, the steric hindrance around the metal hydride can effectively prevent enone reduction rendering the tandem hydrogen borrowing-acceptorless dehydrogenation pathway inaccessible.

1.4 Quaternary Stereocentres

1.4.1 Importance of Quaternary Stereocentres

Quaternary stereocentres are an important motif which can confer favourable properties onto molecules containing them. Within a synthetic chemistry setting, the inclusion of a quaternary stereocentre can help to bias the conformation of the molecule, which may result in more favourable reactivity. For example, inclusion of a *gem*-dialkyl group has been shown to increase the rate of cyclisation to access a range of different ring sizes.^{54, 55} This conformational bias has also been exploited in a medicinal chemistry setting to either increase the population of the bioactive conformation or confer rigidity onto the molecule and therefore provide an improvement in compound potency, as the entropic penalty of binding to the biological target is reduced (**Figure 1. 1**).⁵⁶ Equally, the departure from planarity and further exploration of chemical space can increase interactions with the biological target, helping to improve both the potency and selectivity of the compound.^{57, 58} The inclusion of a quaternary stereocentre can also improve the pharmacokinetic profile of a compound, either by blocking sites that are a metabolic liability, or by preventing racemisation *in vivo*. However, the synthesis of such motifs is relatively challenging compared to their sp^2 -rich counterparts and therefore the development of new methods for the synthesis of quaternary stereocentres is highly desirable.

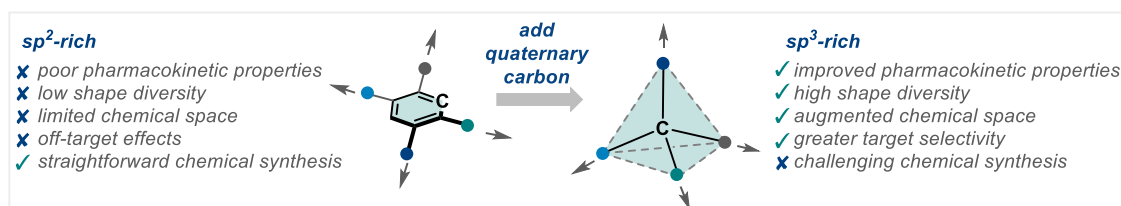


Figure 1. 1 Advantages of using quaternary carbons in medicinal chemistry, compared to sp^2 -rich analogues.

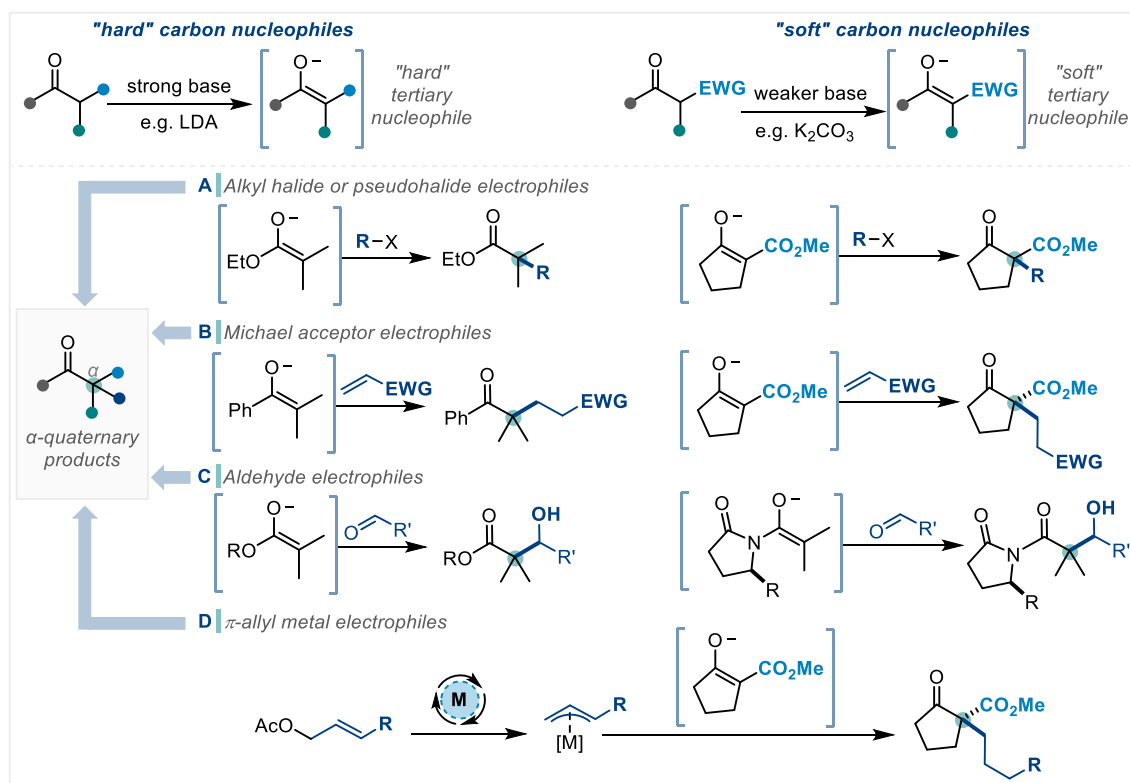
1.4.2 Quaternary Stereocentres *via* alkylation

The α -alkylation of carbonyl compounds is a very common strategy for the formation of quaternary stereocentres. However, this approach is often thwarted by harsh reaction conditions or limited substrate scope for milder variants: this section will briefly address some of the most commonly used methods for single step α -alkylation to generate a quaternary stereocentre. The classical approach employs a stoichiometric amount of strong base to deprotonate α -to the carbonyl to form the corresponding enolate, which acts as a tertiary carbanion and can then be reacted with a simple alkyl halide or pseudohalide to form an α -quaternary stereocentre (**Scheme 1. 17A**).⁵⁹⁻⁶¹ More recently, such enolates have been exploited in transition-metal catalysed cross-coupling with aryl halide electrophiles, however the mechanistic requirement for stoichiometric enolate formation still necessitates the use of stoichiometric strong base.⁶² This can limit the functional group tolerance in these processes and can lead to unwanted side-reactions. An alternative approach is to alkylate carbonyls with more acidic α -protons, which can afford the desired α -quaternary products under milder reaction conditions using weaker bases. Such softer tertiary nucleophiles can be reacted directly with halide or pseudohalide electrophiles to give quaternary stereocentres.^{63, 64} However, this approach results in a more limited substrate scope by way of restricting the nucleophiles that can be accessed *via* deprotonation. In addition, the use of stoichiometric amounts of halide or pseudohalide electrophiles in these approaches generates stoichiometric amounts of toxic waste.

The tertiary carbanion nucleophiles generated by carbonyl α -deprotonation can also be intercepted by Michael acceptors to access α -quaternary stereocentres (**Scheme 1. 17B**),

however, it should be noted that softer enolate nucleophiles are more commonly employed in this chemistry.⁶⁵ A wide range of enantioselective methods have also been developed for this process, using both metal catalysis and organocatalysis in order to access α -quaternary carbonyl compounds *via* conjugate addition.⁶⁶

The direct addition of tertiary nucleophiles to aldehydes has also been employed for the synthesis of quaternary stereocentres, forming β -hydroxy carbonyl products *via* aldol reactions (**Scheme 1. 17C**).⁶⁷⁻⁶⁹ Although such α -quaternary products are susceptible to retro-aldol processes at high temperature to relieve strain, some examples have been isolated using Evans-aldol chemistry.^{70, 71} This aldol approach has also been employed in an intramolecular fashion, to form cyclic β -hydroxy ketone products, which are less susceptible to retro-aldol on account of the reduced entropic driving force for this intramolecular process.^{72, 73}



Scheme 1. 17 Common approaches for the formation of quaternary stereocentres via ketone alkylation.

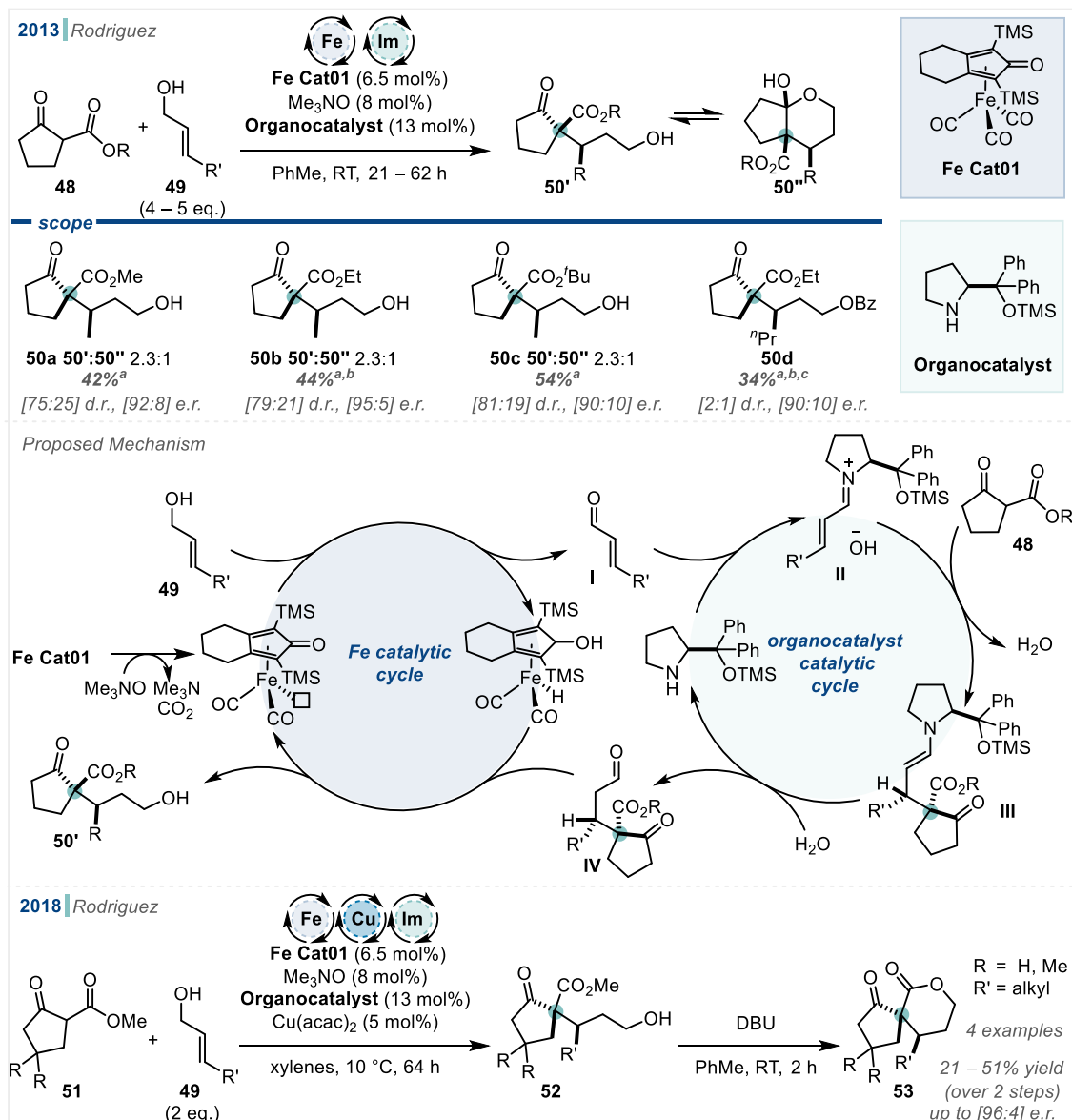
More recently, similar soft tertiary nucleophiles have also been employed in Tsuji-Trost-type reactions, enabling the synthesis of α -quaternary stereocentres (**Scheme 1. 17D**). Many enantioselective variants of these reactions have also been developed.^{74, 75} While this approach

typically employs carbonyl compounds with more acidic α -protons, some examples using branched ester enolates have been reported.⁷⁶⁻⁷⁸ Recently, a particularly elegant example of this has been reported by Carreira and co-workers using a chiral ruthenium complex for the construction of vicinal quaternary centres using lithium ester enolates.⁷⁹

1.4.3 Quaternary Stereocentres *via* Hydrogen Borrowing Methods

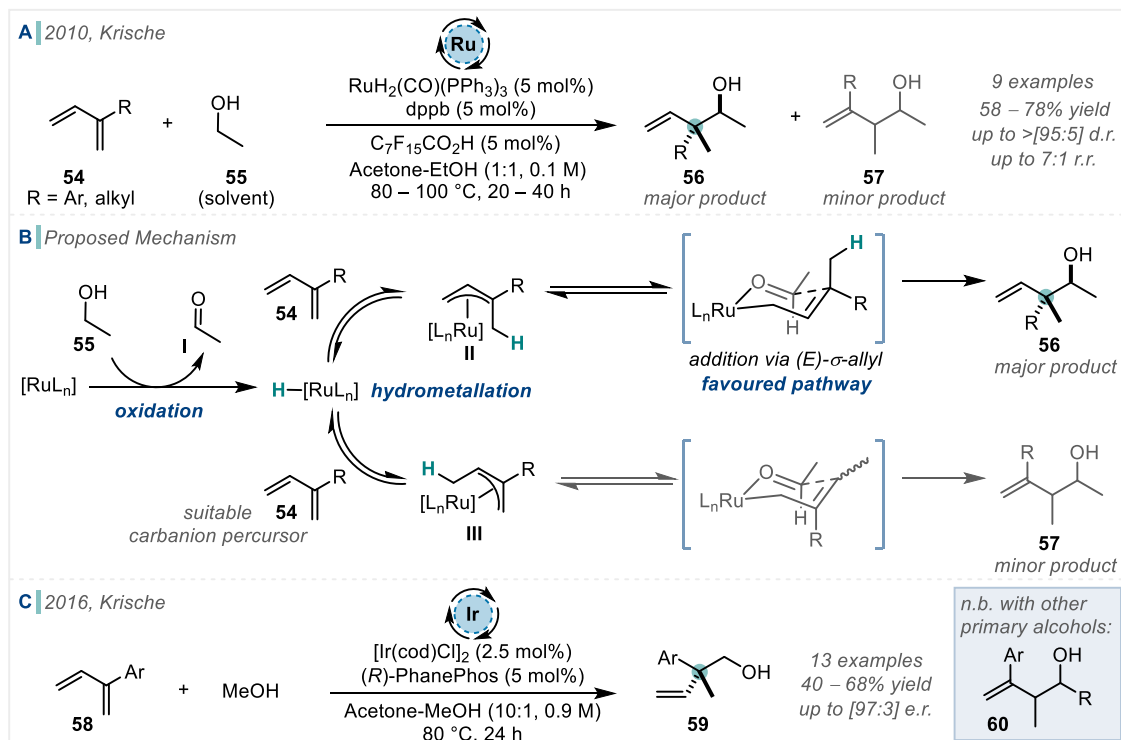
Since quaternary stereocentres can be formed *via* ketone α -alkylation, it follows that this motif should be accessible within the hydrogen borrowing manifold. However, in the hydrogen borrowing catalytic cycle (see **Scheme 1. 2**), the reduction step results in the addition of hydrogen to both the α - and β - positions, precluding the direct synthesis of quaternary stereocentres at these positions. As a result of this, the formation of quaternary stereocentres *via* hydrogen borrowing catalysis is underexplored in the literature, with only a few previously reported examples.

In 2013, Rodriguez and co-workers pioneered a dual catalysis approach for the enantioselective functionalisation of allylic alcohols using β -keto ester nucleophiles (**Scheme 1. 18**).⁸⁰ Using an iron-based catalyst, **Fe Cat01**, an allylic alcohol **49** can be oxidised to the corresponding aldehyde **I**, which can then condense with the organocatalyst to form iminium ion **II**. Addition of the β -ketoester nucleophile **48** from the least hindered face results in the formation of enamine **III**, which can undergo hydrolysis to give the corresponding aldehyde **IV** and regenerate the organocatalyst. The aldehyde **IV** can then be reduced by the iron-hydride species to generate the corresponding alcohol **50'**, which was found to exist in equilibrium with the ring-closed form, **50''**. This method was successfully employed for a small range of nucleophiles and two allylic alcohols, giving the corresponding products in moderate yields and diastereoselectivity, but with good enantioselectivity.



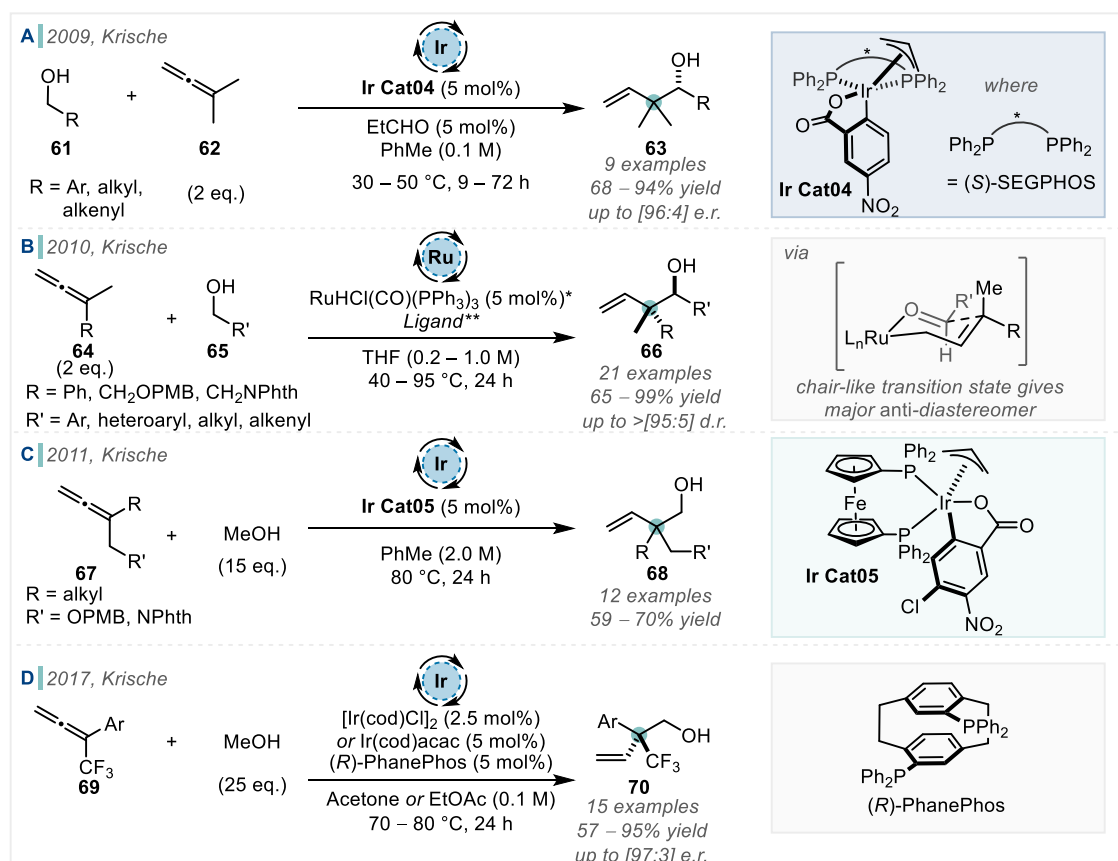
Rodriguez and co-workers subsequently extended this approach to enable the enantioselective synthesis of spirolactones (**Scheme 1. 18**).⁸¹ In 2018, they employed a triple catalytic system, with the inclusion of a copper co-catalyst, to effect a hydrogen borrowing-conjugate addition cascade reaction to access a β -ketoester bearing a pendant alcohol, **52**. The authors reported that this product could be cyclised in a separate step under basic conditions to give the corresponding spirolactone **53** in low-to-moderate yields over two steps, but in high enantiomeric purity.

Krische and co-workers took a different approach for the synthesis of quaternary stereocentres by using a transfer hydrogenation to generate a tertiary carbanion *in situ* (**Scheme 1. 19A**).⁸² The method works by initial oxidation of ethanol to form acetaldehyde **I**, generating a metal-hydride species (**Scheme 1. 19B**). The diene substrate **54** can then undergo hydrometallation to form the corresponding π -allyl metal complex, **II**, which can react with the aldehyde at the most hindered end to generate products containing a quaternary stereocentre, **56**, with high diastereoselectivity, which the authors proposed to be a result of a chair-like transition state. In 2016, Krische and co-workers developed an asymmetric variant of this reaction using an iridium catalyst in combination with a chiral PhanePhos ligand, which enabled the formation of products containing a quaternary stereocentre, **59**, with high enantioselectivity (**Scheme 1. 19C**).⁸² However, this method could only be employed when using methanol as the alcohol, with other primary alcohols favouring the formation of the isomeric product **60**, presumably as a result of increased steric hindrance.



Scheme 1. 19 Quaternary stereocentres via hydrogen transfer to a diene and subsequent carbonyl addition.

Krische and co-workers have also demonstrated that allenes are suitable carbanion precursors that can form analogous π -allyl metal complexes and therefore can be employed in a similar approach for the synthesis of quaternary stereocentres (**Scheme 1. 20**). Initially using 1,1-dimethylallene **62** as the carbanion precursor, a range of alcohols underwent reverse prenylation to give the corresponding secondary alcohol products, **63**, with high enantioselectivity (**Scheme 1. 20A**).⁸³

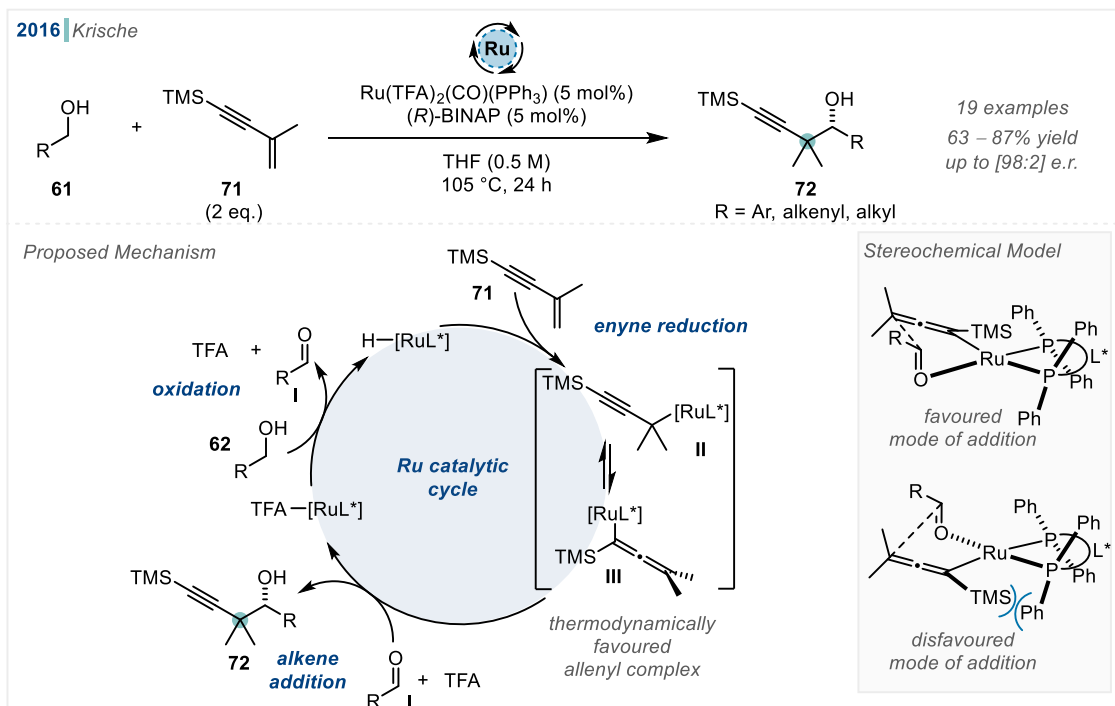


Scheme 1. 20 Quaternary stereocentres via hydrogen transfer to an allene and subsequent carbonyl addition. (S)-SEGPHOS = (S)-(-)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole; *other similar ruthenium catalysts with alternative counterions were also used for high diastereoselectivity with some substrates. ** Ligand = dippf (1,1'-bis(diisopropylphosphino)ferrocene, 5 mol%), dCypf (1,1'-bis(dicyclohexylphosphino)ferrocene, 5 mol%), or PPh₂Cy (15 mol%).

In 2010, Krische and co-workers extended this approach to enable a wider range of allene carbanion precursors to be employed in a diastereoselective approach using a ruthenium catalyst (here the observed diastereoselectivity was attributed to a chair-like transition state for the carbonyl addition, **Scheme 1. 20B**).⁸⁴ A related iridium-catalysed system was later developed for the coupling of methanol with a range of different allenes, affording examples with a variety of different substituents at the quaternary position (**Scheme 1. 20C**).⁸⁵ In 2017, Krische and

co-workers reported a highly enantioselective variant of this reaction to control the absolute stereochemistry at the quaternary centre, using trifluoromethylated allenes **69** as carbanion precursors (**Scheme 1. 20D**).⁸⁶

Furthermore, in 2016, Krische and co-workers reported another enantioselective method for the formation of quaternary stereocentres, this time using enynes as tertiary carbanion precursors which could be employed using a variety of primary alcohol substrates (**Scheme 1. 21**).⁸⁷ In this case, the generated metal-hydride reacts with the enyne to form the tertiary complex **II** which isomerises to the thermodynamically favoured metal-allenyl complex **III**. This can then add to aldehyde **I** through the tertiary centre to access the α -quaternary propargylic alcohol product. The authors proposed that the addition of the aldehyde **I** to the metal-allenyl complex **III** is responsible for the high enantioselectivity, and suggested that the allene substituent occupies the open quadrant, preventing steric clash of the ligand with the silyl group. This leaves the more hindered, “closed” quadrant to be occupied by the aldehyde, with the R group oriented to minimise steric interactions. Overall, this method enables the enantioselective synthesis of a range of α -quaternary propargylic alcohols from simple primary alcohol starting materials, however the scope of the tertiary carbanion precursor was limited to the simple enyne **71**, limiting the range of substituents at the quaternary position.



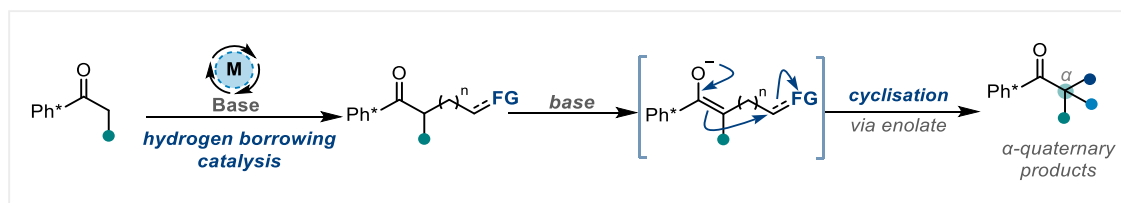
Scheme 1. 21 Quaternary stereocentres via hydrogen transfer to an enyne and subsequent carbonyl addition. Axial ligands are omitted in the ruthenium complexes for clarity.

1.5 Project Aims and General Strategy

Although a few examples of the synthesis of quaternary stereocentres using hydrogen borrowing methods have been reported, compared to the wealth of methods disclosed for the formation of simple branched ketones, this area is underexplored. Given the utility of such motifs in synthesis and the high prevalence of quaternary stereocentres in biologically-relevant molecules, this presents a serious limitation of hydrogen borrowing methodology that requires further study. The few systems that have been developed for the synthesis of quaternary stereocentres using this approach have indicated some of the challenges associated with the synthesis of this motif, in some cases demonstrating that the system may act to avoid the formation of such sterically congested centres if there is a viable alternative. Thus, there is an opportunity for the improvement of the hydrogen borrowing method to enable the synthesis of quaternary stereocentres using a general strategy.

The objective of the research described in this thesis was to design and develop approaches for the synthesis of quaternary stereocentres within the hydrogen borrowing manifold. Since hydrogen borrowing catalysis is unable to furnish quaternary stereocentres directly as a result

of the mechanism, our approach was to exploit as many of the key steps of the hydrogen borrowing cycle as possible to access this motif. Given the nucleophilic nature of ketones at the α -position *via* enolate formation, which is already exploited within the hydrogen borrowing process, this thesis focusses on harnessing this reactivity to enable the synthesis of α -quaternary Ph* ketones. Ultimately, we aimed to synthesise α -quaternary stereocentres *via* a cyclisation approach, to ensure that the formation of the desired motif was entropically favourable (**Scheme 1. 22**). Overall, our strategy centred on using established hydrogen borrowing methods for the synthesis of α -branched ketone intermediates, resulting in the formation of tertiary nucleophiles which could cyclise *in situ* *via* the enolate to give a variety of structures with an all-carbon α -quaternary stereocentre, expanding the chemical space accessible *via* this methodology.

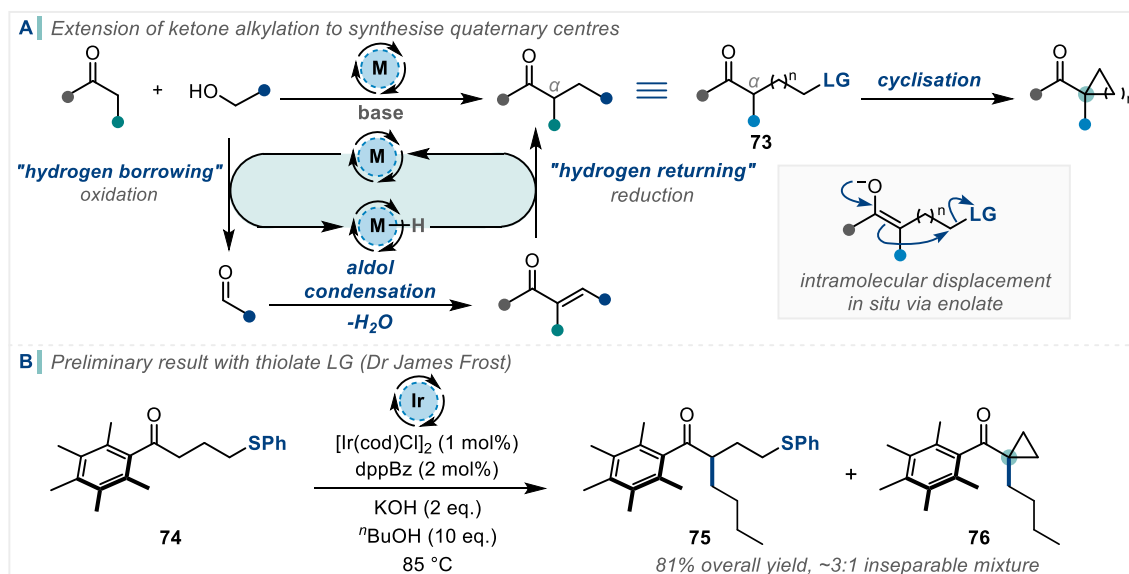


Scheme 1. 22 General strategy for the synthesis of α -quaternary stereocentres.

2. Intramolecular Displacement Strategies

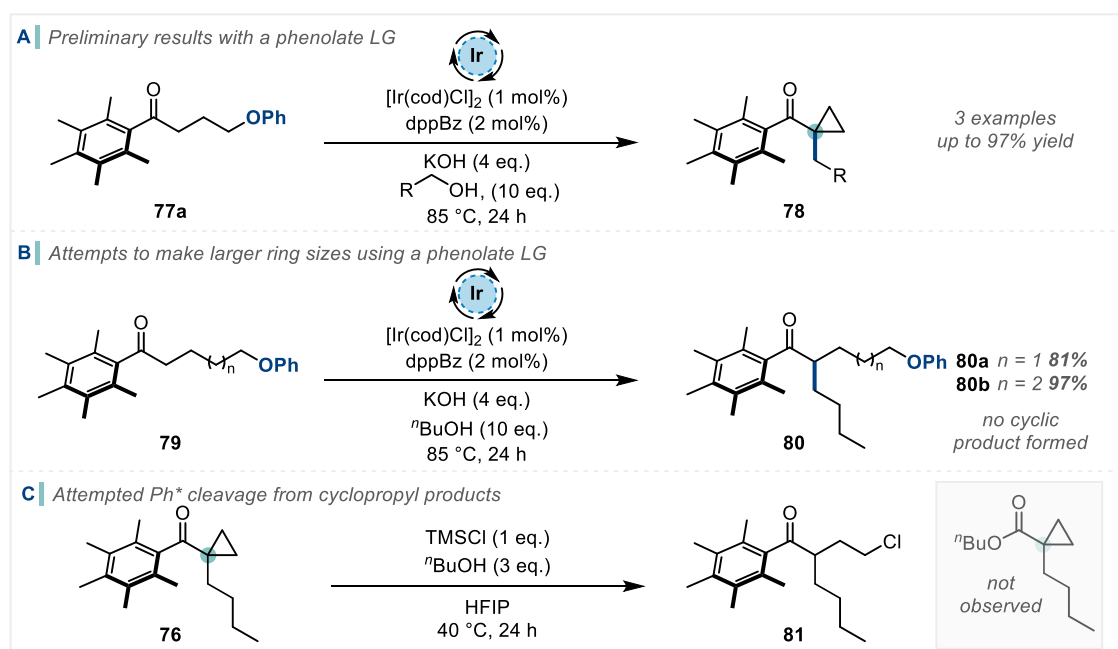
2.1 Introduction

The synthesis of α -branched ketones *via* hydrogen borrowing catalysis is well established in the literature, enabling alkylation of a range of compounds. It was hypothesised that we could extend this established chemistry to enable the synthesis of quaternary stereocentres by inclusion of a suitable leaving group (LG, **Scheme 2. 1A**). It was envisioned that such substrates could undergo alkylation to give an α -branched ketone, **73**, and then, under the highly basic reaction conditions typical of C–C hydrogen borrowing reactions, the corresponding enolate could displace the leaving group in an intramolecular fashion. Such intramolecular displacement approaches are well known in the literature for the synthesis of cycloalkanes.⁸⁸⁻⁹⁰ Indeed, while investigating the scope of α -alkylation, Dr James Frost discovered that thiolate leaving groups enabled this transformation: when substrate **74** was subjected to hydrogen borrowing conditions, displacement of the thiolate leaving group was observed, giving an inseparable mixture of α -branched product **75** and cyclopropane **76** (**Scheme 2. 1B**). It was proposed that the nucleophilic nature of the thiolate released upon displacement could result in cyclopropane ring opening *via* homo-conjugate addition, giving **75**.⁹¹



Scheme 2. 1 A) Proposal for extension of hydrogen borrowing methodology to access quaternary stereocentres. B) Preliminary result with thiolate leaving group, conducted by Dr James Frost.

With this proof-of-concept in hand, a preliminary screen of leaving groups was carried out by Dr James Frost (**Scheme 2. 2A**). It was found that by employing a phenoxide leaving group, employed in substrate **77a**, full conversion to the corresponding cyclopropane **78** could be achieved, presumably as the less nucleophilic phenoxide anion could not intercept the ring-closed product. Unfortunately, cyclobutanes and cyclopentanes could not be formed in an analogous process by simple homologation of the starting material containing this leaving group (**Scheme 2. 2B**). In addition, preliminary efforts to cleave the key Ph* protecting group from the α -cyclopropyl products were unsuccessful using established conditions, due to cyclopropane ring-opening (observed in product **81**, (**Scheme 2. 2C**)).³⁴

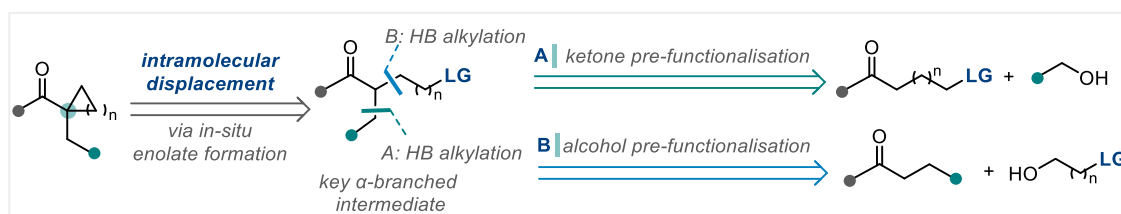


Scheme 2. 2 A) & B) Preliminary investigation with LG = OPh. **C)** Attempt to cleave Ph* from cyclopropyl products. Work conducted by Dr James Frost.

2.2 Project Aims

Given these preliminary results, we considered various approaches to make carbocycles *via* this intramolecular displacement strategy. By considering the proposed α -branched intermediate, we suggested two different disconnections (**Scheme 2. 3**): firstly, the ketone component of the hydrogen borrowing alkylation could be pre-functionalised with an appropriate leaving group. Alternatively, the alcohol substrate could be pre-functionalised with a leaving group, therefore presenting two complementary approaches for the synthesis of cyclopropyl ketones. At the

outset of this project, we aimed to fully investigate both approaches, including the extension of the method to enable the synthesis of larger and more complex carbocycles containing quaternary stereocentres. It was also vital that the key Ph* protecting group could be cleaved to enable the synthesis of synthetically useful fragments; therefore, transformations of the α -cyclopropyl ketone products required further investigation.

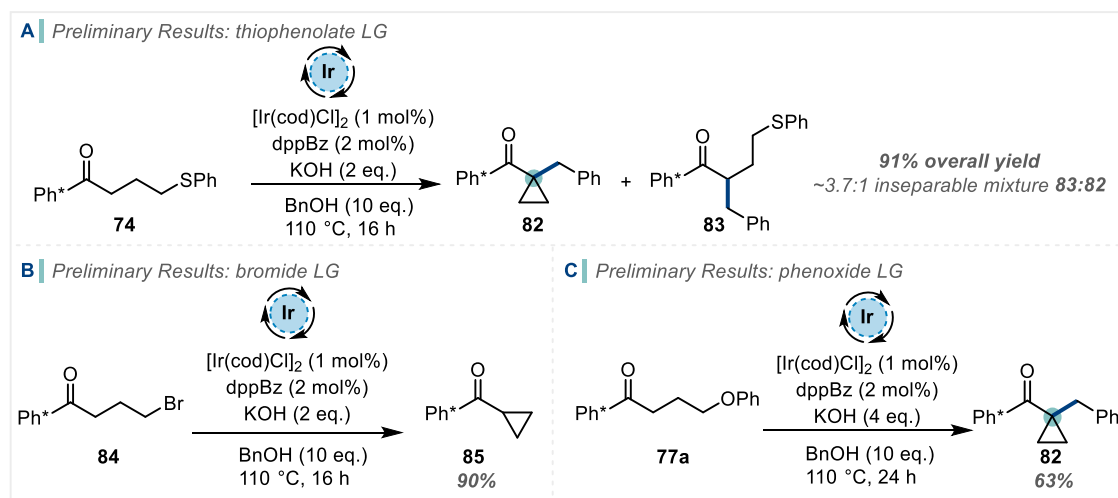


Scheme 2.3 Proposed complementary approaches towards the synthesis of α -quaternary ketones via intramolecular displacement.

2.3 Preliminary Work

Since proof-of concept had been established for forming α -cyclopropyl ketones, it was decided to begin our studies focussing on the synthesis of this motif. Work began by repeating some of the key reactions conducted by Dr James Frost (**Scheme 2.4**). Substrate **74**, bearing a thiolate leaving group, underwent hydrogen borrowing alkylation in high yield to give an inseparable mixture of cyclopropane **82** and ring-opened product **83** (**Scheme 2.4A**). Next, we investigated the use of bromide, a better leaving group, however, under the strongly basic hydrogen borrowing conditions, displacement of the bromide outcompeted hydrogen borrowing alkylation of ketone **84**, giving cyclopropane **85** in 90% yield (**Scheme 2.4B**). Pleasingly, use of the phenoxide leaving group employed by Dr James Frost gave the desired product **82** in 63% yield (**Scheme 2.4C**). These preliminary results gave us a list of criteria for alternative leaving groups: firstly, for displacement to occur in an intramolecular fashion to furnish an α -cyclopropyl ketone, a sufficiently labile leaving group is required. However, the leaving group must also be sufficiently unreactive to allow sufficient time for hydrogen borrowing alkylation to occur prior to displacement. In addition, the anion released upon displacement must not be so nucleophilic that it can intercept the product cyclopropane in a homo-conjugate addition reaction (as demonstrated by the formation of products **75** and **83**). This delicate balance of properties is

key due to the challenge that this reaction presents: developing an intermolecular hydrogen borrowing alkylation which can outcompete cyclisation.

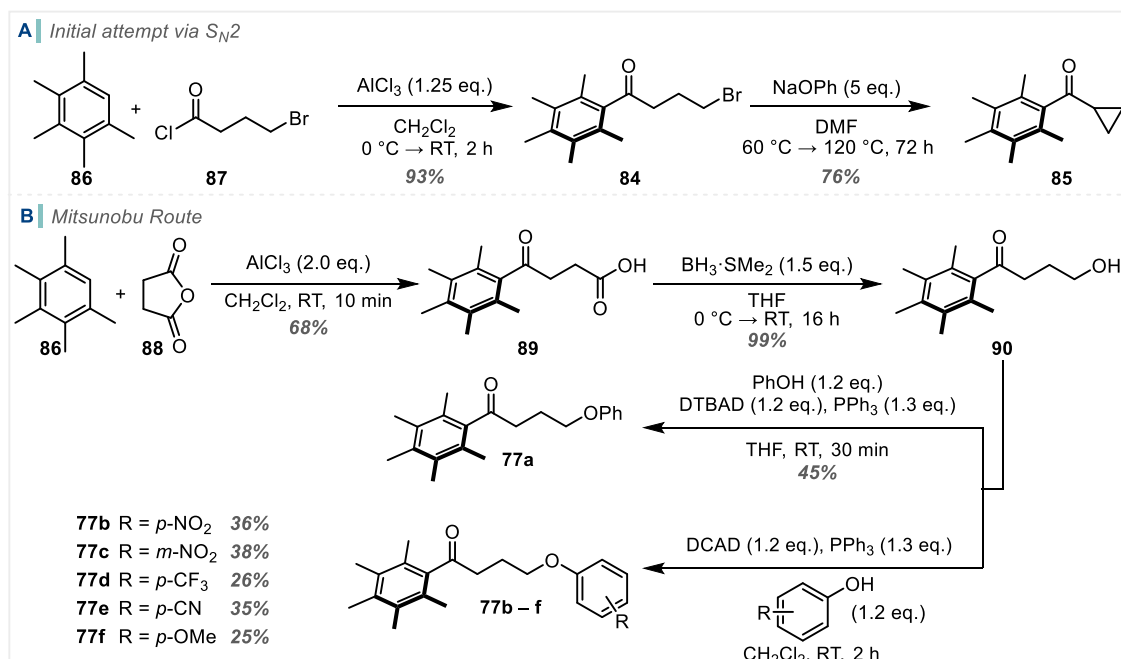


Scheme 2. 4 Preliminary results using a range of different LGs.

2.4 Starting Material Synthesis I

Thus far, phenol-based leaving groups had been shown to have adequate properties to enable the formation of α -cyclopropyl ketones bearing a quaternary stereocentre. Therefore, we aimed to synthesise a panel of pre-functionalised ketone substrates in order to screen a range of different phenoxide leaving groups. Our initial attempt to synthesise such precursors was *via* the S_N2 reaction of alkyl bromide **84** with NaOPh: however, no reaction was observed at 60 °C, presumably as a result of the poor nucleophilicity of phenoxide (**Scheme 2. 5A**). Heating the reaction further to 120 °C resulted in the formation of cyclopropyl ketone **85** in 76% yield, illustrating that this approach was not feasible for the formation of pre-functionalised ketones. Therefore, we embarked on an alternative route using the Mitsunobu reaction (**Scheme 2. 5B**). Friedel–Crafts acylation of pentamethylbenzene **86** with succinic anhydride gave acid **89** in 68% yield, which then underwent chemoselective reduction with borane to give alcohol **90** in 99% yield. Alcohol **90** could then be coupled with a variety of different phenols to give ketones **77a – f** in 25% – 45% yield. The yields for the final Mitsunobu reactions were generally low, as a significant amount of cyclopropyl ketone **85** was formed as a side product; this is likely due to intramolecular displacement of the intermediate alkoxy phosphonium ion by the enol, and

represents a key limitation of this synthetic strategy. Nonetheless, this method enabled the synthesis of a panel of different pre-functionalised ketones for screening.



Scheme 2.5 Starting material synthesis. A) Unsuccessful attempt to synthesise pre-functionalised ketones by direct displacement. B) First-generation route for synthesis of panel of pre-functionalised ketones **77a–f** via Mitsunobu reaction. DTBAD = di-*tert*-butyl azodicarboxylate, DCAD = di-(4-chlorobenzyl)azodicarboxylate.

2.5 Optimisation

2.5.1 Ketone pre-functionalisation approach

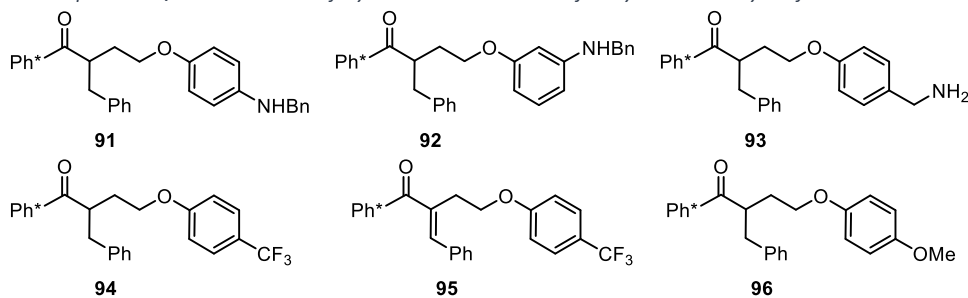
Initial optimisation studies were carried out by screening the panel of pre-functionalised ketones **77a–f** (Table 2. 1). Unsubstituted phenol ether **77a** gave the product **82** in a moderate 63% yield (Entry 1). In an effort to improve conversion, a range of more electron-deficient phenoxide leaving groups were screened (Entries 2 – 5). Unfortunately, these resulted in a decreased yield of desired product **82**, due to the formation of various side products **91–93**. Where reducible functional groups were incorporated in the phenoxide leaving group (R = NO₂, CN), reduction of these groups occurred to give the corresponding amines. As amines are themselves competent nucleophiles, the reduction products can undergo a well-studied amine hydrogen borrowing alkylation, demonstrated by the formation of side products **91** and **92**. When trifluoromethyl-substituted substrate **77e** was employed, side products **94** and **95** were observed by ¹H NMR analysis of the crude reaction mixture, indicative of slow enone reduction

and displacement. This suggested that electron-deficient phenoxide leaving groups were unsuitable for the reaction. However, using electron-rich *p*-methoxyphenoxy substituted ketone **77f** resulted in an improved yield of 67% (Entry 6). Notably, the proposed intermediate **96** was formed in 23% ^1H NMR yield, therefore substrate **77f** was taken forwards for further optimisation, in the hope of increasing conversion of this intermediate to product **82**.

Table 2. 1 Phenoxide-based leaving group screening.

Entry	Substrate	Leaving Group, R =	pKaH (LG) (DMSO) ^{92, 93}	Yield 82 (%)	Side Product	
					Compound	Yield (%) ^a
1	77a	H	18.0	(63)	-	-
2	77b	<i>p</i> -NO ₂	10.8	(30)	91	4
3	77c	<i>m</i> -NO ₂	14.4	(25)	92	(21)
4	77d	<i>p</i> -CN	13.2	(43)	93	6
5	77e	<i>p</i> -CF ₃	15.3	(40)	94 & 95	27, 11
6	77f	<i>p</i> -OMe	18.9	(67)	96	23

^aYield determined via ^1H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Compounds **93**, **94** & **95** were not fully characterised but identified by ^1H NMR analysis of the crude reaction mixtures.



Using *p*-methoxyphenoxy substrate **77f** as the starting material, a range of hydroxide and alkoxide bases typically used in similar hydrogen borrowing processes were then screened (Table 2. 2). Decreasing the equivalents of KOH to two equivalents resulted in a decreased yield, giving desired product **82** in 24% yield (Entry 2). Using KO^tBu also gave a decrease in yield, giving **82** in 58% yield (Entry 3), however, once again, decreasing the equivalents of base proved detrimental to the yield (Entry 4). An alternative counterion was also trialled: using NaOH

resulted in the formation of **82** in a moderate 51% yield (Entry 5), however when NaO^tBu was employed, the yield decreased significantly to form **82** in only 26% yield. It was proposed that the preference for bases with a potassium counterion was likely a result of forming a less-tightly bound enolate in the reaction and therefore the enolate formed is more reactive. None of the alternative bases screened offered any improvement on the original KOH conditions, which gave product **82** in 67% isolated yield, therefore these conditions were taken forwards for further optimisation.

Table 2. 2 Base screening.

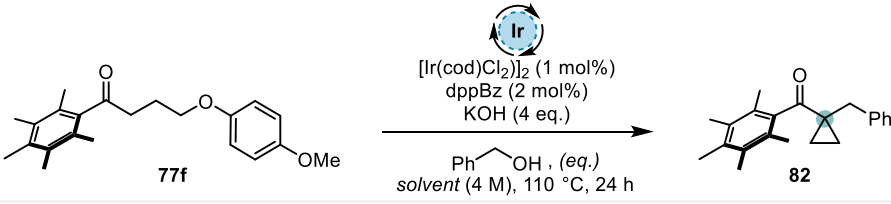
Entry	Base	Base Equivalents	Yield 82 (%) ^a
1	KOH	4	68 (67)
2	KOH	2	24
3	KO ^t Bu	4	58
4	KO ^t Bu	2	13
5	NaOH	4	51
6	NaO ^t Bu	4	26

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Entry 1 repeated from **Table 2. 1** for comparison.

Next, we investigated the addition of a solvent, with a view to decreasing the alcohol equivalents used in the reaction (**Table 2. 3**). Adding either PhMe or ^tBuOH (4.0 M) resulted in a decreased yield of product **82** compared to the neat reaction (Entries 2 – 3). This is presumably a result of the overall decrease in reaction concentration when using a relatively large volume of BnOH as a reagent in combination with a solvent. However, when the equivalents of BnOH were also decreased, the yield was much improved, giving **82** in 53% and 50% when using five equivalents and two equivalents, respectively (Entries 4 – 5). Although this represents a decrease in the yield of **82** compared to the neat reaction, these conditions could be employed if a valuable alcohol was being used in the hydrogen borrowing reaction. Running the reaction neat with reduced

equivalents was not trialled because stirring of the reactions was difficult when only a small amount of liquid reagent was used.

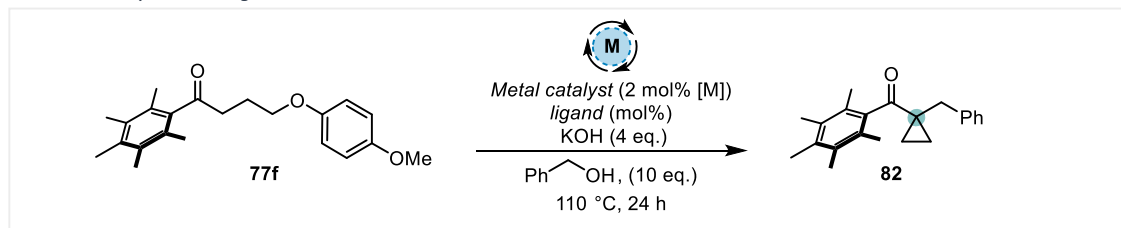
Table 2. 3 Solvent and BnOH equivalents screen.

			
Entry	BnOH Equivalents	Solvent	Yield 82 (%) ^a
1	10	-	68 (67)
2	10	PhMe	43
3	10	^t BuOH	25
4	5	^t BuOH	53
5	2	^t BuOH	50

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Entry 1 repeated from **Table 2. 1** for comparison.

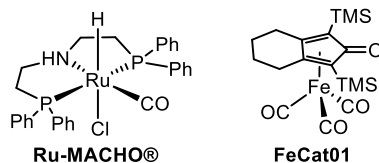
Alternative metal catalysts were also screened in this process (**Table 2. 4**). Using an iridium (III) source, [IrCp*Cl₂]₂, gave a similar yield of product, forming **82** in 65% yield (Entry 2). However, the analogous rhodium and ruthenium-based catalysts resulted in a decrease in yield, giving **82** in 55% and 43% yield, respectively. Surprisingly, Ru-MACHO[®] gave the desired product in 64% isolated yield, which was comparable with the iridium catalysts. Alternative earth-abundant metal catalysts Ni(OAc)₂ and iron Knöllker catalyst **FeCat01** were also screened,^{9, 94} however product **82** was formed in only 39% and 23% yield, respectively (Entries 6 – 7). Given the greater natural abundance of ruthenium, Ru-MACHO[®] was taken forwards as a more sustainable option as well as the [Ir(cod)Cl₂]₂ and [IrCp*Cl₂]₂ catalytic systems for further optimisation.

Table 2. 4 Catalyst screening.



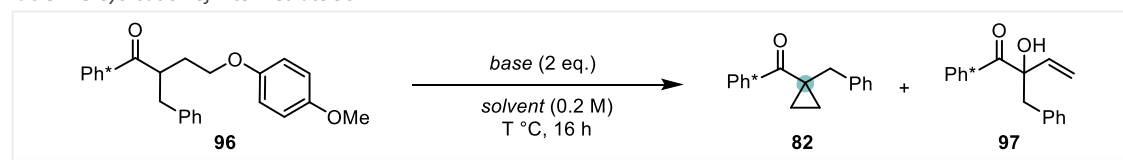
Entry	Catalyst	Catalyst Loading (mol%)	Ligand	Ligand Loading (mol%)	Yield 82 (%) ^a
1	[Ir(cod)Cl ₂] ₂	1	dppBz	2	68 (67)
2	[IrCp*Cl ₂] ₂	1	-	-	65
3	[RhCp*Cl ₂] ₂	1	-	-	55
4	[RuCp*Cl ₂] _n	2	-	-	43
5	Ru-MACHO®	2	-	-	72 (64)
6	Ni(OAc) ₂	2	P ^t Bu ₃	4	39
7 ^b	FeCat01*	2	-	-	23

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b Me₃NO (4 mol%) was added at the start of the reaction. Entry 1 repeated from Table 2. 1 for comparison.



Given that a significant amount of proposed intermediate **96** was observed in the reaction when using substrate **77f**, we investigated ways to drive the cyclisation. Proposed intermediate **96** was prepared separately (see Table 2. 8, Chapter 2.5.2) and subjected to various basic reaction conditions (Table 2. 6). Most of the conditions tested did not result in cyclisation and in some cases small amounts of alkene product **97** were formed instead, presumably *via* reaction with adventitious oxygen and elimination of the leaving group. However, it was found that when treated with KO^tBu in ^tBuOH, substrate **77f** underwent cyclisation to form cyclopropane **82** in high yield. This supported the working hypothesis that the reaction mechanism proceeds *via* initial hydrogen borrowing to give **96** as an intermediate. The enolate then displaces the *p*-methoxyphenoxy leaving group to generate cyclopropane **82**.

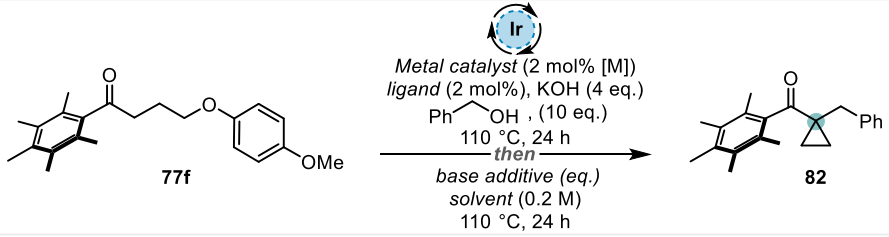
* This catalyst was prepared by Dr. Chris Hall

Table 2. 5 Cyclisation of intermediate **96**.

Entry	Base	Solvent	Reaction Temperature (°C)	Yield (%) ^a		
				96	82	97
1	NaH	THF	RT	18	-	5 (9)
2	KOH	PhMe	110	46	-	-
3	KO ^t Bu	PhMe	110	31	-	-
4	KHMDS	PhMe	110	41	-	5
5	KO ^t Bu	^t BuOH	110	-	80 (81)	-

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses.

Having conducted the cyclisation in a separate step, we investigated ways of driving this cyclisation *in situ* in an effort to increase the yield of cyclopropane **82** in one pot. It was envisaged that adding a second portion of base and solvent after the initial 24 h reaction period could increase cyclisation of intermediate **96** (Table 2. 6). Adding another four equivalents of KOH, and ^tBuOH as the solvent resulted in a decrease in yield (52%) of cyclopropane **82** (Entry 1). However, adding only two equivalents of KOH with ^tBuOH gave an improved yield of 75% (Entry 2). Employing KO^tBu (two equivalents) instead of KOH resulted in a decreased yield (Entry 3). Equally, when ^tBuOH was replaced by the addition of PhMe, the product was formed in a lower, 52% yield (Entry 4). Therefore, the addition of a second portion of KOH (two equivalents) and ^tBuOH was taken forwards and alternative catalysts were trialled in this system. A similar increase in yield was observed when using either Ru-MACHO® or [IrCp*Cl₂]₂ (Entries 5 – 6). Therefore, both the [Ir(cod)Cl₂] and Ru-MACHO® systems were taken forwards to explore the scope of the transformation.

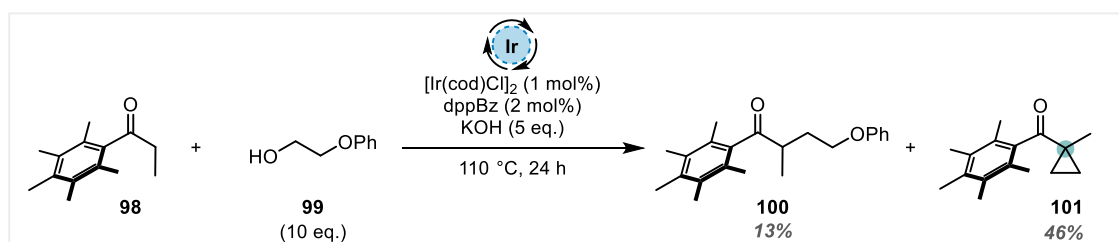
Table 2. 6 Addition of additional base and solvent to drive conversion to **82** in situ.


Entry	Catalyst (mol%)	Ligand (mol%)	Base Additive (eq.)	Solvent	Yield 82 (%) ^a
1	[Ir(cod)Cl] ₂ (1)	dppBz (2)	KOH (4)	^t BuOH	52
2	[Ir(cod)Cl] ₂ (1)	dppBz (2)	KOH (2)	^t BuOH	75 (75)
3	[Ir(cod)Cl] ₂ (1)	dppBz (2)	KO ^t Bu (2)	^t BuOH	62
4	[Ir(cod)Cl] ₂ (1)	dppBz (2)	KOH (2)	PhMe	52
5	Ru-MACHO®	-	KOH (2)	^t BuOH	73 (75)
6	[IrCp*Cl] ₂	-	KOH (2)	^t BuOH	74

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses.

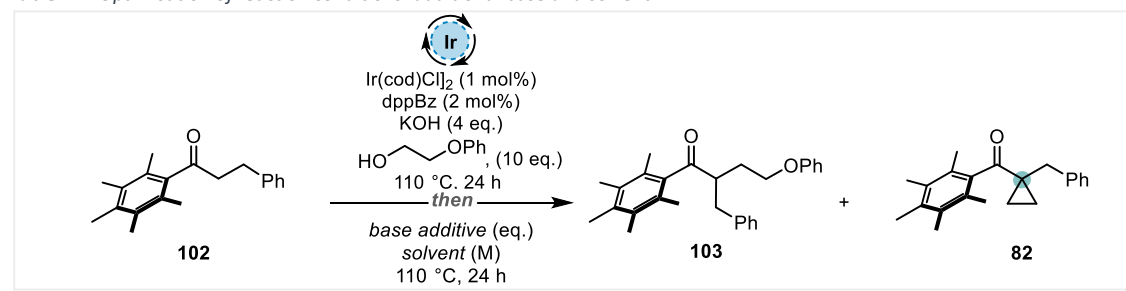
2.5.2 Alcohol pre-functionalisation approach

As described in Chapter 2.2, an alternative approach towards the synthesis of α -cyclopropyl ketones involves pre-functionalisation of the alcohol component of the hydrogen borrowing. To determine the feasibility this approach, Ph* ketone **98** was reacted with 2-phenoxyethanol (**99**) under hydrogen borrowing conditions (**Scheme 2. 6**). Pleasingly, a mixture of intermediate **100** and cyclopropane **101** was formed, demonstrating proof-of-concept for this strategy.

**Scheme 2. 6** Proof-of-concept for cyclopropane synthesis via alcohol pre-functionalisation.

With this preliminary result in hand, we decided employ a different model substrate in order to carry out further reaction optimisation. Substrate **102** was chosen for this purpose as while still a simple substrate for optimisation, the resulting cyclopropane would carry a larger substituent, hopefully allowing the method to be applicable to a wider range of Ph* ketone substrates with higher steric demands α -to the quaternary centre than a simple methyl group. The reaction time was also increased to 48 h, in the hope of improving conversion. However, when ketone **102**

was subjected to the reaction, product **82** was formed in only 20% ^1H NMR yield (Table 2. 7, Entry 1). When additional solvent was added after 24 h, and the reaction heated for a further 24 h, no improvement in yield was observed (Entry 2). In an approach similar to the reaction using a pre-functionalised ketone, the addition of a second portion of base and solvent was investigated. While adding an additional portion of KO^tBu (four equivalents) did not increase the yield of product **82** significantly, a large amount of intermediate **103** remained (Entry 3). Interestingly, halving the equivalents of base added after the first 24 h of the reaction to two equivalents enabled greater conversion to product **82**, which was isolated in 60% yield (Entry 4). Decreasing the equivalents of added base further resulted in a slight decrease in yield to 50% (Entry 5). The amount of added solvent was also investigated, and it was found that diluting the reaction to either 0.5 M or 0.1 M after 24 h resulted in poorer yields, giving **82** in 46% and 41%, respectively (Entries 6, 7). Adding PhMe instead of $^t\text{BuOH}$ gave no further improvement (Entry 8), and using KOH in place of the alkoxide base resulted in a decrease in yield of cyclopropane **82** (Entry 9), presumably as a result of poorer solubility, as no additional conversion was observed c.f. when no additional base was added. We also trialled a shorter reaction time after the addition of the second portion of base and solvent, however limited product formation suggested that a longer reaction time was necessary to enable efficient cyclisation (Entry 10). It was also suggested that KO^tBu could be employed as an alternative to KOH in the initial reaction; this gave a poor yield of 20%, although a significant amount of intermediate **103** remained (55%) (Entry 11). Finally, we considered the operational simplicity of the reaction, and investigated whether the additional base could be added at the start of the reaction, with addition of only solvent *via* syringe after the first 24 h (Entry 12). Unfortunately, this did not give good conversion, forming product **82** in only 26% yield.

Table 2. 7 Optimisation of reaction conditions: additional base and solvent.

Entry	Base Additive (eq.)	Solvent (M)	Yield (%) ^a	
			103	82
1	-	-	15	20
2	-	<i>t</i> BuOH (0.2)	7	22
3	KO ^{<i>t</i>} Bu (4)	<i>t</i> BuOH (0.2)	52	26
4	KO ^{<i>t</i>} Bu (2)	<i>t</i> BuOH (0.2)	24	48 (60)
5	KO ^{<i>t</i>} Bu (1)	<i>t</i> BuOH (0.2)	25	36 (50)
6	KO ^{<i>t</i>} Bu (2)	<i>t</i> BuOH (0.5)	27	44 (46)
7	KO ^{<i>t</i>} Bu (2)	<i>t</i> BuOH (0.1)	24	38 (41)
8	KO ^{<i>t</i>} Bu (2)	PhMe (0.2)	37	43
9	KOH (2)	<i>t</i> BuOH (0.2)	38	26
10^b	KO ^{<i>t</i>} Bu (2)	<i>t</i> BuOH (0.2)	15	23
11^c	KO ^{<i>t</i>} Bu (2)	<i>t</i> BuOH (0.2)	55	20
12^d	-	<i>t</i> BuOH (0.2)	12	26

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Intermediate **103** was not isolated but identified by ¹H NMR ^b After second portion of base and solvent added, reaction heated for a further 6 h. ^c KO^{*t*}Bu (4 eq.) used instead of KOH (4 eq.) in the initial reaction, ^d Additional KO^{*t*}Bu (2 eq.) added at the start of the reaction.

After studying various different leaving groups for the ketone pre-functionalisation reaction (see Chapter 2.5.1), we investigated the use of a *p*-methoxyphenoxide leaving group in this approach. Mono-protected diol **104** was synthesised and employed in the reaction (Table 2. 8). Since this pre-functionalised alcohol was not commercially available, we also investigated decreasing the equivalents of diol employed in the reaction. A significant decrease in isolated yield was observed when using diol **104**, which gave product **82** in only 40% isolated yield (Entry 1). Decreasing the equivalents of this diol to five and then two equivalents resulted in lower conversion to product **82**, which was formed in 34% and 19% yield, respectively (Entries 2 – 3). Notably, a large amount of intermediate **96** (approximately 50% yield) was formed in these

reactions, and a variant on these conditions was therefore employed to access intermediate **96** for mechanistic investigation (see **Table 2. 5**). Since diol **104** was a solid, we also investigated the effect of adding a small amount of PhMe to the initial hydrogen borrowing reaction to aid initial stirring of the reaction (Entry 4). This offered no improvement on the yield, giving cyclopropane **82** in 31% yield, potentially as a result of decreasing the reaction concentration. We postulate that using the poorer *p*-methoxyphenoxide leaving group does not improve this reaction as much as in the previous approach, as the leaving group is intrinsic to the alcohol and so the desired hydrogen borrowing reaction does not have to compete kinetically with alternate cyclisation processes. However, in the previous approach, using a poorer leaving group allows more time for hydrogen borrowing alkylation prior to displacement; we proposed that premature cyclisation to form the corresponding cyclopropyl ketone was a plausible pathway which could contribute to the reduced yields.

Table 2. 8 Investigation of alternative leaving group and diol equivalents.

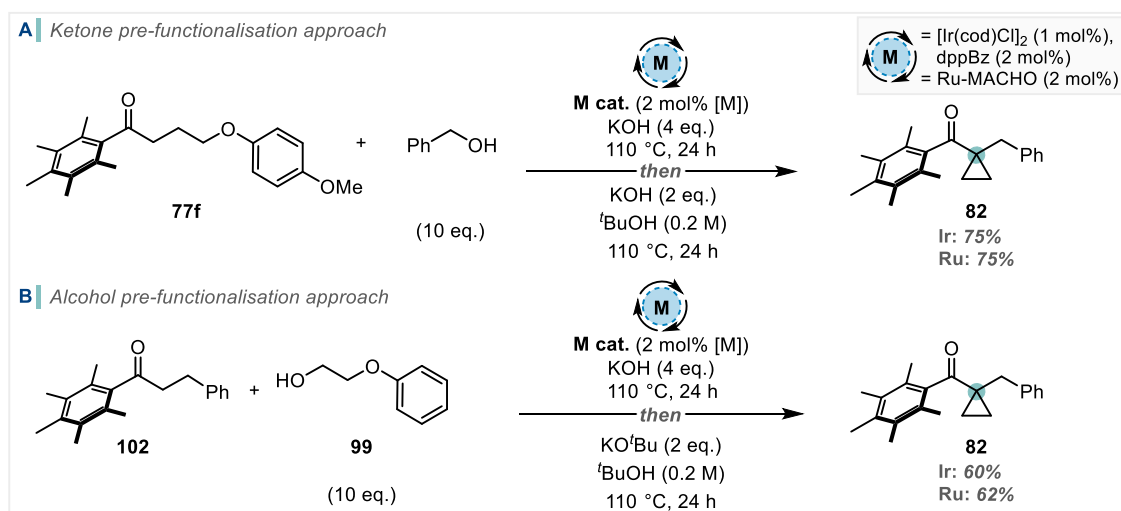
Entry	Diol	R =	Diol Equivalents	Yield (%) ^a		
				96	103	82
1	104	OMe	10	36 (33)	–	59 (40)
2	104	OMe	5	50	–	34
3	104	OMe	2	51	–	19
4 ^b	104	OMe	10	(31)	–	(31)
5	99	H	10	–	24	48 (60)
6	99	H	5	–	48	31
7	99	H	2	–	72	18

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b PhMe (4 M) added to initial reaction. Entry 5 is repeated from **Table 2. 7** for comparison.

We also investigated the effect of decreasing the equivalents of commercially available alcohol **99** on the yield of product **82** (**Table 2. 8**, Entries 6 – 7). Unfortunately, the yield of cyclised

product **99** decreased significantly with decreasing equivalents, giving 31% yield of **82** when using five equivalents, and only 18% yield when using two equivalents, although the hydrogen borrowing alkylation still worked well in both cases, as significant amounts (48% and 72% yield, respectively) of intermediate **103** were observed.

Finally, we investigated whether the alternative, Ru-MACHO[®] catalyst was effective in this reaction. Pleasingly when this catalyst was employed, product **82** was isolated in 62% yield, which is comparable to the original iridium-catalysed system. Our final optimised conditions are shown in **Scheme 2. 7**. Using either an iridium- or ruthenium-based catalyst, cyclopropane **82** could be made in two distinct approaches, where either the ketone or alcohol component of the reaction were pre-functionalised with a phenoxide leaving group, allowing intramolecular displacement to occur after hydrogen borrowing alkylation.

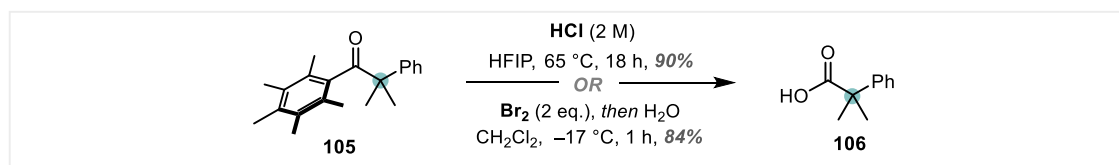


Scheme 2. 7 Optimised reaction conditions for cyclopropane formation.

2.6 Strategies for Derivatisation

Previous strategies employed within the Donohoe group for the removal of the key Ph* protecting group relied upon a retro-Friedel–Crafts acylation reaction.³⁵ However, it was suggested that this strategy could be problematic for the deprotection of α-quaternary Ph* ketones as it is well known in the literature that α-quaternary acid derivatives may undergo decarbonylation under Friedel–Crafts conditions.⁹⁵ In order to probe whether this approach was feasible, acyclic α-quaternary ketone **105** was prepared and subjected to a range of

conditions for Ph* cleavage. Pleasingly, the Ph* group could be removed from **105** to give acid **106** in high yields under typical acidic or oxidative Ph* cleavage conditions (**Scheme 2. 8**).



Scheme 2. 8 Cleavage of Ph* group from acyclic α-quaternary ketone **105**.

However, preliminary studies by Dr James Frost had indicated that the cyclopropane products were vulnerable to ring opening by nucleophilic counterions under these cleavage conditions. Therefore, a range of alternative acids bearing non-nucleophilic counterions were investigated (**Table 2. 9**). Pleasingly, a range of these acids enabled Ph* cleavage from model ketone **105** to give acid **106**. While the addition of phosphoric acid resulted in no conversion (Entry 3), sulfuric acid and tetrafluoroboric acid were able to furnish acid **106** in quantitative yield (Entries 2, 5).

Table 2. 9 Cleavage of Ph* group with acids with a non-nucleophilic counterion.

Entry	Acid	Yield 106 (%) ^a
1	HCl	(90)
2	H ₂ SO ₄	quant.
3	H ₃ PO ₄	-
4	HClO ₄	23
5	HBF ₄	quant.

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Entry 1 is repeated from **Scheme 2. 8** for comparison.

Therefore, the conditions employing sulfuric acid and tetrafluoroboric acid were each applied to α-cyclopropyl ketone **82** (**Table 2. 10**). Unfortunately, a complex mixture of products was formed, including only trace amounts of desired α-cyclopropyl acid **107**. A small amount of rearranged product **108** was also formed under both sets of reaction conditions, likely a result of cyclopropane ring-opening by a nucleophile to generate the corresponding enol, which then ring closes in a 5-*exo-tet* fashion. We hypothesised that such Ph* cyclopropyl ketones are particularly vulnerable to ring-opening as a result of the Ph* group being twisted out of

conjugation and therefore that a cyclopropane σ -bond is conjugated with the carbonyl and is possibly weaker than in its non-Ph* analogue. This is evidenced by the IR (C=O) stretches for compounds **102** and **82** (Figure 2. 1) which demonstrate that the Ph* ketone C=O bond is weaker with the addition of an α -cyclopropane (other branching substituents do not give a similar effect, as illustrated by acyclic compound **105**). It was also observed that significant decomposition occurred under these Ph* cleavage conditions, indicating that these strongly acidic conditions were unsuitable for derivatisation of the cyclopropane products. We therefore investigated other ways of derivatising these α -quaternary ketones.

Table 2. 10 Acidic cleavage conditions for Ph* removal using α -cyclopropyl ketone **82**.

Entry	Acid	Yield (%) ^a		
		82	107	108
1	H ₂ SO ₄	-	12	16
2	HBF ₄	25	4	14

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

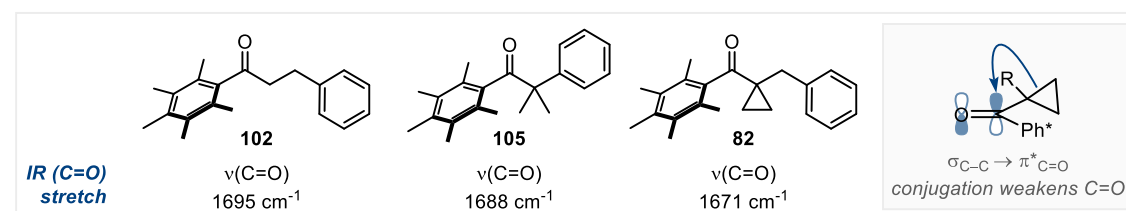
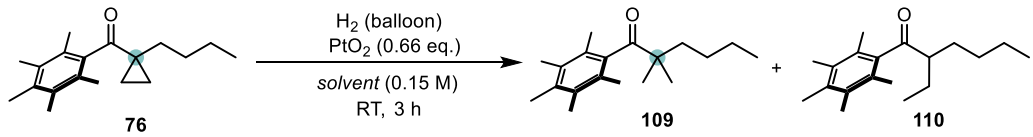


Figure 2. 1 IR stretches of Ph* ketones and α -cyclopropyl Ph* ketones.

It was suggested that the cyclopropane could be further derivatised prior to Ph* cleavage. We initially tried to cleave the cyclopropane C–C bond, in an effort to access an acyclic α -quaternary centre (Table 2. 11).⁹⁶ Cyclopropane **76** did undergo cleavage using PtO₂ as a hydrogenation catalyst in AcOH, however the product was identified as singly α -branched ketone **110** and the desired *gem*-dimethyl product **109** was not observed (Entry 1). It was proposed that the acidic solvent could contribute to this selectivity by protonation of the ketone, weakening the cyclopropane C–C bond further. Therefore, other hydrogenation solvents were investigated. Unfortunately, using either MeOH or EtOAc also gave high yields of ketone **110** (Entries 2 – 3).

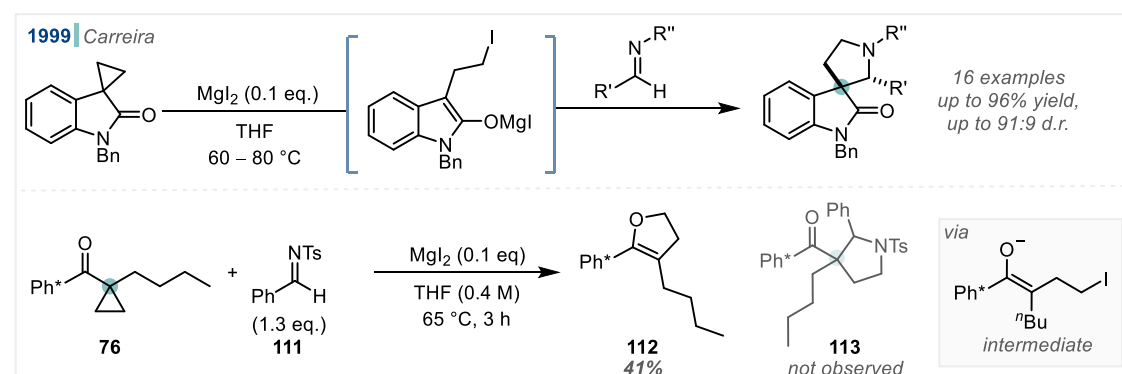
Alternative hydrogenation catalysts such as Pd/C and Rh/C were also investigated; however, no conversion of starting material **76** was observed under these conditions.

Table 2. 11 Hydrogenation of cyclopropyl ketone **76**.

				
Entry	Solvent	Yield (%) ^a		
		109	110	
1	AcOH	-	(79)	
2	MeOH	-	89	
3	EtOAc	-	84	

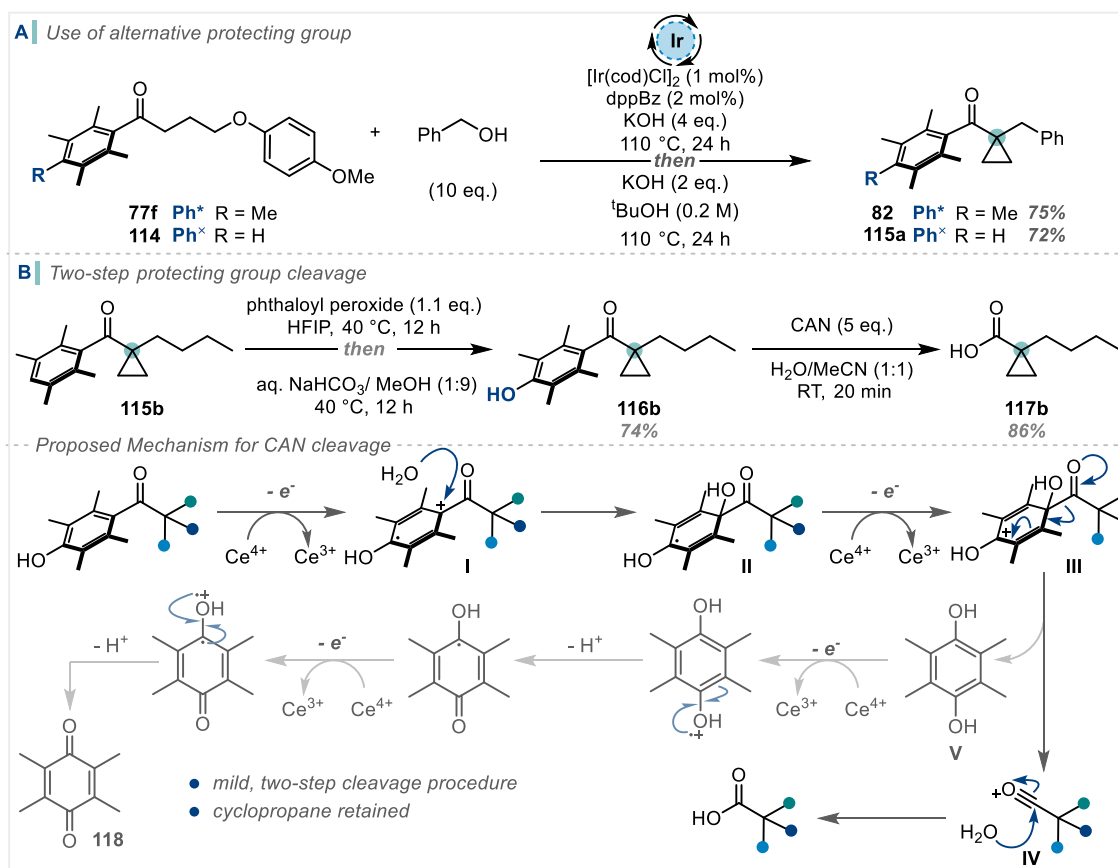
^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses.

It was hypothesised that the intrinsic ring-opening reactivity of the cyclopropane could be harnessed to allow further derivatisation. Based on methodology developed by Carreira and co-workers, it was suggested that the intermediate ring-opened enolate could intercept an imine to give ring expansion product **113** (Scheme 2. 9).⁹⁷ However, under these conditions, no ring expansion product was observed. Instead, dihydrofuran **112** was formed in 41% yield, indicating that the iodide is intercepted in an intramolecular manner to give the *O*-alkylated product faster than the enolate can react with the imine.



Scheme 2. 9 Attempted ring expansion of cyclopropane products.

Since attempts to functionalise the cyclopropane prior to Ph* cleavage had been unsuccessful, we next investigated the use of a 2,3,5,6-tetramethylphenyl (Ph^x) protecting group. This group had been shown to behave similarly to Ph* in hydrogen borrowing alkylation, demonstrated by the synthesis of Ph^x cyclopropyl ketone **115a** *via* the optimised ketone pre-functionalisation approach in 72% using [Ir(cod)Cl]₂ as the catalyst (c.f. 75% with the Ph* analogue, (**Scheme 2. 10A**)). However, previous work within the group had indicated that Ph^x protecting groups can be cleaved in a mild two-step sequence *via* the corresponding phenol.^{98, 99} Therefore, cyclopropyl ketone **115b** was prepared and then subjected to the two-step cleavage protocol (**Scheme 2. 10B**). Pleasingly, the hindered aryl protecting group could be oxidised to the corresponding phenol **116b** in 74% yield. This phenol could then undergo oxidative cleavage using CAN to access the corresponding acid **117b** in 86% yield, with retention of the cyclopropane. We propose that this step proceeds as follows: the phenol is oxidised by the cerium(IV) to give the radical cation **I**, which is intercepted by H₂O to give radical species **II**. This is further oxidised by Ce⁴⁺ to give cation **III** which fragments to give acylium ion **IV**, which is captured by H₂O to give the product carboxylic acid. The hydroquinone **V** can then be oxidised further by CAN to give quinone **118** which is isolated as a by-product. The ability to cleave the key protecting group would enable the synthesis of a variety of α-cyclopropyl acid derivatives. Therefore, this protecting group was employed for all further work with α-cyclopropyl ketones.

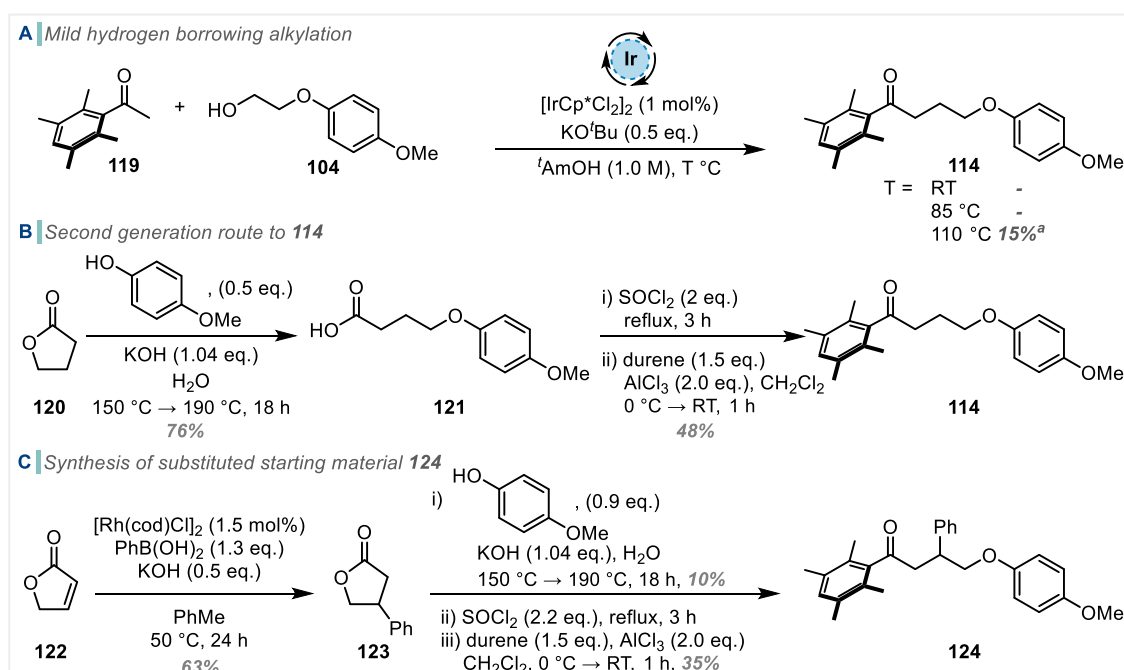


Scheme 2. 10 A) Use of Ph^* protecting group in synthesis of cyclopropyl ketones. B) Cleavage of Ph^* protecting group.

2.7 Starting Material Synthesis II

Although the first-generation starting material synthesis route was sufficient for optimisation, this route was unsuitable for the preparation of large quantities of pre-functionalised ketone **114**. Therefore, alternative strategies for the synthesis of **114** were explored (**Scheme 2. 11**). We first investigated the synthesis of ketone **114** itself *via* hydrogen borrowing alkylation, however it was suggested that the basic reaction conditions may promote premature cyclisation to the cyclopropane (see **Scheme 2. 4**). To avoid this fate, we employed milder conditions using sub-stoichiometric amounts of base, which had been recently developed within the group, to investigate the hydrogen borrowing alkylation with alcohol **104** (**Scheme 2. 11A**).¹⁶ Unfortunately, conversion was low when using this method, and **114** was formed in only 15% ^1H NMR yield at 110 °C. Ultimately, ketone **114** was prepared in two-step process: lactone **120** underwent ring-opening at the γ -centre with *p*-methoxyphenoxide to give functionalised acid **121** in 76% (**Scheme 2. 11B**). This acid was then converted into the corresponding acyl chloride

and acylated to yield pre-functionalised ketone **114** in 48% yield over two steps. This route enabled the synthesis of **114** on multi-gram scale and also presented an opportunity to easily access precursors bearing backbone substitution; unsaturated lactone **122** underwent rhodium-catalysed conjugate addition to generate phenyl-substituted lactone **123** in 63% yield (**Scheme 2. 11C**). This could then be employed in the second-generation route to access substituted ketone **124**. Although the yields were low for the lactone ring opening and Friedel–Crafts acylation in this case, a sufficient amount of material was obtained for further investigation of the method.



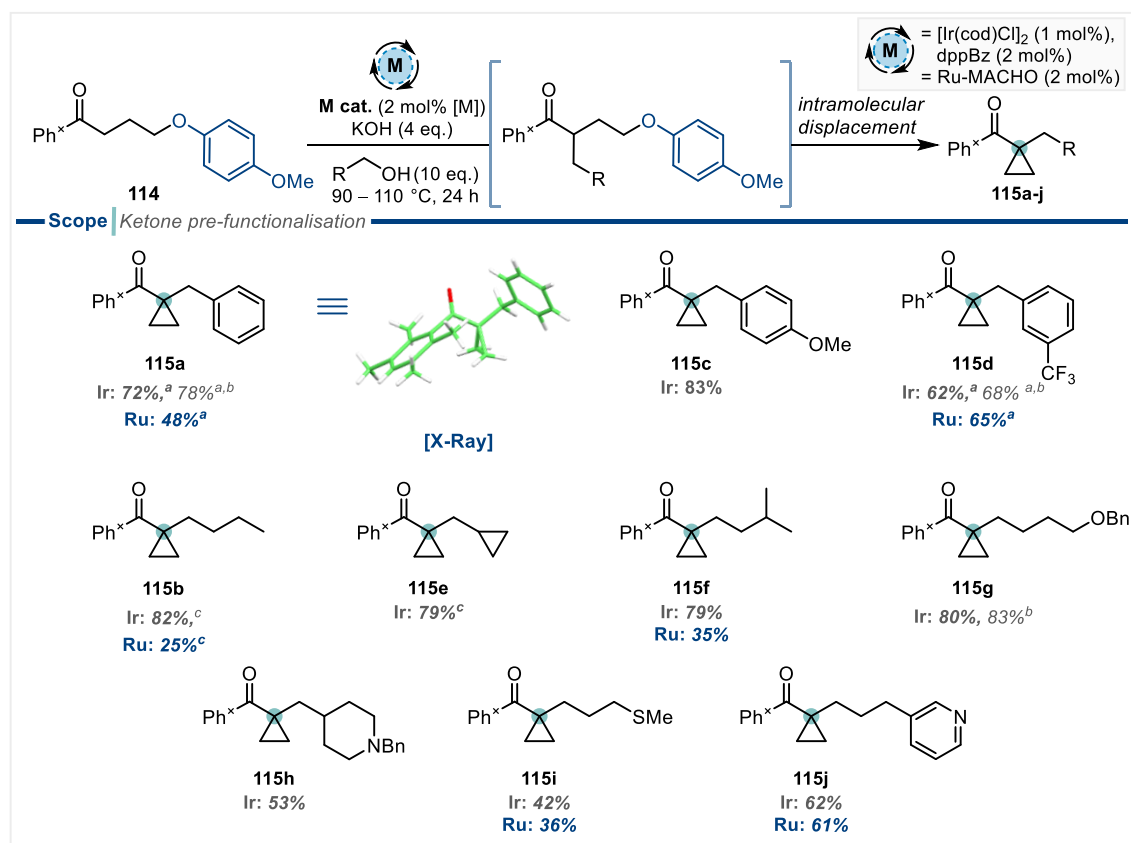
Scheme 2. 11 Second-generation synthesis of starting material **114**. ^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

2.8 Reaction Scope

2.8.1 Ketone pre-functionalisation approach

With the optimised reaction conditions and ketone protecting group in hand, the scope of the transformation was examined. A variety of alcohols were subjected to the optimised conditions with ketone **114** (**Scheme 2. 12**). Pleasingly, for many of the alcohols investigated, it was not necessary to add a second portion of base and solvent after the initial 24 h reaction time in order to synthesise the cyclopropyl ketone products in good yields. Under iridium catalysis, a range of benzylic alcohols, including those bearing electron-donating and electron-withdrawing

substituents were tolerated to give α -cyclopropyl ketones **115a**, **115c**, and **115d** in 62% – 83% yield. Simple unactivated alkyl alcohols were also successful, giving compounds **115b**, **115e**, and **115f** in 79% – 82% yield. Protected heteroatoms were also tolerated, resulting in the synthesis of ketones **115g** – **i** in 42% – 80% yield. An alcohol bearing a pendant pyridine was also a successful substrate, giving **115j** in 62% yield.

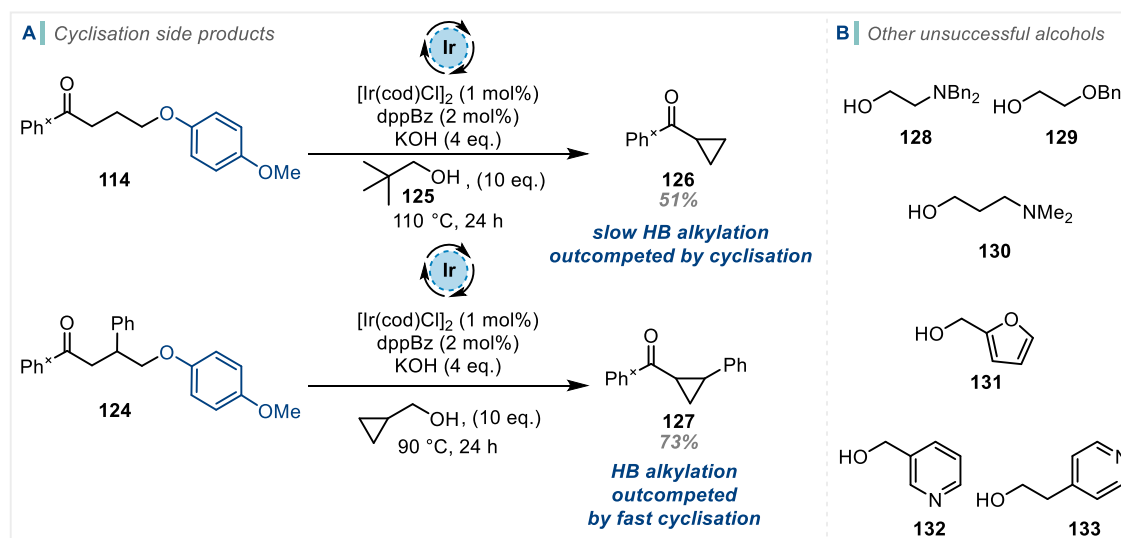


Scheme 2.12 Ketone pre-functionalisation scope. Reactions were performed on a 0.30 – 0.60 mmol scale unless otherwise stated. Isolated yields are reported. X-ray crystallography data and analysis were provided by Dr Kirsten E. Christensen. ^a KOH (2 eq.) and ^tBuOH added after 24 h; reaction heated for a further 24 h. ^b Reaction was performed on a 1.00 mmol scale. ^c Reaction performed at 90 °C.

A selection of these alcohol substrates was also subjected to the reaction conditions using the Ru-MACHO[®] catalyst (**Scheme 2.12**). While some cyclopropyl ketone products were synthesised in comparable yield to the iridium-catalysed system (**115d** and **115j**), for certain substrates, the Ru-MACHO[®] catalytic system resulted in a significant decrease in yield compared to the iridium-catalysed system (demonstrated by examples **115a**, **115b** and **115f**). We postulate that this is due to the Ru-MACHO[®] catalyst being less reducing than the iridium system, therefore the hydrogen borrowing alkylation is slower, leading to a complex mixture of other products,

including the α -branched ketone and corresponding enone. Indeed, the corresponding enone was observed in the crude ^1H NMR spectra in reactions with *n*-butanol and 3-methylbutan-1-ol when using Ru-MACHO[®], which is consistent with this hypothesis.

However, certain substrates were not tolerated in this reaction (**Scheme 2. 13A**). Sterically encumbered neopentyl alcohol **125** did not undergo hydrogen borrowing alkylation, instead furnishing cyclopropane **126** in 51% yield. We propose that in this case, the alkylation is slow due to the high steric demand of this alcohol and is therefore outcompeted by displacement of the leaving group, giving cyclopropane **126**. Backbone substituted cyclopropanes were not accessible *via* this method, as when substrate **124** was subjected to the optimised reaction conditions, cyclopropane **127** was isolated in 73% yield. It was suggested that adding substitution to the backbone serves to increase the rate of cyclisation *via* a Thorpe–Ingold-type effect, therefore the hydrogen borrowing alkylation step is outcompeted. A range of alcohol substrates were also unsuccessful (**Scheme 2. 13B**). Alcohols bearing proximal protected heteroatoms and proximal heterocycles, **128** – **133**, gave complex mixtures of products. It was suggested that all of these unsuccessful substrates could potentially coordinate to the metal catalyst, inhibiting its function. The aldehyde intermediate may also be unstable for some alcohols, for example, the aldehyde generated by amino alcohol **130** may be vulnerable to degradation *via* an E1cB reaction under the basic reaction conditions and the aldehyde of **133** may be particularly susceptible to self-condensation processes due to the acidity of its α -protons.

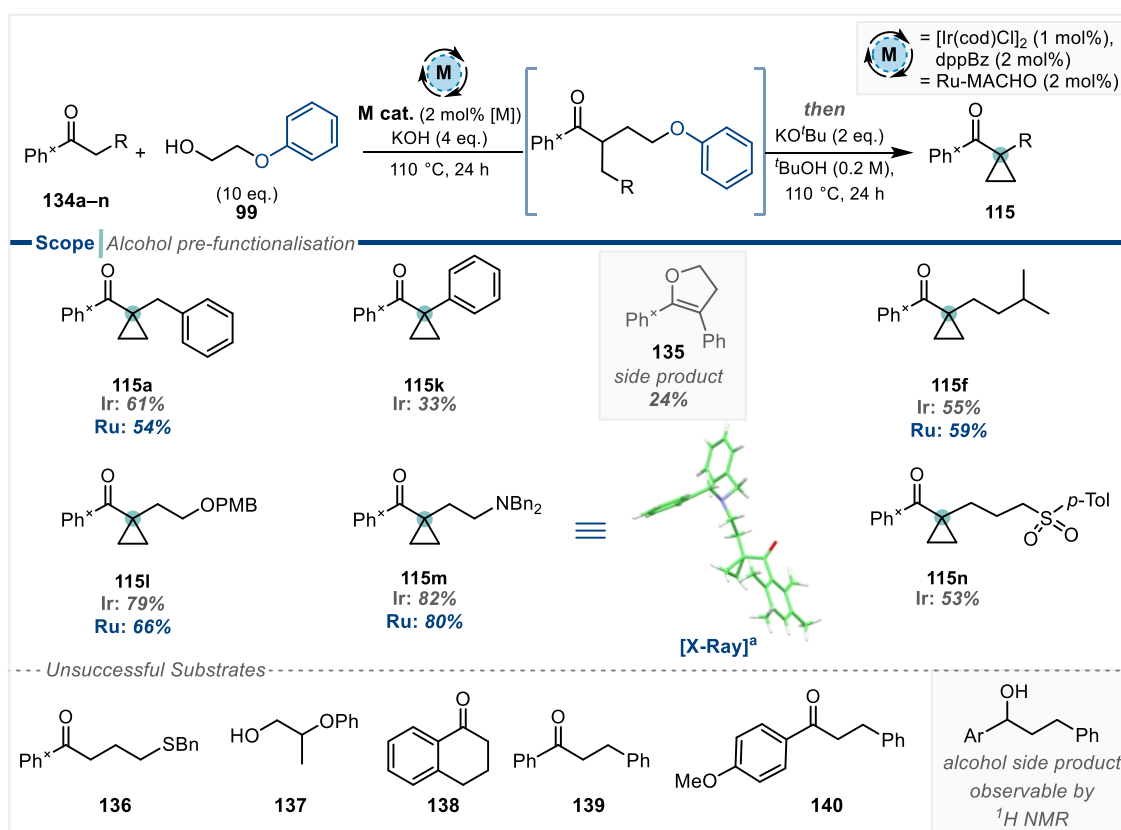


Scheme 2. 13 Unsuccessful Substrates: ketone pre-functionalisation approach.

2.8.2 Alcohol pre-functionalisation approach

Having determined the tolerance limits of the ketone pre-functionalisation approach, the substrate scope of the alcohol pre-functionalisation approach was investigated (**Scheme 2. 12**). Under the iridium-catalysed conditions, pendant phenyl groups were tolerated, giving **115a** and **115k** in 61% and 33% yield, respectively. The decrease in yield observed between these two examples reflects the increased steric congestion about the quaternary stereocentre. Indeed, an appreciable amount of side product **135** was isolated in the synthesis of cyclopropane **115k**. This product was not observed during the synthesis of any of the other examples and therefore demonstrates one way in which the system can avoid the formation of such a sterically hindered centre: by *O*-alkylation. Although the isolated yield of **115k** is low, this example illustrates the complementarity of the two approaches, as this cyclopropane does not possess the α -methylene unit which is a mechanistic necessity of the ketone pre-functionalisation approach. A ketone bearing a simple alkyl group could also be employed in this approach, giving **115f** in 55% yield. Protected heteroatoms were also tolerated, enabling the synthesis of **115l** and **115m** in 79% and 82% yield, respectively. These examples also demonstrate the complementary nature of the method, as the β -heteroatom-functionalised alcohols necessary to synthesise these molecules *via* the ketone pre-functionalised method were unsuitable substrates (see **Scheme 2. 13**). A pendant sulfone was also tolerated, giving **115n** in 53% yield. Given that the sulfone itself could

be a competent nucleophile, this result indicates that the ketone is significantly more reactive than the sulfone towards the intermediate aldehyde in the aldol step. A selection of these substrates was also subjected to the Ru-MACHO[®]-catalysed conditions. Pleasingly, similar yields were obtained for compounds **115a**, **115f**, **115l**, and **115m** using this system. It was suggested that the more consistent yields observed using this approach (c.f. the ketone pre-functionalisation approach) may be a result of the same alcohol being used in each example for this reaction, maintaining a similar solvent environment and more similar enone intermediates for the reduction step throughout all examples.



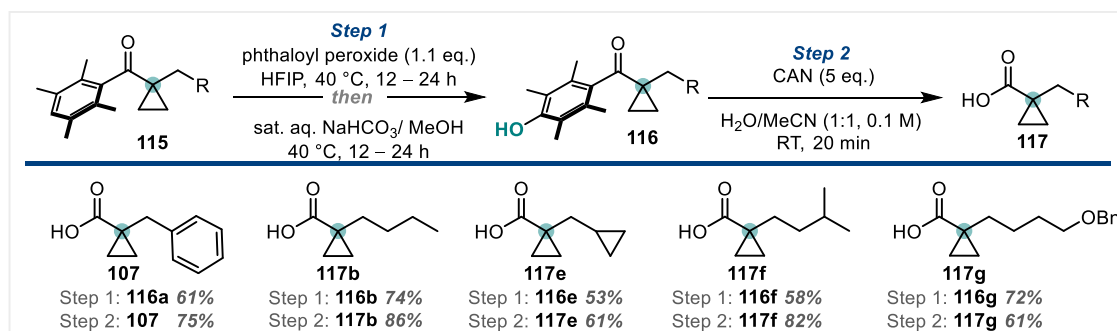
Scheme 2. 14 Alcohol pre-functionalisation scope. Reactions were carried out on a 0.30 mmol scale, isolated yields are reported. X-ray crystallography data and analysis were provided by Dr Kirsten E. Christensen^a Disorder is omitted for clarity.

A range of ketone substrates were unsuccessful in the reaction to install an α -cyclopropyl group. Thioether **136** gave a complex mixture of products when subjected to the reaction conditions, presumably a result of the –S_{Bn} substituent being a competent leaving group itself and the generated thiolate being sufficiently nucleophilic to ring-open any formed cyclopropane. Pre-functionalised alcohol **137** was also investigated in an effort to add further substitution to

the cyclopropane, this reaction gave a complex mixture of products. Simple ketones, which did not bear the key Ph^x protecting group, were also investigated. When using tetralone **138**, trace amounts of α -cyclopropyl ketone product were observed *via* ¹H NMR analysis of the crude reaction mixture. However, ketones **139** and **140** showed no conversion to product and the corresponding alcohol was observed by ¹H NMR analysis of the crude reaction mixture in each case. This demonstrates the need for the hindered Ph^x protecting group, as the *ortho*-methyl groups act to shield the carbonyl from undesirable overreduction processes.

2.9 Derivatisation

Having synthesised a range of α -cyclopropyl ketones, removal of the Ph^x protecting group was investigated, in the hope of accessing a range of useful carboxylic acid fragments (**Scheme 2. 15**). Following the two-step procedure outlined in Chapter 2.6, a range of cyclopropyl ketones **115** were oxidised to the corresponding phenols **116a – g** in 53% – 74% yield. These phenols could be oxidatively cleaved using CAN, to give the corresponding carboxylic acids **107** and **117b – g** in 61% – 86% yield. This cleavage method enabled the formation of a range of carboxylic acids from the corresponding Ph^x ketones, with retention of the cyclopropyl group.



Scheme 2. 15 Cleavage of Ph^x group to access a range of α -cyclopropyl acids.

2.10 Extension of the Method to Larger Carbocycle Synthesis

Having successfully synthesised a range of α -cyclopropyl ketones using this strategy, the extension of the method to enable the synthesis of larger carbocycles bearing quaternary stereocentres was investigated. Dr James Frost had shown that homologation of the pre-functionalised ketone starting materials while maintaining a phenoxide leaving group

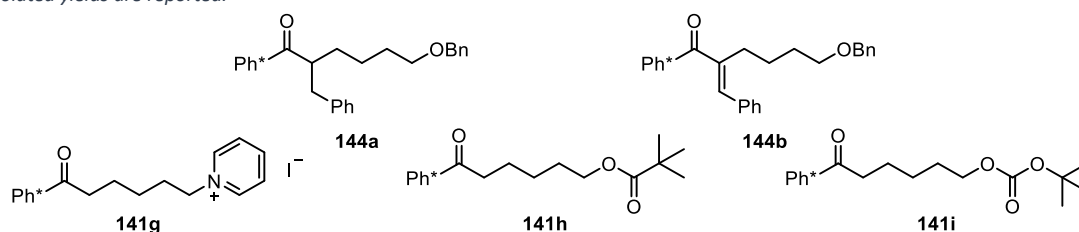
resulted in hydrogen borrowing alkylation but no leaving group displacement (see **Scheme 2. 2B**). We therefore investigated the use of a range of better leaving groups, using the pKa of the conjugate acid as a guide for leaving group ability.⁹² Given the faster rate of cyclisation for 5-membered rings compared to 4-membered rings, we decided to focus our efforts on the synthesis of cyclopentanes.¹⁰⁰ Ph* ketones were employed for these investigations, as it was hypothesised that there would be less ring strain in the desired products, enabling single-step protecting group cleavage.

Starting with the ketone pre-functionalisation approach, a range of ketones bearing different leaving groups were synthesised and subjected to the optimised reaction conditions (**Table 2. 12**). Halide leaving groups were unsuccessful, with pre-functionalised ketones **141a** and **141b** giving the cyclised product **142** in 62% and 56%, respectively (Entries 1, 2). This indicated that these leaving groups are too labile, as displacement could occur prior to hydrogen borrowing alkylation. The mesylate **141c** was also investigated, however displacement of the mesylate leaving group by the alcohol starting material formed the corresponding benzyl ether (Entry 3). This ether subsequently underwent hydrogen borrowing alkylation itself to give side products **144a** and **144b** in 36% and 14% yield. Thiophenolate leaving groups were also investigated, however these were found to be insufficiently labile, as only hydrogen borrowing products **143a** and **143b** were formed in 84% and 76% yield (Entries 4, 5). The use of sulfinate as a leaving group was also explored, however when pre-functionalised ketone **141f** was subjected to the reaction conditions, only hydrogen borrowing product **143c** was isolated in 61% yield (Entry 6). A range of other pre-functionalised ketones were also investigated, however when ketones **141g** and **141h** were employed in the reaction, a complex mixture of products was formed, including cyclised product **142**. Similarly, ketone **141i** gave a complex mixture of degradation products.

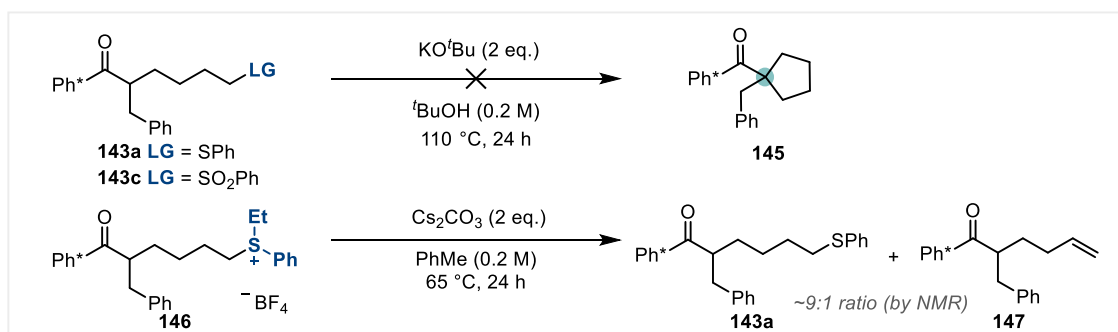
Table 2. 12 Leaving group screening to access cyclopentane products.

Entry	Substrate	LG =	Yield (%)		Side Products	
			142	143	Identity	Yield
1	141a	–Br	(62)	-	-	N/A
2	141b	–Cl	(56)	-	-	N/A
3	141c	–OMs	-	-	144a,b	(36), (14)
4	141d	–SPh	-	143a (84)	-	N/A
5	141e	–S(C ₆ H ₄)CF ₃	-	143b (76)	-	N/A
6	141f	–SO ₂ pTol	-	143c (61)	-	N/A

Isolated yields are reported.

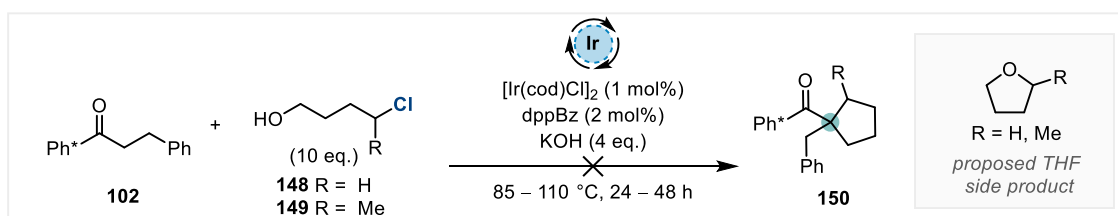


In an attempt to drive cyclisation of the hydrogen borrowing products **143** in a separate step, compounds **143a** and **143c** were treated with base (Scheme 2. 16). Unfortunately, no conversion to the desired product **145** was observed with either substrate. To further improve LG ability, the thioether was alkylated to give sulfonium salt **146**. Upon treatment with mild base, **146** gave a mixture of the thioether **143a** and alkene **147** (this was not fully characterised but identified by ¹H NMR analysis of the crude reaction mixture). Both of these products were likely formed *via* eliminations suggesting that this is an ineffective strategy to effect cyclisation.



Scheme 2.16 Attempts to drive hydrogen borrowing product cyclisation via treatment with base.

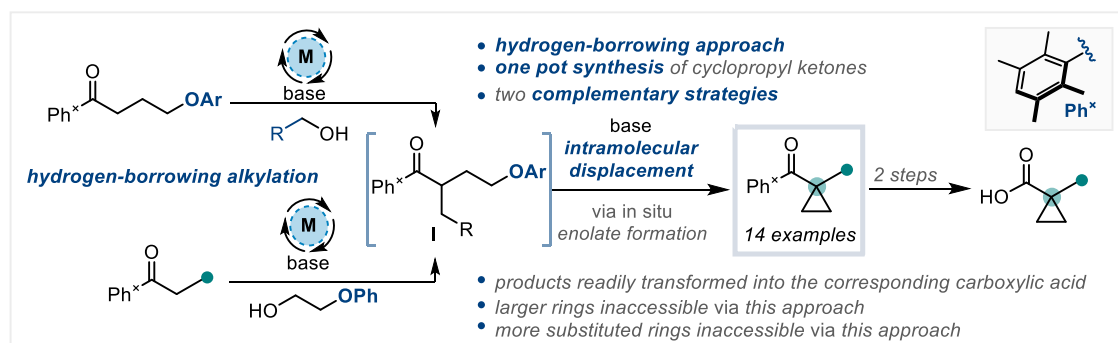
Since all attempts to form cyclopentanes *via* the ketone pre-functionalisation approach had been unsuccessful, we turned our attention to the alcohol pre-functionalisation approach. It was hypothesised that more labile leaving groups may be safely employed here, as provided cyclisation of the alcohol itself could be prevented, the hydrogen borrowing product could undergo fast cyclisation while still incorporating a quaternary centre into the final product. Therefore, 4-chlorobutan-1-ol **148** was employed as the alcohol substrate (**Scheme 2.17**) at 110 °C. Unfortunately, no cyclised product was observed, presumably as a result of alcohol cyclisation to give THF. In an effort to slow down this cyclisation, the secondary alkyl chloride **149** was employed at 85 °C. Once again, no ketone cyclisation product (**150**) was formed and 2-Me-THF was observed by ¹H NMR analysis of the crude reaction mixture as a side product. Since none of the potential leaving groups investigated had shown any conversion to the desired cyclopentane product, other approaches (described in Chapters 3 and 4) were explored in order to access larger, more complex ring systems.



Scheme 2.17 Attempts to form cyclopentanes using the alcohol pre-functionalisation approach.

2.11 Conclusion

This chapter describes the synthesis of α -quaternary ketones *via* hydrogen borrowing catalysis (**Scheme 2. 18**). The method works by hydrogen borrowing alkylation using either an iridium- or ruthenium-based catalyst to access an α -branched intermediate bearing a pendant phenoxide leaving group (I). Under the basic reaction conditions, this intermediate can cyclise *in situ* to give a cyclopropyl ketone product. Either the ketone or alcohol component of the hydrogen borrowing could be pre-functionalised with the appropriate leaving group, giving two complementary approaches to access a range of cyclopropyl ketone products. Unfortunately, this strategy could not be extended to allow access to larger rings or more substituted cyclopropanes. While the Donohoe group typically employs Ph^{*} ketone protecting groups in hydrogen borrowing reactions, in this scenario this group could not be removed without degradation of the cyclopropane. An alternative Ph^{*} protecting group was therefore used and could be removed in a two-step sequence, *via* the corresponding phenol, to access a range of α -cyclopropyl carboxylic acid fragments.



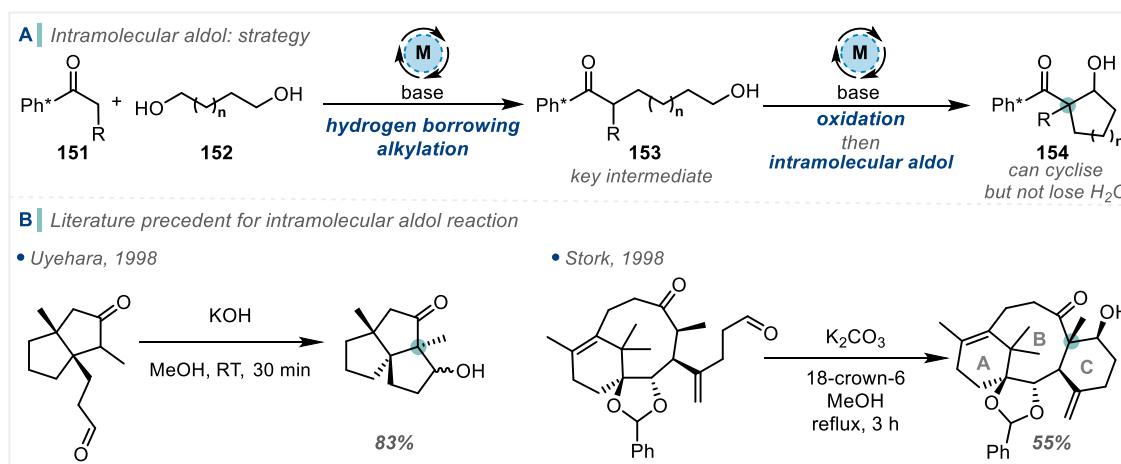
Scheme 2. 18 Summary of formation of α -quaternary ketones using an intramolecular displacement strategy.

3. Intramolecular Conjugate Addition

3.1 Introduction and Preliminary Work

3.1.1 Introduction: intramolecular aldol reaction

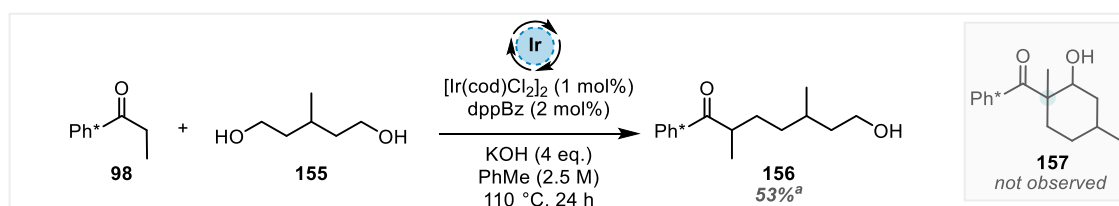
While the initial intramolecular displacement strategy for the synthesis of quaternary stereocentres had been successful for the synthesis of α -cyclopropyl ketones, several key limitations were identified. Firstly, the method could not be extended to enable the synthesis of larger carbocycles bearing quaternary stereocentres. Backbone substitution was also not tolerated, limiting the product complexity. We therefore set about investigating alternative strategies to address these issues. Our initial strategy was based upon an intramolecular aldol reaction (**Scheme 3. 1A**): it was proposed that the hydroxy ketone **153** could be accessed *via* hydrogen borrowing alkylation of a Ph* ketone **151** with a diol **152**. Under hydrogen borrowing conditions, this key intermediate could cyclise in an aldol reaction to generate a β -hydroxy ketone **154**, but would not eliminate due to the presence of the quaternary centre α -to the ketone. Although we were initially concerned about the possibility of the desired product undergoing an unwanted retro-aldol process, there were multiple examples of stable cyclic β -hydroxy ketones in the literature, notably in Stork's enantioselective synthesis of the ABC system of Taxol (**Scheme 3. 1B**).^{72, 73, 101}



Scheme 3. 1 A) Strategy for intramolecular aldol approach to quaternary stereocentres and B) literature precedent for cyclisation.

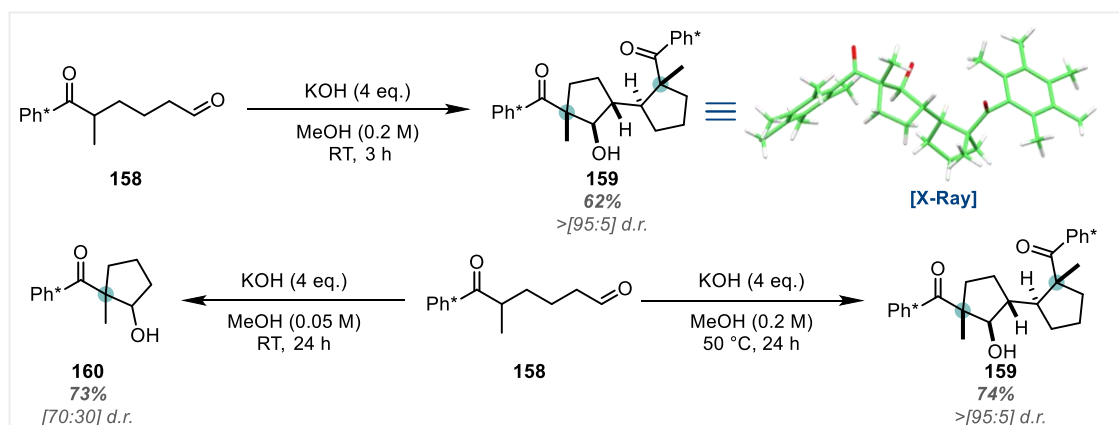
3.1.2 Preliminary work

To probe whether this approach would be successful in the context of hydrogen borrowing, Ph* ethyl ketone **98** and diol **155** were subjected to typical hydrogen borrowing conditions. (Scheme 3. 2). While no cyclic product **157** was observed, a significant amount (53%) of mono-alkylation product **156** was observed *via* ^1H NMR analysis of the crude reaction mixture, demonstrating proof-of-concept for the initial hydrogen borrowing to access the proposed key intermediate.



Scheme 3. 2 Hydrogen borrowing alkylation of ketone **98** to give proposed hydroxy ketone intermediate **156**. ^a Yield determined via ^1H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

With this result in hand, the feasibility of the cyclisation to access the desired β -hydroxy ketone product was assessed. The proposed intermediate aldehyde, **158**, was synthesised and treated with base (Scheme 3. 3). Surprisingly, the major product was identified as dimer **159**, and was formed in 62% yield as a single diastereomer. To further probe this system, the factors involved in determining the cyclisation product distribution were investigated. The desired product **160** could be accessed in 73% yield as a mixture of diastereomers at higher dilution and without the formation of dimer. The yield of dimer **159** could be improved to 74% by increasing the reaction temperature, suggesting that this product was thermodynamically favoured.



Scheme 3. 3 Cyclisations of aldehyde **158**. X-ray crystallography data and analysis were provided by Dr. Kirsten E. Christensen.

This suggested that the distribution of products could be affected by whether the system was operating under kinetic or thermodynamic control. To investigate this hypothesis, a small amount of β -hydroxy ketone **160** was resubjected to the reaction conditions at different temperatures (**Table 3. 1**). At room temperature, the simple β -hydroxy ketone was retained, though evidence for ring opening *via* a retro-aldol process was observed: aldehyde **158** was identified in 20% ^1H NMR yield and the β -hydroxy ketone was formed in 74% ^1H NMR yield and in [70:30] d.r. However, when **160** was resubjected at 60 °C, the only product observed was dimer **159**, which was formed in 28% ^1H NMR yield. The low yield observed here likely reflects the importance of reaction concentration for dimer formation. Given that at higher temperatures and reaction concentrations dimer **159**, and not β -hydroxy ketone **160**, was favoured, it was suggested that this approach would not be compatible with hydrogen borrowing catalysis, which typically requires high temperatures and concentrated reactions.³ Therefore, the intramolecular aldol approach was not pursued further.

Table 3. 1 Re-subjection experiment.

Entry	Temperature (°C)	Yield (%) ^a		
		158	160	159
1	RT	20	74 ([70:30] d.r.)	-
2	60	-	-	28 (>[95:5] d.r.)

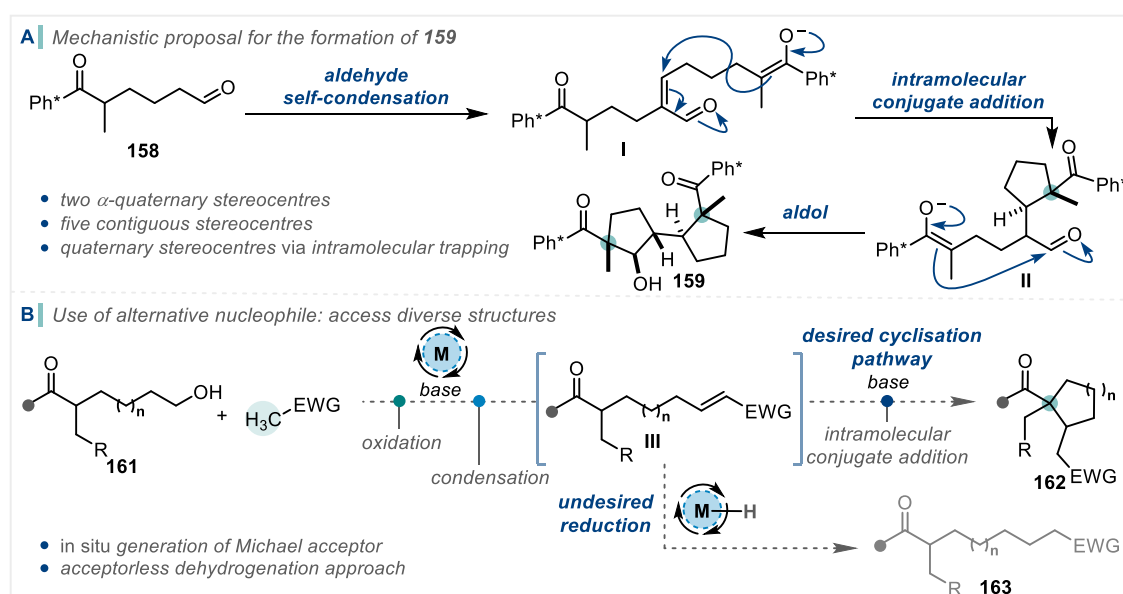
^a Yield determined via ^1H quantitative NMR using 1,1,1,2-tetrachloroethane as an internal standard.

3.1.3 Mechanistic considerations

Although the intramolecular aldol approach was deemed incompatible with typical hydrogen borrowing conditions, we were intrigued by the formation of dimer **159**. This compound was formed with high diastereoselectivity, despite containing two α -quaternary stereocentres and five contiguous stereocentres. It was proposed that dimer **159** could be formed *via* the following pathway: aldehyde **158** could undergo self-condensation to form intermediate **I** (**Scheme 3. 4A**).

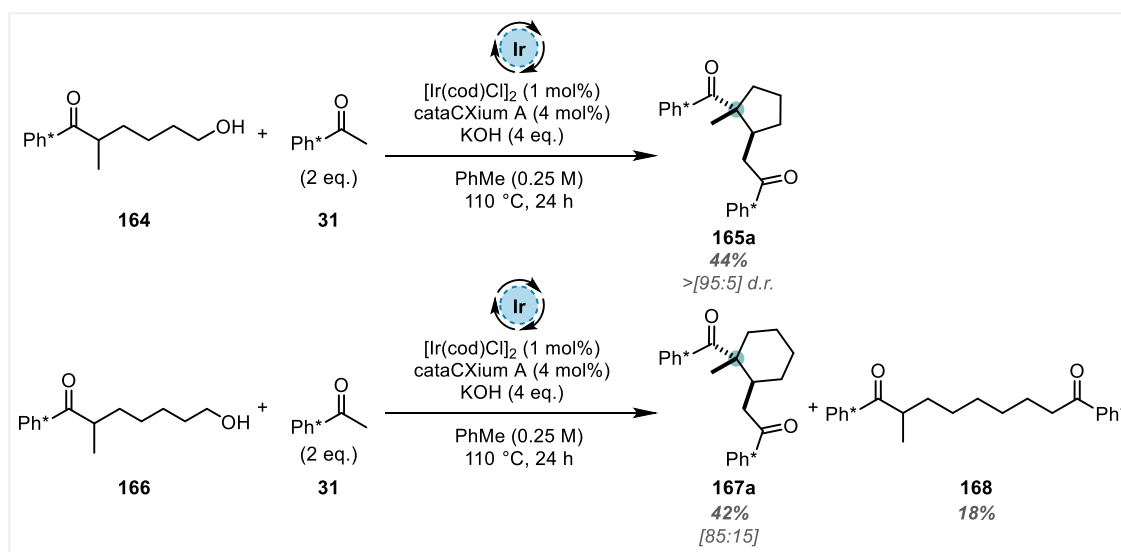
The formed Michael acceptor (intermediate **I**) could then be intercepted by the enolate in a *5-exo-trig* fashion to give intermediate **II**, which could cyclise *via* aldol reaction to give the β -hydroxy ketone motif observed in **159**.

While it was noted that compound **159** was of limited utility, it was hypothesised that the intrinsic reactivity of these substrates could be harnessed with the addition of an additional nucleophile (**Scheme 3. 4B**). Under hydrogen borrowing conditions, a hydroxy ketone **161** could be oxidised to give the corresponding aldehyde in low concentrations, this could condense with an appropriate nucleophile to give a Michael acceptor, **III**, *in situ*. Under the basic conditions of the reaction, it was proposed that this intermediate could undergo *5-exo-trig* cyclisation to give **162**, bearing an α -quaternary stereocentre. It was noted that intermediate **III** could also be reduced by the metal hydride to give acyclic side product **163**. We proposed that the use of an intramolecular nucleophile (here a tethered enolate) for the conjugate addition step would enable the cyclisation to outcompete the intermolecular reduction process and thereby prevent the formation of acyclic side product **163**. As hydrogen is not returned to the molecule in the desired cyclisation pathway, this is a net oxidative approach and would therefore be an example of an acceptorless dehydrogenative coupling.



Scheme 3. 4 A) Mechanistic proposal for formation of dimer **159**. B) Strategy for synthesis of quaternary stereocentres via intramolecular conjugate addition.

To assess the feasibility of this approach within the hydrogen borrowing manifold, hydroxy ketone **164** and Ph* methyl ketone **31** were subjected to acceptorless dehydrogenation conditions similar to those previously used in the group for the formation of cyclohexenes (Scheme 3. 5).⁵¹ Pleasingly, α -quaternary ketone **165a** was formed in 44% yield with high diastereoselectivity, demonstrating proof-of-concept for this approach. This approach could also be used to synthesise cyclohexane **167a** in 42% yield by employing the homologous starting material **166**, although some (18%) of the acyclic side product **168** was also isolated.



Scheme 3. 5 Proof-of-concept for the formation of quaternary stereocentres via intramolecular conjugate addition using acceptorless dehydrogenation.

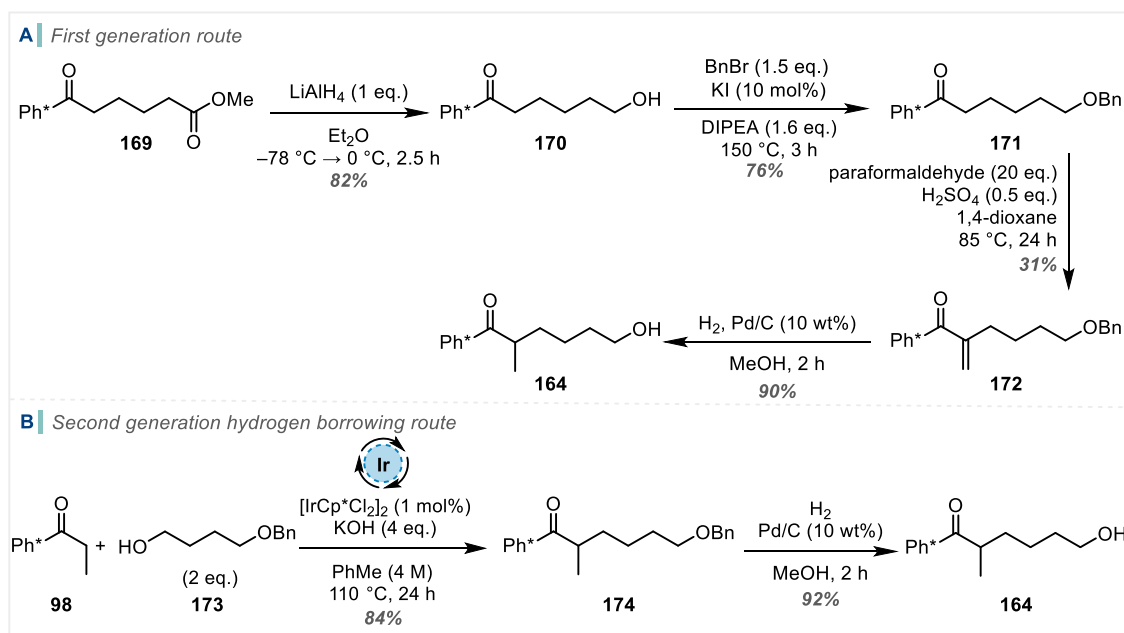
3.2 Project Aims

At the outset of this project, we aimed to develop the acceptorless dehydrogenation–intramolecular conjugate addition cascade reaction in order to address the key limitations of the previous approach (see Chapter 2). In this way, we hoped to access a wide range of complex carbocycles bearing α -quaternary stereocentres. It was proposed that the process could be made more efficient by using a sterically encumbered catalyst to prevent reduction of the key Michael acceptor intermediate and therefore hinder the formation of the acyclic side product.

3.3 Synthesis of Linear Hydroxy Ketones

The synthesis of hydroxy ketone **164** was initially carried out using hydroxy ketone **170**, which had been prepared *via* Friedel–Crafts acylation (to give keto-ester **169**) and subsequent

chemoselective reduction for investigation of the intramolecular displacement approach (**Scheme 3. 6A**). Benzylation of this alcohol proceeded in 76% yield to give **171**, which then underwent an aldol reaction with paraformaldehyde to give enone **172**. The enone was reduced alongside removal of the benzyl group to give the desired starting material **164** in 90% yield. While this route enabled the formation of **164**, the low yield obtained for the aldol step severely limited the amount of material that could be prepared *via* this route. Therefore, we investigated the preparation of starting material **164** using hydrogen borrowing catalysis. This strategy was very attractive as, combined with the intramolecular conjugate addition reaction, it would enable the synthesis of complex fragments from simple starting materials in only a few steps *via* hydrogen borrowing catalysis and related methods. Pleasingly, Ph* ethyl ketone **98** and mono-protected diol **173** underwent hydrogen borrowing alkylation to give α -branched ketone **174** in 84% yield (**Scheme 3. 6B**). The benzyl protecting group could then be removed *via* hydrogenation to give **164** in high yield. This modular and scalable route could be employed for the synthesis of a diverse range of hydroxy ketone substrates that contained Ph* ketone protecting groups. Although the first-generation route was not used for the synthesis of the majority of Ph* ketone substrates investigated, it could be employed when hydrogen borrowing alkylation could not be used, for example when preparing 5-hydroxy ketones (here the corresponding mono-protected 1,3-diol would be susceptible to E1cB at the aldehyde stage in the hydrogen borrowing reaction).



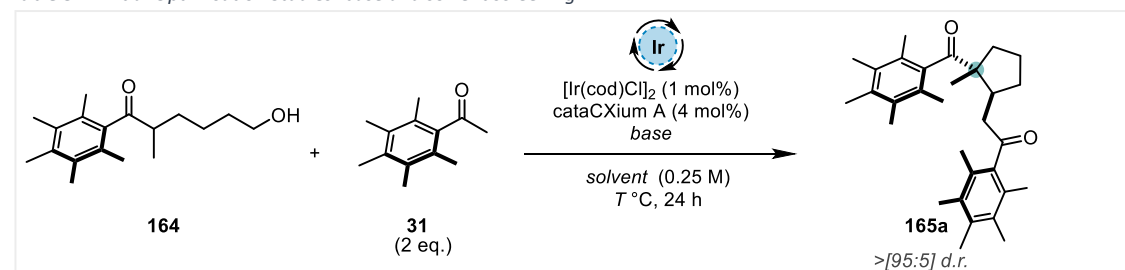
Scheme 3. 6 Starting material synthesis: A) First generation route, B) Second generation route using hydrogen borrowing.

3.4 Optimisation I

Having demonstrated proof-of-concept for the formation of quaternary stereocentres *via* an acceptorless dehydrogenation–intramolecular conjugate addition cascade, we set about optimising the process (**Table 3. 2**). Hydroxy ketone **164** and Ph* methyl ketone **31** were employed in a model system as the substrate and nucleophile, respectively. Lowering the reaction temperature to 85 °C was detrimental to the reaction (Entry 2), which is consistent with the literature as many acceptorless dehydrogenation reactions are carried out at high temperature to drive the release of H₂(g).¹⁰² The identity of the base also proved to be influential on the yield; bases with a sodium counterion, NaOH and NaO^tBu, resulted in limited formation of product **165a** (Entries 3, 4), while using KO^tBu gave a comparable yield to KOH (Entry 5, 61%). Here, we suggest that using bases with a potassium counterion favours product formation due to the enolate being less tightly bound and therefore more reactive. Both of these bases were therefore screened using ^tBuOH as the solvent (Entries 6, 7). It was found that switching to this solvent gave a much cleaner reaction, giving **165a** in 53% isolated yield when using KOH as the base (Entry 6). However, using KO^tBu as the base in combination with ^tBuOH as the solvent gave a large improvement in yield, forming **165a** in 88% isolated yield. Despite having greater

solubility in t BuOH, NaO^tBu still gave poor conversion of starting material (Entry 8). It should be noted that high diastereoselectivity, $>[95:5 \text{ d.r.}]$, was observed in all optimisation reactions.

Table 3. 2 Initial Optimisation Studies: base and solvent screening.



Entry	Base (eq.)	Solvent	Temperature (°C)	Yield (%) ^a	
				164	165a
1	KOH (4)	PhMe	110	-	58 (44)
2	KOH (4)	PhMe	85	45	13
3	NaOH (4)	PhMe	110	14	8
4	NaO^tBu (4)	PhMe	110	42	8
5 ^b	KO^tBu (4)	PhMe	110	9	61
6	KOH (4)	t BuOH	110	-	56 (53)
7 ^b	KO^tBu (4)	t BuOH	110	-	82 (88)
8	NaO^tBu (4)	t BuOH	110	39	23

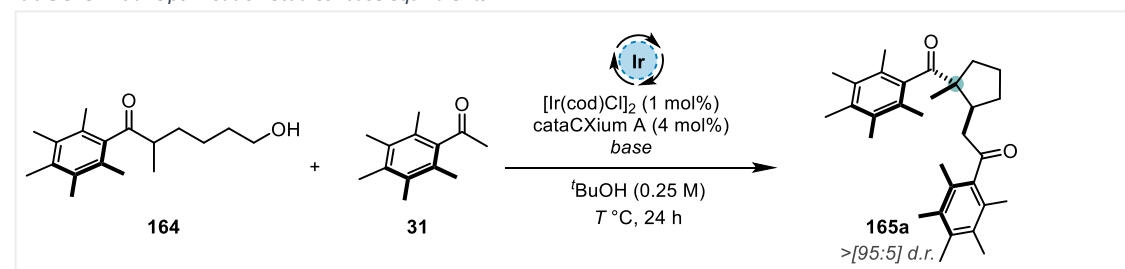
^a Yield determined using ^1H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b KO^tBu 95% (Sigma Aldrich) Lot: S44188-387.

At this point, it was observed that the results using KO^tBu were not reproducible when using different batches of KO^tBu of the same grade; similar irreproducibility issues had been encountered previously by other students in the group when using this base.^{103, 104} The 95% grade had also been recently discontinued by Sigma Aldrich, therefore a more permanent source of KO^tBu needed to be identified. When four equivalents of KO^tBu (99.99% grade, trace metals basis) was employed in the reaction, the reaction did not give full conversion (**Table 3. 3**, Entry 1). We propose that the difference between the two grades of KO^tBu is due to the major form present in the solid state. When KO^tBu is synthesised using excess t BuOH, a highly soluble alcohol adduct, $[\text{KO}^t\text{Bu} \cdot t\text{BuOH}]_\infty$ is formed, which adopts a ribbon-like one-dimensional chain in the solid state.¹⁰⁵ However, after further purification by sublimation, the KO^tBu exists as tetramer in a cubane-like structure, $[\text{KO}^t\text{Bu}]_4$. We hypothesise that the 95% grade contains the

more soluble $[\text{KO}^t\text{Bu}\cdot^t\text{BuOH}]_\infty$ and therefore is more effective than the 99.99% grade, which was prepared *via* sublimation by the supplier and therefore contains the tetramer. In an effort to improve the solubility of the KO^tBu (99.99% grade), we investigated decreasing the equivalents of this base. While decreasing amount of base to three equivalents reduced the conversion of starting material **164** to the desired product **165a** even further (Entry 2), using two equivalents gave an improved isolated yield of 74% (Entry 3). Further decreasing the equivalents of base to one equivalent resulted in a decrease in yield (Entry 4). Although it was not possible to completely reproduce the original result when using the 99.99% KO^tBu, we decided to use this base in further optimisation as it gave reproducible results, therefore all further reference to KO^tBu in this thesis refers to the 99.99% grade.

In an effort to ease the purification of the reaction, we next investigated the effect of decreasing the equivalents of nucleophile **31**. Decreasing the equivalents of **31** to 1.5 equivalents initially seemed to offer an improved yield of **165a** (Entry 5a), however this result was shown to be irreproducible (Entry 5b). The addition of norbornene as a sacrificial hydride acceptor was also investigated in an effort to encourage greater turnover (Entry 6), in the hope of improving reproducibility. However, this proved detrimental to the yield of **165a**. Increased temperature has also been shown to favour hydrogen evolution, therefore, the reaction temperature was increased to 115 °C.^{102, 106} Pleasingly, this gave product **165a** in a reliable yield of 80%.

Table 3. 3 Initial Optimisation Studies: base equivalents.



Entry	Equivalents 31	Base (eq.)	Temperature (°C)	Yield (%) ^a	
				164	165a
1	2	KO ^t Bu (4)	110	41	44
2	2	KO ^t Bu (3)	110	57	16
3	2	KO ^t Bu (2)	110	-	72 (74)
4	2	KO ^t Bu (1)	110		(66)
5a	1.5	KO ^t Bu (2)	110		83 (85)
5b	1.5	KO ^t Bu (2)	110	62	13
6 ^b	1.5	KO ^t Bu (2)	110	64	22
7	1.5	KO ^t Bu (2)	115	-	70 (80) ^c

KO^tBu refers to KO^tBu 99.99% (Sigma Aldrich) ^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b norbornene (2 eq.) added to reaction. ^c A repeat of this result yielded product **165a** in 83% yield.

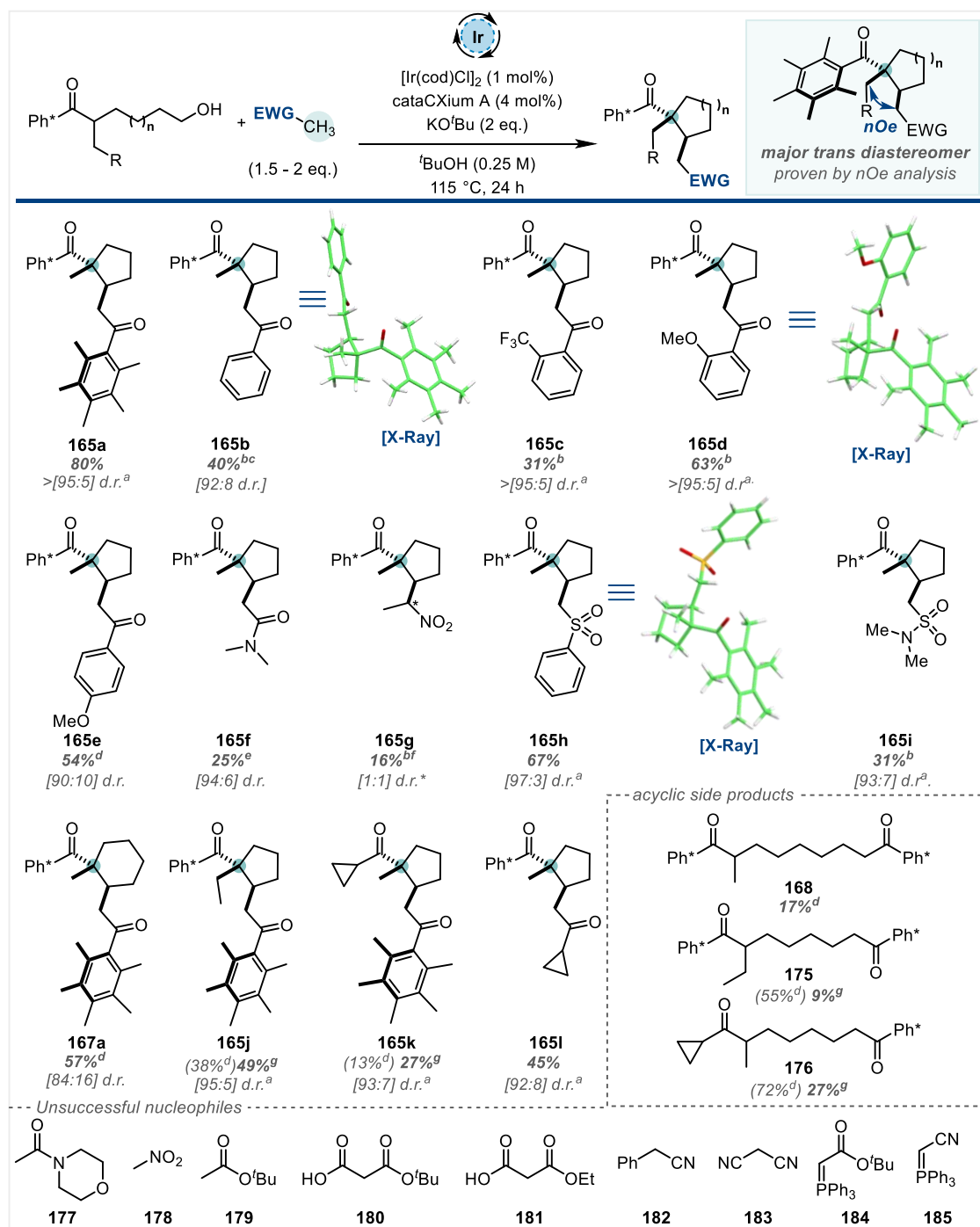
3.5 Preliminary Substrate Scope

With the optimised reaction conditions in hand, we examined the preliminary scope of the transformation (**Scheme 3. 7**). Less hindered acetophenones bearing a range of different substituents were tolerated as nucleophiles, giving diketones **165b – e** in 31% – 63% yield. The reduced yield in these examples compared to the reaction using Ph* methyl ketone to give **165a** can be attributed to overreduction of the ketone nucleophile prior to reaction, however, the corresponding overreduction of the products was not observed. An amide nucleophile was also investigated, this resulted in limited conversion to **165f**, giving 25% isolated yield.* The strategy was also applied to a known catalytic system for the formation of nitroalkenes *via* acceptorless dehydrogenation, developed by Williams and co-workers.¹⁰⁷ The desired nitroalkane product

* It was later found that these conditions gave irreproducible results with a variety of ketone nucleophiles. After further optimisation to give reproducible yields with Ph* ketones (*vide infra*), the newly optimised conditions could not be employed to give products with unhindered aryl ketone or amide nucleophiles in comparable yields to those obtained using this method (**Scheme 3.7**). The scope of the reaction when using the updated conditions will be discussed in Chapter 3.7.

165g was isolated in 16% yield, however no stereocontrol was observed at the exocyclic stereocentre. Sulfur-based nucleophiles were also successful substrates, with methyl phenyl sulfone giving product **165h** in 67% yield and *N,N*-dimethylmethanesulfonamide giving the corresponding product **165i** in 31% yield. All α -quaternary ketone products were formed with high diastereoselectivity; at this stage we tentatively proposed that this was a result of the reaction being under thermodynamic control to give the most stable *trans*-product, which was assigned using nOe and single crystal X-ray analysis, where possible.

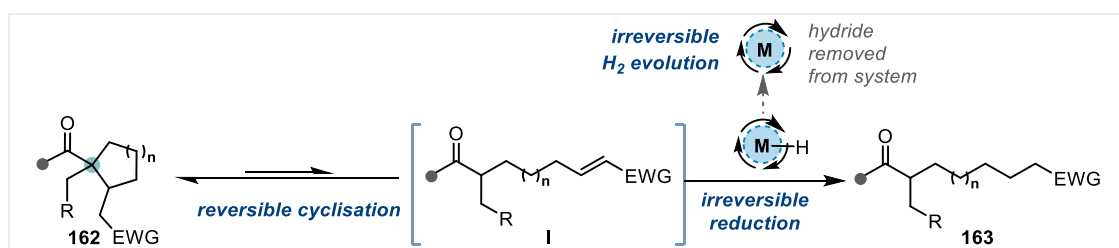
However, a variety of nucleophiles were not tolerated. Despite the successful synthesis of **165f** using *N,N*-dimethylacetamide, using morpholine amide **177** as the nucleophile gave a complex mixture of reaction products. Although nitroethane was successfully employed in the synthesis of **165g**, nitromethane **178** gave a complex mixture, possibly as a result of unwanted Nef-type reactivity in any cyclic product formed. Ester **179** and ester enolate precursors **180** and **181** also proved unsuitable nucleophiles, and nitriles **182** and **183** were also unsuccessful substrates. In a related approach, we investigated alternative reactions of the intermediate aldehyde to generate the necessary Michael acceptor. Inspired by the indirect Wittig reaction developed by Williams and co-workers, phosphonium ylides **184** and **185** were investigated as nucleophiles, however, these reactions gave complex mixtures of products.¹⁰⁸



Scheme 3. 7 Preliminary Substrate Scope. Reactions carried out on 0.30 mmol scale unless otherwise stated, major isomer shown for clarity. Isolated yields are reported. X-ray crystallography data and analysis were provided by Dr. K. E. Christensen and Timothy C. Jenkins. ^a d.r. determined post-purification due to overlapping peaks, ^b yield of isolated major trans-diastereomer(s) reported. Deviation from stated conditions as follows: ^c Base: KOH (2 eq.), Solvent: PhMe; ^d Base: KOH (4 eq.), Solvent: PhMe; ^e Solvent: PhMe; ^f Catalyst: Ru(PPh₃)₃(CO)H₂ (2.5 mol%), Ligand: XantPhos (2.5 mol%), Base Replacement: Piperidinium Acetate (1 eq.), crotononitrile (2 eq.), Solvent: PhMe; ^g Ligand: PAd₃, Base: KOH (4 eq.), Solvent: PhMe.

The effect of backbone modification was also investigated (**Scheme 3. 7**), and it was found that when the homologous hydroxy ketone starting material was employed, cyclohexane **167a** was formed in 57% yield, however acyclic side product **168** (17%) was also isolated. We suggest that the differing amounts of reduced side product formed is the result of a delicate balance of

factors (**Scheme 3. 8**). Firstly, given that we have shown the cyclisation of the key Michael acceptor intermediate **I** is reversible (see Chapter 3.8), and assuming that the rate of reduction for both intermediate acyclic Ph* enones is approximately equal, the relative concentration of the Michael acceptor at equilibrium should determine the relative amount of side product formed by reduction from the metal hydride. Therefore, if the position of equilibrium is further towards the cyclised product **162** for the 5-membered ring, relative to the 6-membered ring, less of the acyclic side product **163** is formed because there will be less enone to reduce *in situ*. In addition, the opportunity to reduce any enone present is temporary because evolution of hydrogen gas from the metal hydride over the course of the reaction reduces the amount of [M-H] present, thus resulting in less reduction of intermediate **I**.

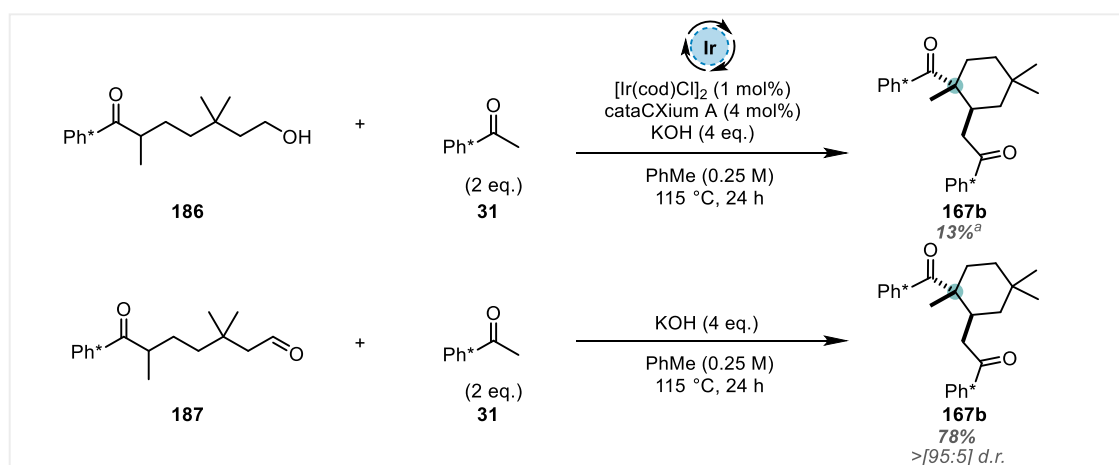


Scheme 3. 8 Factors governing the formation of the acyclic side product.

A larger, ethyl group was also tolerated in the reaction, giving compound **165j** in 38% yield (**Scheme 3.7**). The Ph* protecting group could also be replaced by a cyclopropyl ketone in either the hydroxy ketone substrate or the nucleophile, giving products **165k** and **165l** in 13% and 45%, respectively. For the reactions forming diketones **165j** and **165k**, significant amounts of acyclic side products **175** and **176** (55% and 72%, respectively) were also formed. Again, we suggest that the cyclised form is less favoured for these substrates, possibly as a result of increased steric hindrance in the cyclised products **165j** and **165k**, thus increasing the concentration of the Michael acceptor at equilibrium, allowing more reduction to give **175** and **176**, respectively. As the position of equilibrium for a given substrate cannot be easily controlled, we investigated ways in which the reduction of the intermediate Michael acceptor might be impeded. It was found that the product distribution could be shifted towards the desired cyclic products **165j** and **165k** by employing the very sterically encumbered ligand PAd₃ to hinder reduction of the

intermediate Michael acceptor and so encourage hydrogen evolution. This modification successfully reduced the amount of acyclic side products **175** (9%) and **176** (27%) formed, resulting in the formation of cyclic products **165j** and **165k** in 49% and 27% yield, respectively, representing a modest improvement.

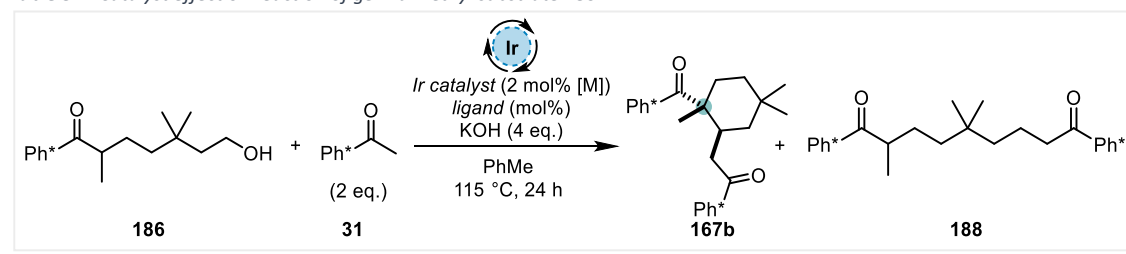
Having investigated the preliminary scope of the transformation, we aimed to further improve the method to give higher yields with a wider range of substrates under a more general set of reaction conditions (see **Scheme 3. 7**). Hoping to improve the yield by taking advantage of the Thorpe–Ingold Effect to favour the cyclised form, hydroxy ketone substrate **186** was synthesised and subjected to the optimised reaction conditions for the formation of **167a** (**Scheme 3. 9**).⁵⁴ Surprisingly, the cyclised product **167b** was formed in only 13% ¹H NMR yield (c.f. unsubstituted cyclohexane **167a** which was obtained in 57% yield under the same conditions). To probe whether the cyclisation itself was high yielding, the proposed intermediate aldehyde **187** was synthesised and subjected to the reaction conditions, in the absence of catalyst. Pleasingly, the aldehyde underwent aldol reaction with the ketone nucleophile and subsequent intramolecular conjugate addition to give the desired product **167b** in 78% isolated yield. It was therefore proposed that the hindered nature of the [Ir(cod)Cl]₂/cataCXium® A catalytic system was incompatible with the *gem*-dimethyl group on the substrate backbone, impeding initial substrate oxidation.



Scheme 3. 9 Cyclisation reactions to give *gem*-dimethyl substituted product **167b**. ^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Therefore, we investigated the effect of using the less hindered $[\text{IrCp}^*\text{Cl}_2]_2$ catalyst in combination with this substrate (**Table 3. 4**). Unfortunately, no improvement was seen when using $[\text{IrCp}^*\text{Cl}_2]_2$ compared to the more sterically encumbered catalytic system (Entries 1, 2). However, when the reaction mixture was concentrated to 4.0 M, the yield of cyclised product **167b** doubled to 26%. The acyclic product **188** was not observed under any of these reaction conditions, despite concentrated reaction conditions typically favouring the reduction of enone intermediates.⁵¹ It was therefore proposed that the *gem*-dimethyl group was having the desired effect of increasing cyclisation, however this did not result in increased or viable yield due to slow oxidation by the metal catalyst.

Table 3. 4 Catalyst effect on reaction of *gem*-dimethyl substrate **186**.



Entry	Catalyst	Ligand (mol%)	Reaction Concentration (M)	Yield (%) ^a	
				167b	188
1	$[\text{Ir}(\text{cod})\text{Cl}]_2$	cataCXium® A (4)	0.25	13	-
2	$[\text{IrCp}^*\text{Cl}_2]_2$	-	0.25	12	-
3	$[\text{IrCp}^*\text{Cl}_2]_2$	-	4.0	26	-

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

3.6 Optimisation II

3.6.1 Optimisation of cyclohexane synthesis

At this point, it was decided to focus further optimisation efforts on the formation of simple cyclohexane **167a**. We initially investigated the use of hydride acceptors to prevent the formation of side product **168** *via* reduction of the enone intermediate (**Table 3. 5**). This transfer hydrogenation approach had been well explored in the literature for the oxidation of primary and secondary alcohols.^{107, 109-111} The less hindered $[\text{IrCp}^*\text{Cl}_2]_2$ catalytic system was used for this study, as the aim was to encourage faster reduction of the hydride acceptors compared to the enone intermediate; this catalyst was therefore employed in the absence of a hydride acceptor

as a control experiment, giving 28% cyclised product **167a** and 10% acyclic side product **168** (Entry 1). Using benzoquinone as a hydride acceptor completely prevented catalytic activity, giving only 71% starting material (Entry 2). Employing either *tert*-butyl ethene or crotononitrile offered no improvement on the yield of cyclic product **167a** compared to the control (Entries 3,4), with the reaction using crotononitrile giving a greater proportion of the undesired acyclic hydrogen borrowing product **168** (31%, Entry 4). Given that the yields of cyclised product were less than those obtained using the acceptorless dehydrogenation strategy (using a sterically hindered catalytic system), this approach was not pursued further.

Table 3. 5 Investigation of hydride acceptors.

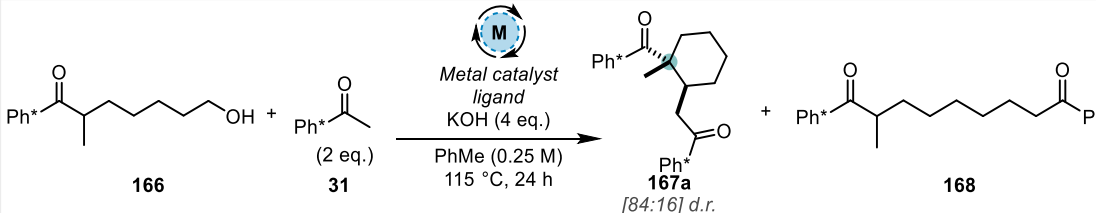
Entry	Hydride Acceptor	Yield (%) ^a		
		166	167a	168
1	none	24	28	10
2	benzoquinone	71	-	-
3	<i>tert</i> -butyl ethene	46	22	4
4	crotononitrile	32	30	31

^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. The d.r. of the product **167a** was not determined.

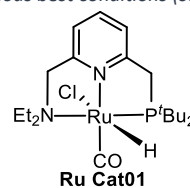
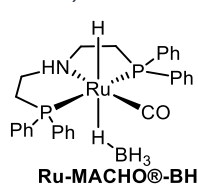
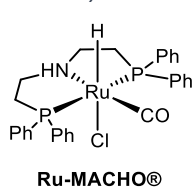
We instead turned our attention to the further optimisation of the acceptorless dehydrogenation strategy. A variety of different catalytic systems were investigated (Table 3. 6). Doubling the ligand loading resulted in reduced conversion to the desired product **167a**, potentially as a result of greater catalyst saturation with the ligand, preventing binding of the hydroxy ketone substrate **166** for oxidation (Entry 2). Similar phosphine ligands bearing alternative large groups were also investigated; while P^tBu₃ gave a similar isolated yield to the cataCXium® A system (58%, Entry 3), using isosteric PAd₃ as a ligand gave a marked decrease in formation of the desired product **167a** (32%, Entry 4).^{112, 113} The effect of alternative metal

precatalysts was also investigated. Using either $[\text{Rh}(\text{cod})\text{Cl}]_2$ or $[\text{Ru}(\text{cod})\text{Cl}]_n$ resulted in decreased conversion of starting material **166**, giving cyclised product **167a** in only 22% and 21%, respectively (Entries 5, 6). Ru-MACHO® and Ru-MACHO®-BH were found to give exclusively the acyclic side product **167a** in 35% and 80% yield, respectively (Entries 7, 8). Similarly, Milstein's catalyst **Ru Cat01** gave only the acyclic side product **168** in 70% yield (Entry 9); this was somewhat surprising given that this catalyst was originally employed by Milstein and co-workers for the acceptorless dehydrogenation of primary alcohols to give esters.¹¹⁴

Table 3. 6 Catalyst screen for the synthesis of cyclohexane **167a**.

					
Entry	M Catalyst (mol%)	Ligand (mol%)	Yield (%) ^a		
			166	167a	168
1	$[\text{Ir}(\text{cod})\text{Cl}]_2$ (1)	cataCXium® A (4)	17	55 (57)	15 (17)
2	$[\text{Ir}(\text{cod})\text{Cl}]_2$ (1)	cataCXium® A (8)	52	30	2
3	$[\text{Ir}(\text{cod})\text{Cl}]_2$ (1)	P^tBu_3 (4)	12	63 (58)	11
4	$[\text{Ir}(\text{cod})\text{Cl}]_2$ (1)	PAd_3 (4)	35	32	2
5	$[\text{Rh}(\text{cod})\text{Cl}]_2$ (1)	cataCXium® A (4)	45	22	2
6	$[\text{Ru}(\text{cod})\text{Cl}]_n$ (2)	cataCXium® A (4)	35	21	13
7	Ru-MACHO® (2)	-	-	-	35
8	Ru-MACHO®-BH (2)	-	-	-	80
9	Ru Cat01	-	-	-	70
10	$\text{Ir}(\text{cod})\text{acac}$ (2)	cataCXium® A (4)	8	69 (72)	10 (11)
11	$\text{Ir}(\text{cod})\text{acac}$ (4)	cataCXium® A (8)	5	69	13
12 ^b	$\text{Ir}(\text{cod})\text{acac}$ (2)	cataCXium® A (4)	6	43	6

^a Yield determined via ^1H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b 1.5 eq. of Ph^* methyl ketone **31** employed. Entry 1 indicates the previous best conditions (see Scheme 3. 7).



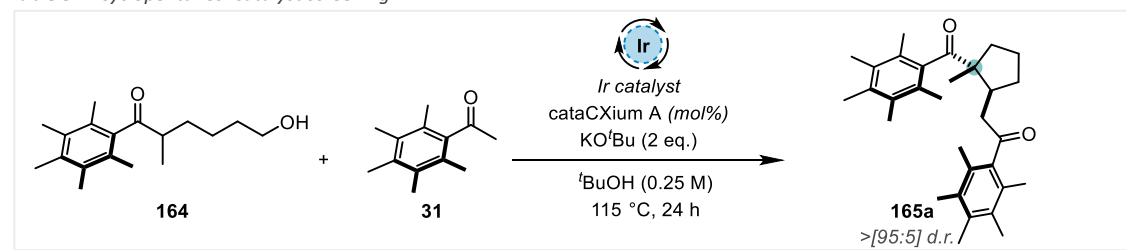
Since none of the other metals investigated offered any improvement on the iridium-catalysed system, an alternative iridium precatalyst, Ir(cod)acac, was investigated. Pleasingly, this gave a small improvement and product **167a** was isolated in 72% yield (**Table 3. 6**, Entry 10). Doubling the loading of this catalytic system offered no further improvement (Entry 11) and decreasing the equivalents of nucleophile resulted in the formation of **167a** in only 43% yield and significant decomposition of starting material (Entry 12). We propose that this may be due to the intermediate aldehyde being prone to decomposition, therefore using a larger excess of **31** increases the nucleophile concentration, shortening the lifetime of this intermediate prior to productive aldol condensation. As a result of this optimisation, the Ir(cod)acac system (Entry 10) was employed for the synthesis of cyclohexanes using ketone nucleophiles moving forwards.

3.6.2 Reproducibility issues in cyclopentane synthesis

In optimising the synthesis for cyclohexane **167a**, it was found that using an alternative iridium precatalyst, Ir(cod)acac, offered an improved yield (see **Table 3. 6**). Therefore, this catalytic system was screened in the reaction to make cyclopentane **165a** (**Table 3. 7**). While using the Ir(cod)acac system initially seemed to give a decrease in yield compared to the optimised conditions (Entry 2a), this result was shown to be very irreproducible (Entries 2a – 2d). Switching back to the [Ir(cod)Cl]₂ system using two equivalents of ketone **31** as the nucleophile, it was found that the previously isolated yield of 74% (Entry 3a) could not be replicated, and product **165a** was formed in only 20% yield (Entry 3b). Using Ir(cod)acac in combination with two equivalents of nucleophile gave similarly low yields (Entry 4). After extensive optimisation (see **Appendix I**), it was found that changing the catalyst and ligand loading was able to give more reliable yields (Entries 5 – 7). Doubling the catalyst loading gave **165a** in 59% yield, however the acyclic side product **189** was isolated in 40% yield (Entry 5). In an effort to impede reduction of the key enone intermediate and therefore suppress the formation of the side product **189**, the ligand loading was increased (Entries 6, 7a, 7b). It was found that using a higher ligand loading of 16 mol% improved the yield, giving the desired product **165a** in a reliable yield of

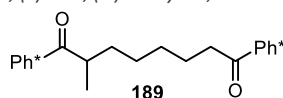
approximately 67% (averaged over two runs, see Entries 7a, b). Therefore, these conditions were employed for the future synthesis of cyclopentanes using ketone nucleophiles.

Table 3. 7 Cyclopentanes: catalyst screening.



Entry	Eq. 31	Ir catalyst (mol%)	Ligand Loading (mol%)	Yield (%) ^a	
				164	165a
1	1.5	[Ir(cod)Cl] ₂ (1)	4	-	70 (80)
2a	1.5	Ir(cod)acac (2)	4	-	75 (69)
2b	1.5	Ir(cod)acac (2)	4	37	37
2c	1.5	Ir(cod)acac (2)	4	50	26
2d	1.5	Ir(cod)acac (2)	4	51	15
3a	2	[Ir(cod)Cl] ₂ (1)	4	-	72 (74)
3b	2	[Ir(cod)Cl] ₂ (1)	4	43	20
4	2	Ir(cod)acac (2)	4	61	23
5	2	Ir(cod)acac (4)	8	-	59 (59) ^{b(i)}
6	2	Ir(cod)acac (4)	10	2	60
7a	2	Ir(cod)acac (4)	16	15	66 (64) ^{b(ii)}
7b	2	Ir(cod)acac (4)	16	10	70 (69) ^{b(iii)}

^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b side-product **189** isolated in (i) 40%, (ii) 12%, (iii) 10% yield, Entries 1 and 3a repeated from Table 3. 3 for comparison.

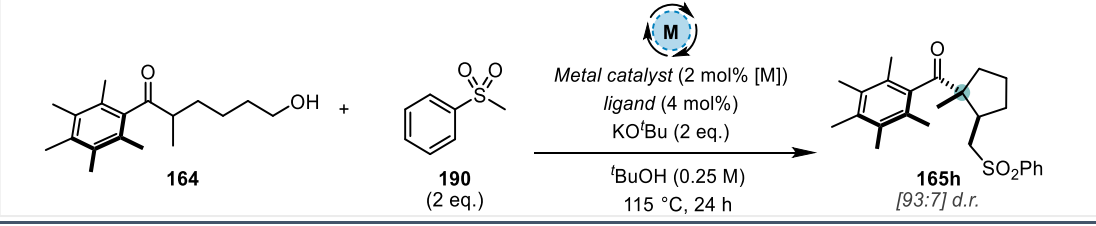


3.6.3 Optimisation using sulfone nucleophiles

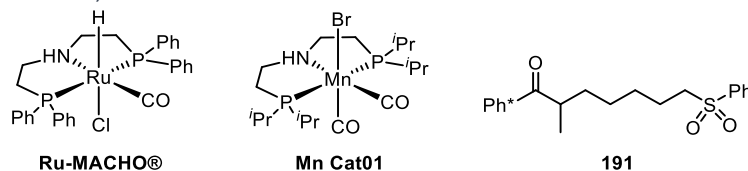
While addressing the issue of irreproducibility in the synthesis of cyclopentanes using Ph* methyl ketone **31** as a nucleophile (see Table 3. 7), it was observed that the reaction proceeded reliably when using methyl phenyl sulfone as the nucleophile, giving 67% yield of sulfone **165h** when using the conditions employed for the preliminary scope (see Scheme 3. 7). As a result of this more reliable behaviour, it was decided that we would focus on this class of nucleophile when investigating the scope of the reaction. To this end, we set about re-optimising the

reaction using a sulfone nucleophile, **190**. Given the different nature of this system, particularly regarding the different alkenyl sulfone intermediate, a range of catalysts were screened for this reaction (**Table 3. 8**). Using two equivalents of the sulfone nucleophile and Ir(cod)acac instead of [Ir(cod)Cl]₂ offered a small improvement in isolated yield, giving product **165h** in 70% isolated yield (Entry 2). Interestingly, while less hindered ligands dppBz and PPh₃ did not result in a significant decrease in yield (Entries 3, 4), using the Ir(III) catalyst, [IrCp*Cl₂]₂, gave a significant decrease in yield, forming product **165h** in 50% yield (Entry 5).

Table 3. 8 Optimisation using sulfone nucleophiles: catalysts.

				
Entry	Catalyst	Ligand	Yield (%) ^a	
			164	165h
1 ^b	[Ir(cod)Cl] ₂	cataCXium® A	-	67 (67)
2	Ir(cod)acac	cataCXium® A	-	82 (70)
3	Ir(cod)acac	dppBz	4	71
4	Ir(cod)acac	PPh ₃	5	73
5	[IrCp*Cl ₂] ₂	-	20	50
6	Ru-MACHO®	-	4	26 ^c
7	Mn Cat01	-	-	74 (75)
8	-	-	79	-

^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b 1.5 eq. of nucleophile **190** employed. ^c acyclic side product **191** isolated in 55% yield. Entry 1 indicates the previous best conditions (see **Scheme 3. 7**).

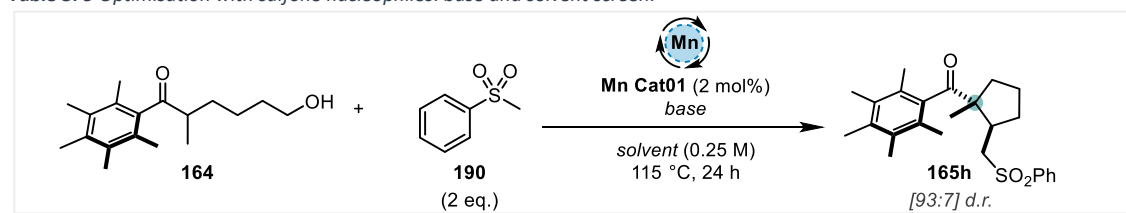


In an effort to identify catalysts using other, more sustainable metals, other transition metal catalysts were also investigated. Ru-MACHO® only formed the desired product **165h** in 26% yield, however a significant amount of the acyclic side product **191** (55%) was isolated (**Table 3. 8**, Entry 6). The related manganese catalyst **MnCat01** was also screened (Entry 7);

pleasingly, this catalyst gave **165h** in 75% isolated yield and these conditions were therefore taken forwards for further optimisation.

Next, a range of solvents and base conditions were screened (**Table 3. 9**). Decreasing the equivalents of KO^tBu to one equivalent gave a significant decrease in yield, forming product **165h** in 64% (Entry 2). Using substoichiometric equivalents of base was detrimental to the catalytic activity (Entry 3). Using NaO^tBu as the base was unsuccessful, resulting in the formation of product **165h** in only 17% yield. Since the analogous reaction to form cyclohexane **167a** using Ph* methyl ketone **31** as the nucleophile worked well using KOH as the base and PhMe as the solvent, these conditions were also investigated in combination with this catalyst. Using two equivalents of KOH gave a decrease in yield, forming product **165h** in 57% yield. Increasing the equivalents of KOH was detrimental to the yield, giving **165h** in only 38% yield.

Table 3. 9 Optimisation with sulfone nucleophiles: base and solvent screen.



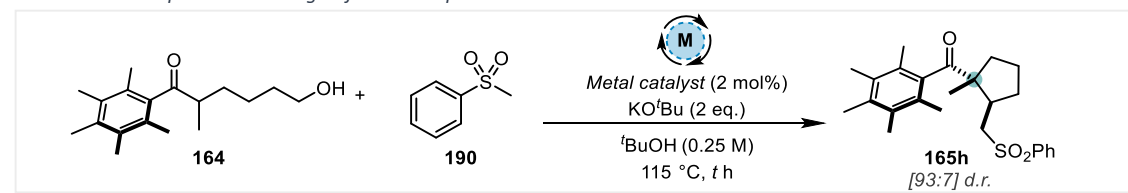
Entry	Base (eq.)	Solvent	Yield (%) ^a	
			164	165h
1	KO ^t Bu (2)	^t BuOH	-	74 (75)
2	KO ^t Bu (1)	^t BuOH	-	64
3	KO ^t Bu (0.5)	^t BuOH	84	-
4	NaO ^t Bu (2)	^t BuOH	51	17
5	KOH (2)	PhMe	11	57
6	KOH (4)	PhMe	4	38

^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Entry 1 repeated from **Table 3. 8** for comparison.

Finally, a variety of other factors were investigated (**Table 3. 10**). Throughout the optimisation, it was noted that purification of the product could be challenging due to difficult separation of the excess nucleophile. In an effort to ease purification, the effect of decreasing the equivalents of sulfone nucleophile was investigated. Unfortunately, decreasing the equivalents of sulfone

nucleophile **190** to 1.5 equivalents gave product **165h** in a slightly reduced yield (64%, Entry 2). However, it was found that reducing the reaction time to 16 h gave an improvement in yield, giving the cyclised product **165h** in 80% isolated yield (Entry 3). Reducing the reaction time further to 6 h resulted in a lower yield of 69% (Entry 4). The new manganese system was also compared to the previous Ir(cod)acac/cataCXium A[®] system under analogous conditions (Entry 5). After a reaction time of 16 h, the iridium catalysed system gave a slightly lower yield of 69%, therefore the manganese system was taken forwards to examine the scope of the transformation with sulfur-based nucleophiles.

Table 3. 10 Final optimisation using sulfone nucleophiles.

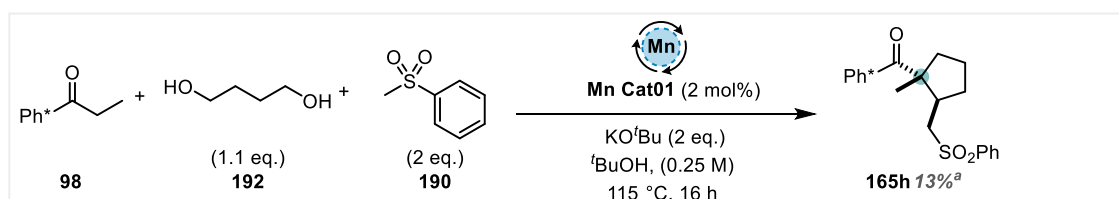


Entry	Eq. 190	Catalyst	Reaction time (h)	Yield (%) ^a	
				164	165h
1	2	Mn Cat01	24	-	74 (75)
2	1.5	Mn Cat01	24	-	64
3	2	Mn Cat01	16	-	77 (80)
4	2	Mn Cat01	6	4	69 (69)
5	2	Ir(cod)acac cataCXium [®] A (4 mol%)	16	2	69

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. Entry 1 repeated from Table 3. 8 for comparison.

Since the hydroxy ketone substrates for this reaction were prepared *via* hydrogen borrowing alkylation, we investigated whether the cyclic products could be prepared in a single step, multi-component reaction. This was an ambitious undertaking as the reaction conditions would first have to accomplish a hydrogen borrowing alkylation, typically favoured at high concentrations, and then an acceptorless dehydrogenative coupling of the corresponding hydroxy ketone, favoured by dilute reaction conditions.⁵¹ To probe whether a multi-component approach was feasible, Ph* ethyl ketone **98**, 1,4-butanediol **192** and methyl phenyl sulfone **190** were subjected to the optimised reaction conditions for the acceptorless dehydrogenation–

intramolecular cyclisation cascade (**Scheme 3. 10**). Despite formation of a complex mixture of products, cyclised product **165h** was observed in 13% ^1H NMR yield. However, due to the complex mixture obtained and multiple conflicting factors governing success of both the hydrogen borrowing and subsequent acceptorless dehydrogenation processes, this multi-component approach was not explored further and the scope was investigated using the hydroxy ketone substrates.

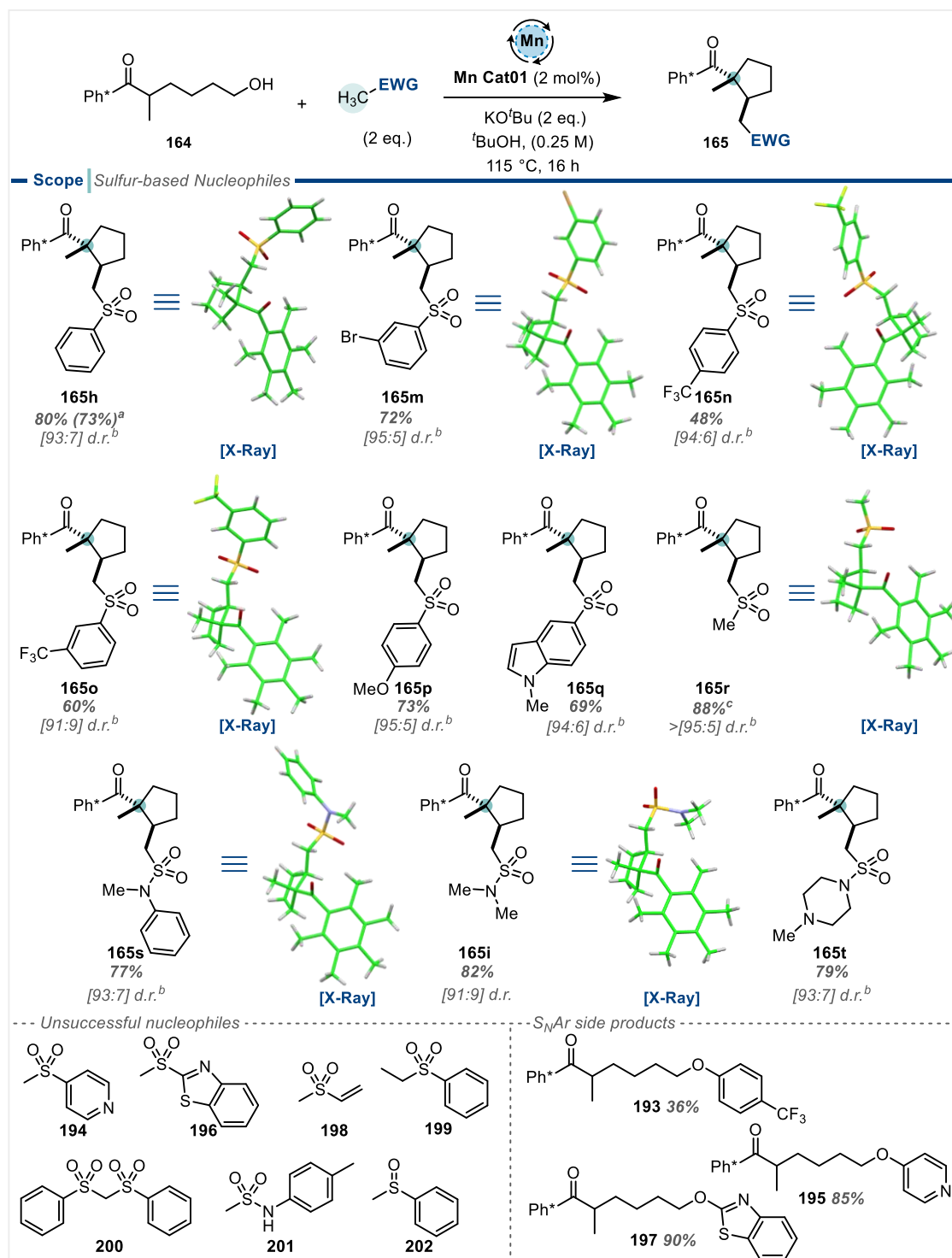


Scheme 3. 10 Attempted multi-component reaction. ^a Yield determined via ^1H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, the product d.r. was not determined.

3.7 Substrate Scope

With the optimised reaction conditions using a sulfone nucleophile in hand, the scope of the sulfur-based nucleophiles was examined (**Scheme 3.11**). An aryl bromide-substituted sulfone was found to be a good nucleophile, giving **165m** in 72% yield. Electron-withdrawing trifluoromethyl substituents were also tolerated, giving **165n** and **165o** in 48% and 60% yield, respectively. These sulfones were susceptible to a deleterious $\text{S}_{\text{N}}\text{Ar}$ process, identified by the formation of side product **193** in 36% yield. More electron-withdrawing sulfones bearing electron-deficient heterocycles, **194** and **196**, were poor substrates for cyclisation, instead undergoing the undesired $\text{S}_{\text{N}}\text{Ar}$ reaction to form products **195** and **197** in 85% and 90% yield, respectively. However, electron-rich aryl and heteroaryl sulfones proved to be excellent substrates, forming cyclised products **165p** and **165q** in 73% and 69% yield, respectively. A simple dialkyl sulfone could also be employed to access product **165r** in 88% yield, though a large excess of nucleophile was employed to prevent bis-alkylation of the sulfone nucleophile. The reaction could also be carried out on a 1.10 g (4.00 mmol) scale using methyl phenyl sulfone **190**, giving product **165h** in 73% yield and [94:6] d.r., which could be further purified by

recrystallisation to access the major *trans*-diastereomer as a single diastereomer that was used for further derivatisation (see Chapter 3.9).



Scheme 3. 11 Scope of sulfur-based nucleophiles. Reactions carried out on 0.30 mmol scale, isolated yields are reported, major isomer is shown for clarity. X-ray crystallography data and analysis provided by Timothy C. Jenkins. ^a Reaction carried out on 1.10 g scale, product d.r. = [94:6] ^b d.r. was determined post-purification due to overlapping peaks in the crude ¹H NMR. ^c 5 eq. nucleophile used.

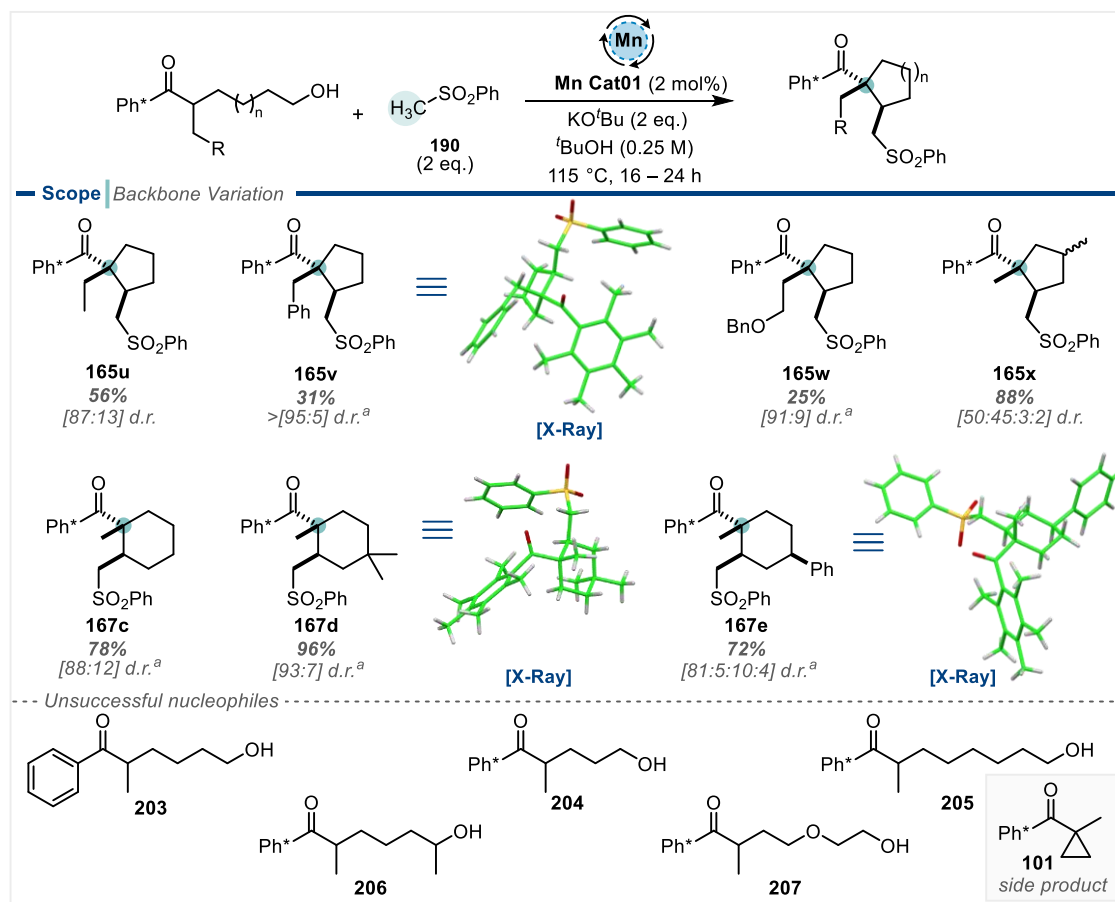
Given the success of electron-rich aryl sulfones, sulfonamide nucleophiles were also investigated (**Scheme 3. 11**). Pleasingly, tertiary sulfonamides were excellent substrates, giving

products **165i**, **165s** and **165t** in 77% – 82% yield. For all examples, high *trans*-diastereoselectivity was observed, presumably due to thermodynamic control arranging the Ph* ketone and sulfone group to minimise the steric interaction (see Chapter 3.8).

However, a range of sulfone substrates were not compatible with the method. Electrophilic sulfones, such as **198** were incompatible with the reaction conditions due to unwanted Michael acceptor reactivity. Substituted sulfones such as **199** and **200** were also not tolerated, presumably as a result of more challenging condensation reactions with the additional steric demand. Other unsuitable nucleophiles included the secondary sulfonamide **201**, likely due to the presence of the acidic N–H bond, and sulfoxide **202**.

Having examined the scope with respect to the sulfur-based nucleophile component, we investigated the scope of hydroxy ketone substrates that could be employed in the reaction (**Scheme 3. 12**). In addition to a methyl group (see product **165h**), more sterically demanding ethyl, benzyl and benzyloxy ethyl groups could be incorporated at the quaternary position, giving compounds **165u – w** in 25% – 56% yield. The reduced yields obtained when employing larger groups at the quaternary position is likely a testament to the challenge of synthesising such sterically congested quaternary stereocentres *via* cyclisation. Further backbone substitution could also be tolerated, as demonstrated by the formation of methyl-substituted product **165x** in 88%, however the stereochemistry at this additional centre was uncontrolled, giving the product in [50:45:3:2] d.r. By employing a homologous hydroxy ketone starting material **166**, the simple cyclohexane product **167c** could be formed in 78% yield. Pleasingly, incorporating a *gem*-dimethyl group in the backbone served to increase the yield, giving **167d** in 96% yield, presumably as the Thorpe–Ingold effect favours the cyclised product.⁵⁴ Addition of a single substituent to the backbone of the hydroxy ketone was also successful, forming **167e** in 72% yield. Notably, the diastereoselectivity was much improved in this case compared to the

similar cyclopentane **165x**, this is likely due to the stronger conformational preference for equatorial substituents in cyclohexanes compared with their cyclopentane counterparts.

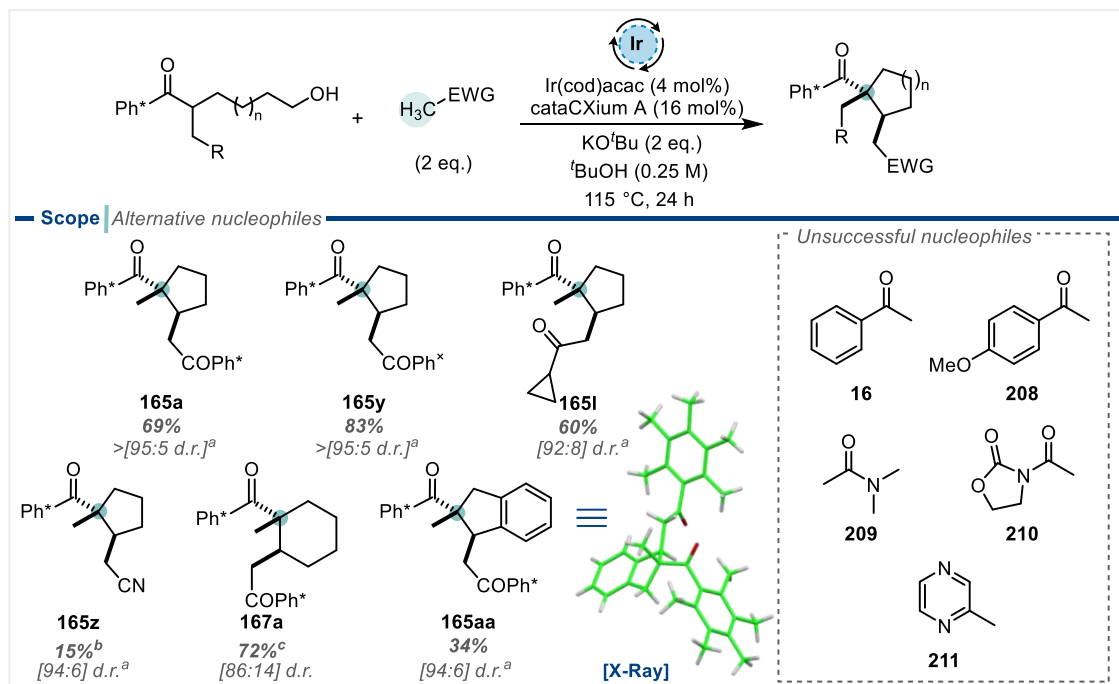


Scheme 3. 12 Scope of hydroxy ketone substrates. Reactions carried out on a 0.30 mmol scale, isolated yields are reported, major isomer is shown for clarity. X-ray crystallography data and analysis were provided by Timothy C. Jenkins. ^a d.r. was determined post-purification.

Although a range of cyclopentane and cyclohexane products could be formed, a range of other hydroxy ketone nucleophiles were not compatible with the method (**Scheme 3. 12**). Using non-Ph* ketone substrate **203** resulted in a complex reaction mixture, illustrating the need for the key Ph* ketone protecting group to prevent unwanted nucleophilic attack at the carbonyl. The method could also not be extended to enable the formation of cyclobutanes or cycloheptanes by employing analogues **204** or **205**. Secondary alcohols were also unsuitable, resulting in no conversion of starting material **206** to the desired cyclic product. Preliminary investigations regarding the installation of heteroatoms in the backbone were also unsuccessful; when **207** was subjected to the optimised reaction conditions, no desired intramolecular conjugate addition product was observed. The major product was identified as cyclopropyl

ketone **101**, which was isolated in 43% yield. This cyclopropane is likely formed as the result of intramolecular displacement of the alkoxide from starting material **207** under the basic reaction conditions.

A range of alternative nucleophiles were also investigated (**Scheme 3. 13**). First, we examined the scope of ketone nucleophiles, using the conditions optimised for the formation of cyclopentane **165a** (see **Table 3. 7**).^a Hindered aryl methyl ketones, such as Ph^{*} methyl ketone and Ph^x methyl ketone were suitable nucleophilic partners, giving products **165a** and **165y** in 69% and 83% yield, respectively. Cyclopropyl methyl ketone was also tolerated, giving diketone **165l** in 60% yield. Acetonitrile could also be employed as a substrate in combination with the manganese catalyst **Mn Cat01**, however the desired product **165z** was formed in only 15% yield. Backbone modification was also possible using these conditions, allowing the formation of simple cyclohexane **167a** in 72%. Unsaturation could also be incorporated into the backbone, giving bicyclic diketone product **165aa** in 34% yield.



Scheme 3. 13 Alternative nucleophile scope. Reactions carried out on a 0.30 mmol scale, isolated yields are reported, major isomer is shown for clarity. X-ray crystallography data and analysis were provided by Timothy C. Jenkins ^a d.r. was determined post-purification. ^b**Mn Cat01** (2 mol%), MeCN (5 eq.) KO^tBu (2 eq.), ^tBuOH (0.25 M), 115 °C, 16 h. ^cCatalyst: Ir(cod)acac (2 mol%), cataCXium® A (4 mol%), Base: KOH (4 eq.), Solvent: PhMe (0.25 M).

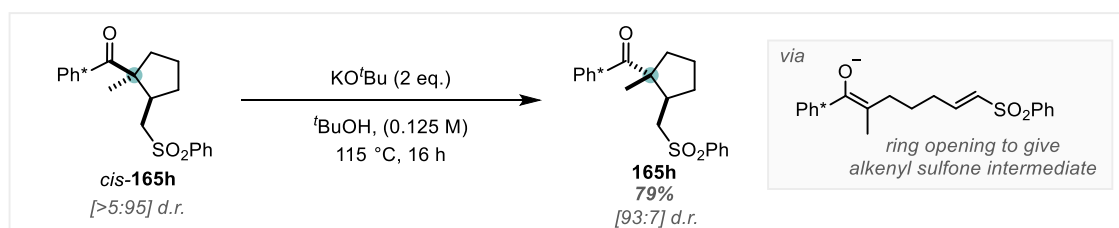
* Ir(cod)acac/cataCXium® A was employed here as using **Mn Cat01** in combination with Ph^{*}COME (**31**) as the nucleophile gave only 60% ¹H NMR yield of diketone **165h** alongside 33% of the acyclic side product **189**.

Although simple aryl ketones **16** and **208** had been successful substrates in the preliminary reaction scope (see **Scheme 3. 7**), these results could not be replicated in the modified system. Similarly, the amide **209** did not show any conversion to the desired product. The oxazolidinone **210** was investigated with a view to using a chiral auxiliary to control the absolute stereochemistry in the cyclisation reaction; unfortunately, this nucleophile underwent hydrolysis in the reaction. Methylpyrazine **211** was also investigated as acidic heterocycles had been previously employed as nucleophiles in similar acceptorless dehydrogenative coupling reactions, however, no significant conversion to the corresponding cyclic product was observed.¹¹⁵

3.8 Mechanistic Experiments

3.8.1 Cause of diastereoselectivity

Throughout our investigation of the reaction scope, high levels of diastereoselectivity were observed. We proposed that this was a result of the reaction being under thermodynamic control, thereby favouring the product that minimises the steric interaction between the Ph* ketone and the sulfone substituent. To provide evidence for this, the *cis*-diastereomer *cis*-**165h** was isolated and then re-subjected to the reaction conditions, in the absence of a metal catalyst (**Scheme 3. 14**). Pleasingly, full conversion to give **165h** in [93:7] d.r. was observed, with *trans*-**165h** as the major isomer, presumably formed *via* ring opening to give the intermediate alkenyl sulfone. This diastereomeric ratio is identical to that obtained in the reaction that forms **165h**, supporting the hypothesis that the reaction is under thermodynamic control, and that the thermodynamic product ratio is governed by the relative stabilities of the product diastereomers.



Scheme 3. 14 Re-subjection of *cis*-**165h** to the basic reaction conditions, indicating thermodynamic control in the reaction.

3.8.2 Gas evolution experiments

Given that the reaction used to form **165h** is an acceptorless dehydrogenation reaction, this reaction should evolve hydrogen gas. To demonstrate that this was the case, we recorded the amount of gas evolved during the reaction by piercing the microwave vial septum with a cannula and collecting the gas evolved in an inverted measuring cylinder. The results of this experiment are depicted in **Figure 3. 1** (for tabulated data, see **Appendix II**). Since heating the reaction solvent to 115 °C in a microwave vial would cause an increase in vapour pressure, we first heated t AmOH under our gas collection apparatus.* The expansion of the reaction headspace was complete within 1 h and constituted approximately 6.5 mL of gas. This volume was subtracted from all readings in the hydrogen evolution experiment to give an accurate representation of the amount of gas evolved in the reaction. Over the course of the reaction, a total of approximately 7 cm³ of gas was evolved (averaged over two repeats). Using the ideal gas law, which states that 1 mmol of an ideal gas at 298 K and 1 atm occupies a volume of 24.2 cm³, we calculated that full oxidation of the alcohol and should give a volume of 7.26 cm³ of evolved hydrogen gas. Therefore, the results of the gas collection experiment are consistent with the alcohol undergoing almost full conversion to the corresponding aldehyde and one equivalent of hydrogen gas being evolved to enable catalyst turnover. Despite the gas evolution experiment implying near-quantitative conversion to the aldehyde, the average ¹H NMR yield of the desired product **165h** formed in these experiments was 71%, with no significant starting material observed by ¹H NMR analysis of the crude NMR spectrum. Taken in conjunction, the gas evolution experiment and corresponding ¹H NMR yields suggest that some decomposition occurs after the oxidation takes place; presumably, the reactive aldehyde intermediate can undergo unwanted side reactions, resulting in slightly lower yields of product.

* t AmOH was used for this study in place of t BuOH as the lower boiling point of t BuOH was incompatible with the experimental setup. A control experiment indicated that the product **165h** was formed in comparable (77% ¹H NMR) yield when using t AmOH as the solvent.

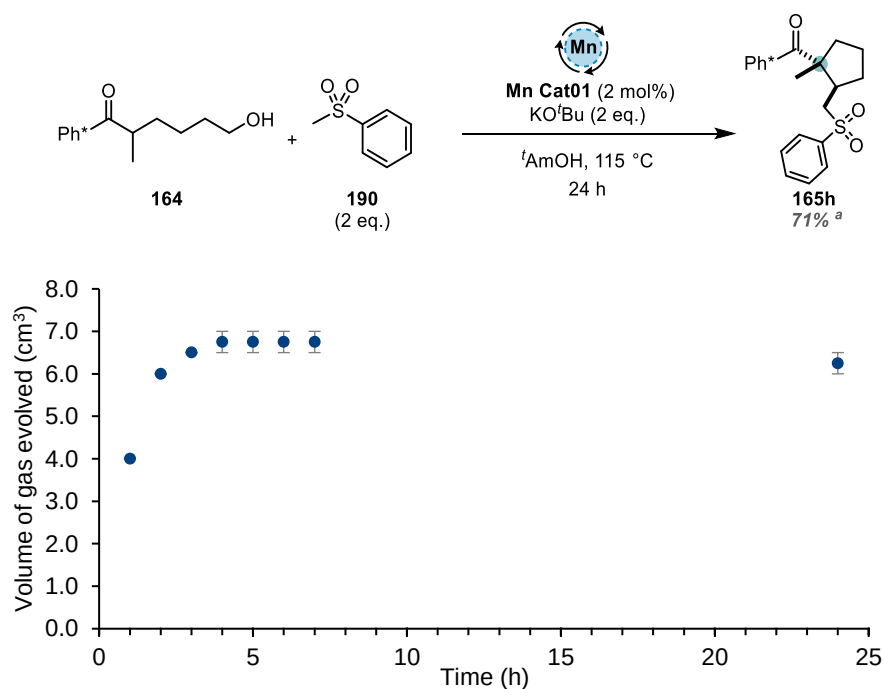
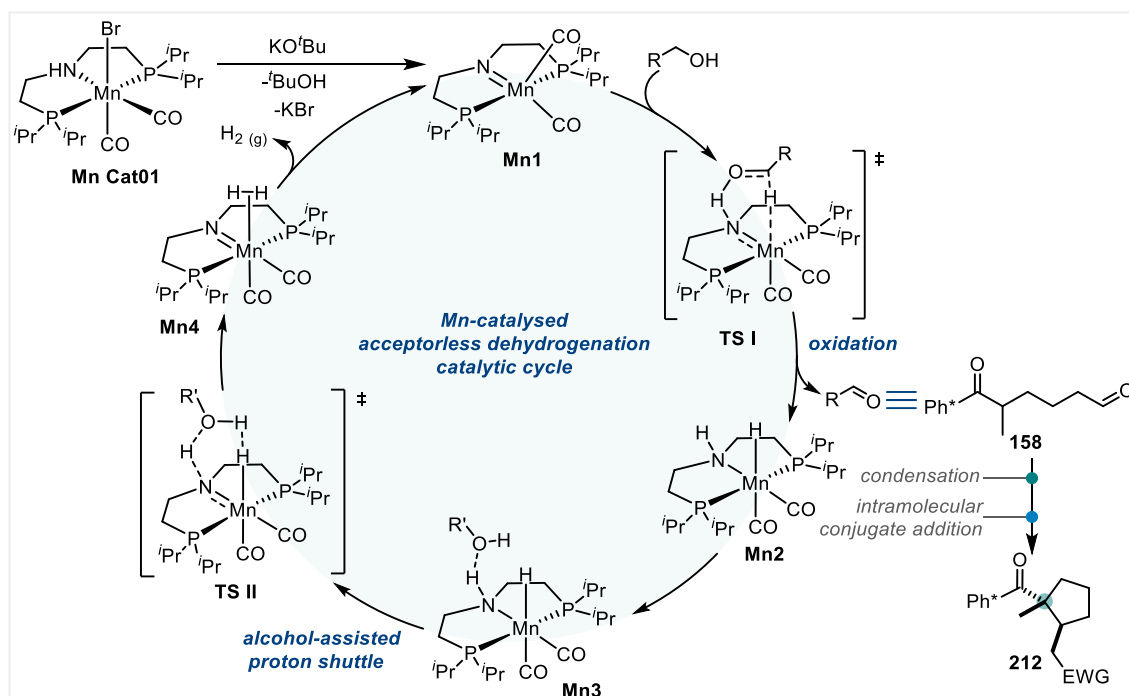


Figure 3. 1 Graph showing gas evolution over the course of the acceptorless dehydrogenative coupling reaction to give **165h**. ^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, the product d.r. was not determined.

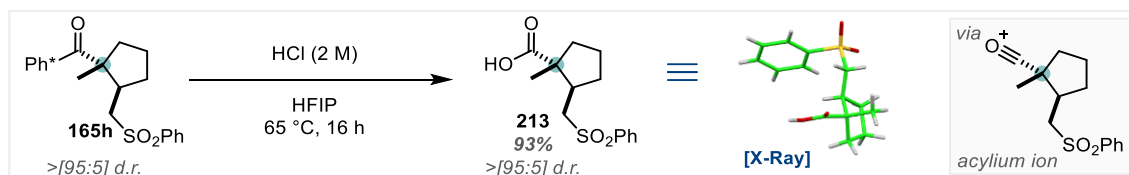
This is consistent with literature reports using **Mn Cat01** in acceptorless dehydrogenation reactions, which suggest that ligand-metal cooperation is key to the reactivity of this complex (and other similar pincer complexes).^{43, 116} It is proposed that **Mn Cat01** acts as a pre-catalyst that undergoes elimination of HBr under the basic reaction conditions to generate the catalytically active Mn-amido complex **Mn1** (Scheme 3. 15). The alcohol substrate is oxidised *via* proton transfer from the alcohol to the nitrogen in the pincer ligand and hydride transfer from the alcohol α -methylene unit to the metal centre (**TS I**) to give the manganese hydride species **Mn2** and the corresponding aldehyde, which in our system then undergoes condensation with the nucleophile and intramolecular conjugate addition to give the α -quaternary ketone **212**. Gauvin and co-workers then propose that the dihydrogen σ -complex **Mn4** is generated by an alcohol-assisted proton shuttle (**TS II**), which is calculated to be favoured over direct combination of the N–H proton with the Mn–H by 2.1 kcalmol⁻¹. Hydrogen can then be lost from this species to regenerate the active catalyst **Mn1**. We propose that such metal-ligand co-operation means that hydrogen evolution is relatively fast and therefore the reduction of the unsaturated intermediate by the metal-hydride is outcompeted.



Scheme 3. 15 Proposed catalytic cycle for the oxidation of hydroxy ketone substrates using **Mn Cat01**.

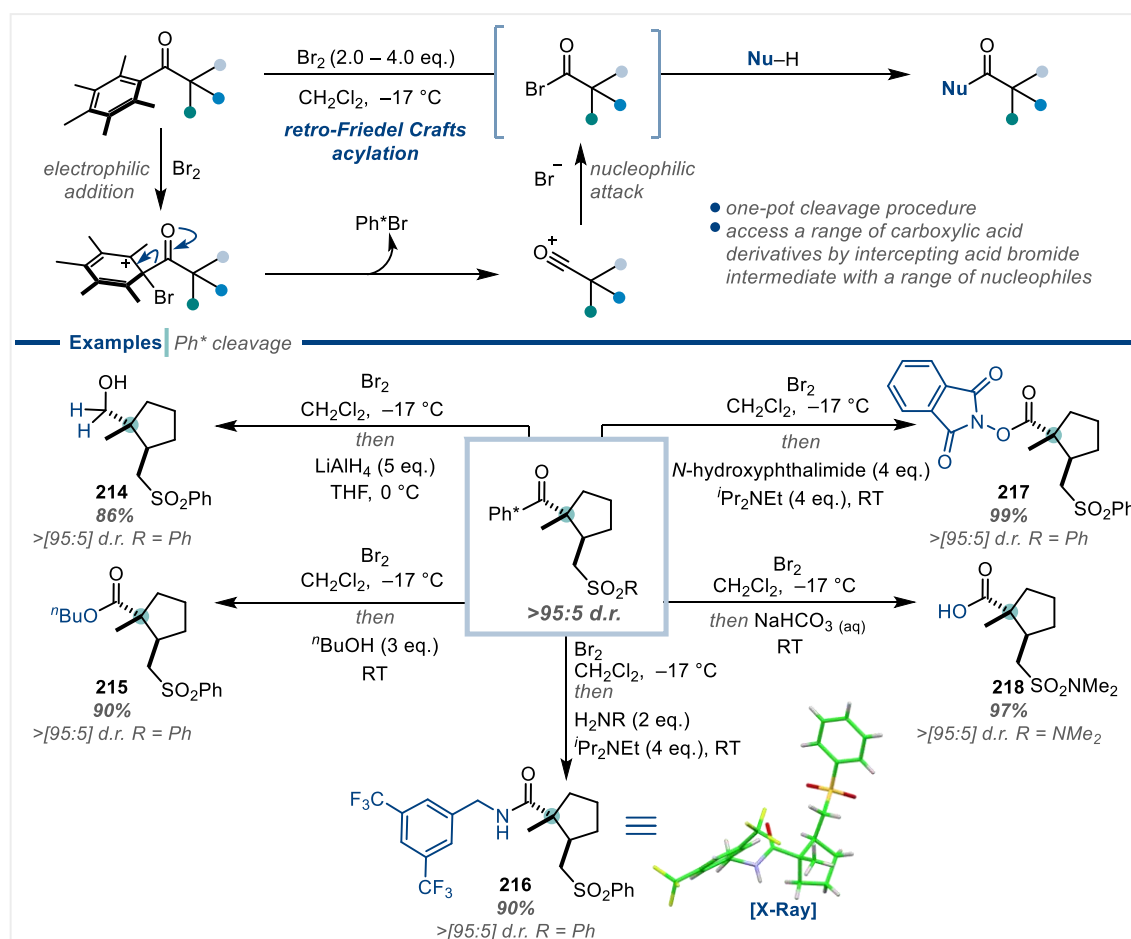
3.9 Product Derivatisation

To demonstrate the utility of the method, the key Ph^* protecting group should be removable in high yield to allow access to a useful functional handle for derivatisation. The Donohoe group has previously reported various methods for the cleavage of Ph^* ketones *via* retro-Friedel–Crafts acylation. The process works by attack of the electron-rich pentamethylphenyl ring with an electrophile, followed by collapse of the generated Wheland intermediate to give the corresponding acylium ion. This can then be intercepted by a nucleophile, giving access to a range of carboxylic acid derivatives. We first subjected product **155h** to established acidic cleavage conditions using HFIP as the solvent (Scheme 3. 16). Pleasingly, the corresponding carboxylic acid **213** was formed in 93% yield. Importantly, the relative stereochemistry was maintained with complete fidelity, as proven by nOe and single crystal X-ray analysis.



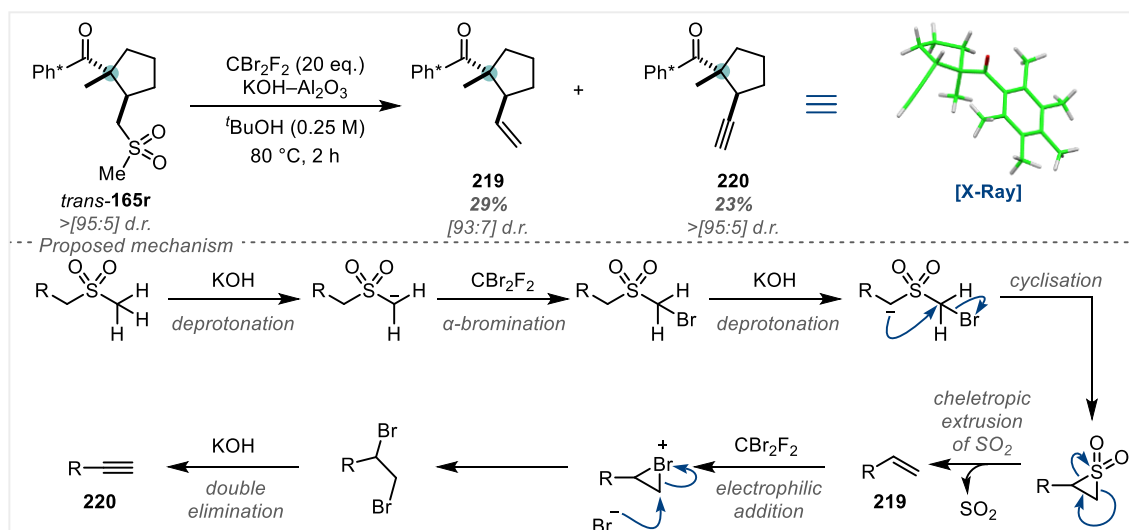
Scheme 3. 16 Ph^* cleavage from product **165h** under acidic conditions. X-ray crystallography data and analysis were provided by Timothy C. Jenkins.

An alternative method which has been employed within the Donohoe group for Ph* cleavage involves the use of bromine as the electrophile to generate an acid bromide *in situ* (Scheme 3. 17). Product **165h** was subjected to these conditions and successfully reacted with a variety of different nucleophiles to give a range of carboxylic acid derivatives in a single step: alcohol **214**, ester **215**, amide **216** and *N*-hydroxyphthalimide ester **217** were all formed in high yields using this method. Pleasingly, the key Ph* protecting group could also be cleaved from sulfonamide product **165i** to give the corresponding acid **218** in 97% yield with retention of the sulfonamide. This example demonstrates the complementarity between the acidic cleavage and the Br₂-mediated cleavage as it illustrates that acid-sensitive functional groups can be employed in hydrogen borrowing alkylation and retained in the subsequent cleavage step.



Scheme 3. 17 Ph* cleavage using bromine to generate the corresponding acid bromide which can be intercepted with a range of nucleophiles. Typical conditions for the bromination step: Br₂ (2.0 – 4.0 eq.), CH₂Cl₂, –17 °C, 40 min, then addition of nucleophile as indicated. X-ray crystallography data and analysis were provided by Timothy C. Jenkins.

Having demonstrated successful Ph* cleavage from the α -quaternary products, alternative derivatisation reactions were explored. We briefly investigated the derivatisation of dialkyl sulfone **165r** via a one-pot Ramberg-Bäcklund reaction (Scheme 3. 18). When the major *trans*-diastereomer, *trans*-**165r**, was subjected to conditions developed by Chan and co-workers, both alkene **219** and alkyne **220** were formed in 29% and 23% yield respectively.¹¹⁷ We propose that the alkyne is formed by electrophilic addition of bromine across the double bond of Ramberg-Bäcklund product **219** to form the corresponding dibromide, which undergoes two consecutive eliminations to form the alkyne **220**. It should also be noted that the alkene **219** was formed in [93:7] d.r., suggesting that ring opening of the starting material occurs under the basic reaction conditions leading to equilibration to the thermodynamic ratio. Although this reaction demonstrated proof-of-concept for derivatisation of the sulfone products, this approach was not explored further due to time constraints.

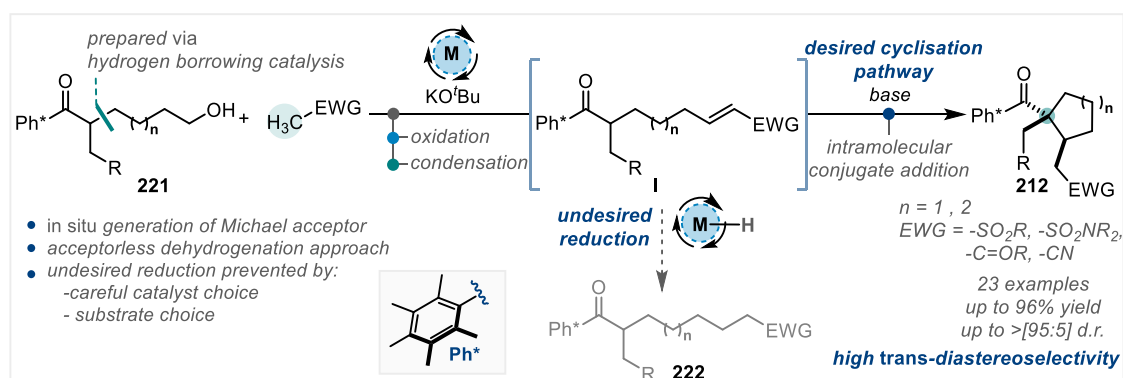


Scheme 3. 18 Preliminary work: derivatisation of alkyl sulfone product **165r** using a one-pot Ramberg-Bäcklund reaction. X-ray crystallography data and analysis were provided by Timothy C. Jenkins.

3.10 Conclusions

This chapter describes the synthesis of α -quaternary ketones using an acceptorless dehydrogenation–intramolecular cyclisation cascade reaction (Scheme 3. 19). Using a commercial manganese catalyst, hydroxy ketones, such as **221**, could be oxidised and undergo condensation with an appropriate nucleophile to give an intermediate Michael acceptor, **I**.

Under the basic reaction conditions, intermediate **1** could cyclise *via* the corresponding enolate in an intramolecular conjugate addition to give α -quaternary ketone **212**. By careful choice of the catalyst and substrate, we could prevent the undesired reduction of the unsaturated intermediate **1** to the acyclic side product **222**. A range of nucleophiles could be employed, including sulfones, sulfonamides and ketones to access a variety of complex cyclopentane and cyclohexane fragments with high *trans*-diastereoselectivity. Since the hydroxy ketone starting materials were themselves easily prepared using hydrogen borrowing catalysis, this approach enabled the synthesis of complex fragments including quaternary stereocentres in a short synthetic sequence using both hydrogen borrowing catalysis and acceptorless dehydrogenation (or interrupted hydrogen borrowing). Finally, the key Ph* protecting group could be removed in a one-pot process using either bromine- or acid-mediated conditions to access a range of carboxylic acid derivatives with complete retention of the relative stereochemistry.

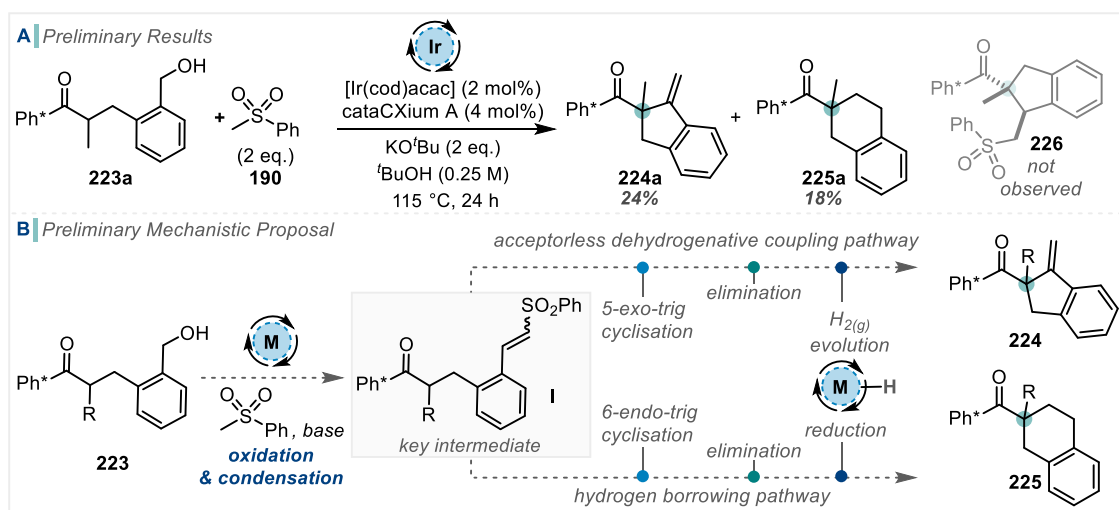


Scheme 3. 19 Summary of formation of α -quaternary ketones via an acceptorless dehydrogenation–intramolecular conjugate addition cascade.

4. Quaternary Centres using Benzylic Alcohol Substrates

4.1 Introduction and Preliminary Results

Given the strong literature precedent for acceptorless dehydrogenation with activated, benzylic alcohols, starting material **223a** was synthesised for use in the acceptorless dehydrogenation–intramolecular conjugate addition cascade (see Chapter 3). While the use of a benzylic alcohol did not improve the yield of this process compared to a simple aliphatic alcohol (when Ph* methyl ketone **31** was employed as a nucleophile (see **Scheme 3. 13**, Chapter 3.7)), unexpected reactivity was observed when using methyl phenyl sulfone **190** as the nucleophile (**Scheme 4. 1A**). The expected sulfone-containing product **226** was not observed, however, two α -quaternary ketone products, **224a** and **225a**, were isolated. Initially, we postulated that both products could be formed *via* the same vinyl sulfone intermediate **I** (**Scheme 4. 1B**), where the 5-membered ring product **224a** could be formed *via* a 5-*exo-trig* cyclisation with subsequent elimination of sulfinate in an acceptorless dehydrogenative coupling pathway. In contrast, the 6-membered ring product **225a** could be formed *via* a pathway involving a 6-*endo-trig* cyclisation, elimination of sulfinate, and reduction of the formed C=C bond by the metal-hydride, though further investigation would be required in order to determine the order of these steps.



Scheme 4. 1 A) Preliminary result: formation of α -quaternary ketones **224a** and **225a**. B) Initial mechanistic proposal.

4.2 Project Aims

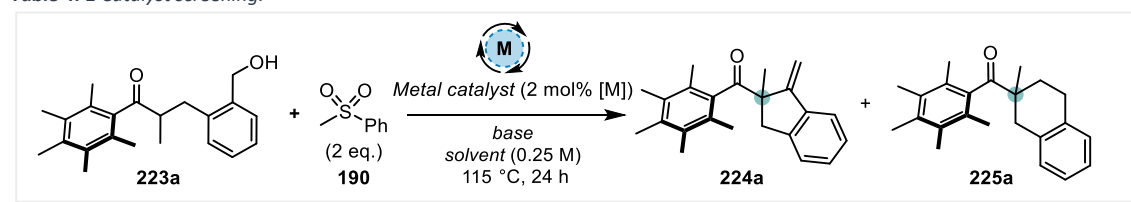
The aim at the start of this project was to investigate the formation of each of these two classes of α -quaternary ketones, particularly to assess whether the formation of either product could be favoured depending on the reaction conditions, enabling divergent synthesis. Given that the formation of the 6-membered ring product **225** requires an additional reduction step compared to the formation of the 5-membered ring product **224**, it was envisaged that by modulating the catalyst reducing ability, such divergent reaction conditions would be achievable. However, since both products could be formed in the reaction, this approach presented a significant challenge. It was also suggested that mechanistic investigations would help elucidate the mechanism by which each of the two different products are formed.

4.3 Reaction Optimisation

To begin the reaction optimisation process, we investigated the use of KOH (four equivalents) as the base and PhMe as the solvent (**Table 4. 1**); this system had been successfully employed in the acceptorless dehydrogenation–intramolecular conjugate addition reaction. Pleasingly, the 6-membered ring product **225a** was formed in an improved 40% isolated yield, while the amount of the 5-membered ring product **224a** remained approximately constant (Entry 2). Since it was proposed that catalyst reducing ability could be useful in modulating the product distribution of the reaction, an initial catalyst screen was conducted. Although we anticipated that using a less sterically hindered catalytic system would favour the reduction process and thereby promote the formation of 6-membered ring product **225a**, using the less hindered ligand dppBz favoured the formation of the 5-membered ring product **224a** (Entry 3). Using $[\text{IrCp}^*\text{Cl}_2]_2$ (Entry 4) resulted in a similar isolated yield (41%) as the more sterically encumbered $[\text{Ir}(\text{cod})\text{acac}]/\text{cataCXium}^\text{®}$ A catalytic system (Entry 2); therefore, both of these systems were taken forwards for further optimisation.

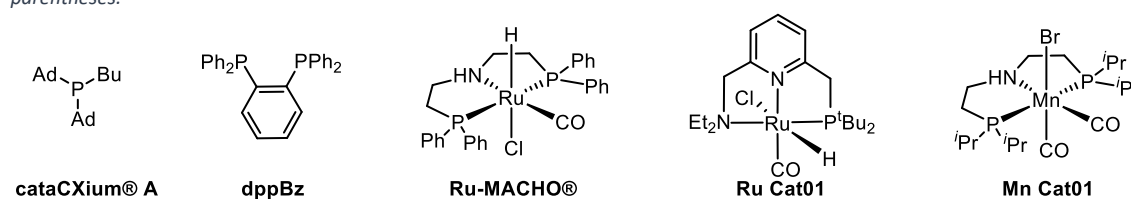
A range of catalysts that are more typically employed in acceptorless dehydrogenation reactions were also screened in an effort to favour the formation of 5-membered ring product **224a** (Entries 5 – 7).^{43, 114, 118, 119} While Milstein's catalyst precursor **Ru Cat01** resulted in minimal formation of the desired product (24% yield, Entry 5), both Ru-MACHO[®] and **Mn Cat01** selectively gave product **224a** (62% and 50% yield, respectively, Entries 7 & 8). Ru-MACHO[®] gave the highest yield of **224a** (62%) and was therefore taken forward for further optimisation.

Table 4. 1 Catalyst screening.



Entry	Catalyst (mol%)/ligand (mol%)	Base (eq.)	Solvent	Yield (%) ^a		
				223a	224a	225a
1	[Ir(cod)acac] (2)/cataCXium [®] A (4)	KO ^t Bu (2)	^t BuOH	31	21 (24)	18 (18)
2	[Ir(cod)acac] (2)/cataCXium [®] A (4)	KOH (4)	PhMe	-	19 (22)	45 (40)
3	[Ir(cod)acac] (2)/dppBz (4)	KOH (4)	PhMe	3	41	23
4	[IrCp*Cl ₂] ₂ (1)	KOH (4)	PhMe	11	21	44 (41)
5	Ru Cat01 (2)	KOH (4)	PhMe	-	24	-
6	Ru-MACHO [®] (2)	KOH (4)	PhMe	-	62	-
7	Mn Cat01 (2)	KOH (4)	PhMe	-	50	-

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses.



4.3.1 Optimisation for formation of 6-membered ring product **225**

Another factor that is known to govern whether reduction or H₂ evolution occurs in a hydrogen borrowing system is the reaction concentration, with more dilute systems favouring H₂ evolution in a formal acceptorless dehydrogenation process.⁵¹ Therefore, we increased the reaction concentration in an effort to increase the proportion of reduced product **225a** formed (Table 4. 2). Increasing the reaction concentration to 0.5 M while employing the

[Ir(cod)acac]/cataCXium® A catalytic system had no effect on the product distribution (42% yield **225a**, Entry 3), presumably as the sterically encumbered ligand acts to prevent further reduction, demonstrating that both the ligand identity as well as reaction concentration play an important role in governing whether reduction occurs. However, increasing the reaction concentration to 0.5 M while using the [IrCp*Cl₂]₂ catalytic system gave a large improvement in the yield of the desired reduced product **225a** (70% isolated yield, Entry 4). Further increasing the reaction concentration to 1.0 M and 2.0 M resulted in a decrease in the yield of the reduced product, giving **225a** in yields of 50% and 55%, respectively.

Table 4. 2 Reaction concentration screening with iridium catalysts.

Entry	Catalyst (mol%)/ligand (mol%)	Reaction Concentration (M)	Yield (%) ^a			
			223a	224a	225a	
1	[Ir(cod)acac] (2)/cataCXium® A (4)	0.25	-	19 (22)	45 (40)	
2	[IrCp*Cl ₂] ₂ (1)	0.25	11	21	44 (41)	
3	[Ir(cod)acac] (2)/cataCXium® A (4)	0.5	-	20	42	
4	[IrCp*Cl ₂] ₂ (1)	0.5	1	12	71 (70)	
5	[IrCp*Cl ₂] ₂ (1)	1.0	-	13	50	
6	[IrCp*Cl ₂] ₂ (1)	2.0	-	11	55	

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. Entries 1 and 2 are repeated from Table 4.1 for comparison.

High Temperatures are also known to favour hydrogen gas evolution, as evidenced by the large number of literature methods for acceptorless dehydrogenation that are carried out at high temperature,^{102, 106} possibly due to the entropic advantage of liberating a gas. Therefore, we investigated whether decreasing the reaction temperature would disfavour hydrogen evolution and therefore promote the formation of the reduced product **225a** (Table 4. 3). Lowering the reaction temperature to 100 °C and 80 °C reduced conversion of the starting material **223a** and had a detrimental effect on the yield of the reduced product **225a**. KI was also trialled as an additive, as iodide ions have been shown to increase the reducing ability of transition metal

catalysts, including iridium-based catalysts.¹²⁰⁻¹²² Unfortunately, the addition of KI (20 mol%) reduced the yield of desired product **225a** significantly and resulted in significant decomposition.

Table 4. 3 Reaction temperature and additive screening.

Entry	Temperature (°C)	Additive (mol%)	Yield (%) ^a		
			223a	224a	225a
1	115	-	1	12	71 (70)
2	100	-	17	14	46
3	80	-	37	31	-
4	115	KI (20)	7	6	39

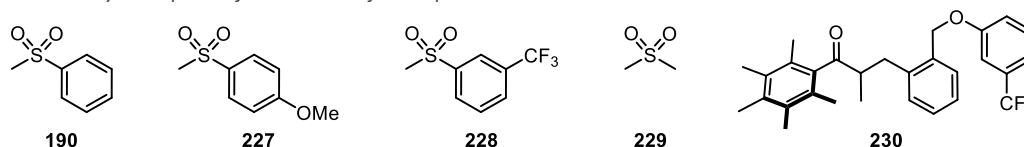
^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. Entry 1 is repeated from **Table 4.2** for comparison.

Finally, the nature of the nucleophilic reaction partner was investigated (**Table 4. 4**). Employing either an electron-rich (**227**, Entry 2) or an electron-deficient sulfone (**228**, Entry 3) gave a significant decrease in yield to 55% and 10%, respectively. Notably, using sulfone **228** as the nucleophile resulted in the formation of an S_NAr side product, **230**, in 18% yield; this was presumably formed *via* attack of alcohol **223a** and subsequent elimination of methanesulfinate. Use of commercially available dimethyl sulfone (**229**) did result in the formation of **225a** as the major product, but in only moderate yield (43%). MeCN was considered as an alternative nucleophile that could eliminate cyanide in a similar manner, however no significant conversion to product was observed. Therefore, PhSO₂Me (**190**) was used to investigate the scope of the transformation; this reagent presented many advantages as it is commercially available, does not generate toxic waste and the sulfinate by-product is easily removed.

Table 4. 4 Nucleophilic reaction partner screening for [IrCp*Cl₂]₂ reaction.

Entry	Nucleophile	Yield (%) ^a			
		223a	224a	225a	Side product
1	190	1	12	71 (70)	-
2	227	5	19	55	-
3	228		19	10	230, (18)
4	229	-	26	43	-
5	MeCN	42	complex mixture		-

^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. Entry 1 is repeated from Table 4.2 for comparison.

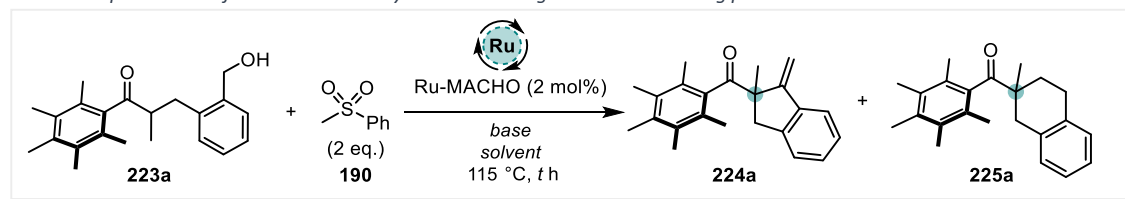


4.3.2 Optimisation for formation of 5-membered ring product 224

We next turned our attention to optimisation of the reaction to favour the formation of 5-membered ring product **224**. The preliminary catalyst screen had indicated that a Ru-MACHO[®] catalyst favoured the formation of this product, therefore we employed this catalyst in further screening (Table 4. 5). Since the proposed mechanism would require a proton transfer in order to enable the elimination of sulfinate from the 5-*exo-trig* cyclisation product, we investigated a protic system (as employed in Chapter 3) using ^tBuOH as the solvent and KO^tBu as the base. This gave a small improvement in the yield of 5-membered ring product **224a** (70%, Entry 2). As full conversion of starting material was observed in these reactions, the reaction time was decreased (Entries 3 – 6). Pleasingly, the yield of **224a** increased slightly to 79% on decreasing the reaction time to 6 h (Entry 3). The yield of **224a** was not severely affected by decreasing the reaction time further, with a reaction time of 3 h giving the best isolated yield of 81% (Entry 5). Finally, the reaction concentration was decreased to 0.5 M, which gave a slightly improved yield of 85%. The lack of dependence of product distribution on the reaction concentration is

consistent with the literature, which suggests that both the reaction concentration and the nature of the metal catalyst is responsible for dictating the fate of the metal-hydride species in this reaction.⁵¹ Indeed, it has been proposed that the Ru-MACHO® catalyst favours hydrogen evolution over reduction due to metal-ligand co-operation, in an analogous process to that demonstrated by **MnCat01** (for a full discussion see Chapter 3.8.1).¹²³

Table 4. 5 Optimisation of Ru-MACHO®-catalysed reaction to give 5-membered ring product **224a**.

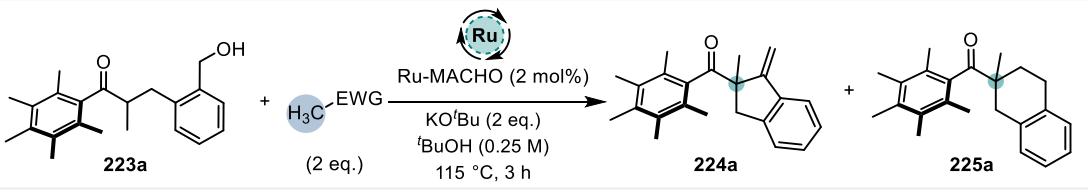


Entry	Base (eq.)	Solvent (M)	Reaction time (h)	Yield (%) ^a		
				223a	224a	225a
1	KOH (4)	PhMe (0.25)	24	-	62	-
2	KO ^t Bu (2)	^t BuOH (0.25)	24	-	70	-
3	KO ^t Bu (2)	^t BuOH (0.25)	6	2	79	-
4	KO ^t Bu (2)	^t BuOH (0.25)	4	4	78	-
5	KO ^t Bu (2)	^t BuOH (0.25)	3	5	80 (81)	-
6	KO ^t Bu (2)	^t BuOH (0.25)	2	7	77 (76)	-
7	KO ^t Bu (2)	^t BuOH (0.5)	3	1	85 (85)	-

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. Entry 1 is repeated from **Table 4.1** for comparison.

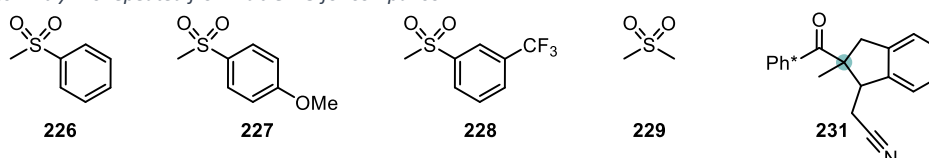
Once again, a range of different nucleophiles were also investigated (**Table 4. 6**). The yield of desired product **224a** decreased when using electron-rich aryl sulfone **227** (71%, Entry 2) and electron-poor sulfone **228** (69%, Entry 3). Using dimethyl sulfone **229** as the nucleophile gave an acceptable yield of product **224a** (74%), though this was still lower than the yield which was obtained using the commercially available PhSO₂Me as the nucleophilic partner. In this scenario, when MeCN was employed as an alternative nucleophile, a cyclised product did form, however no elimination of cyanide was observed, resulting in the isolation of nitrile **231** as the major product from the complex reaction mixture. Due to the commercial availability and optimal yields observed in both processes to form products **224a** and **225a**, it was decided to use PhSO₂Me **190** as the nucleophile in all reactions moving forwards.

Table 4. 6 Nucleophilic partner screening for Ru-MACHO® reaction.

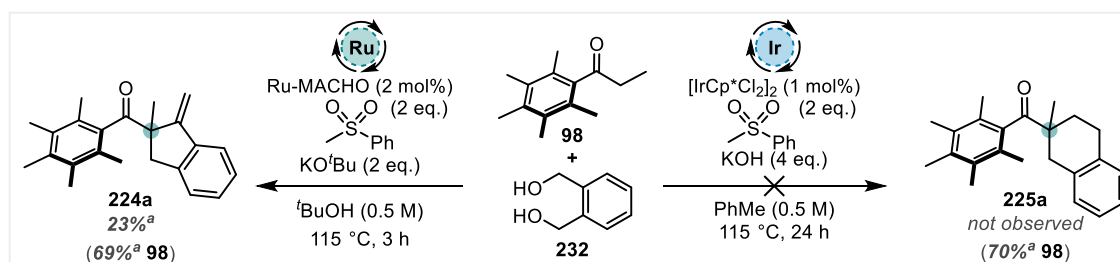


Entry	Nucleophile	Yield (%) ^a			
		223a	224a	225a	Side product
1	190	-	85 (85)	-	-
2	227	-	71	-	-
3	228	-	69	-	-
4	229	-	79 (74)	-	-
5	MeCN	-	Complex mixture		231, (20) (>[95:5] d.r).

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. Entry 1 is repeated from Table 4.5 for comparison.

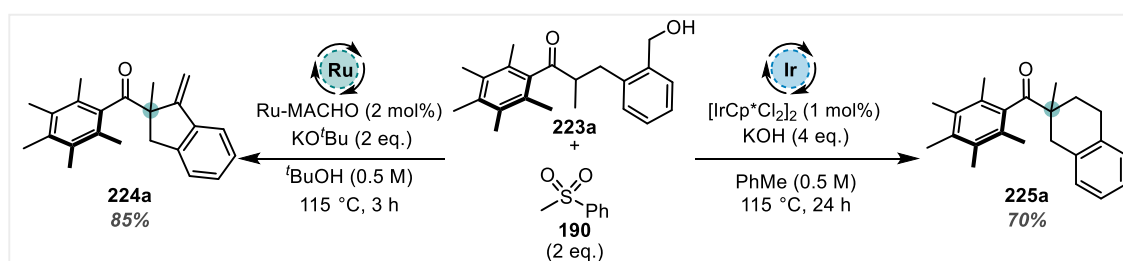


Thus far, our studies had focussed on the use of hydroxy ketone **223a** which is itself synthesised via hydrogen borrowing alkylation, to form products **224a** and **225a**. However, we considered whether this initial hydrogen borrowing reaction to preform α -tertiary precursor **223** was necessary. Therefore, control experiments were carried out using Ph* ethyl ketone **98** and diol **232** in place of hydroxy ketone **223a** (Scheme 4. 2). Although a small amount of product **224a** (23% ¹H NMR yield) was formed under the Ru-catalysed conditions, 6-membered carbocyclic product **225a** was not formed under the Ir-catalysed conditions, demonstrating the need for pre-formation of the first C–C bond. This is not entirely surprising, given the difference in reaction concentration between these optimised conditions and those employed in the formation of starting material **223a** (see Scheme 4. 6).



Scheme 4. 2 Control experiment: multicomponent reaction without preformation of α -tertiary ketone **223a**. ^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

In summary, we were able to develop divergent conditions to transform hydroxy ketone **223a** into two different products, **224a** and **225a**, each containing an α -quaternary stereocentre (**Scheme 4. 3**). The 5-membered ring product **224a** could be favoured by employing Ru-MACHO[®] as the catalyst in a protic solvent system, whereas the 6-membered ring product **225a** could be favoured when using [IrCp*Cl₂]₂ as the catalyst in PhMe. It was hypothesised that the observed selectivity is governed by the choice of metal catalyst, rather than the other differences between the two systems, however further work was necessary to determine the mechanistic pathways involved.



Scheme 4. 3 Summary of optimised reaction conditions.

4.4 Mechanistic Studies

With the optimised reaction conditions in hand, we wanted to understand how each of the two products were formed under the reaction conditions, and the root cause of the selectivity. Since each set of optimised reaction conditions differed in the reaction solvent and base employed as well as the metal catalyst used, control crossover experiments were carried out to confirm whether the metal catalyst or the wider reaction conditions were responsible for the divergent selectivity (**Table 4. 7**). When starting material **223a** was treated with [IrCp*Cl₂]₂ with the base and solvent system usually employed for the formation of 5-membered ring product **224a**, KO^tBu (two equivalents) in ^tBuOH for 3 h, only trace amounts of both products **224a** and **225a** were observed (Entry 1). However, when the same reaction conditions were employed in combination with Ru-MACHO[®], the 5-membered ring product **224a** was formed in 81% yield (Entry 2). This demonstrates that the identity of the catalyst is key for the selective formation of product **224a**. Surprisingly, the yield of 5-membered ring product **224a** was unaffected by

switching to the KOH/PhMe reaction system while using Ru-MACHO[®] as the catalyst, which gave **224a** in a similar 82% yield (Entry 3). Importantly, no 6-membered ring product **225a** was observed with Ru-MACHO[®] under these conditions, highlighting the key role of the catalyst in determining the product distribution. This is consistent with the literature, as similar PNP-pincer compounds have been shown to favour hydrogen evolution over alkene reduction.^{43, 116}

Table 4. 7 Crossover experiments with each catalyst in different reaction conditions.

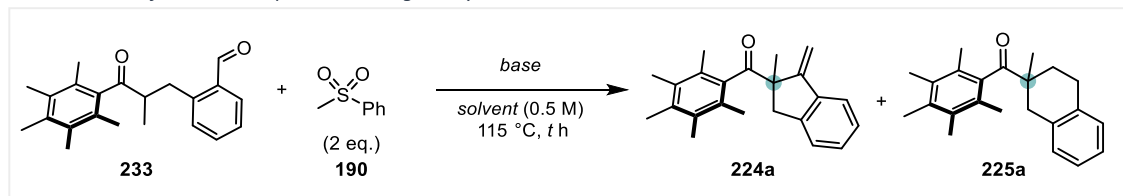
Entry	Catalyst	Base (eq.)	Solvent (M)	Time (h)	Yield (%) ^a		
					223a	224a	225a
1	[IrCp*Cl ₂] ₂	KO ^t Bu (2)	^t BuOH (0.25)	3	42	3	5
2	Ru-MACHO [®]	KO ^t Bu (2)	^t BuOH (0.25)	3	5	80 (81)	-
3	Ru-MACHO [®]	KOH (4)	PhMe (0.5)	24	-	82 (82)	-
4	[IrCp*Cl ₂] ₂	KOH (4)	PhMe (0.5)	24	1	12	71 (70)

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. Entries 1 and 4 repeated from Table 4.5 and Table 4.2 for comparison.

It was hypothesised that the different product distribution observed with the two catalysts was a result of differing relative rates of hydrogen evolution and reduction. Due to the product distribution observed with each catalyst, we proposed that with Ru-MACHO[®] the rate of hydrogen evolution is fast compared to the rate of reduction, preferentially releasing H_{2(g)} and forming the acceptorless dehydrogenation product. By contrast, with [IrCp*Cl₂]₂, we hypothesise that reduction is faster compared to hydrogen evolution, and so the hydrogen borrowing product is favoured. Therefore, we synthesised the proposed aldehyde intermediate **233** and subjected it to the reaction conditions (Table 4. 8). Using aldehyde **233**, the oxidised form of the hydroxy ketone starting material **223a**, avoids the generation of a metal-hydride in the reaction and so eliminates the option of hydrogen return. As such, we would expect only the acceptorless dehydrogenation product to form under these conditions. Pleasingly, when aldehyde **233** was reacted with PhSO₂Me under metal-free versions of both sets of reaction

conditions, only 5-membered ring product **224a** was formed in high yield. This implies that it is the higher reducing power of the iridium-hydride species (compared to the analogous ruthenium species) that results in the favoured formation of 6-membered ring product **225a** when using this catalyst.

Table 4. 8 Metal-free control experiments using aldehyde **233**.

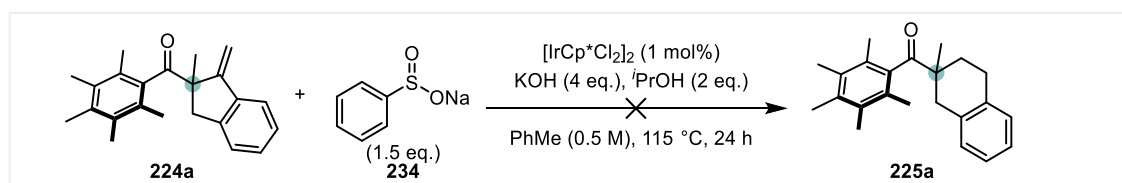


Entry	Base (eq.)	Solvent	Time (h)	Yield (%)	
				224a	225a
1	KO ^t Bu (2)	^t BuOH	3	(96)	-
2	KOH (4)	PhMe	24	(83)	-

Isolated yields are reported.

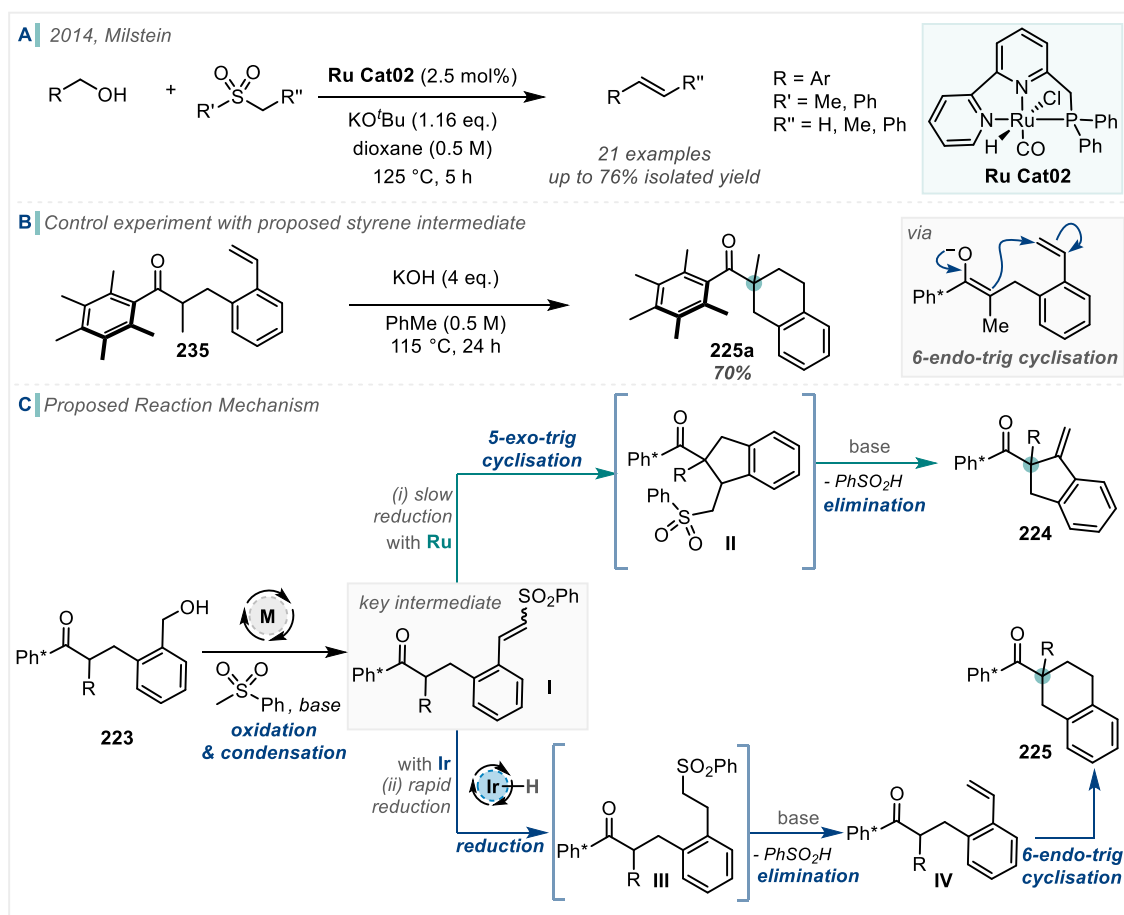
Having established that the catalyst reducing ability was crucial in determining the observed divergent reactivity, our attention turned to more fully understanding the reaction pathway. By considering the product structure, it was hypothesised that the products were formed *via* the following steps: for the formation of either product, oxidation of alcohol **223** to the corresponding aldehyde must occur, followed by condensation with the sulfone nucleophile to form the key vinyl sulfone intermediate **I** (see **Scheme 4. 1B**). From here product **224** could be formed *via* 5-*exo-trig* cyclisation, proton transfer to form a benzylic anion and subsequent elimination of sulfinate, with the metal complex evolving hydrogen gas to enable catalyst turnover. Given the similarity to the acceptorless dehydrogenation–intramolecular conjugate addition cascade that was discussed in Chapter 3, we were fairly confident in this proposed sequence of steps. The mechanistic pathway which was operative to access 6-membered ring product **225** was less clear. From key intermediate **I**, three steps must occur to access **225**: a 6-*endo-trig* cyclisation, sulfinate elimination and a reduction, however, the precise order of these steps was unknown. We first considered whether sulfinate elimination was reversible, which would enable regeneration of key intermediate **I** *via* ring opening, and would be

consistent with the observation that the 5-membered ring product **224a** was found to form much faster than **225a** (see Chapter 4.3). In order to test this hypothesis, 5-membered ring product **224a** and benzenesulfinate **234** were subjected to the Ir-catalysed reaction conditions (using *i*PrOH as a hydride source to allow the key reduction step to occur) (**Scheme 4. 4**). No formation of 6-membered ring product **225a** was observed and the starting material **224a** was recovered in 90% yield, suggesting that this pathway does not contribute to the formation of 6-membered ring product **225a**.



Scheme 4. 4 Probing the reversibility of the elimination step.

Turning to the literature, we found that Milstein and co-workers had already employed sulfones in the synthesis of styrenes from benzylic alcohols (**Scheme 4. 5A**).¹²⁴ We considered whether a similar reaction may form part of the mechanistic pathway to form **225a**. Styrene **235** was synthesised and subjected to the reaction conditions, in the absence of the iridium catalyst (**Scheme 4. 5B**). Pleasingly, the desired 6-membered ring product **225a** was formed in 70% yield, suggesting that the styrene is the final intermediate prior to the formation of **225a**. Our mechanistic proposal is therefore as follows: as previously outlined, starting material **223** undergoes oxidation to the corresponding aldehyde which undergoes condensation with the sulfone nucleophile to form key intermediate **I** (**Scheme 4. 5C**). We propose that under the ruthenium-catalysed reaction conditions, the key intermediate undergoes 5-*exo-trig* cyclisation *via* the enolate to give intermediate **II**. Under the basic reaction conditions, phenylsulfinate is eliminated from this intermediate to give **224**. We propose that reduction of the alkenyl sulfone intermediate **I** is relatively slow with the Ru-MACHO® catalyst, allowing time for the cyclisation and irreversible elimination steps to occur to form **224**, which removes the site for conjugate reduction. The metal catalyst can then easily lose H₂, likely assisted by metal-ligand co-operation *via* an analogous mechanism to that proposed for **Mn Cat01** (see Chapter 3.8.2).^{116, 125}



Scheme 4. 5 Mechanistic studies. A) Direct formation of styrenes from benzylic alcohols. B) 6-endo-trig cyclisation of proposed styrene intermediate **235**. C) Proposed mechanisms for the formation of **224** and **225**.

By contrast, when $[\text{IrCp}^*\text{Cl}_2]_2$ is employed as the catalyst, reduction of the alkenyl sulfone is fast (compared to the cyclisation and irreversible elimination steps), forming intermediate **III** which eliminates phenylsulfinate to give styrene **IV** (Scheme 4. 5C). This intermediate can then undergo 6-endo-trig cyclisation to give 6-membered ring product **225**. It should be noted that analogues of products **224** and **225** are not observed in the tandem acceptorless dehydrogenation–intramolecular conjugate addition cascade reaction (discussed in Chapter 3). We propose that the phenyl ring present in the backbone is key to the observed reactivity here, as the elimination steps within the mechanism are facilitated by the lower pKa of the benzylic protons. In addition, the phenyl ring likely acts to stabilise the anion formed in the 6-endo-trig cyclisation, where no other stabilising groups are present.

4.5 Starting Material Synthesis

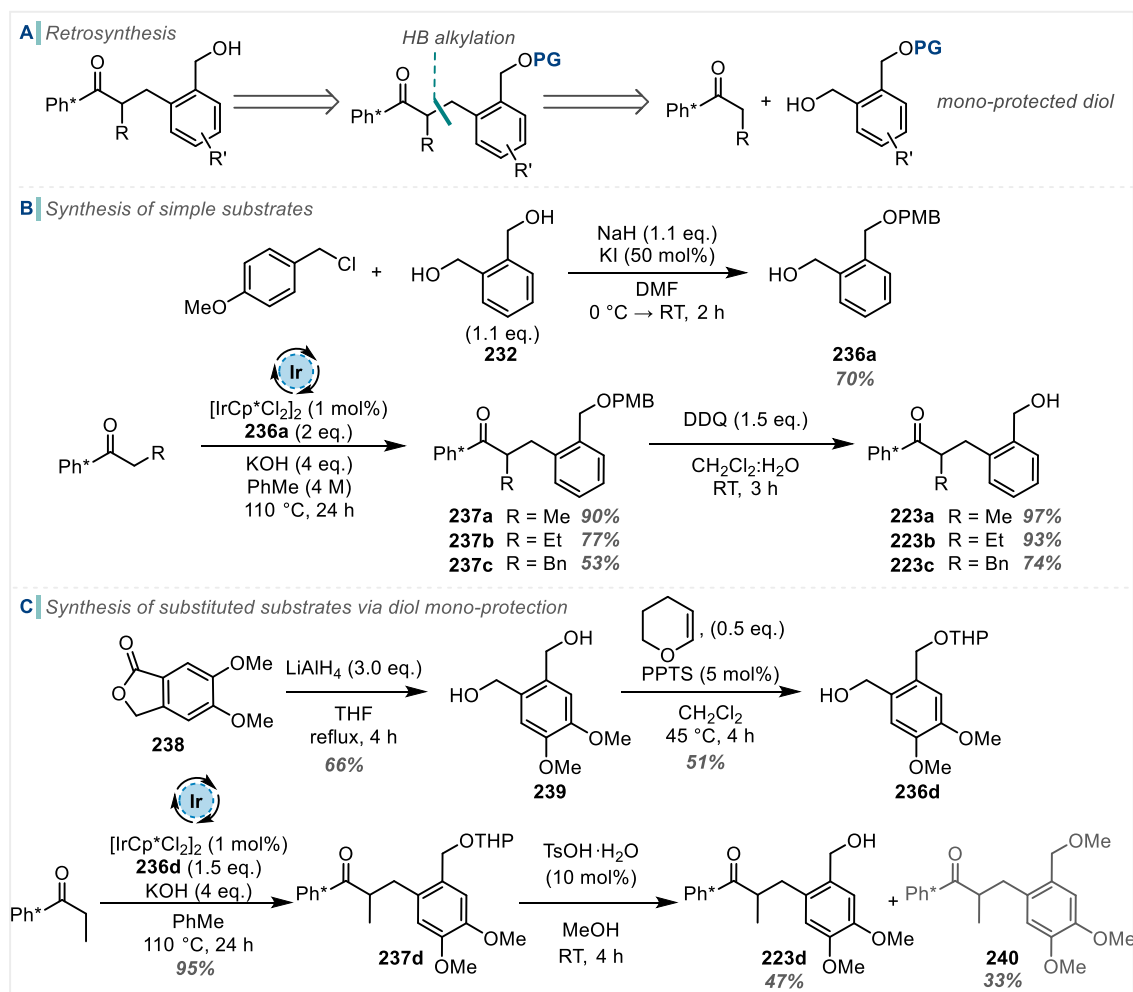
Given the nature of the starting materials for these reactions, we aimed to prepare them *via* hydrogen borrowing alkylation (**Scheme 4. 6A**). This would hopefully allow us to build complexity from relatively simple starting materials in a short synthetic sequence, as had been previously demonstrated in the intramolecular conjugate addition reaction (see Chapter 3.3). Therefore, it was necessary to devise a synthetic route to be able to access a range of different mono-protected diols to enable investigation of the substrate scope.

4.5.1 Diol mono-protection route

Our first approach to access mono-protected diol precursors was *via* simple protection of the symmetrical diol **232** with a PMB group to give **236a** (**Scheme 4. 6B**). A variety of Ph* ketone substrates were then employed in hydrogen borrowing reactions with **236** to give compounds **237a – c** in 53% – 90% yield. The PMB group could then be easily removed using DDQ to give starting materials **223a – c** in high yields. For simple substrates, this route provided a highly modular approach for the synthesis of a range of substrates, with a view to investigating the effect of multiple different groups at the quaternary position.

This mono-protection approach was also adapted for the synthesis of starting materials bearing substituents on the backbone aromatic ring. Using the dimethoxy-substituted diol **239**, substrate **223d** was accessed in a synthetically useful yield (**Scheme 4. 6C**), although the reaction stoichiometry required for the mono-protection step resulted in limited conversion to desired THP-protected diol **236d**. While the diol proved an excellent substrate in the hydrogen borrowing reaction to give **237d** in 95% yield, on removal of the THP group, we noted that a significant amount (33%) of side product **240** was formed, either *via* direct displacement of the THP group or substitution of the benzylic alcohol product with MeOH. Given these limitations, it was clear that a more general solution for the synthesis of mono-protected diol starting

materials was required, especially due to the lack of suitable, symmetrical, and commercially available diol precursors.

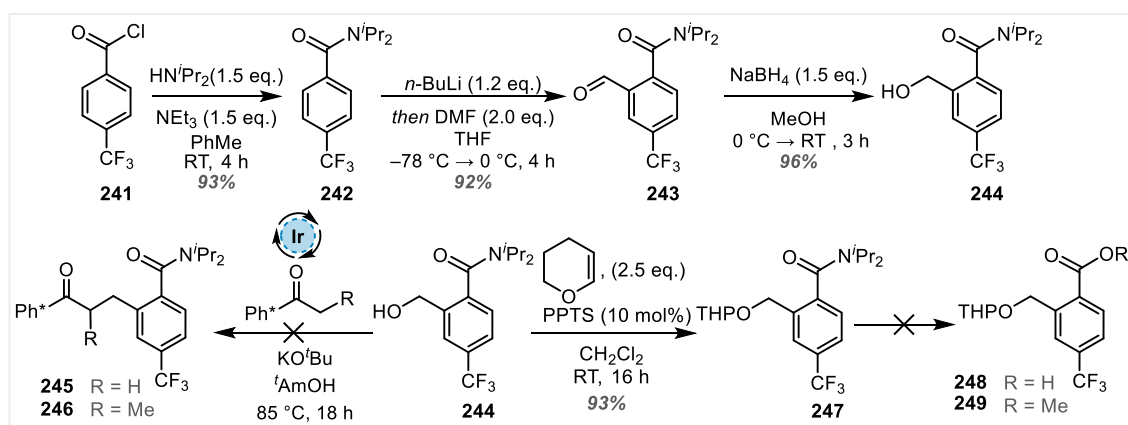


Scheme 4. 6 A) Starting material retrosynthesis. B) & C) Synthesis of substrates via hydrogen borrowing catalysis with mono-protected diols..

4.5.2 *ortho*-Lithiation route

Next, we investigated an alternative route for the synthesis of mono-protected diols for initial hydrogen borrowing to access substrates for the cyclisation reactions. We chose to explore a route based on directed *ortho*-lithiation chemistry for a number of reasons: firstly, there was strong literature precedent for the formation of alcohols *via* this route (**Scheme 4. 7**).¹²⁶ This route was also attractive due to the large number of diverse, commercially available aryl acid precursors which could easily undergo amide coupling to access compounds bearing the required directing group. Therefore, aryl amide **242** was synthesised in high yield and successfully underwent directed *ortho*-lithiation, quenching with DMF to access the required

aldehyde **243** in 93% yield. Subsequent reduction of this aldehyde gave alcohol **244** in 96% yield, however this alcohol did not undergo hydrogen borrowing with either Ph* methyl ketone **31** or Ph* ethyl ketone **98** to give the corresponding alkylated products **245** or **246**. This lack of reactivity could either be a result of the electron-deficient nature of the benzylic alcohol, or due to increased steric hindrance from the *ortho*-amide. Alcohol **244** was therefore protected with a THP group to give **247**, in the hope of converting the amide to the corresponding alcohol prior to hydrogen borrowing alkylation. Unfortunately, the amide could not be hydrolysed under basic reaction conditions to give **248** or converted to the corresponding methyl ester, **249**.^{127, 128} As a result, this route was not pursued further as a method of accessing mono-protected diols for the initial hydrogen borrowing step.

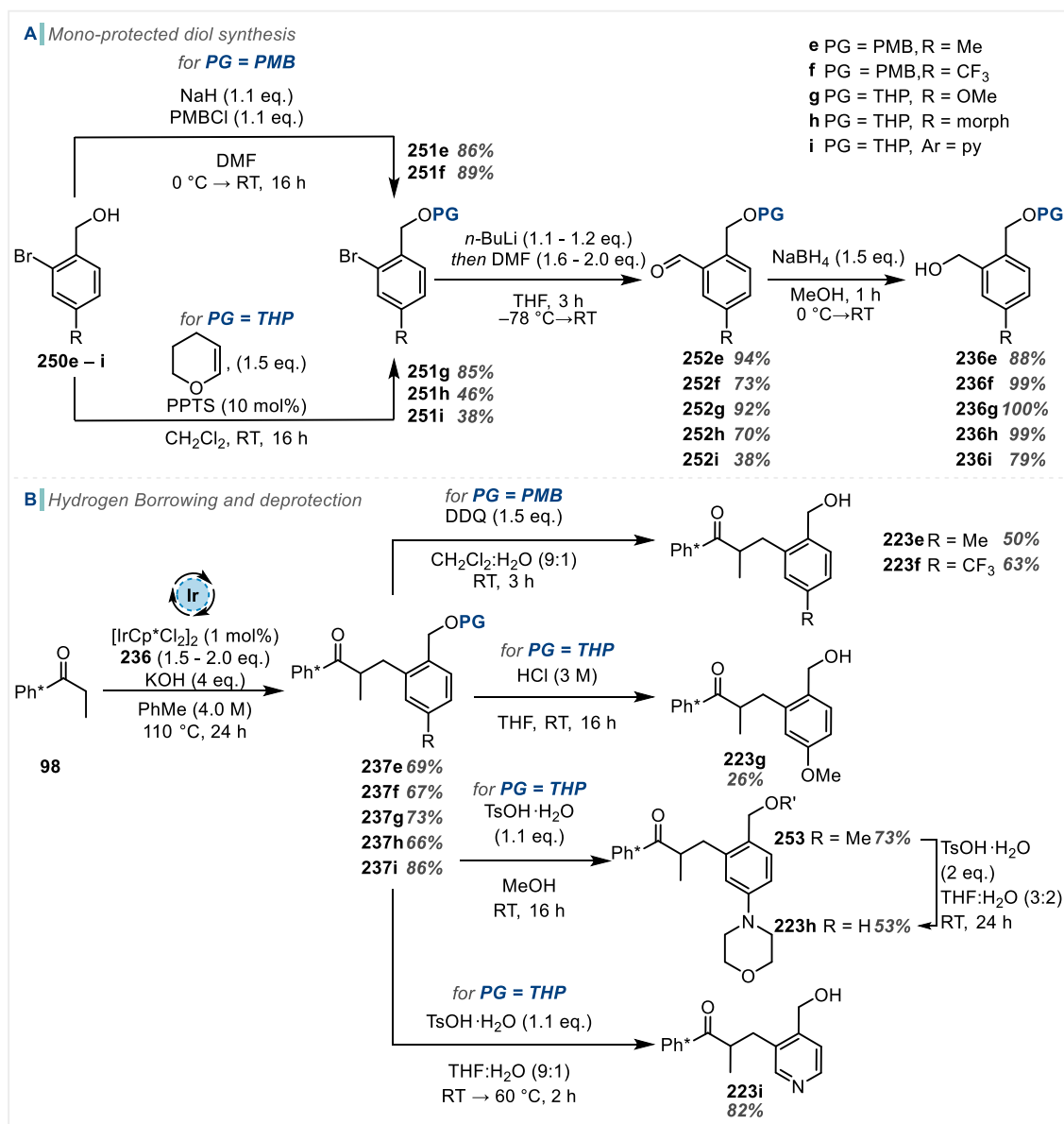


Scheme 4. 7 Attempted synthesis of mono-protected diols via directed *ortho*-lithiation.

4.5.3 Lithium-halogen exchange route

Encouraged by the high yields observed for the lithiation step in the previous approach, an alternative strategy based on lithium-halogen exchange was devised (Scheme 4. 8A). *ortho*-Bromo benzylic alcohols **250e – h** could be easily prepared or purchased and protected with a PMB or THP protecting group, as appropriate, to give aryl bromides **251e – h**, which could then undergo Li-halogen exchange to give the corresponding organolithium, which was quenched with DMF to give formylated products **252e – h** in 70% – 92% yield. Pyridyl aldehyde **252i** was also prepared *via* this sequence, however side reactions resulted in a lower yield for

the formylation step (38%). Aldehydes **252e – i** were all reduced using NaBH_4 to form the corresponding mono-protected diols **236e – i** in high yields.



Scheme 4. 8 Synthesis of alcohol substrates via lithium-halogen exchange. morph = morpholine.

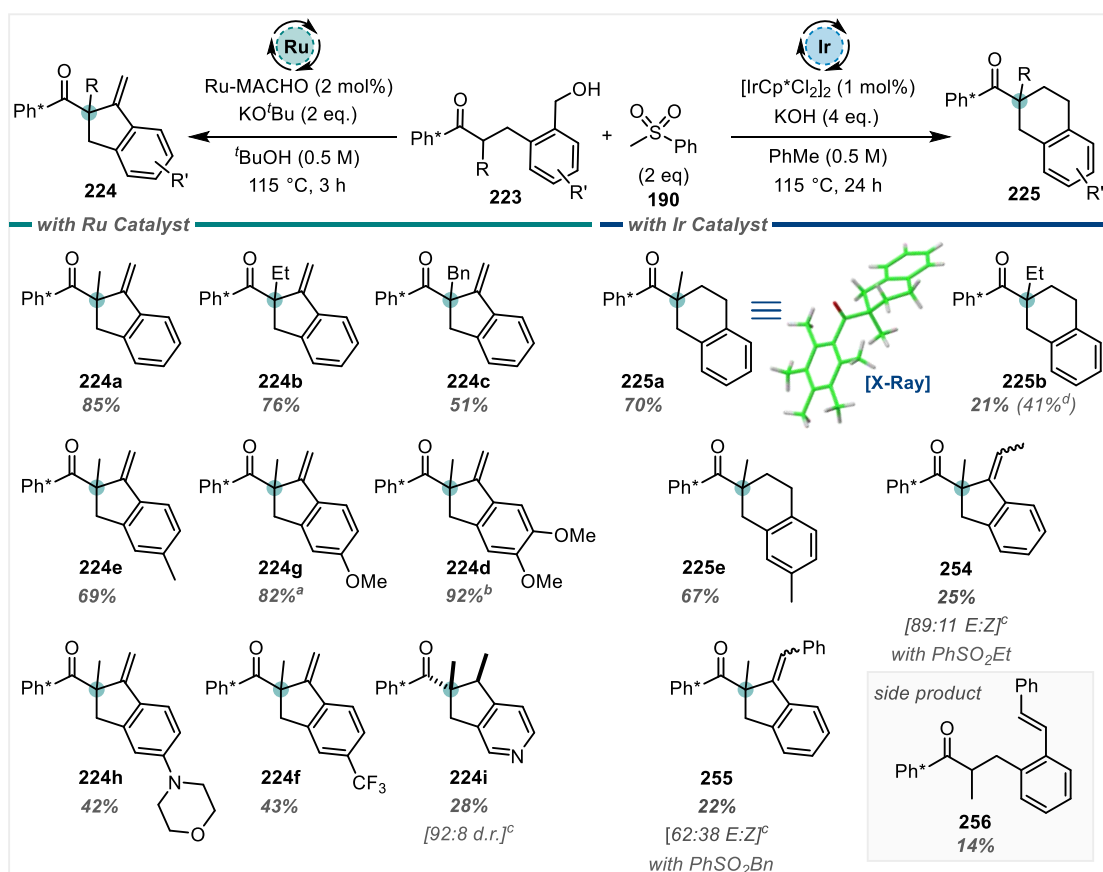
The mono protected diols **236e – i** all served as excellent alcohol substrates for hydrogen borrowing with Ph^* ethyl ketone **98**, giving the corresponding alkylated products **237e – i** in 66% – 86% yield (Scheme 4. 8B). However, deprotection of the alcohol proved problematic for a number of substrates. Methyl-substituted PMB ether **237e** did undergo deprotection with DDQ to give desired product **223e**, however a significant amount of the corresponding aldehyde was also generated, demonstrating poor selectivity in the cleavage of the ether bond.

Unfortunately, the corresponding aldehyde was inseparable from the anisaldehyde by-product, resulting in a low overall yield for the transformation. The more electron-deficient trifluoromethyl-substituted PMB ether **237f** did not present the same issue, giving alcohol **223f** in 63% yield. Informed by previous approaches, where the formation of side product **240** was observed when deprotecting dimethoxy analogue **237d**, alternative conditions were trialled for the deprotection of the THP group in **237g**, in the absence of MeOH. While a sufficient amount of product **223g** was obtained for further study, a large amount of decomposition occurred, resulting in a poor 26% yield. Since THP ether **237h** contained a less electron-rich aromatic ring than **237d**, the THP ether **237h** was subjected to methanolysis conditions. Unfortunately, this resulted in smooth conversion to the methyl ether **253**, presumably *via* nucleophilic substitution. However, it was found that hydrolysis of the methyl ether was possible under mild conditions using TsOH·H₂O in aqueous THF, giving desired alcohol **223h** in 53% yield. A variant on these conditions was successfully applied to THP ether **237i**, giving alcohol **223i** in 82% yield.

4.6 Substrate Scope

With the hydroxy ketone starting materials (**223a – i**) in hand, we set about investigating the scope of the reactions (**Scheme 4. 9**). Under the ruthenium-catalysed conditions, methyl, ethyl and benzyl groups were tolerated at the quaternary position, to give **224a**, **224b** and **224c** in 85%, 76% and 51% respectively. The isolated yield was observed to decrease as the size of the group increases, demonstrating the challenge of forming quaternary stereocentres with substituents that have a higher steric demand. Simple alkyl substitution was also tolerated on the backbone aromatic ring, giving **224e** in 69% yield. Methoxy-substituted benzylic alcohols proved to be excellent substrates, giving **224g** and **224d** in 82% and 92% yield, respectively. However, the related electron-rich morpholine substituted benzylic alcohol substrate gave a lower yield of **224h** (42%). Electron-deficient groups were also tolerated, as exemplified by the formation of **224f** in moderate yield (43%); the lower yield observed here is possibly a result of

slower oxidation of the electron-deficient benzylic alcohol. Interestingly, when the pyridyl alcohol substrate **223i** was employed, the expected exocyclic alkene product was not observed, however, a further reduced analogue **224i** was isolated in 28% yield, with high diastereoselectivity. We hypothesise that the final reduction step occurs in this case as the pyridine nitrogen is more electron-withdrawing and suitably positioned to stabilise the anion formed *via* conjugate reduction by the metal-hydride. The relative stereochemistry was tentatively assigned by analogy with reduced carbocyclic derivative **262** (see **Scheme 4.12**) and is consistent with forming the thermodynamically favoured product by base-promoted equilibration.



Scheme 4.9 Substrate Scope using benzylic alcohol substrates. Unless otherwise stated, reactions carried out on 0.30 mmol scale and isolated yields are stated. ^a Reaction conducted on 0.15 mmol scale. ^b Reaction conducted on 0.20 mmol scale. ^c Ratio determined post-purification due to overlapping peaks. ^d Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard. X-ray crystallography data and analysis were provided by Timothy C. Jenkins.

Unfortunately, the substrate scope was found to be much more limited when using the iridium-catalysed system. A significant decrease in yield was observed with increasing steric congestion at the quaternary position, as the corresponding ethyl compound **225b** was formed

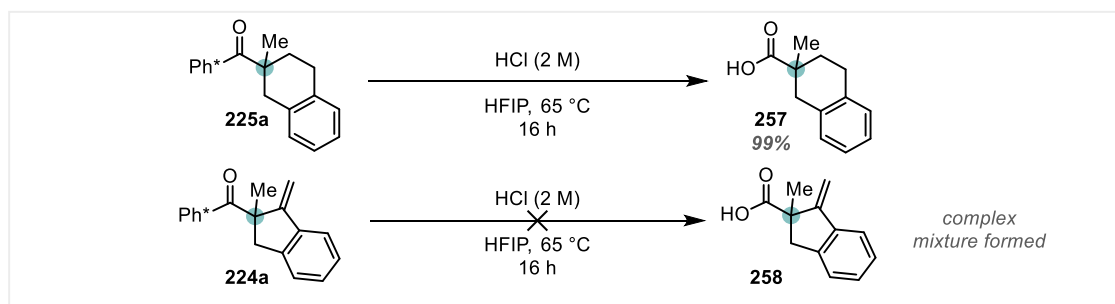
in 41% ^1H NMR yield, however challenging purification procedure resulted in a much lower isolated yield of 21%. The corresponding benzyl-substituted compound could not be formed under these conditions. While a simple methyl substituent was tolerated on the backbone aromatic ring, giving **224e** in 67% yield, more electron-donating or electron-withdrawing groups were not tolerated; when either dimethoxy substrate **223d** or trifluoromethyl-substituted substrate **223f** were subjected to these conditions, a complex mixture of products was formed.

A range of alternative sulfone nucleophiles were also investigated, in the hope of transferring larger groups to the products. Surprisingly, when PhSO_2Et and PhSO_2Bn nucleophiles were employed under both sets of reaction conditions, only the system with $[\text{IrCp}^*\text{Cl}_2]_2$ gave any cyclised product, resulting in the formation of alkenes **254** and **255** in poor yields, with modest *E:Z* ratios. We propose that these products are formed with these sulfone substrates due to more challenging reduction of the alkenyl sulfone intermediate, *via* a mechanistic pathway analogous to the one that forms exocyclic alkene **224**. Interestingly, when PhSO_2Bn was employed as the nucleophile, alkene side product **256** was also isolated in 14% yield. The formation of this product is consistent with the mechanism proposed for the formation of the 6-membered ring product **225** *via* reduction and sulfinate elimination to give a styrene prior to *6-endo-trig* cyclisation (see Chapter 4.4). In this case, no 6-membered ring product was observed, indicating that in this case, *6-endo-trig* cyclisation is unfavourable, presumably as a result of increased steric congestion in the transition state.

4.7 Product Derivatisation

Having explored the substrate scope of both the ruthenium- and iridium-catalysed approaches to form 5- and 6-membered rings respectively, we set about investigating ways in which the products could be derivatised. We initially attempted to cleave the key Ph^* protecting group using established acidic conditions for *retro*-Friedel–Crafts acylation (**Scheme 4. 10**).⁵¹ While the Ph^* group was easily cleaved from 6-membered ring product **225a** to give acid **257** in excellent

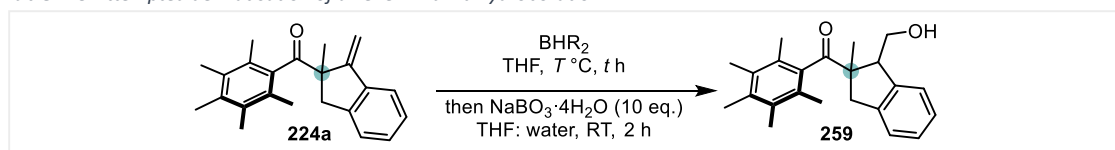
yield, when 5-membered ring compound **224a** was subjected to the same reaction conditions, a complex mixture was formed, presumably due to participation of the reactive exocyclic alkene.



Scheme 4. 10 Ph* cleavage reactions of 5- and 6- membered ring products.

A variety of different reactions were considered for further derivatisation of exocyclic alkene **224a** to enable downstream Ph* cleavage. We initially investigated hydroboration of alkene **224a**, as the corresponding products could deliver a range of highly substituted lactones upon Ph* cleavage (Table 4. 9). Unfortunately, despite screening a range of conditions, no conversion to desired product **259** was observed.

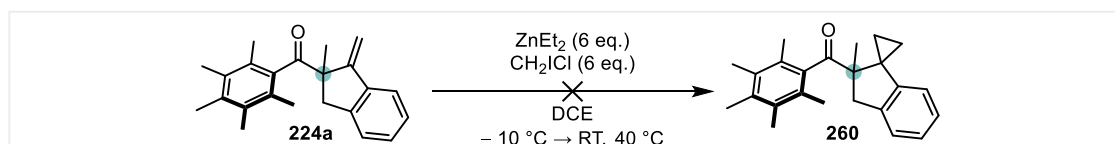
Table 4. 9 Attempted derivatisation of alkene **224a** via hydroboration.



Entry	Borane reagent (eq.)	Temperature (°C)	Time (h)	Yield (%) ^a	
				224a	259
1	9-BBN (2)	RT	16	77	-
2	BH ₃ ·SMe ₂ (2)	RT	16	complex mixture	
3	BH ₃ ·SMe ₂ (1)	0	2	92	-
4	BH ₃ ·SMe ₂ (1)	RT	2	85	-

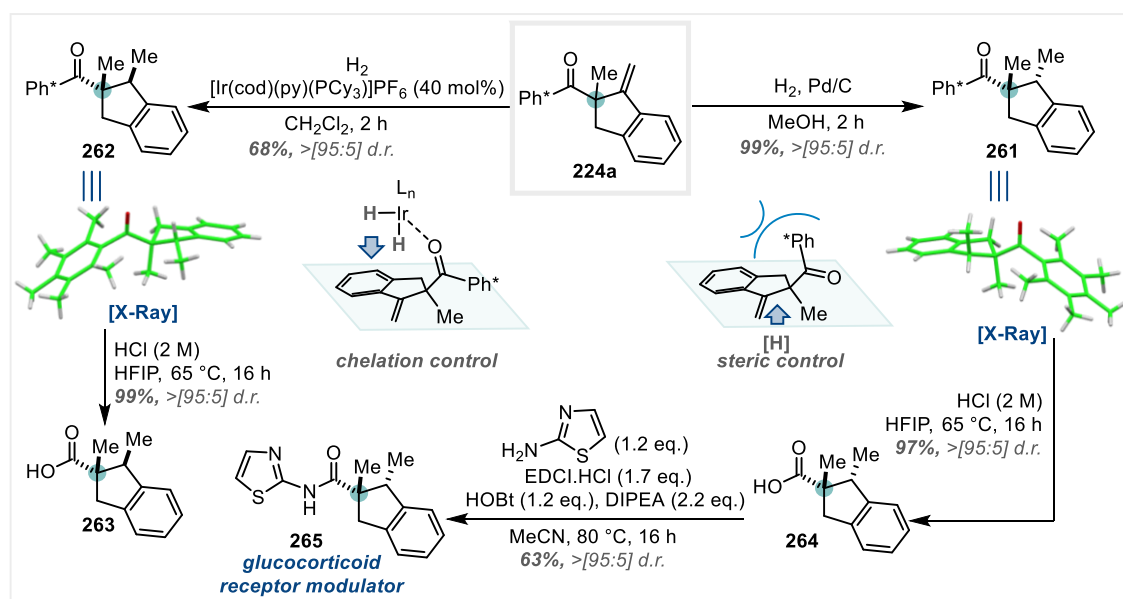
^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Cyclopropanation was also trialled in an effort to form more complex, tricyclic products (Scheme 4. 11). Again, no conversion of the starting material was observed at room temperature, and a complex mixture of products was formed when the reaction was heated.



Scheme 4. 11 Attempted derivatisation of product **224a** via cyclopropanation.

Finally, we considered derivatisation of the alkene product **224a** *via* reduction (**Scheme 4. 12**). Pleasingly, simple hydrogenation could be carried out under steric control using Pd/C to give *cis*-substituted product **261** as a single diastereomer in high yield; the relative stereochemistry of the product was proven by both nOe analysis and single crystal X-ray analysis. It was proposed that the high degree of selectivity was derived from addition of hydrogen to the least hindered face. Crabtree's catalyst could also be employed for the hydrogenation to access the *trans*-diastereomer under chelation control, giving **262** in 68% yield, with the relative stereochemistry again proven by single crystal X-ray analysis. In the absence of the reactive exocyclic alkene, the Ph* protecting group could be removed from both of the reduced compounds **261** and **262** to give the corresponding acids **263** and **264** in excellent yield. Finally, the *cis*-diastereomer **264** was coupled with 2-aminothiazole to give amide **265**, which has been studied as a glucocorticoid receptor modulator in the patent literature.^{129, 130}

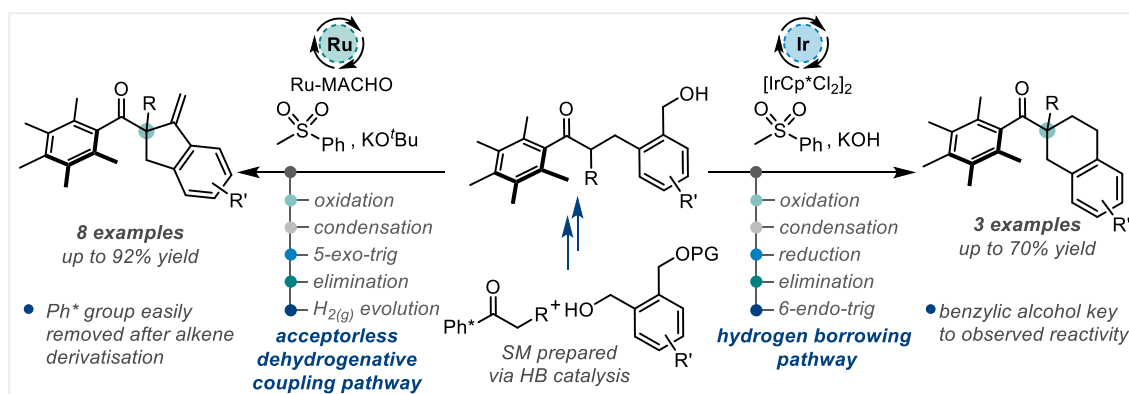


Scheme 4. 12 Derivatization of alkene product **224a**. X-ray crystallography data and analysis were provided by Timothy C. Jenkins.

4.8 Conclusion

This chapter describes the synthesis of α -quaternary ketones using benzylic alcohol starting materials (**Scheme 4. 13**). In a divergent approach, either 5- or 6-membered carbocyclic products could be accessed by employing either a Ru-MACHO® or $[\text{IrCp}^*\text{Cl}_2]_2$ catalyst, respectively. After conducting mechanistic investigations to elucidate the origin of this

selectivity, it was proposed that this was due to a difference in the reducing ability of the metal-hydride formed in the catalytic cycle: when the more reducing iridium-hydride is present, the key intermediate alkenyl sulfone intermediate is reduced, allowing elimination of sulfinate prior to 6-*endo-trig* cyclisation of the formed styrene intermediate. Using a range of substrates accessible *via* hydrogen borrowing alkylation of mono-protected diols, a range of α -quaternary ketone products could be formed. Importantly, the key Ph* protecting group could be removed to give a range of useful acid fragments, each bearing an α -quaternary stereocentre.



Scheme 4.13 Summary of formation of α -quaternary ketones using benzylic alcohol substrates.

In this thesis, the successful synthesis of quaternary stereocentres within the hydrogen borrowing manifold has been described. This work expands the chemical space accessible *via* this methodology, enabling the formation of a variety of different structures containing an α -quaternary ketone. A range of approaches has been explored which are all based on the same underpinning strategy: using hydrogen borrowing catalysis to access an α -branched ketone which is activated in some way towards cyclisation (**Scheme 5. 1**).



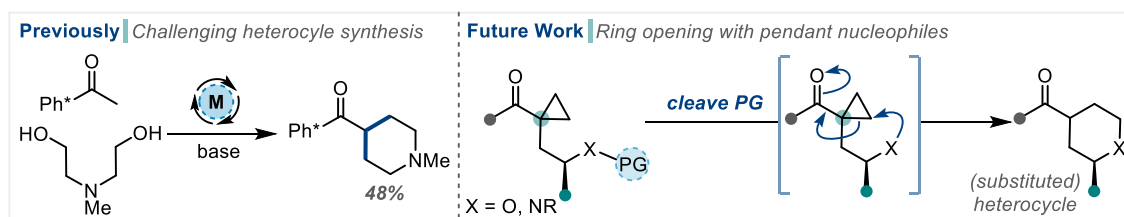
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hydrogen borrowing reaction and the key Ph^{*} protecting group could be removed in a two-step sequence with retention of the cyclopropane.

Acceptorless dehydrogenation was then investigated as an alternative way of activating a substrate towards cyclisation (**Scheme 5. 1B**). An α -branched ketone substrate bearing a pendant alcohol could be converted into a Michael acceptor by oxidation and condensation with an appropriate nucleophile, which could then be intercepted by a pendant enolate. This gave the corresponding cyclopentane and cyclohexane products bearing a quaternary stereocentre with high *trans*-diastereoselectivity. Importantly, substituents could be incorporated at both the quaternary position and on the hydroxy ketone substrate backbone, enabling the synthesis of a wide range of complex fragments in a short sequence using hydrogen borrowing and acceptorless dehydrogenation.

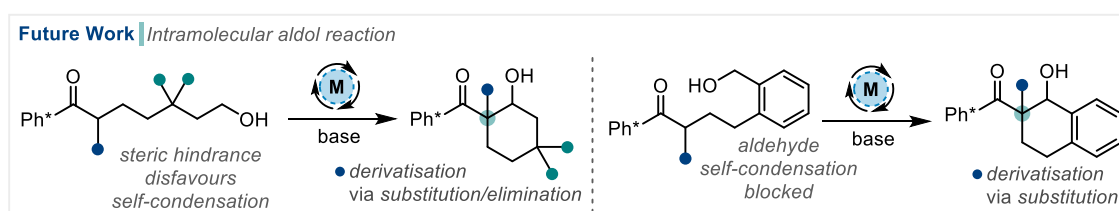
Finally, it was found that benzylic substrates behaved anomalously in the previous reaction when employed in combination with sulfone nucleophiles (**Scheme 5. 1C**). It was discovered that the product distribution could be altered depending on which metal catalyst was used. Mechanistic studies were conducted to elucidate the cause of this divergent reactivity and it was shown that the relative rate of reduction of a common alkenyl sulfone intermediate compared to cyclisation and sulfinate elimination dictated the product distribution. It was also demonstrated that, for reactions employing a Ph^{*} protecting group (**Scheme 5. 1B & C**), this group could be removed from the products or their derivatives in high yield.

Having developed a general strategy for the synthesis of quaternary stereocentres using hydrogen borrowing methods, future work could explore many avenues. The utility of the α -cyclopropyl products could be further explored, for example, by harnessing the ring-opening reactivity observed in this study (**Scheme 5. 2**). Using an intramolecular nucleophile, this would allow the synthesis of heterocycles, which has been challenging using C–C hydrogen borrowing catalysis, providing an alternative approach for their synthesis.⁴⁵



Scheme 5. 2 Ring-opening derivatisation of cyclopropane products to synthesise heterocycles.

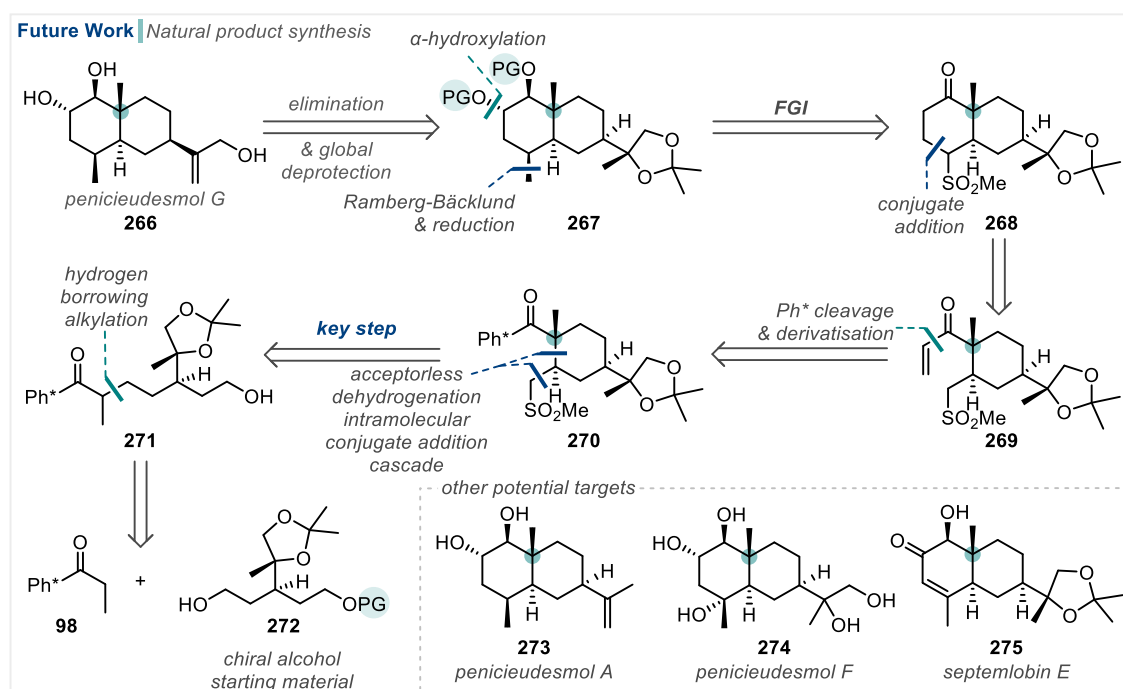
In this thesis, the synthesis of quaternary stereocentres *via* intramolecular aldol reaction was not thoroughly explored due to the discovery of the acceptorless dehydrogenation–intramolecular conjugate addition reaction and the observation that the desired intermediate aldehyde was susceptible to self-condensation to form an unwanted dimer in the 5-membered ring system (see Chapter 3. 1). We propose that the desired intramolecular cyclisation could be encouraged by engineering the substrates to disfavour the undesirable aldehyde self-condensation process (**Scheme 5. 3**). In this way, a class of β -hydroxy ketone products may be accessed which could be further derivatised to access other products bearing an α -quaternary ketone. This work has also highlighted the many alternative catalysts that can be employed in hydrogen borrowing methods and has showcased catalysts containing earth-abundant metals and P,N,P-pincer ligands which are particularly effective for acceptorless dehydrogenative couplings and that are effective at high dilution, which would likely favour the formation of the desired intramolecular aldol product.



Scheme 5. 3 Synthesis of quaternary stereocentres using an intramolecular aldol reaction.

Given the ubiquity of quaternary stereocentres in biologically-relevant compounds, this general strategy could also be employed in the total synthesis of some natural products. Fortuitously, the *trans*-substitution pattern accessed in high diastereoselectivity in the acceptorless dehydrogenation–intramolecular conjugate addition cascade reaction is prevalent in many natural products containing a cyclohexane ring. This reaction could therefore form part of a

synthetic strategy to make eudesmane-type natural products, such as penicieudesmol G, **266** (Scheme 5. 4).¹³¹ We propose that by using an enantioenriched hydroxy ketone starting material, such as **271**, in the key step, the desired cyclohexane product **270** will be formed as a single enantiomer. The sulfone group incorporated in this key step could then act as the nucleophile in a second intramolecular conjugate addition reaction to close the second ring and give the core structure **268**; the sulfone functional handle could then be removed using a Ramberg-Bäcklund reaction and subsequent reduction. The starting material for the key step could itself be prepared *via* hydrogen borrowing alkylation using a chiral mono-protected diol, **272**. The Ph* group would be key to enabling the hydrogen borrowing and acceptorless dehydrogenation reaction, driving high *trans*-diastereoselectivity in the latter step. In addition, the removable nature of this group will allow easy access to the required enone, *via* single step cleavage of the Ph* group to the Weinreb amide.



Scheme 5. 4 Application of the acceptorless dehydrogenation–intramolecular conjugate addition cascade to total synthesis.

Overall, the development of a general strategy for the synthesis of quaternary stereocentres within the hydrogen borrowing manifold is transformative for the hydrogen borrowing methodology and will allow these techniques to be employed in the synthesis of a much wider range of structures than has previously been possible.

6. Experimental

6.1 General Experimental

Glassware: Microwave vials and vial caps (containing a resealing silicone/PTFE septum) were purchased from Kinesis (Cole-Palmer) and were used without flame-drying. All other reactions were carried out in flame-dried glassware under an atmosphere of nitrogen unless stated otherwise.

Temperature and Heating: Room temperature (RT) refers to 20 – 25 °C. Temperatures of 0 °C were obtained using an ice/water bath, temperatures of –17 °C were obtained using an ice/NaCl bath, and temperatures of –78 °C were obtained using a dry ice/acetone bath. Heating was achieved using an oil bath equipped with a contact thermometer or DrySyn® heating blocks.

Reagents and Solvents: PhMe, CH₂Cl₂, Et₂O, tetrahydrofuran (THF), MeCN, and 1,4-dioxane were purified by filtration through activated alumina columns employing the method of Grubbs *et al.*¹³² Water was purified by an Elix® UV-10 system. All other solvents and reagents were used as supplied by major chemical suppliers without prior purification.

Chromatography: Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F₂₅₄ 0.25 mm pre-coated aluminium plates. TLC plates were visualised under UV light (λ = 254 nm) and/or by staining with potassium permanganate solution, phosphomolybdic acid stain, bromocresol green stain or vanillin in acidic ethanol (Vanillin stain). Flash column chromatography was performed using VWR silica gel 60 (particle size 40 – 63 μ m or 15 – 40 μ m) using head pressure by means of a nitrogen line.

NMR Spectroscopy: NMR spectroscopy was carried out using Bruker 400 MHz, 500 MHz, 600 MHz (with helium-cooled broadband cryoprobe) or 700 MHz (with inverse TCI cryoprobe) spectrometers 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), pentet (p), hextet (h), heptet (hept.), or

multiplet (m). Higher multiplicities are indicated by combinations of these abbreviations, for example: doublet of doublets (dd). The abbreviation br. denotes broad. Coupling constants, J , are rounded to the nearest 0.1 Hz and are presented as observed. Unless otherwise stated, all NMR experiments were performed at 298 K. Where a pentamethylphenyl (Ph*) group is employed, peak broadening and splitting of signals from carbons numbered C(2), C(3), C(6) and C(7), and any associated protons may be observed in both the ^1H and ^{13}C NMR spectra due to restricted rotation, resulting in more resonances than initially expected based upon symmetry. Similar peak broadening and splitting may be observed when a 2,3,5,6-tetramethylphenyl (Ph $\times$) group is employed, where signals for carbons numbered C(2), C(3), C(5) and C(6) and any associated protons may be affected. For inseparable mixtures of diastereomers (>[75:25] d.r.), both isomers are reported separately and the structure of the major diastereomer is shown. When ^1H and ^{13}C NMR data for the major diastereoisomer is reported, any signals that overlap with the minor isomer have been integrated without the contribution from the minor isomer being included. When ^1H and ^{13}C NMR data for the minor diastereoisomer is reported, assignments are given where possible. For equimolar mixtures of diastereomers (d.r. $\leq$ [75:25]), ^1H NMR data for isomers is reported together.

Compound names and atom numbering: Systematic names were generated by the computer software ChemDraw 23.0.1 according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). The atom numbering shown does not follow IUPAC numbering and is therefore different to the compound name.

Melting Points and Infrared Spectroscopy: Melting points were determined using a Griffin melting point apparatus and are uncorrected. Infrared spectra were recorded neat or as a thin film on a Bruker Tensor 27 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (λ_{max}) are quoted in wavenumbers (cm^{-1}). The abbreviation br. denotes broad.

Mass Spectrometry: Low-resolution mass spectra were recorded on a Waters LCT Premier XE bench-top orthogonal acceleration time-of-flight LC-MS system (loop injection mode). High resolution mass spectrometry (HRMS) was carried out using flow injection analysis and was performed on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe and a TOF mass analyser. In positive ion mode, the flow rate was set to 0.300 mL/min using a 50% methanol_(aq) + 0.1% formic acid eluent. Scan parameters were set as follows: analyser mode, full scan; scan range, 50 2000 m/z; scan rate, 2 Hz; cone voltage, 30 V; capillary voltage, 1.5 kV; desolvation temperature, 550 °C; and intelligent data capture, on. In negative ion mode, the flow rate was set to 0.300 mL/min using a 50% methanol_(aq) + 0.1% formic acid eluent. Scan parameters were set as follows: analyser mode, full scan; scan range, 50 2000 m/z; scan rate, 2 Hz; cone voltage, 40 V; capillary voltage, 0.8 kV; desolvation temperature, 550 °C; and intelligent data capture, on. Electrospray ionisation (ESI) HRMS were also recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using a water:methanol:formic acid (10:89.9:0.1) eluent. The system uses an orbitrap mass analyser and 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.

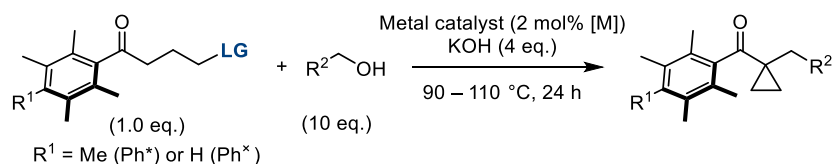
X-Ray Crystallography: Single crystal X-ray data collection and structure determination were performed by Dr. Kirsten E. Christensen or Timothy C. Jenkins in the Chemistry Research Laboratory, University of Oxford. Crystals were mounted on MiTeGen loops using perfluoropolyether oil and rapidly transferred to a goniometer head on a diffractometer fitted with an Oxford CryoSystems CryoStream open-flow nitrogen cooling device.¹³³ Data collections were either carried out at 150 K using an (Rigaku) Oxford Diffraction Supernova A

diffractometer, or at 100 K using a high flux Rigaku Synergy DW rotating anode diffractometer using mirror-monochromated Cu K α radiation ($\lambda = 1.54184 \text{ \AA}$). Data were processed using CryAlisPro, the structure was then solved using charge-flipping algorithm SUPERFLIP¹³⁴ and refined by full-matrix least squares using CRYSTALS.^{135, 136} Structures are visualised and represented using the software Mercury.

6.2 Experimental for Chapter 2

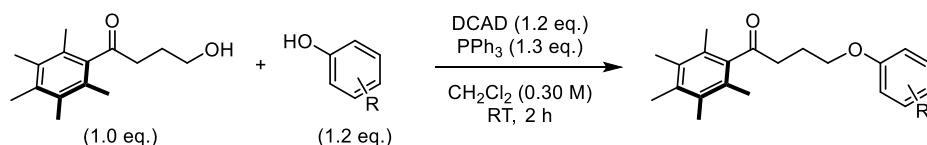
6.2.1 General Procedures

General Procedure A: Hydrogen borrowing using pre-functionalised ketones to give α -cyclopropyl ketones

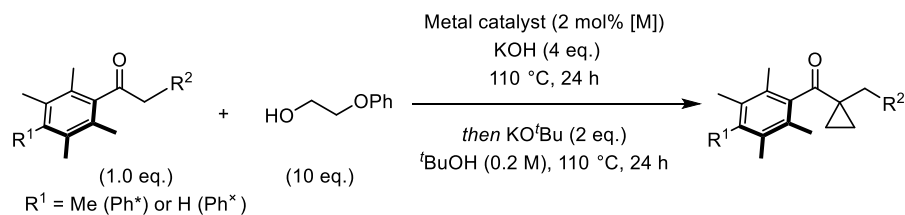


Ph* or Ph[×] ketone substrate (1.00 eq.), metal catalyst (2.0 mol% [M]) and KOH (4.00 eq.) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and alcohol (10.0 eq., degassed with Ar (balloon)) was added. The reaction was heated at 90 – 110 °C for 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

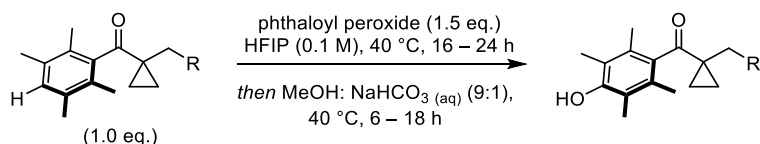
General Procedure B: Mitsunobu Reaction for the synthesis of pre-functionalised ketones



A substituted phenol (1.20 eq.) was added to a solution of alcohol **90** (1.00 eq.) in CH₂Cl₂ (0.30 M). PPh₃ (1.30 eq.) and di-(4-chlorobenzyl)azodicarboxylate (DCAD, 1.20 eq.) were added and the reaction was stirred at RT for 2 h. The reaction mixture was filtered under reduced pressure and the filtrate was concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

General Procedure C: Hydrogen borrowing using 2-phenoxyethanol as a cyclopropane surrogate to give α -cyclopropyl ketones


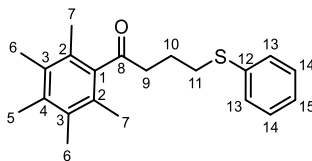
Ph* or Ph^x ketone substrate (0.300 mmol, 1.00 eq.), metal catalyst (2.0 mol% [M]) and KOH (1.20 mmol, 4.00 eq.) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and 2-phenoxyethanol (3.00 mmol, 10.0 eq., degassed with Ar (balloon)) was added. The reaction was heated at 110 °C for 24 h, cooled to RT and KO^tBu (0.600 mmol, 2.00 eq.) was added. The vial was re-sealed and purged with Ar (balloon) for 5 min. ^tBuOH (0.2 M) was added and the reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

General Procedure D: Oxidation of Ph^x group using phthaloyl peroxide


Phthaloyl peroxide **S4** (1.50 eq.) was added to a solution of Ph^x ketone (1.00 eq.) in 1,1,1,3,3,3-hexafluoro-2-propanol (0.1 M, degassed with Ar (balloon)). The resulting mixture was purged with Ar (balloon) and heated at 40 °C for 16 – 24 h. The crude reaction mixture was concentrated *in vacuo* and deoxygenated MeOH and sat. aq. NaHCO₃ (9:1, 0.1 M, degassed with Ar (balloon)) were added. The mixture was heated at 40 °C for a further 6 – 18 h, cooled to RT and diluted with brine and CH₂Cl₂. The layers were separated and the aqueous layer extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

6.2.2 Preparation and Characterisation of Compounds

74 1-(2,3,4,5,6-Pentamethylphenyl)-4-(phenylthio)butan-1-one



Triethylamine (0.94 mL, 6.72 mmol) was added dropwise to a solution of 4-bromo-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one **84** (1.00 g, 3.36 mmol) and thiophenol (0.41 mL, 4.0 mmol) in EtOAc (35 mL) at RT. The mixture was heated to 65 °C and stirred at this temperature for 16 h. The mixture was cooled to RT and concentrated *in vacuo*. Purification via column chromatography (eluent, pentane → pentane/Et₂O, 95:5) gave the *title compound* as a white solid (893 mg, 81%).

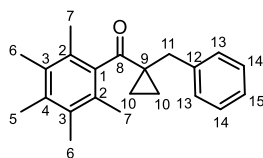
¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.33 (m, 2H, 2 × C(Ph)H), 7.32 – 7.26 (m, 2H, 2 × C(Ph)H), 7.22 – 7.15 (m, 1H, C(15)H), 3.05 (t, *J* = 7.0 Hz, 2H, C(11)H₂), 2.85 (t, *J* = 7.1 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H 2 × C(Ph*)H₃), 2.12 – 2.00 (m, 8H, 2 × C(Ph*)H₃, C(10)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.3 C(8), 140.6 C(Ar(Ph*)), 136.2, C(12), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 129.7 2 × C(Ph), 129.1 2 × C(Ph), 127.4 2 × C(Ar(Ph*)), 126.2 C(15), 43.9 C(9), 33.3 C(11), 22.7 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2916, 1699, 1481, 1399, 1112, 739, 692;

HRMS (ESI⁺) Found [M+Na]⁺ = 349.1598; C₂₁H₂₆OSNa requires 349.1600, Δ 0.38 ppm.

82 (1-Benzylcyclopropyl)(2,3,4,5,6-pentamethylphenyl)methanone



Ir-catalysed: Ketone **77a** (102 mg, 0.300 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol, degassed with Ar (balloon)) were added to a 2 – 5 mL microwave vial. The vial was sealed and evacuated and back-filled with argon (3 times). The reaction was heated at 110 °C for 24 h, cooled to RT and

KOH (34 mg, 0.60 mmol) and ^tBuOH (1.5 mL) were added. The reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 95:5) gave the *title compound* as a colourless oil (69 mg, 75%).

Ru-catalysed: Ketone **77a** (102 mg, 0.300 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol, degassed with Ar (balloon)) were added to a 2 – 5 mL microwave vial. The vial was sealed and evacuated and back-filled with argon (3 times). The reaction was heated at 110 °C for 24 h, cooled to RT and KOH (34 mg, 0.60 mmol) and ^tBuOH (1.5 mL) were added. The reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 95:5) gave the *title compound* as a colourless oil (69 mg, 75%).

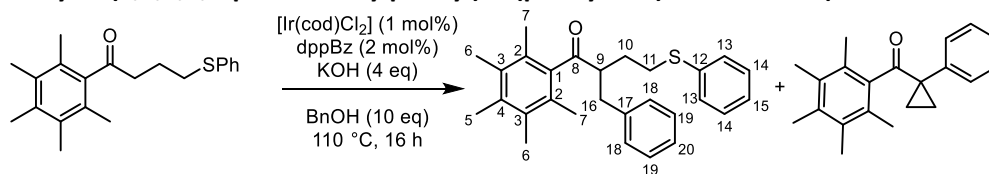
m.p. = 69 – 71 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.17 (m, 3H, 2 × C(14)*H* & C(15)*H*), 7.13 – 7.08 (m, 2H, 2 × C(13)*H*), 3.06 (s, 2H, C(11)*H*₂), 2.21 (s, 3H, C(Ph*)*H*₃), 2.13 (s, 6H, 2 × C(Ph*)*H*₃), 1.97 (s, 6H, 2 × C(Ph*)*H*₃), 1.24 – 1.15 (m, 2H, 2 × C(10)*H*_A*H*_B), 1.05 – 0.92 (m, 2H, 2 × C(10)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.6 C(8), 139.1 C(12), 137.3 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 132.9 2 × C(Ar(Ph*)), 130.1 2 × C(13), 128.6 2 × C(Ar(Ph*)), 128.0 2 × C(14), 126.3 C(15), 37.8 C(11), 34.4 C(9), 17.6 2 × C(Me(Ph*)), 17.1 2 × C(10), 16.8 C(Me(Ph*)), 16.0 2 × C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 3027, 2921, 1671, 917, 749, 701;

HRMS (ESI⁺) C₂₂H₂₇O⁺ ([M+H]⁺) requires 307.2056; found 307.2057, Δ 0.33 ppm.

83 2-Benzyl-1-(2,3,4,5,6-pentamethylphenyl)-4-(phenylthio)butan-1-one (mixture with 82)

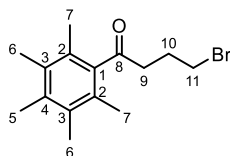
Ketone **74** (89 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2) gave the *title compound* as a colourless oil (as an inseparable mixture with ketone **82**, ratio 3.7:1, **83:82**) (107 mg, 91% overall yield).

Selected data for 83 (from the mixture with **82**):

¹H NMR (400 MHz, CDCl₃) δ 7.17 – 6.88 (m, 10H, 10 $\times$ C(Ph)H), 3.24 (dq, J = 8.6, 5.8 Hz, 1H, C(9)H), 3.12 (dd, J = 13.7, 5.5 Hz, 1H, C(16)H_AH_B), 2.87 – 2.68 (m, 2H, C(11)H₂), 2.53 (dd, J = 13.7, 8.7 Hz, 1H, C(16)H_AH_B), 2.16 (s, 3H, C(Ph*)H₃), 2.08 (s, 6H, 2 $\times$ C(Ph*)H₃), 1.98 – 1.83 (m, 7H, 2 $\times$ C(Ph*)H₃, C(10)H_AH_B), 1.61 (ddt, J = 14.1, 8.3, 5.9 Hz, 1H, C(10)H_AH_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.5 C(8), 139.7 C(17), 139.2 C(Ar(Ph*)), 135.8 C(Ar(Ph*)), 135.8 C(12), 133.3 2 $\times$ C(Ar(Ph*)), 129.8 2 $\times$ C(Ph), 129.4 2 $\times$ C(Ph), 128.9 2 $\times$ C(Ph), 128.6 2 $\times$ C(Ar(Ph*)) & 2 $\times$ C(Ph), 126.4 C(15), 126.1 C(20), 54.5 C(9), 35.9 C(16), 32.1 C(11), 28.8 C(10), 18.0 2 $\times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 $\times$ C(Me(Ph*));

HRMS (ESI⁺) C₂₈H₃₂NaOS⁺ ([M+Na]⁺) requires 439.2066; found 439.2064, Δ 0.48 ppm.

84 4-Bromo-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one

A solution of pentamethylbenzene (4.45 g, 30.0 mmol) and 4-bromobutyryl chloride (3.8 mL, 33 mmol) in CH₂Cl₂ (150 mL) was cooled to 0 °C in an ice bath. AlCl₃ (5.00 g, 37.5 mmol) was added portion-wise over 5 min and the resulting mixture was allowed to warm to RT and stirred for 2 h. After completion, crushed ice (approx. 150 g) was added and the reaction mixture was

stirred vigorously until the ice had melted. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×100 mL), the combined organic layers were washed with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 $\rightarrow$ 95:5) gave the *title compound* as a white solid (8.26 g, 93%).

m.p. = 70 – 72 °C;

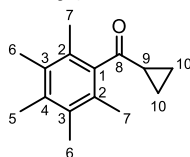
^1H NMR (400 MHz, CDCl_3) 3.57 (t, J = 6.4 Hz, 2H, C(11) H_2), 2.88 (t, J = 6.9 Hz, 2H, C(9) H_2), 2.29 (p, J = 6.7 Hz, 2H, C(10) H_2), 2.24 (s, 3H, C(Ph*) H_3), 2.19 (s, 6H, $2 \times$ C(Ph*) H_3), 2.11 (s, 6H, $2 \times$ C(Ph*) H_3);

^{13}C NMR (101 MHz, CDCl_3) 210.8 C(8), 140.4 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.3 $2 \times$ C(Ar(Ph*)), 127.4 $2 \times$ C(Ar(Ph*)), 43.5 C(9), 33.5 C(11), 26.4, C(10), 17.3 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2922, 1698, 1575, 1436, 1402, 1383, 1313, 1278, 1242, 1108, 997, 922;

HRMS (ESI⁺) $\text{C}_{15}\text{H}_{22}^{79}\text{BrO}^+$ ([M+H]⁺) requires 297.0849; found 297.0850, Δ 0.34 ppm.

85 Cyclopropyl(2,3,4,5,6-pentamethylphenyl)methanone



Ketone **84** (89 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98.5:1.5 $\rightarrow$ 98:2) gave the *title compound* as a white solid (58 mg, 90%).

m.p. = 68 – 70 °C;

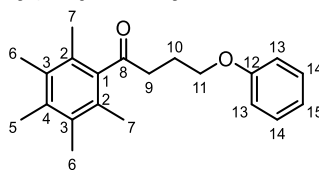
^1H NMR (400 MHz, CDCl_3) δ 2.24 (s, 3H, C(Ph*) H_3), 2.20 (s, 6H, $2 \times$ C(Ph*) H_3), 2.19 – 2.16 (m, 7H, C(9) H & $2 \times$ C(Ph*) H_3), 1.33 – 1.18 (m, 2H, $2 \times$ C(10) $H_{\text{A}}H_{\text{B}}$), 1.13 – 1.00 (m, 2H, $2 \times$ C(10) $H_{\text{A}}H_{\text{B}}$);

^{13}C NMR (101 MHz, CDCl_3) δ 212.1 C(8), 141.1 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.1 $2 \times$ C(Ar(Ph*)), 127.9 $2 \times$ C(Ar(Ph*)), 23.8 C(9), 17.6 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*)), 12.3 $2 \times$ C(10);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3007, 2925, 1682, 1365, 1120, 1064, 1030, 993, 937;

HRMS (ESI^+) $\text{C}_{15}\text{H}_{21}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 217.1587; found 217.1587, Δ 0.14 ppm.

77a 1-(2,3,4,5,6-Pentamethylphenyl)-4-phenoxybutan-1-one



Phenol (1.39 g, 14.8 mmol) was added to a solution of alcohol **90** (3.00 g, 12.3 mmol) in THF (40 mL). Triphenylphosphine (4.19 g, 16.0 mmol) and DTBAD (di-*tert*-butyl azodicarboxylate, 3.40 g, 14.8 mmol) were added and the reaction was stirred at RT for 2 h. The crude reaction mixture was concentrated *in vacuo* and triturated with pentane/ Et_2O (approx. 5:1), filtered (washed with pentane) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 $\rightarrow$ 95:5) and subsequent recrystallisation from a minimum amount of boiling hexane gave the *title compound* as a white solid (1.73 g, 45%).

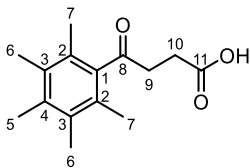
m.p. = 74 – 75 $^{\circ}\text{C}$;

^1H NMR (400 MHz, CDCl_3) δ 7.27 (dd, J = 8.7, 7.3 Hz, 2H, $2 \times$ C(14)H), 6.94 (tt, J = 7.4, 1.0 Hz, 1H, C(15)H), 6.91 – 6.86 (m, 2H, $2 \times$ C(13)H), 4.09 (t, J = 6.1 Hz, 2H, C(11) H_2), 2.91 (t, J = 7.0 Hz, 2H, C(9) H_2), 2.26 – 2.18 (m, 5H, C(10) H_2 , C(Ph*) H_3), 2.18 (s, 6H, $2 \times$ C(Ph*) H_3), 2.09 (s, 6H, $2 \times$ C(Ph*) H_3);

^{13}C NMR (126 MHz, CDCl_3) δ 211.6 C(8), 159.0 C(12), 140.7 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 129.6 $2 \times$ C(14), 127.4 $2 \times$ C(Ar(Ph*)), 120.8 C(15), 114.6 $2 \times$ C(13), 66.7 C(11), 41.8 C(9), 23.2 C(10), 17.3 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 1699, 1600, 1493, 1473, 1245, 1171, 1127, 1047, 944, 825, 755, 692;

HRMS (ESI^+) $\text{C}_{21}\text{H}_{27}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 311.2006; found 311.2007.

89 4-Oxo-4-(2,3,4,5,6-pentamethylphenyl)butanoic acid

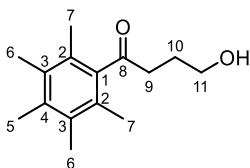
AlCl_3 (9.00 g, 67.5 mmol) was added portion-wise (over 5 min) to a stirred solution of succinic anhydride (3.10 g, 30.9 mmol) and pentamethylbenzene (5.00 g, 33.7 mmol) in CH_2Cl_2 (100 mL) at RT. The reaction was stirred for 5 min and then poured into cold 1 M HCl (100 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 $\times$ 100 mL). The combined organic layers were washed with 1 M HCl (2 $\times$ 100 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3 $\rightarrow$ 95:5) gave the *title compound* as a white solid (5.25 g, 68%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.02 (t, J = 6.4 Hz, 2H, C(9) H_2), 2.78 (t, J = 6.4 Hz, 2H, C(10) H_2), 2.24 (s, 3H, C(Ph*) H_3), 2.19 (s, 6H, 2 $\times$ C(Ph*) H_3), 2.12 (s, 6H, 2 $\times$ C(Ph*) H_3);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 209.6 C(8), 178.4 C(11), 139.8 C(Ar(Ph*)), 135.8 C(Ar(Ph*)), 133.3 2 $\times$ C(Ar(Ph*)), 127.7 2 $\times$ C(Ar(Ph*)), 40.1 C(9), 27.6 C(10), 17.2 2 $\times$ C(Ph*(Me)), 16.8 C(Ph*(Me)), 16.1 2 $\times$ C(Ph*(Me));

m/z (ESI $^+$) Found ([M+Na] $^+$) = 271, $\text{C}_{15}\text{H}_{20}\text{NaO}_3$ requires 271.

The spectroscopic data were consistent with that reported in the literature.³⁴

90 4-Hydroxy-1-(2,3,4,5,6-Pentamethylphenyl)butan-1-one

$\text{BH}_3\cdot\text{SMe}_2$ (3.1 mL, 33 mmol) was added dropwise (over 5 min) to a solution of acid **89** (5.38 g, 21.6 mmol) in THF (100 mL) at 0 $^\circ\text{C}$. The resulting solution was allowed to warm slowly to RT over 16 h, cooled to 0 $^\circ\text{C}$ and was then quenched with MeOH (16 mL) and water (40 mL). The mixture was concentrated *in vacuo*, diluted further with water (100 mL) and extracted with EtOAc (3 $\times$ 100 mL). The combined organic layers were washed with sat. aq. NaHCO_3 , dried over

MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 60:40 → 30:70) gave the *title compound* as a white solid (5.05 g, 99%)

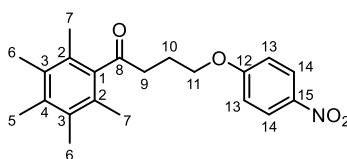
¹H NMR (400 MHz, CDCl₃) δ 3.75 (t, *J* = 6.1 Hz, 2H, C(11)H₂), 2.82 (t, *J* = 6.9 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.19 (s, 6H, 2 × C(Ph*)H₃), 2.10 (s, 6H, 2 × C(Ph*)H₃), 2.06 – 1.94 (m, 2H, C(10)H₂), 1.78 (br. s, 1H, OH);

¹³C NMR (101 MHz, CDCl₃) δ 212.6 C(8), 140.6 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 62.5 C(11), 42.6 C(9), 26.3 C(10), 17.3 2 × C(Ph*(Me)), 16.8 C(Ph*(Me)), 16.1 2 × C(Ph*(Me));

m/z (ESI⁺) Found ([M+Na]⁺) = 257, C₁₅H₂₂NaO₂ requires 257.

The spectroscopic data were consistent with that reported in the literature.³⁴

77b 4-(4-Nitrophenoxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



4-Nitrophenol (713 mg, 5.10 mmol), alcohol **90** (1.00 g, 4.27 mmol), PPh₃ (1.47 g, 5.61 mmol) and di-(4 chlorobenzyl)azodicarboxylate (1.87 g, 5.13 mmol) were subjected to **General Procedure B**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 90:10 → 80:20) gave a mixture of the *title compound* and 4-nitrophenol, which was purified further *via* recrystallisation from a minimum amount of boiling MeOH to give the *title compound* as a white solid (554 mg, 36%).

m.p. = 89 – 90 °C;

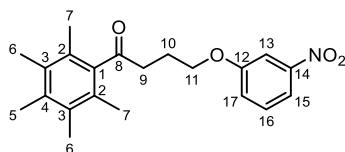
¹H NMR (400 MHz, CDCl₃) δ 8.37 – 8.04 (m, 2H, 2 × C(14)H), 7.02 – 6.80 (m, 2H, 2 × C(13)H), 4.21 (t, *J* = 6.1 Hz, 2H, C(11)H₂), 2.90 (t, *J* = 6.8 Hz, 2H, C(9)H₂), 2.30 – 2.24 (m, 2H, C(10)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.08 (s, 6H, 2 × C(Ph*)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 210.9 C(8), 163.9 C(12), 141.6 C(15), 140.3 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.2 $2 \times$ C(Ar(Ph*)), 126.0 $2 \times$ C(14), 114.4 $2 \times$ C(13), 67.6 C(11), 41.3 C(9), 22.8 C(10), 17.1 $2 \times$ C(Me(Ph*)), 16.7 C(Me(Ph*)), 15.9 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2929, 1698, 1593, 1511, 1498, 1471, 1405, 1338, 1299, 1260;

HRMS (ESI⁺) $\text{C}_{21}\text{H}_{26}\text{NO}_4^+$ ([M+H]⁺) requires 356.1856; found 356.1859, Δ 0.84 ppm.

77c 4-(3-Nitrophenoxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



3-Nitrophenol (357 mg, 2.55 mmol), alcohol **90** (500 mg, 2.14 mmol), PPh_3 (735 mg, 2.81 mmol) and di-(4-chlorobenzyl)azodicarboxylate (935 mg, 2.55 mmol) were subjected to **General Procedure B**. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 92:8 $\rightarrow$ 90:10) gave a mixture of the *title compound* and 3-nitrophenol, which was purified further *via* recrystallisation from a minimum amount of boiling MeOH to give the *title compound* as an off-white solid (275 mg, 38%).

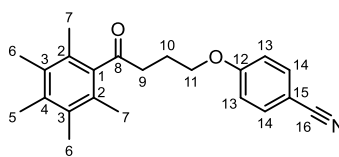
m.p. = 87 – 89 °C;

^1H NMR (400 MHz, CDCl_3) δ 7.82 (ddd, J 8.0, 2.1, 0.9 Hz, 1H, C(15)*H*), 7.72 (t, J = 2.3 Hz, 1H, C(13)*H*), 7.42 (t, J = 8.2 Hz, 1H, C(16)*H*), 7.22 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H C(17)*H*), 4.18 (t, J = 6.1 Hz, 2H, C(11)*H*₂), 2.91 (t, J = 7.0 Hz, 2H, C(9)*H*₂), 2.30 – 2.24 (m, 2H, C(10)*H*₂), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, $2 \times$ C(Ph*)*H*₃), 2.09 (s, 6H, $2 \times$ C(Ph*)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 211.0 C(8), 159.4 C(12), 149.3 C(14), 140.3 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 130.0 C(16), 127.2 $2 \times$ C(Ar(Ph*)), 121.4 C(17), 115.8 C(15), 108.9 C(13), 67.5 C(11), 41.4 C(9), 22.8 C(10), 17.1 $2 \times$ C(Me(Ph*)), 16.7 C(Me(Ph*)), 16.0 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2935, 1699, 1529, 1471, 1405, 1350, 1321, 1286, 1247;

HRMS (ESI⁺) $\text{C}_{21}\text{H}_{26}\text{NO}_4^+$ ([M+H]⁺) requires 356.1856; found 356.1858, Δ 0.56 ppm.

77d 4-(4-Oxo-4-(2,3,4,5,6-pentamethylphenyl)butoxy)benzonitrile

4-Cyanophenol (305 mg, 2.56 mmol), alcohol **90** (500 mg, 2.15 mmol), PPh_3 (725 mg, 2.77 mmol) and di-(4-chlorobenzyl)azodicarboxylate (974 mg, 2.56 mmol) were subjected to **General Procedure B**. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 80:20 $\rightarrow$ 70:30) gave a mixture of the *title compound* and 4-cyanophenol, which was purified further *via* recrystallisation from a minimum amount of boiling MeOH to give the *title compound* as an off-white solid (265 mg, 35%).

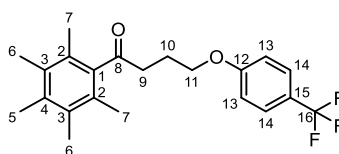
m.p. = 117 – 120 °C;

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.72 – 7.37 (m, 2H, $2 \times \text{C}(14)\text{H}$), 7.03 – 6.78 (m, 2H, $2 \times \text{C}(13)\text{H}$), 4.15 (t, $J = 6.1$ Hz, 2H, $\text{C}(11)\text{H}_2$), 2.89 (t, $J = 6.9$ Hz, 2H, $\text{C}(9)\text{H}_2$), 2.29 – 2.20 (m, 5H, $\text{C}(10)\text{H}_2$ & $\text{C}(\text{Ph}^*)\text{H}_3$), 2.18 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 2.08 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 211.1 C(8), 162.3 C(12), 140.4 C(Ar(Ph^*)), 135.8 C(Ar(Ph^*)), 134.2 $2 \times \text{C}(14)$, 133.3 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 127.3 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 119.4 C(16), 115.3 $2 \times \text{C}(13)$, 104.1 C(15), 67.2 C(11), 41.5 C(9), 22.9 C(10), 17.2 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.8 C(Me(Ph^*)), 16.1 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2938, 2224, 1698, 1606, 1509, 1257, 1172, 836;

HRMS (ESI^+) $\text{C}_{21}\text{H}_{26}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$) requires 336.1958; found 336.1960, Δ 0.59 ppm.

77e 1-(2,3,4,5,6-Pentamethylphenyl)-4-(4-(trifluoromethyl)phenoxy)butan-1-one

4-(Trifluoromethyl)phenol (415 mg, 2.56 mmol), alcohol **90** (500 mg, 2.15 mmol), PPh_3 (725 mg, 2.77 mmol) and di-(4-chlorobenzyl)azodicarboxylate (974 mg, 2.65 mmol) were subjected to **General Procedure B**. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 97:3 $\rightarrow$ 95:5) gave a mixture of the *title compound* and 4-(trifluoromethyl)phenol, which was

purified further *via* recrystallisation from a minimum amount of boiling MeOH to give the *title compound* as an off-white solid (213 mg, 26%).

m.p. = 88 – 90 °C;

¹H NMR (500 MHz, CDCl₃) δ 7.63 – 7.46 (m, 2H, 2 × C(14)H), 7.05 – 6.69 (m, 2H, 2 × C(13)H), 4.14 (t, *J* = 6.1 Hz, 2H, C(11)H₂), 2.90 (t, *J* = 7.0 Hz, 2H, C(9)H₂), 2.30 – 2.21 (m, 5H, C(10)H₂, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃);

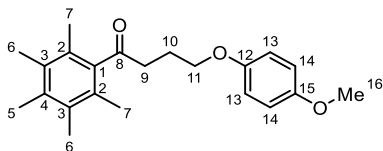
¹³C NMR ({¹⁹F} 126 MHz, CDCl₃) δ 211.3 C(8), 161.4 C(12), 140.5 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 127.0 2 × C(14), 124.6 C(16), 123.0 C(15), 114.5 2 × C(13), 67.0 C(11), 41.6 C(9), 23.0 C(10), 17.2 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

¹⁹F NMR (471 MHz, CDCl₃) δ -61.5;

IR (film) ν_{max} /cm⁻¹ 3020, 2936, 1699, 1616, 1328, 1257, 1111, 1069, 943, 837;

HRMS (ESI⁺) C₂₂H₂₆F₃O₂⁺ ([M+H]⁺) requires 379.1890; found 379.1880, Δ 2.63 ppm.

77f 4-(4-Methoxyphenoxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



3-Methoxyphenol (320 mg, 2.58 mmol), alcohol **90** (500 mg, 2.15 mmol), PPh₃ (735 mg, 2.81 mmol) and di-(4-chlorobenzyl)azodicarboxylate (935 mg, 2.55 mmol) were subjected to **General Procedure B**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 92:8) gave the *title compound* as a white solid (180 mg, 25%).

m.p. = 72 – 74 °C;

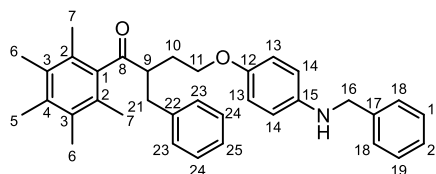
¹H NMR (400 MHz, CDCl₃) δ 6.83 (s, 4H, 2 × C(13)H & 2 × C(14)H), 4.04 (t, *J* = 6.0 Hz, 2H, C(11)H₂), 3.77 (s, 3H, C(16)H₃), 2.90 (t, *J* = 7.0, 2H, C(9)H₂), 2.24 (s, 3H, C(Ph*)H₃), 2.22 – 2.15 (m, 8H, C(10)H₂ & 2 × C(Ph*)H₃), 2.10 (s, 6H, 2 × C(Ph*)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 211.5 C(8), 154.0 C(Ar), 153.2 C(Ar), 140.7 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.4 $2 \times$ C(Ar(Ph*)), 115.6 $2 \times$ C(Ar), 114.8 $2 \times$ C(Ar), 67.5 C(11), 55.9 C(16), 41.8 C(9), 23.3 C(10), 17.2 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2935, 1699, 1508, 1231, 1041, 824;

HRMS (ESI^+) $\text{C}_{22}\text{H}_{29}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 341.2109; found 341.2112, Δ 0.88 ppm.

91 2-Benzyl-4-(4-(benzylamino)phenoxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



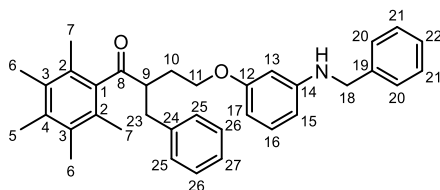
Ketone **77b** (107 mg, 0.300 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 $\rightarrow$ 88:12) gave the *title compound* as a yellow oil (inseparable from BnOH, ratio 11:1 BnOH: *title compound*) (isolated in conjunction with 30% **82**).

^1H NMR (400 MHz, CDCl_3) δ 7.31– 7.06 (m, 10H, $10 \times$ C(Ph)*H*), 6.60 – 6.48 (m, 2H, $2 \times$ C(13)*H*), 6.48 – 6.30 (m, 2H, $2 \times$ C(14)*H*), 4.17 (s, 2H, C(16)*H*₂), 3.77 (td, J = 6.4, 1.4 Hz, 2H, C(11)*H*₂), 3.42 – 3.23 (m, 1H, C(9)*H*), 3.14 (dd, J = 13.7, 5.4 Hz, 1H, C(21)*H*_A*H*_B), 2.58 (dd, J = 13.7, 8.8 Hz, 1H, C(21)*H*_A*H*_B), 2.16 (s, 4H, C(10)*H*_A*H*_B & C(Ph*)*H*₃), 2.09 (s, 6H, $2 \times$ C(Ph*)*H*₃), 1.91 (br. s, 6H, $2 \times$ C(Ph*)*H*₃), 1.81 – 1.64 (m, 1H, C(10)*H*_A*H*_B) (BnOH peaks omitted for clarity);

^{13}C NMR (101 MHz, CDCl_3) δ 213.1 C(8), 151.3 C(12), 142.5 C(15), 141.0 C(Ar), 139.7 C(Ar), 135.8 C(Ar), 133.2 C(Ar), 129.3 C(Ar), 128.6 C(Ar), 128.4 C(Ar), 127.6 C(Ar), 127.2 C(Ar), 126.2 C(Ar), 115.9 $2 \times$ C(13), 114.2 $2 \times$ C(14), 66.4 C(11), 52.3 C(9), 49.3 C(16), 36.2 C(21), 29.0 C(10), 17.8 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*)) (BnOH peaks omitted for clarity);

N.B. Two fewer C(Ar) signals are reported due to overlap with inseparable BnOH signals.

HRMS (ESI^+) $\text{C}_{35}\text{H}_{40}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$) requires 506.3054; found 506.3052, Δ 0.40 ppm.

92 2-Benzyl-4-(3-(benzylamino)phenoxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one

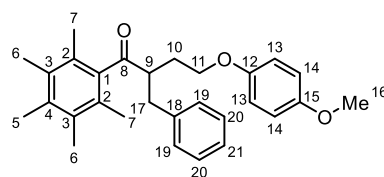
Ketone **77c** (107 mg, 0.300 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 90:10) gave the *title compound* as a yellow oil (32 mg, 21%, isolated in conjunction with 25% **82**).

¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.31 (m, 4H, 4 × C(Ph)*H*), 7.28 (m, 1H, C(Ph)*H*), 7.25 – 7.21 (m, 2H, 2 × C(Ph)*H*), 7.21 – 7.12 (m, 3H, 3 × C(Ph)*H*), 7.01 (t, *J* = 8.0 Hz, 1H, C(16)*H*), 6.31 – 6.17 (m, 1H, C(15)*H*), 6.14 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H, C(17)*H*), 6.07 (t, *J* = 2.3 Hz, 1H, C(13)*H*), 4.29 (s, 2H, C(18)*H*₂), 3.90 – 3.80 (m, 2H, C(11)*H*₂), 3.41 – 3.28 (m, 1H, C(9)*H*), 3.21 (dd, *J* = 13.7, 5.2 Hz, 1H, C(23)*H*_A*H*_B), 2.64 (dd, *J* = 13.7, 9.0 Hz, 1H, C(23)*H*_A*H*_B), 2.29 – 2.14 (m, 10H, C(10)*H*_A*H*_B, 3 × C(Ph*)*H*₃, overlapped), 2.08 (s, 6H, 2 × C(Ph*)*H*₃), 1.83 (dtd, *J* = 12.3, 6.8, 5.5 Hz, 1H, C(10)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 213.1 C(8), 160.4 C(12), 149.9 C(14), 140.0 C(Ar), 139.8 C(Ar), 139.6 C(Ar), 136.2 C(Ar), 133.6 C(Ar), 130.3 C(Ar), 129.6 C(16), 129.1 C(Ar), 129.0 C(Ar), 128.8 C(Ar), 128.0 C(Ar), 127.7 C(Ar), 126.7 C(Ar), 106.3 C(15), 104.0 C(17), 99.8 C(13), 65.9 C(11), 52.7 C(9), 48.8 C(18), 36.7 C(23), 29.2, C(10), 18.3 2 × C(Me(Ph*))₂, 17.2 C(Me(Ph*))₂, 16.5 2 × C(Me(Ph*))₂;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3416, 2921, 1689, 1614, 1163, 731, 699;

HRMS (ESI⁺) C₃₅H₄₀NO₂⁺ ([M+H]⁺) requires 506.3054; found 506.3050, Δ 0.79 ppm.

96 2-Benzyl-4-(4-methoxyphenoxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one

Ketone **102** (84 mg, 0.30 mmol), alcohol **104** (504 mg, 3.00 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), and KOH (67 mg, 1.20 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) for 10 min. PhMe (75 μL) was added and the reaction (complete with balloon) was heated for 48 h at 110 $^\circ\text{C}$, cooled to RT, filtered through a silica plug (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 95:5 $\rightarrow$ 92:8) gave the *title compound* as a yellow solid (55 mg, 43%).

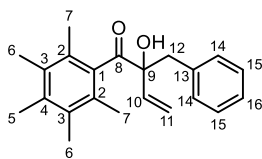
m.p. = 95 – 97 $^\circ\text{C}$;

^1H NMR (600 MHz, CDCl_3) δ 7.26 – 7.22 (m, 2H, 2 $\times$ C(Ph)*H*), 7.20 – 7.15 (m, 3H, 3 $\times$ C(Ph)*H*), 6.82 – 6.73 (m, 2H, 2 $\times$ C(14)*H*), 6.71 – 6.59 (m, 2H, 2 $\times$ C(13)*H*), 3.92 – 3.82 (m, 2H, C(11)*H*₂), 3.75 (s, 3H, C(16)*H*₃), 3.37 (ddt, J = 9.1, 7.0, 5.4 Hz, 1H, C(9)*H*), 3.22 (dd, J = 13.7, 5.2 Hz, 1H, C(17)*H*_A*H*_B), 2.63 (dd, J = 13.7, 9.1 Hz, 1H, C(17)*H*_A*H*_B), 2.26 – 2.19 (m, 4H, C(10)*H*_A*H*_B, C(Ph*)*H*₃), 2.16 (s, 6H, 2 $\times$ C(Ph*)*H*₃), 2.12 – 1.92 (br. s, 6H 2 $\times$ C(Ph*)*H*₃), 1.83 (dtd, J = 12.3, 6.7, 5.5 Hz, 1H, C(10)*H*_A*H*_B);

^{13}C NMR (151 MHz, CDCl_3) δ 212.6 C(8), 153.7 C(15), 152.8 C(12), 139.6 C(18), 139.1 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.2 2 $\times$ C(Ar(Ph*)), 129.2 2 $\times$ C(19), 128.6 (br.) 2 $\times$ C(Ar(Ph*)), 128.4 2 $\times$ C(20), 126.2 C(21), 115.4 2 $\times$ C(14), 114.5 2 $\times$ C(13), 66.2 C(11), 55.7 C(16), 52.2 C(9), 36.3 C(17), 28.8 C(10), 17.8 2 $\times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.0 2 $\times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3026, 2932, 1691, 1508, 1231;

HRMS (ESI⁺) $\text{C}_{29}\text{H}_{34}\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 453.2400; found 453.2401, Δ 0.22 ppm.

97 2-Benzyl-2-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)but-3-en-1-one

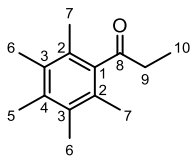
Ketone **96** (86 mg, 0.20 mmol) was dissolved in THF (1.0 mL) and the solution was cooled to 0 °C in an ice bath. NaH (60% dispersed in mineral oil, 16 mg, 0.40 mmol) was added, the reaction was warmed to RT and allowed to stir for 20 h. The reaction was quenched with the dropwise addition of MeOH (0.5 mL) and diluted with CH₂Cl₂ (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 97:3 → 95:5) gave the *title compound* as a solid glass (6 mg, 9%).

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.15 (m, 5H, 5 × C(Ph)*H*), 6.07 (dd, *J* = 17.1, 10.6 Hz, 1H, C(10)*H*), 5.19 – 4.99 (m, 2H, C(11)*H*₂), 3.24 (d, *J* = 13.3 Hz, 1H, C(12)*H*_A*H*_B), 3.16 (d, *J* = 13.3 Hz, 1H, C(12)*H*_A*H*_B), 2.56 (s, 1H, OH), 2.24 (s, 3H, C(Ph*)*H*₃), 2.19 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 2.10 (s, 3H, C(Ph*)*H*₃), 2.08 (s, 3H, C(Ph*)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 213.4 C(8), 138.7 C(10), 136.6 C(Ar(Ph*)), 136.1 C(Ar(Ph*)), 135.2 C(13), 133.3 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 131.1 2 × C(14), 129.0 C(Ar(Ph*)), 128.8 C(Ar(Ph*)), 127.9 2 × C(15), 126.8 C(16), 115.9 C(11), 84.6 C(9), 44.4 C(12), 19.3 C(Me(Ph*)), 19.1 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3568, 2925, 1697;

HRMS (ESI⁺) C₂₂H₂₆NaO⁺ ([M+Na]⁺) requires 345.1825; found 345.1826, Δ 0.25 ppm.

98 1-(2,3,4,5,6-Pentamethylphenyl)propan-1-one

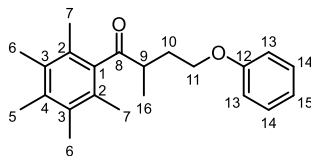
Pentamethylbenzene (5.00 g, 33.7 mmol) and propionyl chloride (3.2 mL, 37 mmol) were dissolved in CH_2Cl_2 (150 mL) and the mixture was cooled to 0 °C. AlCl_3 (5.43 g, 40.8 mmol) was added portion-wise and the reaction was allowed to warm to RT and stirred for 1 h. The crude reaction mixture was poured onto ice (approx. 150 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic layers were washed with sat. aq. NaHCO_3 , dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 → 96:4) gave the *title compound* as a white solid (5.63 g, 81%).

^1H NMR (400 MHz, CDCl_3) δ 2.69 (q, J = 7.2 Hz, 2H, C(9) H_2), 2.23 (s, 3H, C(Ph*) H_3), 2.19 (s, 6H, 2 × C(Ph*) H_3), 2.09 (s, 6H, 2 × C(Ph*) H_3), 1.20 (t, J = 7.2 Hz, 3H, C(10) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 212.9 C(8), 141.0 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.5 2 × C(Ar(Ph*)), 38.9 C(9), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 7.7 C(10);

m/z (ESI⁺) Found ($[\text{M}+\text{H}]^+$) = 205, $\text{C}_{14}\text{H}_{21}\text{O}$ requires 205.

The spectroscopic data were consistent with that reported in the literature.¹³⁷

100 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-4-phenoxybutan-1-one

Ph* ethyl ketone **98** (102 mg, 0.50 mmol), $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ (4.0 mg, 1.0 mol%), dppBz (5.0 mg, 2.0 mol%), KOH (140 mg, 5.00 mmol), 2-phenoxyethanol (0.62 mL, 5.0 mmol) and PhMe (0.15 mL) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) for 5 min. The reaction (complete with balloon) was heated at 115 °C for 48 h, cooled to RT, filtered through a silica plug (elution with CH_2Cl_2) and concentrated *in vacuo*. Purification

via flash column chromatography (eluent pentane/Et₂O, 99:1 → 95:5) gave the *title compound* as a colourless oil (21 mg, 13%, isolated in conjunction with 53 mg, 46% **101**).

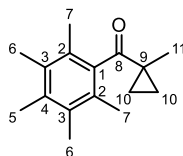
¹H NMR (400 MHz, CDCl₃) 7.32 – 7.22 (m, 2H, 2 × C(14)H), 6.93 (tt, 1H, *J* = 7.3, 1.1 Hz, C(15)H), 6.90 – 6.83 (m, 2H, 2 × C(13)H), 4.19 – 3.97 (m, 2H, C(11)H₂), 3.17 (m, 1H, C(9)H), 2.37 (m, 1H, C(10)H_AH_B), 2.24 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.83 (m, 1H, C(10)H_AH_B), 1.20 (d, *J* = 7.2 Hz, 3H, C(16)H₃);

¹³C NMR (151 MHz, CDCl₃) 213.4 C(8), 157.7 C(12), 138.5 C(Ar(Ph*)), 134.5 C(Ar(Ph*)), 132.1 2 × C(Ar(Ph*)), 128.4 2 × C(Ar(Ph*)) & 2 × C(14), 119.6 C(15), 113.4 2 × C(13), 64.3 C(11), 43.9 C(9), 30.1 C(10), 16.8 C(Me(Ph*)), 15.7 C(16), 15.0 2 × C(Me(Ph*)), 14.8 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2950, 2875, 1693, 1600, 1497, 1475, 1301, 1244, 1173, 1081, 1032, 920, 885;

HRMS (ESI⁺) C₂₂H₂₉O₂⁺ ([M+H]⁺) requires 325.2162; found 325.2162.

101 (1-Methylcyclopropyl)(2,3,4,5,6-pentamethylphenyl)methanone



Ph* ethyl ketone **98** (102 mg, 0.50 mmol), [Ir(cod)Cl₂]₂ (4.0 mg, 1.0 mol%), dppBz (5.0 mg, 2.0 mol%), KOH (140 mg, 5.00 mmol), 2-phenoxyethanol (0.62 mL, 5.0 mmol) and PhMe (0.15 mL) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) for 5 min. The reaction (complete with balloon) was heated at 115 °C for 48 h, cooled to RT, filtered through a silica plug (elution with CH₂Cl₂) and concentrated *in vacuo*. Purification via flash column chromatography (eluent pentane/Et₂O, 99:1 → 95:5) gave the *title compound* as a white solid (53 mg, 46%, isolated in conjunction with 21 mg, 13% **100**).

m.p. = 89 – 90 °C;

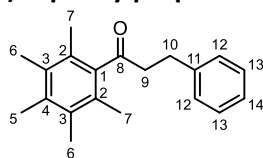
¹H NMR (400 MHz, CDCl₃) δ 2.21 (s, 3H, C(Ph*)H₃), 2.17 (s, 6H, 2 × C(Ph*)H₃), 2.10 (s, 6H, 2 × C(Ph*)H₃), 1.30 (q, *J* = 3.7 Hz, 2H, 2 × C(10)H_AH_B), 1.27 (s, 3H, C(11)H₃), 0.89 (q, *J* = 3.3 Hz, 2H, 2 × C(10)H_AH_B);

^{13}C NMR (101 MHz, CDCl_3) δ 214. $\text{C}(8)$, 138.3 $\text{C}(\text{Ar}(\text{Ph}^*))$, 135.1 $\text{C}(\text{Ar}(\text{Ph}^*))$, 133.0 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 127.9 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 28.7 $\text{C}(9)$, 20.0 $2 \times \text{C}(10)$, 19.8 $\text{C}(11)$, 17.7 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.8 $\text{C}(\text{Me}(\text{Ph}^*))$, 16.1 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2930, 1674, 1448, 1389, 1320, 1150, 1111, 1028, 919;

HRMS (ESI^+) $\text{C}_{16}\text{H}_{23}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 231.1743; found 231.1743, Δ 0.26 ppm.

102 1-(2,3,4,5,6-Pentamethylphenyl)-3-phenylpropan-1-one



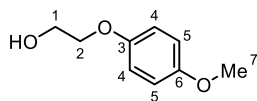
3-Phenylpropanoic acid (4.50 g, 30.0 mmol) was dissolved in thionyl chloride (5.3 mL, 73 mmol) and the mixture was refluxed for 16 h. Once cooled to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH_2Cl_2 (10 mL) and added to a solution of pentamethylbenzene (4.40 g, 29.7 mmol) in CH_2Cl_2 (90 mL) at 0 °C. AlCl_3 (5.00 g, 37.5 mmol) was added portion-wise and to mixture was stirred at RT for 1 h. The crude reaction mixture was poured onto ice (approx. 150 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and the combined organic layers were washed sequentially with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane: Et_2O , 98:2) gave the title compound as a pale yellow solid (3.88 g, 46%).

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.12 (m, 5H, $5 \times \text{C}(\text{Ph})\text{H}$), 3.11 – 3.04 (m, 2H, $\text{C}(10)\text{H}_2$), 3.04 – 2.95 (m, 2H, $\text{C}(9)\text{H}_2$), 2.24 (s, 3H, $\text{C}(\text{Ph}^*)\text{H}_3$), 2.18 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 2.06 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 210.9 $\text{C}(8)$, 141.0 $\text{C}(\text{Ar})$, 140.5 $\text{C}(\text{Ar})$, 135.5 $\text{C}(\text{Ar})$, 133.1 $\text{C}(\text{Ar})$, 128.5 $2 \times \text{C}(\text{Ph})$, 128.5 $2 \times \text{C}(\text{Ph})$, 127.4 $\text{C}(\text{Ar})$, 126.1 $\text{C}(14)$, 47.1 $\text{C}(9)$, 29.4 $\text{C}(10)$, 17.1 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.7 $\text{C}(\text{Me}(\text{Ph}^*))$, 15.9, $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

m/z (ESI^+) Found ($[\text{M}+\text{H}]^+$) = 281, $\text{C}_{20}\text{H}_{25}\text{O}$ requires 281.

The spectroscopic data were consistent with that reported in the literature.³⁴

104 2-(4-Methoxyphenoxy)ethan-1-ol

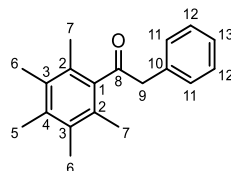
4-Methoxyphenol (2.48 g, 20.0 mmol) was dissolved in aqueous NaOH (50 mL, 30.0 mmol). 2-Bromoethanol (2.2 mL, 30.0 mmol) was added and the reaction was heated to 105 °C for 40 h. The reaction mixture was cooled to RT, diluted with 15 mL water and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed sequentially with 10% aq. NaOH, water and brine, dried over Na₂SO₄, and concentrated *in vacuo* to give the *title compound* as an off-white solid which was used without further purification (2.72 g, 81%).

¹H NMR (400 MHz, CDCl₃) δ 6.91 – 6.77 (m, 4H, 2 × C(4)H & 2 × C(5)H), 4.08 – 3.99 (m, 2H, C(2)H₂), 3.98 – 3.87 (m, 2H, C(1)H₂), 3.77 (s, 3H, C(7)H₃), 2.08 (t, *J* = 6.2 Hz, 1H, OH);

¹³C NMR (101 MHz, CDCl₃) δ 154.3 C(Ar), 152.9 C(Ar), 115.8 2 × C(Ar), 114.9 2 × C(Ar), 70.1 C(2), 61.7 C(1), 55.9 C(7);

m/z (ESI⁺) Found ([M+Na⁺] = 191, C₉H₁₂NaO₃ requires 191.

The spectroscopic data were consistent with that reported in the literature.¹³⁸

S1 1-(2,3,4,5,6-Pentamethylphenyl)-2-phenylethan-1-one

Pentamethylbenzene (5.00 g, 33.7 mmol) and phenylacetylchloride (3.8 mL, 29 mmol) were dissolved in CH₂Cl₂ (130 mL) and the mixture was cooled to 0 °C. AlCl₃ (4.38 g, 32.9 mmol) was added portion-wise and the reaction was allowed to warm to RT and stirred for 15 min. The crude reaction mixture was poured onto ice (approx. 150 g) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 100 mL) and the combined organic layers were washed sequentially with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* recrystallisation from a minimum amount of boiling hexane gave the *title compound* as a white solid (6.72 g, 87%).

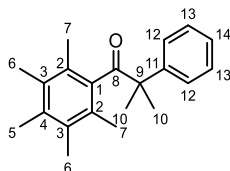
^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.22 (m, 5H, 5 $\times$ C(Ph)H), 3.99 (s, 2H, C(9)H₂), 2.25 (s, 3H, C(Ph*)H₃), 2.19 (s, 6H, 2 $\times$ C(Ph*)H₃), 2.09 (s, 6H, 2 $\times$ C(Ph*)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 208.7 C(8), 140.3 C(Ar), 135.6 C(Ar), 133.4 C(Ar), 133.1 C(Ar), 130.0 2 $\times$ C(Ph), 128.5 2 $\times$ C(Ph), 127.5 C(Ar), 127.0 C(Ar), 52.4 C(9), 17.3 2 $\times$ C(Me(Ph*)), 16.7 C(Me(Ph*)), 16.0 2 $\times$ C(Me(Ph*));

m/z (ESI⁺) Found ([M+H]⁺) = 267, C₁₉H₂₃O requires 267.

The spectroscopic data were consistent with that reported in the literature.¹³⁷

105 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-2-phenylpropan-1-one



Ketone **S1** (1.33 g, 5.00 mmol) was dissolved in THF (25 mL) and the resulting solution was cooled to 0 °C. NaH (60% dispersed in mineral oil, 1.00 g, 25.0 mmol) was added portion-wise and the mixture was allowed to warm to RT and stirred for 30 min. MeI (1.6 mL, 25 mmol) was added and the reaction was stirred at RT for 16 h. The reaction mixture was cooled to 0 °C and quenched with the dropwise addition of MeOH (10 mL) and water (10 mL). The mixture was concentrated *in vacuo* and diluted with Et₂O (30 mL) and water (30 mL), the layers separated and the aqueous phase extracted with Et₂O (2 $\times$ 30 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1) gave the *title compound* as a white solid (920 mg, 63%).

m.p. = 92 – 93 °C;

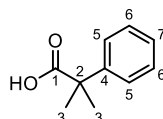
^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.40 (m, 2H, 2 $\times$ C(12)H), 7.31 – 7.22 (m, 2H, 2 $\times$ C(13)H), 7.22 – 7.13 (m, 1H, C(14)H), 2.16 (s, 3H, C(Ph*)H₃), 2.06 (s, 6H, 2 $\times$ C(Ph*)H₃), 1.66 (s, 6H, 2 $\times$ C(Ph*)H₃), 1.57 (s, 6H, 2 $\times$ C(10)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 216.1 C(8), 143.8 C(Ar), 139.4 C(Ar), 134.7 C(Ar), 132.8 $2 \times \text{C(Ph}^*(\text{Ar}))$, 128.1 $2 \times \text{C(13)}$, 127.7 $2 \times \text{C(Ph}^*(\text{Ar}))$, 127.4 $2 \times \text{C(12)}$, 126.7 C(14), 52.2 C(9), 26.7 $2 \times \text{C(10)}$, 18.4 $2 \times \text{C(Me(Ph}^*))$, 16.6 C(Me(Ph*)), 16.02 $\times \text{C(Me(Ph}^*))$;

IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2984, 2942, 2360, 1688, 1459, 1439, 1390, 1079, 902, 699;

HRMS (ESI⁺) $\text{C}_{21}\text{H}_{27}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 295.2056; found 295.2057, Δ 0.34 ppm.

106 2-Methyl-2-phenylpropanoic acid



Ketone **105** (88 mg, 0.30 mmol), 1,1,1,3,3,3-hexafluoroisopropanol (3.0 mL) and 37% aq. HCl (12 M, 0.6 mL) were added to a 2 – 5 mL microwave vial. The resulting mixture was stirred at 65 °C for 16 h, cooled to RT and diluted with CH_2Cl_2 (10 mL) and water (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 80:20 $\rightarrow$ Et_2O) gave the *title compound* as an off-white solid (44 mg, 90%).

Alternative Method: A 2 – 5 mL microwave vial was charged with ketone **105** (88 mg, 0.30 mmol) and CH_2Cl_2 (1.5 mL) was added. The vessel was sealed and cooled to -17 °C using an ice/ NaCl bath. Bromine (30 μL , 0.60 mmol) was added dropwise and the mixture stirred for 15 min. Water (0.2 mL) was added, the mixture warmed to RT and stirred for 1 h. The reaction was diluted with EtOAc (10 mL) and HCl (1 M, 10 mL), the layers were separated and the aqueous layer extracted with EtOAc (2×10 mL). The combined organic layers were washed sequentially with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 90:10) gave the *title compound* as an off-white solid (41 mg, 84%).

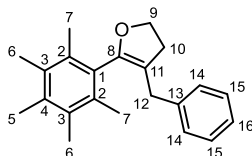
^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.38 (m, 2H, $2 \times \text{C(5)H}$), 7.38 – 7.31 (m, 2H, $2 \times \text{C(6)H}$), 7.30 – 7.22 (m, 1H, C(7)H), 1.61 (s, 6H, $2 \times \text{C(3)H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 182.1 C(1), 144.0 C(4), 128.6 2 $\times$ C(6), 127.1 C(7), 125.9 2 $\times$ C(5), 46.4 C(2), 26.4 2 $\times$ C(3);

m/z (ESI⁺) Found ($[\text{M}+\text{Na}^+] = 187$, $\text{C}_{10}\text{H}_{12}\text{NaO}_2$ requires 187.

The spectroscopic data were consistent with that reported in the literature.¹³⁹

108 4-Benzyl-5-(2,3,4,5,6-pentamethylphenyl)-2,3-dihydrofuran



Cyclopropyl ketone **82** (61 mg, 0.20 mmol) was added to a 2 – 5 mL microwave vial and HFIP (1.75 mL) and 2 M HCl (0.26 mL) were added. The vial was sealed and heated to 65 °C for 16 h. The reaction was cooled to RT, diluted with water and extracted with CH_2Cl_2 (3 $\times$ 10 mL), dried over MgSO_4 and concentrated in vacuo. Purification *via* flash column chromatography (eluent pentanes/ Et_2O , 99:1) gave the *title compound* as a colourless oil (5 mg, 7%).

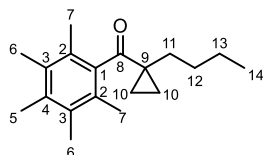
^1H NMR (400 MHz, CDCl_3) 7.28 – 7.23 (m, 2H, 2 $\times$ C(Ph)*H*), 7.20 – 7.14 (m, 1H, C(16)*H*), 7.13 – 7.06 (m, 2H, 2 $\times$ C(Ph)*H*), 4.39 (t, $J = 9.3$ Hz, 2H, C(9)*H*₂), 3.17 (s, 2H, C(12)*H*₂), 2.66 (tt, $J = 9.2, 1.0$ Hz, 2H, C(10)*H*₂), 2.26 (s, 6H, 2 $\times$ C(Ph*)*H*₃), 2.24 (s, 3H, C(Ph*)*H*₃), 2.22 (s, 6H, 2 $\times$ C(Ph*)*H*₃);

^{13}C NMR (101 MHz, CDCl_3) 150.8 C(8), 140.3 C(Ar), 135.4 C(Ar), 133.2 C(Ar), 132.4 C(Ar), 128.6 2 $\times$ C(Ph), 128.4 C(Ar), 128.2 2 $\times$ C(Ph), 125.8 C(16), 109.6 C(11), 68.6 C(9), 33.1 C(12), 33.0 C(10), 17.7 2 $\times$ C(Me(Ph*))₃, 16.8 C(Me(Ph*))₃, 16.5 2 $\times$ C(Me(Ph*))₃;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2922, 1691, 1494, 1453, 1380, 1262, 1220, 1145, 1075, 1023, 1003, 952, 700;

HRMS (ESI⁺) $\text{C}_{22}\text{H}_{27}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 307.2056; found 307.2057, Δ 0.33 ppm.

76 (1-Butylcyclopropyl)(2,3,4,5,6-pentamethylphenyl)methanone



Ketone **77a** (186 mg, 0.600 mmol), $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ (4.0 mg, 1.0 mol%), dppBz (6.0 mg, 2.0 mol%), KOH (134 mg, 2.40 mmol) and *n*-butanol (0.55 mL, 6.0 mmol) were subjected to

General Procedure A at 85 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2) gave the *title compound* as a white solid (116 mg, 71%).

m.p. = 47 – 49 °C;

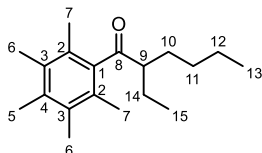
¹H NMR (400 MHz, CDCl₃) 2.20 (s, 3H, C(Ph*)H₃), 2.15 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.68 – 1.59 (m, 2H, C(11)H₂), 1.48 – 1.37 (m, 2H, C(12)H₂), 1.35 – 1.23 (m, 2H, C(13)H₂), 1.13 – 1.04 (m, 2H, 2 × C(10)H_AH_B), 0.94 – 0.90 (m, 2H, 2 × C(10)H_AH_B), 0.87 (t, *J* = 7.3 Hz, 3H, C(14)H₃);

¹³C NMR (101 MHz, CDCl₃) 212.7 C(8), 136.7 C(Ar(Ph*)), 135.0 C(Ar(Ph*)), 132.7 2 × C(Ar(Ph*)), 128.5 2 × C(Ar(Ph*)), 34.1 C(9), 33.2 C(11), 29.4 C(12), 23.1 C(13), 17.7 2 × C(Me(Ph*)), 17.5 2 × C(10), 16.6 C(Me(Ph*)), 15.9 2 × C(Me(Ph*)), 14.0 C(14);

IR (film) ν_{max} /cm⁻¹ 3005, 2931, 1671, 1455, 1347, 1120, 1079, 915, 832, 731, 701;

HRMS (ESI⁺) C₁₉H₂₉O⁺ ([M+H]⁺) requires 273.2213; found 273.2213.

110 2-Ethyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



A mixture of cyclopropyl ketone **76** (82 mg, 0.30 mmol) and PtO₂ (45 mg, 0.20 mmol) was stirred in acetic acid (2 mL) under H₂ (balloon) for 3 h. The mixture was filtered through a Celite® pad (washed with CH₂Cl₂) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 97:3) gave the *title compound* as a colourless oil (65 mg, 79%).

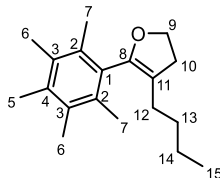
¹H NMR (400 MHz, CDCl₃) 2.77 – 2.63 (m, 1H, C(9)H), 2.25 (s, 3H, C(Ph*)H₃), 2.19 (s, 6H, 2 × C(Ph*)H₃), 2.11 (s, 6H, 2 × C(Ph*)H₃), 1.83 – 1.65 (m, 2H, C(10)H_AH_B & C(14)H_AH_B), 1.61 – 1.44 (m, 2H, C(10)H_AH_B & C(14)H_AH_B), 1.43 – 1.26 (m, 4H, C(11)H₂ & C(12)H₂), 0.97 (t, *J* = 7.4 Hz, 3H, C(15)H₃), 0.90 (t, *J* = 7.2 Hz, 3H, C(13)H₃);

¹³C NMR (101 MHz, CDCl₃) 214.1 C(8), 140.2 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.1 2 × C(Ar(Ph*)), 128.6 2 × C(Ar(Ph*)), 54.9 C(9), 29.5 C(11)/C(12), 28.5 29.5 C(11)/C(12), 23.1 C(10), 22.2 C(14), 17.9 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 14.1 C(13), 11.9 C(15);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2931, 1691, 1457, 1381, 1300, 1090, 996, 912, 832, 731, 701;

HRMS (ESI⁺) $\text{C}_{19}\text{H}_{31}\text{O}^+$ ([M+H]⁺) requires 275.2369; found 275.2369.

112 4-Butyl-5-(2,3,4,5,6-pentamethylphenyl)-2,3-dihydrofuran



A solution of cyclopropyl ketone **76** (109 mg, 0.398 mmol), *N*-benzylidene-*p*-toluene-sulfonimide* (135 mg, 0.521 mmol) and MgI_2 (11 mg, 10 mol%) in THF (1 mL) was heated at 60 °C for 28 h. The reaction mixture was allowed to cool to RT, quenched with water (1 mL) and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (1 mL) and diluted with EtOAc (20 mL) and water (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with 1 M NaOH (20 mL) and brine, dried over MgSO_4 , and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1) gave the *title compound* as a colourless oil (45 mg, 41%).

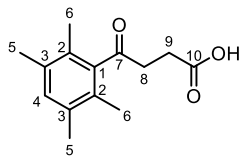
¹H NMR (400 MHz, CDCl_3) 4.39 (t, J = 9.2 Hz, 2H, C(9) H_2), 2.76 (tt, J = 9.2, 1.0 Hz, 2H, C(10) H_2), 2.24 (s, 3H, C(Ph*) H_3), 2.21 (s, 6H, 2 × C(Ph*) H_3), 2.20 (s, 6H, 2 × C(Ph*) H_3), 1.86 (tt, J = 6.9, 1.1 Hz, 2H, C(12) H_2), 1.38 – 1.30 (m, 2H, C(13) H_2), 1.28 – 1.21 (m, 2H, C(14) H_2), 0.83 (t, J = 7.2 Hz, 3H, C(15) H_3);

¹³C NMR (101 MHz, CDCl_3) 149.4 C(8), 135.2 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 132.3 2 × C(Ar(Ph*)), 129.0 C(Ar(Ph*)), 110.7 C(11), 68.4 C(9), 33.3 C(10), 30.4 C(13), 26.2 C(12), 22.7 C(14), 17.7 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.6 2 × C(Me(Ph*)), 14.1 C(15);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2926, 1691, 1456, 1152, 1104, 1068, 1046, 1019, 1001, 953, 894, 873;

HRMS (ESI⁺) $\text{C}_{19}\text{H}_{29}\text{O}^+$ ([M+H]⁺) requires 273.2213; found 273.2213.

* Prepared by Dr Anna Chamberlain

S2 4-Oxo-4-(2,3,5,6-tetramethylphenyl)butanoic acid

AlCl_3 (16.0 g, 120 mmol) was added portion-wise (over 5 min) to a stirred solution of succinic anhydride (6.00 g, 60.0 mmol) and 1,2,4,5-tetramethylbenzene (8.86 g, 66.0 mmol) in CH_2Cl_2 (200 mL) at RT. The reaction was stirred for 45 min at RT and then poured onto ice (approx. 200 g) and diluted with 1 M HCl (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×300 mL). The combined organic layers were washed with 1 M HCl (200 mL), brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{MeOH}$, 90:10) gave the *title compound* as a white solid (12.2 g, 87%).

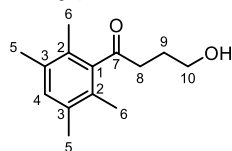
m.p. = 155 – 157 °C;

^1H NMR (400 MHz, CDCl_3) δ 6.90 (s, 1H, C(4)H), 2.94 (t, $J = 6.4$ Hz, 2H, C(8)H₂), 2.71 (t, $J = 6.4$ Hz, 2H, C(9)H₂), 2.13 (s, 6H, $2 \times \text{C}(\text{Ph}^\times)\text{CH}_3$), 2.00 (s, 6H, $2 \times \text{C}(\text{Ph}^\times)\text{CH}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 209.2 C(7), 178.5 C(10), 141.8 C(1), 134.5 $2 \times \text{C}(\text{Ar}(\text{Ph}^\times))$, 131.8 C(4), 128.2 $2 \times \text{C}(\text{Ar}(\text{Ph}^\times))$, 39.7 C(8), 27.4 C(9), 19.4 $2 \times \text{C}(\text{Me}(\text{Ph}^\times))$, 15.8, $2 \times \text{C}(\text{Me}(\text{Ph}^\times))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3046, 2941, 1716, 1699;

HRMS (ESI⁺) $\text{C}_{14}\text{H}_{18}\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 257.1148; found 257.1148, Δ 0.03 ppm.

S3 4-Hydroxy-1-(2,3,5,6-tetramethylphenyl)butan-1-one

$\text{BH}_3 \cdot \text{SMe}_2$ (3.6 mL, 38 mmol) was added dropwise (over 5 min) to a solution of acid **S2** (5.85 g, 25.0 mmol) in THF (125 mL) at 0 °C. The resulting solution was allowed to warm slowly to RT for 16 h and was subsequently cooled to 0 °C and quenched with MeOH (16 mL) and water (40 mL). The mixture was concentrated *in vacuo*, diluted further with water (200 mL) and extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine, dried over MgSO_4

and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 55:45 → Et₂O) gave the *title compound* as a white solid (5.09 g, 93%).

m.p. = 78 – 80 °C;

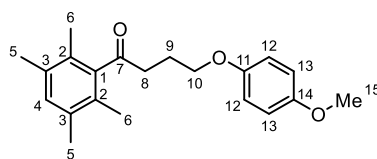
¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1H, C(4)*H*), 3.75 (q, *J* = 5.8 Hz, 2H, C(10)*H*₂), 2.83 (t, *J* = 6.9 Hz, 2H, C(8)*H*₂), 2.20 (s, 6H, 2 × C(Ph[×])CH₃), 2.06 (s, 6H, 2 × C(Ph[×])CH₃), 2.04 – 1.94 (m, 2H, C(9)*H*₂), 1.83 (t, *J* = 5.1 Hz, 1H, OH);

¹³C NMR (101 MHz, CDCl₃) δ 212.3 C(7), 142.8 C(1), 134.5 2 × C(Ar(Ph[×])), 131.7 C(4), 128.0 2 × C(Ar(Ph[×])), 62.4 C(10), 42.2 C(8), 26.3 C(9), 19.6 2 × C(Me(Ph[×])), 16.1 2 × C(Me(Ph[×]));

IR (film) ν_{max} /cm⁻¹ 3370, 2939, 1695, 1469, 1054, 1020;

HRMS (ESI⁺) C₁₄H₂₁O₂⁺ ([M+H]⁺) requires 221.1536; found 221.1536, Δ 0.16 ppm.

114 4-(4-Methoxyphenoxy)-1-(2,3,5,6-tetramethylphenyl)butan-1-one



3-Methoxyphenol (1.70 mg, 13.7 mmol), alcohol **S3** (2.50 g, 11.4 mmol), PPh₃ (3.88 g, 14.8 mmol) and di-4-chlorobenzyl)azodicarboxylate (5.03 g, 13.7 mmol) were subjected to **General Procedure B** Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 92.5:7.5) gave the *title compound* as a white solid (931 mg, 25%).

Alternative Method: Carboxylic acid **121** (5.00 g, 23.8 mmol) was dissolved in thionyl chloride (3.5 mL, 48 mmol) and the mixture was refluxed for 3 h. After cooling to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH₂Cl₂ (20 mL) and added to a solution of durene (4.83 g, 36.0 mmol) in CH₂Cl₂ (100 mL) at 0 °C. AlCl₃ (6.38 g, 48.0 mmol) was added portion-wise and to mixture was stirred at RT for 1 h. The crude reaction mixture was poured onto ice (approx. 150 g) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 × 150 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent

pentane: Et₂O, 96:4 → 90:10) gave a pale yellow solid, which was recrystallised from a minimum amount of boiling hexane to give the *title compound* as a white solid (3.75 g, 48%).

m.p. = 59 – 61 °C;

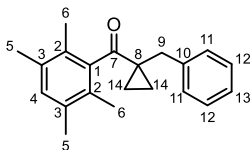
¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1H, C(4)H), 6.83 (s, 4H, 2 × C(12)H & 2 × C(13)H), 4.03 (t, *J* = 6.0 Hz, 2H, C(10)H₂), 3.77 (s, 3H, C(15)H₃), 2.90 (t, *J* = 7.0 Hz, 2H, C(8)H₂), 2.24 – 2.15 (m, 8H, 2 × C(Ph^{*})CH₃ & C(9)H₂), 2.05 (s, 6H, 2 × C(Ph^{*})CH₃);

¹³C NMR (101 MHz, CDCl₃) δ 211.4 C(7), 154.0 C(Ar), 153.1 C(Ar), 142.8 C(Ar), 134.5 2 × C(Ar(Ph^{*})), 131.7 C(4), 128.1 2 × C(Ar(Ph^{*})), 115.6 2 × C(Ar(PMP)), 114.8 2 × C(Ar(PMP)), 67.5 C(10), 55.9 C(15), 41.6 C(8), 23.2 C(9), 19.6 2 × C(Me(Ph^{*})), 16.0 2 × C(Me(Ph^{*}));

IR (film) ν_{max} /cm⁻¹ 2936, 1698, 1508, 1470, 1291, 1231, 1040, 825;

HRMS (ESI⁺) C₂₁H₂₇O₂⁺ ([M+H]⁺) requires 327.1955; found 327.1954, Δ 0.21 ppm.

115a (1-Benzylcyclopropyl)(2,3,5,6-tetramethylphenyl)methanone



Ketone Pre-functionalisation method:

Ir-catalysed: Ketone **114** (102 mg, 0.300 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol, degassed with Ar) were added to a 2 – 5 mL microwave vial. The vial was sealed and evacuated and back-filled with Argon (3 times). The reaction was heated at 110 °C for 24 h, cooled to RT and KOH (34 mg, 0.60 mmol) and ^tBuOH (1.5 mL) were added. The reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 95:5) gave the *title compound* as a colourless oil (69 mg, 75%).

Ru-catalysed: Ketone **114** (102 mg, 0.300 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol, degassed with Ar) were added to a 2 – 5 mL microwave vial. The vial was sealed and evacuated and back-filled with Argon (3 times). The

reaction was heated at 110 °C for 24 h, cooled to RT and KOH (34 mg, 0.60 mmol) and ^tBuOH (1.5 mL) were added. The reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 95:5) gave the *title compound* as a colourless oil (69 mg, 75%).

Alcohol Pre-functionalisation method:

Ir-catalysed: Ketone **134a** (80 mg, 0.30 mmol), [Ir(cod)Cl]₂ (4.0 mg, 1.0 mol%), dppBz (6.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5) gave the *title compound* as a colourless oil (54 mg, 61%).

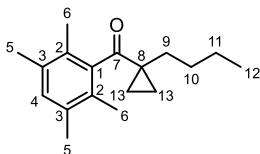
Ru-catalysed: Ketone **134a** (80 mg, 0.30 mmol), Ru-MACHO[®] (3.6 mg, 2.0 mol%) KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5) gave the *title compound* as a colourless oil (48 mg, 54%).

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.24 (m, 1H, C(13)*H*), 7.16 – 7.07 (m, 2H, 2 × C(Ph)*H*), 7.03 – 6.96 (m, 2H, 2 × C(Ph)*H*), 6.83 (s, 1H, C(4)*H*), 2.95 (s, 2H, C(9)*H*₂), 2.07 (s, 6H, 2 × C(Ph^x)CH₃), 1.83 (s, 6H, 2 × C(Ph^x)CH₃), 1.23 – 1.12 (m, 2H, 2 × C(14)*H*_A*H*_B), 0.98 – 0.88 (m, 2H, 2 × C(14)*H*_A*H*_B);

¹³C NMR (151 MHz, CDCl₃) δ 212.3 C(7), 139.6 C(Ar), 139.0 C(Ar), 134.1 C(Ar), 131.4 C(4), 129.9 2 × C(Ph), 129.1 C(Ar), 127.9 2 × C(Ph), 126.2 C(13), 37.8 C(9), 34.1 C(8), 19.4 2 × C(Me(Ph^x)), 17.4 2 × C(14), 16.2 2 × C(Me(Ph^x));

IR (film) ν_{max}/cm⁻¹ 2922, 2862, 1671, 1469, 700;

HRMS (ESI⁺) C₂₁H₂₅O⁺ ([M+H]⁺) requires 293.1900; found 293.1900, Δ 0.04 ppm.

115b (1-Butylcyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Ir-catalysed: Ketone **114** (98 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 3.0 mmol) and *n*-butanol (0.27 mL, 3.0 mmol) were subjected to **General Procedure A** at 90 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5) gave the *title compound* as a colourless oil (64 mg, 82%).

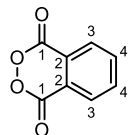
Ru-catalysed: Ketone **114** (98 mg, 0.30 mmol) Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and *n*-butanol (0.27 mL, 3.0 mmol) were subjected to **General Procedure A** at 90 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1 → 98.5:1.5) gave the *title compound* as a colourless oil (19 mg, 25%).

¹H NMR (400 MHz, CDCl₃) δ 6.91 (s, 1H, C(4)*H*), 2.17 (s, 6H, 2 × C(Ph^{*})CH₃), 2.05 (s, 6H, 2 × C(Ph^{*})CH₃), 1.68 – 1.59 (m, 2H, C(9)*H*₂), 1.47 – 1.35 (m, 2H, C(10)*H*₂), 1.35 – 1.23 (m, 2H, C(11)*H*₂), 1.13 – 1.06 (m, 2H, 2 × C(13)*H*_A*H*_B), 0.96 – 0.90 (m, 2H, 2 × C(13)*H*_A*H*_B), 0.86 (t, *J* = 7.3 Hz, 3H, C(12)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 212.6 C(7), 139.3 C(1), 134.2 2 × C(Ar(Ph^{*})), 131.4 C(4), 129.2 2 × C(Ar(Ph^{*})), 34.1 C(8), 33.4 C(9), 29.6 C(10), 23.2 C(11), 19.6 2 × C(Me(Ph^{*})), 17.9 2 × C(13), 16.6 2 × C(Me(Ph^{*})), 14.1 C(12);

IR (film) ν_{max} /cm⁻¹ 2956, 2932, 2861, 1670, 1468, 964;

HRMS (ESI⁺) C₁₈H₂₇O⁺ ([M+H]⁺) requires 259.2054; found 259.2057, Δ 0.95 ppm.

S4 Phthaloyl peroxide

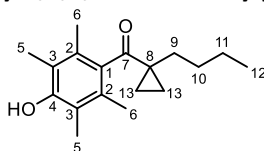
Phthaloyl chloride (1.45 mL, 10.0 mmol) was added to a vigorously stirred suspension of $\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$ (2.36 g, 15.0 mmol) and Na_2CO_3 (530 mg, 5.00 mmol) in water-saturated CH_2Cl_2 * (50 mL) and the resulting mixture was stirred vigorously for 3 h. The crude reaction mixture was filtered through a Celite® pad, eluting with CH_2Cl_2 and the filtrate was concentrated *in vacuo*, ensuring that the water bath temperature did not exceed 30 °C. The residue was re-dissolved in a minimum amount of warm benzene and poured into ice-cold pentane (100 mL). The resulting solid was filtered under reduced pressure and washed with ice-cold pentane (3 × 30 mL) to give the *title compound* as a white solid (1.37 g, 83%).

^1H NMR (400 MHz, CDCl_3) δ 8.35 – 8.25 (m, 2H, 2 × C(3)H), 8.07 – 7.98 (m, 2H, 2 × C(4)H);

^{13}C NMR (101 MHz, CDCl_3) δ 162.1 2 × C(1), 136.6 2 × C(4), 130.3 2 × C(3), 123.8 2 × C(2);

m/z (ESI⁺) Found ($[\text{M}+\text{H}]^+$) = 165, $\text{C}_8\text{H}_5\text{O}_4$ requires 165.

The spectroscopic data were consistent with that reported in the literature.¹⁴⁰

116b (1-Butylcyclopropyl)(4-hydroxy-2,3,5,6-tetramethylphenyl)methanone

Phthaloyl peroxide **S4** (58 mg, 0.35 mmol) was added to a solution of ketone **115b** (70 mg, 0.27 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (2.7 mL) under Ar. The resulting mixture was purged with Ar and heated at 40 °C for 16 h. The crude reaction mixture was concentrated *in vacuo* and deoxygenated MeOH (2.7 mL) and sat. aq. NaHCO_3 (0.29 mL) were added. The mixture was heated at 40 °C for a further 6 h, cooled to RT and diluted with brine and CH_2Cl_2 . The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined

* Water-saturated CH_2Cl_2 was easily prepared by putting CH_2Cl_2 and deionised H_2O in a separating funnel and shaking it vigorously, then removing only the organic phase and avoiding any obvious water droplets.

organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent pentane/ Et_2O , 85:15) gave the *title compound* as an off-white solid (55 mg, 74%).

m.p. = 111 – 113 °C, *via* oxidation to the corresponding quinone (yellow solid);

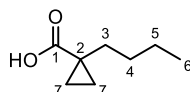
^1H NMR (600 MHz, CDCl_3) δ 4.67 (br. s, 1H, OH), 2.11 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{CH}_3$), 2.08 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{CH}_3$), 1.66 – 1.59 (m, 2H, $\text{C}(9)\text{H}_2$), 1.44 – 1.32 (m, 2H, $\text{C}(10)\text{H}_2$), 1.32 – 1.21 (m, 2H, $\text{C}(11)\text{H}_2$), 1.08 (q, $J = 4.0$ Hz, 2H, $2 \times \text{C}(13)\text{H}_\text{A}\text{H}_\text{B}$), 0.94 – 0.88 (m, 2H, $2 \times \text{C}(13)\text{H}_\text{A}\text{H}_\text{B}$), 0.87 (t, $J = 7.3$ Hz, 3H, $\text{C}(12)\text{H}_3$);

^{13}C NMR (151 MHz, CDCl_3) δ 212.6 $\text{C}(7)$, 151.7 $\text{C}(4)$, 132.1 $\text{C}(1)$, 130.2 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 119.6 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 34.3 $\text{C}(8)$, 33.5 $\text{C}(9)$, 29.6 $\text{C}(10)$, 23.2 $\text{C}(11)$, 17.8 $2 \times \text{C}(13)$, 17.3 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 14.1 $\text{C}(12)$, 11.8 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3433, 2955, 2932, 2860, 1650, 1124, 1098;

HRMS (ESI^+) $\text{C}_{18}\text{H}_{27}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 275.2006; found 275.2006, Δ 0.02 ppm.

117b 1-Butylcyclopropane-1-carboxylic acid



CAN (ceric ammonium nitrate) (548 mg, 1.00 mmol) in water (1.0 mL) was added into a stirred suspension of compound **116b** (55 mg, 0.20 mmol) in MeCN (1.0 mL) and the resulting mixture was stirred at RT for 5 min. Water (6.0 mL) was added and the reaction was stirred for a further 10 min. The reaction was diluted with CH_2Cl_2 (10 mL) and water (4 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). NaOH (3 M, 30 mL) was added to the combined organic layers, the layers were separated and the aqueous layer acidified with HCl (3 M, 35 mL) and extracted with CH_2Cl_2 (3×60 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the *title compound* as a yellow oil which required no further purification (24.5 mg, 86%).

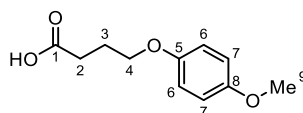
^1H NMR (600 MHz, CDCl_3) δ 1.54 – 1.47 (m, 2H, C(3) H_2), 1.47 – 1.39 (m, 2H, C(4) H_2), 1.33 – 1.28 (m, 2H, C(5) H_2), 1.28 – 1.22 (m, 2H, 2 $\times$ C(7) H_AH_B), 0.89 (t, J = 7.3 Hz, 3H, C(6) H_3), 0.81 – 0.67 (m, 2H, 2 $\times$ C(7) H_AH_B);

^{13}C NMR (151 MHz, CDCl_3) δ 182.2 C(1), 33.5 C(3), 29.9 C(4), 23.5 C(2), 23.0 C(5), 16.6 2 $\times$ C(7), 14.2 C(6);

m/z (ESI^-) Found ($[\text{M}-\text{H}]^-$) = 141, $\text{C}_8\text{H}_{13}\text{O}_2$ requires 141.

The spectroscopic data were consistent with that reported in the literature.¹⁴¹

121 4-(4-Methoxyphenoxy)butanoic acid



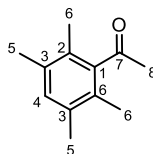
KOH (2.92 g, 52.0 mmol) was added to a stirred suspension of 4-methoxyphenol (6.20 g, 50.0 mmol) in water (2 mL). γ -Butyrolactone (7.7 mL, 100 mmol) was added, a Dean-Stark trap was attached and the mixture was heated under N_2 at 150 $^\circ\text{C}$ for 2 h and then at 190 $^\circ\text{C}$ for 18 h. After cooling to RT, water (50 mL) was added and the mixture was heated to reflux until all of the solid had dissolved. The resulting hot brown solution was poured into ice-cold HCl (1.5 M, 200 mL) and the mixture was cooled at 0 $^\circ\text{C}$ for 2 h. The crystals were collected by filtering under reduced pressure (washing with cold water) and then re-dissolved in CH_2Cl_2 (500 mL). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the *title compound* as a white solid which required no further purification (7.97 g, 76%).

^1H NMR (400 MHz, CDCl_3) δ 6.83 (s, 4H, 2 $\times$ C(6) H & 2 $\times$ C(7) H), 3.97 (t, J = 6.1 Hz, 2H, C(4) H_2), 3.77 (s, 3H, C(9) H_3), 2.59 (t, J = 7.3 Hz, 2H, C(2) H_2), 2.17 – 2.01 (m, 2H, C(3) H_2);

^{13}C NMR (101 MHz, CDCl_3) δ 179.5 C(1), 154.0 C(Ar), 153.0 C(Ar), 115.6 2 $\times$ C(Ar), 114.8 2 $\times$ C(Ar), 67.3 C(4), 55.9 C(9), 30.7 C(2), 24.6 C(3);

m/z (ESI^-) Found ($[\text{M}-\text{H}]^-$) = 209, $\text{C}_{11}\text{H}_{13}\text{O}_4$ requires 209.

The spectroscopic data were consistent with that reported in the literature.¹⁴²

119 1-(2,3,5,6-Tetramethylphenyl)ethan-1-one

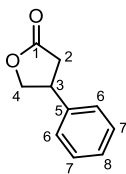
Aluminium trichloride (2.97 g, 22.3 mmol) was added portion-wise to a solution of durene (2.50 g, 18.6 mmol) and acetyl chloride (1.34 mL, 20.5 mmol) in CH_2Cl_2 (75 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 30 min and was then poured onto crushed ice (approx. 100 g). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed sequentially with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 → 90:10) gave the *title compound* as a white solid (3.07 g, 94%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.95 (s, 1H, C(4)H), 2.46 (s, 3H, C(8)H₃), 2.21 (s, 6H, 2 × C(Ph^{*})H₃), 2.09 (s, 6H, 2 × C(Ph^{*})H₃);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 210.0 C(7), 143.2 C(1), 134.5 2 × C(Ar(Ph^{*})), 131.6 C(4), 127.7 2 × C(Ar(Ph^{*})), 32.9 C(8), 19.6 2 × C(Me(Ph^{*})), 16.0 2 × C(Me(Ph^{*}));

m/z (ESI⁺) Found ([M+H]⁺) = 177, $\text{C}_{12}\text{H}_{17}\text{O}$ requires 177.

The spectroscopic data were consistent with that reported in the literature.¹⁴³

123 4-Phenyldihydrofuran-2(3H)-one

$[\text{Rh}(\text{cod})\text{Cl}]_2$ (21 mg, 1.5 mol%) was dissolved in PhMe (65 mL) and stirred for 5 mins. Aqueous KOH (2.0 M, 7.0 mL, 14 mmol) was added and the mixture was stirred vigorously for 30 min. Phenylboronic acid (4.47 g, 36.6 mmol) and furan-2(5H)-one (2.0 mL, 28 mmol) were added and the mixture was heated at 50 °C for 24 h. After cooling to RT, the reaction mixture was diluted with sat. aq. NaHCO_3 (150 mL) and CH_2Cl_2 (100 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine, dried

over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 65:35 $\rightarrow$ 50:50) gave the *title compound* as an off-white solid (2.87 g, 63%).

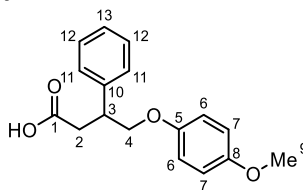
^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.34 (m, 2H, 2 $\times$ C(Ph)H), 7.33 – 7.28 (m, 1H, C(8)H), 7.26 – 7.21 (m, 2H, 2 $\times$ C(Ph)H), 4.67 (dd, J = 9.1, 7.9 Hz, 1H, C(4) H_AH_B), 4.27 (dd, J = 9.1, 7.9 Hz, 1H, C(4) H_AH_B), 3.79 (p, J = 8.4 Hz, 1H, C(3)H), 2.93 (dd, J = 17.5, 8.7 Hz, 1H, C(2) H_AH_B), 2.68 (dd, J = 17.5, 9.1 Hz, 1H, C(2) H_AH_B);

^{13}C NMR (101 MHz, CDCl_3) δ 176.5 C(1), 139.5 C(5), 129.3 2 $\times$ C(Ph), 127.8 C(8), 126.8 2 $\times$ C(Ph), 74.2 C(4), 41.2 C(3), 35.8 C(2);

m/z (ESI $^+$) Found ($[\text{M}+\text{H}]^+$) = 163, $\text{C}_{10}\text{H}_{11}\text{O}$ requires 163.

The spectroscopic data were consistent with that reported in the literature.¹⁴⁴

S5 4-(4-Methoxyphenoxy)-3-phenylbutanoic acid



KOH (561 mg, 10.0 mmol) was added to a stirred suspension of 4-methoxyphenol (1.13 g, 9.11 mmol) in water (0.4 mL). Lactone **123** (1.62 g, 10.0 mmol) was added and the reaction was heated to 150 $^{\circ}\text{C}$ for 2 h, then 190 $^{\circ}\text{C}$ for 16 h. After cooling to RT, the reaction mixture was diluted with 1.5 M HCl (20 mL) and CH_2Cl_2 (20 mL) and the layers separated. The organic layer was basified using 3 M NaOH, the layers separated and the aqueous layer was acidified using 3 M HCl, and extracted with CH_2Cl_2 (3 $\times$ 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{MeOH}$, 95:5:0 $\rightarrow$ 98:0:2) gave the *title compound* as a tan solid (290 mg, 10%).

m.p. = 102 – 103 $^{\circ}\text{C}$;

^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.26 (m, 5H, 5 $\times$ C(Ph)H), 6.80 (s, 4H, 2 $\times$ C(6)H, 2 $\times$ C(7)H), 4.10 (dd, J = 9.3, 5.2 Hz, 1H, C(4) H_AH_B), 3.97 (dd, J = 9.3, 8.1 Hz, 1H, C(4) H_AH_B), 3.76 (s, 3H, C(9) H_3),

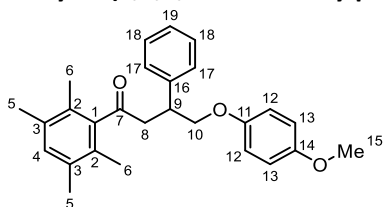
3.67 – 3.53 (m, 1H, C(3)*H*), 3.07 (dd, 1H, $J = 16.2, 6.5$ Hz, 1H, C(2)*H_AH_B*), 2.77 (dd, $J = 16.2, 8.2$ Hz, 1H, C(2)*H_AH_B*);

¹³C NMR (101 MHz, CDCl₃) δ 176.9 C(1), 154.0 C(Ar(Ph)), 152.7 C(Ar(Ph)), 140.5 C(10), 128.7 2 $\times$ C(Ph), 127.8 2 $\times$ C(Ph), 127.3 C(13), 115.5 2 $\times$ C(Ar(PMP)), 114.6 2 $\times$ C(Ar(PMP)), 72.0 C(4), 55.7 C(9), 41.6 C(2), 37.0 C(3);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3031, 2919, 1708, 1509, 1230;

HRMS (ESI[−]) C₁₇H₁₇O₄[−] ([M-H][−]) requires 285.1132; found 285.1133, Δ 0.24 ppm.

124 4-(4-Methoxyphenoxy)-3-phenyl-1-(2,3,5,6-tetramethylphenyl)butan-1-one



Carboxylic acid **S5** (250 mg, 0.874 mmol) was dissolved in thionyl chloride (0.15 mL, 2.1 mmol) and the mixture was refluxed for 3 h. After cooling to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH₂Cl₂ (3.0 mL), durene (181 mg, 1.34 mmol) was added and the mixture was cooled to 0 °C. AlCl₃ (240 mg, 1.80 mmol) was added portion-wise and to mixture was stirred at RT for 2 h. The crude reaction mixture was poured onto ice (approx. 10 g) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 10 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂, 20:80 $\rightarrow$ pentane/Et₂O, 90:10) gave the *title compound* as an off-white solid (101 mg, 35%).

m.p. = 84 – 86 °C;

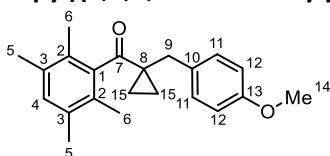
¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.21 (m, 5H, 5 $\times$ C(Ph)*H*), 6.86 (s, 1H, C(4)*H*), 6.74 (s, 4H, 2 $\times$ C(12)*H*, 2 $\times$ C(13)*H*), 4.13 (dd, $J = 9.2, 5.2$ Hz, 1H, C(10)*H_AH_B*), 4.01 (dd, $J = 9.2, 6.7$ Hz, 1H, C(10)*H_AH_B*), 3.84 – 3.76 (m, 1H, C(9)*H*), 3.69 (s, 3H, C(15)*H₃*), 3.45 – 3.30 (m, 1H, C(8)*H_AH_B*), 3.11 – 2.93 (m, 1H, C(8)*H_AH_B*), 2.09 (s, 6H, 2 $\times$ C(Ph*)*CH₃*), 1.83 (s, 6H, 2 $\times$ C(Ph*)*CH₃*);

^{13}C NMR (126 MHz, CDCl_3) δ 209.8 C(7), 154.1 C(14), 153.0 C(11), 142.5 C(1), 142.1 C(16), 134.5 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 131.7 C(4), 128.6 $2 \times \text{C}(18)$, 128.4 $2 \times \text{C}(17)$, 128.2 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 127.0 C(19), 115.7 $2 \times \text{C}(\text{Ar}(\text{PMP}))$, 114.8 $2 \times \text{C}(\text{Ar}(\text{PMP}))$, 71.7 C(10), 55.9 C(15), 47.9 C(8), 39.9 C(9), 19.6 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 15.8 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2938, 1701, 1508, 1289, 1230;

HRMS (ESI^+) $\text{C}_{27}\text{H}_{31}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 403.2266; found 403.2268, Δ 0.37 ppm.

115c (1-(4-Methoxybenzyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone



Ketone **114** (98 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and anisyl alcohol (0.37 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 97:3 $\rightarrow$ 95:5) gave the *title compound* as a colourless oil which solidified on standing (80 mg, 83%).

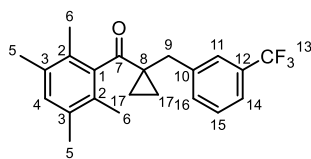
m.p. = 92 – 94 °C;

^1H NMR (400 MHz, CDCl_3) δ 7.03 – 6.93 (m, 2H, C(11) H_2), 6.90 (s, 1H, C(4) H), 6.78 – 6.66 (m, 2H, C(12) H_2), 3.78 (s, 3H, C(14) H_3), 2.96 (s, 2H, C(9) H_2), 2.15 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{CH}_3$), 1.91 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{CH}_3$), 1.26 – 1.16 (m, 2H, $2 \times \text{C}(15)H_AH_B$), 1.10 – 0.88 (m, 2H, $2 \times \text{C}(15)H_AH_B$);

^{13}C NMR (101 MHz, CDCl_3) δ 212.5 C(7), 158.1 C(13), 139.6 C(Ar), 134.1 C(Ar), 131.4 C(4), 131.0 C(Ar), 130.9 $2 \times \text{C}(\text{Ar}(\text{PMP}))$, 129.1 C(Ar), 113.3 $2 \times \text{C}(\text{Ar}(\text{PMP}))$, 55.2 C(14), 36.9 C(9), 34.3 C(8), 19.4 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 17.3 $2 \times \text{C}(15)$, 16.2 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3006, 2917, 1671, 1611, 1511, 1247;

HRMS (ESI^+) $\text{C}_{22}\text{H}_{26}\text{O}_2\text{Na}^+$ ($[\text{M}+\text{Na}]^+$) requires 345.1825; found 345.1831, Δ 1.70 ppm.

115d (2,3,5,6-Tetramethylphenyl)(1-(3-(trifluoromethyl)benzyl)cyclopropyl)methanone

Ir-catalysed: Ketone **114** (98 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and (3-(trifluoromethyl)phenyl)methanol (0.40 mL, 3.0 mmol, degassed with Ar (balloon)) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, and KOH (34 mg, 0.15 mmol) and ^tBuOH (1.5 mL) were added. The reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5 → 98:2) gave the *title compound* as a colourless oil (67 mg, 62%).

Ru-catalysed: Ketone **114** (98 mg, 0.30 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and (3-(trifluoromethyl)phenyl)methanol (0.40 mL, 3.0 mmol, degassed with Ar (balloon)) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, and KOH (34 mg, 0.15 mmol) and ^tBuOH (1.5 mL) were added. The reaction was heated at 110 °C for a further 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5 → 98:2) gave the *title compound* as a colourless oil (70 mg, 65%).

¹H NMR (500 MHz, CDCl₃) δ 7.45 – 7.42 (m, 1H, C(14)H), 7.36 – 7.30 (m, 3H, C(11)H, C(15)H, C(16)H), 6.90 (s, 1H, C(4)H), 3.05 (s, 2H, C(9)H₂), 2.12 (s, 6H, 2 × C(Ph^{*})CH₃), 1.87 (s, 6H, 2 × C(Ph^{*})CH₃), 1.30 (q, *J* = 4.1 Hz, 2H, 2 × C(17)H_AH_B), 1.12 – 1.02 (m, 2H, 2 × C(17)H_AH_B);

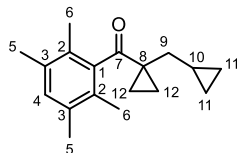
¹³C NMR ({¹⁹F} 126 MHz, CDCl₃) δ 211.8 C(7), 140.5 C(10), 139.2 C(1), 134.4 2 × C(Ar(Ph^{*})), 133.2 C(11), 131.8 C(4), 130.4 C(12), 129.1 2 × C(Ar(Ph^{*})), 128.5 C(15), 126.3 C(16), 124.3 C(13), 123.2 C(14), 38.4 C(9), 34.3 C(8), 19.5 2 × C(Me(Ph^{*})), 17.9 2 × C(17), 16.3 2 × C(Me(Ph^{*}));

¹⁹F NMR (471 MHz, CDCl₃) δ –62.6;

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2925, 2866, 1672, 1450, 1329, 1198, 1163, 1125;

HRMS (ESI⁺) $\text{C}_{22}\text{H}_{23}\text{F}_3\text{NaO}^+$ ($[\text{M}+\text{Na}]^+$) requires 383.1593; found 383.1607, Δ 3.59 ppm.

115e (1-(Cyclopropylmethyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone



Ketone **114** (196 mg, 0.600 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (4.0 mg, 1.0 mol%), dppBz (6.0 mg, 2.0 mol%), KOH (135 mg, 1.20 mmol) and cyclopropanemethanol (0.55 mL, 6.0 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2) gave the *title compound* as a colourless oil (122 mg, 79%).

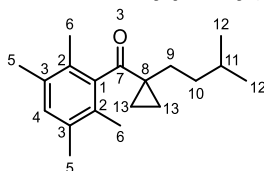
¹H NMR (400 MHz, CDCl₃) δ 6.91 (s, 1H, C(4)*H*), 2.18 (s, 6H, 2 × C(Ph^{*})CH₃), 2.07 (s, 6H, 2 × C(Ph^{*})CH₃), 1.64 (d, J = 6.9 Hz, 2H, C(9)*H*₂), 1.19 – 1.10 (m, 2H, 2 × C(12)*H*_A*H*_B), 1.10 – 1.01 (m, 2H, 2 × C(12)*H*_A*H*_B), 0.84 – 0.67 (m, 1H, C(10)*H*), 0.46 – 0.26 (m, 2H, 2 × C(11)*H*_A*H*_B), 0.03 (dd, J = 5.0, 1.4 Hz, 2H, 2 × C(11)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.9 C(7), 139.6 C(1), 134.2 2 × C(Ar(Ph^{*})), 131.5 C(4), 129.2 2 × C(Ar(Ph^{*})), 37.1 C(9), 34.0 C(8), 19.6 2 × C(Me(Ph^{*})), 17.1 2 × C(12), 16.5 2 × C(Me(Ph^{*})), 8.6 C(10), 4.5 2 × C(11);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3078, 3003, 2923, 1671, 1469, 1011, 964;

HRMS (ESI⁺) $\text{C}_{18}\text{H}_{25}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 257.1900; found 257.1900, Δ 0.08 ppm.

115f (1-Isopentylcyclopropyl)(2,3,5,6-tetramethylphenyl)methanone



Ketone Pre-functionalisation method:

Ir-catalysed: Ketone **114** (98 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 3-methylbutan-1-ol (0.35 mL, 3.0 mmol) were subjected

to **General Procedure A** at 90 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.5:0.5 → 99:1) gave the *title compound* as a white solid (64 mg, 79%).

Ru-catalysed: Ketone **114** (98 mg, 0.30 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 3-methylbutan-1-ol (0.35 mL, 3.0 mmol) were subjected to **General Procedure A** at 90 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.5:0.5 → 99:1) gave the *title compound* as a white solid (28 mg, 35%).

Alcohol Pre-functionalisation method:

Ir-catalysed: Ketone **134f** (74 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5) gave the *title compound* as a colourless oil which solidified on standing (45 mg, 55%).

Ru-catalysed: Ketone **134f** (74 mg, 0.30 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5) gave the *title compound* as a colourless oil which solidified on standing (48 mg, 59%).

m.p. = 48 – 50 °C;

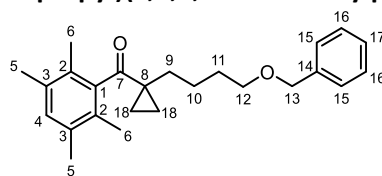
¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1H, C(4)*H*), 2.17 (s, 6H, 2 × C(Ph^{*})CH₃), 2.05 (s, 6H, 2 × C(Ph^{*})CH₃), 1.67 – 1.58 (m, 2H, C(9)*H*₂), 1.45 (m, 1H, C(11)*H*), 1.37 – 1.23 (m, 2H, C(10)*H*₂), 1.11 (q, *J* = 4.0 Hz, 2H, 2 × C(13)*H*_A*H*_B), 0.91 (q, *J* = 4.0 Hz, 2H, 2 × C(13)*H*_A*H*_B), 0.83 (d, *J* = 6.6 Hz, 6H, 2 × C(12)*H*₃);

¹³C NMR (126 MHz, CDCl₃) δ 212.6 C(7), 139.3 C(1), 134.2 2 × C(Ar(Ph^x)), 131.4 C(4), 129.2 2 × C(Ar(Ph^x)), 36.4 C(10), 34.1 C(8), 31.5 C(9), 28.4 C(11), 22.6 2 × C(12), 19.6 2 × C(Me(Ph^x)), 18.0 2 × C(13), 16.6 2 × C(Me(Ph^x));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2953, 2869, 1670 1468, 966;

HRMS (ESI⁺) C₁₉H₂₉O⁺ ([M+H]⁺) requires 273.2211; found 273.2213 Δ 0.59 ppm.

115g (1-(4-(Benzyloxy)butyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone



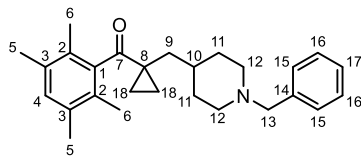
Ketone **114** (98 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 4-benzyloxybutan-1-ol (0.53 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 94:6) gave the *title compound* as a colourless oil (87 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.20 (m, 5H, 5 × C(Ph)*H*), 6.83 (s, 1H, C(4)*H*), 4.42 (s, 2H, C(13)*H*₂), 3.37 (t, *J* = 6.5 Hz, 2H, C(12)*H*₂), 2.09 (s, 6H, 2 × C(Ph^x)CH₃), 1.97 (s, 6H, 2 × C(Ph^x)CH₃), 1.62 – 1.38 (m, 6H, C(9)*H*₂, C(10)*H*₂, C(11)*H*₂), 1.02 (q, *J* = 3.6 Hz, 2H, 2 × C(18)*H*_A*H*_B), 0.93 – 0.81 (m, 2H, 2 × C(18)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.5 C(7), 139.1 C(Ar), 138.8 C(Ar), 134.2 2 × C(Ar(Ph^x)), 131.5 C(4), 129.2 2 × C(Ar(Ph^x)), 128.5 2 × C(Ph), 127.8 2 × C(Ph), 127.6 C(17), 73.0 C(13), 70.4 C(12), 34.0 C(8), 33.5 C(9), 30.2 C(11), 24.0 C(10), 19.6 2 × C(Me(Ph^x)), 17.8 2 × C(18), 16.6 2 × C(Me(Ph^x));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3029, 2939, 2861, 1669, 1469, 1105, 736, 698;

HRMS (ESI⁺) C₂₅H₃₃O₂⁺ ([M+H]⁺) requires 365.2475; found 365.2474, Δ 0.36 ppm.

115h (1-((1-Benzylpiperidin-4-yl)methyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Ketone **114** (98 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 1-benzyl-4-piperidyl methanol (616 mg, 3.00 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 50:50) gave the *title compound* as a colourless oil which solidified on standing to give an off-white solid (62 mg, 53%).

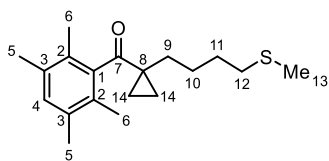
m.p. = 85 – 87 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.14 (m, 5H, 5 × C(Ph)*H*), 6.83 (s, 1H, C(4)*H*), 3.41 (s, 2H, C(13)*H*₂), 2.79 (d, *J* = 11.1 Hz, 2H, 2 × C(12)*H*_A*H*_B), 2.10 (s, 6H, 2 × C(Ph^{*})CH₃), 1.98 (s, 6H, 2 × C(Ph^{*})CH₃), 1.93 – 1.78 (m, 2H, 2 × C(12)*H*_A*H*_B), 1.77 – 1.54 (m, 3H, C(10)*H*, 2 × C(11)*H*_A*H*_B), 1.49 (d, *J* = 6.3 Hz, 2H, C(9)*H*₂), 1.26 – 1.11 (m, 2H, 2 × C(11)*H*_A*H*_B), 1.03 (q, *J* = 4.0 Hz, 2H, 2 × C(18)*H*_A*H*_B), 0.93 – 0.78 (m, 2H, 2 × C(18)*H*_A*H*_B);

¹³C NMR (151 MHz, CDCl₃) δ 212.3 C(7), 139.2 C(1), 138.6 br. C(14) 134.3 2 × C(Ar(Ph^{*})), 131.5 C(4), 129.4 2 × C(Ar(Ph^{*})), 129.2 2 × C(15) 128.3 2 × C(16), 127.1 C(17), 63.6 C(13), 54.0 2 × C(12), 40.8 C(9), 34.5 C(10), 33.3 2 × C(11), 32.2 C(8), 19.6 2 × C(Me(Ph^{*})), 18.0 2 × C(18), 16.7, 2 × C(Me(Ph^{*}));

IR (film) ν_{max} /cm⁻¹ 2922, 2799, 2756, 1669, 738, 699;

HRMS (ESI⁺) C₂₇H₃₅NONa⁺ ([M+Na]⁺) requires 412.2611; found 412.2625, Δ 3.40 ppm.

115i 1-(4-(Methylthio)butyl)cyclopropyl(2,3,5,6-tetramethylphenyl)methanone

Ir-catalysed: Ketone **114** (98 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 4-(methylthio)butan-1-ol (0.36 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C for 24 h, filtered through a silica plug (elution with Et₂O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 96:4) gave the *title compound* as a colourless oil (39 mg, 43%).

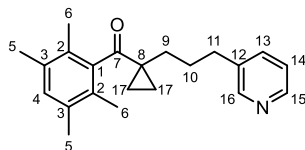
Ru-catalysed: Ketone **114** (98 mg, 0.30 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 4-(methylthio)butan-1-ol (0.36 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 96:4) gave the *title compound* as a colourless oil (31 mg, 36%).

¹H NMR (400 MHz, CDCl₃) δ 6.91 (s, 1H, C(4)*H*), 2.46 (t, *J* = 6.9 Hz, 2H, C(12)*H*₂), 2.17 (s, 6H, 2 × C(Ph[×])*H*₃), 2.07 (s, 3H, C(13)*H*₃), 2.05 (s, 6H, 2 × C(Ph[×])*H*₃), 1.68 – 1.61 (m, 2H, C(9)*H*₂), 1.61 – 1.49 (m, 4H, C(10)*H*₂, C(11)*H*₂), 1.14 – 1.06 (m, 2H, 2 × C(14)*H*_A*H*_B), 0.98 – 0.89 (m, 2H, 2 × C(14)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.5 C(7), 139.0 C(1), 134.3 2 × C(Ar(Ph[×])), 131.5 C(4), 129.2 2 × C(Ar(Ph[×])), 34.2 C(12), 34.0 C(8), 33.3 C(9), 29.6 C(11), 26.6 C(10), 19.6 2 × C(Me(Ph[×])), 17.9 2 × C(14), 16.6 2 × C(Me(Ph[×])), 15.7 C(13);

IR (film) ν_{max} /cm⁻¹ 2938, 2861, 1670, 1469, 1097, 965, 872, 760;

HRMS (ESI⁺) C₁₉H₂₉OS⁺ ([M+H]⁺) requires 305.1934; found 305.1943, Δ 3.06 ppm.

115j (1-(3-(Pyridin-3-yl)propyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Ir-catalysed: Ketone **114** (98 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 3-pyridinepropanol (0.39 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 40:60 → 20:80) gave the *title compound* as a colourless oil (60 mg, 62%).

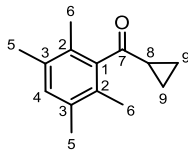
Ru-catalysed: Ketone **114** (98 mg, 0.30 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 3-pyridinepropanol (0.39 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 40:60 → 20:80) gave the *title compound* as a colourless oil (59 mg, 61%).

¹H NMR (500 MHz, CDCl₃) δ 8.45 (d, *J* = 4.9 Hz, 1H, C(15)*H*), 8.42 (d, *J* = 2.3 Hz, 1H, C(16)*H*), 7.46 (dd, *J* = 7.8, 2.5 Hz, 1H, C(13)*H*), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H, C(14)*H*), 6.93 (s, 1H, C(4)*H*), 2.61 (t, *J* = 7.6 Hz, 2H, C(11)*H*₂), 2.19 (s, 6H, 2 × C(Ph^x)CH₃), 2.07 (s, 6H, 2 × C(Ph^x)CH₃), 1.87 – 1.75 (m, 2H, C(9)*H*₂), 1.72 – 1.63 (m, 2H, C(10)*H*₂), 1.15 (q, *J* = 4.1 Hz, 2H, 2 × C(17)*H*_A*H*_B), 0.93 (q, *J* = 4.2 Hz, 2H, 2 × C(17)*H*_A*H*_B);

¹³C NMR (126 MHz, CDCl₃) δ 212.2 C(7), 149.7 C(16), 147.1 C(15), 138.8 C(1), 137.5 C(12), 135.9 C(13), 134.2 2 × C(Ar(Ph^x)), 131.5 C(4), 129.0 2 × C(Ar(Ph^x)), 123.4 C(14) 33.7 C(8), 33.3 C(10), 33.2 C(11), 28.6 C(9), 19.4 2 × C(Me(Ph^x)), 17.9 2 × C(17), 16.5 2 × C(Me(Ph^x));

IR (film) ν_{max} /cm⁻¹ 2938, 2862, 1667, 1470, 1377, 1343, 1308, 715;

HRMS (ESI⁺) C₂₂H₂₈NO⁺ ([M+H]⁺) requires 322.2165; found 322.2164, Δ 0.44 ppm.

126 Cyclopropyl(2,3,5,6-tetramethylphenyl)methanone

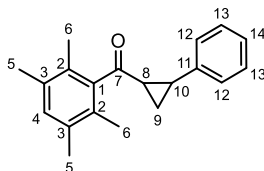
Ketone **114** (98 mg, 0.30 mmol) [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and neopentyl alcohol **125** (264 mg, 3.00 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5) gave the *title compound* as a colourless oil (31 mg, 51%).

¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1H, C(4)*H*), 2.21 (s, 6H, 2 × C(Ph[×])CH₃), 2.20 – 2.14 (m, 1H, C(8)*H*), 2.13 (s, 6H, 2 × C(Ph[×])CH₃), 1.31 – 1.20 (m, 2H, 2 × C(9)*H_AH_B*), 1.10 – 1.02 (m, 2H, 2 × C(9)*H_AH_B*);

¹³C NMR (101 MHz, CDCl₃) δ 211.9 C(7), 143.3 C(1), 134.4 2 × C(Ar(Ph[×])), 131.7 C(4), 128.5 2 × C(Ar(Ph[×])), 23.6 C(8), 19.7 2 × C(Me(Ph[×])), 16.4, 2 × C(Me(Ph[×])), 12.4 2 × C(9);

IR (film) ν_{max} /cm⁻¹ 3008, 2923, 1681, 1470, 1442, 1381, 1363, 1294, 1118, 979;

HRMS (ESI⁺) C₁₄H₁₉O⁺ ([M+H]⁺) requires 203.1430; found 203.1431, Δ 0.50 ppm.

127 (2-Phenylcyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Ketone **124** (75 mg, 0.19 mmol), [Ir(cod)Cl]₂ (1.3 mg, 1.0 mol%), dppBz (1.8 mg, 2.0 mol%), KOH (45 mg, 0.8 mmol) and cyclopropanemethanol (0.17 mL, 2.0 mmol) were subjected to **General Procedure A** at 90 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.5:0.5 → 99:1) gave the *title compound* as an off-white solid (38 mg, 73%).

m.p. = 108 – 110 °C;

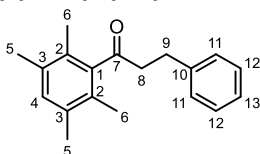
¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.24 (m, 2H, 2 × C(13)*H*), 7.24 – 7.15 (m, 1H, C(14)*H*), 7.14 – 7.06 (m, 2H, 2 × C(12)*H*), 6.95 (s, 1H, C(4)*H*), 2.77 (ddd, *J* = 9.1, 6.7, 4.0 Hz, 1H, C(10)*H*), 2.42 (ddd, *J* = 8.0, 5.3, 4.0 Hz, 1H, C(8)*H*), 2.20 (s, 6H, 2 × C(Ph[×])CH₃), 2.13 (s, 6H, 2 × C(Ph[×])CH₃), 1.94 (ddd, *J* = 9.3, 5.3, 4.1 Hz, 1H, C(9)*H_AH_B*), 1.63 – 1.52 (m, 1H, C(9)*H_AH_B*);

^{13}C NMR (101 MHz, CDCl_3) δ 209.7 C(7), 143.3 C(1), 140.1 C(11), 134.5 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 131.8 C(4), 128.7 $2 \times \text{C}(13)$, 128.5 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 126.8 C(14), 126.2 $2 \times \text{C}(12)$, 35.3 C(8), 30.9 C(10), 20.0 C(9), 19.6 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.4 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2922, 1686, 1470, 1456, 1398, 980, 669;

HRMS (ESI^+) $\text{C}_{20}\text{H}_{23}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 279.1743; found 219.1743, Δ 0.20 ppm.

134a 3-Phenyl-1-(2,3,5,6-tetramethylphenyl)propan-1-one



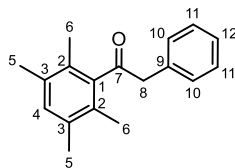
3-Phenylpropanoic acid (4.50 g, 30.0 mmol) was dissolved in thionyl chloride (5.3 mL, 75 mmol) and the mixture was refluxed for 16 h. Once cooled to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH_2Cl_2 (10 mL) and added to a solution of durene (4.40 g, 32.8 mmol) in CH_2Cl_2 (90 mL) at 0 °C. AlCl_3 (5.00 g, 37.6 mmol) was added portion-wise and to mixture was stirred at RT for 1 h. The crude reaction mixture was poured onto ice (approx. 150 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and the combined organic layers were washed sequentially with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Pentane: Et_2O , 98:2) gave the title compound as an off-white solid (1.30 g, 16%).

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.17 (m, 5H, $5 \times \text{C}(\text{Ph})\text{H}$), 6.95 (s, 1H, C(4)H), 3.12 – 3.04 (m, 2H, C(9)H₂), 3.04 – 2.94 (m, 2H, C(8)H₂), 2.19 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{CH}_3$), 2.00 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{CH}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 210.8 C(7), 142.7 C(Ar), 141.1 C(Ar), 134.5 C(Ar), 131.7 C(4), 128.6 C(Ar(Ph)), 128.6 C(Ar(Ph)), 128.1 C(Ar), 126.2 C(13), 46.9 C(8), 29.4 C(9), 19.6 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.0 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

m/z (ESI^+) Found ($[\text{M}+\text{Na}]^+$) = 289, $\text{C}_{19}\text{H}_{22}\text{NaO}$ requires 289.

The spectral data matched that previously reported in the literature.⁹⁹

134k 2-Phenyl-1-(2,3,5,6-tetramethylphenyl)ethan-1-one

Durene (2.50 g, 18.6 mmol) and phenylacetylchloride (2.7 mL, 21 mmol) were dissolved in CH_2Cl_2 (65 mL) and the mixture was cooled to 0 °C. AlCl_3 (3.11 g, 23.2 mmol) was added portion-wise over 15 min, the reaction warmed to RT and stirred for 30 min. The crude reaction mixture was poured onto ice (approx. 75 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL) and the combined organic layers were washed with sat. aq. NaHCO_3 , dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* recrystallisation from a minimum amount of boiling hexane gave the *title compound* as a white solid (3.70 g, 79%).

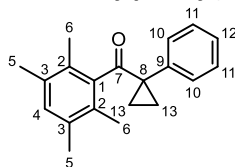
m.p. = 104 – 106 °C;

^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.13 (m, 5H, 5 × C(Ph)*H*), 6.91 (s, 1H, C(4)*H*), 3.92 (s, 2H, C(8)*H*₂), 2.14 (s, 6H, 2 × C(Ph^x)*H*₃), 1.96 (s, 6H, 2 × C(Ph^x)*H*₃);

^{13}C NMR (101 MHz, CDCl_3) δ 208.7 C(7), 142.4 C(Ar(Ph^x)), 134.5 2 × C(Ar(Ph^x)), 133.3 C(9), 131.9 C(4), 130.1 2 × C(Ph), 128.7 2 × C(Ph), 128.3 2 × C(Ar(Ph^x)), 127.2 C(12), 52.3 C(8), 19.6 2 × C(Me(Ph^x)), 16.2 2 × C(Me(Ph^x));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 1703, 1320, 1104, 979, 710;

HRMS (ESI⁺) $\text{C}_{18}\text{H}_{21}\text{O}^+$ ([M+H]⁺) requires 253.1587; found 253.1575 Δ 4.72 ppm.

115k (1-Phenylcyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Ketone **134k** (76 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and $^t\text{BuOH}$ (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column

chromatography (eluent pentane/Et₂O, 99.5:0.5 → 98:2) gave the *title compound* as a white solid (27 mg, 33%, isolated in conjunction with 20 mg, 24% **135**).

m.p. = 94 – 96 °C;

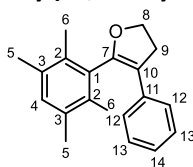
¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.27 (m, 2H, 2 × C(11)*H*), 7.24 – 7.14 (m, 3H, 2 × C(10)*H*, C(12)*H*), 6.81 (s, 1H, C(4)*H*), 2.12 (s, 6H, 2 × C(Ph^{*})*H*₃), 2.11 (s, 6H, 2 × C(Ph^{*})*H*₃), 1.68 (q, *J* = 3.7 Hz, 2H, 2 × C(13)*H*_A*H*_B), 1.47 – 1.35 (m, 2H, 2 × C(13)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 211.6 C(7), 140.3 C(Ar), 139.9 C(Ar), 134.1 2 × C(Ar(Ph^{*})), 131.4 C(4), 130.7 2 × C(11), 128.5 2 × C(Ar(Ph^{*})), 128.0 2 × C(10), 127.3 C(12), 39.7 C(8), 19.5 2 × C(13), 19.5 2 × C(Me(Ph^{*})), 17.1 2 × C(Me(Ph^{*}));

IR (film) ν_{max}/cm⁻¹ 2939, 1676, 1306, 1257, 975, 701;

HRMS (ESI⁺) C₂₀H₂₂NaO⁺ ([M+Na]⁺) requires 301.1563; found 301.1570 Δ 2.36 ppm.

135 4-Phenyl-5-(2,3,5,6-tetramethylphenyl)-2,3-dihydrofuran



Ketone **134k** (76 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.5:0.5 → 98:2) gave the *title compound* as a white solid (20 mg, 24%, isolated in conjunction with 27 mg, 33%, **115k**).

m.p. = 105 – 107 °C;

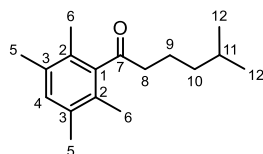
¹H NMR (400 MHz, CDCl₃) δ 7.13 (dd, *J* = 8.5, 7.0 Hz, 2H, 2 × C(Ph)*H*), 7.08 – 6.96 (m, 2H, C(4)*H*, C(Ph)*H*), 6.96 – 6.86 (m, 2H, 2 × C(Ph)*H*), 4.55 (t, *J* = 9.3 Hz, 2H, C(8)*H*₂), 3.25 (t, *J* = 9.3 Hz, 2H, C(9)*H*₂), 2.23 (s, 6H, 2 × C(Ph^{*})*H*₃), 2.10 (s, 6H, 2 × C(Ph^{*})*H*₃);

^{13}C NMR (101 MHz, CDCl_3) δ 152.3 C(7), 135.2 C(Ar), 134.1 2 $\times$ C(Ar(Ph *)), 133.0 2 $\times$ C(Ar(Ph *)), 132.3 C(Ar), 132.2 C(4), 128.3 2 $\times$ C(Ph), 125.0 C(14), 124.7 2 $\times$ C(Ph), 110.8 C(10), 68.7 C(8), 33.4 C(9), 20.1 2 $\times$ C(Me(Ph *)), 16.2 2 $\times$ C(Me(Ph *));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2924, 1651, 1601, 1471, 1152, 1011, 760, 694;

HRMS (ESI^+) $\text{C}_{20}\text{H}_{23}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 279.1743; found 279.1730 Δ 4.82 ppm.

134f 5-Methyl-1-(2,3,5,6-tetramethylphenyl)hexan-1-one



5-Methylhexanoic acid (2.2 mL, 15 mmol) was dissolved in thionyl chloride (2.3 mL, 31 mmol) and the mixture was refluxed for 3 h. Once cooled to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH_2Cl_2 (10 mL) and added to a solution of durene (3.10 g, 23.1 mmol) in CH_2Cl_2 (50 mL) at 0 °C. AlCl_3 (3.28 g, 24.6 mmol) was added portion-wise and to mixture was stirred at RT for 1 h. The crude reaction mixture was poured onto ice (approx. 50 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 50 mL) and the combined organic layers were washed sequentially with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane: Et_2O , 99:1) gave the title compound as a white solid (1.31 g, 35%).

m.p. = 43 – 46 °C;

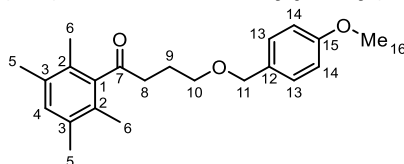
^1H NMR (400 MHz, CDCl_3) δ 6.95 (s, 1H, C(Ph *)H), 2.75 – 2.55 (m, 2H, C(8) H_2), 2.20 (s, 6H, 2 $\times$ C(Ph *) H_3), 2.06 (s, 6H, 2 $\times$ C(Ph *) H_3), 1.83 – 1.64 (m, 2H, C(9) H_2), 1.65 – 1.50 (m, 1H, C(11)H), 1.36 – 1.16 (m, 2H, C(10) H_2), 0.91 (d, J = 6.5 Hz, 6H, 2 $\times$ C(12) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 212.1 C(7), 143.1 C(1), 134.5 2 $\times$ C(Ar(Ph *)), 131.6 C(4), 128.0 2 $\times$ C(Ar(Ph *)), 45.7 C(8), 38.5 C(10), 28.1 C(11), 22.7 2 $\times$ C(12), 21.2 C(9), 19.6 2 $\times$ C(Me(Ph *)), 16.1 2 $\times$ C(Me(Ph *));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2955, 2871, 1704, 1544, 1469, 1385;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{27}\text{O}^+$ ([M+H]⁺) requires 247.2056; found 247.2057, Δ 0.22 ppm.

134l 4-((4-Methoxybenzyl)oxy)-1-(2,3,5,6-tetramethylphenyl)butan-1-one



Alcohol **S2** (330 mg, 1.50 mmol), 4-methoxybenzyl chloride (0.41 mL, 3.0 mmol), *N,N*-diisopropylethylamine (0.42 mL, 2.4 mmol) and KI (50 mg, 0.30 mmol) were heated at 110 °C for 3 h. The mixture was cooled to RT and diluted with EtOAc (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 93:7 → 92:8) gave the *title compound* as a white solid (402 mg, 79%).

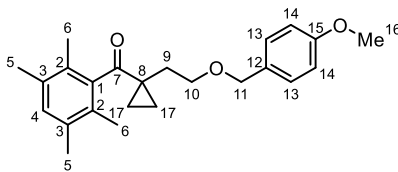
m.p. = 48 – 50 °C;

¹H NMR (400 MHz, CDCl_3) δ 7.33 – 7.20 (m, 2H, 2 × C(13) H_2), 6.95 (s, 1H, C(4) H), 6.90 – 6.83 (m, 2H, 2 × C(14) H_2), 4.43 (s, 2H, C(11) H_2), 3.80 (s, 3H, C(16) H_3), 3.55 (t, J = 6.1 Hz, 2H, C(10) H_2), 2.80 (t, J = 7.2 Hz, 2H, C(8) H_2), 2.20 (s, 6H, 2 × C(Ph^{*}) H_3), 2.10 – 1.98 (m, 8H, 2 × C(Ph^{*}) H_3 , C(9) H_2);

¹³C NMR (101 MHz, CDCl_3) δ 211.7 C(7), 159.3 C(15), 142.9 C(Ar(Ph^{*})), 134.5 2 × C(Ar(Ph^{*})), 131.6 C(4), 130.6 C(12), 129.4 2 × C(13), 128.0 2 × C(Ar(Ph^{*})), 113.9 2 × C(14), 72.7 C(11), 69.1 C(10), 55.4 C(16), 41.9 C(8), 23.5 C(9), 19.6 2 × C(Me(Ph^{*})), 16.1 2 × C(Me(Ph^{*}));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2937, 2862, 1699, 1613, 1514, 1248, 1098, 1036, 820;

HRMS (ESI⁺) $\text{C}_{22}\text{H}_{28}\text{NaO}_3^+$ ([M+Na]⁺) requires 363.1931; found 363.1933, Δ 0.63 ppm.

115I (1-(2-((4-Methoxybenzyl)oxy)ethyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Ir-catalysed: Ketone **134I** (102 mg, 0.300 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 92:8) gave the *title compound* as an off-white solid (85 mg, 79%).

Ru-catalysed: Ketone **134I** (102 mg, 0.300 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 92:8) gave the *title compound* as an off-white solid (72 mg, 66%).

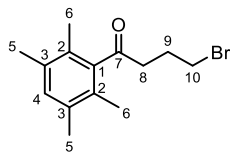
m.p. = 81 – 83 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.20 (m, 2H, 2 × C(13)*H*), 6.91 (s, 1H, C(4)*H*), 6.89 – 6.84 (m, 2H, 2 × C(14)*H*), 4.40 (s, 2H, C(11)*H*₂), 3.81 (s, 3H, C(16)*H*₃), 3.61 (t, *J* = 6.8 Hz, 2H, C(10)*H*₂), 2.16 (s, 6H, 2 × C(Ph^{*})*CH*₃), 2.03 (s, 6H, 2 × C(Ph^{*})*CH*₃), 1.99 (t, *J* = 6.9 Hz, 2H, C(9)*H*₃), 1.15 – 1.09 (m, 2H, 2 × C(17)*H*_A*H*_B), 1.09 – 1.03 (m, 2H, 2 × C(17)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.4 C(7), 159.2 C(15), 138.9 C(1), 134.3 2 × C(Ar(Ph^{*})), 131.6 C(4), 130.8 C(12), 129.3 2 × C(13), 129.2 2 × C(Ar(Ph^{*})), 113.9 2 × C(14), 72.7 C(11), 68.6 C(10), 55.4 C(16), 33.4 C(9), 31.7 C(8), 19.6 2 × C(Me(Ph^{*})), 17.8 2 × C(17), 16.6 2 × C(Me(Ph^{*}));

IR (film) ν_{max} /cm⁻¹ 2938, 2863, 1669, 1514, 1249;

HRMS (ESI⁺) C₂₄H₃₀NaO₃⁺ ([M+Na]⁺) requires 389.2087; found 389.2088 Δ 0.20 ppm.

S6 4-Bromo-1-(2,3,5,6-tetramethylphenyl)butan-1-one

Durene (3.36 g, 25.0 mmol) and 4-bromobutyryl chloride (3.2 mL, 27.5 mmol) were dissolved in CH_2Cl_2 (85 mL) and the mixture was cooled to 0 °C. AlCl_3 (4.16 g, 31.3 mmol) was added portion-wise over 15 min, the reaction warmed to RT and stirred for 1 h. The crude reaction mixture was poured onto ice (approx. 100 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed with sat. aq. NaHCO_3 , dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98.5:1.5 → 97.5:2.5) gave the *title compound* as a white solid (6.64 g, 94%).

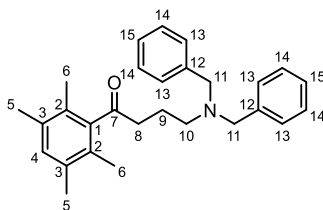
m.p. = 50 – 52 °C;

^1H NMR (400 MHz, CDCl_3) δ 6.96 (s, 1H, C(4)*H*), 3.58 (t, J = 6.3 Hz, 2H, C(10)*H*₂), 2.88 (t, J = 6.9 Hz, 2H, C(8)*H*₂), 7.00 – 6.92 (m, 2H, C(9)*H*₂), 2.21 (s, 6H, 2 × C(Ph^x)*H*₃), 2.07 (s, 6H, 2 × C(Ph^x)*H*₃);

^{13}C NMR (101 MHz, CDCl_3) δ 210.7 C(7), 142.5 C(1), 134.6 2 × C(Ar(Ph^x)), 131.8 C(4), 128.0 2 × C(Ar(Ph^x)), 43.2 C(8), 33.5 C(10), 26.3 C(9), 19.6 2 × C(Me(Ph^x)), 16.1 2 × C(Me(Ph^x));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2922, 1703, 1471, 1106, 874;

HRMS (ESI⁺) $\text{C}_{14}\text{H}_{20}^{79}\text{BrO}^+$ ([*M*+*H*]⁺) requires 283.0692; found 283.0681, Δ 3.91 ppm.

134m 4-(Dibenzylamino)-1-(2,3,5,6-tetramethylphenyl)butan-1-one

Alkyl bromide **S6** (1.42 g, 5.00 mmol), KI (83 mg, 0.50 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) were added sequentially to a solution of Bn_2NH (1.0 mL, 5.25 mmol) in *N,N*-dimethylformamide (2.9 mL). The resulting mixture was heated to 85 °C for 18 h, cooled to RT and diluted with EtOAc (30 mL) and water (30 mL). The layers were separated and the aqueous layer was extracted with

EtOAc (2 × 30 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 94:6) gave the *title compound* as a white solid (1.49 g, 75%).

m.p. = 67 – 69 °C;

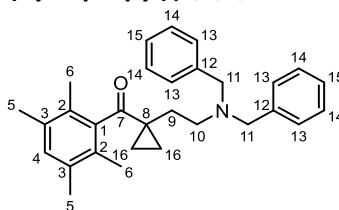
¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.26 (m, 8H, 4 × C(13)H, 4 × C(14)H), 7.26 – 7.18 (m, 2H, 2 × C(15)H), 6.95 (s, 1H, C(4)H), 3.57 (s, 4H, 2 × C(11)H₂), 2.69 (t, *J* = 7.5 Hz, 2H, C(8)H₂), 2.50 (t, *J* = 6.9 Hz, 2H, C(10)H₂), 2.20 (s, 6H, 2 × C(Ph^x)H₃), 2.00 (s, 6H, 2 × C(Ph^x)H₃), 2.00 – 1.89 (m, 2H, C(9)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 212.1 C(7), 143.0 C(1), 139.8 2 × C(12), 134.5 2 × C(Ar(Ph^x)), 131.6 C(4), 128.9 4 × C(14), 128.3 4 × C(13), 128.0 2 × C(Ar(Ph^x)), 127.0 2 × C(15), 58.3 2 × C(11), 52.8 C(10), 43.1 C(8), 20.7 C(9), 19.6 2 × C(Me(Ph^x)), 16.1 2 × C(Me(Ph^x));

IR (film) ν_{max} /cm⁻¹ 2941, 1699, 1453, 746, 699;

HRMS (ESI⁺) C₂₈H₃₃NNaO⁺ ([M+Na]⁺) requires 422.2454; found 422.2445, Δ 2.22 ppm.

115m (1-(2-(Dibenzylamino)ethyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone



Ir-catalysed: Ketone **134m** (120 mg, 0.300 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5) gave the *title compound* as a colourless oil which solidified on standing (105 mg, 82%).

Ru-catalysed: Ketone **134m** (120 mg, 0.300 mmol), Ru-MACHO[®] (3.6 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol)

and t BuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5) gave the *title compound* as a colourless oil which solidified on standing (102 mg, 80%).

m.p. = 81 – 83 °C;

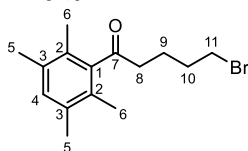
¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.27 (m, 8H, 4 $\times$ C(13)H, 4 $\times$ C(14)H), 7.25 – 7.16 (m, 2H, 2 $\times$ C(15)H), 6.87 (s, 1H, C(4)H), 3.52 (s, 4H, 2 $\times$ C(11)H₂), 2.63 – 2.49 (m, 2H, C(10)H₂), 2.14 (s, 6H, 2 $\times$ C(Ph^x)H₃), 1.97 (s, 6H, 2 $\times$ C(Ph^x)H₃), 1.90 – 1.80 (m, 2H, C(9)H₂), 1.07 (q, J = 4.0 Hz, 2H, 2 $\times$ C(16)H_AH_B), 0.86 (q, J = 4.1 Hz, 2H, 2 $\times$ C(16)H_AH_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.4 C(7), 139.9 C(1), 134.2 C(12), 131.5 C(4), 129.1 2 $\times$ C(Ar(Ph^x)), 128.8 4 $\times$ C(Ph), 128.3 4 $\times$ C(Ph) & 2 $\times$ C(Ar(Ph^x)), 126.9 2 $\times$ C(15), 58.3 2 $\times$ C(11), 51.6 C(10), 32.5 C(8), 31.0 C(9), 19.6 2 $\times$ C(Me(Ph^x)), 18.1 2 $\times$ C(16), 16.6 2 $\times$ C(Me(Ph^x));

IR (film) ν_{max} /cm⁻¹ 2925, 1671, 1495, 1454, 737, 699;

HRMS (ESI⁺) C₃₀H₃₆NO⁺ ([M+H]⁺) requires 426.2791; found 426.2794 Δ 0.60 ppm.

S7 5-Bromo-1-(2,3,5,6-tetramethylphenyl)pentan-1-one



5-Bromovaleric acid (2.72 g, 15.0 mmol) was dissolved in thionyl chloride (2.2 mL, 30 mmol) and the mixture was heated at 85 °C for 2 h. Once cooled to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH₂Cl₂ (10 mL) and added to a solution of durene (2.62 g, 19.5 mmol) in CH₂Cl₂ (40 mL) at 0 °C. AlCl₃ (2.59 g, 19.5 mmol) was added portion-wise and to mixture was stirred at RT for 10 min. The crude reaction mixture was poured onto ice (approx. 50 g) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 $\times$ 50 mL) and the combined organic layers were washed sequentially with sat. aq. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane: Et₂O, 98:2 $\rightarrow$ 95:5) gave the *title compound* as a white solid (4.21 g, 94%).

m.p. = 54 – 56 °C;

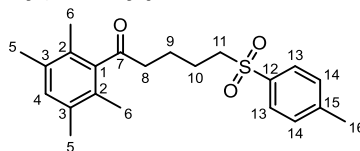
¹H NMR (400 MHz, CDCl₃) δ 6.88 (s, 1H, C(4)*H*), 3.38 (t, *J* = 6.5 Hz, 2H, C(11)*H*₂), 2.64 (t, *J* = 7.1 Hz, 2H, C(8)*H*₂), 2.13 (s, 6H, 2 × C(Ph[×])*H*₃), 1.98 (s, 6H, 2 × C(Ph[×])*H*₃), 1.94 – 1.86 (m, 2H, C(10)*H*₂), 1.86 – 1.76 (m, 2H, C(9)*H*₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.1 C(7), 142.8 C(1), 134.6 2 × C(Ar(Ph[×])), 131.7 C(4), 128.0 2 × C(Ar(Ph[×])), 44.3 C(8), 33.4 C(11), 32.2 C(10), 22.0 C(9), 19.6 2 × C(Me(Ph[×])), 16.1 2 × C(Me(Ph[×]));

IR (film) $\nu_{\max}$ /cm⁻¹ 2941, 1702, 1470, 1402, 1302, 1256, 1229, 1107;

HRMS (ESI⁺) C₁₅H₂₂⁷⁹BrO⁺ ([M+H]⁺) requires 297.0849; found 297.0843, Δ 1.87 ppm.

134n 1-(2,3,5,6-Tetramethylphenyl)-5-tosylpentan-1-one



Alkyl bromide **57** (1.49 g, 5.00 mmol) and sodium *p*-toluene sulfonate were dissolved in *N,N*-dimethylformamide (8.0 mL) and the reaction was heated at 80 °C for 4 h. The mixture was cooled to RT and diluted with CH₂Cl₂ (100 mL). The organic phase was washed with brine (5 × 100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 70:20:10) gave the *title compound* as a white solid (1.40 g, 75%).

m.p. = 111 – 113 °C;

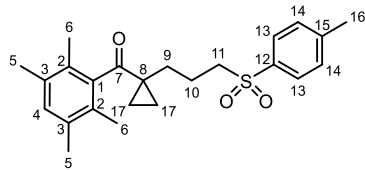
¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.66 (m, 2H, 2 × C(13)*H*), 7.44 – 7.31 (m, 2H, 2 × C(14)*H*), 6.94 (s, 1H, C(4)*H*), 3.21 – 3.00 (m, 2H, C(11)*H*₂), 2.77 – 2.57 (m, 2H, C(8)*H*₂), 2.45 (s, 3H, C(16)*H*₃), 2.19 (s, 6H, 2 × C(Ph[×])*H*₃), 2.00 (s, 6H, 2 × C(Ph[×])*H*₃), 1.88 – 1.70 (m, 4H, C(9)*H*₂, C(10)*H*₂);

¹³C NMR (101 MHz, CDCl₃) δ 210.7 C(7), 144.9 C(15), 142.6 C(1), 136.3 C(12), 134.6 2 × C(Ar(Ph[×])), 131.8 C(4), 130.1 2 × C(14), 128.2 2 × C(13), 127.9 2 × C(Ar(Ph[×])), 56.4 C(11), 44.6 C(8), 22.5 C(9)/C(10), 22.1 C(9)/C(10), 21.8 C(16), 19.6 2 × C(Me(Ph[×])), 16.1 2 × C(Me(Ph[×]));

IR (film) $\nu_{\max}$ /cm⁻¹ 2925, 1698, 1300, 1148, 1088, 818, 732;

HRMS (ESI⁺) C₂₂H₂₈O₃S⁺ ([M+H]⁺) requires 373.1832; found 373.1831, Δ 0.26 ppm.

115n (2,3,5,6-Tetramethylphenyl)(1-(3-tosylpropyl)cyclopropyl)methanone



Ketone **134n** (112 mg, 0.300 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and 2-phenoxyethanol (0.37 mL, 3.0 mmol) were subjected to **General Procedure C** at 110 °C for 24 h, with subsequent addition of KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.5 mL) before heating at 110 °C for a further 24 h. Purification *via* sequential flash column chromatography (eluent PhMe/Et₂O, 98.5:1.5 → 97:3) and preparative TLC (eluent PhMe/Et₂O, 80:20) gave the *title compound* as a white solid (63 mg, 53%).

m.p. = 88 – 90 °C;

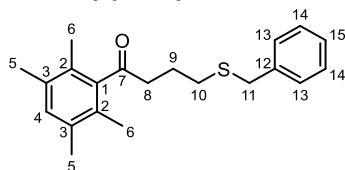
¹H NMR (600 MHz, CDCl₃) δ 7.83 – 7.72 (m, 2H, 2 × C(13)*H*), 7.41 – 7.31 (m, 2H, 2 × C(14)*H*), 6.90 (s, 1H, C(4)*H*), 3.15 – 2.99 (m, 2H, C(11)*H*₂), 2.45 (s, 3H, C(16)*H*₃), 2.15 (s, 6H, 2 × C(Ph^x)*H*₃), 1.99 (s, 6H, 2 × C(Ph^x)*H*₃), 1.92 (m, 2H, C(10)*H*₂), 1.76 – 1.66 (m, 2H, C(9)*H*₂), 1.14 – 1.04 (m, 2H, 2 × C(17)*H*_A*H*_B), 0.97 – 0.88 (m, 2H, 2 × C(17)*H*_A*H*_B);

¹³C NMR (151 MHz, CDCl₃) δ 211.8 C(7), 144.8 C(15), 138.3 C(1), 136.4 C(12), 134.4 2 × C(Ar(Ph^x)), 131.7 C(4), 130.0 2 × C(14), 129.1 2 × C(Ar(Ph^x)), 128.2 2 × C(13), 56.6 C(11), 33.8 C(8), 32.5 C(9), 21.8 C(16), 21.0 C(10), 19.5 2 × C(Me(Ph^x)), 17.7 2 × C(17), 16.6 2 × C(Me(Ph^x));

IR (film) ν_{max}/cm⁻¹ 2923, 1667, 1301, 1149, 1089, 735;

HRMS (ESI⁺) C₂₄H₃₀NaO₃S⁺ ([M+Na]⁺) requires 421.1808; found 421.1824, Δ 3.82 ppm.

136 4-(Benzylthio)-1-(2,3,5,6-tetramethylphenyl)butan-1-one



Alkyl bromide **56** (1.42 g, 5.00 mmol), KI (83 mg, 0.50 mmol) and K₂CO₃ (1.38 g, 10.0 mmol) were added sequentially to a solution of benzyl mercaptan (0.62 mL, 5.3 mmol) in

N,N-dimethylformamide (2.9 mL). The resulting mixture was heated to 85 °C for 18 h, cooled to RT and diluted with EtOAc (30 mL) and water (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1 → 96:4) gave the *title compound* as a white solid (1.31 g, 80%).

m.p. = 69 – 71 °C;

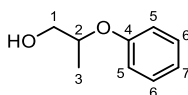
¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.27 (m, 4H, 2 × C(13)H, 2 × C(14)H), 7.25 – 7.21 (m, 1H, C(15)H), 6.95 (s, 1H, C(4)H), 3.72 (s, 2H, C(11)H₂), 2.78 (t, *J* = 7.2 Hz, 2H, C(8)H₂), 2.53 (t, *J* = 7.0 Hz, 2H, C(10)H₂), 2.20 (s, 6H, 2 × C(Ph^{*})H₃), 2.03 (s, 6H, 2 × C(Ph^{*})H₃), 1.98 (p, *J* = 7.0 Hz, 2H, C(9)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.3 C(7), 142.7 C(1), 138.5 C(12), 134.5 2 × C(Ar(Ph^{*})), 131.7 C(4), 129.0 2 × C(13), 128.6 2 × C(14), 128.0 2 × C(Ar(Ph^{*})), 127.1 C(15), 43.9 C(8), 36.1 C(11), 30.8 C(10), 22.6 C(9), 19.6 2 × C(Me(Ph^{*})), 16.1 2 × C(Me(Ph^{*}));

IR (film) ν_{max} /cm⁻¹ 2921, 1699, 1454, 1108, 874, 770, 702;

HRMS (ESI⁺) C₂₁H₂₆NaO⁺ ([M+Na]⁺) requires 349.1579; found 349.1587, Δ 2.76 ppm.

137 2-Phenoxypropan-1-ol



BH₃·SMe₂ (4.3 mL, 45 mmol) was added dropwise to a solution of 2-phenoxypropionic acid (5.00 g, 30 mmol) in THF (150 mL) at 0 °C. The reaction was allowed to warm to RT, cooled to 0 °C and quenched with the addition of MeOH (20 mL) and water (40 mL). The crude reaction mixture was concentrated *in vacuo* and diluted with EtOAc (150 mL) and water (100 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 75:25 → 70:30) gave the *title compound* as a colourless oil (4.06 g, 89%).

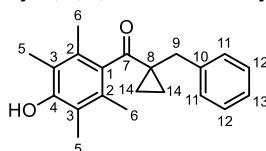
¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.11 (m, 2H, 2 × C(6)H), 7.07 – 6.80 (m, 3H, 2 × C(5)H, C(7)H), 4.66 – 4.31 (m, 1H, C(2)H), 4.02 – 3.54 (m, 2H, C(1)H₂), 1.90 (s, 1H, OH), 1.28 (d, *J* = 6.2 Hz, 3H, C(3)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 157.8 C(4), 129.7 2 × C(6), 121.4 C(7), 116.2 2 × C(5), 74.8 C(2), 66.5 C(1), 15.9 C(3);

m/z (ESI⁺) Found ([M+Na]⁺) = 175, C₉H₁₂NaO₂ requires 175;

The spectroscopic data were consistent with that reported in the literature.¹⁴⁵

116a (1-Benzylcyclopropyl)(4-hydroxy-2,3,5,6-tetramethylphenyl)methanone



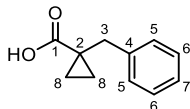
Phthaloyl peroxide **S4** (111 mg, 0.675 mmol) and ketone **115a** (131 mg, 0.450 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (4.5 mL) were subjected to **General Procedure D** (heated at 40 °C for 18 h, after the addition of MeOH (4.0 mL) and sat. aq. NaHCO₃ (0.5 mL) the mixture was heated at 40 °C for a further 18 h). Purification *via* flash column chromatography (eluent pentane/Et₂O, 85:15) gave the *title compound* as a colourless oil (85 mg, 61%).

¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.14 (m, 3H, 3 × C(Ph)H), 7.11 – 7.05 (m, 2H, 2 × C(Ph)H), 4.68 (s, 1H, OH), 3.02 (s, 2H, C(9)H₂), 2.08 (s, 6H, 2 × C(Ph^x)CH₃), 1.92 (s, 6H, 2 × C(Ph^x)CH₃), 1.23 – 1.16 (m, 2H, 2 × C(14)H_AH_B), 1.02 – 0.98 (m, 2H, 2 × C(14)H_AH_B);

¹³C NMR (101 MHz, CDCl₃) δ 212.2 C(7), 151.7 C(4), 139.1 C(1), 130.0 2 × C(2), 129.9 2 × C(11), 127.9 2 × C(12), 126.2 C(10) & C(13), 119.5 2 × C(3), 37.9 C(9), 34.4 C(8), 17.3 2 × C(14), 16.9 2 × C(Me(Ph^x)), 11.6 2 × C(Me(Ph^x));

IR (film) ν_{max} /cm⁻¹ 3567, 2921, 2861, 1699, 1653, 1455, 1296, 1107, 745, 701;

HRMS (ESI⁺) C₂₁H₂₅O₂⁺ ([M+H]⁺) requires 309.1849; found 309.1849, Δ 0.10 ppm.

107 1-Benzylcyclopropane-1-carboxylic acid

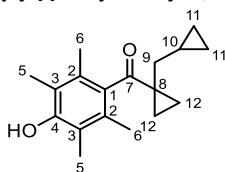
A solution of CAN (ceric ammonium nitrate) (1.01 g, 1.85 mmol) in water (1.85 mL) was added to a stirred solution of phenol **116a** (115 mg, 0.373 mmol) in MeCN (1.85 mL) and the resulting mixture was stirred at RT for 15 min. Water (6.0 mL) was added and the reaction was stirred for a further 15 min. The reaction was diluted with CH₂Cl₂ (20 mL) and water (15 mL) was added. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH₂Cl₂ → CH₂Cl₂/EtOAc/AcOH, 94:95:5:0.05) gave the *title compound* as a yellow solid (48.4 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.14 (m, 5H, 5 × C(Ph)H), 2.99 (s, 2H, C(3)H₂), 1.35 (q, *J* = 4.1 Hz, 2H, 2 × C(8)H_AH_B), 0.90 – 0.85 (m, 2H, 2 × C(8)H_AH_B);

¹³C NMR (101 MHz, CDCl₃) δ 181.6 C(1), 139.3 C(4), 129.4 2 × C(5), 128.3 2 × C(6), 126.4 C(7), 37.9 C(3), 23.6 C(2), 16.1 2 × C(8);

m/z (ESI[−]) Found ([M-H][−]) = 175, C₁₁H₁₁O₂ requires 175.

The spectroscopic data were consistent with that reported in the literature.¹⁴⁶

116e (1-(Cyclopropylmethyl)cyclopropyl)(4-hydroxy-2,3,5,6-tetramethylphenyl)methanone

Phthaloyl peroxide **S4** (148 mg, 0.900 mmol) and ketone **115e** (166 mg, 0.650 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (6.0 mL) were subjected to **General Procedure D** (heated at 40 °C for 24 h, after the addition of MeOH (5.4 mL) and sat. aq. NaHCO₃ (0.6 mL) the mixture was heated at 40 °C for a further 18 h). Purification *via* flash column chromatography (eluent pentane/Et₂O, 85:15) gave the *title compound* as a white solid (94 mg, 53%).

m.p. = 89 – 91 °C;

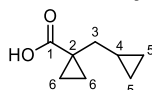
^1H NMR (400 MHz, CDCl_3) δ 4.80 (br. s, 1H, OH), 2.10 (s, 6H, $2 \times \text{C(Ph}^*)\text{CH}_3$), 2.09 (s, 6H, $2 \times \text{C(Ph}^*)\text{CH}_3$), 1.63 (d, $J = 6.9$ Hz, 2H, $\text{C(9)}\text{H}_2$), 1.14 – 1.08 (m, 2H, $2 \times \text{C(12)}\text{H}_\text{A}\text{H}_\text{B}$), 1.07 – 1.00 (m, 2H, $2 \times \text{C(12)}\text{H}_\text{A}\text{H}_\text{B}$), 0.76 (m, 1H, $\text{C(10)}\text{H}$), 0.45 – 0.31 (m, 2H, $2 \times \text{C(11)}\text{H}_\text{A}\text{H}_\text{B}$), 0.06 – –0.01 (m, 2H, $2 \times \text{C(11)}\text{H}_\text{A}\text{H}_\text{B}$);

^{13}C NMR (101 MHz, CDCl_3) δ 213.0 C(7) , 151.7 C(4) , 132.3 C(1) , 130.1 $2 \times \text{C(Ar(Ph}^*))$, 119.8 $2 \times \text{C(Ar(Ph}^*))$, 37.2 C(9) , 34.2 C(8) , 17.2 $2 \times \text{C(Me(Ph}^*))$, 17.1 $2 \times \text{C(12)}$, 11.8 $2 \times \text{C(Me(Ph}^*))$, 8.6 C(10) , 4.5 $2 \times \text{C(11)}$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3433, 2922, 1653, 1350, 1299, 1219, 1103, 1014, 930, 762;

HRMS (ESI^+) $\text{C}_{18}\text{H}_{25}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 273.1849; found 273.1844, Δ 1.69 ppm.

117e 1-(Cyclopropylmethyl)cyclopropane-1-carboxylic acid



A solution of CAN (ceric ammonium nitrate) (822 mg, 1.50 mmol) in water (1.5 mL) was added to a stirred suspension of phenol **116e** (82 mg, 0.30 mmol) in MeCN (1.5 mL) and the resulting mixture was stirred at RT for 5 min. Water (6.0 mL) was added and the reaction was stirred for a further 10 min. The reaction was diluted with CH_2Cl_2 (10 mL) and water (4 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). NaOH (3 M, 30 mL) was added to the combined organic layers, the layers separated and the aqueous layer acidified with HCl (3 M, 35 mL) and extracted with CH_2Cl_2 (3×60 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{HCO}_2\text{H}$, 97:95:2:0.05) gave the *title compound* as a colourless oil (25.5 mg, 61%).

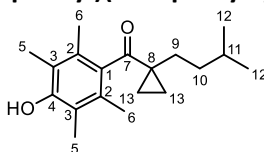
^1H NMR (400 MHz, MeOD) δ 1.52 (d, $J = 6.8$ Hz, 2H, $\text{C(3)}\text{H}_2$), 1.13 (p, $J = 3.6$ Hz, 2H, $2 \times \text{C(6)}\text{H}_\text{A}\text{H}_\text{B}$), 0.95 – 0.83 (m, 1H, $\text{C(4)}\text{H}$), 0.83 – 0.72 (m, 2H, $2 \times \text{C(6)}\text{H}_\text{A}\text{H}_\text{B}$), 0.46 – 0.35 (m, 1H, $2 \times \text{C(5)}\text{H}_\text{A}\text{H}_\text{B}$), 0.17 – 0.00 (m, 1H, $2 \times \text{C(5)}\text{H}_\text{A}\text{H}_\text{B}$);

^{13}C NMR (101 MHz, MeOD) δ 179.6 C(1) , 38.9 C(3) , 24.3 C(2) , 15.2 $2 \times \text{C(6)}$, 9.7 C(4) , 4.6 $2 \times \text{C(5)}$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3080, 3010, 2911, 2840, 1689, 1425, 1340, 1248, 1202, 1031, 929;

HRMS (ESI⁻) C₈H₁₀O₂⁻ ([M-H]⁻) requires 139.0765; mass not found.

116f (4-Hydroxy-2,3,5,6-tetramethylphenyl)(1-isopentylcyclopropyl)methanone



Phthaloyl peroxide **54** (111 mg, 0.675 mmol) and ketone **115f** (122 mg, 0.450 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (4.5 mL) were subjected to **General Procedure D** (heated at 40 °C for 24 h, after the addition of MeOH (4.0 mL) and sat. aq. NaHCO₃ (0.5 mL), the mixture was heated at 40 °C for a further 18 h). Purification *via* flash column chromatography (eluent pentane/Et₂O, 85:15) gave the title compound as a white solid (75 mg, 58%).

m.p. = 83 – 84 °C;

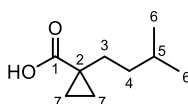
¹H NMR (600 MHz, CDCl₃) δ 4.81 – 4.44 (m, 1H, OH), 2.11 (s, 6H, 2 × C(Ph^{*})H₃), 2.08 (s, 6H, 2 × C(Ph^{*})H₃), 1.64 – 1.57 (m, 2H, C(9)H₂), 1.50 – 1.42 (m, 1H, C(11)H), 1.34 – 1.24 (m, 2H, C(10)H₂), 1.09 (q, *J* = 3.6 Hz, 2H, 2 × C(13)H_AH_B), 0.92 – 0.87 (m, 2H, 2 × C(13)H_AH_B), 0.84 (d, *J* = 6.6 Hz, 6H, 2 × C(12)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 212.5 C(7), 151.7 C(4), 132.2 C(1), 130.2 2 × C(Ar(Ph^{*})), 119.6 2 × C(Ar(Ph^{*})), 36.4 C(10), 34.3 C(8), 31.5 C(9), 28.4 C(11), 22.6 2 × C(12), 17.9 2 × C(13), 17.3 2 × C(Me(Ph^{*})), 11.8 2 × C(Me(Ph^{*}));

IR (film) ν_{max}/cm⁻¹ 3480, 2955, 2870, 1654, 1458, 1124, 1102, 762, 737;

HRMS (ESI⁺) C₁₉H₂₈NaO₂⁺ ([M+Na]⁺) requires 311.1982; found 311.1984, Δ 0.79 ppm.

117f 1-Isopentylcyclopropane-1-carboxylic acid



A solution of CAN (ceric ammonium nitrate) (548 mg, 1.00 mmol) in water (1.0 mL) was added to a stirred suspension of phenol **116f** (58 mg, 0.20 mmol) in MeCN (1.0 mL) and the resulting mixture was stirred at RT for 5 min. Water (6.0 mL) was added and the reaction was stirred for a further 10 min. The reaction was diluted with CH₂Cl₂ (10 mL) and water (4 mL) was added. The

layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). NaOH (3 M, 30 mL) was added to the combined organic layers, the layers separated and the aqueous layer acidified with HCl (3 M, 35 mL) and extracted with CH_2Cl_2 (3×60 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{HCO}_2\text{H}$, 97.95:2:0.05) gave the *title compound* as a colourless oil (25.5 mg, 82%).

m.p. = 27 – 29 °C;

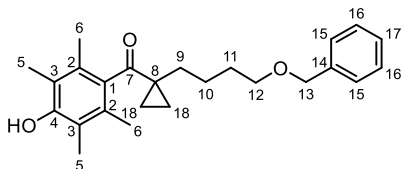
^1H NMR (400 MHz, CDCl_3) δ 1.55 – 1.45 (m, 3H, C(3) H_2 , C(5) H), 1.38 – 1.30 (m, 2H, $2 \times \text{C}(4)H_2$), 1.29 – 1.22 (m, 2H, $2 \times \text{C}(7)H_AH_B$), 0.87 (d, J = 6.6 Hz, 6H, $2 \times \text{C}(6)H_3$), 0.77 – 0.71 (m, 2H, $2 \times \text{C}(7)H_AH_B$);

^{13}C NMR (101 MHz, CDCl_3) δ 182.3 C(1), 36.5 C(4), 31.4 C(3), 28.2 C(5), 23.5 C(2), 22.5 $2 \times \text{C}(6)$, 16.5 $2 \times \text{C}(7)$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3017, 2957, 1693, 1458, 1346, 1293, 1229, 1190;

HRMS (ESI $^-$) $\text{C}_9\text{H}_{15}\text{O}_2^-$ ($[\text{M}-\text{H}]^-$) requires 155.1078; mass not found.

116g (1-(4-(Benzyloxy)butyl)cyclopropyl)(4-hydroxy-2,3,5,6-tetramethylphenyl)methanone



Phthaloyl peroxide **S4** (175 mg, 1.07 mmol) and ketone **115g** (259 mg, 0.710 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (7.0 mL) were subjected to **General Procedure D** (heated at 40 °C for 24 h, after the addition of MeOH (2.7 mL) and sat. aq. NaHCO_3 (0.29 mL) the mixture was heated at 40 °C for a further 18 h). Purification *via* flash column chromatography (eluent pentane/ Et_2O , 80:20 $\rightarrow$ 70:30) gave the *title compound* as an off-white solid (195 mg, 72%).

m.p. = 83 – 84 °C;

^1H NMR (600 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H, $5 \times \text{C}(\text{Ph})H$), 4.49 (s, 2H, C(13) H_2), 3.44 (t, J = 6.5 Hz, 2H, C(12) H_2), 2.10 (s, 6H, $2 \times \text{C}(\text{Ph}^*)H_3$), 2.07 (s, 6H, $2 \times \text{C}(\text{Ph}^*)H_3$), 1.68 – 1.55 (m, 4H,

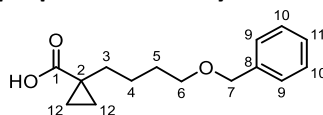
$C(9)H_2$, $C(11)H_2$, 1.55 – 1.47 (m, 2H, $C(10)H_2$), 1.08 (q, $J = 4.0$ Hz, 2H, $2 \times C(18)H_AH_B$), 0.95 – 0.88 (m, 2H, $2 \times C(18)H_AH_B$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.5 $C(7)$, 151.7 $C(4)$, 138.8 $C(14)$, 132.0 $C(1)$, 130.2 $2 \times C(Ar(Ph^*))$, 128.5 $2 \times C(16)$, 127.8 $2 \times C(15)$, 127.6 $C(17)$, 119.7 $2 \times C(Ar(Ph^*))$, 73.0 $C(13)$, 70.4 $C(2)$, 34.3 $C(8)$, 33.6 $C(9)$, 30.2 $C(11)$, 24.1 $C(10)$, 17.8 $2 \times C(18)$, 17.3 $2 \times C(Me(Ph^*))$, 11.8 $2 \times C(Me(Ph^*))$;

IR (film) ν_{max}/cm^{-1} 3449, 2942, 2863, 1719, 1120, 737, 699;

HRMS (ESI^+) $C_{25}H_{32}NaO_3^+$ ($[M+Na]^+$) requires 403.2244; found 403.2243, Δ 0.17 ppm.

117g 1-(4-(Benzyloxy)butyl)cyclopropane-1-carboxylic acid



A solution of CAN (ceric ammonium nitrate) (822 mg, 1.50 mmol) in water (1.5 mL) was added to a stirred solution of phenol **116g** (114 mg, 0.300 mmol) in MeCN (1.5 mL) and the resulting mixture was stirred at RT for 15 min. Water (6.0 mL) was added and the reaction was stirred for a further 15 min. The reaction was diluted with CH_2Cl_2 (20 mL) and water (15 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CH_2Cl_2/EtOAc/AcOH$, 94:5:1) gave the *title compound* as a yellow oil which solidified on standing (46 mg, 61%).

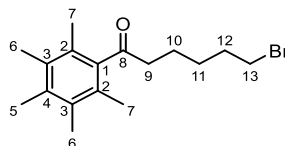
m.p. = 46 – 48 °C;

^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H, $5 \times C(Ph)H$), 4.50 (s, 2H, $C(7)H_2$), 3.46 (t, $J = 6.3$ Hz, 2H, $C(6)H_2$), 1.70 – 1.47 (m, 6H, $C(3)H_2$, $C(4)H_2$, $C(5)H_2$), 1.26 (q, $J = 3.9$ Hz, 2H, $2 \times C(12)H_AH_B$), 0.81 – 0.64 (m, 2H, $2 \times C(12)H_AH_B$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.0 $C(1)$, 138.7 $C(8)$, 128.5 $2 \times C(10)$, 127.8 $2 \times C(9)$, 127.6 $C(11)$, 73.1 $C(7)$, 70.4 $C(6)$, 33.5 $C(3)$, 30.0 $C(5)$, 24.4 $C(4)$, 23.4 $C(2)$, 16.6 $2 \times C(12)$;

IR (film) ν_{max}/cm^{-1} 3089, 2942, 2864, 1687, 1456, 1213, 1104, 737, 698;

HRMS (ESI^-) $C_{15}H_{19}O_3^-$ ($[M-H]^-$) requires 247.1340; found 247.1339, Δ 0.26 ppm.

141a 6-Bromo-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

A solution of pentamethylbenzene (3.00 g, 20.2 mmol), and 6-hexanoyl chloride (3.4 mL, 22 mmol) in CH_2Cl_2 (100 mL) was cooled in an ice bath, AlCl_3 (3.37 g, 25.3 mmol) was added portion-wise over 10 mins. The mixture was allowed to warm to RT and stirred for 30 min, then poured onto ice (approx. 100 g) and stirred rapidly until the ice melted. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were washed with sat. aq. NaHCO_3 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 97:3 $\rightarrow$ 95:5) gave the *title compound* as a white solid (5.65 g, 84%).

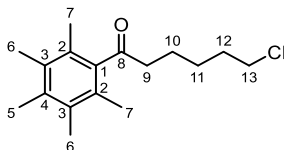
m.p. = 46 – 47 °C;

^1H NMR (400 MHz, CDCl_3) δ 3.43 (t, J = 6.8 Hz, 2H, C(13) H_2), 2.69 (t, J = 7.3 Hz, 2H, C(9) H_2), 2.23 (s, 3H, C(Ph*) H_3), 2.19 (s, 6H, $2 \times$ C(Ph*) H_3), 2.10 (s, 6H, $2 \times$ C(Ph*) H_3), 1.97 – 1.86 (m, 2H, C(12) H_2), 1.83 – 1.67 (m, 2H, C(10) H_2), 1.60 – 1.43 (m, 2H, C(11) H_2);

^{13}C NMR (101 MHz, CDCl_3) δ 211.8 C(8), 140.8 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.4 $2 \times$ C(Ar(Ph*)), 45.5 C(9), 33.7 C(13), 32.9 C(12), 27.9 C(11), 22.6 C(10), 17.3 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2936, 2866, 1699;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{26}^{79}\text{BrO}^+$ ($[\text{M}+\text{H}]^+$) requires 325.1162; found 325.1174, Δ 3.83 ppm.

141b 6-Chloro-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

6-Chlorohexanoic acid (3.80 g, 25.0 mmol) was dissolved in thionyl chloride (4.6 mL, 63 mmol) and the mixture was refluxed for 2 h. Once cooled to RT, the reaction mixture was concentrated *in vacuo*. The crude acyl chloride was dissolved in CH_2Cl_2 (10 mL) and added to a solution of pentamethylbenzene (4.10 g, 27.5 mmol) in CH_2Cl_2 (70 mL) at 0 °C. AlCl_3 (4.20 g, 31.3 mmol) was added portion-wise and to mixture was stirred at RT for 30 min. The crude reaction mixture was poured onto ice (approx. 150 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed sequentially with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 → 92:8) gave the title compound as a yellow solid (5.70 g, 81%).

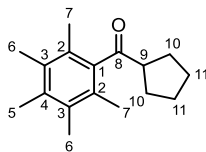
m.p. = 43 – 45 °C;

^1H NMR (400 MHz, CDCl_3) δ 3.57 (t, J = 6.7 Hz, 2H, C(13) H_2), 2.70 (t, J = 7.3 Hz, 2H, C(9) H_2), 2.24 (s, 3H, C(Ph*) H_3), 2.19 (s, 6H, 2 × C(Ph*) H_3), 2.10 (s, 6H, 2 × C(Ph*) H_3), 1.87 – 1.80 (m, 2H, C(12) H_2), 1.79 – 1.72 (m, 2H, C(10) H_2), 1.61 – 1.46 (m, 2H, C(11) H_2);

^{13}C NMR (101 MHz, CDCl_3) δ 211.8 C(8), 140.8 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 45.5 C(9), 45.0 C(13), 32.7 C(12), 26.6 C(11), 22.7 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2937, 2867, 1699, 1457, 1115;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{26}^{35}\text{ClO}^+ ([(^{35}\text{Cl})\text{M}+\text{H}]^+)$ requires 281.1667; found 281.1668, Δ 0.36 ppm.

142 Cyclopentyl(2,3,4,5,6-pentamethylphenyl)methanone

Ketone **141b** (84 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.00 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1 → 98.5:1.5) gave the *title compound* as a white solid (41 mg, 56%).

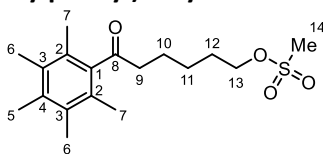
m.p. = 71 – 73 °C;

¹H NMR (400 MHz, CDCl₃) δ 3.18 (p, J = 8.1 Hz, 1H, C(9)*H*), 2.24 (s, 3H, C(Ph*)*H*₃), 2.19 (s, 6H, 2 × C(Ph*)*H*₃), 2.12 (s, 6H, 2 × C(Ph*)*H*₃), 1.97 – 1.81 (m, 4H, 2 × C(11)*H*₂), 1.81 – 1.71 (m, 2H, 2 × C(10)*H*_A*H*_B), 1.67 – 1.53 (m, 2H, 2 × C(10)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 215.1 C(8), 141.2 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.1 2 × C(Ar(Ph*)), 127.8 2 × C(Ar(Ph*)), 54.4 C(9), 29.7 2 × C(11), 25.9 2 × C(10), 17.8 2 × C(Me(Ph*)), 16.7 C(Me(Ph*)), 16.0 2 × C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2869, 1688, 1448, 1122, 1067, 1019;

HRMS (ESI⁺) C₁₇H₂₅O⁺ ([M+H]⁺) requires 245.1900; found 245.1900, Δ 0.02 ppm.

141c 6-Oxo-6-(2,3,4,5,6-pentamethylphenyl)hexyl methanesulfonate

Triethylamine (0.8 mL, 5.7 mmol) was added dropwise to a solution of hydroxy ketone **170** (500 mg, 1.91 mmol) and methanesulfonic anhydride (499 mg, 2.87 mmol) in CH₂Cl₂ (10 mL) at 0 °C. The reaction was allowed to warm to RT and stirred for 2 h, then diluted with water (30 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* recrystallisation from a minimum amount of boiling MeOH gave the *title compound* as an off-white solid (589 mg, 91%).

m.p. = 84 – 86 °C;

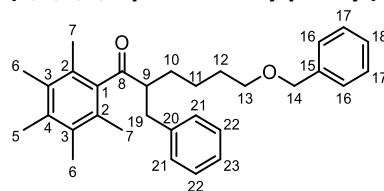
¹H NMR (400 MHz, CDCl₃) δ 4.25 (t, *J* = 6.5 Hz, 2H, C(13)H₂), 3.01 (s, 3H, C(14)H₃), 2.69 (t, *J* = 7.2 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.88 – 1.71 (m, 4H, C(10)H₂, C(12)H₂), 1.56 – 1.45 (m, 2H, C(11)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.7 C(8), 140.7 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 70.0 C(13), 45.4 C(9), 37.5 C(14), 29.3 C(12), 25.2 C(11), 22.8 C(10), 17.3 2 × C(Ph*(Me)), 16.8 C(Me(Ph*)), 16.1 2 × C(Ph*(Me));

IR (film) ν_{max} /cm⁻¹ 3022, 2938, 1698, 1352, 1174, 1126, 974, 944;

HRMS (ESI⁺) C₁₈H₂₉O₄S⁺ ([M+H]⁺) requires 341.1781; found 341.1781; Δ 0.08 ppm.

144a 2-Benzyl-6-(benzyloxy)-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



Ketone **141c** (102 mg, 0.300 mmol), Ir(cod)Cl₂]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4) gave the *title compound* as a colourless oil (48 mg, 36%, isolated in conjunction with 19 mg, 14% **144b**).

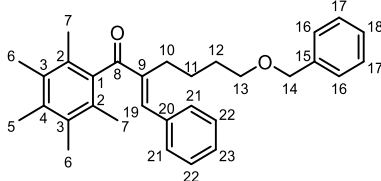
¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.13 (m, 10H, 10 × C(Ph)H), 4.44 (s, 2H, C(14)H₂), 3.38 (t, *J* = 6.4 Hz, 2H, C(13)H), 3.17 (dd, *J* = 13.5, 6.2 Hz, 1H, C(19)H_AH_B), 3.06 (ddd, *J* = 11.6, 7.4, 5.7 Hz, 1H, C(9)H), 2.68 (dd, *J* = 13.5, 7.5 Hz, 1H, C(19)H_AH_B), 2.23 (s, 3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.12 – 1.78 (br. s, 6H, 2 × C(Ph*)H₃), 1.78 – 1.66 (m, 1H, C(10)H_AH_B), 1.57 – 1.48 (m, 2H, C(12)H₂), 1.48 – 1.33 (m, 3H, C(10)H_AH_B & C(11)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 212.9 C(8), 140.4 C(Ar), 139.6 C(Ar), 138.7 C(Ar), 135.7 C(Ar), 133.2 C(Ar), 129.5 2 × C(Ar(Ph)), 128.7 C(Ar), 128.5 2 × C(Ar(Ph)), 128.4 2 × C(Ar(Ph)), 127.7 2 × C(Ar(Ph)), 127.6 C(Ar(Ph)), 126.2 C(Ar(Ph)), 73.0 C(14), 70.2 C(13), 56.0 C(9), 35.6 C(19), 30.0 C(12), 29.5 C(10), 24.0 C(11), 17.8 2 × C(Me(Ph*)), 16.9 2 × C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2936, 2859, 1691, 1454, 1100, 735, 699;

HRMS (ESI⁺) $\text{C}_{31}\text{H}_{39}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 443.2945; found 443.2946, Δ 0.29 ppm.

144b 2-Benzylidene-6-(benzyloxy)-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



Ketone **141c** (102 mg, 0.300 mmol), $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4) gave the *title compound* as a colourless oil (19 mg, 14%, isolated in conjunction with 48 mg, 36% **144a**).

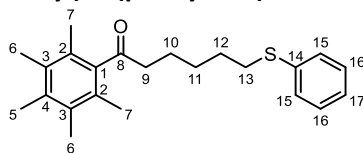
¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.20 (m, 10H, 10 $\times$ C(Ph)H), 7.10 (s, 1H, C(19)H), 4.47 (s, 2H, C(14)H₂), 3.49 (t, J = 6.1 Hz, 2H, C(13)H₂), 2.66 (2.71 – 2.56 (m, 2H, C(10)H₂), 2.20 (s, 3H, C(Ph*)H₃), 2.14 (s, 6H, 2 $\times$ C(Ph*)H₃), 2.00 (s, 6H, 2 $\times$ C(Ph*)H₃), 1.79 – 1.60 (m, 4H, C(11)H₂ & C(12)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 204.3 C(8), 144.4 C(19), 143.0 C(9), 138.7 C(Ar), 137.9 C(Ar), 135.8 C(Ar), 135.1 C(Ar), 132.7 C(Ar), 129.4 C(Ar), 129.3 C(Ar), 128.8 C(Ar), 128.5 C(Ar), 128.4 C(Ar), 127.6 C(Ar), 127.5 C(Ar), 72.9 C(14), 70.0 C(13), 30.1 C(12), 25.7 C(10), 25.6 C(11), 17.4 2 $\times$ C(Me(Ph*)), 16.7 C(Me(Ph*)), 16.0, 2 $\times$ C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2927, 2858, 1651, 1618, 1454, 1107, 1028, 806, 735;

HRMS (ESI⁺) $\text{C}_{31}\text{H}_{37}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 441.2788; found 441.2787, Δ 0.27 ppm.

141d 1-(2,3,4,5,6-Pentamethylphenyl)-6-(phenylthio)hexan-1-one



Triethylamine (2.8 mL, 20 mmol) was added dropwise to a solution of ketone **141a** (3.24 g, 10.0 mmol) and thiophenol (1.3 mL, 12 mmol) in EtOAc (100 mL). The reaction mixture was

stirred at 65 °C for 18 h, cooled to RT and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 95:5) gave the *title compound* as a white solid (3.51 g, 99%).

m.p. 48 – 50 °C;

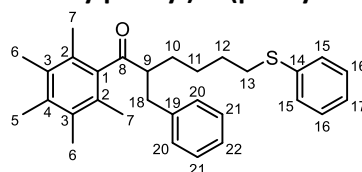
¹H NMR (400 MHz, CDCl₃) δ 7.27 – 7.23 (m, 2H, 2 × C(15)H), 7.22 – 7.15 (m, 2H, 2 × C(16)H), 7.11 – 7.06 (m, 1H, C(17)H), 2.91 – 2.79 (m, 2H, C(13)H₂), 2.59 (t, *J* = 7.3 Hz, 2H, C(9)H₂), 2.15 (s, 3H, C(Ph*)H₃), 2.10 (s, 6H, 2 × C(Ph*)H₃), 2.02 (s, 6H, 2 × C(Ph*)H₃), 1.74 – 1.57 (m, 4H, C(10)H₂ & C(12)H₂), 1.51 – 1.37 (m, 2H, C(11)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.9 C(8), 140.8 C(Ar(Ph*)), 136.9 C(Ar(Ph*)), 135.5 C(14), 133.2 2 × C(Ar(Ph*)), 129.2 C(17), 129.0 2 × C(15), 127.4 2 × C(Ar(Ph*)), 125.9 2 × C(16), 45.5 C(9), 33.6 C(13), 29.3 C(12), 28.5 C(11), 22.9 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\max}$ /cm⁻¹ 2931, 1699, 1584, 1480, 1439, 738, 691;

HRMS (ESI⁺) C₂₃H₃₀NaOS⁺ ([M+Na]⁺) requires 377.1910; found 377.1913, Δ 0.80 ppm.

143a 2-Benzyl-1-(2,3,4,5,6-pentamethylphenyl)-6-(phenylthio)hexan-1-one



Ketone **141d** (106 mg, 0.300 mmol), [Ir(cod)Cl₂]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 97.5:2.5) gave the *title compound* as a colourless oil (109 mg, 84%).

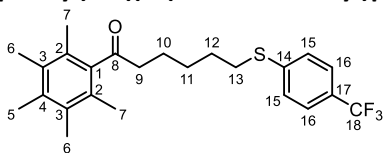
¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.20 (m, 5H, 5 × C(Ph)H), 7.20 – 7.11 (m, 5H, 5 × C(Ph)H), 3.15 (dd, *J* = 13.5, 6.0 Hz, 1H, C(18)H_AH_B), 3.08 – 2.97 (m, 1H, C(9)H), 2.79 (t, *J* = 7.1 Hz, 2H, C(13)H₂), 2.64 (dd, *J* = 13.5, 7.9 Hz, 1H, C(18)H_AH_B), 2.21 (s, 3H, C(Ph*)H₃), 2.15 (s, 6H, 2 × C(Ph*)H₃), 2.00 – 1.90 (br. s, 6H, 2 × C(Ph*)H₃), 1.69 (m, 2H, C(10)H₂), 1.61 – 1.32 (m, 4H, C(11)H₂, C(12)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 212.8 C(8), 140.3 C(Ar), 139.6 C(Ar), 136.9 C(Ar), 135.8 C(Ar), 133.3 2 × C(Ar), 129.4 2 × C(Ar(Ph)), 129.1 2 × C(Ar(Ph)), 129.0 2 × C(Ar(Ph)), 128.7 2 × C(Ar), 128.4 2 × C(Ar(Ph)), 126.2 C(Ar(Ph)), 125.9 2 × C(Ar), 55.8 C(9), 35.7 C(18), 33.4 C(13), 29.4 C(10), 29.1 C(12), 26.5 C(11), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 2981, 1691, 1382, 1302, 1259, 1154, 955, 819, 738, 700;

HRMS (ESI⁺) C₃₀H₃₆OS⁺ ([M+H]⁺) requires 467.2379; found 467.2379.

141e 1-(2,3,4,5,6-Pentamethylphenyl)-6-((4-(trifluoromethyl)phenyl)thio)hexan-1-one



Triethylamine (0.43 mL, 3.1 mmol) was added dropwise to a stirred solution of ketone **141a** (500 mg, 1.54 mmol) and 4-(trifluoromethyl)benzenethiol (0.22 mL, 1.9 mmol) in CH₂Cl₂ (15 mL). The reaction mixture was heated at 65 °C for 18 h, cooled to RT and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4 → 92:8) gave the *title compound* as a white solid (643 mg, 99%).

m.p. = 68 – 70 °C;

¹H NMR (500 MHz, CDCl₃) δ 7.58 – 7.43 (m, 2H, 2 × C(16)H), 7.42 – 7.27 (m, 2H, 2 × C(15)H), 3.00 (t, *J* = 7.3 Hz, 2H, C(13)H₂), 2.68 (t, *J* = 7.3 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.88 – 1.67 (m, 4H, C(10)H₂ & C(12)H₂), 1.66 – 1.46 (m, 2H, C(11)H₂);

¹³C NMR ({¹⁹F} 126 MHz, CDCl₃) δ 211.8 C(8), 142.7 C(Ar), 140.8 C(Ar), 135.6 C(Ar), 133.2 C(Ar), 127.4 2 × C(15), 125.7 2 × C(16), 124.3 C(18), 45.4 C(9), 32.4 C(13), 28.9 C(12), 28.5 C(11) 22.9 C(10), 17.3 2 × C(Me(Ph*)) 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

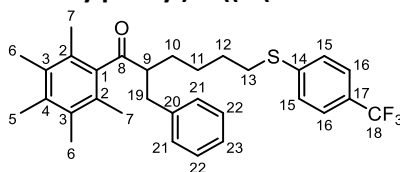
N.B. Fewer ¹³C signals observed than expected based on symmetry due to overlapping peaks in the aromatic region.

¹⁹F NMR (471 MHz, CDCl₃) δ -62.4;

IR (film) ν_{max}/cm⁻¹ 2934, 1699, 1327, 1163, 1120, 1096, 1064, 1012;

HRMS (ESI⁺) C₂₄H₃₀F₃OS⁺ ([M+H]⁺) requires 423.1964; found 423.1963, Δ 0.24 ppm.

143b 2-Benzyl-1-(2,3,4,5,6-pentamethylphenyl)-6-((4-(trifluoromethyl)phenyl)thio)hexan-1-one



Ketone **141e** (127 mg, 0.300 mmol), [Ir(cod)Cl₂]₂ (2.0 mg, 1.0 mol%), dppBz (3.0 mg, 2.0 mol%), KOH (67 mg, 1.2 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. The reaction mixture was cooled to RT and filtered through a silica plug (CH₂Cl₂ elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.5:1.5 → 98:2) gave the *title compound* as a colourless oil (117 mg, 76%).

¹H NMR (500 MHz, CDCl₃) δ 7.49 (d, *J* = 8.2 Hz, 2H, 2 × C(16)*H*), 7.28 (d, *J* = 8.2 Hz, 2H, 2 × C(15)*H*), 7.25 – 7.22 (m, 2H, 2 × C(21)*H*), 7.21 – 7.09 (m, 3H, 2 × C(22)*H* & C(23)*H*), 3.16 (dd, *J* = 13.6, 5.7 Hz, 1H, C(19)*H_AH_B*), 3.09 – 2.97 (m, 1H, C(9)*H*), 2.85 (t, *J* = 7.1 Hz, 2H, C(13)*H₂*), 2.63 (dd, *J* = 13.6, 8.2 Hz, 1H, C(19)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 6H, 2 × C(Ph*)*H₃*), 2.12 – 1.79 (m, 6H, 2 × C(Ph*)*H₃*), 1.81 – 1.66 (m, 1H, C(10)*H_AH_B*), 1.66 – 1.49 (m, 3H, C(10)*H_AH_B* & C(12)*H₂*), 1.47 – 1.29 (m, 2H, C(11)*H₂*);

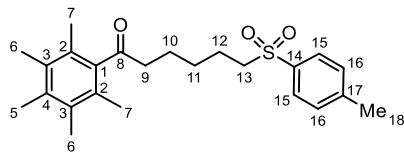
¹³C NMR ({¹⁹F} 126 MHz, CDCl₃) δ 212.8 C(8), 142.6 C(Ar), 140.2 C(Ar), 139.5 C(Ar), 135.9 C(Ar), 133.3 C(Ar), 129.4 2 × C(22), 128.7 C(Ar), 128.5 2 × C(21), 127.4 2 × C(15), 126.3 C(23), 125.7 2 × C(16), 124.3 C(18), 55.7 C(9), 35.8 C(19), 32.2 C(13), 29.0 C(12), 28.9 C(10), 26.5 C(11), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

N.B. Fewer ¹³C signals observed than expected based on symmetry due to overlapping peaks.

¹⁹F NMR (471 MHz, CDCl₃) δ –62.4;

IR (film) ν_{max}/cm^{–1} 2937, 1691, 1606, 1327, 1164, 1122, 1096, 1064;

HRMS (ESI⁺) C₃₁H₃₅F₃NaOS⁺ ([M+Na]⁺) requires 535.2253; found 535.2253, Δ 0.02 ppm.

141f 1-(2,3,4,5,6-Pentamethylphenyl)-6-tosylhexan-1-one

Sodium *p*-toluenesulfinate (824 mg, 4.62 mmol) was added to a solution of ketone **141a** (1.00 g, 3.08 mmol) in *N,N*-dimethylformamide (5 mL) and the mixture was heated at 85 °C for 3.5 h. After cooling to RT, the reaction mixture was diluted with CH₂Cl₂ (50 mL) and washed with water (4 × 50 mL). The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 70:30 → Et₂O) gave the *title compound* as an off-white solid (1.05 g, 85%).

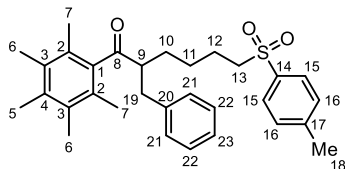
m.p. = 94 – 96 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.64 (m, 2H, 2 × C(15)*H*), 7.41 – 7.30 (m, 2H, 2 × C(16)*H*), 3.17 – 2.97 (m, 2H, C(13)*H*₂), 2.63 (t, *J* = 7.2 Hz, 2H, C(9)*H*₂), 2.46 (s, 3H, C(18)*H*₃), 2.22 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 6H, 2 × C(Ph*)*H*₃), 2.05 (s, 6H, 2 × C(Ph*)*H*₃), 1.82 – 1.60 (m, 4H, C(10)*H*₂ & C(12)*H*₂), 1.53 – 1.40 (m, 2H, C(11)*H*₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.6 C(8), 144.8 C(Ar), 140.6 C(Ar), 136.4 C(Ar), 135.6 C(Ar), 133.2 C(Ar), 130.0 2 × C(16), 128.2 2 × C(15), 127.3 C(Ar), 56.3 C(13), 45.1 C(9), 27.9 C(11), 22.9 C(10), 22.8 C(12), 21.8 C(18), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2938, 2869, 1698, 1301, 1146, 1088;

HRMS (ESI⁺) C₂₄H₃₃O₃S⁺ ([M+H]⁺) requires 401.2145; found 401.2142, Δ 0.64 ppm.

143c 2-Benzyl-1-(2,3,4,5,6-pentamethylphenyl)-6-tosylhexan-1-one

Ketone **141f** (500 mg, 1.25 mmol), [Ir(cod)Cl]₂ (8.4 mg, 1.0 mol%), dppBz (11.2 mg, 2.00 mol%), KOH (280 mg, 5.00 mmol) and benzyl alcohol (1.3 mL, 13 mmol) were subjected to **General Procedure A** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 90:10) gave the *title compound* as a pale yellow oil (373 mg, 61%).

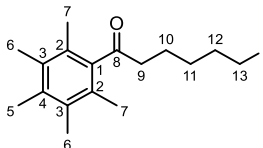
¹H NMR (600 MHz, CDCl₃) δ 7.76 – 7.71 (m, 2H, 2 × C(15)H), 7.38 – 7.32 (m, 2H, 2 × C(16)H), 7.26 – 7.21 (m, 2H, 2 × C(22)H), 7.21 – 7.15 (m, 1H, C(23)H), 7.12 – 7.08 (m, 2H, 2 × C(21)H), 3.11 (dd, *J* = 13.6, 5.4 Hz, 1H, C(19)H_AH_B), 3.04 – 2.96 (m, 1H, C(9)H), 2.96 – 2.89 (m, 2H, C(13)H₂), 2.53 (dd, *J* = 13.6, 8.7 Hz, 1H, C(19)H_AH_B), 2.45 (s, 3H, C(18)H₃), 2.23 (s, 3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.03 (br. s, 6H, 2 × C(Ph*)H₃), 1.70 – 1.56 (m, 3H, C(11)H_AH_B, C(12)H₂), 1.47 – 1.15 (m, 3H, C(10)H₂, C(11)H_AH_B);

¹³C NMR (151 MHz, CDCl₃) δ 212.6 C(8), 144.7 C(17), 139.9 C(20), 139.3 C(Ar(Ph*)), 136.3 C(14), 135.9 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 130.0 2 × C(16), 129.3 2 × C(21), 128.5 2 × C(22), 128.5 2 × C(Ar(Ph*)), 128.2 2 × C(15), 126.4 C(23), 56.2 C(13), 55.5 C(9), 35.9 C(19), 28.7 C(10), 26.1 C(11), 22.9 C(12), 21.8 C(18), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2923, 2868, 1691, 1454, 1302, 1185, 1147, 1088;

HRMS (ESI⁺) C₃₁H₃₉O₃S⁺ ([M+H]⁺) requires 491.2614; found 491.2614, Δ 0.12 ppm.

S8 6-Iodo-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



Ketone **141b** (1.50 g, 5.36 mmol) was added to a solution of NaI (1.22 g, 8.10 mmol) in acetone (10 mL) in a 10 – 20 mL microwave vial. The vial was sealed and the reaction mixture heated at 60 °C for 24 h. The crude reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (20 mL) and diluted with water (20 mL), the layers separated and the aqueous layer extracted with CH₂Cl₂ (2 × 20 mL). The combined organic extracts were washed with sat. aq. Na₂S₂O₃ and brine, dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* as a tan solid (1.57 g, 78%), which required no further purification.

m.p. = 47 – 49 °C;

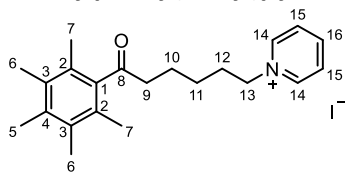
¹H NMR (400 MHz, CDCl₃) δ 3.21 (t, *J* = 7.0 Hz, 2H, C(13)H₂), 2.69 (t, *J* = 7.4 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.88 (m, 2H, C(12)H₂), 1.75 (m, 2H, C(10)H₂), 1.50 (m, 2H, C(11)H₂);

^{13}C NMR (101 MHz, CDCl_3) δ 211.8 C(8), 140.8 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.4, $2 \times$ C(Ar(Ph*)), 45.4 C(9), 33.6 C(12), 30.2 C(11), 22.4 C(10), 17.3 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*)), 6.8 C(13);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2981, 1699, 1457, 1382, 1304, 1264, 1199, 1165, 1071, 913, 731;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{26}\text{IO}^+$ ($[\text{M}+\text{H}]^+$) requires 373.1021; found 373.1023, Δ 0.46 ppm.

141g 1-(6-Oxo-6-(2,3,4,5,6-pentamethylphenyl)hexyl)pyridin-1-ium iodide



Pyridine (0.32 mL, 4.0 mmol) was added to a solution of ketone **58** (744 mg, 2.00 mmol) in 1,4-dioxane (4 mL) and the resulting mixture was heated at 90 °C for 65 h. The crude reaction mixture was diluted with CH_2Cl_2 (20 mL) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 90:10) gave the *title compound* as a pale brown solid (505 mg, 61%).

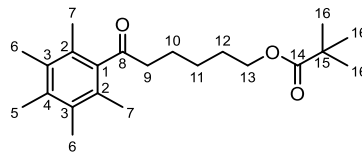
m.p. = 132 – 135 °C;

^1H NMR (400 MHz, CDCl_3) δ 9.59 – 9.30 (m, 2H, $2 \times$ C(14)H), 8.53 (tt, J = 7.8, 1.4 Hz, 1H, C(16)H), 8.24 – 7.91 (m, 2H, $2 \times$ C(15)H), 5.04 (t, J = 7.4 Hz, 2H, C(13)H₂), 2.70 (t, J = 6.8 Hz, 2H, C(9)H₂), 2.22 (s, 3H, C(Ph*)H₃), 2.17 (m, 8H, $2 \times$ C(Ph*)H₃ & C(12)H₂, overlapped), 2.04 (s, 6H, $2 \times$ C(Ph*)H₃), 1.78 (m, 2H, C(10)H₂), 1.56 – 1.39 (m, 2H, C(11)H₂);

^{13}C NMR (101 MHz, CDCl_3) δ 212.1 C(8), 145.4 C(16), 145.2 $2 \times$ C(14), 140.4 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.3 $2 \times$ C(Ar(Ph*)), 128.6 $2 \times$ C(15), 127.3 $2 \times$ C(Ar(Ph*)), 61.9 C(13), 45.0 C(9), 31.9 C(12), 25.3 C(11), 22.4 C(10), 17.4 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*));

IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 3052, 2936, 1694, 1636, 1486, 770, 680;

HRMS (ESI⁺) $\text{C}_{22}\text{H}_{30}\text{ON}^+$ ($[\text{M}]^+$) requires 324.2322; found 324.2320, Δ 0.61 ppm.

141h 6-Oxo-6-(2,3,4,5,6-pentamethylphenyl)hexyl pivalate

Pyridine (0.94 mL, 12 mmol) was added dropwise to a solution of alcohol **170** (500 mg, 1.91 mmol) and pivaloyl chloride (0.52 mL, 4.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was allowed to warm to RT, stirred for 16 h and diluted with CH_2Cl_2 (10 mL) and water (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed with sat. aq. NaHCO_3 , dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 92:8) gave a mixture of the *title compound* and pivalic acid, which was removed under high vacuum (0.2 mmHg, 180 °C, 4 h) to give the *title compound* as a white solid (513 mg, 78%).

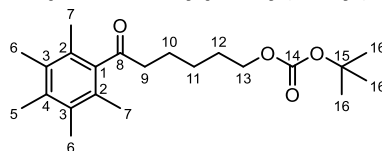
m.p. = 31 – 33 °C;

^1H NMR (400 MHz, CDCl_3) δ 4.07 (t, J = 6.5 Hz, 2H, $\text{C}(13)\text{H}_2$), 2.68 (t, J = 7.3 Hz, 2H, $\text{C}(9)\text{H}_2$), 2.23 (s, 3H, $\text{C}(\text{Ph}^*)\text{H}_3$), 2.18 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 2.09 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 1.83 – 1.71 (m, 2H, $\text{C}(10)\text{H}_2$), 1.71 – 1.62 (m, 2H, $\text{C}(12)\text{H}_2$), 1.51 – 1.37 (m, 2H, $\text{C}(11)\text{H}_2$), 1.19 (s, 9H, $3 \times \text{C}(16)\text{H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 211.9 $\text{C}(8)$, 178.8 $\text{C}(14)$, 140.8 $\text{C}(\text{Ar}(\text{Ph}^*))$, 135.5 $\text{C}(\text{Ar}(\text{Ph}^*))$, 133.2 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 127.4 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 64.3 $\text{C}(13)$, 45.6 $\text{C}(9)$, 38.9 $\text{C}(15)$, 28.7 $\text{C}(12)$, 27.4 $3 \times \text{C}(16)$, 25.8 $\text{C}(11)$, 23.1 $\text{C}(10)$, 17.3 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.8 $\text{C}(\text{Me}(\text{Ph}^*))$, 16.1 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2935, 1728, 1701, 1480, 1459, 1399, 1284, 1155;

HRMS (ESI^+) $\text{C}_{22}\text{H}_{35}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 347.2581; found 347.2581, Δ 0.05 ppm.

141i *tert*-Butyl (6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexyl) carbonate

Pyridine (0.19 mL, 2.4 mmol) was added dropwise to a solution of alcohol **170** (500 mg, 1.91 mmol), DMAP (46 mg, 0.38 mmol) and di-*tert*-butyl dicarbonate (500 mg, 2.29 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 2 h and

then diluted with water (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 90:10 $\rightarrow$ 65:35) gave the *title compound* as a white solid (212 mg, 31%).

m.p. = 57 – 59 °C;

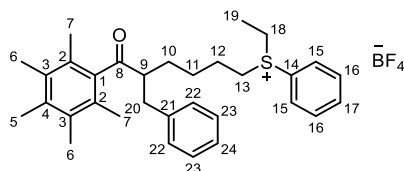
^1H NMR (400 MHz, CDCl_3) δ 4.07 (t, J = 6.6 Hz, 2H, C(13) H_2), 2.68 (t, J = 7.4 Hz, 2H, C(9) H_2), 2.23 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, $2 \times$ C(Ph*) H_3), 2.09 (s, 6H, $2 \times$ C(Ph*) H_3), 1.86 – 1.63 (m, 4H, C(10) H_2 , C(12) H_2), 1.48 (s, 11H, C(11) H_2 , $3 \times$ C(16) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 211.9 C(8), 153.8 C(14), 140.8 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.4 $2 \times$ C(Ar(Ph*)), 82.0 C(15), 67.0 C(13), 45.6 C(9), 28.9 C(12), 27.9 $3 \times$ C(16), 25.6 C(11), 23.1 C(10), 17.3 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2859, 1739, 1700, 1278, 1255, 1164;

HRMS (ESI^+) $\text{C}_{22}\text{H}_{34}\text{NaO}_4^+$ ($[\text{M}+\text{Na}]^+$) requires 385.2349; found 385.2345, Δ 1.05 ppm.

146 (5-Benzyl-6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexyl)(ethyl)(phenyl)sulfonium tetrafluoroborate



Ketone **143a** (166 mg, 0.300 mmol) and silver tetrafluoroborate (58 mg, 0.30 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and ethyl iodide (48 μL , 0.60 mmol) and 1,2-dichloroethane (0.75 mL) were added. The reaction mixture was stirred at RT overnight, filtered through a Celite[®] pad (washed with MeCN) and the filtrate was partitioned between MeCN: hexane (1:3). The phases were separated and the hexane layer extracted with MeCN (2×10 mL), the MeCN layer was then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3) gave the *title compound* as a colourless gum (64 mg, 38%).

¹H NMR (400 MHz, CDCl₃) 7.94 – 7.86 (m, 4H, 2 × C(15')H, 2 × C(15'')H), 7.82 – 7.76 (m, 2H, C(17')H, C(17'')H), 7.71 (m, 4H, 2 × C(16')H, 2 × C(16'')H), 7.22 (m, 4H, 2 × C(23')H, 2 × C(23'')H), 7.19 – 7.12 (m, 2H, C(24')H, C(24'')H), 7.11 – 7.01 (m, 4H, 2 × C(22')H, 2 × C(22'')H), 3.92 – 3.57 (m, 8H, C(13')H₂, C(13'')H₂, C(18')H₂, C(18'')H₂) 3.14 – 3.03 (m, 2H, C(20')H_AH_B, C(20'')H_AH_B), 2.99 (2 H, m, C(9')H, C(9'')H), 2.56 – 2.41 (m, 2H, C(20')H_AH_B, C(20'')H_AH_B), 2.22 (s, 6H, 2 × C(Ph*)H₃), 2.16 (s, 12H, 4 × C(Ph*)H₃), 1.99 (s, 12H, 4 × C(Ph*)H₃), 1.69 – 1.47 (m, 12H, C(10')H₂, C(10'')H₂, C(11')H₂, C(11'')H₂, C(12')H₂, C(12'')H₂), 1.31 (t, *J* = 7.3 Hz, 6H, C(19')H₃, C(19'')H₃);

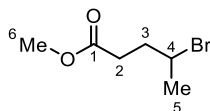
¹³C NMR (151 MHz, CDCl₃) 212.8 C(8') & C(8''), 139.7 C(21') & C(21''), 139.1 2 × C(Ar(Ph*)), 136.0 2 × C(Ar(Ph*)), 135.3 C(17') & C(17''), 133.4 4 × C(Ar(Ph*)), 131.8 2 × C(16') & 2 × C(16''), 131.5 2 × C(15'), 131.5 2 × C(15''), 129.2 2 × C(22') & 2 × C(22''), 128.6 2 × C(23') & 2 × C(23'') & 4 × C(Ar(Ph*)), 126.4 C(24'), 126.4 C(24''), 120.6 C(14'), 120.5 C(14''), 55.4 C(9') & C(9''), 44.1 C(18'), 44.0 C(18''), 39.6 C(13'), 39.5 C(13''), 36.0 C(20') & C(20''), 28.2 C(12'), 28.1 C(12''), 25.7 C(11'), 25.6 C(11''), 24.9 C(10') & C(10''), 18.0 4 × C(Me(Ph*)), 16.9 2 × C(Me(Ph*)), 16.2 4 × C(Me(Ph*)), 9.8 C(19') & C(19'');

IR (film) ν_{max} /cm⁻¹ 2942, 2362, 1688, 1449, 1385, 1261, 1063, 914, 751, 703, 688;

HRMS (ESI⁺) C₃₂H₄₂OS⁺ ([M+H]⁺) requires 473.2873; found 473.2871, Δ 0.42 ppm.

N.B. the labels ' and '' indicate peaks belonging to different diastereomers and are assigned arbitrarily.

S9 Methyl 4-bromopentanoate



γ -Valerolactone (5.0 mL, 52 mmol) was added to a solution of HBr in AcOH (33 wt%, 13 mL). The resulting mixture was heated to 75 °C and stirred for 5 h. After cooling to RT, MeOH (21 mL) was added and the reaction stirred at RT overnight. The crude reaction mixture was concentrated *in vacuo* and re-dissolved in EtOAc (100 mL), washed with sat. aq. NaHCO₃ (3 × 100 mL) and brine. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column

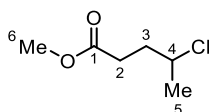
chromatography (eluent pentane/Et₂O, 98:2) gave the *title compound* as a colourless oil (4.94 g, 49%) which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ 4.16 (dq, *J* = 9.1, 6.6, 4.0 Hz, 1H, C(4)*H*), 3.68 (s, 3H, C(6)*H*₃), 2.68 – 2.40 (m, 2H, C(2)*H*₂), 2.24 – 1.97 (m, 2H, C(3)*H*₂), 1.73 (d, *J* = 6.6 Hz, 3H, C(5)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 173.2 C(1), 51.7 C(6), 50.3 C(4), 35.9 C(3), 32.3 C(2), 26.4 C(5);

m/z (ESI⁺) C₆H₁₂⁷⁹BrO₂⁺ ([M+H]⁺) requires 195; mass not found.

S10 Methyl 4-chloropentanoate



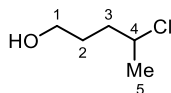
Ester **S9** (3.00 g, 15.3 mmol) was dissolved in DMF, LiCl (1.97 g, 46.5 mmol) was added in one portion and the reaction was stirred at 90 °C for 24 h. The mixture was cooled to RT, diluted with Et₂O (100 mL) and washed with 1 M HCl (3 × 100 mL). The remaining organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo* to give the *title compound* as a pale yellow oil (1.56 g, 67%), which was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ 4.08 (dq, *J* = 9.1, 6.6, 3.9 Hz, 1H, C(4)*H*), 3.68 (s, 3H, C(6)*H*₃), 2.63 – 2.42 (m, 2H, C(2)*H*₂), 2.17 – 2.03 (m, 1H, C(3)*H*_A*H*_B), 2.01 – 1.87 (m, 1H, C(3)*H*_A*H*_B), 1.53 (d, *J* = 6.5 Hz, 3H, C(5)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 173.5 C(1), 57.8 C(4), 51.8 C(6), 35.2 C(3), 31.2 C(2), 25.5 C(5);

m/z (ESI⁺) C₆H₁₂³⁵ClO₂⁺ ([M+H]⁺) requires 151; mass not found.

149 4-Chloropentan-1-ol



A solution of ester **S10** (1.00 g, 6.62 mmol) in THF (5 mL) was added dropwise to a suspension of LiAlH₄ (378 mg, 9.96 mmol) in THF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min, allowed to warm to RT and stirred for 1 h. The reaction was quenched with sequential dropwise addition of water (0.38 mL), aq. NaOH (15% w/v, 0.38 mL) and water (1.14 mL) at 0 °C and the mixture was filtered over Celite® and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent pentane/Et₂O, 60:40) gave the *title compound* as a pale yellow oil (739 mg, 91%).

¹H NMR (400 MHz, CDCl₃) δ 4.15 – 3.99 (m, 1H, C(4)H), 3.67 (t, *J* = 6.0 Hz, 2H, C(1)H₂), 1.90 – 1.59 (m, 4H, C(2)H₂, C(3)H₂), 1.52 (d, *J* = 6.6 Hz, 3H, C(5)H₃), 1.49 (br. s, 1H, OH);

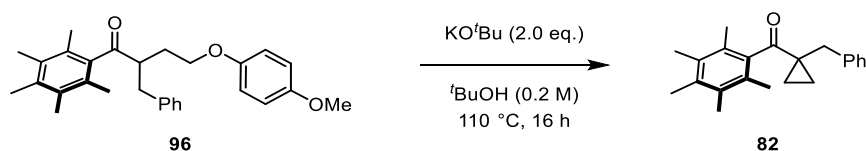
¹³C NMR (101 MHz, CDCl₃) δ 62.4 C(1), 58.7 C(4), 36.8 C(3), 29.9 C(2), 25.6 C(5);

m/z (ESI⁺) C₅H₁₂³⁵ClO⁺ ([M+H]⁺) requires 123; mass not found.

The spectroscopic data were consistent with that reported in the literature.¹⁴⁷

6.2.3 Mechanistic Experiments

Cyclisation of α-branched ketone **96** to give cyclopropyl ketone **82**

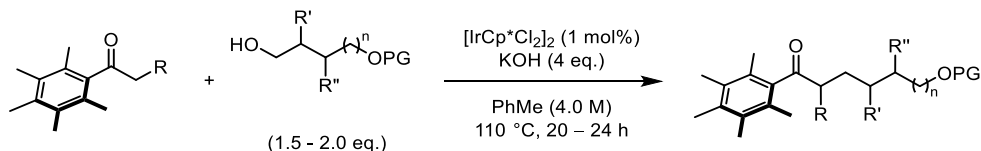


Ketone **96** (43 mg, 0.10 mmol) and KO^tBu (22 mg, 0.20 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon). ^tBuOH (0.5 mL) was added and the reaction was heated to 110 °C overnight. The reaction was cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O 98:2) gave the ketone **82** as a white solid (25 mg, 81%). The spectroscopic data matched that reported for compound **82**.

6.3 Experimental for Chapter 3

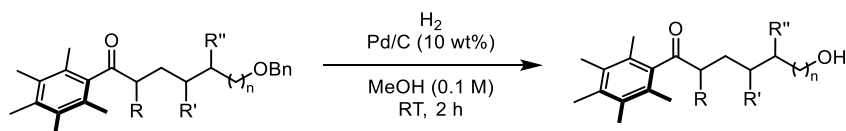
6.3.1 General Procedures

General Procedure E: Hydrogen borrowing alkylation with mono-protected diols

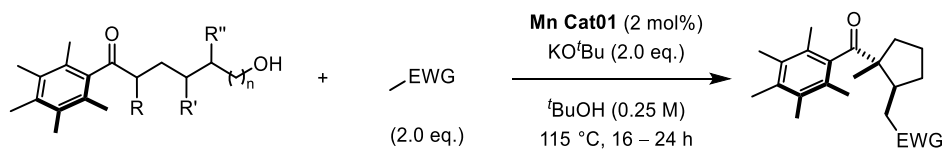


Ph* ketone (1.00 eq.), mono-protected diol (1.50 – 2.00 eq.), [IrCp*Cl₂]₂ (1.0 mol%) and KOH (4.00 eq.) were added to a 10 – 20 mL microwave vial. The vial was sealed, evacuated, and back-filled with Ar (3 times) and PhMe (4.0 M, degassed with Ar (balloon)) was added. The reaction was heated at 110 °C for 20 – 24 h, cooled to RT, filtered through a silica plug (elution with Et₂O) and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

General Procedure F: Benzyl deprotection

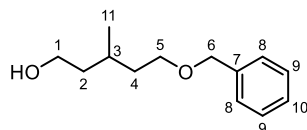


Benzyl ether substrate (1.00 eq.) was dissolved in MeOH (0.1 M) and the solution was degassed with nitrogen (balloon) for 10 min. Pd (10% on carbon, 10 wt%) was added and a balloon of hydrogen gas was attached. H₂ was bubbled through the reaction mixture for 10 min and then the mixture was stirred vigorously at RT for 2 h. The crude reaction mixture was filtered through a Celite® pad (washed with CH₂Cl₂) and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

General Procedure G: Acceptorless dehydrogenation–intramolecular conjugate addition

Hydroxy ketone substrate (0.30 mmol, 1.00 eq.), nucleophile (0.60 mmol, 2.00 eq.), bromodicarbonyl[bis[2-(diisopropylphosphino)ethyl]amine]manganese(I), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol, 2.00 eq.) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and ^tBuOH (1.2 mL, 0.25 M, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 16 – 24 h, cooled to RT, filtered through a silica pad (Et₂O/CH₂Cl₂ elution) and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

6.3.2 Preparation and Characterisation of Compounds

S11 5-(Benzyloxy)-3-methylpentan-1-ol

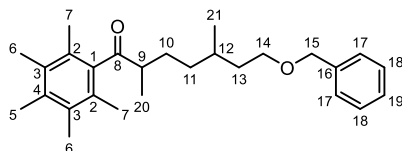
Benzyl bromide (5.0 mL, 42 mmol) and KOH (10.0 g, 178 mmol) were added in two equal portions to 3-methyl-1,5-pentanediol (20 mL, 170 mmol) in THF (20 mL) at RT over 30 mins. The resulting suspension was stirred vigorously for 4 h and diluted with water (100 mL). The mixture was extracted with Et₂O (3 × 100 mL) and the combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 60:40 → 50:50) gave the *title compound* as a pale yellow oil (7.33 g, 84%).

¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.27 (m, 5H, 5 × C(Ph)H), 4.50 (s, 2H, C(6)H₂), 3.81 – 3.58 (m, 2H, C(1)H₂), 3.58 – 3.25 (m, 2H, C(5)H₂), 1.81 – 1.73 (m, 1H, C(3)H), 1.73 – 1.64 (m, 1H, C(4)H_AH_B), 1.64 – 1.54 (m, 1H, C(2)H_AH_B), 1.54 – 1.38 (m, 3H, C(2)H_AH_B, C(4)H_AH_B), 0.98 – 0.83 (m, 3H, C(11)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 138.6 C(7), 128.5 2 × C(Ph), 127.8 2 × C(Ph), 127.7 C(10), 73.1 C(6), 68.6 C(5), 61.1 C(1), 40.0 C(2), 36.8 C(4), 26.9 C(3), 20.0 C(11);

m/z (ESI⁺) Found ([M+Na]⁺) = 209, C₁₃H₂₁O₂ requires 209.

The spectroscopic data matched that previously reported in the literature.¹⁴⁸

S12 7-(Benzyloxy)-2,5-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one

Ketone **98** (1.02 g, 5.00 mmol), [IrCp*Cl₂]₂ (40 mg, 1.0 mol%) and KOH (1.12 g, 20.0 mmol) were added to a 10 – 20 mL microwave vial. The vial was sealed, purged with Ar (balloon) and alcohol **S11** (1.56 g, 7.50 mmol) and PhMe (1.25 mL, 4 M) were added. The reaction was heated at 110 °C for 18 h, cooled to room temperature, filtered through a silica plug (elution with Et₂O) and

concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 97:3 → 95:5) gave the *title compound* as a pale yellow oil (905 mg, 46%, [50:50] d.r.)

The relative stereochemistry is unassigned. The spectroscopic data were collected on the diastereomeric mixture.

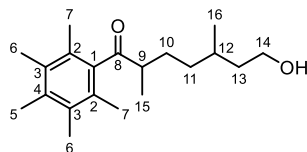
¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.26 (m, 10H, 10 × C(Ph)H), 4.49 (s, 4H, C(15')H₂, C(15'')H₂), 3.61 – 3.34 (m, 4H, C(14')H₂, C(14'')H₂), 2.81 – 2.52 (m, 2H, C(9')H, C(9'')H), 2.23 (2 × s, 6H, C(Ph*)H₃, C(Ph'')H₃), 2.18 (2 × s, 12H, 2 × C(Ph*)H₃, 2 × C(Ph'')H₃), 2.08 (s, 12H, 2 × C(Ph*)H₃, 2 × C(Ph'')H₃), 1.95 – 1.58 (m, 6H, C(10')H_AH_B, C(10'')H_AH_B, C(12')H, C(12'')H, C(13')H_AH_B, C(13'')H_AH_B), 1.49 – 1.16 (m, 8H, C(10')H_AH_B, C(10'')H_AH_B, C(11')H₂, C(11'')H₂, C(13')H_AH_B, C(13'')H_AH_B), 1.13 (dd, *J* = 7.0, 1.0 Hz, 6H, C(20')H₃, C(20'')H₃), 0.88 (t, *J* = 6.5 Hz, 6H, C(21')H₃, C(21'')H₃);

¹³C NMR (151 MHz, CDCl₃) δ 215.3 C(8'), 215.2 C(8''), 140.2 2 × C(Ar(Ph*)), 138.8 C(16'), 138.8 C(16''), 135.5 C(Ar(Ph*')), C(Ar(Ph*')), 133.2 2 × C(Ar(Ph*')), 2 × C(Ar(Ph*')), 128.5 2 × C(18'), 2 × C(18''), 128.4 2 × C(Ar(Ph*')), 2 × C(Ar(Ph*')), 127.8 2 × C(17'), 2 × C(17''), 127.6 C(19'), C(19''), 73.0 C(15'), 73.0 C(15''), 68.7 C(14'), 68.7 C(14''), 48.7 C(9'), 48.6 C(9''), 37.1 C(13'), 36.6 C(13''), 34.8 C(11'), 34.7 C(11''), 30.3 C(12'), 30.1 C(12''), 29.3 C(10'), 29.3 C(10''), 19.9 C(21'), 19.5 C(21''), 18.1 2 × C(Me(Ph*')), 18.1 2 × C(Me(Ph*')), 16.8 C(Me(Ph*')), C(Me(Ph*')), 16.2 2 × C(Me(Ph*')), 2 × C(Me(Ph*')), 15.6 C(20'), 15.3 C(20'');

IR (film) ν_{max}/cm⁻¹ 2932, 2870, 1694, 1455, 1099, 924, 736, 698;

HRMS (ESI⁺) C₂₇H₃₉O₂⁺ ([M+H]⁺) requires 395.2945; found 395.2943, Δ 0.41 ppm.

* N.B. the labels ' and '' indicate peaks belonging to different diastereomers and are assigned arbitrarily.

156 7-Hydroxy-2,5-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one

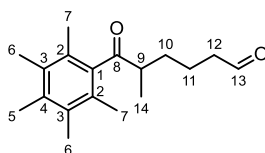
Benzyl ether **S12** (517 mg, 1.31 mmol) and Pd (10% on carbon) (52 mg, 10 wt%) were subjected to **General Procedure F** in MeOH (15 mL) for 3 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 70:30) gave the *title compound* as a colourless oil (398 mg, 99%, [50:50] d.r.)

¹H NMR (400 MHz, CDCl₃) δ 3.81 – 3.49 (m, 4H, C(14')H₂, C(14'')H₂), 2.83 – 2.67 (m, 2H, C(9')H, C(9'')H), 2.23 (s, 6H, C(Ph*)H₃, C(Ph'')H₃), 2.18 (s, 12H, 2 × C(Ph*)H₃, 2 × C(Ph'')H₃), 2.09 (s, 12H, 2 × C(Ph*)H₃, 2 × C(Ph'')H₃), 1.92 – 1.71 (m, 2H, C(10')H_AH_B, C(10'')H_AH_B), 1.67 – 1.49 (m, 4H, C(12')H, C(12'')H, C(13')H_AH_B, C(13'')H_AH_B), 1.49 – 1.16 (m, 8H, C(10')H_AH_B, C(10'')H_AH_B, C(11')H₂, C(11'')H₂, C(13')H_AH_B, C(13'')H_AH_B), 1.14 (d, *J* = 7.0 Hz, 6H, C(15')H₃, C(15'')H₃), 0.90 (t, *J* = 6.2 Hz, 6H, C(16')H₃, C(16'')H₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.3 C(8'), 215.2 C(8''), 140.1 C(Ar(Ph*')), 140.1 C(Ar(Ph'')), 135.6 C(Ar(Ph*')), C(Ar(Ph'')), 133.2 2 × C(Ar(Ph*')), 2 × C(Ar(Ph'')), 128.4 2 × C(Ar(Ph*')), 2 × C(Ar(Ph'')), 61.2 C(14'), 61.2 C(14''), 48.7 C(9'), 48.6 C(9''), 40.2 C(13'), 39.7 C(13''), 34.8 C(11'), 34.7 C(11''), 29.9 C(12'), 29.8 C(12''), 29.3 C(10'), 29.3 C(10''), 19.9 C(16'), 19.5 C(16''), 18.1 2 × C(Me(Ph*')), 2 × C(Me(Ph'')), 16.9 C(Me(Ph*')), C(Me(Ph'')), 16.2 2 × C(Me(Ph*')), 2 × C(Me(Ph'')), 15.7 C(15'), 15.4 C(15'');

IR (film) ν_{max} /cm⁻¹ 3421, 2933, 1692, 1460, 1064, 924;

HRMS (ESI⁺) C₂₀H₃₃O₂⁺ ([M+H]⁺) requires 305.2475; found 305.2474, Δ 0.36 ppm.

158 5-Methyl-6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexanal

Dess-Martin periodinane (275 mg, 0.648 mmol) was added to a solution of **164a** (149 mg, 0.540 mmol) in CH₂Cl₂ (3 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 3 h.

The reaction was quenched with the addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL), the layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 85:15) gave the *title compound* as a colourless oil (127 mg, 86%).

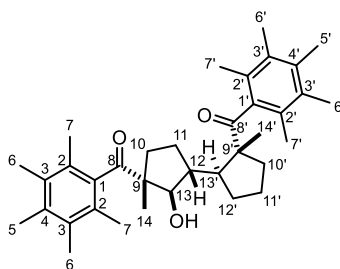
^1H NMR (600 MHz, CDCl_3) δ 9.77 (t, $J = 1.6$ Hz, 1H, C(13)H), 2.84 – 2.75 (m, 1H, C(9)H), 2.46 (m, 2H, C(12)H₂), 2.24 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, $2 \times$ C(Ph*)H₃), 2.08 (s, 6H, $2 \times$ C(Ph*)H₃), 1.87 – 1.73 (m, 2H, C(10)H_AH_B, C(11)H_AH_B), 1.70 – 1.58 (m, 1H, C(11)H_AH_B), 1.50 – 1.37 (m, 1H, C(10)H_AH_B), 1.16 (d, $J = 7.1$ Hz, 3H, C(14)H₃);

^{13}C NMR (151 MHz, CDCl_3) δ 214.6 C(13), 202.3 C(8), 139.9 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.3 $2 \times$ C(Ar(Ph*)), 128.3 br. $2 \times$ C(Ar(Ph*)), 48.3 C(9), 44.1 C(12), 31.3 C(10), 20.1 C(11), 18.1 $2 \times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 $2 \times$ C(Me(Ph*)), 15.5 C(14);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 1724, 1692, 1457, 1303, 1195, 1091, 990, 923, 742, 623;

HRMS (ESI⁺) $\text{C}_{18}\text{H}_{26}\text{NaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 297.1825; found 297.1825, Δ 0.08 ppm.

159 ((1*SR*,1'*RS*,2*RS*,2'*RS*,3'*RS*)-2'-Hydroxy-2,3'-dimethyl-[1,1'-bi(cyclopentane)]-2,3'-diyl)bis((2,3,4,5,6-pentamethylphenyl)methanone)



KOH (236 mg, 4.20 mmol) was added to a solution of aldehyde **156** (287 mg, 1.05 mmol) in MeOH (5 mL) and the resulting mixture was stirred at 50 °C for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL) and water (20 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 80:20) gave the *title compound* as a white solid (207 mg, 74%, >[95:5] d.r.)

m.p. = 64 – 66 °C;

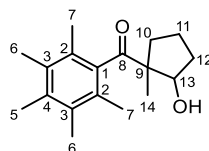
^1H NMR (400 MHz, CDCl_3) δ 4.12 (dd, $J = 9.9, 6.3$ Hz, 1H, C(13) H), 2.50 (ddd, $J = 10.0, 8.1, 3.6$ Hz, 1H, C(13') H), 2.22 (s, 6H, $2 \times \text{C(Ph}^*)\text{H}_3$), 2.17 (s, 12H, $4 \times \text{C(Ph}^*)\text{H}_3$), 2.13 (s, 3H, C(Ph*) H_3), 2.10 – 1.94 (m, 12H, $3 \times \text{C(Ph}^*)\text{H}_3$, C(12) H , C(10) H_AH_B , C(10') H_AH_B), 1.84 (m, 1H, C(12') H_AH_B), 1.76 (m, 1H, C(11) H_AH_B), 1.70 – 1.48 (m, 6H, C(11) H_AH_B , C(10) H_AH_B , C(12') H_AH_B , C(11') H_2 , C(10') H_AH_B), 1.19 (s, 3H, C(14) H_3), 1.08 (s, 3H, C(14') H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 220.6 C(8), 219.9 C(8'), 140.0 C(Ar(Ph*)), 139.6 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 134.8 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 132.8 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 127.3 C(Ar(Ph*)), 81.4 C(13), 58.5 C(9), 57.6 C(9'), 46.3 C(13'), 43.8 C(12), 39.6 C(10), 36.4 C(10'), 25.9 C(11), 23.6 C(12'), 22.4 C(11'), 21.6 C(14), 19.1 C(Me(Ph*)), 19.0 C(Me(Ph*)), 18.2 C(Me(Ph*)), 18.0 C(Me(Ph*)), 17.1 C(14'), 16.7 C(Me(Ph*)), 16.6 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*)), 16.0 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2927, 2875, 1681, 1559, 918;

HRMS (ESI⁺) $\text{C}_{36}\text{H}_{51}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 531.3833; found 531.3831, Δ 0.41 ppm.

160 (2-Hydroxy-1-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



KOH (27 mg, 0.48 mmol) was added to a solution of aldehyde **158** (33 mg, 0.12 mmol) in MeOH (2.4 mL) and the resulting mixture was stirred at RT for 24 h. The mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 95:5 $\rightarrow$ 60:40) gave separable diastereomers of the *title compound* as white solids (24 mg, 73%, [70:30] d.r.)*

* Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification. The relative stereochemistry of each diastereomer could not be assigned.

Major diastereomer:

m.p. = 127 – 129 °C;

¹H NMR (400 MHz, CDCl₃) δ 4.48 (td, *J* = 8.4, 4.9 Hz, 1H, C(13)*H*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 2.12 – 2.06 (m, 7H, 2 × C(Ph*)*H*₃, C(12)*H_AH_B*), 2.03 – 1.94 (m, 1H, C(10)*H_AH_B*), 1.92 (d, *J* = 4.9 Hz, 1H, OH), 1.79 – 1.60 (m, 4H, C(10)*H_AH_B*, C(11)*H*₂, C(12)*H_AH_B*), 1.19 (s, 3H, C(14)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 220.1 C(8), 139.4 C(Ar(Ph*)), 135.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 77.7 C(13), 58.8 C(9), 36.5 C(10), 31.6 C(12), 19.4 C(11), 18.6 C(Me(Ph*)), 18.5 C(Me(Ph*)), 17.1 C(14), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}$ /cm⁻¹ 3459, 2942, 2875, 1679, 1454, 1079, 920;

HRMS (ESI⁺) C₁₈H₂₆NaO₂⁺ ([M+Na]⁺) requires 297.1825; found 297.1826, Δ 0.18 ppm.

Minor diastereomer:

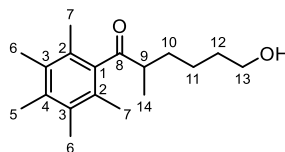
m.p. = 119 – 120 °C;

¹H NMR (600 MHz, CDCl₃) δ 4.14 – 4.10 (m, 1H, C(13)*H*), 4.08 (d, *J* = 3.7 Hz, 1H, OH), 2.48 – 2.35 (m, 1H, C(12)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, 2 × C(Ph*)*H*₃), 2.11 (s, 3H, C(Ph*)*H*₃), 2.08 (s, 3H, C(Ph*)*H*₃), 2.02 (m, 2H, C(10)*H_AH_B* & C(11)*H_AH_B*), 1.94 – 1.85 (m, 1H, C(11)*H_AH_B*), 1.79 – 1.59 (m, 2H, C(10)*H_AH_B*, C(12)*H_AH_B*), 0.98 (s, 3H, C(14)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 223.3 C(8), 139.8 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 127.3 C(Ar(Ph*)) 127.3 C(Ar(Ph*)), 81.7 C(13), 59.0 C(9), 38.2 C(12), 34.7 C(11), 22.5 C(14), 21.5 C(10), 18.0 C(Me(Ph*)), 17.7 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}$ /cm⁻¹ 3463, 2959, 2918, 1684, 1458, 1080, 927;

HRMS (ESI⁺) C₁₈H₂₆NaO₂⁺ ([M+Na]⁺) requires 297.1825; found 297.1825, Δ 0.12 ppm.

164 6-Hydroxy-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

Enone **172** (93 mg, 0.26 mmol) was dissolved in MeOH (2.5 mL), Pd (10% on carbon) (9 mg, 10 wt%) was added and a balloon of hydrogen gas was attached. H₂ was bubbled through the reaction mixture for 15 min and then the mixture was stirred vigorously under an atmosphere of H₂ at RT for 2 h. The crude reaction mixture was filtered through a Celite® pad (washed with CH₂Cl₂) and concentrated *in vacuo* to obtain the *title compound* as a white solid which was used without further purification (65 mg, 90%).

Alternative Route:

Benzyl ether **174** (2.09 g, 5.70 mmol) and Pd (10% on carbon) (209 mg, 10 wt%) were subjected to **General Procedure F** in MeOH (10 mL) for 2 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 70:30 → 60:40) gave the *title compound* as a white solid (1.44 g, 92%).

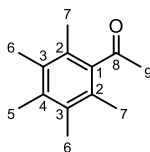
m.p. = 39 – 41 °C;

¹H NMR (400 MHz, CDCl₃) δ 3.64 (t, *J* = 6.5 Hz, 2H, C(13)H₂), 2.87 – 2.71 (m, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.88 – 1.75 (m, 1H, C(10)H_AH_B), 1.63 – 1.32 (m, 5H, C(10)H_AH_B, C(11)H₂, C(12)H₂), 1.15 (d, *J* = 7.0 Hz, 3H, C(14)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.1 C(8), 140.1 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 128.3 2 × C(Ar(Ph*)), 62.8 C(13), 48.5 C(9), 32.9 C(12), 31.6 C(10), 23.6 C(11), 18.0 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 15.4 C(14);

IR (film) ν_{max} /cm⁻¹ 3371, 2935, 2360, 2342, 1692, 1575, 1457, 1070, 923;

HRMS (ESI⁺) C₁₈H₂₉O₂⁺ ([M+H]⁺) requires 277.2162; found 277.2163, Δ 0.26 ppm.

31 1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one

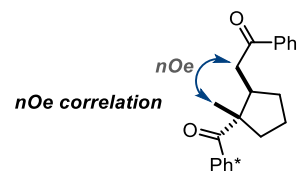
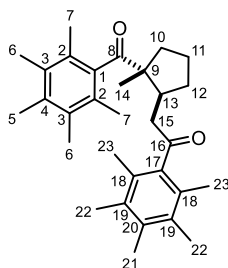
A solution of pentamethylbenzene (5.00 g, 33.7 mmol) and acetyl chloride (2.1 mL, 29 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C. AlCl_3 (4.38 g, 32.9 mmol) was added portion-wise over 5 min, the resulting mixture was allowed to warm to RT and stirred for 90 min. After completion, the reaction mixture was poured onto crushed ice (approx. 200 g). Once the ice had melted, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 97:3 → 90:10) gave the *title compound* as a white solid (4.66 g, 85%).

^1H NMR (400 MHz, CDCl_3) δ 2.46 (3 H, s, C(9) H_3), 2.24 (3 H, s, C(Ph*) H_3), 2.19 (6 H, s, 2 × C(Ph*) H_3), 2.13 (6 H, s, 2 × C(Ph*) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 210.2 C(8), 141.1 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.1 2 × C(Ar(Ph*)), 33.3 C(9), 17.2 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

m/z (ESI $^+$) Found ([M+Na] $^+$) = 213, $\text{C}_{13}\text{H}_{18}\text{NaO}$ requires 213.

The spectroscopic data matched that previously reported in the literature.¹⁴⁹

165a 2-((1S,2R)-2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one

Hydroxy ketone **164** (83 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.600 mmol), Ir(cod)acac (2.0 mg, 1.0 mol%), cataCXium® A (17.2 mg, 16.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar and $^t\text{BuOH}$ (1.2 mL) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, filtered

through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 92:8) gave the *title compound* as a white solid (93 mg, 69%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe analysis.

m.p. = 159 – 161 °C;

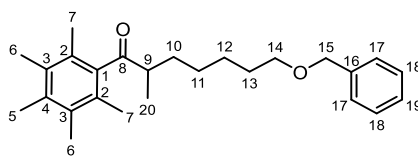
¹H NMR (400 MHz, CDCl₃) δ 2.95 (dd, *J* = 19.1, 1.7 Hz, 1H, C(15)*H_AH_B*), 2.80 – 2.62 (m, 1H, C(13)*H*), 2.52 (dd, *J* = 19.1, 11.3 Hz, 1H, C(15)*H_AH_B*), 2.32 – 2.21 (m, 1H, C(12)*H_AH_B*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.15 (s, 3H, C(Ph*)*H₃*), 2.20 – 2.17 (m, 9H, 3 × C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.08 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 9H, 3 × C(Ph*)*H₃*), 1.92 – 1.84 (m, 1H, C(10)*H_AH_B*), 1.68 – 1.56 (m, 3H, C(10)*H_AH_B*, C(11)*H₂*), 1.31 – 1.17 (m, 1H, C(12)*H_AH_B*), 1.05 (s, 3H, C(14)*H₃*);

¹³C NMR (101 MHz, CDCl₃) δ 218.0 C(8), 210.8 C(16), 140.8 C(Ar(Ph*)), 139.0 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 135.0 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 132.8 C(Ar(Ph*)), 128.5 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.3 C(Ar(Ph*)), 58.3 C(9), 47.0 C(15), 39.7 C(13), 37.3 C(10), 30.4 C(12), 22.0 C(11), 19.3 C(Me(Ph*)), 18.2 C(Me(Ph*)), 18.1 C(14), 17.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.1 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2988, 2942, 1700, 1677, 1462, 1447, 1407, 1382, 1303, 1262, 1226, 1111, 998;

HRMS (ESI⁺) C₃₁H₄₃O₂⁺ ([M+H]⁺) requires 447.3258; found 447.3255, Δ 0.51 ppm.

S13 7-(Benzyloxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one



Ph* ethyl ketone **98** (1.63 g, 8.00 mmol), [IrCp*Cl₂]₂ (64 mg, 1.0 mol%), KOH (1.80 g, 32.0 mmol), 5-benzyloxypentan-1-ol (3.1 mL, 16 mmol) and PhMe (2.0 mL) were subjected to **General Procedure E** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 92:8) gave the *title compound* as a colourless oil which solidified on standing (2.71 g, 89%).

m.p. = 66 – 68 °C;

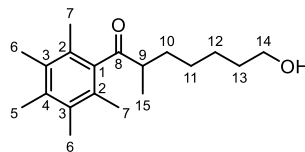
¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.26 (m, 5H, 5 × C(Ph)H), 4.49 (s, 2H, C(15)H₂), 3.45 (t, *J* = 6.5 Hz, 2H, C(14)H₂), 2.90 – 2.67 (m, 1H, C(9)H), 2.23 (s, 3H, (Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.08 (s, 6H, 2 × C(Ph*)H₃), 1.85 – 1.71 (m, 1H, C(10)H_AH_B), 1.66 – 1.59 (m, 2H, C(13)H₂), 1.50 – 1.22 (m, 5H, C(10)H_AH_B, C(11)H₂, C(12)H₂), 1.14 (d, *J* = 7.0 Hz, 3H, C(20)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.2 C(8), 140.2 C(Ar), 138.8 C(Ar), 135.5 C(Ar), 133.2 C(Ar), 128.5 2 × C(Ar(Ph)), 128.4 C(Ar), 127.8 2 × C(Ar(Ph)), 127.6 C(19), 73.0 C(15), 70.5 C(14), 48.5 C(9), 31.8 C(10), 29.8 C(13), 27.3 C(11), 26.4 C(12), 18.1 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.3 C(20);

IR (film) $\nu_{\max}$ /cm⁻¹ 2935, 2858, 1693, 1454, 1100, 1028, 990, 923, 735, 698;

HRMS (ESI⁺) C₂₆H₃₇O₂⁺ ([M+H]⁺) requires 381.2788; found 381.2788, Δ 0.08 ppm.

166 7-Hydroxy-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one



Benzyl ether **S13** (2.53 g, 6.66 mmol) was subjected to **General Procedure F** in MeOH (70 mL) with Pd (10% on carbon) (253 mg, 10 wt%) for 2 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 70:30 → 60:40) gave the *title compound* as a white solid (1.35 g, 70%).

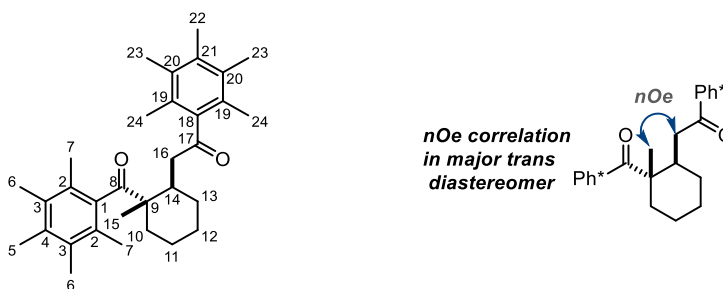
m.p. = 31 – 33 °C;

¹H NMR (400 MHz, CDCl₃) δ 3.63 (t, *J* = 6.6 Hz, 2H, C(14)H₂), 2.78 (dq, *J* = 8.3, 6.9, 4.4 Hz, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.85 – 1.74 (m, 1H, C(10)H_AH_B), 1.56 (tdd, *J* = 8.2, 6.7, 3.8 Hz, 2H, C(13)H₂), 1.51 – 1.22 (m, 6H, C(10)H_AH_B, C(11)H₂, C(12)H₂, OH), 1.14 (d, *J* = 7.0 Hz, 3H, C(15)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.2 C(8), 140.1 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 128.4 2 × C(Ar(Ph*)), 63.1 C(14), 48.5 C(9), 32.8 C(13), 31.8 C(10), 27.3 C(11), 26.0 C(12), 18.1 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.3 C(15);

IR (film) $\nu_{\max}$ /cm⁻¹ 3367 br., 2934, 2860, 1692, 1456, 1382, 1304, 1260, 1055, 990, 925, 732, 688;

HRMS (ESI⁺) C₁₉H₃₁O₂⁺ ([M+H]⁺) requires 291.2318; found 291.2319, Δ 0.05 ppm.

167a 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one

Hydroxy ketone **166** (87 mg, 0.30 mmol), *Ph** methyl ketone **31** (114 mg, 0.600 mmol), [Ir(cod)acac] (2.4 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%) and KOH (67 mg, 1.2 mmol) were added to 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and PhMe (1.2 mL, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 94:6) gave the *title compound* as a white solid (100 mg, 72%, [86:14] d.r., isolated in conjunction with 15 mg **168**).

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by *nOe* analysis.

m.p. = 203 – 205 °C;

Major (1*SR*, 2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 3.44 – 3.38 (m, 1H, *J* = 19.7, 1.3 Hz, C(16)*H_AH_B*), 2.75 (dddd, *J* = 11.6, 10.4, 4.0, 1.2 Hz, 1H, C(14)*H*), 2.49 (dd, *J* = 19.8, 10.4 Hz, 1H, C(16)*H_AH_B*), 2.24 (s, 3H, C(*Ph**)*H*₃), 2.22 (s, 3H, C(*Ph**)*H*₃), 2.19 (s, 9H, 3 × C(*Ph**)*H*₃), 2.16 (s, 3H, C(*Ph**)*H*₃), 2.12 (s, 3H, C(*Ph**)*H*₃), 2.10 (s, 6H, 2 × C(*Ph**)*H*₃), 2.02 (s, 4H, C(*Ph**)*H*₃ & C(13)*H_AH_B*), 1.69 – 1.65 (m, 1H, C(12)*H_AH_B*), 1.62 – 1.58 (m, 1H, C(10)*H_AH_B*), 1.54 – 1.45 (m, 2H, C(10)*H_AH_B*, C(11)*H_AH_B*), 1.42 – 1.28 (m, 2H, C(11)*H_AH_B*, C(12)*H_AH_B*), 1.19 (m, 4H, C(13)*H_AH_B*, C(15)*H*₃, overlapped),

¹³C NMR (151 MHz, CDCl₃) δ 219.1 C(8), 210.6 C(17), 140.9 C(Ar(*Ph**)), 139.7 C(Ar(*Ph**)), 135.4 C(Ar(*Ph**)), 134.8 C(Ar(*Ph**)), 133.4 (br.) C(Ar(*Ph**)), 133.2 C(Ar(*Ph**)), 132.9 C(Ar(*Ph**)), 128.0 C(Ar(*Ph**)), 127.8 C(Ar(*Ph**)), 127.6 (br.) C(Ar(*Ph**)), 51.2 C(9), 48.1 C(16), 35.8 C(10), 34.7 C(14),

29.1 C(13), 25.8 C(12), 21.4 C(11), 19.4 C(Me(Ph*)), 19.3 C(Me(Ph*)), 16.9 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 16.1 C(15), 16.1 C(Me(Ph*));

Selected characteristic peaks for the minor (1*RS*, 2*RS*) diastereomer (from the mixture):

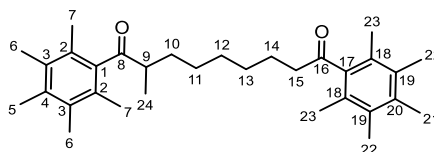
¹H NMR (600 MHz, CDCl₃) δ 3.13 (d, *J* = 6.0 Hz, 1H, C(16)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.06 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 3H, C(Ph*)*H₃*), 2.00 (br. s, 6H, 2 × C(Ph*)*H₃*), 1.93 – 1.87 (m, 1H, C(14)*H*), 1.16 (s, 3H, C(15)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 218.2 C(8), 211.1 C(17), 141.0 C(Ar(Ph*)), 139.9 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.5 C(Ar(Ph*)), 51.9 C(9), 46.3 C(16), 27.3 C(14), 24.1 C(15), 19.3 C(Me(Ph*)), 18.9 C(Me(Ph*)), 17.0 C(Me(Ph*)), 16.3 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2931, 2860, 1699, 1677, 1447, 1381, 1304, 1270, 1256, 1171, 1116, 909;

HRMS (ESI⁺) C₃₂H₄₅O₂⁺ ([M+H]⁺) requires 461.3414; found 461.3414, Δ 0.05 ppm.

168 2-Methyl-1,9-bis(2,3,4,5,6-pentamethylphenyl)nonane-1,9-dione



Hydroxy ketone **166** (87 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.600 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar and PhMe (1.2 mL) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1 → 95:5) gave the *title compound* as a colourless oil which solidified on standing (25 mg, 18%, isolated in conjunction with 62 mg, 42% **167a**).

m.p. = 65 – 67 °C;

¹H NMR (400 MHz, CDCl₃) δ 2.89 – 2.73 (m, 1H, C(9)*H*), 2.66 (t, *J* = 7.4 Hz, 2H, C(15)*H₂*), 2.24 (m, 6H, 2 × C(Ph*)*H₃*), 2.19 (s, 12H, 4 × C(Ph*)*H₃*), 2.09 (s, 12H, 4 × C(Ph*)*H₃*), 1.83 – 1.74 (m, 1H,

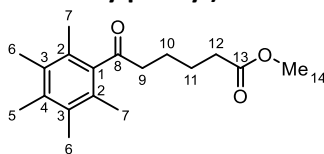
$C(10)H_AH_B$, 1.74 – 1.65 (m, 2H, $C(14)H_2$), 1.42 – 1.27 (m, 7H, $C(10)H_AH_B$, $C(11)H_2$, $C(12)H_2$, $C(13)H_2$), 1.14 (d, $J = 7.0$ Hz, 3H, $C(24)H_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 $C(8)$, 212.2 $C(16)$, 140.9 $C(Ar(Ph^*))$, 140.2 $C(Ar(Ph^*))$, 135.5 $C(Ar(Ph^*))$, 135.4 $C(Ar(Ph^*))$, 133.2 $4 \times C(Ar(Ph^*))$, 128.4 $C(Ar(Ph^*))$, 127.4 $2 \times C(Ar(Ph^*))$, 48.5 $C(9)$, 45.7 $C(15)$, 31.8 $C(10)$, 29.7 $C(12)$, 29.2 $C(13)$, 27.3 $C(11)$, 23.3 $C(14)$, 18.1 $2 \times C(Me(Ph^*))$, 17.3 $2 \times C(Me(Ph^*))$, 16.9 $C(Me(Ph^*))$, 16.8 $C(Me(Ph^*))$, 16.2 $2 \times C(Me(Ph^*))$, 16.1 $2 \times C(Me(Ph^*))$, 15.3 $C(24)$;

IR (film) ν_{max}/cm^{-1} 2929, 2856, 1692, 1456, 1382, 1304, 1261, 1121, 1090, 992, 915, 735, 644;

HRMS (ESI⁺) $C_{32}H_{47}O_2^+$ ($[M+H]^+$) requires 463.3571; found 461.3571, Δ 0.13 ppm.

169 Methyl 6-oxo-6-(2,3,4,5,6-pentamethylphenyl)hexanoate



Pentamethylbenzene (1.57 g, 10.6 mmol) and methyl adipoyl chloride (1.2 mL, 7.7 mmol) were dissolved in CH_2Cl_2 (30 mL) and the mixture was cooled to 0 °C. $AlCl_3$ (1.92 g, 14.4 mmol) was added portionwise and the reaction was allowed to warm to RT and stirred for 15 min. The crude reaction mixture was poured onto ice (approx. 50 g) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 95:5 $\rightarrow$ 85:15) gave the *title compound* as a white solid (1.74 g, 78%).

m.p. = 54 – 56 °C;

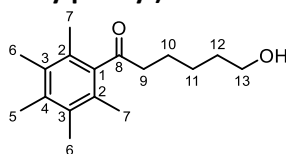
^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H, $C(14)H_3$), 2.76 – 2.64 (m, 2H, $C(9)H_2$), 2.41 – 2.29 (m, 2H, $C(12)H_2$), 2.23 (s, 3H, $C(Ph^*)H_3$), 2.18 (s, 6H, $2 \times C(Ph^*)H_3$), 2.09 (s, 6H, $2 \times C(Ph^*)H_3$), 1.84 – 1.64 (m, 4H, $C(10)H_2$ & $C(11)H_2$);

^{13}C NMR (101 MHz, CDCl_3) δ 211.6 C(8), 174.0 C(13), 140.7 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.4 $2 \times$ C(Ar(Ph*)), 51.7 C(14), 45.3 C(9), 34.1 C(12), 24.6 C(11), 22.9 C(10), 17.3 $2 \times$ C(Ph*(Me)), 16.8 C(Ph*(Me)), 16.1 $2 \times$ C(Ph*(Me));

IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2952, 1729, 1683, 1192, 1068;

HRMS (ESI^+) $\text{C}_{18}\text{H}_{27}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 291.1955; found 291.1955.

170 6-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



A solution of ester **169** (1.50 g, 5.17 mmol) in Et_2O (10 mL) was added dropwise to a stirred suspension of LiAlH_4 (196 mg, 5.17 mmol) in Et_2O (25 mL) at -78°C . The resulting mixture was stirred at -78°C for 2.5 h and then at 0°C for 10 min. The reaction was quenched with sequential dropwise addition of water (0.2 mL), aq. NaOH (15% w/v, 0.2 mL) and water (0.6 mL) at 0°C . The resulting mixture was diluted with Et_2O (10 mL) and MgSO_4 was added. The mixture was vigorously stirred for 15 min, then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 55:45 $\rightarrow$ 45:55) gave the *title compound* as a white solid (1.11 g, 82%).

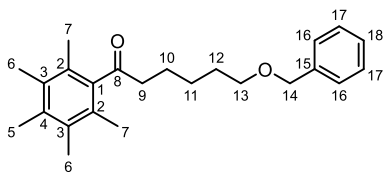
m.p. = $74 - 75^\circ\text{C}$;

^1H NMR (400 MHz, CDCl_3) δ 3.68 (td, $J = 6.5, 5.3$ Hz, 2H, C(13) H_2), 2.69 (t, $J = 7.3$ Hz, 2H, C(9) H_2), 2.23 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, $2 \times$ C(Ph*) H_3), 2.09 (s, 6H, $2 \times$ C(Ph*) H_3), 1.75 (dt, $J = 15.1, 7.3$ Hz, 2H, C(10) H_2), 1.68 – 1.59 (m, 2H, C(12) H_2), 1.55 – 1.40 (m, 2H, C(11) H_2), 1.32 (t, $J = 5.4$ Hz, 1H, OH);

^{13}C NMR (101 MHz, CDCl_3) δ 212.1 C(8), 140.9 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.4 $2 \times$ C(Ar(Ph*)), 62.9 C(13), 45.7 C(9), 32.7 C(12), 25.5 C(11), 23.1 C(10), 17.3 $2 \times$ C(Ph*(Me)), 16.8 C(Ph*(Me)), 16.1 $2 \times$ C(Ph*(Me));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3394 br., 2935, 2864, 1698, 1466, 1122, 1071, 1053;

HRMS (ESI^+) $\text{C}_{17}\text{H}_{27}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 263.2006; found 263.1993; Δ 4.94 ppm.

171 6-(Benzyloxy)-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

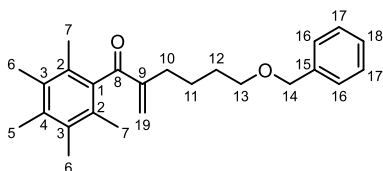
Alcohol **170** (393 mg, 1.50 mmol) and potassium iodide (25 mg, 0.15 mmol) were added to a reaction vessel. Benzyl bromide (0.28 mL, 2.25 mmol) and *N,N*-diisopropylethylamine (0.42 mL, 2.4 mmol) were added and the reaction mixture was heated at 150 °C for 2 h. After cooling to RT, the reaction mixture was diluted with EtOAc (5 mL) and water (5 mL), the layers separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5) gave the *title compound* as a colourless oil (400 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.15 (m, 5H, 5 × C(Ph)H), 4.43 (s, 2H, C(14)H₂), 3.42 (t, *J* = 6.5 Hz, 2H, C(13)H₂), 2.61 (t, *J* = 7.4 Hz, 2H, C(9)H₂), 2.16 (s, 3H, C(Ph*)H₃), 2.11 (s, 6H, 2 × C(Ph*)H₃), 2.02 (s, 6H, 2 × C(Ph*)H₃), 1.72 – 1.64 (m, 2H, C(10)H₂), 1.64 – 1.55 (m, 2H, C(12)H₂), 1.45 – 1.34 (m, 2H, C(11)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 212.1 C(8), 140.9 C(Ar), 138.8 C(Ar), 135.4 C(Ar), 133.2 C(Ar), 128.5 2 × C(Ar(Ph)), 127.8 2 × C(Ar(Ph)), 127.6 C(18), 127.4 C(Ar), 73.0 C(14), 70.3 C(13), 45.7 C(9), 29.8 C(12), 26.0 C(11), 23.2 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 2936, 2861, 1699, 1454, 1404, 1362, 1306, 1268, 1205, 1103, 736, 698;

HRMS (ESI⁺) C₂₄H₃₂NaO₂⁺ ([M+Na]⁺) requires 375.2295; found 375.2993, Δ 0.22 ppm.

172 6-(Benzyloxy)-2-methylene-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

Concentrated sulfuric acid (98%, 0.5 mL) was added to a stirred suspension of paraformaldehyde (300 mg, 10.0 mmol) and ketone **171** (704 mg, 2.00 mmol) in 1,4-dioxane (5.0 mL) and the resulting mixture was heated at 85 °C for 16 h. A further portion of paraformaldehyde (300 mg,

10.0 mmol) was added and the mixture heated at 85 °C for a further 8 h. The crude reaction mixture was concentrated *in vacuo* and the residual gum was diluted with water (20 mL) and extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4) gave the *title compound* as a colourless oil (228 mg, 31%).

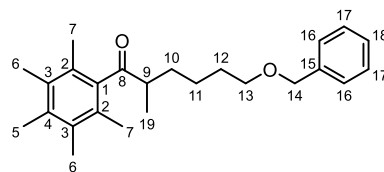
¹H NMR (600 MHz, CDCl₃) δ 7.44 – 7.29 (m, 5H, 5 × C(Ph)H), 5.87 – 5.70 (m, 1H, C(19)H_AH_B), 5.56 (s, 1H, C(19)H_AH_B), 4.55 (s, 2H, C(14)H₂), 3.55 (t, *J* = 6.4 Hz, 2H, C(13)H₂), 2.63 – 2.41 (m, 2H, C(10)H₂), 2.26 (s, 3H, C(Ph*)H₃), 2.20 (s, 6H, 2 × C(Ph*)H₃), 2.03 (s, 6H, 2 × C(Ph*)H₃), 1.79 – 1.72 (m, 2H, C(12)H₂), 1.72 – 1.63 (m, 2H, C(11)H₂);

¹³C NMR (151 MHz, CDCl₃) δ 204.0 C(8), 149.6 C(9), 138.8 C(Ar), 138.0 C(Ar), 135.3 C(Ar), 132.8 C(Ar), 129.6 C(19), 129.2 C(Ar), 128.5 2 × C(Ar(Ph)), 127.8 2 × C(Ar(Ph)), 127.7 C(18), 73.1 C(14), 70.3 C(13), 29.8 C(12), 29.7 C(10), 25.1 C(11), 17.5 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2981, 2936, 2864, 1662, 1455, 1382, 1327, 1263, 1113, 942, 736, 698;

HRMS (ESI⁺) C₂₅H₃₃O₂⁺ ([M+H]⁺) requires 365.2475; found 365.2475, Δ 0.03 ppm.

174 6-(Benzyloxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



Ketone **98** (2.04 g, 10.0 mmol), [IrCp*Cl₂]₂ (80 mg, 1.0 mol%), KOH (2.24 g, 40.0 mmol), 4-benzyloxy-1-butanol (3.5 mL, 20 mmol) and PhMe (2.5 mL) were subjected to **General Procedure E** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4 → 90:10) gave the *title compound* as a colourless oil (3.10 g, 85%).

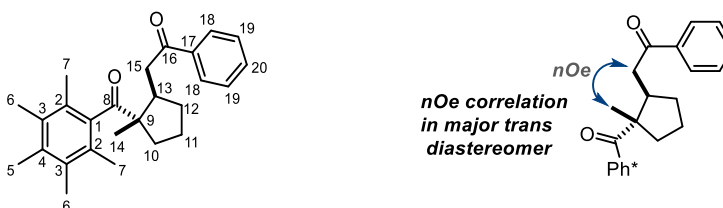
¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.26 (m, 5H, 5 × C(Ph)H), 4.49 (s, 2H, C(14)H₂), 3.46 (t, *J* = 6.4 Hz, 2H, C(13)H₂), 2.91 – 2.69 (m, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.08 (s, 6H, 2 × C(Ph*)H₃), 1.86 – 1.76 (m, 1H, C(10)H_AH_B), 1.71 – 1.47 (m, 3H, C(11)H_AH_B, C(12)H₂), 1.45 – 1.30 (m, 2H, C(10)H_AH_B, C(11)H_AH_B), 1.14 (d, *J* = 7.0 Hz, 3H, C(19)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 215.1 C(8), 140.2 C(Ar), 138.7 C(Ar), 135.5 C(Ar), 133.2 C(Ar), 128.5 $2 \times$ C(Ph), 128.4 C(Ar), 127.8 $2 \times$ C(Ph), 127.6 C(18), 73.1 C(14), 70.3 C(13), 48.5 C(9), 31.7 C(11), 30.0 C(12), 24.2 C(11), 18.1 $2 \times$ C(Me(Ph*)) , 16.8 C(Me(Ph*)), 16.2 $2 \times$ C(Me(Ph*)), 15.3 C(19);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2935, 2862, 1693, 1100, 734, 698;

HRMS (ESI⁺) $\text{C}_{25}\text{H}_{35}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 367.2632; found 367.2639, Δ 1.98 ppm.

165b 2-((1*RS*,2*SR*)-2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-1-phenylethan-1-one



Hydroxy ketone **164** (83 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and PhMe (1.2 mL) and acetophenone (70 μL , 0.60 mmol) were added. The reaction was heated at 110 $^\circ\text{C}$ for 24 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 $\rightarrow$ 96:4) gave the major diastereomer of the *title compound* as a white solid (45 mg, 40%).

A [92:8] d.r. was calculated from the crude ^1H quantitative NMR, however the minor diastereomer could not be isolated. The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

m.p. = 153 – 155 $^\circ\text{C}$;

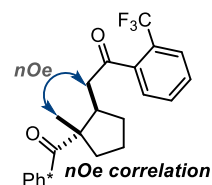
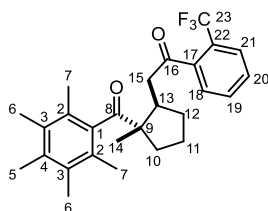
^1H NMR (600 MHz, CDCl_3) δ 7.98 – 7.91 (m, 2H, $2 \times$ C(18)*H*), 7.61 – 7.53 (m, 1H, C(20)*H*), 7.46 (t, J = 7.7 Hz, 2H, $2 \times$ C(19)*H*), 3.38 (dd, J = 16.8, 2.1 Hz, 1H, C(15)*H*_A*H*_B), 2.85 (dd, J = 16.8, 11.2 Hz, 1H, C(15)*H*_A*H*_B), 2.73 (tdd, J = 10.6, 8.1, 2.1 Hz, 1H, C(13)*H*), 2.22 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 2.16 (s, 3H, C(Ph*)*H*₃), 2.11 (ddd, J = 12.6, 8.4, 4.1 Hz, 1H, C(12)*H*_A*H*_B), 2.08 (s, 3H, C(Ph*)*H*₃), 2.02 (s, 3H, C(Ph*)*H*₃), 2.00 – 1.89 (m, 1H, C(10)*H*_A*H*_B), 1.76 – 1.58 (m, 3H, C(10)*H*_A*H*_B & C(11)*H*₂), 1.34 – 1.27 (m, 1H, C(12)*H*_A*H*_B), 1.26 (s, 3H, C(14)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 218.2 C(8), 199.6 C(16), 138.9 C(Ar(Ph*)), 137.3 C(17), 135.1 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.1 C(20), 132.9 C(Ar(Ph*)), 128.7 $2 \times$ C(19), 128.5 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 128.2 $2 \times$ C(18), 58.6 C(9), 40.9 C(13), 39.8 C(15), 37.6 C(10), 30.3 C(12), 21.9 C(11), 19.2 C(Me(Ph*)), 18.4 C(Me(Ph*)), 18.0 C(14), 16.7 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2961, 1685, 1521, 1448, 1373, 1292, 1262, 1215, 1110, 1073, 986, 925;

HRMS (ESI^+) $\text{C}_{26}\text{H}_{33}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 377.2475; found 377.2475, Δ 0.06 ppm.

165c 2-((1*RS*,2*SR*)-2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-1-(2-(trifluoromethyl)phenyl)ethan-1-one



Hydroxy ketone **164** (83 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%) and KO^tBu (135 mg, 1.20 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and $^t\text{BuOH}$ (1.2 mL) and 2'-(trifluoromethyl)acetophenone (90 μL , 0.60 mmol) were added. The reaction was heated at 115 $^\circ\text{C}$ for 24 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/PhMe, 20:80) gave the *title compound* as a white solid (41 mg, 31%, $>[95:5]$ d.r.)

The relative stereochemistry was assigned by nOe analysis.

m.p. = 158 – 160 $^\circ\text{C}$;

^1H NMR (400 MHz, CDCl_3) δ 7.80 – 7.66 (m, 1H, C(18)*H*), 7.66 – 7.49 (m, 2H, C(19)*H*, C(20)*H*), 7.45 – 7.31 (m, 1H, C(21)*H*), 3.25 (d, J = 17.0 Hz, 1H, C(15)*H*_A*H*_B), 2.82 – 2.62 (m, 2H, C(13)*H*, C(15)*H*_A*H*_B), 2.23 (s, 4H, C(Ph*)*H*₃, C(12)*H*_A*H*_B), 2.17 (s, 3H, C(Ph*)*H*₃), 2.16 (s, 3H, C(Ph*)*H*₃), 2.05 (s, 3H, C(Ph*)*H*₃), 2.03 (s, 3H, C(Ph*)*H*₃), 1.91 (dt, J = 13.0, 7.0 Hz, 1H, C(10)*H*_A*H*_B), 1.76 – 1.62 (m,

3H, C(10) H_AH_B , C(11) H_2), 1.32 (ddd, $J = 10.0, 8.5, 6.5$ Hz, 1H, C(12) H_AH_B) 1.20 – 1.12 (m, 3H, C(14) H_3);

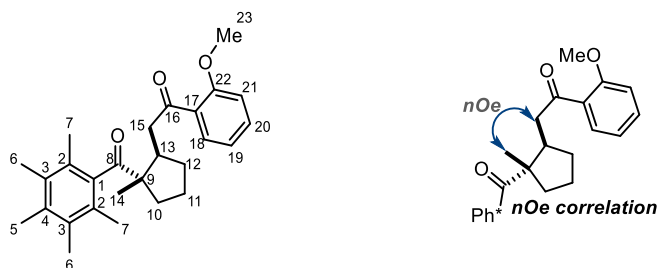
^{13}C NMR ($\{^{19}\text{F}\}$ 126 MHz, CDCl_3) δ 218.0 C(8), 203.4 C(16), 140.6 C(17), 138.7 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 133.6 C(Ar(Ph*)), 132.9 C(Ar(Ph*)), 131.9 C(20), 130.1 C(19), 128.5 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 127.1 C(21), 127.0 C(22), 126.9 C(18), 123.7 C(23), 58.4 C(9), 44.4 C(15), 40.1 C(13), 37.1 C(10), 29.9 C(12), 21.8 C(11), 19.3 C(Me(Ph*)), 18.2 C(Me(Ph*)), 17.9 C(14), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.0 C(Me(Ph*));

^{19}F NMR (377 MHz, CDCl_3) δ -58.0;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2927, 1709, 1678, 1315, 1170, 1136, 1066, 1036, 991, 914, 770, 739;

HRMS (ESI $^+$) $\text{C}_{27}\text{H}_{32}\text{F}_3\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 445.2349; found 445.2358, Δ 2.00 ppm.

165d 1-(2-Methoxyphenyl)-2-((1*RS*,2*SR*)-2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)ethan-1-one



Hydroxy ketone **164** (83 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), cataCXium $^{\text{®}}$ A (4.3 mg, 4.0 mol%) and KO^tBu (135 mg, 1.20 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar and $^t\text{BuOH}$ (1.2 mL) and 2'-methoxyacetophenone (90 μL , 0.60 mmol) were added. The reaction was heated at 115 $^{\circ}\text{C}$ for 24 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/PhMe/ Et_2O , 25:75:0 $\rightarrow$ 0:99:1) and preparative TLC (eluent PhMe/ Et_2O , 95:5) gave the *title compound* as a white solid (76 mg, 63%, $>[95:5]$ d.r.)

The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

m.p. = 92 – 95 $^{\circ}\text{C}$;

^1H NMR (600 MHz, CDCl_3) δ 7.59 (dd, $J = 7.6, 1.8$ Hz, 1H, C(18) H), 7.44 (ddd, $J = 8.9, 7.4, 1.8$ Hz, 1H, C(20) H), 7.04 – 6.89 (m, 2H, C(19) H , C(21) H), 3.92 (s, 3H, C(23) H_3), 3.39 (dd, $J = 17.5, 2.1$ Hz,

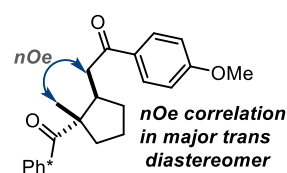
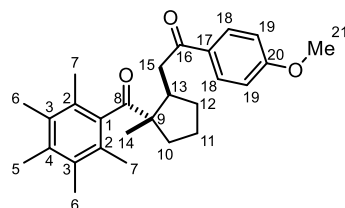
^1H , C(15) H_AH_B), 2.86 (dd, $J = 17.5, 11.3$ Hz, 1H, C(15) H_AH_B), 2.77 – 2.66 (m, 1H, C(13) H), 2.21 (s, 3H, C(Ph*) H_3), 2.16 (s, 3H, C(Ph*) H_3), 2.15 (s, 3H, C(Ph*) H_3), 2.14 – 2.08 (m, 1H, C(12) H_AH_B), 2.06 (s, 3H, C(Ph*) H_3), 2.01 (s, 3H, C(Ph*) H_3), 1.97 – 1.87 (m, 1H, C(10) H_AH_B), 1.72 – 1.59 (m, 3H, C(10) H_AH_B , C(11) H_2), 1.34 – 1.22 (m, 1H, C(12) H_AH_B), 1.18 (s, 3H, C(14) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 218.1 C(8), 202.4 C(16), 158.4 C(22), 139.0 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 133.5 C(17), 133.2 C(20), 132.7 C(Ar(Ph*)), 130.0 C(18), 129.1 C(Ar(Ph*)), 128.6 C(Ar(Ph*)), 128.4 C(Ar(Ph*)), 120.7 C(19), 111.7 C(21), 58.7 C(9), 55.7 C(23), 45.1 C(15), 41.1 C(13), 37.8 C(10), 30.3 C(12), 22.1 C(11), 19.2 C(Me(Ph*)), 18.3 C(Me(Ph*)), 17.7 C(14), 16.7 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2943, 2874, 1677, 1598, 1465, 1437, 1245, 758;

HRMS (ESI $^+$) $\text{C}_{27}\text{H}_{34}\text{NaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 429.2400; found 429.2403, Δ 0.65 ppm.

165e 1-(4-Methoxyphenyl)-2-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)ethan-1-one



Hydroxy ketone **164** (83 mg, 0.30 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), cataCXium $^{\text{®}}$ A (4.3 mg, 4.0 mol%) and KOH (67 mg, 1.2 mmol) and 4'-methoxyacetophenone (90 mg, 0.60 mmol) were added to 2 – 5 mL microwave vial. The vial was sealed, purged with Ar and PhMe (1.2 mL) was added. The reaction was heated at 110 $^{\circ}\text{C}$ for 24 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent PhMe/ Et_2O , 99.5:0.5 $\rightarrow$ 99:1) gave the *title compound* as an off-white solid (65 mg, 54%, [90:10] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by nOe analysis.

m.p. = 127 – 129 $^{\circ}\text{C}$;

Major (RS,SR) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 7.95 – 7.89 (m, 2H, 2 × C(18)H), 6.98 – 6.87 (m, 2H, 2 × C(19)H), 3.88 (s, 3H, C(21)H₃), 3.32 (dd, *J* = 16.2, 1.9 Hz, 1H, C(15)H_AH_B), 2.82 – 2.74 (m, 1H, C(15)H_AH_B), 2.74 – 2.67 (m, 1H, C(14)H), 2.22 (s, 3H, C(Ph*)H₃), 2.17 (s, 3H, C(Ph*)H₃), 2.16 (s, 3H, C(Ph*)H₃), 2.13 – 2.04 (m, 4H, C(12)H_AH_B, C(Ph*)H₃), 2.02 (s, 3H, C(Ph*)H₃), 1.98 – 1.89 (m, 1H, C(10)H_AH_B), 1.76 – 1.59 (m, 3H, C(10)H_AH_B, C(11)H₂), 1.35 – 1.26 (m, 1H, C(12)H_AH_B), 1.25 (s, 3H, C(14)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 218.4 C(8), 198.2 C(16), 163.5 C(20), 139.0 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 132.8 C(Ar(Ph*)), 130.5 2 × C(18), 130.4 C(17), 128.5 C(Ar(Ph*)), 128.3 C(Ar(Ph*)), 113.8 2 × C(19), 58.7 C(9), 55.6 C(21), 41.1 C(13), 39.5 C(15), 37.7 C(10), 30.3 C(12), 21.9 C(11), 19.2 C(Me(Ph*)), 18.5 C(Me(Ph*)), 18.1 C(14), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

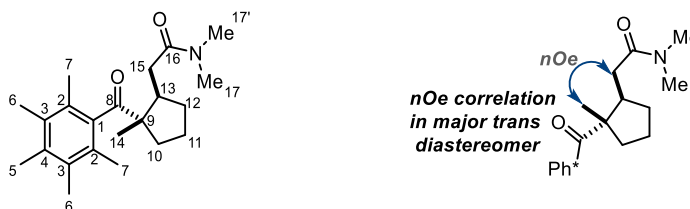
Selected characteristic peaks for the minor (SR,SR) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 8.02 (dd, *J* = 9.0, 2.6 Hz, 2H, 2 × C(18)H), 3.15 (dd, *J* = 16.9, 2.8 Hz, 1H, C(15)H_AH_B), 2.62 – 2.55 (m, 1H, C(13)H);

¹³C NMR (151 MHz, CDCl₃) δ 219.0 C(8), 199.0 C(16), 140.6, 134.9, 133.3, 129.1, 128.8, 58.8 C(9), 46.8 C(13), 40.0 C(15), 39.4, 31.6, 30.5, 24.8, 21.6, 18.3, 18.3, 16.8, 16.3, 16.0;

IR (film) ν_{max} /cm⁻¹ 2961, 1677, 1601, 1261, 1172;

HRMS (ESI⁺) C₂₇H₃₅O₃⁺ ([M+H]⁺) requires 407.2851; found 407.2851, Δ 0.06 ppm.

165f *N,N*-Dimethyl-2-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)acetamide

Hydroxy ketone **164** (83 mg, 0.30 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and *N,N*-dimethylacetamide (56 μL, 0.60 mmol) and PhMe (1.2 mL) were added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through

a silica pad (EtOAc elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 85:15 → 70:30) gave the *title compound* as a white solid (25 mg, 25%, [94:6] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by nOe analysis.

m.p. = 140 – 143 °C;

Major (1*RS*, 2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 3.00 (s, 3H, C(17)*H*₃), 2.93 (s, 3H, C(17')*H*₃), 2.70 (dd, *J* = 15.6, 2.3 Hz, 1H, C(15)*H_AH_B*), 2.61 (tdd, *J* = 10.7, 8.3, 2.4 Hz, 1H, C(13)*H*), 2.21 (s, 3H, C(Ph*)*H*₃), 2.19 – 2.10 (m, 8H, C(12)*H_AH_B*, C(15)*H_AH_B*, 2 × C(Ph*)*H*₃), 2.08 – 2.02 (m, 6H, 2 × C(Ph*)*H*₃), 1.94 – 1.81 (m, 1H, C(10)*H_AH_B*), 1.69 – 1.55 (m, 3H, C(10)*H_AH_B*, C(11)*H*₂), 1.34 – 1.22 (m, 1H, C(12)*H_AH_B*), 1.17 (s, 3H, C(14)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 218.4 C(8), 172.2 C(16), 139.0 C(Ar(Ph*)), 135.0 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 132.7 C(Ar(Ph*)), 128.4 C(Ar(Ph*)), 128.4 C(Ar(Ph*)), 58.5 C(9), 41.7 C(13), 37.6 C(10), 37.3 C(17), 35.5 C(17'), 34.2 C(15), 30.5 C(12), 21.8 C(11), 19.2 C(Me(Ph*)), 18.5 C(Me(Ph*)), 17.8 C(14), 16.7 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

Selected characteristic peaks for the minor (1*SR*, 2*SR*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 3.07 (s, 3H, C(17)*H*₃), 2.96 (s, 3H, C(17')*H*₃), 2.53 (dd, *J* = 15.8, 3.1 Hz, 1H, C(15)*H_AH_B*), 2.51 – 2.45 (m, 1H, C(13)*H*), 1.12 (s, 3H, C(14)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 219.1 C(8), 172.9 C(16), 140.6 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 132.8 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 127.5 C(Ar(Ph*)), 58.7 C(9), 47.7 C(13), 39.5 C(10), 34.7 C(15), 31.5 C(12), 24.7 C(14), 21.6 C(11), 18.3 C(Me(Ph*)), 18.2 C(Me(Ph*)), 16.8 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2939, 1676, 1650, 1458, 1397, 1302, 1262, 1141, 1110, 924;

HRMS (ESI⁺) C₂₂H₃₄NO₂⁺ ([M+H]⁺) requires 344.2584; found 344.2585, Δ 0.21 ppm.

N.B. the labels ' and '' refer to peaks which are split due to restricted rotation about the amide bond.

165g ((1*SR*,2*SR*)-1-Methyl-2-(1-nitroethyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), Ru(PPh₃)(CO)H₂ (7.0 mg, 2.5 mol%), and XantPhos (4.3 mg, 2.5 mol%) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and PhMe (1.2 mL), nitroethane (43 µL, 0.60 mmol), crotononitrile (49 µL, 0.60 mmol), piperidine (30 µL, 0.30 mmol), and acetic acid (17 µL, 0.30 mmol) were added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4) gave separable diastereomers of the *title compound* as a solid glass (16 mg, 16%, [1:1] d.r.) Only the major “*trans*” diastereomers were isolated, the relative stereochemistry between the cyclopentane substituents was assigned by nOe analysis. The stereochemistry at the exocyclic centre could not be assigned.

First diastereomer:

¹H NMR (600 MHz, CDCl₃) δ 4.81 (p, *J* = 6.8 Hz, 1H, C(15)*H*), 2.77 (ddd, *J* = 9.9, 8.1, 6.8 Hz, 1H, C(13)*H*), 2.24 (s, 3H, C(Ph*)*H*₃), 2.19 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 3H, C(Ph*)*H*₃), 2.12 (s, 3H, C(Ph*)*H*₃), 2.08 (s, 3H, C(Ph*)*H*₃), 2.08 – 2.00 (m, 1H, C(10)*H*_A*H*_B), 1.96 – 1.88 (m, 1H, C(12)*H*_A*H*_B), 1.72 – 1.63 (m, 5H, C(11)*H*_A*H*_B, C(12)*H*_A*H*_B, C(16)*H*₃ (obscured d)), 1.60 – 1.50 (m, 2H, C(10)*H*_A*H*_B, C(11)*H*_A*H*_B), 1.20 (s, 3H, C(13)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.2 C(8), 139.0 C(Ar(Ph*)), 135.2 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 127.4 C(Ar(Ph*)), 85.6 C(15), 58.4 C(9), 48.1 C(13), 39.9 C(10), 27.4 C(12), 21.8 C(11), 20.4 C(16), 19.3 C(Me(Ph*)), 19.2 C(Me(Ph*)), 19.1 C(14), 16.6 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3011, 2942, 1684, 1551;

HRMS (ESI⁺) C₂₀H₂₉NNaO₃⁺ ([M+Na]⁺) requires 354.2040; found 354.2041, Δ 0.39 ppm.

Second diastereomer:

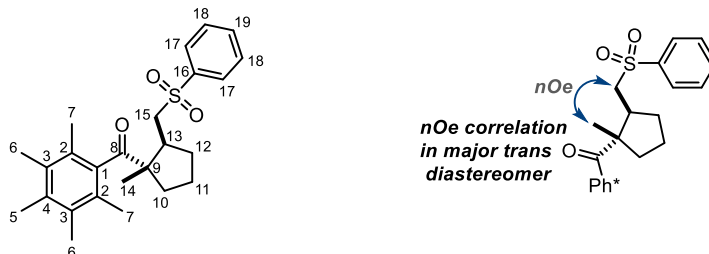
¹H NMR (600 MHz, CDCl₃) δ 4.91 (qd, *J* = 6.8, 4.8 Hz, 1H, C(15)*H*), 3.00 (ddd, *J* = 9.8, 8.0, 4.7 Hz, 1H, C(13)*H*), 2.22 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 2.16 (s, 3H, C(Ph*)*H*₃), 2.08 (s, 3H, C(Ph*)*H*₃), 2.05 (s, 3H, C(Ph*)*H*₃), 2.04 – 1.95 (m, 2H, C(10)*H*_A*H*_B, C(12)*H*_A*H*_B), 1.72 – 1.58 (m, 6H, C(11)*H*₂, C(12)*H*₂, C(16)*H*₃), 1.58 – 1.49 (m, 1H, C(10)*H*_A*H*_B), 1.22 (s, 3H, C(14)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 216.7 C(8), 138.9 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 128.3 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 83.1 C(15), 58.2 C(9), 47.2 C(13), 38.5 C(10), 25.6 C(12), 21.6 C(11), 20.1 C(14), 19.3 C(Me(Ph*)), 18.8 C(Me(Ph*)), 18.1 C(16), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 2927, 1685, 1551, 1507, 1457, 1389, 1359, 1302, 988;

HRMS (ESI⁺) C₂₀H₃₀NO₃⁺ ([M+H]⁺) requires 322.2220; found 322.2220, Δ 0.08 ppm.

165h (1-Methyl-2-((phenylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* reverse phase flash column chromatography (eluent water/MeCN 70:30 → MeCN) gave the *title compound* as a white solid (99 mg, 80%, [93:7] d.r.)*

*Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 164 – 166 °C;

¹H NMR (500 MHz, CDCl₃) δ 7.92 – 7.86 (m, 2H, 2 × C(17)H), 7.70 – 7.62 (m, 1H, C(19)H), 7.60 – 7.53 (m, 2H, 2 × C(18)H), 3.56 (dd, *J* = 13.8, 2.1 Hz, 1H, C(15)H_AH_B), 2.99 (dd, *J* = 13.8, 11.9 Hz, 1H, C(15)H_AH_B), 2.62 – 2.52 (m, 1H, C(13)H), 2.35 – 2.25 (m, 1H, C(12)H_AH_B), 2.22 (s, 3H, C(Ph*)H₃), 2.14 (s, 6H, 2 × C(Ph*)H₃), 2.01 (s, 3H, C(Ph*)H₃), 1.92 (s, 3H, C(Ph*)H₃), 1.90 – 1.76 (m, 1H, C(10)H_AH_B), 1.75 – 1.53 (m, 4H, C(10)H_AH_B, C(11)H₂, C(12)H_AH_B), 1.12 (s, 3H, C(14)H₃);

¹³C NMR (126 MHz, CDCl₃) δ 217.4 C(8), 140.3 C(16), 138.7 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.7 C(19), 133.5 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 129.4 2 × C(18), 128.1 C(Ar(Ph*)), 128.0 2 × C(17), 127.9 C(Ar(Ph*)), 58.6 C(9), 58.1 C(15), 39.5 C(13), 36.7 C(10), 29.6 C(12), 22.1 C(11), 19.2 C(Me(Ph*)), 18.5 C(Me(Ph*)), 18.4 C(14), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2926, 1678, 1447, 1306, 1147, 756;

HRMS (ESI⁺) C₂₅H₃₂NaO₃S⁺ ([M+Na]⁺) requires 435.1964; found 435.1975, Δ 2.47 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

m.p. = 138 – 140 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.97 – 7.90 (m, 2H, 2 × C(17)H), 7.69 – 7.63 (m, 1H, C(19)H), 7.60 – 7.54 (m, 2H, 2 × C(18)H), 3.65 – 3.32 (m, 2H, C(15)H₂), 2.34 (dtd, *J* = 10.3, 7.5, 2.4 Hz, 1H, C(13)H), 2.21 (s, 3H, C(Ph*)H₃), 2.19 – 2.15 (m, 4H, C(10)H_AH_B, C(Ph*)H₃), 2.14 (s, 3H, C(Ph*)H₃), 2.12 – 2.04 (m, 1H, C(12)H_AH_B), 2.04 – 1.98 (m, 4H, C(12)H_AH_B, C(Ph*)H₃), 1.94 (s, 3H, C(Ph*)H₃), 1.80 – 1.70 (m, 2H, C(11)H₂), 1.56 – 1.50 (m, 1H, C(10)H_AH_B), 1.12 (s, 3H, C(14)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.6 C(8), 140.3 C(16), 139.4 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.7 C(19), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 129.4 2 × C(18), 128.1 2 × C(17), 127.9 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 60.2 C(9), 58.5 C(15), 45.0 C(13), 39.0 C(10), 31.0 C(12), 24.2 C(14), 22.0 C(11), 18.7 C(Me(Ph*)), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2967, 1679, 1448, 1306, 1150, 1087, 917, 738;

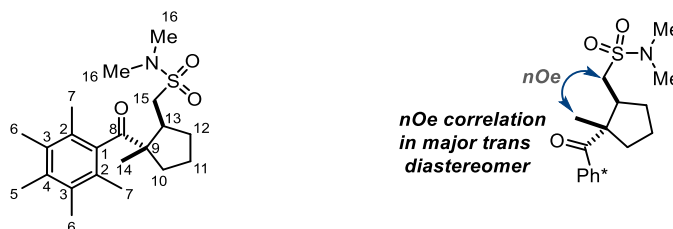
HRMS (ESI⁺) C₂₅H₃₃O₃S⁺ ([M+H]⁺) requires 413.2145; found 413.2148, Δ 0.73 ppm.

Scale-up Procedure: Hydroxy Ketone **164** (1.10 g, 4.00 mmol), methyl phenyl sulfone (1.25 g, 8.00 mmol), **Mn Cat01** (40 mg, 2.0 mol%) and KO^tBu (898 mg, 8.00 mmol) were added to a 125 mL pressure tube. The vial was evacuated and back-filled with Ar (3 times), ^tBuOH (degassed with Ar (balloon) (16 mL)) was added and the pressure tube was sealed under an Ar atmosphere. The reaction was heated at 115 °C for 16 h, cooled to RT, filtered through a silica pad (Et₂O/CH₂Cl₂ elution) and concentrated *in vacuo*. Purification *via* reverse phase flash column chromatography (eluent water: MeCN 70:30 → MeCN) gave the *title compound* as a white solid (1.20 g, 73%, [94:6] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The spectroscopic data was identical to that given above.

165i *N,N*-Dimethyl-1-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)methanesulfonamide



Hydroxy ketone **164** (83 mg, 0.30 mmol), *N,N*-dimethylmethanesulfonamide (74 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 80:20 → 72:28) gave separable diastereomers of the *title compound* as a white solid (93 mg, 82%, [91:9] d.r.)

The relative stereochemistry was assigned by *nOe* and X-ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 138 – 140 °C;

¹H NMR (600 MHz, CDCl₃) δ 3.33 (dd, *J* = 13.3, 2.2 Hz, 1H, C(15)*H_AH_B*), 2.85 (s, 6H, 2 × C(16)*H₃*), 2.72 (dd, *J* = 13.3, 11.9 Hz, 1H, C(15)*H_AH_B*), 2.61 (dddd, *J* = 12.1, 10.2, 8.2, 2.2 Hz, 1H, C(13)*H*), 2.30 (dtd, *J* = 12.8, 8.4, 3.8 Hz, 1H, C(12)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.17

(s, 3H, C(Ph*)H₃), 2.12 (s, 3H, C(Ph*)H₃), 2.06 (s, 3H, C(Ph*)H₃), 1.93 – 1.82 (m, 1H, C(10)H_AH_B), 1.75 – 1.51 (m, 4H, C(10)H_AH_B, C(11)H₂, C(12)H_AH_B), 1.16 (s, 3H, C(14)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.6 C(8), 138.7 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.6 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 58.8 C(9), 48.7 C(15), 39.9 C(13), 37.5 2 × C(16), 36.9 C(10), 29.7 C(12), 21.9 C(11), 19.3 C(Me(Ph*)), 18.6 C(Me(Ph*)), 18.2 C(14), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2967, 1679, 1461, 1357, 1333, 1260, 1218, 1150, 1094, 960, 926;

HRMS (ESI⁺) C₂₁H₃₃NaNO₃S⁺ ([M+Na]⁺) requires 402.2073; found 402.2061, Δ 2.97 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

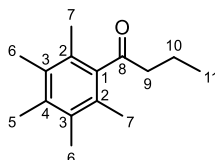
¹H NMR (600 MHz, CDCl₃) δ 3.26 (dd, *J* = 14.0, 2.1 Hz, 1H, C(15)H_AH_B), 3.17 (dd, *J* = 13.9, 11.2 Hz, 1H, C(15)H_AH_B), 2.88 (s, 6H, 2 × C(16)H₃), 2.47 – 2.34 (m, 1H, C(13)H), 2.27 – 2.19 (m, 5H, C(10)H_AH_B, C(12)H_AH_B, C(Ph*)H₃), 2.18 (s, 3H, C(Ph*)H₃), 2.17 (s, 3H, C(Ph*)H₃), 2.13 (ddt, *J* = 13.6, 9.4, 5.9 Hz, 1H, C(12)H_AH_B), 2.07 (s, 3H, C(Ph*)H₃), 2.06 (s, 3H, C(Ph*)H₃), 1.88 – 1.71 (m, 2H, C(11)H₂), 1.62 (ddd, *J* = 13.2, 8.6, 6.7 Hz, 1H, C(10)H_AH_B), 1.18 (s, 3H, C(14)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 218.4 C(8), 139.7 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 127.6 C(Ar(Ph*)), 59.9 C(9), 49.3 C(15), 45.4 C(13), 39.2 C(10), 37.6 2 × C(16), 31.0 C(12), 24.6 C(14), 21.9 C(11), 18.5 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2959, 1679, 1650, 1461, 1333, 1266, 1219, 1151, 1097, 960, 923, 898;

HRMS (ESI⁺) C₂₁H₃₄NO₃S⁺ ([M+H]⁺) requires 380.2254; found 380.2244, Δ 2.71 ppm.

S14 1-(2,3,4,5,6-Pentamethylphenyl)butan-1-one



AlCl₃ (5.43 g, 40.8 mmol) was added portion-wise (over 5 min) to a stirred solution of butyryl chloride (3.94 g, 38.0 mmol) and pentamethylbenzene (5.00 g, 33.8 mmol) in CH₂Cl₂ (160 mL) at 0 °C. The reaction was allowed to warm to RT and stirred for 2 h and was then poured onto ice

(approx. 200 g) and diluted with sat. aq. NaHCO_3 (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with sat. aq. NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane $\rightarrow$ pentane/ Et_2O , 96:4) gave the *title compound* as a white solid (5.95 g, 80%).

m.p. = 76 – 78 °C;

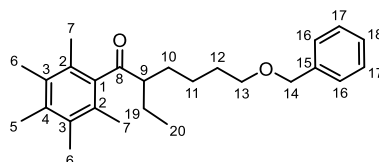
^1H NMR (400 MHz, CDCl_3) δ 2.66 (t, J = 7.3 Hz, 2H, C(9) H_2), 2.23 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, $2 \times$ C(Ph*) H_3), 2.10 (s, 6H, $2 \times$ C(Ph*) H_3), 1.75 (h, J = 7.4 Hz, 2H, C(10) H_2), 1.01 (t, J = 7.4 Hz, 3H, C(11) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 212.2 C(8), 140.9 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 127.5 $2 \times$ C(Ar(Ph*)), 47.7 C(9), 17.3 $2 \times$ C(Me(Ph*)), 16.8 C(10) & C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*)), 13.9 C(11);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 1700, 1456, 1133, 913, 742;

HRMS (ESI $^+$) $\text{C}_{15}\text{H}_{23}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 219.1743; found 219.1744, Δ 0.09 ppm.

S15 6-(Benzyloxy)-2-ethyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



Ketone **S14** (1.65 g, 7.50 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (50 mg, 1.0 mol%), dppBz (67 mg, 2.0 mol%) and KOH (1.68 g, 30.0 mmol) were added to a 10 – 20 mL microwave vial. The vial was sealed and purged with Ar (balloon) for 5 min. PhMe (1.9 mL, 4 M) and 4-benzyloxy-butan-1-ol (2.91 g, 15.0 mmol) were added. The reaction was heated at 110 °C for 18 h, cooled to RT, filtered through a silica plug (elution with Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 96:4) gave the *title compound* as a colourless oil (2.22 g, 78%).

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.26 (m, 5H, $5 \times$ C(Ph) H), 4.48 (s, 2H, C(14) H_2), 3.45 (t, J = 6.6 Hz, 2H, C(13) H_2), 2.68 (p, J = 6.2 Hz, 1H, C(9) H), 2.23 (s, 3H, C(Ph*) H_3), 2.17 (s, 6H,

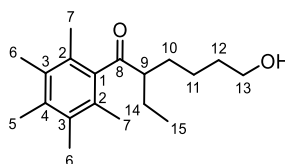
$2 \times \text{C(Ph}^*)\text{H}_3$), 2.09 (s, 6H, $2 \times \text{C(Ph}^*)\text{H}_3$), 1.83 – 1.66 (m, 2H, $\text{C(10)}\text{H}_\text{A}\text{H}_\text{B}$, $\text{C(19)}\text{H}_\text{A}\text{H}_\text{B}$), 1.66 – 1.57 (m, 2H, $\text{C(12)}\text{H}_2$), 1.54 – 1.40 (m, 4H, $\text{C(10)}\text{H}_\text{A}\text{H}_\text{B}$, $\text{C(11)}\text{H}_2$, $\text{C(19)}\text{H}_\text{A}\text{H}_\text{B}$), 0.94 (t, $J = 7.4$ Hz, 3H, $\text{C(20)}\text{H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 214.0 C(8) , 140.1 C(Ar) , 138.8 C(Ar) , 135.5 C(Ar) , 133.2 C(Ar) , 128.6 C(Ar) , 128.5 $2 \times \text{C(Ph)}$, 127.8 $2 \times \text{C(Ph)}$, 127.6 C(18) , 73.1 C(14) , 70.3 C(13) , 54.9 C(9) , 30.2 C(12) , 28.6 C(19) , 24.0 C(10) , 22.2 C(11) , 18.0 $2 \times \text{C(Me(Ph}^*))}$, 16.9 $\text{C(Me(Ph}^*))}$, 16.2 $2 \times \text{C(Me(Ph}^*))}$, 11.9 C(20) ;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2937, 2862, 1691, 1454, 1100, 1028, 996, 910;

HRMS (ESI^+) $\text{C}_{26}\text{H}_{37}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 381.2788; found 318.2786, Δ 0.64 ppm.

S16 2-Ethyl-6-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



Benzyl ether **S15** (1.94 g, 5.11 mmol) was subjected to **General Procedure F** in MeOH (55 mL) with Pd (10% on carbon) (194 mg, 10 wt%) for 1 h. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 60:40 $\rightarrow$ 50:50) gave the *title compound* as a white solid (1.36 g, 92%).

m.p. = 55 – 57 °C;

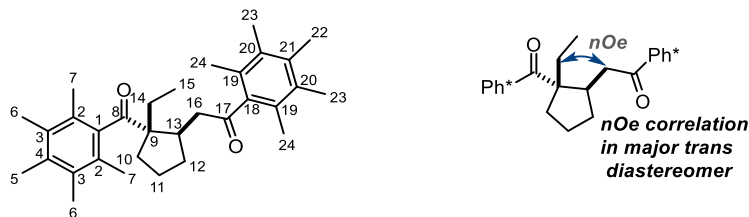
^1H NMR (400 MHz, CDCl_3) δ 3.65 (t, $J = 6.5$ Hz, 2H, $\text{C(13)}\text{H}_2$), 2.73 – 2.56 (m, 1H, $\text{C(9)}\text{H}$), 2.23 (s, 3H, $\text{C(Ph}^*)\text{H}_3$), 2.18 (s, 6H, $2 \times \text{C(Ph}^*)\text{H}_3$), 2.09 (s, 6H, $2 \times \text{C(Ph}^*)\text{H}_3$), 1.82 – 1.66 (m, 2H, $\text{C(10)}\text{H}_\text{A}\text{H}_\text{B}$, $\text{C(14)}\text{H}_\text{A}\text{H}_\text{B}$), 1.63 – 1.37 (m, 6H, $\text{C(10)}\text{H}_\text{A}\text{H}_\text{B}$, $\text{C(11)}\text{H}_2$, $\text{C(12)}\text{H}_2$, $\text{C(14)}\text{H}_\text{A}\text{H}_\text{B}$), 0.95 (t, $J = 7.4$ Hz, 3H, $\text{C(15)}\text{H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 214.1 C(8) , 140.0 $\text{C(Ar(Ph}^*))}$, 135.6 $\text{C(Ar(Ph}^*))}$, 133.2 $2 \times \text{C(Ar(Ph}^*))}$, 128.6 $2 \times \text{C(Ar(Ph}^*))}$, 62.8 C(13) , 54.9 C(9) , 33.1 C(10) , 28.3 C(14) , 23.5 C(12) , 22.3 C(11) , 18.0 $2 \times \text{C(Me(Ph}^*))}$, 16.9 $\text{C(Me(Ph}^*))}$, 16.2 $2 \times \text{C(Me(Ph}^*))}$, 12.0 C(15) ;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3400, 2936, 2873, 1693, 1458, 1383, 1300, 1263, 1071, 997;

HRMS (ESI^+) $\text{C}_{19}\text{H}_{30}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 291.2319; found 291.2318, Δ 0.26 ppm.

165j 2-(2-Ethyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



Hydroxy ketone **S16** (83 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.60 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), PAd₃ (5.2 mg, 4.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and PhMe (1.2 mL) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 92:8) gave the *title compound* as a white solid (68 mg, 49%, [95:5] d.r.*, isolated in conjunction with 12.6 mg, 9% **175**).

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The spectroscopic data were collected on the mixture. The relative stereochemistry was assigned by nOe analysis.

m.p. = 208 – 210 °C;

Major (1*RS*,2*SR*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 2.85 – 2.79 (dd, *J* = 19.0, 1.6 Hz, 1H, C(16)*H_AH_B*), 2.79 – 2.71 (m, 1H, C(13)*H*), 2.70 – 2.59 (dd, *J* = 19.0, 11.4 Hz, 1H, C(16)*H_AH_B*), 2.28 (ddt, *J* = 12.3, 8.5, 4.2 Hz, 1H, C(12)*H_AH_B*), 2.23 (s, 6H, 2 × C(Ph*)*H₃*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.18 (s, 6H, 2 × C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.08 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 4H, C(Ph*)*H₃*, C(10)*H_AH_B*), 2.02 (br. s, 7H, 2 × C(Ph*)*H₃*, C(14)*H_AH_B*, overlapped), 1.89 – 1.75 (m, 1H, C(10)*H_AH_B*), 1.68 – 1.60 (m, 2H, C(11)*H₂*), 1.30 (tdd, *J* = 15.0, 10.9, 5.7 Hz, 1H, C(12)*H_AH_B*), 1.19 (dq, *J* = 14.6, 7.5 Hz, 1H, C(14)*H_AH_B*), 0.95 (t, *J* = 7.5 Hz, 3H, C(15)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 215.9 C(8), 210.5 C(17), 140.8 C(Ar(Ph*)), 137.8 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 132.6 C(Ar(Ph*)), 129.5, C(Ar(Ph*)), 129.0 C(Ar(Ph*)), 127.3 2 × C(Ar(Ph*)), 62.9 C(9), 46.6 C(16), 40.1 C(13), 31.7 C(10),

30.3 C(12), 22.2 C(11), 21.6 C(14), 18.9 C(Me(Ph*)), 18.2 C(Me(Ph*)), 17.0 (br.) 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.5, C(Me(Ph*)) 16.1 2 × C(Me(Ph*)), 15.9 C(Me(Ph*)), 9.5 C(15);

Selected characteristic peaks for the minor (1*SR*,2*SR*) diastereomer (from the mixture):

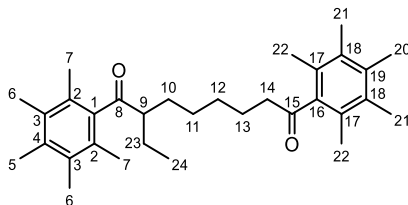
¹H NMR (600 MHz, CDCl₃) δ 3.06 – 3.02 (m, 2H, C(16)H₂), 2.21 (s, 3H, C(Ph*)H₃), 2.12 (s, 3H, C(Ph*)H₃), 0.76 (t, *J* = 7.4 Hz, 3H, C(15)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 218.2 C(8), 211.7 C(17), 141.0 C(Ar(Ph*)), 140.5 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 132.9 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 127.4 C(Ar(Ph*)), 125.7 C(Ar(Ph*)), 62.1 C(9), 47.5 C(16), 41.4 C(13), 35.0, 31.9, 29.8, 27.9, 22.4, 17.2, 16.3, 8.7 C(15);

IR (film) ν_{max}/cm⁻¹ 2927, 2877, 1701, 1674, 1451, 1408, 1383, 1302, 1260, 1113, 1068, 996, 911;

HRMS (ESI⁺) C₃₂H₄₅O₂⁺ ([M+H]⁺) requires 461.3414; found 461.3413, Δ 0.15 ppm.

175 2-Ethyl-1,8-bis(2,3,4,5,6-pentamethylphenyl)octane-1,8-dione



Hydroxy ketone **S16** (83 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.600 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%), and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and PhMe (1.2 mL) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 92:8) gave the *title compound* as a white solid (77 mg, 55%, isolated in conjunction with 38% **165j**).

m.p. = 110 – 112 °C;

¹H NMR (400 MHz, CDCl₃) δ 2.73 – 2.62 (m, 3H, C(9)H, C(14)H₂), 2.23 (s, 6H, 2 × C(Ph*)H₃), 2.18 (s, 12H, 4 × C(Ph*)H₃), 2.10 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.81 – 1.64 (m, 4H,

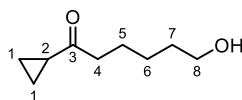
$C(10)H_AH_B$, $C(13)H_2$, $C(23)H_AH_B$, 1.55 – 1.44 (m, 2H, $C(10)H_AH_B$, $C(23)H_AH_B$), 1.39 (m, 4H, $C(11)H_2$, $C(12)H_2$), 0.95 (t, $J = 7.4$ Hz, 3H, $C(24)H_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.1 C(8), 212.2 C(15), 140.9 C(Ar(Ph*)), 140.1 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 4 $\times$ C(Ar(Ph*)), 128.6 2 $\times$ C(Ar(Ph*)), 127.4 2 $\times$ C(Ar(Ph*)), 54.9 C(9), 45.7 C(14), 29.6 C(12), 28.6 C(10), 27.2 C(11), 23.2 C(13), 22.2 C(23), 18.0 2 $\times$ C(Me(Ph*)), 17.3 2 $\times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 2 $\times$ C(Me(Ph*)), 16.1 2 $\times$ C(Me(Ph*)), 11.9 C(24);

IR (film) ν_{max}/cm^{-1} 2934, 2863, 1693, 1573, 1453;

HRMS (ESI⁺) $C_{32}H_{47}O_2^+$ ($[M+H]^+$) requires 463.3571; found 463.3587, Δ 3.50 ppm.

S17 1-Cyclopropyl-6-hydroxyhexan-1-one



Mg turnings (2.92 g, 120 mmol) were heated with stirring under vacuum in a two-necked flask for 5 min and allowed to cool to RT. THF (10 mL) and a single iodine crystal were added and bromocyclopropane (4.8 mL, 60 mmol) was added slowly. The mixture was refluxed for a further 5 min, cooled to RT and diluted with THF (20 mL). ϵ -Caprolactone (1.11 mL, 10.0 mmol), *N,O*-dimethylhydroxyamine hydrochloride (1.17 g, 12.0 mmol) and THF (70 mL) were added to a round-bottomed flask and cooled to -20 °C. The cooled Grignard reagent was added slowly *via* cannula and the reaction mixture was allowed to warm to RT overnight (16 h). HCl (30 mL) was added slowly and the reaction was stirred at RT for 2 h. The crude reaction mixture was concentrated *in vacuo* and then diluted with Et_2O (150 mL) and water (10 mL). The layers were separated and the organic layer washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ $EtOAc$, 70:30 $\rightarrow$ 60:40) gave the *title compound* as a colourless oil (884 mg, 57%).

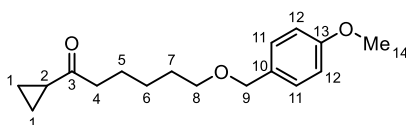
¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, *J* = 6.5 Hz, 2H, C(8)H₂), 2.56 (t, *J* = 7.3 Hz, 2H, C(4)H₂), 2.02 – 1.81 (m, 1H, C(2)H), 1.73 – 1.51 (m, 4H, C(5)H₂, C(7)H₂), 1.48 (s, 1H, OH), 1.44 – 1.30 (m, 2H, C(6)H₂), 1.07 – 0.95 (m, 2H, 2 × C(1)H_AH_B), 0.90 – 0.77 (m, 2H, 2 × C(1)H_AH_B);

¹³C NMR (101 MHz, CDCl₃) δ 211.1 C(3), 62.7 C(8), 43.3 C(4), 32.4 C(5), 25.4 C(6), 23.6 C(7), 20.4 C(2), 10.6 2 × C(1);

IR (film) ν_{max} /cm⁻¹ 3467, 3010, 2938, 2867, 1697, 1392, 1324, 1174, 1143, 1089, 1063, 1016;

HRMS (ESI⁺) C₉H₁₇O₂⁺ ([M+H]⁺) requires 157.1223; found 157.1222, Δ 0.65 ppm.

S18 1-Cyclopropyl-6-((4-methoxybenzyl)oxy)hexan-1-one



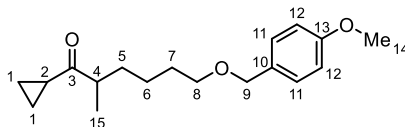
Alcohol **S17** (873 mg, 5.60 mmol), PMBCl (1.2 mL, 8.4 mmol), KI (93 mg, 0.56 mmol) and DIPEA (1.6 mL, 9.0 mmol) were added to a round-bottomed flask and the mixture was heated at 150 °C for 3 h. The mixture was cooled to RT and diluted with EtOAc (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed sequentially with 1 M HCl and brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 90:10 → 88:12) gave the *title compound* as a colourless oil (1.34 g, 87%).

¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.16 (m, 2H, 2 × C(11)H), 7.04 – 6.80 (m, 2H, 2 × C(12)H), 4.42 (s, 2H, C(9)H₂), 3.80 (s, 3H, C(14)H₃), 3.44 (t, *J* = 6.5 Hz, 2H, C(8)H₂), 2.60 – 2.46 (m, 2H, C(4)H₂), 1.90 (tt, *J* = 7.8, 4.6 Hz, 1H, C(2)H), 1.70 – 1.48 (m, 4H, C(5)H₂, C(7)H₂), 1.46 – 1.26 (m, 2H, C(6)H₂), 1.02 – 0.94 (m, 2H, 2 × C(1)H_AH_B), 0.89 – 0.74 (m, 2H, 2 × C(1)H_AH_B);

¹³C NMR (101 MHz, CDCl₃) δ 211.2 C(3), 159.3 C(13), 130.9 C(10), 129.4 2 × C(11), 113.9 2 × C(12), 72.7 C(9), 70.0 C(8), 55.4 C(14), 43.5 C(4), 29.7 C(7), 26.0 C(6), 23.9 C(5), 20.5 C(2), 10.7 2 × C(1);

IR (film) ν_{max} /cm⁻¹ 2939, 2861, 1699, 1614, 1514, 1464, 1389, 1303, 1250, 1175, 1101, 1037;

HRMS (ESI⁺) C₁₇H₂₅O₃⁺ ([M+H]⁺) requires 277.1798; found 277.1796, Δ 0.83 ppm.

S19 1-Cyclopropyl-6-((4-methoxybenzyl)oxy)-2-methylhexan-1-one

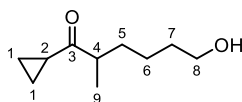
n-BuLi (1.93 mL, 5.31 mmol, 2.5 M in hexane) was added slowly to a solution of *N,N*-diisopropylamine (DIPA) (0.74 mL, 5.31 mmol) in THF (20 mL) at -78°C . The mixture was warmed to RT and stirred for 1 h. The mixture was cooled to -78°C and ketone **S18** (1.33 g, 4.82 mmol) in THF (30 mL) was added dropwise. The reaction was warmed to 0°C and stirred for 2 h. MeI (0.90 mL, 14.5 mmol) was added dropwise, the reaction mixture warmed to RT and stirred for 4 h. The reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 94:6 $\rightarrow$ 93:7) gave the *title compound* as a colourless oil (995 mg, 71%).

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.14 (m, 2H, $2 \times \text{C}(11)\text{H}$), 6.96 – 6.81 (m, 2H, $2 \times \text{C}(12)\text{H}$), 4.42 (s, 2H, $\text{C}(9)\text{H}_2$), 3.80 (s, 3H, $\text{C}(14)\text{H}_3$), 3.43 (t, $J = 6.6$ Hz, 2H, $\text{C}(8)\text{H}_2$), 2.64 (p, $J = 6.8$ Hz, 1H, $\text{C}(4)\text{H}$), 2.01 – 1.92 (m, 1H, $\text{C}(2)\text{H}$), 1.80 – 1.69 (m, 1H, $\text{C}(5)\text{H}_\text{A}\text{H}_\text{B}$), 1.68 – 1.55 (m, 2H, $\text{C}(7)\text{H}_2$), 1.48 – 1.27 (m, 3H, $\text{C}(5)\text{H}_\text{A}\text{H}_\text{B}$, $\text{C}(6)\text{H}_2$), 1.12 (d, $J = 6.9$ Hz, 3H, $\text{C}(15)\text{H}_3$), 1.06 – 0.91 (m, 2H, $2 \times \text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$), 0.90 – 0.74 (m, 2H, $2 \times \text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$);

^{13}C NMR (101 MHz, CDCl_3) δ 214.6 $\text{C}(3)$, 159.3 $\text{C}(13)$, 130.8 $\text{C}(10)$, 129.4 $2 \times \text{C}(11)$, 113.9 $2 \times \text{C}(12)$, 72.7 $\text{C}(9)$, 70.0 $\text{C}(8)$, 55.4 $\text{C}(14)$, 47.3 $\text{C}(4)$, 32.9 $\text{C}(5)$, 30.0 $\text{C}(7)$, 24.2 $\text{C}(6)$, 19.2 $\text{C}(2)$, 16.4 $\text{C}(15)$, 10.8 $\text{C}(1)$, 10.8 $\text{C}(1')$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3007, 2937, 2860, 1696, 1614, 1514, 1462, 1388, 1249, 1175, 1100, 1037, 822;

HRMS (ESI^+) $\text{C}_{18}\text{H}_{27}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 291.1955; found 291.1951, Δ 1.19 ppm.

S20 1-Cyclopropyl-6-hydroxy-2-methylhexan-1-one

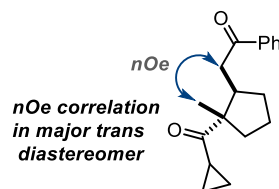
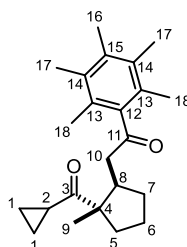
Ketone **S19** (988 mg, 3.41 mmol) was dissolved in a mixture of CH_2Cl_2 (32 mL)/water (3.5 mL) and DDQ (1.16 g, 5.11 mmol) was added at RT. The mixture was stirred at RT for 3 h, quenched with sat. aq. NaHCO_3 (20 mL) and diluted with water (20 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 60:40 $\rightarrow$ 50:50) gave the *title compound* as a colourless oil (553 mg, 95%).

^1H NMR (400 MHz, CDCl_3) δ 3.64 (t, $J = 6.5$ Hz, 2H, C(8) H_2), 2.74 – 2.53 (m, 1H, C(4) H), 2.09 – 1.86 (m, 1H, C(2) H), 1.80 – 1.67 (m, 1H, C(5) H_AH_B), 1.64 – 1.52 (m, 2H, C(7) H_2), 1.49 – 1.26 (m, 3H, C(5) H_AH_B , C(6) H_2), 1.14 (d, $J = 7.0$ Hz, 3H, C(9) H_3), 1.06 – 0.90 (m, 2H, $2 \times$ C(1) H_AH_B), 0.89 – 0.82 (m, 2H, $2 \times$ C(1) H_AH_B);

^{13}C NMR (101 MHz, CDCl_3) δ 214.7 C(3), 62.8 C(8), 47.3 C(4), 32.8 C(7), 32.7 C(5), 23.7 C(6), 19.2 C(2), 16.6 C(9), 10.9 C(1'), 10.9 C(1'');

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3437, 2936, 2860, 1696, 1455, 1387, 1068, 1013;

HRMS (ESI $^+$) $\text{C}_{10}\text{H}_{19}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 171.1380; found 171.1380, Δ 0.23 ppm.

165k 2-(2-(Cyclopropanecarbonyl)-2-methylcyclopentyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one

Hydroxy ketone **S20** (51 mg, 0.30 mmol), Ph * methyl ketone **31** (114 mg, 0.600 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.0 mg, 1.0 mol%), PAD_3 (5.2 mg, 4.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and $^t\text{BuOH}$ (1.2 mL) was added. The reaction was heated at 115 $^\circ\text{C}$ for 24 h, cooled to RT, filtered through a

silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 94:6) gave the *title compound* as a white solid (28 mg, 27% [93:7] d.r.*, isolated in conjunction with 28 mg, 27% **176**).

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The spectroscopic data were collected on the mixture. The relative stereochemistry was assigned by nOe analysis.

m.p. = 92 – 94 °C;

Major (1*RS*, 2*SR*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 2.94 (tdd, *J* = 10.6, 7.6, 2.3 Hz, 1H, C(8)*H*), 2.79 (dd, *J* = 19.1, 2.3 Hz, 1H, C(10)*H_AH_B*), 2.47 (dd, *J* = 19.1, 10.7 Hz, 1H, C(10)*H_AH_B*), 2.38 (dtd, *J* = 12.2, 7.6, 4.4 Hz, 1H, C(7)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 7H, C(5)*H_AH_B*, 2 × C(Ph*)*H₃*), 2.15 – 2.11 (m, 1H, C(2)*H*), 2.08 (s, 6H, 2 × C(Ph*)*H₃*), 1.87 – 1.75 (m, 2H, C(6)*H₂*), 1.66 – 1.50 (m, 1H, C(5)*H_AH_B*), 1.43 – 1.30 (m, 1H, C(7)*H_AH_B*), 1.03 (s, 3H, C(9)*H₃*), 0.99 – 0.88 (m, 2H, 2 × C(1)*H_AH_B*), 0.87 – 0.80 (m, 2H, 2 × C(1)*H_AH_B*);

¹³C NMR (151 MHz, CDCl₃) δ 214.4 C(3), 211.1 C(11), 140.8 C(Ar(Ph*)), 135.5 C(Ar(Ph*)) 133.2 2 × C(Ar(Ph*)), 127.3 2 × C(Ar(Ph*)), 57.2 C(4), 47.1 C(10), 40.3 C(8), 36.9 C(5), 30.9 C(7), 22.9 C(6), 17.9 C(9), 17.2 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.5 C(2), 16.1 2 × C(Me(Ph*)), 11.1 C(1'), 10.9 C(1'');

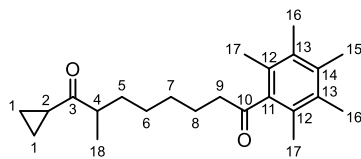
Selected characteristic peaks for the minor (1*SR*, 2*SR*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 2.74 – 2.70 (m, 1H, C(10)*H_AH_B*), 2.70 – 2.62 (m, 1H, C(10)*H_AH_B*);

¹³C NMR (151 MHz, CDCl₃) δ 214.3 C(3), 58.5 C(4), 46.4 C(10), 43.2 C(8), 34.8, 29.9, 29.4, 27.3, 23.9, 23.2, 21.9, 14.0, 11.6;

IR (film) ν_{max} /cm⁻¹ 2959, 1701, 1688, 1458, 1381, 1038, 771, 669, 650;

HRMS (ESI⁺) C₂₃H₃₃O₂⁺ ([M+H]⁺) requires 341.2475; found 341.2480, Δ 1.43 ppm.

176 1-Cyclopropyl-2-methyl-8-(2,3,4,5,6-pentamethylphenyl)octane-1,8-dione

Hydroxy ketone **S20** (51 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.600 mmol), [Ir(cod)Cl]₂ (2.0 mg, 1.0 mol%), cataCXium® A (4.3 mg, 4.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged with Ar (balloon) and ^tBuOH (1.2 mL) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 97:3 → 94:6) gave the *title compound* as a white solid (74 mg, 72%, isolated in conjunction with 13% **165k**).

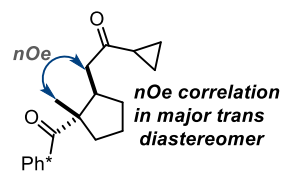
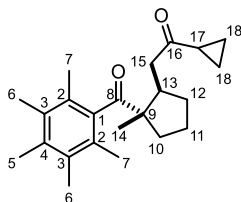
m.p. = 42 – 44 °C;

¹H NMR (400 MHz, CDCl₃) δ 2.73 – 2.59 (m, 3H, C(4)*H*, C(9)*H*₂), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, 2 × C(Ph*)*H*₃), 2.09 (s, 6H, 2 × C(Ph*)*H*₃), 1.96 (tt, *J* = 8.0, 4.5 Hz, 1H, C(2)*H*), 1.80 – 1.66 (m, 3H, C(5)*H*_A*H*_B, C(8)*H*₂), 1.46 – 1.27 (m, 5H, C(5)*H*_A*H*_B, C(6)*H*₂, C(7)*H*₂), 1.12 (d, *J* = 7.0 Hz, 3H, C(18)*H*₃), 1.07 – 0.93 (m, 2H, 2 × C(1)*H*_A*H*_B), 0.85 (dt, *J* = 8.0, 4.0 Hz, 2H, 2 × C(1)*H*_A*H*_B);

¹³C NMR (101 MHz, CDCl₃) δ 214.6 C(3), 212.1 C(10), 140.9 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 47.3 C(4), 45.7 C(9), 33.0 C(5), 29.4 C(7), 27.4 C(6), 23.2 C(8), 19.1 C(2), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.5 C(18), 16.1 2 × C(Me(Ph*)), 10.8 C(1'), 10.8 C(1'');

IR (film) ν_{max} /cm⁻¹ 2935, 1699, 1459, 1386, 1062, 1012, 648, 633;

HRMS (ESI⁺) C₂₃H₃₄NaO₂⁺ ([M+Na]⁺) requires 365.2451; found 365.2465, Δ 3.82 ppm.

165I 1-Cyclopropyl-2-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)ethan-1-one

Hydroxy ketone **164** (83 mg, 0.30 mmol), Ir(cod)acac (4.8 mg, 4.0 mol%), cataCXium® A (17.2 mg, 16.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and evacuated and back-filled with Ar (3 times). ^tBuOH (1.2 mL, degassed with Ar (balloon)) and cyclopropyl methyl ketone (59 μ L, 0.60 mmol) were added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 92:8) gave inseparable diastereomers of the *title compound* as a colourless solid (61 mg, 60%, [92:8] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by nOe analysis.

m.p. = 61 – 63 °C;

Major (1*SR*, 2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 2.95 (dd, J = 16.6, 2.2 Hz, 1H, C(15)*H_AH_B*), 2.63 – 2.54 (m, 1H, C(13)*H*), 2.42 (dd, J = 16.6, 11.4 Hz, 1H, C(15)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.16 (m, 6H, 2 $\times$ C(Ph*)*H₃*), 2.08 – 2.03 (m, 4H, C(12)*H_AH_B*, C(Ph*)*H₃*), 2.02 (s, 3H, C(Ph*)*H₃*), 1.95 – 1.79 (m, 2H, C(10)*H_AH_B*, C(17)*H*), 1.72 – 1.59 (m, 3H, C(10)*H_AH_B*, C(11)*H₂*), 1.34 – 1.19 (m, 1H, C(12)*H_AH_B*), 1.15 (s, 3H, C(14)*H₃*), 1.05 – 0.91 (m, 2H, 2 $\times$ C(18)*H_AH_B*), 0.92 – 0.73 (m, 2H, C(18)*H_AH_B*);

¹³C NMR (151 MHz, CDCl₃) δ 218.0 C(8), 210.0 C(16), 138.7 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 132.7 C(Ar(Ph*)), 128.4 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 58.4 C(9), 44.5 C(15), 40.6 C(13), 37.5 C(10), 30.2 C(12), 21.8 C(11), 20.6 C(17), 19.1 C(Me(Ph*)), 18.2 C(Me(Ph*)), 17.6 C(14), 16.6 C(Me(Ph*)), 16.2 C(Me(Ph*)), 15.9 C(Me(Ph*)), 10.7 C(18'), 10.4 C(18'');

Selected characteristic peaks for the minor (1*RS*, 2*RS*) diastereomer (from the mixture):

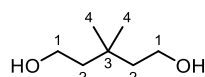
¹H NMR (600 MHz, CDCl₃) δ 2.91 – 2.87 (m, 2H, C(15)*H₂*), 1.10 (s, 3H, C(14)*H₃*);

^{13}C NMR (151 MHz, CDCl_3) δ 218.7 C(8), 210.9 C(16), 140.6 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 127.5 C(Ar(Ph*)), 58.5 C(9), 46.4, 45.5 C(15), 39.3, 31.5, 24.7 C(14), 21.5, 21.3, 18.2, 16.8, 16.3, 10.8 C(18'), 10.7 C(18'');

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 1699, 1678, 1447, 1386, 1302, 1261, 1196, 1114, 1071, 1016, 924;

HRMS (ESI⁺) $\text{C}_{23}\text{H}_{32}\text{NaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 363.2295; found 363.2299, Δ 1.20 ppm.

S21 3,3-Dimethylpentane-1,5-diol



3,3-Dimethylpentanedioic acid (3.50 g, 21.9 mmol) was added portion-wise to a suspension of LiAlH_4 (2.49 g, 65.7 mmol) in THF (110 mL) at 0 °C. A condenser was added and the mixture was heated to reflux for 16 h, cooled to 0 °C and diluted with Et_2O (50 mL). The reaction was quenched with sequential dropwise addition of water (2.5 mL), aqueous NaOH (15% w/v, 2.5 mL) and water (7.5 mL). MgSO_4 was added, the mixture was stirred vigorously for 15 min and filtered under reduced pressure. The filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 40:60) gave the *title compound* as a colourless oil (2.79 g, 96%).

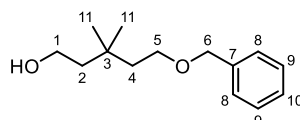
^1H NMR (400 MHz, CDCl_3) δ 3.93 – 3.60 (m, 4H, 2 $\times$ C(1) H_2), 2.06 (br. s, 2H, 2 $\times$ OH), 1.57 (t, J = 7.0 Hz, 4H, 2 $\times$ C(2) H_2), 0.94 (s, 6H, 2 $\times$ C(4) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 59.8 2 $\times$ C(1), 44.2 2 $\times$ C(2), 31.8 C(3), 28.2 2 $\times$ C(4);

m/z (ESI⁺) Found ($[\text{M}+\text{Na}]^+$) = 155, $\text{C}_7\text{H}_{16}\text{NaO}_2$ requires 155;

The spectroscopic data were consistent with that reported in the literature.⁴⁴

S22 5-(Benzyloxy)-3,3-dimethylpentan-1-ol



Diol **S21** (2.48 g, 19 mmol) was dissolved in dry THF (20 mL) and NaH (60% dispersed in mineral oil, 752 mg, 19 mmol) was added at RT. The mixture was stirred at RT for 1 h, cooled to 0 °C and benzyl bromide (2.3 mL, 19 mmol) was added dropwise. The resulting mixture was allowed to

warm to RT overnight, cooled to 0 °C and quenched with the addition of sat. aq. NH_4Cl (5 mL) and diluted with EtOAc (50 mL) and water (50 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 60:40) gave the *title compound* as a colourless oil (1.48 g, 35%).

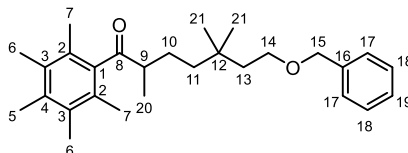
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40 – 7.28 (m, 5H, 5 × C(Ph)H), 4.50 (s, 2H, C(6) H_2), 3.70 (t, J = 7.2 Hz, 2H, C(1) H_2), 3.55 (t, J = 6.9 Hz, 2H, C(5) H_2), 1.71 – 1.59 (m, 3H, C(4) H_2 , OH), 1.56 (t, J = 7.2 Hz, 2H, C(2) H_2), 0.93 (s, 6H, 2 × C(11) H_3);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 138.4 C(7), 128.5 2 × C(9), 127.8 2 × C(8), 127.8 C(10), 73.3 C(6), 67.5 C(5), 59.9 C(1), 44.5 C(2), 41.3 C(4), 31.8 C(3), 28.2 2 × C(11);

m/z (ESI $^+$) Found ($[\text{M}+\text{H}]^+$) = 223, $\text{C}_{14}\text{H}_{23}\text{O}_2$ requires 223;

The spectroscopic data were consistent with that reported in the literature.¹⁵⁰

S23 7-(Benzyloxy)-2,5,5-trimethyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one



Ph* ethyl ketone **98** (612 mg, 3.00 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (20 mg, 1.0 mol%), dppBz (27 mg, 2.0 mol%) and KOH (673 mg, 12.0 mmol) were added to a 5 – 10 mL microwave vial. The vial was sealed and purged with Ar (balloon) for 5 min. PhMe (0.75 mL) and alcohol **S22** (1.00 g, 4.50 mmol) were added. The reaction was heated at 110 °C for 18 h, cooled to RT, filtered through a silica plug (elution with Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 96:4 → 95:5) gave the *title compound* as a colourless oil (1.12 g, 91%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.38 – 7.27 (m, 5H, 5 × C(Ph)H), 4.48 (s, 2H, C(15) H_2), 3.51 (t, J = 7.5 Hz, 2H, C(14) H_2), 2.78 – 2.63 (m, 1H, C(9)H), 2.23 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, 2 × C(Ph*) H_3), 2.08 (s, 6H, 2 × C(Ph*) H_3), 1.88 – 1.76 (m, 1H, C(10) $\text{H}_\text{A}\text{H}_\text{B}$), 1.65 – 1.54 (m, 2H,

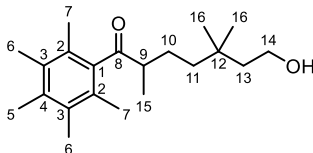
$C(13)H_2$), 1.37 – 1.24 (m, 2H, $C(10)H_AH_B$, $C(11)H_AH_B$), 1.22 – 1.14 (m, 1H, $C(11)H_AH_B$), 1.11 (d, $J = 7.1$ Hz, 3H, $C(20)H_3$), 0.89 (s, 6H, $2 \times C(21)H_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 $C(8)$, 140.2 $C(Ar(Ph^*))$, 138.8 $C(16)$, 135.5 $C(Ar(Ph^*))$, 133.2 $2 \times C(Ar(Ph^*))$, 128.5 $2 \times C(Ar(Ph^*))$ & $2 \times C(17)$, 127.7 $2 \times C(18)$, 127.6 $C(19)$, 73.1 $C(15)$, 67.6 $C(14)$, 49.0 $C(9)$, 41.0 $C(13)$, 40.1 $C(11)$, 32.3 $C(12)$, 27.6 $C(21')$, 27.5 $C(21'')$, 26.4 $C(10)$, 18.1 $2 \times C(Me(Ph^*))$, 16.8 $2 \times C(Me(Ph^*))$, 16.2 $2 \times C(Me(Ph^*))$, 15.7 $C(20)$;

IR (film) ν_{max}/cm^{-1} 2936, 2869, 1694, 1454, 1101, 1028, 924, 736, 698, 630;

HRMS (ESI⁺) $C_{28}H_{41}O_2^+$ ($[M+H]^+$) requires 409.3101; found 409.3107, Δ 1.44 ppm.

186 7-Hydroxy-2,5,5-trimethyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one



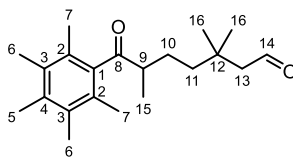
Benzyl ether **S23** (1.11 g, 2.70 mmol) was subjected to **General Procedure F** in MeOH (25 mL) with Pd (10% on carbon) (111 mg, 10 wt%) for 2 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 65:35) gave the *title compound* as a colourless oil (859 mg, 99%).

^1H NMR (600 MHz, $CDCl_3$) δ 3.69 (t, $J = 8.0$ Hz, 2H, $C(14)H_2$), 2.70 (td, $J = 7.5$, 5.1 Hz, 1H, $C(9)H$), 2.24 (s, 3H, $C(Ph^*)H_3$), 2.18 (s, 6H, $2 \times C(Ph^*)H_3$), 2.09 (s, 6H, $2 \times C(Ph^*)H_3$), 1.87 – 1.78 (m, 1H, $C(10)H_AH_B$), 1.55 – 1.47 (m, 2H, $C(13)H_2$), 1.37 – 1.29 (m, 2H, $C(10)H_AH_B$, $C(11)H_AH_B$), 1.25 – 1.17 (m, 1H, $C(11)H_AH_B$), 1.13 (d, $J = 7.1$ Hz, 3H, $C(15)H_3$), 0.90 (s, 6H, $2 \times C(16)H_3$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 215.2 $C(8)$, 140.2 $C(Ar(Ph^*))$, 135.6 $C(Ar(Ph^*))$, 133.2 $2 \times C(Ar(Ph^*))$, 128.4 $2 \times C(Ar(Ph^*))$, 60.0 $C(14)$, 49.0 $C(9)$, 44.5 $C(13)$, 40.0 $C(11)$, 32.4 $C(12)$, 27.6 $C(16')$, 27.5 $C(16'')$, 26.4 $C(10)$, 18.1 $2 \times C(Me(Ph^*))$, 16.9 $C(Me(Ph^*))$, 16.2 $2 \times C(Me(Ph^*))$, 15.9 $C(15)$;

IR (film) ν_{max}/cm^{-1} 3358, 2938, 1693, 1459, 1385, 1302, 1261, 1146, 1123, 1051, 1021, 988, 925;

HRMS (ESI⁺) $C_{21}H_{35}O_2^+$ ($[M+H]^+$) requires 319.2632; found 319.2638, Δ 2.00 ppm.

187 3,3,6-Trimethyl-7-oxo-7-(2,3,4,5,6-pentamethylphenyl)heptanal

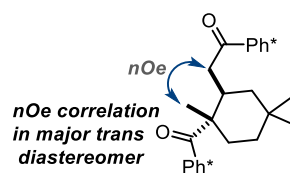
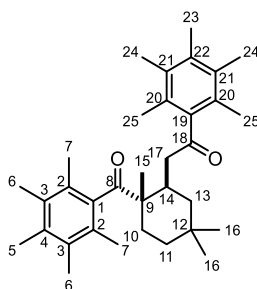
Dess-Martin periodinane (400 mg, 0.940 mmol) was added to a solution of alcohol **186** (250 mg, 0.78 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was allowed to warm to RT and stirred for 3 h. The reaction was quenched with the addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL), the layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 92:8 $\rightarrow$ 90:10) gave the *title compound* as a colourless oil (209 mg, 84%).

^1H NMR (400 MHz, CDCl_3) δ 9.83 (t, $J = 3.1$ Hz, 1H, C(14)H), 2.77 – 2.62 (m, 1H, C(9)H), 2.28 (d, $J = 3.1$ Hz, 2H, C(13)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, $2 \times \text{C(Ph*)H}_3$), 2.09 (s, 6H, $2 \times \text{C(Ph*)H}_3$), 1.90 – 1.80 (m, 1H, C(10)H_AH_B), 1.49 – 1.29 (m, 3H, C(10)H_AH_B, C(11)H₂), 1.13 (d, $J = 7.0$ Hz, 3H, C(15)H₃), 1.06 (s, 6H, $2 \times \text{C(16)H}_3$);

^{13}C NMR (151 MHz, CDCl_3) δ 214.9 C(14), 203.6 C(8), 140.0 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.3 $2 \times \text{C(Ar(Ph*))}$, 128.3 $2 \times \text{C(Ar(Ph*))}$, 54.8 C(13), 48.8 C(9), 40.2 C(11), 33.7 C(12), 27.6 C(16'), 27.5 C(16''), 26.3 C(10), 18.1 $2 \times \text{C(Me(Ph*))}$, 16.9 C(Me(Ph*)), 16.2 $2 \times \text{C(Me(Ph*))}$, 15.9 C(15);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 1721, 1694, 1466, 991, 925;

HRMS (ESI⁺) $\text{C}_{19}\text{H}_{33}\text{O}_2^+$ ([M+H]⁺) requires 317.2475; found 317.2485, Δ 3.12 ppm.

167b 1-(2,3,4,5,6-Pentamethylphenyl)-2-((1*RS*, 2*SR*)-2,5,5-trimethyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclohexyl)ethan-1-one

Keto-aldehyde **187** (95 mg, 0.30 mmol), Ph* methyl ketone **31** (86 mg, 0.45 mmol) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed and purged

with Ar (balloon) and PhMe (1.2 mL) was added. The reaction was heated at 110 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 96:4) gave the *title compound* as a white solid (115 mg, 78%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe analysis.

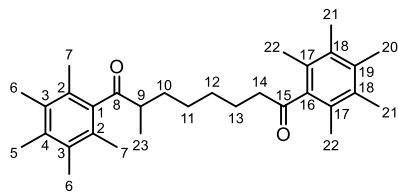
m.p. = 198 – 200 °C;

¹H NMR (600 MHz, CDCl₃) δ 3.45 (dd, *J* = 19.7, 1.3 Hz, 1H, C(17)*H_AH_B*), 3.02 – 2.93 (m, 1H, C(14)*H*), 2.44 (dd, *J* = 19.6, 10.4 Hz, 1H, C(17)*H_AH_B*), 2.24 (s, 3H, C(Ph*)*H₃*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.19 (s, 9H, 3 × C(Ph*)*H₃*), 2.15 (s, 3H, C(Ph*)*H₃*), 2.14 (s, 3H, C(Ph*)*H₃*), 2.10 (s, 6H, 2 × C(Ph*)*H₃*), 2.02 (s, 3H, C(Ph*)*H₃*), 1.75 (td, *J* = 13.8, 4.1 Hz, 1H, C(10)*H_AH_B*), 1.70 – 1.64 (m, 1H, C(13)*H_AH_B*), 1.39 (dt, *J* = 13.5, 3.5 Hz, 1H, C(10)*H_AH_B*), 1.32 (td, *J* = 14.0, 4.0 Hz, 1H, C(11)*H_AH_B*), 1.24 – 1.17 (m, 1H, C(11)*H_AH_B*), 1.16 (s, 3H, C(15)*H₃*), 1.12 (t, *J* = 12.5 Hz, 1H, C(13)*H_AH_B*), 1.01 (s, 3H, C(16')*H₃*), 0.92 (s, 3H, C(16'')*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 219.4 C(8), 210.3 C(18), 141.0 C(Ar(Ph*)), 139.9 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 134.8 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 133.1 (br.) 2 × C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 127.6 (br.) 2 × C(Ar(Ph*)), 50.9 C(9), 47.9 C(17), 42.1 C(13), 34.3 C(11), 33.1 C(16''), 31.8 C(10), 30.7 C(12), 30.4 C(14), 24.7 C(16'), 19.3 C(Me(Ph*)), 19.3 C(Me(Ph*)), 17.0 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 15.8 C(15);

IR (film) ν_{max} /cm⁻¹ 2947, 1701, 1678, 1470, 1302, 1259, 1217, 1066, 911, 759;

HRMS (ESI⁺) C₃₄H₄₉O₂⁺ ([M+H]⁺) requires 489.3730; found 489.3727, Δ 0.51 ppm.

189 2-Methyl-1,8-bis(2,3,4,5,6-pentamethylphenyl)octane-1,8-dione

Hydroxy ketone **164** (83 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.600 mmol), [Ir(cod)acac] (2.4 mg, 1.0 mol%), and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and ^tBuOH (1.2 mL) and tri-*tert*-butylphosphine (12 μ L, 1.0 M in PhMe, 4.0 mol%) were added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 $\rightarrow$ 94:6) gave the *title compound* as a white solid (65 mg, 48%).

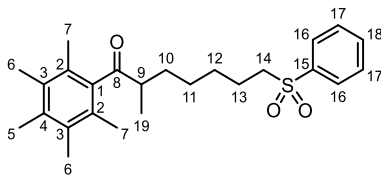
m.p. = 136 – 138 °C;

¹H NMR (400 MHz, CDCl₃) δ 2.85 – 2.72 (m, 1H, C(9)*H*), 2.66 (t, *J* = 7.4 Hz, 2H, C(14)*H*₂), 2.24 (s, 3H, C(Ph*)*H*₃), 2.23 (s, 3H, C(Ph*)*H*₃), 2.19 (s, 12H, 4 $\times$ C(Ph*)*H*₃), 2.09 (s, 6H, 2 $\times$ C(Ph*)*H*₃), 2.09 (s, 6H, 2 $\times$ C(Ph*)*H*₃), 1.85 – 1.76 (m, 1H, C(10)*H*_A*H*_B), 1.76 – 1.65 (m, 2H, C(13)*H*₂), 1.53 – 1.28 (m, 5H, C(10)*H*_A*H*_B, C(11)*H*₂, C(12)*H*₂), 1.15 (d, *J* = 7.0 Hz, 3H, C(23)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.2 C(8), 212.1 C(15), 140.9 C(Ar(Ph*)), 140.1 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.2 4 $\times$ C(Ar(Ph*)), 128.3 2 $\times$ C(Ar(Ph*)), 127.4 2 $\times$ C(Ar(Ph*)), 48.5 C(9), 45.6 C(14), 31.7 C(10), 29.4 C(12), 27.4 C(11), 23.2 C(13), 18.1 2 $\times$ C(Me(Ph*)), 17.3 2 $\times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 2 $\times$ C(Me(Ph*)), 16.1 2 $\times$ C(Me(Ph*)), 15.3 C(23);

IR (film) ν_{max} /cm⁻¹ 2934, 1756, 1697, 1463, 1385, 1306, 1260, 1099, 758;

HRMS (ESI⁺) C₃₂H₄₅O₂⁺ ([M+H]⁺) requires 461.3414; found 461.3414, Δ 0.05 ppm.

191 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-7-(phenylsulfonyl)heptan-1-one

Hydroxy ketone **164** (83 mg, 0.30 mmol), methyl phenyl sulfone **190** (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and ^tBuOH (1.2 mL) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 87:5:8 → 85:5:10) gave the *title compound* as a white solid (68 mg, 55%, isolated in conjunction with 35 mg, 28% cyclised product **165h**, [89:11] d.r.)

m.p. = 82 – 84 °C;

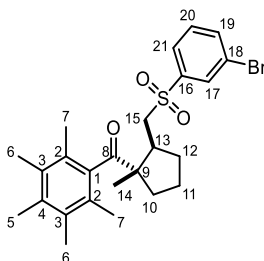
¹H NMR (600 MHz, CDCl₃) δ 7.92 – 7.86 (m, 2H, 2 × C(16)H), 7.69 – 7.61 (m, 1H, C(18)H), 7.60 – 7.53 (m, 2H, 2 × C(17)H), 3.14 – 3.02 (m, 2H, C(14)H₂), 2.80 – 2.67 (m, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.06 (s, 6H, 2 × C(Ph*)H₃), 1.78 – 1.66 (m, 3H, C(10)H_AH_B, C(13)H₂), 1.45 – 1.20 (m, 5H, C(10)H_AH_B, C(11)H₂, C(12)H₂), 1.10 (d, *J* = 7.0 Hz, 3H, C(19)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.8 C(8), 140.0 C(Ar(Ph*)), 139.4 C(15), 135.6 C(Ar(Ph*)), 133.8 C(18), 133.2 2 × C(Ar(Ph*)), 129.4 2 × C(17), 128.3 2 × C(Ar(Ph*)), 128.2 2 × C(16), 56.3 C(14), 48.3 C(9), 31.5 C(10), 28.6 C(11), 26.9 C(12), 22.7 C(13), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.4 C(19);

IR (film) ν_{max} /cm⁻¹ 2940, 1691, 1447, 1306, 1148, 1088, 922, 733, 690;

HRMS (ESI⁺) C₂₅H₃₄NaO₃S⁺ ([M+Na]⁺) requires 437.2121; found 437.2120, Δ 0.21 ppm.

165m (2-(((3-Bromophenyl)sulfonyl)methyl)-1-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), 3-bromophenyl methyl sulfone (141 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $^t\text{BuOH}$ (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/ CH_2Cl_2 /EtOAc, 91:5:4) gave separable diastereomers of the *title compound* as a white solid (106 mg, 72%, [95:5] d.r.)*

*Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification. The relative stereochemistry was assigned by X-ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 118 – 120 °C;

^1H NMR (600 MHz, CDCl_3) δ 8.03 (t, J = 1.9 Hz, 1H, C(17) H), 7.84 – 7.80 (m, 1H, C(21) H), 7.80 – 7.75 (m, 1H, C(19) H), 7.45 (t, J = 7.9 Hz, 1H, C(20) H), 3.57 (dd, J = 13.8, 2.1 Hz, 1H, C(15) H_AH_B), 3.00 (dd, J = 13.8, 11.9 Hz, 1H, C(15) H_AH_B), 2.63 – 2.54 (m, 1H, C(13) H), 2.34 – 2.27 (m, 1H, C(12) H_AH_B), 2.23 (s, 3H, C(Ph*) H_3), 2.18 – 2.12 (m, 6H, 2 $\times$ C(Ph*) H_3), 2.02 (s, 3H, C(Ph*) H_3), 1.96 (s, 3H, C(Ph*) H_3), 1.87 – 1.79 (m, 1H, C(10) H_AH_B), 1.76 – 1.54 (m, 4H, C(10) H_AH_B , C(11) H_2 , C(12) H_AH_B), 1.13 (s, 3H, C(14) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 217.4 C(8), 142.2 C(16), 138.7 C(Ar(Ph*)), 136.9 C(19), 135.4 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 131.0 C(20), 131.0 C(17), 128.1 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 126.6 C(21), 123.4 C(18), 58.6 C(9), 58.3 C(15), 39.4 C(13), 36.6 C(10), 29.7 C(12), 22.1 C(11), 19.2 C(Me(Ph*)), 18.5 C(14), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm $^{-1}$ 2968, 1677, 1572, 1412, 1318, 1217, 1149, 1099, 926 ;

HRMS (ESI⁺) C₂₅H₃₂⁷⁹BrO₃S⁺ ([M+H]⁺) requires 491.1250; found 491.1244, Δ 1.32 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

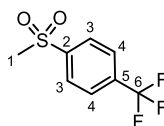
¹H NMR (600 MHz, CDCl₃) δ 8.08 (t, *J* = 1.8 Hz, 1H, C(17)*H*), 7.87 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H, C(21)*H*), 7.79 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H, C(19)*H*), 7.46 (t, *J* = 7.9 Hz, 1H, C(20)*H*), 3.58 – 3.42 (m, 2H, C(15)*H*₂), 2.36 (dtd, *J* = 10.3, 7.4, 2.3 Hz, 1H, C(13)*H*), 2.22 (s, 3H, C(Ph*)*H*₃), 2.20 – 2.17 (m, 1H, C(10)*H*_A*H*_B), 2.16 (s, 3H, C(Ph*)*H*₃), 2.15 (s, 3H, C(Ph*)*H*₃), 2.13 – 2.05 (m, 1H, C(12)*H*_A*H*_B), 2.04 – 1.97 (m, 4H, C(15)*H*_A*H*_B & C(Ph*)*H*₃), 1.96 (s, 3H, C(Ph*)*H*₃), 1.83 – 1.71 (m, 2H, C(11)*H*₂), 1.61 – 1.49 (m, 1H, C(10)*H*_A*H*_B), 1.14 (s, 3H, C(14)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.7 C(8), 142.3 C(16), 139.3 C(Ar(Ph*)), 136.9 C(19), 135.3 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 131.1 C(17), 131.0 C(20), 127.9 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 126.7 C(21), 123.5 C(18), 60.2 C(9), 58.6 C(15), 44.8 C(13), 39.0 C(10), 31.1 C(12), 24.3 C(14), 22.0 C(11), 18.7 C(Me(Ph*)), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 2930, 1679, 1572, 1461, 1414, 1318, 1217, 1150, 1097;

HRMS (ESI⁺) C₂₅H₃₂⁷⁹BrO₃S⁺ ([M+H]⁺) requires 491.1250; found 491.1245, Δ 1.01 ppm.

S24 1-(Methylsulfonyl)-4-(trifluoromethyl)benzene



Mg turnings (608 mg, 24.9 mmol) were heated with stirring under vacuum in a two-necked flask for 10 min and allowed to cool to RT. THF (5 mL) and a single iodine crystal were added and 4-bromobenzotrifluoride (1.40 mL, 10.0 mmol) was added slowly. The mixture was refluxed for a further 5 min, cooled to RT and diluted with THF (5 mL). The cooled Grignard reagent was added slowly to a suspension of 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (2.40 g, 10.0 mmol) in THF (30 mL) at -40 °C. The reaction mixture was stirred at -40 °C for 1 h, allowed to warm to RT and the THF was removed under a stream of N₂. The residue was dissolved in *N,N*-dimethylformamide (40 mL) and MeI (1.9 mL, 30 mmol) was added. The resulting

suspension was heated to 75 °C overnight, cooled to RT, filtered through a Celite® pad and the filtrate concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 75:5:20) gave the *title compound* as a yellow solid (732 mg, 33%).

¹H NMR (600 MHz, CDCl₃) δ 8.23 – 8.00 (m, 2H, 2 × C(3)H), 7.96 – 7.75 (m, 2H, 2 × C(4)H), 3.09 (s, 3H, C(1)H₃);

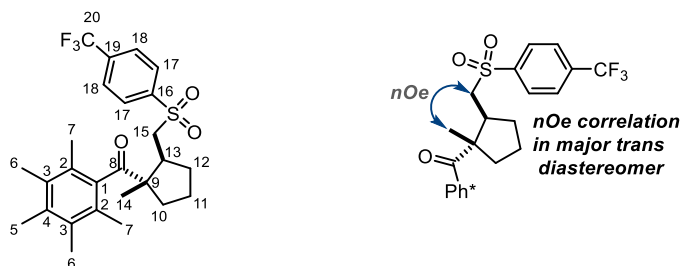
¹³C NMR (151 MHz, CDCl₃) δ 144.0 C(2), 135.6 (q, J^2_{C-F} = 33.2 Hz, C(5)), 128.1 2 × C(3), 126.6 (q, J^3_{C-F} = 3.8 Hz, 2 × C(4)), 123.1 (q, J^1_{C-F} = 273.2 Hz, C(6)), 44.4 C(1);

¹⁹F NMR (471 MHz, CDCl₃) δ –63.2;

HRMS (ESI⁺) C₈H₇F₃NaO₂S⁺ ([M+Na]⁺) requires 247.0011; found 247.0011, Δ 0.01 ppm.

The spectroscopic data were consistent with that reported in the literature.¹⁵¹

165n (1-Methyl-2-(((4-(trifluoromethyl)phenyl)sulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl) methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfone **S24** (134 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 90:5:5) gave separable diastereomers of the *title compound* as a white solid (70 mg, 48%, [94:6] d.r., isolated in conjunction with **193** 45 mg, 36%).*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 140 – 142 °C;

¹H NMR (600 MHz, CDCl₃) δ 8.13 – 7.98 (m, 2H, 2 × C(17)H), 7.93 – 7.73 (m, 2H, 2 × C(18)H), 3.63 (dd, J = 13.9, 2.1 Hz, 1H, C(15)H_AH_B), 3.03 (dd, J = 13.9, 11.9 Hz, 1H, C(15)H_AH_B), 2.54 (dddd,

$J = 12.0, 10.2, 8.3, 2.1$ Hz, 1H, C(13) H), 2.30 (m, 1H, C(12) H_AH_B), 2.22 (s, 3H, C(Ph*) H_3), 2.15 (s, 3H, C(Ph*) H_3), 2.14 (s, 3H, C(Ph*) H_3), 2.02 (s, 3H, C(Ph*) H_3), 1.88 (s, 3H, C(Ph*) H_3), 1.81 (dt, $J = 12.0, 9.5$ Hz, 1H, C(10) H_AH_B), 1.76 – 1.56 (m, 4H, C(10) H_AH_B , C(11) H_2 , C(12) H_AH_B), 1.13 (s, 3H, C(14) H_3);

^{13}C NMR ($\{^{19}\text{F}\}$ 126 MHz, CDCl_3) δ 217.3 C(8), 143.6 C(16), 138.6 C(Ar(Ph*)), 135.5 C(19), 135.4 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 128.7 $2 \times$ C(17), 128.0 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 126.6 $2 \times$ C(18), 123.3 C(20), 58.6 C(9), 58.1 C(15), 39.4 C(13), 36.4 C(10), 29.6 C(12), 22.0 C(11), 19.2 C(Me(Ph*)), 18.5 C(14), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

^{19}F NMR (565 MHz, CDCl_3) δ -63.2;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 1679, 1404, 1325, 1174, 1017, 916, 846;

HRMS (ESI⁺) $\text{C}_{26}\text{H}_{31}\text{F}_3\text{NaO}_3\text{S}^+$ ($[\text{M}+\text{Na}]^+$) requires 503.1838; found 503.1835, Δ 0.58 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

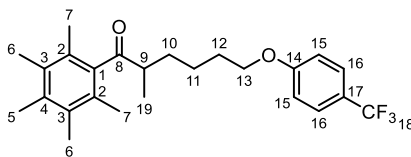
^1H NMR (600 MHz, CDCl_3) δ 8.14 – 8.01 (m, 2H, $2 \times$ C(17) H), 7.86 (d, $J = 8.2$ Hz, 2H, $2 \times$ C(18) H), 3.59 – 3.47 (m, 2H, C(15) H_2), 2.42 – 2.31 (m, 1H, C(13) H), 2.21 (s, 3H, C(Ph*) H_3), 2.20 – 2.15 (m, 4H, C(10) H_AH_B , C(Ph*) H_3), 2.14 (s, 3H, C(Ph*) H_3), 2.12 – 2.07 (m, 1H, C(12) H_AH_B), 2.06 – 1.97 (m, 4H, C(12) H_AH_B , C(Ph*) H_3), 1.92 (s, 3H, C(Ph*) H_3), 1.82 – 1.68 (m, 2H, C(11) H_2), 1.56 (dt, $J = 13.3, 8.1$ Hz, 1H, C(10) H_AH_B), 1.14 (s, 3H, C(14) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 217.6 C(8), 143.9 C(16), 139.2 C(Ar(Ph*)), 135.5 (q, $J_{\text{C-F}}^2 = 33.3$ Hz, C(19)), 135.4 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 128.8 $2 \times$ C(17), 127.9 C(Ar(Ph*)), 127.6 C(Ar(Ph*)), 126.6 (q, $J_{\text{C-F}}^3 = 3.6$ Hz, $2 \times$ C(18)), 123.3 (q, $J_{\text{C-F}}^1 = 273.0$ Hz, C(20)), 60.2 C(9), 58.4 C(15), 44.8 C(13), 38.9 C(10), 31.1 C(12), 24.2 C(14), 22.0 C(11), 18.7 C(Me(Ph*)), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

^{19}F NMR (565 MHz, CDCl_3) δ -63.2;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2945, 1694, 1617, 1520, 1331, 1260, 1179, 1162, 1121, 1069, 639;

HRMS (ESI⁺) $\text{C}_{26}\text{H}_{32}\text{F}_3\text{O}_3\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 481.2019; found 481.2014, Δ 0.90 ppm.

193 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-6-(4-(trifluoromethyl)phenoxy)hexan-1-one

Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfone **S24** (134 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $^t\text{BuOH}$ (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/ $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 90:5:5) gave the *title compound* as a colourless oil (45 mg, 36%, isolated in conjunction with 70 mg, 48% **165n**).

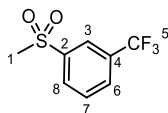
^1H NMR (600 MHz, CDCl_3) δ 7.59 – 7.45 (m, 2H, 2 $\times$ C(16) H), 6.92 (d, J = 8.6 Hz, 2H, 2 $\times$ C(15) H), 3.99 (t, J = 6.4 Hz, 2H, C(13) H_2), 2.89 – 2.75 (m, 1H, C(9) H), 2.24 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, 2 $\times$ C(Ph*) H_3), 2.09 (s, 6H, 2 $\times$ C(Ph*) H_3), 1.91 – 1.74 (m, 3H, C(10) H_AH_B , C(12) H_2), 1.67 – 1.58 (m, 1H, C(11) H_AH_B), 1.53 – 1.39 (m, 2H, C(10) H_AH_B , C(11) H_AH_B), 1.17 (d, J = 7.0 Hz, 3H, C(19) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 214.9 C(8), 161.6 C(14), 140.1 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.3 2 $\times$ C(Ar(Ph*)), 128.4 2 $\times$ C(Ar(Ph*)), 127.0 (q, $J^3_{\text{C-F}}$ = 3.7 Hz, 2 $\times$ C(16)), 123.7 (q, $J^1_{\text{C-F}}$ = 271.4 Hz, C(18)), 122.9 (q, $J^2_{\text{C-F}}$ = 32.7 Hz, C(17)), 114.6 2 $\times$ C(15), 68.1 C(13), 48.4 C(9), 31.6 C(10), 29.4 C(12), 24.0 C(11), 18.1 2 $\times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 $\times$ C(Me(Ph*)), 15.4 C(19);

^{19}F NMR (565 MHz, CDCl_3) δ -61.5;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2946, 1694, 1617, 1520, 1384, 1331, 1260, 1179, 1162, 1121, 1069, 924;

HRMS (ESI $^+$) $\text{C}_{25}\text{H}_{32}\text{F}_3\text{O}_2$ $^+$ ($[\text{M}+\text{H}]^+$) requires 421.2349; found 421.2341, Δ 1.89 ppm.

228 1-(Methylsulfonyl)-3-(trifluoromethyl)benzene

Mg turnings (613 mg, 25.0 mmol) were heated with stirring under vacuum in a two-necked flask for 10 min and allowed to cool to RT. THF (5 mL) and a single iodine crystal were added and 3-bromobenzotrifluoride (1.40 mL, 10.0 mmol) was added slowly. The mixture was refluxed for a further 5 min, cooled to RT and diluted with THF (5 mL). The cooled Grignard reagent was added slowly to a suspension of 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (2.40 g,

10.0 mmol) in THF (30 mL) at $-40\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 2 h, allowed to warm to RT and the THF was removed under a stream of N_2 . The residue was dissolved in *N,N*-dimethylformamide (40 mL) and MeI (1.9 mL, 30 mmol) was added. The resulting suspension was heated to $75\text{ }^{\circ}\text{C}$ overnight, cooled to RT, and Et_2O (50 mL) was added. The resulting suspension was filtered through a Celite[®] pad and the filtrate concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ CH_2Cl_2 / Et_2O , 80:5:15 $\rightarrow$ 75:5:20) gave the *title compound* as a yellow solid (921 mg, 41%).

¹H NMR (500 MHz, CDCl_3) δ 8.23 (s, 1H, C(3)*H*), 8.16 (dt, $J = 7.8, 1.4\text{ Hz}$, 1H, C(8)*H*), 7.93 (dd, $J = 7.5, 1.8\text{ Hz}$, 1H, C(6)*H*), 7.75 (t, $J = 7.8\text{ Hz}$, 1H, C(7)*H*), 3.10 (s, 3H, C(1)*H*₃);

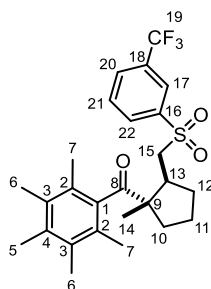
¹³C NMR ($\{^{19}\text{F}\}$ 126 MHz, CDCl_3) δ 141.9 C(2), 132.3 C(4), 130.9 C(8), 130.6 C(6), 130.4 C(7), 124.8 C(3), 123.2 C(5), 44.6 C(1);

¹⁹F NMR (471 MHz, CDCl_3) δ -62.9;

m/z (ESI⁺) Found ($[\text{M}+\text{H}]^+$) = 247, $\text{C}_8\text{H}_7\text{F}_3\text{NaO}_2\text{S}$ requires 247;

The spectroscopic data matched that previously reported in the literature.¹⁵²

165o (1-Methyl-2-((3-(trifluoromethyl)phenyl)sulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfone **228** (134 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $t\text{BuOH}$ (1.2 mL) at $115\text{ }^{\circ}\text{C}$ for 16 h. Purification *via* sequential flash column chromatography (reverse phase (eluent water/ MeCN 30:70 $\rightarrow$ MeCN), then normal phase (eluent pentane/ CH_2Cl_2 / Et_2O , 90:5:5)) gave separable diastereomers of the *title compound* as a white solid (86 mg, 60%, [91:9] d.r.)*

* Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification.

The relative stereochemistry was assigned by X-ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 129 – 131 °C;

^1H NMR (600 MHz, CDCl_3) δ 8.19 – 8.17 (m, 1H, C(17)*H*), 8.13 – 8.07 (m, 1H, C(22)*H*), 7.95 – 7.90 (m, 1H, C(20)*H*), 7.74 (t, J = 7.8 Hz, 1H, C(21)*H*), 3.62 (dd, J = 13.8, 2.1 Hz, 1H, C(15)*H_AH_B*), 3.04 (dd, J = 13.8, 11.9 Hz, 1H, C(15)*H_AH_B*), 2.60 (dddd, J = 12.1, 10.2, 8.3, 2.1 Hz, 1H, C(13)*H*), 2.32 (m, 1H, C(12)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.15 (s, 6H, 2 $\times$ C(Ph*)*H₃*), 2.02 (s, 3H, C(Ph*)*H₃*), 1.93 (s, 3H, C(Ph*)*H₃*), 1.89 – 1.78 (m, 1H, C(10)*H_AH_B*), 1.77 – 1.54 (m, 4H, C(10)*H_AH_B*, C(11)*H₂*, C(12)*H_AH_B*), 1.13 (s, 3H, C(14)*H₃*);

^{13}C NMR (151 MHz, CDCl_3) δ 217.4 C(8), 141.6 C(16), 138.7 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 132.2 (q, $J^2_{\text{C-F}}$ = 33.5 Hz, C(18)), 131.4 C(22), 130.5 (q, $J^3_{\text{C-F}}$ = 3.6 Hz, C(20)), 130.3 C(21), 128.0 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 125.2 (q, $J^3_{\text{C-F}}$ = 3.9 Hz, C(17)), 123.3 (q, $J^1_{\text{C-F}}$ = 273.1 Hz, C(19)), 58.6 C(9), 58.2 C(15), 39.5 C(13), 36.6 C(10), 29.7 C(12), 22.1 C(11), 19.2 C(Me(Ph*)), 18.5 C(14), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

^{19}F NMR (565 MHz, CDCl_3) δ -62.8;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 1677, 1328, 1306, 1175, 1146, 1102, 1073, 771, 755;

HRMS (ESI⁺) $\text{C}_{26}\text{H}_{32}\text{F}_3\text{O}_3\text{S}^+$ ([M+H]⁺) requires 481.2019; found 481.2014, Δ 0.90 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

^1H NMR (400 MHz, CDCl_3) δ 8.25 – 8.17 (m, 1H, C(17)*H*), 8.17 – 8.08 (m, 1H, C(22)*H*), 7.99 – 7.87 (m, 1H, C(20)*H*), 7.83 – 7.67 (m, 1H, C(21)*H*), 3.63 – 3.41 (m, 2H, C(15)*H₂*), 2.44 – 2.33 (m, 1H, C(13)*H*), 2.21 (s, 3H, C(Ph*)*H₃*), 2.20 – 2.15 (m, 4H, C(10)*H_AH_B*, C(Ph*)*H₃*), 2.14 (s, 3H, C(Ph*)*H₃*), 2.13 – 2.05 (m, 1H, C(12)*H_AH_B*), 2.05 – 1.97 (m, 4H, C(12)*H_AH_B*, C(Ph*)*H₃*), 1.95 (s, 3H, C(Ph*)*H₃*), 1.76 (m, 2H, C(11)*H₂*), 1.56 (dt, J = 13.2, 8.1 Hz, 1H, C(10)*H_AH_B*), 1.15 (s, 3H, C(14)*H₃*);

^{13}C NMR (151 MHz, CDCl_3) δ 217.7 C(8), 141.7 C(16), 139.2 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 132.2 (q, $J^2_{\text{C-F}}$ = 33.6 Hz, C(18)), 131.4 C(22), 130.5 (q, $J^3_{\text{C-F}}$ = 3.5 Hz,

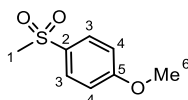
$C(20)$), 130.3 $C(21)$, 127.9 $C(\text{Ar}(\text{Ph}^*))$, 127.7 $C(\text{Ar}(\text{Ph}^*))$, 125.3 (q, $J_{C-F}^3 = 3.9$ Hz, $C(17)$), 123.3 (q, $J_{C-F}^1 = 272.8$ Hz, $C(19)$), 60.2 $C(9)$, 58.6 $C(15)$, 44.8 $C(13)$, 39.0 $C(10)$, 31.1 $C(12)$, 24.3 $C(14)$, 22.0 $C(11)$, 18.6 $C(\text{Me}(\text{Ph}^*))$, 18.4 $C(\text{Me}(\text{Ph}^*))$, 16.8 $C(\text{Me}(\text{Ph}^*))$, 16.3 $C(\text{Me}(\text{Ph}^*))$, 16.0 $C(\text{Me}(\text{Ph}^*))$;

^{19}F NMR (565 MHz, CDCl_3) δ -62.8;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 1680, 1461, 1384, 1329, 1306, 1218, 1175, 1148, 1102, 1073, 762;

HRMS (ESI $^+$) $\text{C}_{26}\text{H}_{32}\text{F}_3\text{O}_3\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 481.2019; found 481.2015, Δ 0.72 ppm.

227 1-Methoxy-4-(methylsulfonyl)benzene



Mg turnings (304 mg, 12.5 mmol) were heated with stirring under vacuum in a two-necked flask for 10 min and allowed to cool to RT. THF (5 mL) and a single iodine crystal were added and 4-bromoanisole (0.63 mL, 5.00 mmol) was added slowly. The mixture was refluxed for a further 5 min, cooled to RT and diluted with THF (5 mL). The cooled Grignard reagent was added slowly to a suspension of 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (1.20 g, 5.00 mmol) in THF (10 mL) at -40 °C. The reaction mixture was stirred at -40 °C for 1 h, allowed to warm to RT and the THF was removed under a stream of N_2 . The residue was dissolved in *N,N*-dimethylformamide (40 mL) and MeI (0.93 mL, 15.0 mmol) was added. The resulting suspension was heated to 75 °C overnight, cooled to RT, filtered through a Celite® pad and the filtrate concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ CH_2Cl_2 / Et_2O , 70:5:25) gave the *title compound* as a white solid (538 mg, 58%).

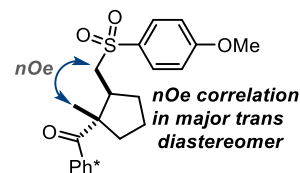
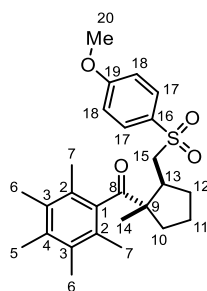
^1H NMR (400 MHz, CDCl_3) δ 7.96 – 7.74 (m, 2H, $2 \times C(3)H$), 7.10 – 6.90 (m, 2H, $2 \times C(4)H$), 3.89 (s, 3H, $C(6)H_3$), 3.03 (s, 3H, $C(1)H_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 163.8 $C(5)$, 132.5 $C(2)$, 129.7 $2 \times C(3)$, 114.6 $2 \times C(4)$, 55.8 $C(6)$, 45.0 $C(1)$;

HRMS (ESI $^+$) $\text{C}_8\text{H}_{11}\text{O}_3\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 187.0423; found 187.0423, Δ 0.51 ppm.

The spectroscopic data were consistent with that reported in the literature.¹⁵³

165p (2-(((4-Methoxyphenyl)sulfonyl)methyl)-1-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfone **227** (112 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $t\text{BuOH}$ (1.2 mL) at 115 °C for 16 h. Purification *via* flash sequential reverse phase flash column chromatography (eluent $\text{H}_2\text{O}/\text{MeCN}$ 80:20 $\rightarrow$ 5:95) and normal phase flash column chromatography (eluent pentane/ $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 80:5:15) gave the *title compound* as a white solid (97 mg, 73%, [95:5] d.r.)*

* Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification. The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by nOe analysis.

m.p. = 143 – 145 °C;

Major (1*RS*, 2*RS*) diastereomer (from the mixture):

^1H NMR (600 MHz, CDCl_3) δ 7.83 – 7.77 (m, 2H, $2 \times \text{C}(17)\text{H}$), 7.05 – 6.99 (m, 2H, $2 \times \text{C}(18)\text{H}$), 3.89 (s, 3H, $\text{C}(20)\text{H}_3$), 3.53 (dd, $J = 13.8, 2.1$ Hz, 1H, $\text{C}(15)\text{H}_\text{A}\text{H}_\text{B}$), 2.96 (dd, $J = 13.8, 11.9$ Hz, 1H, $\text{C}(15)\text{H}_\text{A}\text{H}_\text{B}$), 2.56 (dddd, $J = 12.0, 10.2, 8.3, 2.1$ Hz, 1H, $\text{C}(13)\text{H}$), 2.33 – 2.24 (m, 1H, $\text{C}(12)\text{H}_\text{A}\text{H}_\text{B}$), 2.22 (s, 3H, $\text{C}(\text{Ph}^*)\text{H}_3$), 2.18 – 2.12 (m, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 2.01 (s, 3H, $\text{C}(\text{Ph}^*)\text{H}_3$), 1.94 (s, 3H, $\text{C}(\text{Ph}^*)\text{H}_3$), 1.87 – 1.77 (m, 1H, $\text{C}(10)\text{H}_\text{A}\text{H}_\text{B}$), 1.73 – 1.52 (m, 4H, $\text{C}(10)\text{H}_\text{A}\text{H}_\text{B}$, $\text{C}(11)\text{H}_2$, $\text{C}(12)\text{H}_\text{A}\text{H}_\text{B}$), 1.11 (s, 3H, $\text{C}(14)\text{H}_3$);

^{13}C NMR (151 MHz, CDCl_3) δ 217.4 $\text{C}(8)$, 163.8 $\text{C}(19)$, 138.8 $\text{C}(\text{Ar}(\text{Ph}^*))$, 135.3 $\text{C}(\text{Ar}(\text{Ph}^*))$, 133.5 $\text{C}(\text{Ar}(\text{Ph}^*))$, 133.1 $\text{C}(\text{Ar}(\text{Ph}^*))$, 132.0 $\text{C}(16)$, 130.2 $2 \times \text{C}(17)$, 128.1 $\text{C}(\text{Ar}(\text{Ph}^*))$, 128.0 $\text{C}(\text{Ar}(\text{Ph}^*))$, 114.6 $2 \times \text{C}(18)$, 58.7 $\text{C}(9)$, 58.4 $\text{C}(15)$, 55.8 $\text{C}(20)$, 39.7 $\text{C}(13)$, 36.8 $\text{C}(10)$, 29.7 $\text{C}(12)$, 22.1 $\text{C}(11)$,

19.2 C(Me(Ph*)), 18.4 C(14), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

Selected characteristic peaks for the minor (1*SR*, 2*RS*) diastereomer (from the mixture):

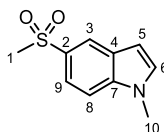
¹H NMR (600 MHz, CDCl₃) δ 7.87 – 7.83 (m, 2H, 2 × C(17)*H*), 3.48 (m, 1H, C(15)*H_AH_B*), 3.44 (dd, *J* = 14.4, 2.4 Hz, 1H, C(15)*H_AH_B*), 2.21 (s, 3H, C(Ph*)*H₃*), 1.96 (s, 3H, C(Ph*)*H₃*), 1.13 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.4 C(8), 163.6 C(19), 139.3, 135.1, 132.8, 131.9, 130.1, 127.7, 60.1, 58.6, 45.1 C(13), 38.9 C(10), 30.8 C(12), 24.1 C(14), 21.9 C(Me(Ph*)), 18.6 C(Me(Ph*)), 16.1 C(Me(Ph*)), 15.9 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3018, 1720, 1676, 1579, 1317, 1297, 1262, 1144, 1091, 1027, 838, 808;

HRMS (ESI⁺) C₂₆H₃₅O₄S⁺ ([M+H]⁺) requires 443.2251; found 443.2246, Δ 1.09 ppm.

S25 1-Methyl-5-(methylsulfonyl)-1*H*-indole



5-Bromo-1-methyl-1*H*-indole (1.99 g, 9.50 mmol) was dissolved in THF (20 mL) and the solution was cooled to −78 °C. *n*-BuLi (4.0 mL, 2.5 M in hexanes, 10 mL) was added dropwise and the resulting mixture allowed to stir at −78 °C for 1 h. The mixture was transferred *via* syringe to a suspension of 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct, (2.40 g, 10.0 mmol) in THF (20 mL) at −40 °C. The reaction mixture was stirred at −40 °C for 2 h, allowed to warm to RT and the THF was removed under a stream of N₂. The residue was dissolved in *N,N*-dimethylformamide (40 mL) and MeI (1.8 mL, 29 mmol) was added. The resulting suspension was heated to 75 °C overnight, cooled to RT, and Et₂O (50 mL) was added. The resulting suspension was filtered through a Celite® pad and the filtrate concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 80:10:10 → 40:10:50) gave the *title compound* as a yellow solid (751 mg, 38%).

m.p. = 112 – 114 °C;

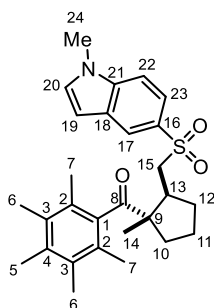
^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 1.8, 0.6$ Hz, 1H, C(3)*H*), 7.76 (dd, $J = 8.7, 1.8$ Hz, 1H, C(9)*H*), 7.45 (dt, $J = 8.7, 0.8$ Hz, 1H, C(8)*H*), 7.21 (d, $J = 3.2$ Hz, 1H, C(6)*H*), 6.64 (dd, $J = 3.2, 0.9$ Hz, 1H, C(5)*H*), 3.86 (s, 3H, C(10) H_3), 3.07 (s, 3H, C(1) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 138.9 C(7), 131.6 C(6), 131.5 C(2), 128.2 C(4), 121.9 C(3), 120.1 C(9), 110.0 C(8), 103.0 C(5), 45.4 C(1), 33.3 C(10);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2927, 1697, 1601, 1574, 1513, 1484, 1449, 1345, 1305, 1209, 1140, 1063, 960;

HRMS (ESI^+) $\text{C}_{10}\text{H}_{11}\text{NNaO}_2\text{S}^+$ ($[\text{M}+\text{Na}]^+$) requires 232.0403; found 232.0402, Δ 0.30 ppm.

165q (1-Methyl-2-(((1-methyl-1*H*-indol-5-yl)sulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfone **S25** (126 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $t\text{BuOH}$ (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/ CH_2Cl_2 /EtOAc, 85:5:10 $\rightarrow$ 83:5:12) gave inseparable diastereomers of the *title compound* as a tan solid (97 mg, 69%, [94:6] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by analogy with other products.

m.p. = 158 – 160 °C;

Major (1*RS*, 2*RS*) diastereomer (from the mixture):

^1H NMR (600 MHz, CDCl_3) δ 8.19 (d, $J = 1.7$ Hz, 1H, C(17)*H*), 7.69 (dd, $J = 8.6, 1.8$ Hz, 1H, C(23)*H*), 7.43 (d, $J = 8.6$ Hz, 1H, C(22)*H*), 7.21 (d, $J = 3.1$ Hz, 1H, C(20)*H*), 6.64 (d, $J = 3.1$ Hz, 1H, C(19)*H*), 3.87 (s, 3H, C(24) H_3), 3.56 (dd, $J = 13.9, 2.1$ Hz, 1H, C(15) $\text{H}_\text{A}\text{H}_\text{B}$), 3.01 (dd, $J = 13.8, 11.9$ Hz, 1H, C(15) $\text{H}_\text{A}\text{H}_\text{B}$), 2.60 (dddd, $J = 12.0, 10.1, 8.2, 2.1$ Hz, 1H, C(13)*H*), 2.37 – 2.26 (m, 1H, C(12) $\text{H}_\text{A}\text{H}_\text{B}$),

2.21 (s, 3H, C(Ph*)H₃), 2.13 (s, 3H, C(Ph*)H₃), 2.11 (s, 3H, C(Ph*)H₃), 2.00 (s, 3H, C(Ph*)H₃), 1.87 (s, 3H, C(Ph*)H₃), 1.85 – 1.77 (m, 1H, C(10)H_AH_B), 1.74 – 1.58 (m, 4H, C(10)H_AH_B, C(11)H₂ C(12)H_AH_B), 1.10 (s, 3H, C(14)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.4 C(8), 139.0 C(21), 138.8 C(Ar(Ph*)), 135.2 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 131.4 C(20), 130.9 C(16), 128.2 C(Ar(Ph*)), 128.1 C(18), 128.1 C(Ar(Ph*)), 122.5 C(17), 120.7 C(23), 109.9 C(22), 103.1 C(19), 58.8 C(9), 58.7 C(15), 39.9 C(13), 36.9 C(10), 33.3 C(24), 29.8 C(12), 22.2 C(11), 19.2 C(Me(Ph*)), 18.4 C(Me(Ph*)), 18.4 C(14), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

Selected characteristic peaks for the minor diastereomer (from the mixture):

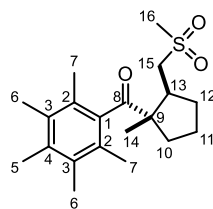
¹H NMR (600 MHz, CDCl₃) δ 8.24 (d, *J* = 1.8 Hz, 1H, C(17)H), 7.74 (dd, *J* = 8.7, 1.8 Hz, 1H, C(23)H), 3.53 – 3.47 (m, 2H, C(15)H₂), 2.15 (s, 3H, C(Ph*)H₃), 2.01 (s, 3H, C(Ph*)H₃), 1.94 (s, 3H, C(Ph*)H₃), 1.11 (s, 3H, C(14)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.5 C(8), 139.5, 135.1, 132.9, 130.9, 128.0, 127.9, 122.6, 120.8, 103.1, 60.2 C(9), 59.1 C(15), 45.4 C(13), 39.0 C(12), 31.0 C(10), 29.8, 24.2 C(14), 22.1, 18.7, 16.0;

IR (film) ν_{max}/cm⁻¹ 2979, 1679, 1608, 1514, 1345, 1328, 1303, 1282, 1138, 1063, 919;

HRMS (ESI⁺) C₂₈H₃₆NO₃S⁺ ([M+H]⁺) requires 466.2410; found 466.2409, Δ 0.24 ppm.

165r (1-Methyl-2-((methylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), dimethyl sulfone **229** (141 mg, 1.50 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 65:10:25 → 60:10:30) gave separable diastereomers of the *title compound* as a white solid (93 mg, 88%, [96:4] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The relative stereochemistry was assigned by X-Ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer

m.p. = 164 – 166 °C;

¹H NMR (600 MHz, CDCl₃) δ 3.51 (dd, *J* = 13.7, 2.1 Hz, 1H, C(15)*H_AH_B*), 2.94 – 2.83 (m, 4H, C(15)*H_AH_B*, C(16)*H₃*), 2.69 (tdd, *J* = 12.2, 9.3, 2.1 Hz, 1H, C(13)*H*), 2.40 – 2.29 (m, 1H, C(12)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.12 (s, 3H, C(Ph*)*H₃*), 2.07 (s, 3H, C(Ph*)*H₃*), 1.93 – 1.88 (m, 1H, C(10)*H_AH_B*), 1.79 – 1.62 (m, 3H, C(11)*H₂*, C(10)*H_AH_B*), 1.62 – 1.53 (m, 1H, C(12)*H_AH_B*), 1.16 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.6 C(8), 138.7 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.7 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 58.8 C(9), 56.5 C(15), 42.0 C(16), 39.4 C(13), 36.8 C(10), 29.8 C(12), 22.1 C(11), 19.3 C(Me(Ph*)), 18.8 C(Me(Ph*)), 18.5 C(14), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2960, 1678, 1588, 1470, 1416, 1385, 1302, 1260, 1227, 1137, 1098;

HRMS (ESI⁺) C₂₀H₃₁O₃S⁺ ([M+H]⁺) requires 351.1988; found 351.1979, Δ 2.68 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

m.p. = 127 – 129 °C;

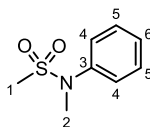
¹H NMR (600 MHz, CDCl₃) δ 3.48 (dd, *J* = 14.0, 11.2 Hz, 1H, C(15)*H_AH_B*), 3.39 (dd, *J* = 14.1, 2.1 Hz, 1H, C(15)*H_AH_B*), 2.97 (s, 3H, C(16)*H₃*), 2.42 (dtd, *J* = 10.6, 7.9, 2.1 Hz, 1H, C(13)*H*), 2.29 – 2.25 (m, 1H, C(12)*H_AH_B*), 2.25 – 2.20 (m, 4H, C(10)*H_AH_B*, C(Ph*)*H₃*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.15 – 2.07 (m, 1H, C(12)*H_AH_B*), 2.06 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 3H, C(Ph*)*H₃*), 1.85 – 1.75 (m, 2H, C(11)*H₂*), 1.63 – 1.57 (m, 1H, C(10)*H_AH_B*), 1.21 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.7 C(8), 139.2 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 60.3 C(9), 56.7 C(15), 44.5 C(13), 42.4 C(16), 38.9 C(10), 31.2 C(12), 24.3 C(14), 22.1 C(11), 18.9 C(Me(Ph*)), 18.5 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2933, 1679, 1461, 1414, 1385, 1303, 1265, 1141, 1097, 965, 916, 842;

HRMS (ESI⁺) C₂₀H₃₁O₃S⁺ ([M+H]⁺) requires 351.1988; found 351.1986, Δ 0.68 ppm.

S26 N-Methyl-N-phenylmethanesulfonamide



A solution of *N*-methylaniline (1.0 mL, 9.2 mmol) and NEt₃ (1.3 mL, 9.2 mmol) in CH₂Cl₂ (20 mL) was cooled to –20 °C. Methanesulfonyl chloride (1.1 mL, 14 mmol) was added dropwise and the reaction was allowed to warm to RT for 6 h. The reaction was quenched with the addition of sat. aq. NH₄Cl (3 mL) and diluted further with CH₂Cl₂ (50 mL) and water (50 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 × 60 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 85:15 → 80:20) gave the title compound as a white solid (1.56 g, 92%).

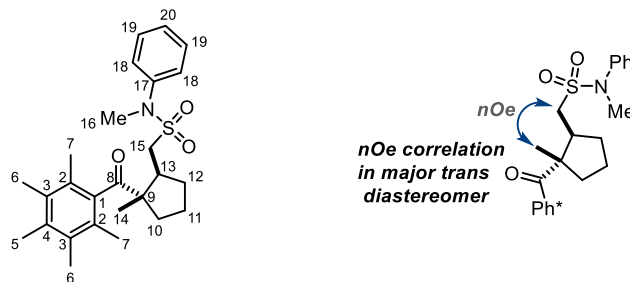
¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.35 (m, 4H, 2 × C(4)H, 2 × C(5)H), 7.33 – 7.27 (m, 1H, C(6)H), 3.33 (s, 3H, C(2)H₃), 2.84 (s, 3H, C(1)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 141.6 C(3), 129.5 2 × C(5), 127.6 C(6), 126.3 2 × C(4), 38.2 C(2), 35.3 C(1);

m/z (ESI⁺) Found ([M+H]⁺) = 186, C₈H₁₂NO₂S requires 186.

The spectroscopic data were consistent with that reported in the literature.¹⁵⁴

165s

***N*-Methyl-1-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-*N*-phenylmethanesulfonamide**

Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfonamide **S26** (111 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 90:5:5) gave separable diastereomers of the *title compound* as a white solid (102 mg, 77%, [93:7] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 118 – 120 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.43 – 7.37 (m, 4H, 2 × C(18)*H*, 2 × C(19)*H*), 7.30 – 7.26 (m, 1H, C(20)*H*), 3.49 (dd, *J* = 13.3, 2.3 Hz, 1H, C(15)*H_AH_B*), 3.33 (s, 3H, C(16)*H₃*), 2.80 (dd, *J* = 13.4, 11.9 Hz, 1H, C(15)*H_AH_B*), 2.65 (dddd, *J* = 12.2, 10.4, 8.2, 2.3 Hz, 1H, C(13)*H*), 2.30 – 2.23 (m, 1H, C(12)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.15 (s, 3H, C(Ph*)*H₃*), 2.00 (s, 6H, 2 × C(Ph*)*H₃*), 1.93 – 1.81 (m, 1H, C(10)*H_AH_B*), 1.73 – 1.59 (m, 3H, C(10)*H_AH_B*, C(11)*H₂*), 1.59 – 1.52 (m, 1H, C(12)*H_AH_B*), 1.10 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.6 C(8), 141.6 C(17), 138.6 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.6 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 129.4 2 × C(19), 128.2 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.3 C(20), 126.5 2 × C(18), 58.8 C(9), 50.3 C(15), 40.1 C(13), 38.3 C(16), 37.1 C(10), 29.6 C(12), 21.9 C(11), 19.2 C(Me(Ph*)), 18.5 C(Me(Ph*)), 18.0 C(14), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3020, 1676, 1597, 1494, 1360, 1146, 1028, 926, 873, 698;

HRMS (ESI⁺) C₂₆H₃₆NO₃S⁺ ([M+H]⁺) requires 442.2410; found 442.2402, Δ 1.97 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

m.p. = 118 – 120 °C;

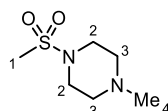
¹H NMR (600 MHz, CDCl₃) δ 7.44 – 7.35 (m, 4H, 2 × C(18)*H*, 2 × C(19)*H*), 7.30 – 7.24 (m, 1H, C(20)*H*), 3.39 – 3.32 (m, 4H, C(15)*H_AH_B*, C(16)*H₃*), 3.26 (dd, *J* = 13.9, 11.3 Hz, 1H, C(15)*H_AH_B*), 2.46 – 2.34 (m, 1H, C(13)*H*), 2.24 – 2.17 (m, 5H, C(10)*H_AH_B*, C(12)*H_AH_B*, C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.14 – 2.09 (m, 4H, C(12)*H_AH_B*, C(Ph*)*H₃*), 2.02 (s, 3H, C(Ph*)*H₃*), 1.86 (s, 3H, C(Ph*)*H₃*), 1.83 – 1.66 (m, 2H, C(11)*H₂*), 1.60 (ddd, *J* = 13.1, 8.6, 6.4 Hz, 1H, C(10)*H_AH_B*), 1.10 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 218.4 C(8), 141.7 C(17), 139.7 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 129.4 2 × C(19), 127.8 C(Ar(Ph*)), 127.5 C(Ar(Ph*)), 127.3 C(20), 126.4 2 × C(18), 59.8 C(9), 50.6 C(15), 45.4 C(13), 39.4 C(10), 38.3 C(16), 30.9 C(12), 24.5 C(14), 22.0 C(11), 18.2 C(Me(Ph*)), 18.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 3026, 2944, 1678, 1493, 1457, 1344, 1268, 1218, 1174, 1077, 920, 898, 869;

HRMS (ESI⁺) C₂₆H₃₆NO₃S⁺ ([M+H]⁺) requires 442.2410; found 442.2401, Δ 2.04 ppm.

S27 1-Methyl-4-(methylsulfonyl)piperazine



1-Methylpiperazine (1.11 mL, 10.0 mmol) and NEt₃ (2.1 mL, 15 mmol) were dissolved in CH₂Cl₂ (70 mL) and the mixture was cooled to 0 °C. Methanesulfonyl chloride (0.81 mL, 10.5 mmol) was added slowly, the mixture allowed to warm to RT and stirred for 1 h. The reaction mixture was diluted with 1 M NaOH (100 mL), the layers separated and the aqueous layer extracted with CH₂Cl₂ (2 × 100 mL). The combined organic layers were washed with sat. aq. NH₄Cl (2 × 100 mL), dried over Na₂SO₄ and concentrated *in vacuo* to give the *title compound* as an off-white solid, which required no further purification (477 mg, 27%).

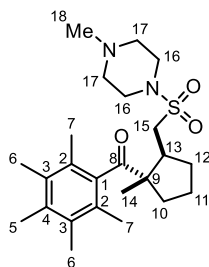
¹H NMR (400 MHz, CDCl₃) δ 3.27 (t, *J* = 5.0 Hz, 4H, 2 × C(2)H₂), 2.78 (s, 3H, C(4)H₃), 2.54 (t, *J* = 5.0 Hz, 4H, 2 × C(3)H₂), 2.35 (s, 3H, C(1)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 54.4 2 × C(3), 45.9 C(4), 45.8 2 × C(2), 34.4 C(1);

m/z (ESI⁺) Found ([M+H]⁺) = 179, C₆H₁₅N₂O₂S requires 179.

The spectroscopic data matched that previously reported in the literature.¹⁵⁵

165t (1-Methyl-2-(((4-methylpiperazin-1-yl)sulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl) methanone



Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfonamide **S27** (107 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent CH₂Cl₂/7 N NH₃ in MeOH, 99.2:0.8 → 99:1) gave inseparable diastereomers of the *title compound* as a white solid (103 mg, 79%, [93:7] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by analogy with other products.

m.p. = 153 – 155 °C;

Major (1*RS*, 2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 3.30 (dd, *J* = 13.0, 2.0 Hz, 1H, C(15)H_AH_B), 3.25 (t, *J* = 5.0 Hz, 4H, 2 × C(16)H₂), 2.69 (dd, *J* = 13.0, 11.8 Hz, 1H, C(15)H_AH_B), 2.62 (dddd, *J* = 11.9, 10.0, 8.0, 1.9 Hz, 1H, C(13)H), 2.48 (t, *J* = 4.9 Hz, 4H, 2 × C(17)H₂), 2.33 (s, 3H, C(18)H₃), 2.31 – 2.25 (m, 1H, C(12)H_AH_B), 2.22 (s, 3H, C(Ph*)H₃), 2.17 (s, 3H, C(Ph*)H₃), 2.16 (s, 3H, C(Ph*)H₃), 2.11 (s, 3H,

$C(Ph^*)H_3$), 2.06 (s, 3H, $C(Ph^*)H_3$), 1.95 – 1.86 (m, 1H, $C(10)H_AH_B$), 1.75 – 1.62 (m, 3H, $C(10)H_AH_B$, $C(11)H_2$), 1.62 – 1.53 (m, 1H, $C(12)H_AH_B$), 1.14 (s, 3H, $C(14)H_3$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 217.5 $C(8)$, 138.8 $C(Ar(Ph^*))$, 135.3 $C(Ar(Ph^*))$, 133.6 $C(Ar(Ph^*))$, 133.1 $C(Ar(Ph^*))$, 128.2 $C(Ar(Ph^*))$, 128.0 $C(Ar(Ph^*))$, 58.8 $C(9)$, 54.7 $2 \times C(17)$, 49.7 $C(15)$, 46.1 $C(18)$, 45.7 $2 \times C(16)$, 39.8 $C(13)$, 37.0 $C(10)$, 29.8 $C(12)$, 21.9 $C(11)$, 19.3 $C(Me(Ph^*))$, 18.7 $C(Me(Ph^*))$, 18.4 $C(14)$, 16.8 $C(Me(Ph^*))$, 16.4 $C(Me(Ph^*))$, 16.1 $C(Me(Ph^*))$);

Selected characteristic peaks for the minor (1*SR*, 2*RS*) diastereomer (from the mixture):

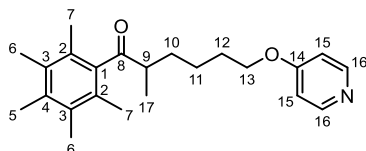
^1H NMR (600 MHz, $CDCl_3$) δ 2.05 (s, 3H, $C(Ph^*)H_3$), 1.18 (s, 3H, $C(14)H_3$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 217.9 $C(8)$, 139.6, 135.3, 133.5, 133.0, 127.9, 127.6, 60.0, 50.5, 45.7, 45.4, 39.2, 31.1, 24.5 $C(14)$, 22.0, 18.6, 18.4, 16.8, 16.3, 16.0;

IR (film) ν_{max}/cm^{-1} 2943, 2799, 1677, 1456, 1341, 1327, 1289, 1164, 1146, 951, 916;

HRMS (ESI⁺) $C_{24}H_{39}N_2O_3S^+$ ($[M+H]^+$) requires 435.2676; found 435.2676, Δ 1.44 ppm.

195 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-6-(pyridin-4-yloxy)hexan-1-one



Hydroxy ketone **164** (83 mg, 0.30 mmol), 4-(methylsulfonyl)pyridine (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and $KOtBu$ (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $tBuOH$ (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/ Et_2O / $EtOAc$, 60:40:0 $\rightarrow$ pentane/ Et_2O / $EtOAc$ 50:0:50) gave the *title compound* as a colourless solid (91 mg, 85% (99% pure by mass)).

m.p. = 60 – 62 °C;

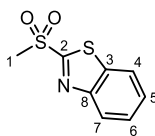
^1H NMR (600 MHz, $CDCl_3$) δ 8.44 (s, 2H, $2 \times C(16)H$), 6.79 (s, 2H, $2 \times C(15)H$), 4.00 (t, J = 6.4 Hz, 2H, $C(13)H_2$), 2.92 – 2.71 (m, 1H, $C(9)H$), 2.23 (s, 3H, $C(Ph^*)H_3$), 2.18 (s, 6H, $2 \times C(Ph^*)H_3$), 2.09 (s, 6H, $2 \times C(Ph^*)H_3$), 1.91 – 1.75 (m, 3H, $C(10)H_AH_B$, $C(12)H_2$), 1.67 – 1.56 (m, 1H, $C(11)H_AH_B$), 1.52 – 1.39 (m, 2H, $C(10)H_AH_B$, $C(11)H_AH_B$), 1.16 (d, J = 7.1 Hz, 3H, $C(17)H_3$);

^{13}C NMR (151 MHz, CDCl_3) δ 214.8 C(8), 165.3 C(14), 151.3 (br.) $2 \times$ C(16), 140.0 C(Ar(Ph*)), 135.6 $2 \times$ C(Ar(Ph*)), 133.3 $2 \times$ C(Ar(Ph*)), 128.3 C(Ar(Ph*)), 110.6 $2 \times$ C(15), 67.8 C(13), 48.4 C(9), 31.5 C(10), 29.1 C(12), 24.0 C(11), 18.1 $2 \times$ C(Me(Ph*)), 16.9 $2 \times$ C(Me(Ph*)), 16.2 C(Me(Ph*)), 15.4 C(17);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 1694, 1595, 1569, 1502, 1471, 1420, 1287, 1212, 1096, 1020, 821, 759;

HRMS (ESI⁺) $\text{C}_{23}\text{H}_{32}\text{NO}_2^+$ ([M+H]⁺) requires 354.2428; found 354.2420, Δ 2.22 ppm.

196 2-(Methylsulfonyl)benzo[d]thiazole



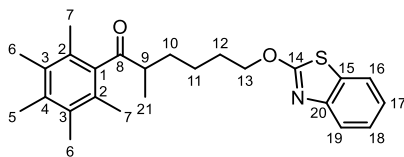
2-Methylthiobenzothiazole (1.00 g, 5.51 mmol) was dissolved in EtOH (30 mL) and the solution was cooled to 0 °C. $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (362 mg, 1.10 mmol) was added and H_2O_2 solution (35 wt%, 6.0 mL, 62 mmol) was added slowly. The reaction was allowed to warm to RT and stirred for 48 h, cooled to 0 °C and quenched with dropwise addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). The mixture was concentrated *in vacuo* and diluted with EtOAc (50 mL) and water (30 mL). The layers were separated and the aqueous layer extracted with EtOAc (2×50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 92:8 $\rightarrow$ 87:13) gave the *title compound* as a white solid (480 mg, 41%).

^1H NMR (400 MHz, CDCl_3) δ 8.22 (ddd, $J = 8.2, 1.4, 0.7$ Hz, 1H, C(7)H), 8.02 (ddd, $J = 7.8, 1.5, 0.7$ Hz, 1H, C(4)H), 7.77 – 7.51 (m, 2H, C(5)H, C(6)H), 3.42 (s, 3H, C(1)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 166.6 C(2), 152.6 C(8), 136.8 C(3), 128.2 C(5), 127.9 C(6), 125.6 C(7), 122.5 C(4), 42.6 C(1);

m/z (ESI⁺) Found ([M+H]⁺) = 214, $\text{C}_8\text{H}_8\text{NO}_2\text{S}_2$ requires 214.

The spectroscopic data were consistent with that reported in the literature.¹⁵⁶

197 6-(Benzo[d]thiazol-2-yloxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

Hydroxy ketone **164** (83 mg, 0.30 mmol), sulfone **196** (128 mg, 0.600 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 90:10) gave the *title compound* as a white solid (110 mg, 90%).

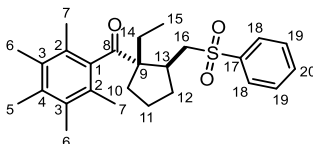
m.p. = 87 – 89 °C;

¹H NMR (500 MHz, CDCl₃) δ 7.67 (dd, *J* = 8.1, 1.2 Hz, 1H, C(19)*H*), 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H, C(16)*H*), 7.36 (ddd, *J* = 8.2, 7.3, 1.3 Hz, 1H, C(18)*H*), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H, C(17)*H*), 4.55 (t, *J* = 6.6 Hz, 2H, C(13)*H*), 2.82 (dq, *J* = 8.0, 6.9, 4.6 Hz, 1H, C(9)*H*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, 2 × C(Ph*)*H*₃), 2.10 (s, 6H, C(Ph*)*H*₃), 1.94 – 1.77 (m, 3H, C(10)*H*_A*H*_B, C(12)*H*₂), 1.69 – 1.57 (m, 1H, C(11)*H*_A*H*_B), 1.56 – 1.38 (m, 2H, C(10)*H*_A*H*_B, C(11)*H*_A*H*_B), 1.17 (d, *J* = 7.0 Hz, 3H, C(21)*H*₃);

¹³C NMR (126 MHz, CDCl₃) δ 214.8 C(8), 173.1 C(14), 149.5 C(20), 140.0 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 131.9 C(15), 128.3 2 × C(Ar(Ph*)), 126.1 C(18), 123.6 C(17), 121.4 C(16), 120.8 C(19), 72.0 C(13), 48.4 C(9), 31.5 C(10), 29.1 C(12), 23.9 C(11), 18.1 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.4 C(21);

IR (film) ν_{max} /cm⁻¹ 2944, 1691, 1598, 1538, 1459, 1443, 1251, 1219, 1125, 1068, 758;

HRMS (ESI⁺) C₂₅H₃₂NO₂S⁺ ([M+H]⁺) requires 410.2148; found 410.2139, Δ 2.35 ppm.

165u (1-Ethyl-2-((phenylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **S16** (87 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 24 h. Purification *via* flash column chromatography (eluent

pentane/CH₂Cl₂/Et₂O, 88:5:7 → 87:5:8) gave the *title compound* as a white solid (72 mg, 56%, [87:13] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by analogy with the other products.

m.p. = 143 – 145 °C;

Major (1*RS*, 2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 7.83 – 7.77 (m, 2H, 2 × C(18)*H*), 7.67 – 7.62 (m, 1H, C(20)*H*), 7.57 – 7.52 (m, 2H, 2 × C(19)*H*), 3.19 (dd, *J* = 13.6, 2.3 Hz, 1H, C(16)*H_AH_B*), 2.97 (dd, *J* = 13.6, 12.2 Hz, 1H, C(16)*H_AH_B*), 2.71 – 2.62 (m, 1H, C(13)*H*), 2.31 – 2.22 (m, 4H, C(12)*H_AH_B*, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.09 – 2.03 (m, 7H, C(10)*H_AH_B*, 2 × C(Ph*)*H₃*), 1.93 – 1.84 (m, 1H, C(14)*H_AH_B*), 1.77 (m, 1H, C(10)*H_AH_B*), 1.69 – 1.58 (m, 3H, C(11)*H₂*, C(12)*H_AH_B*), 1.25 – 1.17 (m, 1H, C(14)*H_AH_B*), 0.94 (t, *J* = 7.4 Hz, 3H, C(15)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 215.3 C(8), 140.8 C(17), 137.4 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.7 C(20), 133.6 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 129.4 2 × C(19), 129.3 C(Ar(Ph*)), 129.0 C(Ar(Ph*)), 127.8 2 × C(18), 63.5 C(9), 57.8 C(16), 39.6 C(13), 31.3 C(10), 29.6 C(12), 22.4 C(11), 21.9 C(14), 19.0 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.0 C(Me(Ph*)), 9.3 C(15);

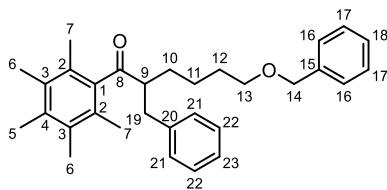
Selected characteristic peaks for the minor (1*SR*, 2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 8.00 – 7.90 (m, 2H), 7.62 – 7.60 (m, 2H), 3.58 – 3.45 (m, 2H, C(16)*H₂*), 2.49 – 2.41 (m, 1H, C(13)*H*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.00 (s, 3H, C(Ph*)*H₃*), 0.68 (t, *J* = 7.4 Hz, 3H, C(15)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.4 C(8), 140.2, 139.4, 135.3, 133.4, 133.1, 128.2, 128.1, 63.6 C(9), 58.6 C(16), 40.5 C(13), 33.6, 26.8, 22.6, 19.1, 18.9, 16.8, 16.3, 16.1, 8.2 C(15);

IR (film) ν_{max} /cm⁻¹ 2965, 2880, 1673, 1448, 1307, 1148, 914, 736;

HRMS (ESI⁺) C₂₆H₃₅O₃S⁺ ([M+H]⁺) requires 427.2301; found 427.2295, Δ 1.46 ppm.

S28 2-Benzyl-6-(benzyloxy)-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

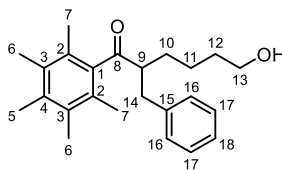
Ketone **102** (840 mg, 3.00 mmol), $[\text{Ir}(\text{cod})\text{Cl}]_2$ (20 mg, 1.0 mol%), dppBz (27 mg, 2.0 mol%), and KOH (673 mg, 12.0 mmol) were added to a 5 – 10 mL microwave vial. The vial was sealed and purged with Ar (balloon) for 5 min and PhMe (0.75 mL, 4 M) and 4-benzyloxy-butanol (1.62 g, 9.00 mmol) were added. The reaction was heated at 110 °C for 28 h, cooled to RT, filtered through a silica plug (elution with Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 95:5) gave the *title compound* as a colourless oil (1.33 g, 95%).

^1H NMR (400 MHz, CDCl_3) δ 7.53 – 6.83 (m, 10H, 10 $\times$ C(Ph)*H*), 4.44 (s, 2H, C(14)*H*₂), 3.37 (t, J = 6.4 Hz, 2H, C(13)*H*₂), 3.17 (dd, J = 13.5, 6.2 Hz, 1H, C(19)*H*_A*H*_B), 3.12 – 3.00 (m, 1H, C(9)*H*), 2.67 (dd, J = 13.5, 7.5 Hz, 1H, C(19)*H*_A*H*_B), 2.22 (s, 3H, C(Ph*)*H*₃), 2.15 (s, 6H, 2 $\times$ C(Ph*)*H*₃), 2.02 (br. s, 6H, 2 $\times$ C(Ph*)*H*₃), 1.78 – 1.67 (m, 1H, C(10)*H*_A*H*_B), 1.57 – 1.48 (m, 2H, C(12)*H*₂), 1.48 – 1.31 (m, 3H, C(10)*H*_A*H*_B, C(11)*H*₂);

^{13}C NMR (101 MHz, CDCl_3) δ 212.9 C(8), 140.4 C(Ar), 139.6 C(Ar), 138.7 C(Ar), 135.7 C(Ar), 133.2 2 $\times$ C(Ar), 129.5 2 $\times$ C(Ar(Ph)), 128.7 2 $\times$ C(Ar), 128.5 2 $\times$ C(Ar(Ph)), 128.4 2 $\times$ C(Ar(Ph)), 127.7 2 $\times$ C(Ar(Ph)), 127.6 C(Ar(Ph)), 126.2 C(Ar(Ph)), 73.0 C(14), 70.2 C(13), 56.0 C(9), 35.6 C(19), 30.0 C(12), 29.5 C(10), 24.0 C(11), 17.8 2 $\times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 2 $\times$ C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2937, 2858, 1691, 1495, 1454, 1362, 1303, 1260, 1204, 1099, 1028, 913;

HRMS (ESI⁺) $\text{C}_{31}\text{H}_{39}\text{O}_2^+$ ([M+H]⁺) requires 443.2945; found 443.2945, Δ 0.15 ppm.

S29 2-Benzyl-6-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

Benzyl ether **S28** (1.24 g, 2.80 mmol) was subjected to **General Procedure F** in MeOH (25 mL) with Pd (10% on carbon) (124 mg, 10 wt%) for 2 h. The *title compound* was obtained as a white solid which was used without further purification (980 mg, 99%).

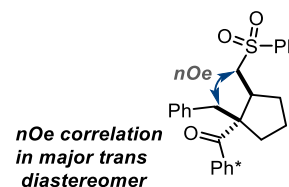
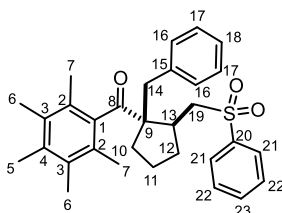
m.p. = 86 – 88 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.22 (m, 2H, 2 × C(Ph)H), 7.21 – 7.14 (m, 3H, 3 × C(Ph)H), 3.63 – 3.49 (m, 2H, C(13)H₂), 3.16 (dd, *J* = 13.5, 5.9 Hz, 1H, C(14)H_AH_B), 3.11 – 2.99 (m, 1H, C(9)H), 2.65 (dd, *J* = 13.5, 8.0 Hz, 1H, C(14)H_AH_B), 2.23 (s, 3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.00 (br. s, 6H, 2 × C(Ph*)H₃), 1.72 (m, 1H, C(10)H_AH_B), 1.54 – 1.30 (m, 5H, C(10)H_AH_B, C(11)H₂, C(12)H₂), 1.24 (t, *J* = 5.5 Hz, 1H, OH);

¹³C NMR (101 MHz, CDCl₃) δ 213.0 C(8), 140.3 C(Ar), 139.6 C(Ar), 135.8 C(Ar), 133.3 2 × C(Ar(Ph*)), 129.4 2 × C(Ar(Ph)), 128.7 2 × C(Ar(Ph*)), 128.4 2 × C(Ar(Ph)), 126.3 C(Ar(Ph)), 62.7 C(13), 56.0 C(9), 35.8 C(14), 32.9 C(12), 29.2 C(10), 23.5 C(11), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3392, 2937, 1689, 1454, 1383, 1302, 1260, 1126, 1070, 1030, 913;

HRMS (ESI⁺) C₂₄H₃₃O₂⁺ ([M+H]⁺) requires 353.2475; found 353.2476, Δ 0.28 ppm.

165v ((1*S*,2*R*))-1-Benzyl-2-((phenylsulfonyl)methyl)cyclopentyl(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **S29** (106 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column

chromatography (eluent pentane/CH₂Cl₂/Et₂O, 89:5:6) gave a single diastereomer of the *title compound* as an off-white solid (45 mg, 31%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

m.p. = 174 – 176 °C;

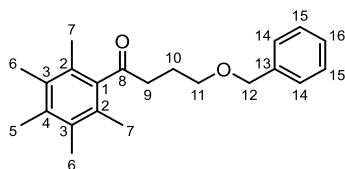
¹H NMR (600 MHz, CDCl₃) δ 7.96 – 7.89 (m, 2H, 2 × C(21)*H*), 7.72 – 7.66 (m, 1H, C(23)*H*), 7.63 – 7.57 (m, 2H, 2 × C(22)*H*), 7.25 – 7.17 (m, 5H, 5 × C(Ph)*H*), 3.51 (dd, *J* = 13.6, 2.3 Hz, 1H, C(19)*H_AH_B*), 3.42 (dd, *J* = 12.9, 1.6 Hz, 1H, C(14)*H_AH_B*), 3.18 (dd, *J* = 13.7, 12.2 Hz, 1H, C(19)*H_AH_B*), 2.73 (dtd, *J* = 12.0, 9.4, 2.3 Hz, 1H, C(13)*H*), 2.42 – 2.35 (m, 1H, C(12)*H_AH_B*), 2.33 (d, *J* = 12.9 Hz, 1H, C(14)*H_AH_B*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.08 (s, 3H, C(Ph*)*H₃*), 2.07 – 2.03 (m, 1H, C(10)*H_AH_B*), 1.96 (s, 3H, C(Ph*)*H₃*), 1.94 – 1.86 (m, 1H, C(11)*H_AH_B*), 1.82 – 1.74 (m, 2H, C(11)*H_AH_B*, C(12)*H_AH_B*), 1.65 – 1.57 (m, 1H, C(10)*H_AH_B*), 1.12 (s, 3H, C(Ph*)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 214.0 C(8), 141.0 C(20), 137.8 C(15), 136.1 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.9 C(23), 133.6 C(Ar(Ph*)), 132.7 C(Ar(Ph*)), 131.6 2 × C(16), 130.3 C(Ar(Ph*)), 129.6 2 × C(22) & C(Ar(Ph*)), 128.2 2 × C(17), 127.9 2 × C(21), 126.8 C(18), 65.1 C(9), 57.6 C(19), 40.1 C(13), 33.1 C(14), 30.6 C(10), 29.1 C(12), 22.1 C(11), 18.0 C(Me(Ph*)), 17.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.5 C(Me(Ph*)), 15.6 C(Me(Ph*));

IR (film) $\nu_{\max}$ /cm⁻¹ 2954, 1673, 1494, 1448, 1308, 1217, 1149, 1112, 1086, 899;

HRMS (ESI⁺) C₃₁H₃₆NaO₃S⁺ ([M+Na]⁺) requires 511.2277; found 511.2272, Δ 1.11 ppm.

S30 4-(Benzyloxy)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



Benzyl bromide (0.54 mL, 4.5 mmol) and DIPEA (0.83 mL, 4.8 mmol) were added to alcohol **90** (702 mg, 3.00 mmol) and KI (50 mg, 0.30 mmol) in a 10 mL round-bottomed flask. The mixture was heated to 150 °C for 3 h, cooled to RT and diluted with EtOAc (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in*

vacuo. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 92:8) gave the *title compound* as a white solid (901 mg, 93%).

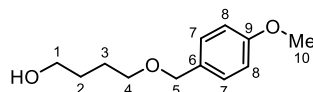
¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.26 (m, 5H, 5 × C(Ph)H), 4.51 (s, 2H, C(12)H₂), 3.59 (t, *J* = 6.1 Hz, 2H, C(11)H₂), 2.81 (t, *J* = 7.2 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 2.07 – 1.99 (m, 2H, C(10)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.8 C(8), 140.8 C(Ar(Ph*)), 138.6 C(13), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 128.5 2 × C(15), 127.8 2 × C(14), 127.7 C(16), 127.5 2 × C(Ar(Ph*)), 73.0 C(12), 69.4 C(11), 42.2 C(9), 23.6 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

m/z (ESI⁺) Found ([M+H]⁺) = 325, C₂₂H₂₉O₂ requires 325.

The spectroscopic data matched that reported in the literature.³⁴

S31 4-((4-Methoxybenzyl)oxy)butan-1-ol



1,4-Butanediol (1.46 mL, 16.5 mmol) was added to a stirred suspension of NaH (660 mg, 16.5 mmol, 60% dispersed in mineral oil) and tetrabutylammonium iodide (1.11 g, 3.00 mmol) in THF (60 mL) at 0 °C. The reaction was warmed to RT, stirred for 1 h, then heated to 60 °C for 16 h. The crude reaction mixture was poured into sat. NaHCO₃ and vigorously stirred for 10 min. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 70:30 → 50:50) gave the *title compound* as a pale yellow oil (2.79 g, 89%).

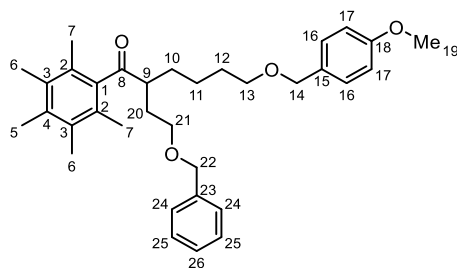
¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.22 (m, 2H, 2 × C(7)H), 6.91 – 6.83 (m, 2H, 2 × C(8)H), 4.45 (s, 2H, C(5)H₂), 3.80 (s, 3H, C(10)H₃), 3.63 (t, *J* = 5.8 Hz, 2H, C(1)H₂), 3.49 (t, *J* = 5.7 Hz, 2H, C(4)H₂), 2.13 (s, 1H, OH), 1.87 – 1.48 (m, 4H, 2 × C(2)H₂ & 2 × C(3)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 159.4 C(9), 130.3 C(6), 129.5 2 × C(7), 114.0 2 × C(8), 72.9 C(5), 70.2 C(4), 62.9 C(1), 55.4 C(10), 30.4 C(3), 26.9 C(2);

m/z (ESI⁺) Found ([M+Na]⁺) = 233, C₁₂H₁₈NaO₃ requires 233;

The spectroscopic data were consistent with that previously reported in the literature.¹⁵⁷

S32 2-(2-(Benzyloxy)ethyl)-6-((4-methoxybenzyl)oxy)-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one



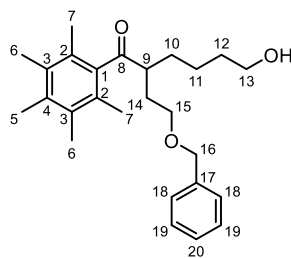
Ketone **S30** (648 mg, 2.00 mmol), alcohol **S31** (840 mg, 4.00 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (16 mg, 1.0 mol%), KOH (449 mg, 8.00 mmol) and PhMe (0.5 mL) were subjected to **General Procedure E** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 85:15 → 80:20) gave the *title compound* as a colourless oil (867 mg, 84%).

¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.30 (m, 2H, 2 × C(24)H), 7.30 – 7.26 (m, 3H, 2 × C(25)H, C(26)H), 7.25 – 7.20 (m, 2H, 2 × C(16)H), 6.88 – 6.84 (m, 2H, 2 × C(17)H), 4.47 – 4.41 (m, 2H, C(22)H₂), 4.39 (s, 2H, C(14)H₂), 3.80 (s, 3H, C(19)H₃), 3.59 – 3.50 (m, 2H, C(21)H₂), 3.38 (t, J = 6.5 Hz, 2H, C(13)H₂), 2.96 (p, J = 6.1 Hz, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.17 (s, 6H, 2 × C(Ph*)H₃), 2.11 (dt, J = 13.9, 6.6 Hz, 1H, C(20)H_AH_B), 2.07 (s, 6H, 2 × C(Ph*)H₃), 1.79 – 1.67 (m, 2H, C(20)H_AH_B, C(10)H_AH_B), 1.65 – 1.50 (m, 2H, C(12)H₂), 1.50 – 1.30 (m, 3H, C(10)H_AH_B, C(11)H₂);

¹³C NMR (151 MHz, CDCl₃) δ 213.7 C(8), 159.3 C(18), 139.8 C(Ar(Ph*)), 138.6 C(23), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 130.8 C(15), 129.4 2 × C(16), 128.6 2 × C(Ar(Ph*)), 128.5 2 × C(25), 127.7 2 × C(24), 127.6 C(26), 113.9 2 × C(17), 72.9 C(22), 72.7 C(14), 70.0 C(13), 68.4 C(21), 55.4 C(19), 50.3 C(9), 30.0 C(12), 29.7 C(10), 29.2 C(20), 24.1 C(11), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2942, 2862, 1689, 1614, 1512, 1455, 1363, 1301, 1247, 1099, 1036, 820;

HRMS (ESI⁺) C₃₄H₄₅O₄⁺ ([M+H]⁺) requires 517.3312; found 517.3322, Δ 1.88 ppm.

S33 2-(2-(Benzyloxy)ethyl)-6-hydroxy-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

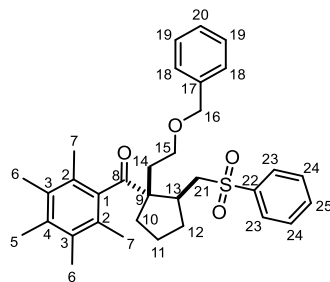
Ketone **S32** (850 mg, 1.65 mmol) was dissolved in a mixture of CH_2Cl_2 (14.5 mL): water (1.5 mL) and DDQ (561 g, 2.47 mmol) was added. The mixture was stirred at RT for 3 h, quenched with sat. aq. NaHCO_3 (20 mL) and diluted with water (20 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 80:20) gave the *title compound* as a colourless oil (544 mg, 83%).

^1H NMR (600 MHz, CDCl_3) δ 7.36 – 7.30 (m, 2H, $2 \times \text{C}(18)\text{H}$), 7.30 – 7.27 (m, 3H, $2 \times \text{C}(19)\text{H}$, $\text{C}(20)\text{H}$), 4.49 – 4.38 (m, 2H, $\text{C}(16)\text{H}_2$), 3.59 (t, $J = 6.4$ Hz, 2H, $\text{C}(13)\text{H}_2$), 3.57 – 3.51 (m, 2H, $\text{C}(15)\text{H}_2$), 2.97 (p, $J = 6.1$ Hz, 1H, $\text{C}(9)\text{H}$), 2.23 (s, 3H, $\text{C}(\text{Ph}^*)\text{H}_3$), 2.17 (s, 6H, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 2.14 – 2.06 (m, 7H, $\text{C}(14)\text{H}_\text{A}\text{H}_\text{B}$, $2 \times \text{C}(\text{Ph}^*)\text{H}_3$), 1.80 – 1.66 (m, 2H, $\text{C}(10)\text{H}_\text{A}\text{H}_\text{B}$, $\text{C}(14)\text{H}_\text{A}\text{H}_\text{B}$), 1.58 – 1.49 (m, 2H, $\text{C}(12)\text{H}_2$), 1.49 – 1.37 (m, 3H, $\text{C}(10)\text{H}_\text{A}\text{H}_\text{B}$, $\text{C}(11)\text{H}_2$);

^{13}C NMR (151 MHz, CDCl_3) δ 213.8 $\text{C}(8)$, 139.7 $\text{C}(\text{Ar}(\text{Ph}^*))$, 138.5 $\text{C}(17)$, 135.7 $\text{C}(\text{Ar}(\text{Ph}^*))$, 133.2 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 128.6 $2 \times \text{C}(\text{Ar}(\text{Ph}^*))$, 128.5 $2 \times \text{C}(19)$, 127.8 $2 \times \text{C}(18)$, 127.7 $\text{C}(20)$, 72.9 $\text{C}(16)$, 68.3 $\text{C}(15)$, 62.7 $\text{C}(13)$, 50.3 $\text{C}(9)$, 32.9 $\text{C}(12)$, 29.3 $\text{C}(10)$, 29.2 $\text{C}(14)$, 23.5 $\text{C}(11)$, 18.0 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$, 16.9 $\text{C}(\text{Me}(\text{Ph}^*))$, 16.2 $2 \times \text{C}(\text{Me}(\text{Ph}^*))$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3441, 3007, 2938, 1689, 1544, 1454, 1218, 1092, 699;

HRMS (ESI^+) $\text{C}_{26}\text{H}_{37}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 397.2737; found 397.2735, Δ 0.49 ppm.

165w (1-(2-(Benzyloxy)ethyl)-2-((phenylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **S33** (119 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in $t\text{BuOH}$ (1.2 mL) at 115 °C for 16 h. Purification *via* sequential flash column chromatography using normal phase (eluent pentane/ $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 88:5:7 $\rightarrow$ pentane/ $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 85:5:10), then reverse phase (eluent water/ MeCN , 70:30 $\rightarrow$ MeCN) gave a mixture of diastereomers of the *title compound* as a colourless oil (40 mg, 25%, [91:9] d.r.)*

*Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification.

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by analogy with the other products.

Major (1*RS*, 2*RS*) diastereomer (from the mixture):

^1H NMR (600 MHz, CDCl_3) δ 7.87 – 7.76 (m, 2H, 2 $\times$ C(23) H), 7.72 – 7.62 (m, 1H, C(25) H), 7.57 (t, J = 7.7 Hz, 2H, 2 $\times$ C(24) H), 7.41 – 7.29 (m, 5H, 2 $\times$ C(18) H , 2 $\times$ C(19) H , C(20) H), 4.56 – 4.45 (m, 2H, C(16) H_2), 3.70 – 3.57 (m, 2H, C(15) H_2), 3.22 (dd, J = 13.7, 2.3 Hz, 1H, C(21) H_AH_B), 3.12 – 2.96 (m, 1H, C(21) H_AH_B), 2.77 – 2.62 (m, 1H, C(13) H), 2.36 – 2.28 (m, 1H, C(12) H_AH_B), 2.27 (s, 3H, C(Ph*) H_3), 2.20 (s, 3H, C(Ph*) H_3), 2.19 – 2.14 (m, 4H, C(14) H_AH_B , C(Ph*) H_3), 2.13 – 2.05 (m, 4H, C(10) H_AH_B , C(Ph*) H_3), 2.03 (s, 3H, C(Ph*) H_3), 1.88 – 1.79 (m, 1H, C(10) H_AH_B), 1.79 – 1.54 (m, 4H, C(11) H_2 , C(12) H_AH_B , C(14) H_AH_B);

^{13}C NMR (151 MHz, CDCl_3) δ 215.0 C(8), 140.8 C(22), 138.3 C(17), 137.2 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.7 C(25), 133.7 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 129.4 2 $\times$ C(24), 129.1 C(Ar(Ph*)), 129.0 C(Ar(Ph*)), 128.5 2 $\times$ C(19), 127.8 2 $\times$ C(18), 127.7 C(20) and 2 $\times$ C(23), 73.3 C(16), 67.1

C(15), 62.1 C(9), 57.8 C(21), 39.9 C(13), 32.5 C(10), 29.4 C(12), 29.1 C(14), 22.4 C(11), 19.1 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.0 C(Me(Ph*));

Fewer ^{13}C resonances observed than expected due to overlapping peaks in the aromatic region.

Selected characteristic peaks of the minor (1*SR*, 2*RS*) diastereomer (from the mixture):

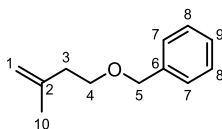
^1H NMR (600 MHz, CDCl_3) δ 7.91 (d, $J = 7.6$ Hz, 2H, $2 \times \text{C}(23)\text{H}$), 7.23 (d, $J = 7.5$ Hz, 2H), 4.28 (s, 2H, C(16) H_2), 3.49 (d, $J = 6.6$ Hz, 2H, C(21) H_2), 3.31 – 3.24 (m, 1H, C(15) $\text{H}_\text{A}\text{H}_\text{B}$), 2.55 – 2.43 (m, 1H, C(13) H), 2.20 (s, 3H, C(Ph*) H_3), 2.14 (s, 3H, C(Ph*) H_3), 2.12 (s, 3H, C(Ph*) H_3), 1.97 (s, 3H, C(Ph*) H_3), 1.95 – 1.88 (m, 4H, contains C(14) H_2);

^{13}C NMR (151 MHz, CDCl_3) δ 216.6 C(8), 140.2, 139.2, 135.4, 133.5, 133.1, 128.5, 128.1, 127.7, 73.1 C(16), 66.6 C(15), 62.5 C(9), 58.4 C(21), 42.3 C(13), 35.0, 34.1 C(14), 30.9, 29.8, 22.4, 19.0, 18.8, 16.8, 16.3, 16.1;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 2877, 1674, 1448, 1306, 1218, 1148, 1086, 690;

HRMS (ESI $^+$) $\text{C}_{33}\text{H}_{41}\text{O}_4\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 533.2720; found 533.2711, Δ 1.79 ppm.

S34 (((3-Methylbut-3-en-1-yl)oxy)methyl)benzene



NaH (60% in mineral oil, 1.58 g, 39.6 mmol) was added to a stirred solution of 3-methyl-3-buten-1-ol (2.0 mL, 20 mmol) in THF (80 mL) at RT and the mixture was stirred at RT for 45 min. The mixture was cooled to 0 °C and benzyl bromide (2.3 mL, 19 mmol) was added dropwise. The reaction was allowed to warm to RT overnight, cooled to 0 °C and quenched with the addition of sat. aq. NH_4Cl (20 mL). The mixture was diluted with EtOAc (50 mL) and water (75 mL), the layers separated and the aqueous layer extracted with EtOAc (2×80 mL). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane: Et_2O , 99.5:0.5 $\rightarrow$ 99:1) gave the *title compound* as a colourless oil (2.54 g, 75%).

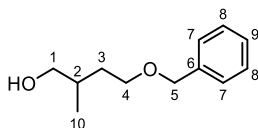
^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.20 (m, 5H, $5 \times \text{C(Ph)H}$), 4.75 – 4.70 (m, 1H, $\text{C(1)H}_\text{A}\text{H}_\text{B}$), 4.67 (dq, $J = 2.1, 1.1$ Hz, 1H, $\text{C(1)H}_\text{A}\text{H}_\text{B}$), 4.46 (s, 2H, C(5)H_2), 3.52 (t, $J = 6.9$ Hz, 2H, C(4)H_2), 2.35 – 2.19 (m, 2H, C(3)H_2), 1.68 (t, $J = 1.2$ Hz, 3H, C(10)H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 142.9 C(2), 138.5 C(6), 128.4 $2 \times \text{C(Ph)}$, 127.7 $2 \times \text{C(Ph)}$, 127.6 C(9), 111.5 C(1), 72.9 C(5), 68.7 C(4), 37.8 C(3), 22.7 C(10);

m/z (ESI⁺) Found ($[\text{M}+\text{Na}]^+$) = 199, $\text{C}_{12}\text{H}_{16}\text{NaO}$ requires 199;

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

S35 4-(Benzyloxy)-2-methylbutan-1-ol



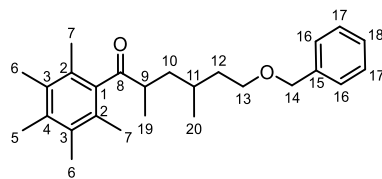
$\text{BH}_3 \cdot \text{SMe}_2$ (2.7 mL, 28 mmol) was added dropwise to a solution of alkene **S34** (1.67 g, 9.53 mmol) in THF (75 mL) at 0 °C. The reaction was allowed to warm to RT and stirred overnight. A suspension of sodium perborate tetrahydrate (7.33 g, 47.6 mmol) in water (20 mL) was added slowly at 0 °C and the reaction was stirred at RT for 4 h. The mixture was diluted with sat. aq. NH_4Cl (70 mL) and Et_2O (50 mL), the layers separated and the aqueous layer extracted with Et_2O (2×100 mL). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 65:35 $\rightarrow$ 50:50) gave the title compound as a colourless oil (1.63 g, 88%).

^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.27 (m, 5H, $5 \times \text{C(Ph)H}$), 4.52 (s, 2H, C(5)H_2), 3.60 (ddd, $J = 9.4, 6.2, 4.9$ Hz, 1H, $\text{C(4)H}_\text{A}\text{H}_\text{B}$), 3.55 – 3.47 (m, 2H, $\text{C(1)H}_\text{A}\text{H}_\text{B}$, $\text{C(4)H}_\text{A}\text{H}_\text{B}$), 3.43 (dd, $J = 10.9, 6.6$ Hz, 1H, $\text{C(1)H}_\text{A}\text{H}_\text{B}$), 2.15 (br. s, 1H, OH), 1.89 – 1.73 (m, 1H, C(2)H), 1.75 – 1.63 (m, 1H, $\text{C(3)H}_\text{A}\text{H}_\text{B}$), 1.58 (dtd, $J = 14.5, 6.1, 4.6$ Hz, 1H, $\text{C(3)H}_\text{A}\text{H}_\text{B}$), 0.92 (d, $J = 7.0$ Hz, 3H, C(10)H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 138.1 C(6), 128.6 $2 \times \text{C(Ph)}$, 127.9 $2 \times \text{C(Ph)}$, 127.9 C(9), 73.3 C(5), 68.8 C(4), 68.3 C(1), 34.3 C(2), 34.2 C(3), 17.4 C(10);

m/z (ESI⁺) Found ($[\text{M}+\text{H}]^+$) = 195, $\text{C}_{12}\text{H}_{19}\text{O}_2$ requires 195.

The spectroscopic data matched that previously reported in the literature.¹⁵⁹

S36 6-(Benzyloxy)-2,4-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

Ph* ethyl ketone **98** (2.10 g, 10.3 mmol), [IrCp*Cl₂]₂ (41 mg, 1.0 mol%) and KOH (1.16 g, 20.6 mmol) were added to a 10 – 20 mL microwave vial. The vial was sealed and evacuated and back-filled with Ar (3 times). Alcohol **S35** (1.00 g, 5.15 mmol) and PhMe (1.3 mL, degassed with Ar (balloon)) were added and the reaction was heated to 110 °C for 30 h. The crude reaction mixture was filtered through a silica plug and concentrated *in vacuo*. The mixture was passed through a silica plug to remove excess Ph* ethyl ketone **98** (elution with pentane/Et₂O, 98:2 → 90:10) and concentrated *in vacuo*. The crude mixture was dissolved in MeOH (40 mL) and degassed with N₂ (balloon). PtO₂ (215 mg, 15 wt%) was added, H₂ was bubbled through the mixture for 15 min and the reaction was left under an atmosphere of H₂ for 3 h. The reaction mixture was filtered through a Celite® pad (washed with CH₂Cl₂) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 97:3 → 95:5) gave the *title compound* as a colourless oil (449 mg, 23%, [78:22] d.r.)*

The relative stereochemistry is unassigned. The spectroscopic data were collected on the diastereomeric mixture.

Major diastereomer (from the mixture):

¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H, 5 × C(Ph)H), 4.49 (s, 2H, C(14)H₂), 3.56 – 3.44 (m, 2H, C(13)H₂), 2.94 – 2.80 (m, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.08 (s, 6H, 2 × C(Ph*)H₃), 1.78 – 1.67 (m, 1H, C(11)H), 1.66 – 1.58 (m, 1H, C(10)H_AH_B), 1.55 – 1.43 (m, 3H, C(10)H_AH_B, C(12)H₂), 1.11 (d, *J* = 7.0 Hz, 3H, C(19)H₃), 0.83 (d, *J* = 6.5 Hz, 3H, C(20)H₃);

¹³C NMR (126 MHz, CDCl₃) δ 215.7 C(8), 140.2 C(Ar(Ph*)), 138.7 C(15), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 128.5 2 × C(Ph), 128.3 2 × C(Ar(Ph*)), 127.8 2 × C(Ph), 127.7 C(18), 73.1 C(14), 68.4 C(13), 46.0 C(9), 38.6 C(10), 37.9 C(12), 27.2 C(11), 18.9 C(20), 18.1 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.1 C(19);

Selected characteristic peaks of the minor diastereomer (from the mixture):

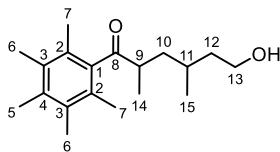
^1H NMR (500 MHz, CDCl_3) δ 4.48 – 4.41 (m, 2H, C(14) H_2), 2.23 (s, 3H, C(Ph*) H_3), 1.13 (d, J = 7.0 Hz, 3H, C(19) H_3), 0.92 (d, J = 6.2 Hz, 3H, C(20) H_3);

^{13}C NMR (126 MHz, CDCl_3) δ 133.1 2 $\times$ C(Ar(Ph*)), 128.5 2 $\times$ C(Ph), 127.7 2 $\times$ C(Ph), 127.6 C(18), 68.6, 46.1, 39.5, 35.6, 27.7, 20.9 C(20), 15.9 C(19);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2932, 2859, 1694, 1455, 1101, 1029, 915, 738, 699, 639;

HRMS (ESI⁺) $\text{C}_{26}\text{H}_{37}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 381.2788; found 381.2789, Δ 0.23 ppm.

*d.r. was calculated after purification and is a result of challenging purification of the diastereomeric mixture from other side products. The d.r. of the crude reaction mixture was [1:1.1], representing an unselective reaction.

S37 6-Hydroxy-2,4-dimethyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one

Ketone **S36** (445 mg, 1.18 mmol, [3.6:1] d.r.) was subjected to **General Procedure F** in MeOH (12 mL) with Pd (10% on carbon) (45 mg, 10 wt%) for 3 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 75:25 $\rightarrow$ 60:40) gave the title compound as a colourless oil (316 mg, 92%, [78:22] d.r.)

Major diastereomer (from the mixture):

^1H NMR (500 MHz, CDCl_3) δ 3.73 – 3.52 (m, 2H, C(13) H_2), 2.97 – 2.83 (m, 1H, C(9) H), 2.23 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, 2 $\times$ C(Ph*) H_3), 2.09 (s, 6H, 2 $\times$ C(Ph*) H_3), 1.76 – 1.66 (m, 1H, C(11) H), 1.64 – 1.41 (m, 4H, C(10) H_2 , C(12) H_2), 1.26 (br. s, 1H, OH), 1.12 (d, J = 7.0 Hz, 3H, C(14) H_3), 0.86 (d, J = 6.5 Hz, 3H, C(15) H_3);

^{13}C NMR (126 MHz, CDCl_3) δ 215.6 C(8), 140.2 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 $\times$ C(Ar(Ph*)), 128.3 2 $\times$ C(Ar(Ph*)), 61.0 C(13), 45.9 C(9), 41.0 C(12), 38.8 C(10), 26.8 C(11), 18.8 C(15), 18.1 2 $\times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 $\times$ C(Me(Ph*)), 15.1 C(14);

Selected characteristic peaks for the minor diastereomer (from the mixture):

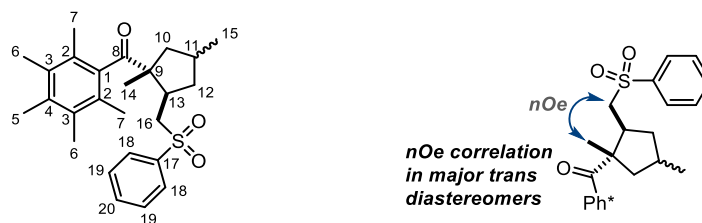
¹H NMR (500 MHz, CDCl₃) δ 3.82 – 3.73 (m, 1H, C(13)*H_AH_B*), 1.88 (dt, *J* = 13.4, 6.5 Hz, 1H, C(10)*H_AH_B*), 1.41 – 1.32 (m, 1H, C(12)*H_AH_B*), 1.17 (dt, *J* = 13.9, 7.1 Hz, 1H, C(10)*H_AH_B*), 0.95 (d, *J* = 6.6 Hz, 3H, C(15)*H*₃);

¹³C NMR (126 MHz, CDCl₃) δ 215.6 C(8), 139.8 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 60.9 C(13), 46.2 C(9), 39.0 C(12), 27.3 C(11), 21.0 C(15), 18.1 2 × C(Me(Ph*)), 16.6 C(14);

IR (film) ν_{max} /cm⁻¹ 3397, 2932, 1693, 1459, 1382, 1062, 921, 736, 647;

HRMS (ESI⁺) C₁₉H₃₁OS⁺ ([M+H]⁺) requires 291.2319; found 291.2320, Δ 0.48 ppm.

165x (1,4-Dimethyl-2-((phenylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **S37** (87 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 80:5:15) gave the *title compound* as a white solid (112 mg, 88%, [50:45:3:2] d.r. ([*trans'*:*trans''*:*cis'*:*cis''*])).*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The two “*trans*” diastereomers were inseparable and therefore the data for both isomers are reported together as observed. Equally, the two “*cis*” diastereomers were inseparable and therefore the data for both isomers are reported together as observed.

The relative stereochemistry between the ketone and sulfone substituents was assigned by nOe analysis.

Data for the major “*trans*” ((1*R*,2*R*,4*S*) & (1*S*,2*S*,4*R*)) diastereomers:

m.p. = 164 – 165 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.97 – 7.77 (m, 4H, 2 × C(18')*H*, 2 × C(18'')*H*), 7.70 – 7.60 (m, 2H, C(20')*H*, C(20'')*H*), 7.60 – 7.49 (m, 4H, 2 × C(19')*H*, 2 × C(19'')*H*), 3.52 (m, 2H, C(16')*H_AH_B*,

$C(16'')H_AH_B$), 3.02 (dd, $J = 13.8, 11.9$ Hz, 1H, $C(16')H_AH_B$), 2.97 (dd, $J = 13.8, 12.0$ Hz, 1H, $C(16'')H_AH_B$), 2.72 (dtd, $J = 11.5, 9.3, 2.1$ Hz, 1H, $C(13'')H$), 2.65 (tdd, $J = 12.0, 6.2, 2.2$ Hz, 1H, $C(13')H$), 2.49 (dt, $J = 12.7, 6.4$ Hz, 1H, $C(12')H_AH_B$), 2.33 (dd, $J = 13.8, 9.8$ Hz, 1H, $C(10')H_AH_B$), 2.22 ($2 \times s$, 6H, $2 \times C(Ph^*)H_3$), 2.21 – 2.12 (m, 13H, $C(11'')H$, $4 \times C(Ph^*)H_3$), 2.02 – 1.96 (m, 7H, $C(11')H$, $2 \times C(Ph^*)H_3$), 1.93 (s, 3H, $C(Ph^*)H_3$), 1.92 – 1.89 (m, 4H, $C(12'')H_AH_B$, $C(Ph^*)H_3$), 1.89 – 1.82 (m, 1H, $C(12'')H_AH_B$), 1.79 (dd, $J = 12.6, 7.2$ Hz, 1H, $C(10'')H_AH_B$), 1.37 (dd, $J = 12.6, 10.3$ Hz, 1H, $C(10'')H_AH_B$), 1.22 (td, $J = 12.4, 11.1$ Hz, 1H, $C(12')H_AH_B$), 1.17 (s, 3H, $C(14')H_3$), 1.16 – 1.10 (m, 4H, $C(10')H_AH_B$, $C(14'')H_3$), 0.99 (d, $J = 6.7$ Hz, 3H, $C(15')H_3$), 0.94 (d, $J = 6.7$ Hz, 3H, $C(15'')H_3$);*

^{13}C NMR (151 MHz, $CDCl_3$) δ 218.1 $C(8')$, 217.3 $C(8'')$, 140.2 $C(17')$ & $C(17'')$, 138.9 $2 \times C(Ar(Ph^*))$, 135.3 $C(Ar(Ph^*))$, 135.3 $C(Ar(Ph^*))$, 133.7 $C(20')/C(20'')$, 133.7 $C(20')/C(20'')$, 133.5 $C(Ar(Ph^*))$, 133.4 $C(Ar(Ph^*))$, 133.1 $C(Ar(Ph^*))$, 133.1 $C(Ar(Ph^*))$, 129.4 $2 \times C(18')/2 \times C(18'')$, 129.4 $2 \times C(18')/2 \times C(18'')$, 128.1 $2 \times C(19')/2 \times C(19'')$, 128.0 $2 \times C(19')/2 \times C(19'')$, 127.9 $C(Ar(Ph^*))$, 127.8 $C(Ar(Ph^*))$, 127.8 $C(Ar(Ph^*))$, 59.5 $C(9'')$, 58.3 $C(16')$, 58.2 $C(9')$, 57.8 $C(16'')$, 46.0 $C(10'')$, 45.6 $C(10')$, 40.7 $C(13')$, 39.9 $C(12')$, 38.5 $C(13'')$, 37.8 $C(12'')$, 32.6 $C(11')$, 30.6 $C(11'')$, 22.5 $C(14')$, 21.8 $C(15'')$, 21.4 $C(15')$, 19.2 $C(Me(Ph^*))$, 19.0 $C(Me(Ph^*))$, 18.6 $C(Me(Ph^*))$, 18.4 $C(14'')$, 18.4 $C(Me(Ph^*))$, 16.8 $C(Me(Ph^*))$, 16.8 $C(Me(Ph^*))$, 16.3 $C(Me(Ph^*))$, 16.3 $C(Me(Ph^*))$, 16.1 $C(Me(Ph^*))$, 16.1 $C(Me(Ph^*))$);*

Fewer peaks than expected due to overlapping signals in aromatic region of the ^{13}C spectrum.

IR (film) ν_{max}/cm^{-1} 2953, 1676, 1448, 1307, 1150, 1088, 923, 791, 760, 690;

HRMS (ESI⁺) $C_{26}H_{35}O_3S^+$ ($[M+H]^+$) requires 427.2301; found 427.2306, Δ 1.06 ppm.

Data for the minor “cis” ((1*S*, 2*R*, 4*SR*) & (1*R*, 2*S*, 4*RS*) diastereomers:

m.p. = 110 – 112 °C;

^1H NMR (600 MHz, $CDCl_3$) δ 7.97 – 7.93 (m, 2H, $2 \times C(18')H$), 7.93 – 7.89 (m, 2H, $2 \times C(18'')H$), 7.69 – 7.63 (m, 2H, $C(20')H$, $C(20'')H$), 7.58 (m, 4H, $2 \times C(19')H$, $2 \times C(19'')H$), 3.61 (dd, $J = 14.3, 11.1$ Hz, 1H, $C(16')H_AH_B$), 3.54 (dd, $J = 14.4, 2.0$ Hz, 1H, $C(16'')H_AH_B$), 3.45 – 3.35 (m, 2H,

$C(16')H_AH_B$, $C(16'')H_AH_B$, 2.50 – 2.43 (m, 1H, $C(13'')H$), 2.44 – 2.36 (m, 2H, $C(12'')H_AH_B$, $C(13')H$), 2.36 – 2.30 (m, 1H, $C(10')H_AH_B$), 2.25 – 2.17 (m, 8H, $C(11')H$, $C(12')H_AH_B$, $2 \times C(Ph^*)H_3$), 2.16 (s, 3H, $C(Ph^*)H_3$), 2.15 (s, 3H, $C(Ph^*)H_3$), 2.14 – 2.11 (m, 7H, $C(11'')H$, $2 \times C(Ph^*)H_3$), 2.02 (s, 3H, $C(Ph^*)H_3$), 2.02 (s, 3H, $C(Ph^*)H_3$), 1.95 (s, 3H, $C(Ph^*)H_3$), 1.91 (s, 3H, $C(Ph^*)H_3$), 1.81 (dd, $J = 9.0$, 3.1 Hz, 2H, $C(10'')H_2$), 1.65 (m, 1H, $C(12')H_AH_B$), 1.57 – 1.53 (m, 1H, $C(12'')H_AH_B$), 1.17 (s, 3H, $C(14')H_3$), 1.13 – 1.07 (m, 4H, $C(10')H_AH_B$, $C(14'')H_3$), 1.04 (d, $J = 6.6$ Hz, 3H, $C(15'')H_3$), 0.99 (d, $J = 6.2$ Hz, 3H, $C(15')H_3$);*

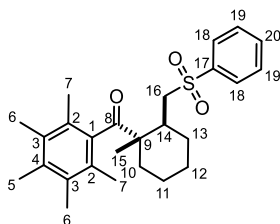
^{13}C NMR (151 MHz, $CDCl_3$) δ 218.9 $C(8'')$, 217.1 $C(8')$, 140.5 $C(17')/C(17'')$, 140.3 $C(17')/C(17'')$, 140.1 $C(Ar(Ph^*))$, 139.0 $C(Ar(Ph^*))$, 135.3 $C(Ar(Ph^*))$, 135.3 $C(Ar(Ph^*))$, 133.7 $C(20')/C(20'')$, 133.7 $C(20')/C(20'')$, 133.5 $C(Ar(Ph^*))$, 133.5 $C(Ar(Ph^*))$, 133.0 $C(Ar(Ph^*))$, 132.9 $C(Ar(Ph^*))$, 129.4 $2 \times C(19')/2 \times C(19'')$, 129.4 $2 \times C(19')/2 \times C(19'')$, 128.1 $2 \times C(18')/2 \times C(18'')$, 128.0 $2 \times C(18')/2 \times C(18'')$, 128.0 $C(Ar(Ph^*))$, 127.5 $C(Ar(Ph^*))$, 127.3 $C(Ar(Ph^*))$, 61.5 $C(9')$, 60.4 $C(16'')$, 59.4 $C(9'')$, 58.2 $C(16')$, 49.0 $C(10'')$, 47.9 $C(10')$, 45.2 $C(13'')$, 44.8 $C(13'')$, 41.5 $C(12'')$, 39.6 $C(12')$, 32.3 $C(11'')$, 30.8 $C(11')$, 26.1 $C(14'')$, 24.8 $C(14')$, 22.0 $C(15')$, 20.8 $C(15'')$, 19.0 $C(Me(Ph^*))$, 18.5 $C(Me(Ph^*))$, 18.3 $C(Me(Ph^*))$, 18.1 $C(Me(Ph^*))$, 16.8 $C(Me(Ph^*))$, 16.8 $C(Me(Ph^*))$, 16.3 $2 \times C(Me(Ph^*))$, 16.0 $2 \times C(Me(Ph^*))$);*

Fewer peaks than expected due to overlapping signals in aromatic region of the ^{13}C spectrum.

IR (film) ν_{max}/cm^{-1} 2955, 1680, 1507, 1385, 1307, 1149, 1087, 999, 921;

HRMS (ESI^+) $C_{26}H_{35}O_3S^+$ ($[M+H]^+$) requires 427.2301; found 427.2313, Δ 2.70 ppm.

* N.B. the labels ' and '' indicate peaks belonging to different diastereomers.

167c (1-Methyl-2-((phenylsulfonyl)methyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **166** (87 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O/CH₂Cl₂, 85:10:5) gave the *title compound* as a white solid (100 mg, 78%, [88:12] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by analogy with other products.

Major (1*RS*,2*RS*) diastereomer (from the mixture):

¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.85 (m, 2H, 2 × C(18)*H*), 7.70 – 7.60 (m, 1H, C(20)*H*), 7.59 – 7.49 (m, 2H, 2 × C(19)*H*), 4.10 (dd, *J* = 14.0, 1.5 Hz, 1H, C(16)*H*_A*H*_B), 2.89 (dd, *J* = 14.0, 10.8 Hz, 1H, C(16)*H*_A*H*_B), 2.62 – 2.49 (m, 1H, C(14)*H*), 2.49 – 2.38 (m, 1H, C(13)*H*_A*H*_B), 2.21 (s, 3H, C(Ph*)*H*₃), 2.19 – 2.10 (m, 6H, 2 × C(Ph*)*H*₃), 1.99 (s, 3H, C(Ph*)*H*₃), 1.97 (s, 3H, C(Ph*)*H*₃), 1.75 – 1.61 (m, 1H, C(12)*H*_A*H*_B), 1.61 – 1.20 (m, 6H, C(10)*H*₂, C(11)*H*₂, C(12)*H*_A*H*_B, C(13)*H*_A*H*_B), 1.19 (s, 3H, C(15)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 219.1 C(8), 140.7 C(17), 139.6 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 133.6 C(20), 133.3 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 129.4 2 × C(19), 128.0 2 × C(18), 127.7 C(Ar(Ph*)), 127.6 C(Ar(Ph*)), 58.3 C(16), 50.5 C(9), 36.3 C(14), 36.2 C(10), 28.6 C(13), 25.4 C(12), 21.0 C(11), 19.2 C(Me(Ph*)), 19.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.7 C(15), 16.3 C(Me(Ph*)), 16.2 C(Me(Ph*));

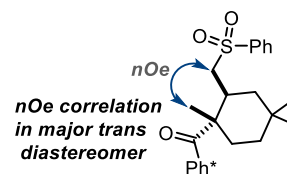
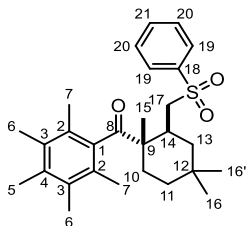
Selected characteristic peaks for the minor (1*RS*,2*SR*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 3.56 (dd, *J* = 14.4, 1.3 Hz, 1H, C(16)*H_AH_B*), 3.46 (dd, *J* = 14.4, 9.2 Hz, 1H, C(16)*H_AH_B*), 2.21 (s, 3H, C(Ph*)*H₃*), 2.14 (s, 3H, C(Ph*)*H₃*), 2.04 (s, 3H, C(Ph*)*H₃*), 2.00 (s, 3H, C(Ph*)*H₃*), 1.05 (s, 3H, C(15)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.4 C(8), 140.5 C(17), 139.1 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 133.7 C(20), 133.4 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 129.4 2 × C(19), 128.2 2 × C(18), 57.8 C(16), 52.6 C(9), 40.0 C(14), 35.2 C(10), 28.0, 24.7 C(15), 23.8, 22.3 C(Me(Ph*)), 19.2 C(Me(Ph*)), 19.0 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2935, 2866, 1680, 1448, 1305, 1150, 1087, 910, 737;

HRMS (ESI⁺) C₂₆H₃₅O₃S⁺ ([M+H]⁺) requires 427.2301; found 427.2309, Δ 1.76 ppm.

167d (2,3,4,5,6-Pentamethylphenyl)(1,4,4-trimethyl-2-(phenylsulfonyl)methyl)cyclohexyl)methanone

Hydroxy ketone **186** (95 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 88:5:7 → 87:5:8) gave inseparable diastereomers of the *title compound* as a white solid (131 mg, 96%, [93:7] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification.

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

m.p. = 175 – 177 °C;

Major (1*RS*,2*RS*) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 7.95 – 7.89 (m, 2H, 2 × C(19)*H*), 7.68 – 7.60 (m, 1H, C(21)*H*), 7.61 – 7.52 (m, 2H, 2 × C(20)*H*), 4.16 (dd, *J* = 14.0, 1.4 Hz, 1H, C(17)*H_AH_B*), 2.85 (dd, *J* = 14.0,

10.8 Hz, 1H, C(17) H_AH_B), 2.68 (dddd, $J = 12.3, 10.8, 4.0, 1.4$ Hz, 1H, C(14) H), 2.21 (s, 3H, C(Ph*) H_3), 2.17 – 2.13 (m, 6H, 2 $\times$ C(Ph*) H_3), 2.13 – 2.08 (m, 1H, C(13) H_AH_B), 2.00 (s, 3H, C(Ph*) H_3), 1.92 (s, 3H, C(Ph*) H_3), 1.62 (td, $J = 14.0, 4.1$ Hz, 1H, C(10) H_AH_B), 1.33 – 1.23 (m, 3H, C(10) H_AH_B , C(11) H_AH_B , C(13) H_AH_B), 1.19 – 1.08 (m, 4H, C(11) H_AH_B , C(15) H_3), 0.92 (s, 3H, C(16) H_3), 0.89 (s, 3H, C(16') H_3); ^{13}C NMR (151 MHz, CDCl_3) δ 219.2 C(8), 140.4 C(18), 139.7 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 133.6 C(21), 133.3 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 129.3 2 $\times$ C(20), 128.2 2 $\times$ C(19), 127.7 C(Ar(Ph*)), 127.5 C(Ar(Ph*)), 58.2 C(17), 50.2 C(9), 41.2 C(13), 33.8 C(11), 32.8 C(16), 32.5 C(14), 32.1 C(10), 30.3 C(12), 24.4 C(16'), 19.1 C(Me(Ph*)), 19.0 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4, C(15), 16.3 C(Me(Ph*)), 16.2 C(Me(Ph*));

Selected characteristic peaks for the minor (1*RS*,2*SR*) diastereomer (from the mixture):

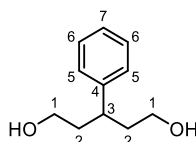
^1H NMR (600 MHz, CDCl_3) δ 3.43 (dd, $J = 14.6, 1.8$ Hz, 1H, C(17) H_AH_B), 3.39 (dd, $J = 14.6, 7.9$ Hz, 1H, C(17) H_AH_B), 2.06 (s, 3H, C(Ph*) H_3), 2.02 (s, 3H, C(Ph*) H_3), 1.86 (dt, $J = 14.2, 3.1$ Hz, 1H, C(10) H_AH_B), 1.50 (dt, $J = 12.2, 2.9$ Hz, 1H, C(13) H_AH_B), 1.43 – 1.34 (m, 2H, C(10) H_AH_B , C(11) H_AH_B), 0.98 (s, 3H, C(16) H_3), 0.88 (s, 3H, C(16') H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 216.3 C(8), 139.9 C(18), 138.5 C(Ar(Ph*)), 135.2 C(Ar(Ph*)), 133.7 C(21), 133.4 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 129.4 2 $\times$ C(20), 128.3 2 $\times$ C(19), 59.4 C(17), 52.6 C(14), 42.8 C(13), 38.5, 35.8 C(11), 33.3 C(10), 32.8 C(16'), 30.5, 26.1 C(16), 24.1 C(15), 19.6 C(Me(Ph*)), 19.0 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2953, 1678, 1473, 1448, 1317, 1305, 1151, 1087, 910, 760;

HRMS (ESI $^+$) $\text{C}_{28}\text{H}_{39}\text{O}_3\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 455.2614; found 415.2608, Δ 1.48 ppm.

S38 3-Phenylpentane-1,5-diol



LiAlH_4 (1.37 g, 36.1 mmol) was added to a stirred solution of 3-phenylglutaric acid (2.50 g, 12.0 mmol) in THF at 0 $^\circ\text{C}$. The resulting suspension was warmed to RT and then heated at reflux for 16 h. The reaction was cooled to 0 $^\circ\text{C}$, diluted with Et_2O and quenched with sequential

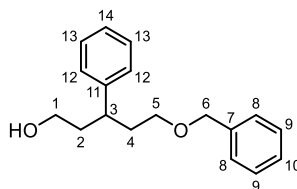
dropwise addition of H₂O (1.4 mL), aq. NaOH (15% w/v, 1.4 mL) and H₂O (4.1 mL). MgSO₄ was added and the resulting suspension was stirred vigorously for 15 min and then filtered under reduced pressure. The filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH₂Cl₂/MeOH, 95:5 → 80:20) gave the *title compound* as a colourless oil (1.84 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.28 (m, 2H, 2 × C(Ph)H), 7.24 – 7.16 (m, 3H, 3 × C(Ph)H), 3.62 – 3.53 (m, 2H, 2 × C(1)H_AH_B), 3.53 – 3.42 (m, 2H, 2 × C(1)H_AH_B), 2.92 (hept, *J* = 5.2 Hz, 1H, C(3)H), 2.02 – 1.91 (m, 2H, 2 × C(2)H_AH_B), 1.91 – 1.77 (m, 2H, 2 × C(2)H_AH_B), 1.36 (s, 2H, 2 × OH);
¹³C NMR (101 MHz, CDCl₃) δ 144.5 C(4), 128.8 2 × C(Ph), 127.7 2 × C(Ph), 126.6 C(7), 61.1 2 × C(1), 39.6 2 × C(2), 39.0 C(3);

m/z (ESI⁺) Found ([M+Na]⁺) = 203, C₁₁H₁₆NaO₂ requires 203;

The spectroscopic data were consistent with that reported in the literature.⁴⁴

S39 5-(Benzyloxy)-3-phenylpentan-1-ol



Diol **S38** (1.79 g, 9.94 mmol) was dissolved in *N,N*-dimethylformamide (20 mL) and cooled to 0 °C. NaH (400 mg, 10.0 mmol, 60% dispersed in mineral oil) was added, the reaction allowed to warm to RT and stirred for 1 h. Benzyl bromide (1.08 mL, 9.04 mmol) was added and the reaction allowed to stir at RT overnight. The reaction was cooled to 0 °C, quenched by addition of sat. aq. NH₄Cl (20 mL) and diluted with EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous layer extracted with EtOAc (100 mL). The combined organic phases were washed with brine (3 times), dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 80:20 → 70:30) gave the *title compound* as a colourless oil (888 mg, 36%).

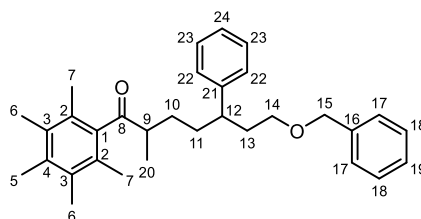
^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.26 (m, 7H, $7 \times \text{C(Ph)H}$), 7.23 – 7.18 (m, 1H, C(Ph)H), 7.18 – 7.14 (m, 2H, $2 \times \text{C(Ph)H}$), 4.42 (d, $J = 11.9$ Hz, 1H, $\text{C(6)}H_AH_B$), 4.38 (d, $J = 11.9$ Hz, 1H, $\text{C(6)}H_AH_B$), 3.54 (ddd, $J = 10.7, 6.9, 5.5$ Hz, 1H, $\text{C(1)}H_AH_B$), 3.47 (ddd, $J = 10.7, 7.2, 6.5$ Hz, 1H, $\text{C(1)}H_AH_B$), 3.37 (ddd, $J = 9.4, 6.7, 5.1$ Hz, 1H, $\text{C(5)}H_AH_B$), 3.27 (ddd, $J = 9.4, 7.9, 6.2$ Hz, 1H, $\text{C(5)}H_AH_B$), 2.92 (tt, $J = 10.0, 5.1$ Hz, 1H, C(3)H), 2.08 – 1.98 (m, 1H, $\text{C(4)}H_AH_B$), 1.94 (dtd, $J = 14.1, 7.2, 5.2$ Hz, 1H, $\text{C(2)}H_AH_B$), 1.90 – 1.77 (m, 2H, $\text{C(2)}H_AH_B$, $\text{C(4)}H_AH_B$), 1.40 (br. s, 1H, OH);

^{13}C NMR (126 MHz, CDCl_3) δ 144.5 C(11), 138.6 C(7), 128.7 $2 \times \text{C(Ph)}$, 128.5 $2 \times \text{C(Ph)}$, 127.8 $2 \times \text{C(Ph)}$, 127.8 $2 \times \text{C(Ph)}$, 127.7 C(Ph), 126.5 C(Ph), 73.1 C(6), 68.4 C(5), 61.2 C(1), 39.7 C(4), 39.2 C(3), 36.9 C(2);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3433, 2935, 2865, 1694, 1495, 1454, 1206, 1052, 912, 736, 702;

HRMS (ESI^+) $\text{C}_{18}\text{H}_{23}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 271.1693; found 271.1690, Δ 1.05 ppm.

S40 7-(Benzyloxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)-5-phenylheptan-1-one



Ph* ethyl ketone **98** (384 mg, 1.88 mmol), alcohol **S39** (888 mg, 3.25 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (15 mg, 1.0 mol%), KOH (422 mg, 7.52 mmol) and PhMe (0.47 mL) were subjected to **General Procedure E** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 95:5 $\rightarrow$ 92:8) gave the *title compound* as a pale yellow oil (769 mg, 90%, [51:49] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry is unassigned.

^1H NMR (600 MHz, CDCl_3) δ 7.35 – 7.26 (m, 10H, $10 \times \text{C(Ph)H}$), 7.25 – 7.20 (m, 4H, $4 \times \text{C(Ph)H}$), 7.20 – 7.13 (m, 2H, $\text{C(24')}H$, $\text{C(24'')}H$), 7.12 – 7.08 (m, 2H, $2 \times \text{C(22')}H$), 7.08 – 7.03 (m, 2H, $2 \times \text{C(22'')}H$), 4.43 – 4.34 (m, 4H, $\text{C(15')}H_2$, $\text{C(15'')}H_2$), 3.34 (m, 2H, $\text{C(14')}H_AH_B$, $\text{C(14'')}H_AH_B$), 3.23 (m, 2H, $\text{C(14')}H_AH_B$, $\text{C(14'')}H_AH_B$), 2.77 – 2.63 (m, 4H, $\text{C(9')}H$, $\text{C(9'')}H$, $\text{C(12')}H$, $\text{C(12'')}H$), 2.23 (s,

3H, C(Ph*)H₃), 2.22 (s, 3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.15 (s, 6H, 2 × C(Ph*)H₃), 2.09 – 1.88 (m, 14H, 4 × C(Ph*)H₃, C(13')H_AH_B, C(13'')H_AH_B), 1.85 – 1.73 (m, 3H, C(11')H_AH_B, C(13')H_AH_B, C(13'')H_AH_B), 1.73 – 1.58 (m, 5H, C(10')H_AH_B, C(10'')H_AH_B, C(11')H_AH_B, C(11'')H₂), 1.34 – 1.25 (m, 1H, C(10')H_AH_B), 1.18 – 1.11 (m, 1H, C(10'')H_AH_B), 1.09 (d, *J* = 7.0 Hz, 3H, C(20')H₃), 1.07 (d, *J* = 6.9 Hz, 3H, C(20'')H₃);*

¹³C NMR (151 MHz, CDCl₃) δ 214.9 C(8') & C(8''), 145.0 C(21'), 144.6 C(21''), 140.1 C(Ar(Ph*)), 140.1 C(Ar(Ph*)), 138.7 C(16'), 138.7 C(16''), 135.5 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 128.5 2 × C(18'), 2 × C(18''), 2 × C(23'), 2 × C(23''), 128.4 C(Ar(Ph*)), 128.3 C(Ar(Ph*)), 127.8 2 × C(17'), 2 × C(17''), 2 × C(22'), 2 × C(22''), 127.6 C(19') & C(19''), 126.2 C(24') & C(24''), 73.1 C(15'), 73.0 C(15''), 68.5 C(14'), 68.5 C(14''), 48.5 C(9'), 48.2 C(9''), 42.9 C(12'), 42.5 C(12''), 37.1 C(13'), 36.6 C(13''), 34.6 C(11'), 34.4 C(11''), 30.0 C(10'), 29.7 C(10''), 18.0 2 × C(Me(Ph*)), 18.0 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 15.6 C(20'), 15.1 C(20'');*

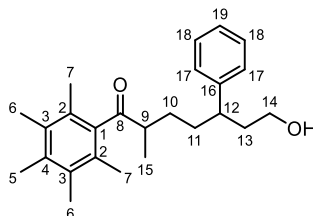
Fewer peaks than expected in the ¹³C spectrum due to overlapping signals of different diastereomers.

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2938, 2863, 1694, 1454, 1115, 1076, 914, 736, 701;

HRMS (ESI⁺) C₃₂H₄₁O₂⁺ ([M+H]⁺) requires 457.3101; found 457.3096, Δ 1.05 ppm.

* N.B. the labels ' and '' indicate peaks belonging to different diastereomers and are assigned arbitrarily.

S41 7-Hydroxy-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)-5-phenylheptan-1-one



Ketone **S40** (753 mg, 1.65 mmol, [51:49] d.r.) was subjected to **General Procedure F** in MeOH (17 mL) with Pd (10% on carbon) (75 mg, 10 wt%) for 3 h. Purification *via* flash column

chromatography (eluent pentane/Et₂O, 65:35 → 60:40) gave the title compound as a colourless oil (560 mg, 93%, [52:48] d.r.)

The spectroscopic data were collected on the diastereomeric mixture. The relative stereochemistry is unassigned.

¹H NMR (600 MHz, CDCl₃) δ 7.30 – 7.22 (m, 4H, 2 × C(18')H, 2 × C(18'')H), 7.20 – 7.15 (m, 2H, C(19')H, C(19'')H), 7.14 – 7.11 (m, 2H, 2 × C(17')H, 7.11 – 7.04 (m, 2H, 2 × C(17'')H), 3.59 – 3.48 (m, 2H, C(14')H_AH_B, C(14'')H_AH_B), 3.48 – 3.39 (m, 2H, C(14')H_AH_B, C(14'')H_AH_B), 2.79 – 2.70 (m, 1H, C(9')H), 2.70 – 2.60 (m, 3H, C(9'')H, C(12')H, C(12'')H), 2.23 (s, 3H, C(Ph*)H₃), 2.22 (s, 3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.15 (s, 6H, 2 × C(Ph*)H₃), 2.00 (br. s, 12H, 4 × C(Ph*)H₃), 1.96 – 1.86 (m, 2H, C(13')H_AH_B, C(13'')H_AH_B), 1.85 – 1.72 (m, 3H, C(11')H_AH_B, C(13')H_AH_B, C(13'')H_AH_B), 1.72 – 1.54 (m, 5H, C(10')H_AH_B, C(10'')H_AH_B, C(11')H_AH_B, C(11'')H₂), 1.40 (br. s, 2H, OH), 1.36 – 1.28 (m, 1H, C(10')H_AH_B), 1.22 – 1.13 (m, 1H, C(10'')H_AH_B), 1.10 (d, *J* = 7.0 Hz, 3H, C(15')H₃), 1.08 (d, *J* = 6.9 Hz, 3H, C(15'')H₃);*

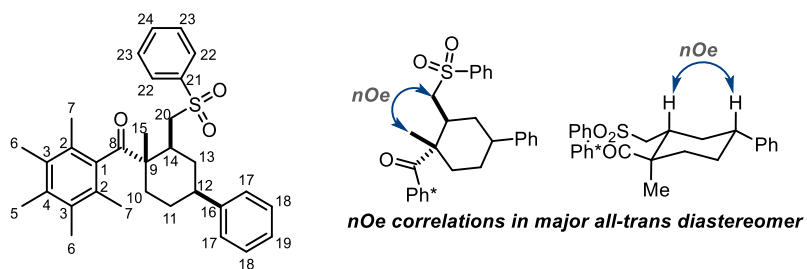
¹³C NMR (151 MHz, CDCl₃) δ 214.9 C(8'), 214.9 C(8''), 144.9 C(16'), 144.5 C(16''), 140.1 C(Ar(Ph*)), 140.1 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.1 2 × C(Ar(Ph*)), 133.1 2 × C(Ar(Ph*)), 128.6 2 × C(18') & 2 × C(18''), 128.3 2 × C(Ar(Ph*)), 128.3 2 × C(Ar(Ph*)), 127.7 2 × C(17') & 2 × C(17''), 126.4 C(19') & C(19''), 61.2 C(14'), 61.2 C(14''), 48.4 C(9'), 48.2 C(9''), 42.9 C(12'), 42.6 C(12''), 39.9 C(13'), 39.4 C(13''), 34.6 C(11'), 34.5 C(11''), 30.0 C(10'), 29.7 C(10''), 18.0 2 × C(Me(Ph*)), 18.0 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 4 × C(Me(Ph*)), 15.6 C(15'), 15.2 C(15'');*

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3458, 2934, 1694, 1541, 1383, 1053, 925, 762, 703, 652;

HRMS (ESI⁺) C₂₅H₃₄NaO₂⁺ ([M+Na]⁺) requires 389.2451; found 389.2441, Δ 2.64 ppm.

* N.B. the labels ' and '' indicate peaks belonging to different diastereomers and are assigned arbitrarily.

167e (1-Methyl-4-phenyl-2-((phenylsulfonyl)methyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **S41** (100 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were subjected to **General Procedure G** in ^tBuOH (1.2 mL) at 115 °C for 16 h. Purification *via* flash column chromatography (eluent pentane/CH₂Cl₂/Et₂O, 97.5:0.5:2 → 80:5:15) gave inseparable diastereomers of the *title compound* as a white solid (108 mg, 72%, [81:5:10:4] d.r. [*trans'*:*trans''*:*cis'*:*cis''*]).*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The labels ' and '' refer to different diastereomers. The labels *cis* and *trans* relate to the relative stereochemistry about the bond between C(9) and C(14). The single prime label indicates the major component with each stereochemistry, and the double prime label indicates the minor component. The *cis* diastereomers were assigned based on the position of the C(20) protons, by analogy with the other *cis* diastereomers. The mixture was further purified by recrystallisation (vapor diffusion over three days using CHCl₃ as the solvent and MeOH as the precipitant) to give the major diastereomer as a single diastereomer which was assigned as (1*RS*,2*RS*,4*RS*) by nOe and X-ray crystallography analysis.

m.p. = 185 – 188 °C;

Major all-*trans* diastereomer (*trans'*) (1*RS*,2*RS*,4*RS*):

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.89 (m, 2H, 2 × C(22)*H*), 7.69 – 7.62 (m, 1H, C(24)*H*), 7.62 – 7.54 (m, 2H, 2 × C(23)*H*), 7.33 – 7.27 (m, 2H, 2 × C(18)*H*), 7.23 – 7.13 (m, 3H, 2 × C(17)*H*, C(19)*H*), 4.17 (dd, *J* = 13.8, 1.3 Hz, 1H, C(20)*H*_A*H*_B), 2.94 (dd, *J* = 13.8, 10.8 Hz, 1H, C(20)*H*_A*H*_B), 2.87 – 2.77 (m, 1H, C(14)*H*), 2.68 (dtd, *J* = 13.7, 3.8, 1.8 Hz, 1H, C(13)*H*_A*H*_B), 2.62 – 2.48 (m, 1H,

C(12)H), 2.24 (s, 3H, C(Ph*)H₃), 2.18 (s, 3H, C(Ph*)H₃), 2.17 (s, 3H, C(Ph*)H₃), 2.06 (s, 3H, C(Ph*)H₃), 2.04 (s, 3H, C(Ph*)H₃), 1.75 – 1.67 (m, 1H, C(10)H_AH_B), 1.67 – 1.53 (m, 4H, C(10)H_AH_B, C(11)H₂, C(13)H_AH_B), 1.28 (s, 3H, C(15)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 218.8 C(8), 145.8 C(16), 140.7 C(21), 139.5 C(Ar(Ph*)), 135.2 C(Ar(Ph*)), 133.6 C(24), 133.4 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 129.4 2 × C(23), 128.6 2 × C(18), 128.0 2 × C(22), 127.6 C(Ar(Ph*)), 127.6 C(Ar(Ph*)), 126.9 2 × C(17), 126.4 C(19), 58.0 C(20), 49.9 C(9), 43.1 C(12), 36.5 C(14), 36.2 C(10), 35.9 C(13), 28.4 C(11), 19.2 C(Me(Ph*)), 19.2 C(Me(Ph*)), 16.9 C(15), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.2 C(Me(Ph*));

Selected characteristic peaks of the minor diastereomers 1*RS*,2*RS*,4*SR* - trans''), (1*RS*,2*SR*,4*RS* - cis') and 1*RS*,2*SR*,4*SR* - cis'') (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 7.91 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.42 (dt, *J* = 8.3, 1.1 Hz, 2H), 7.38 – 7.34 (m, 2H), 4.27 (d, *J* = 14.4 Hz, 1H, C(20)H_AH_B *trans''*), 3.88 (dt, *J* = 14.6, 1.9 Hz, 1H, C(20)H_AH_B *cis''*), 3.72 (dd, *J* = 14.6, 11.5 Hz, 1H, C(20)H_AH_B *cis''*), 3.51 (dd, *J* = 14.5, 1.6 Hz, 1H, C(20)H_AH_B *cis''*), 3.45 (dd, *J* = 14.5, 8.5 Hz, 1H, C(20)H_AH_B *cis''*), 3.12 – 3.06 (m, 2H), 3.02 (dd, *J* = 14.3, 10.5 Hz, 1H, C(20)H_AH_B *trans''*), 2.17 (s, 3H, C(Ph*)H₃), 2.14 (s, 3H, C(Ph*)H₃), 2.12 (s, 3H, C(Ph*)H₃), 2.02 (s, 3H, C(Ph*)H₃), 1.97 (s, 3H, C(Ph*)H₃), 1.49 – 1.43 (m, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.24 – 1.19 (m, 1H), 1.10 (s, 3H, C(15)H₃ *cis'*);

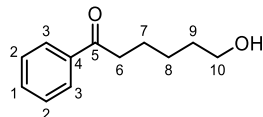
¹³C NMR (151 MHz, CDCl₃) δ 219.0 C(8), 218.6 C(8'), 216.3 C(8''), 146.0, 145.5, 142.8, 140.7, 140.1, 139.7, 139.6, 139.6, 138.5, 135.2, 135.1, 134.8, 133.7, 133.5, 133.4, 133.2, 133.1, 133.0, 133.0, 132.9, 129.4, 129.3, 129.2, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.8, 127.5, 127.4, 127.3, 127.2, 126.9, 126.9, 126.3, 126.2, 125.8, 59.2 C(20)_{*cis'*}, 57.6 C(20)_{*trans''*}, 55.2 C(20)_{*cis''*}, 52.4 C(9)_{*cis'*}, 51.1, 49.3, 44.0, 42.6, 37.7, 37.6, 36.5, 36.1, 35.5, 31.9, 31.7, 31.4, 30.7, 30.6, 27.4, 26.0 C(15)_{*cis'*}, 21.9, 19.5, 19.0, 18.8, 18.7, 18.6, 18.2, 16.6, 16.6, 16.2, 16.0, 16.0;*

IR (film) ν_{max}/cm⁻¹ 3027, 2935, 1680, 1495, 1448, 1306, 1218, 1151, 1086, 910, 839;

HRMS (ESI⁺) C₂₈H₃₉O₃S⁺ ([M+H]⁺) requires 503.2614; found 503.2612, Δ 0.49 ppm.

* N.B. the labels ' and '' are assigned arbitrarily and indicate peaks belonging to different diastereomers.

S42 6-Hydroxy-1-phenylhexan-1-one



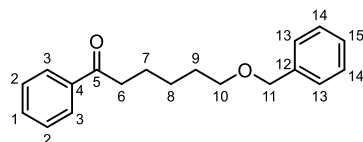
Mg turnings (1.46 g, 60.0 mmol) were heated with stirring under vacuum in a two-necked flask for 5 min and allowed to cool to RT. THF (10 mL) and a single iodine crystal were added and bromobenzene (3.2 mL, 30 mmol) was added slowly. The mixture was refluxed for a further 5 min, cooled to RT and diluted with THF (20 mL). ϵ -Caprolactone (0.55 mL, 5.0 mmol), *N,O*-dimethylhydroxyamine hydrochloride (585 mg, 6.00 mmol) and THF (100 mL) were added to a round-bottomed flask and cooled to $-15\text{ }^{\circ}\text{C}$ (ice/MeOH bath). The cooled Grignard reagent was added slowly *via* cannula and the reaction mixture was allowed to warm to RT overnight (22 h). HCl (15 mL) was added slowly and the reaction was stirred at RT for 1 h. The crude reaction mixture was concentrated *in vacuo* and then diluted with EtOAc (100 mL) and water (100 mL). The layers were separated and the organic layer was washed sequentially with 10% (w/v) aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 70:30 $\rightarrow$ 40:60) gave the *title compound* as a colourless oil (503 mg, 52%, (90% pure by ^1H NMR, (the contaminant was removed after the next step).

^1H NMR (400 MHz, CDCl_3) δ 8.01 – 7.91 (m, 2H, $2 \times \text{C}(3)\text{H}$), 7.60 – 7.51 (m, 1H, $\text{C}(1)\text{H}$), 7.51 – 7.43 (m, 2H, $2 \times \text{C}(2)\text{H}$), 3.67 (t, $J = 6.5\text{ Hz}$, 2H, $\text{C}(10)\text{H}_2$), 2.99 (t, $J = 7.3\text{ Hz}$, 2H, $\text{C}(6)\text{H}_2$), 1.78 (dt, $J = 15.0, 7.4\text{ Hz}$, 2H, $\text{C}(7)\text{H}_2$), 1.70 – 1.57 (m, 2H, $\text{C}(9)\text{H}_2$), 1.47 (m, 2H, $\text{C}(8)\text{H}_2$);

^{13}C NMR (101 MHz, CDCl_3) δ 200.4 $\text{C}(5)$, 137.0 $\text{C}(4)$, 133.0 $\text{C}(1)$, 128.6 $2 \times \text{C}(2)$, 128.1 $2 \times \text{C}(3)$, 62.7 $\text{C}(10)$, 38.5 $\text{C}(6)$, 32.5 $\text{C}(9)$, 25.5 $\text{C}(8)$, 23.9 $\text{C}(7)$;

m/z (ESI $^+$) Found ($[\text{M}+\text{H}]^+$) = 193, $\text{C}_{12}\text{H}_{17}\text{O}_2$ requires 193.

The spectroscopic data were consistent with that reported in the literature.¹⁶⁰

S43 6-(Benzyloxy)-1-phenylhexan-1-one

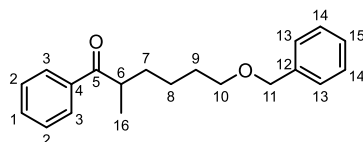
Alcohol **S42** (484 mg, 2.50 mmol, 90% purity by NMR) and KI (42 mg, 0.25 mmol) were added to a round-bottomed flask. Benzyl bromide (0.45 mL, 3.80 mmol) and *N,N*-diisopropylethylamine (0.70 mL, 4.0 mmol) were added and the reaction mixture was heated at 150 °C for 3 h. After cooling to RT, the reaction mixture was diluted with EtOAc (20 mL) and water (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 92:8) gave the *title compound* as a yellow oil (501 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.88 (m, 2H, 2 × C(3)H), 7.61 – 7.51 (m, 1H, C(1)H), 7.50 – 7.41 (m, 2H, 2 × C(2)H), 7.34 (m, 4H, 2 × C(13)H & 2 × C(14)H), 7.31 – 7.27 (m, 1H, C(15)H), 4.50 (s, 2H, C(11)H₂), 3.49 (t, *J* = 6.5 Hz, 2H, C(10)H₂), 3.06 – 2.88 (t, *J* = 7.3 Hz, 2H, C(6)H₂), 1.82 – 1.72 (m, 2H, C(7)H₂), 1.72 – 1.63 (m, 2H, C(9)H₂), 1.53 – 1.42 (m, 2H, C(8)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 200.4 C(5), 138.6 C(Ar(Ph)), 137.1 C(Ar(Ph)), 132.9 C(1), 128.6 2 × C(2), 128.4 2 × C(3), 128.1 2 × C(Ar(Ph)), 127.7 2 × C(Ar(Ph)), 127.5 C(15), 72.9 C(11), 70.2 C(10), 38.5 C(6), 29.7 C(9), 26.0 C(8), 24.2 C(7);

m/z (ESI⁺) Found ([M+Na]⁺) = 305, C₁₉H₂₂NaO₂ requires 305.

The spectroscopic data were consistent with that reported in the literature.¹⁶¹

S44 6-(Benzyloxy)-2-methyl-1-phenylhexan-1-one

n-BuLi (0.7 mL, 1.8 mmol, 2.5 M in hexane) was added slowly to a solution of *N,N*-diisopropylamine (DIPA) (0.41 mL, 2.93 mmol) in THF (10 mL) at –78 °C. The mixture was warmed to RT and stirred for 1 h. The mixture was cooled to –78 °C and ketone **S43** (490 mg,

1.74 mmol) in THF (7.5 mL) was added dropwise. The reaction was warmed to 0 °C and stirred for 2 h. MeI (0.22 mL, 3.48 mmol) was added dropwise, the reaction mixture warmed to RT and stirred for 4 h. The reaction was quenched using sat. aq. NH_4Cl (20 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 96:4) gave the *title compound* as a pale yellow oil (364 mg, 71%).

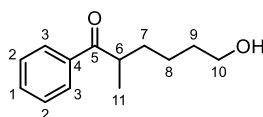
^1H NMR (400 MHz, CDCl_3) δ 8.09 – 7.88 (m, 2H, $2 \times \text{C}(3)\text{H}$), 7.61 – 7.51 (m, 1H, $\text{C}(1)\text{H}$), 7.51 – 7.42 (m, 2H, $2 \times \text{C}(2)\text{H}$), 7.36 – 7.26 (m, 5H, $2 \times \text{C}(13)\text{H}$, $2 \times \text{C}(14)\text{H}$, $\text{C}(15)\text{H}$), 4.47 (s, 2H, $\text{C}(11)\text{H}_2$), 3.61 – 3.36 (m, 3H, $\text{C}(6)\text{H}$, $\text{C}(10)\text{H}_2$), 1.95 – 1.75 (m, 1H, $\text{C}(7)\text{H}_\text{A}\text{H}_\text{B}$), 1.75 – 1.58 (m, 2H, $\text{C}(9)\text{H}_2$), 1.51 – 1.31 (m, 3H, $\text{C}(7)\text{H}_\text{A}\text{H}_\text{B}$, $\text{C}(8)\text{H}_2$), 1.20 (d, $J = 6.8$ Hz, 3H, $\text{C}(16)\text{H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 204.5 $\text{C}(5)$, 138.7 $\text{C}(12)$, 136.8 $\text{C}(4)$, 133.0 $\text{C}(1)$, 128.8 $2 \times \text{C}(2)$, 128.5 $2 \times \text{C}(14)$, 128.4 $2 \times \text{C}(3)$, 127.8 $2 \times \text{C}(13)$, 127.6 $\text{C}(15)$, 73.1 $\text{C}(11)$, 70.3 $\text{C}(10)$, 40.7 $\text{C}(6)$, 33.6 $\text{C}(7)$, 30.0 $\text{C}(9)$, 24.2 $\text{C}(8)$, 17.4 $\text{C}(16)$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2938, 2861, 1683, 1597, 1453, 1365, 1229, 1180, 1103, 1002, 738, 701;

HRMS (ESI^+) $\text{C}_{20}\text{H}_{25}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 297.1849; found 297.1845, Δ 1.25 ppm.

203 6-Hydroxy-2-methyl-1-phenylhexan-1-one



BBr_3 (1.0 M in CH_2Cl_2 , 3.6 mL, 3.6 mmol) was added dropwise to a solution of benzyl ether **S44** (358 mg, 1.21 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and quenched by pouring over ice (approx. 20 g). After the ice had melted, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 80:20 $\rightarrow$ 70:30) gave the *title compound* as a colourless oil (217 mg, 87%).

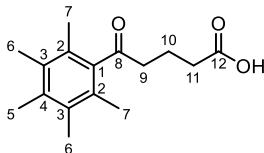
¹H NMR (400 MHz, CDCl₃) δ 7.97 – 7.75 (m, 2H, 2 × C(3)*H*), 7.61 – 7.45 (m, 1H, C(1)*H*), 7.45 – 7.31 (m, 2H, 2 × C(2)*H*), 3.56 (t, *J* = 6.5 Hz, 2H, C(10)*H*₂), 3.42 (h, *J* = 6.8 Hz, 1H, C(6)*H*), 1.88 – 1.68 (m, 1H, C(7)*H*_A*H*_B), 1.50 (m, 2H, C(9)*H*₂), 1.46 – 1.25 (m, 4H, C(7)*H*_A*H*_B, C(8)*H*₂, OH), 1.14 (d, *J* = 6.9 Hz, 3H, C(11)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 204.6 C(5), 136.8 C(4), 133.0 C(1), 128.8 2 × C(2), 128.4 2 × C(3), 62.8 C(10), 40.7 C(6), 33.4 C(7), 32.9 C(9), 23.8 C(8), 17.6 C(11);

IR (film) $\nu_{\max}$ /cm⁻¹ 3399, 2938, 2864, 1682, 1449, 1377, 1180, 1073, 1002, 931, 795;

HRMS (ESI⁺) C₁₃H₁₉O₂⁺ ([M+H]⁺) requires 207.1380; found 207.1380, Δ 0.12 ppm.

S45 5-Oxo-5-(2,3,4,5,6-pentamethylphenyl)pentanoic acid



AlCl₃ (5.12 g, 38.4 mmol) was added portion-wise (over 5 min) to a stirred solution of glutaric anhydride (2.00 g, 17.5 mmol) and pentamethylbenzene (2.85 g, 19.2 mmol) in CH₂Cl₂ (70 mL) at RT. The reaction was stirred for 5 min at RT and was then poured into cold 1 M HCl (100 mL). The layers were separated and the aqueous phase extracted with CH₂Cl₂ (2 × 100 mL). The combined organic layers were washed with 1 M HCl (2 × 100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in MeCN (1 L) and washed with pentane (4 × 300 mL). The MeCN layer was concentrated *in vacuo* to give the *title compound* as a white solid which was used without further purification (3.31 g, 47%).

m.p. = 142 – 145 °C;

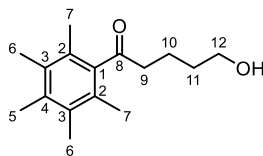
¹H NMR (400 MHz, CDCl₃) δ 2.69 (t, *J* = 7.2 Hz, 2H, C(9)*H*₂), 2.44 (t, *J* = 7.3 Hz, 2H, C(11)*H*₂), 2.16 (s, 3H, C(Ph*)*H*₃), 2.11 (s, 6H, 2 × C(Ph*)*H*₃), 2.00 (m, 8H, 2 × C(Ph*)*H*₃ & C(10)*H*₂, overlapped);

¹³C NMR (101 MHz, CDCl₃) δ 211.2 C(8), 178.7 C(12), 140.5 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 44.3 C(9), 33.0 C(11), 18.4 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\max}$ /cm⁻¹ 3029, 2975, 1694, 1405, 1310, 1233, 1199, 1118, 912;

HRMS (ESI⁻) C₁₆H₂₁O₃⁻ ([M-H]⁻) requires 261.1496; found 261.1493, Δ 1.15 ppm.

S46 5-Hydroxy-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one



BH₃·SMe₂ (0.65 mL, 6.9 mmol) was added dropwise to a solution of acid **S45** (1.20 g, 4.57 mmol) in THF (25 mL) at 0 °C. The reaction mixture was allowed to warm to RT over 16 h and quenched with slow addition of MeOH (3 mL) and water (8 mL). The resulting mixture was concentrated *in vacuo* and the residue was diluted with EtOAc (40 mL) and water (30 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 × 40 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 80:20 → 70:30) gave the *title compound* as a white solid (1.06 g, 93%).

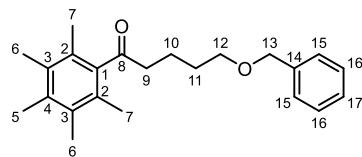
m.p. = 72 – 73 °C;

¹H NMR (400 MHz, CDCl₃) δ 3.69 (t, *J* = 6.9 Hz, 2H, C(12)H₂), 2.72 (t, *J* = 7.1 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.10 (s, 6H, 2 × C(Ph*)H₃), 1.86 – 1.74 (m, 2H, C(10)H₂), 1.72 – 1.61 (m, 2H, C(11)H₂), 1.51 (s, 1H, OH);

¹³C NMR (101 MHz, CDCl₃) δ 212.1 C(8), 140.8 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 127.4 2 × C(Ar(Ph*)), 62.7 C(12), 45.3 C(9), 32.4 C(11), 19.5 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 3463, 2941, 1703, 1681, 1405, 1218, 1182, 1123, 1064, 760;

HRMS (ESI⁺) C₁₆H₂₅O₂⁺ ([M+H]⁺) requires 249.1849; found 249.1848, Δ 0.51 ppm.

S47 5-(Benzyloxy)-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one

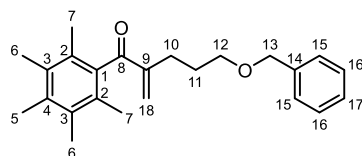
Benzyl Bromide (0.72 mL, 6.0 mmol) and *N,N'*-diisopropylethylamine (1.15 mL, 6.45 mmol) were added to alcohol **S46** (1.00 g, 4.03 mmol) and KI (66 mg, 0.40 mmol) and the mixture was heated to 150 °C for 3 h. The mixture was cooled to RT and diluted with EtOAc (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 90:10) gave the *title compound* as a colourless oil (1.28 g, 94%).

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.31 (m, 4H, 2 × C(15)H, 2 × C(16)H), 7.31 – 7.26 (m, 1H, C(17)H), 4.51 (s, 2H, C(13)H₂), 3.52 (t, *J* = 6.3 Hz, 2H, C(12)H₂), 2.71 (t, *J* = 7.2 Hz, 2H, C(9)H₂), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.08 (s, 6H, 2 × C(Ph*)H₃), 1.89 – 1.76 (m, 2H, C(10)H₂), 1.76 – 1.66 (m, 2H, C(11)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 211.9 C(8), 140.8 C(Ar(Ph*)), 138.7 C(14), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 128.5 2 × C(16), 127.8 2 × C(15), 127.7 C(17), 127.4 2 × C(Ar(Ph*)), 73.1 C(13), 70.3 C(12), 45.5 C(9), 29.4 C(11), 20.2 C(10), 17.3 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2925, 2857, 1702, 1496, 1454, 1404, 1362, 1106, 1028, 738, 699;

HRMS (ESI⁺) C₂₃H₃₁O₂⁺ ([M+H]⁺) requires 339.2319; found 339.2315, Δ 1.13 ppm.

S48 5-(Benzyloxy)-2-methylene-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one

Ketone **S47** (1.28 mg, 3.78 mmol) was dissolved in 1,4-dioxane (15 mL) and paraformaldehyde (2.27 g, 75.6 mmol, prilled) was added. H₂SO₄ (0.3 mL, 5.6 mmol) was added and the reaction mixture was heated to 85 °C for 6 h. A second portion of paraformaldehyde (2.27 g, 75.6 mmol,

prilled) was added and the mixture heated at 85 °C for a further 18 h. The mixture was cooled to RT, diluted with EtOAc (50 ml) and water (60 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 60 mL) and the combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5) gave the *title compound* as a white solid (942 mg, 71%).

m.p. = 43 – 45 °C;

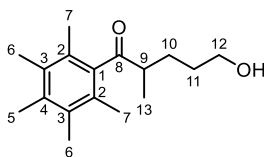
¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.32 (m, 4H, 2 × C(15)*H*, 2 × C(16)*H*₂), 7.32 – 7.27 (m, 1H, C(17)*H*), 5.90 (q, *J* = 1.3 Hz, 1H, C(18)*H*_A*H*_B), 5.65 (br. s, 1H, C(18)*H*_A*H*_B), 4.54 (s, 2H, C(13)*H*₂), 3.57 (t, *J* = 6.5 Hz, 2H, C(12)*H*₂), 2.60 – 2.46 (m, 2H, C(10)*H*₂), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, 2 × C(Ph*)*H*₃), 2.00 (s, 6H, 2 × C(Ph*)*H*₃), 1.96 – 1.77 (m, 2H, C(11)*H*₂);

¹³C NMR (101 MHz, CDCl₃) δ 203.9 C(8), 149.3 C(9), 138.7 C(14), 137.9 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 132.8 2 × C(Ar(Ph*)), 129.9 C(18), 129.1 2 × C(Ar(Ph*)), 128.5 2 × C(16), 127.9 2 × C(15), 127.7 C(17), 73.1 C(13), 70.0 C(12), 28.6 C(11), 26.7 C(10), 17.5 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.0 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3030, 2922, 2865, 1663, 1406, 1205, 1113, 1029, 942, 9102 ;

HRMS (ESI⁺) C₂₄H₃₁O₂⁺ ([M+H]⁺) requires 351.2319; found 351.2313, Δ 1.53 ppm.

204 5-Hydroxy-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one



Enone **S48** (920 mg, 2.63 mmol) and Pd (10% on carbon) (92 mg, 10 wt%) were subjected to **General Procedure F** in MeOH (26 mL) for 2 h. Purification *via* flash column chromatography (eluent pentane/EtOAc, 75:25) gave the *title compound* as a white solid (660 mg, 96%).

m.p. = 54 – 56 °C;

¹H NMR (400 MHz, CDCl₃) δ 3.65 (t, *J* = 6.5 Hz, 2H, C(12)*H*₂), 2.89 – 2.76 (m, 1H, C(9)*H*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, 2 × C(Ph*)*H*₃), 2.09 (s, 6H, C(Ph*)*H*₃), 1.95 – 1.81 (m, 1H, C(10)*H*_A*H*_B),

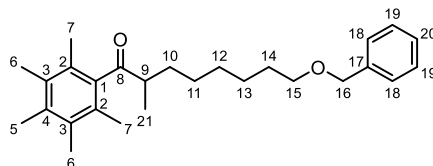
1.79 – 1.65 (m, 1H, C(11) H_AH_B), 1.65 – 1.52 (m, 1H, C(11) H_AH_B), 1.52 – 1.40 (m, 1H, C(10) H_AH_B), 1.16 (d, $J = 7.1$ Hz, 3H, C(13) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 215.0 C(8), 140.0 C(Ar(Ph*)), 135.6 C(Ar(Ph*)), 133.2 $2 \times$ C(Ar(Ph*)), 128.3 $2 \times$ C(Ar(Ph*)), 63.0 C(12), 48.2 C(9), 30.6 C(11), 28.0 C(10), 18.0 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 $2 \times$ C(Me(Ph*)), 15.6 C(13);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3410, 2943, 1693, 1460, 1383, 1303, 1062, 991, 913;

HRMS (ESI $^+$) $\text{C}_{17}\text{H}_{27}\text{O}_2^+$ ([M+H] $^+$) requires 263.2006; found 263.2003, Δ 0.92 ppm.

S49 8-(Benzyloxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)octan-1-one



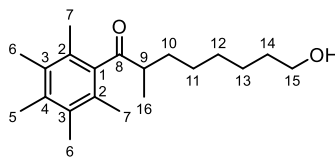
Ph* ethyl ketone **98** (408 mg, 2.00 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (16 mg, 1.0 mol%), KOH (449 mg, 8.00 mmol), 6-(benzyloxy)hexan-1-ol (833 mg, 4.00 mmol) and PhMe (0.5 mL) were subjected to **General Procedure E** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et $_2$ O, 96:4 $\rightarrow$ 94:6) gave the *title compound* as a colourless oil (663 mg, 84%).

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.29 (m, 4H, $2 \times$ C(18) H , $2 \times$ C(19) H), 7.29 – 7.23 (m, 1H, C(20) H), 4.50 (s, 2H, C(16) H_2), 3.45 (t, $J = 6.6$ Hz, 2H, C(15) H_2), 2.83 – 2.69 (m, 1H, C(9) H), 2.23 (s, 3H, C(Ph*) H_3), 2.18 (s, 6H, $2 \times$ C(Ph*) H_3), 2.09 (s, 6H, $2 \times$ C(Ph*) H_3), 1.82 – 1.68 (m, 1H, C(10) H_AH_B), 1.69 – 1.56 (m, 2H, C(14) H_2), 1.47 – 1.20 (m, 7H, C(10) H_AH_B , C(11) H_2 , C(12) H_2 , C(13) H_2), 1.13 (d, $J = 7.0$ Hz, 3H, C(21) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 215.3 C(8), 140.2 C(Ar(Ph*)), 138.8 C(17), 135.5 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 128.5 $2 \times$ C(19), 128.4 C(Ar(Ph*)), 127.8 $2 \times$ C(18), 127.6 C(20), 73.0 C(16), 70.6 C(15), 48.5 C(9), 31.8 C(10), 29.9 C(14), 29.7 C(12), 27.4 C(11), 26.3 C(13), 18.1 $2 \times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 $2 \times$ C(Me(Ph*)), 15.3 C(21);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2935, 2858, 1694, 1572, 1455, 1380, 1102, 990, 925, 698, 646;

HRMS (ESI $^+$) $\text{C}_{27}\text{H}_{39}\text{O}_2^+$ ([M+H] $^+$) requires 395.2945; found 395.2939, Δ 1.53 ppm.

205 8-Hydroxy-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)octan-1-one

Benzyl ether **S49** (652 mg, 1.65 mmol) and Pd (10% on carbon) (65 mg, 10 wt%) was subjected to **General Procedure F** in MeOH (17 mL) for 2 h. Purification *via* flash column chromatography (eluent pentane/EtOAc 70:30 → 55:45) gave the *title compound* as a white solid (482 mg, 96%).

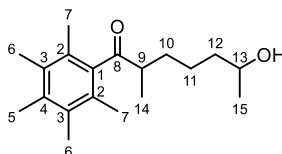
m.p. = 56 – 58 °C;

¹H NMR (400 MHz, CDCl₃) δ 3.62 (t, *J* = 6.6 Hz, 2H, C(15)H₂), 2.85 – 2.68 (m, 1H, C(9)H), 2.23 (s, 3H, C(Ph*)H₃), 2.18 (s, 6H, 2 × C(Ph*)H₃), 2.09 (s, 6H, 2 × C(Ph*)H₃), 1.84 – 1.73 (m, 1H, C(10)H_AH_B), 1.60 – 1.49 (m, 2H, C(14)H₂), 1.48 – 1.21 (m, 8H, C(10)H_AH_B, C(11)H₂, C(12)H₂, C(13)H₂, OH), 1.14 (d, *J* = 7.0 Hz, 3H, C(16)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.2 C(8), 140.2 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 128.4 2 × C(Ar(Ph*)), 63.1 C(15), 48.5 C(9), 32.8 C(14), 31.8 C(10), 29.6 C(12), 27.4 C(11), 25.8 C(13), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.3 C(16);

IR (film) ν_{max} /cm⁻¹ 3484, 2935, 1716, 1695, 1455, 1382, 1310, 1273, 1185, 1035;

HRMS (ESI⁺) C₂₀H₃₃O₂⁺ ([M+H]⁺) requires 305.2475; found 305.2471, Δ 1.44 ppm.

206 6-Hydroxy-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one

Aldehyde **158** (279 mg, 1.02 mmol) was dissolved in Et₂O (5 mL) and the mixture was cooled to –78 °C. MeMgBr (3.0 M in Et₂O, 0.41 mL, 1.2 mmol) was added and the reaction was stirred at –78 °C for 1 h. The mixture was warmed to RT and stirred for 15 min before quenching with sat. aq. NH₄Cl (10 mL) and diluting with EtOAc (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent pentane/Et₂O, 75:25 → 65:35) gave the *title compound* as a white solid (247 mg, 84%, [51:49] d.r.)*

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The spectroscopic data were collected on the diastereomeric mixture and the relative stereochemistry is unassigned.

m.p. = 44 – 46 °C;

¹H NMR (600 MHz, CDCl₃) δ 3.80 (q, *J* = 6.5 Hz, 2H, C(13')H, C(13'')H), 2.90 – 2.71 (m, 2H, C(9')H, C(9'')H), 2.23 (s, 6H, 2 × C(Ph*)H₃), 2.18 (s, 12H, 4 × C(Ph*)H₃), 2.09 (s, 12H, 4 × C(Ph*)H₃), 1.86 – 1.73 (m, 2H, C(10')H_AH_B, C(10'')H_AH_B), 1.64 – 1.60 (m, 2H, 2 × OH), 1.59 – 1.50 (m, 1H, C(11')H_AH_B), 1.49 – 1.26 (m, 9H, C(10')H_AH_B, C(10'')H_AH_B, C(11')H_AH_B, C(11'')H₂, 2 × C(12)H₂), 1.18 (d, *J* = 6.2 Hz, 6H, C(15')H₃, C(15'')H₃), 1.15 (d, *J* = 7.0 Hz, 6H, C(14')H₃, C(14'')H₃);*

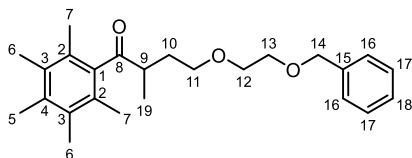
¹³C NMR (151 MHz, CDCl₃) δ 215.1 C(8') & C(8''), 140.1 C(Ar(Ph*)'), 140.1 C(Ar(Ph*)''), 135.6 C(Ar(Ph*)'), 135.6 C(Ar(Ph*)''), 133.2 C(Ar(Ph*)') & C(Ar(Ph*)''), 128.4 C(Ar(Ph*)') & C(Ar(Ph*)''), 68.0 C(13') & C(13''), 48.5 C(9'), 48.5 C(9''), 39.5 C(12'), 39.4 C(12''), 31.8 C(10'), 31.7 C(10''), 23.7 C(11'), 23.7 C(15'), 23.7 C(15''), 23.6 C(11''), 18.1 2 × C(Me(Ph*)') & 2 × C(Me(Ph*)''), 16.9 C(Me(Ph*)') & C(Me(Ph*)''), 16.2 2 × C(Me(Ph*)') & 2 × C(Me(Ph*)''), 15.4 C(14'), 15.3 C(14'');*

IR (film) ν_{max} /cm⁻¹ 3452, 2967, 2938, 1693, 1462, 1379, 1306, 1258, 1097, 924;

HRMS (ESI⁺) C₁₉H₃₁O₂⁺ ([M+H]⁺) requires 291.2319; found 291.2318, Δ 0.27 ppm.

* N.B. the labels ' and '' indicate peaks belonging to different diastereomers and are assigned arbitrarily.

S50 4-(2-(Benzyloxy)ethoxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



Ph* ethyl ketone **98** (816 mg, 4.00 mmol), [IrCp*Cl₂]₂ (32 mg, 1.0 mol%), KOH (898 mg, 16.0 mmol), di(ethylene)glycol benzyl ether (1.5 mL, 8.0 mmol, degassed with Ar) and PhMe (1.0 mL) were subjected to **General Procedure E** at 110 °C for 24 h. Purification *via* flash column

chromatography (eluent pentane/Et₂O, 90:10 → 85:15) gave the *title compound* as a colourless oil (1.27 g, 83%).

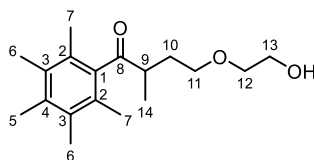
¹H NMR (600 MHz, CDCl₃) δ 7.35 – 7.30 (m, 4H, 2 × C(16)*H*, 2 × C(17)*H*), 7.30 – 7.26 (m, 1H, C(18)*H*), 4.56 (s, 2H, C(14)*H*₂), 3.66 – 3.48 (m, 6H, 2 × C(11)*H*₂, 2 × C(12)*H*₂, 2 × C(13)*H*₂), 3.01 (dq, *J* = 8.4, 7.1, 5.2 Hz, 1H, C(9)*H*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.20 – 2.12 (m, 7H, C(10)*H*_A*H*_B, 2 × C(Ph*)*H*₃), 2.08 (s, 6H, 2 × C(Ph*)*H*₃), 1.67 – 1.56 (m, 1H, C(10)*H*_A*H*_B), 1.15 (d, *J* = 7.1 Hz, 3H, C(19)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.8 C(8), 139.9 C(Ar(Ph*)), 138.4 C(15) 135.5 C(Ar(Ph*)), 133.1 2 × C(Ar(Ph*)), 128.5 2 × C(17), 128.4 2 × C(Ar(Ph*)), 127.8 2 × C(16), 127.7 C(18), 73.4 C(14), 70.3 C(12), 69.5 C(13), 69.1 C(11), 45.2 C(9), 31.6 C(10), 18.0 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)), 15.7 C(19);

IR (film) ν_{max} /cm⁻¹ 2863, 1694, 1497, 1455, 1355, 1107, 920;

HRMS (ESI⁺) C₂₅H₃₅O₃⁺ ([M+H]⁺) requires 383.2581; found 383.2575, Δ 1.48 ppm.

207 4-(2-Hydroxyethoxy)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



Benzyl ether **S50** (1.27 g, 3.32 mmol) and Pd (10% on carbon) (127 mg, 10 wt%) was subjected to **General Procedure F** in MeOH (35 mL) for 2 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 60:40 → pentane/EtOAc 50:50) gave the *title compound* as a colourless oil (876 mg, 90%).

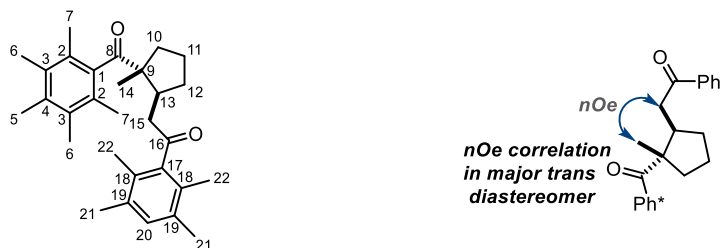
¹H NMR (600 MHz, CDCl₃) δ 3.73 – 3.67 (m, 2H, C(13)*H*₂), 3.63 – 3.53 (m, 2H, C(11)*H*₂), 3.53 – 3.48 (m, 2H, C(12)*H*₂), 3.03 – 2.94 (m, 1H, C(9)*H*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.20 – 2.13 (m, 7H, C(10)*H*_A*H*_B, 2 × C(Ph*)*H*₃), 2.09 (s, 6H, 2 × C(Ph*)*H*₃), 1.98 – 1.90 (m, 1H, OH), 1.63 (ddt, *J* = 14.1, 8.2, 6.1 Hz, 1H, C(10)*H*_A*H*_B), 1.16 (d, *J* = 7.1 Hz, 3H, C(14)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 214.6 C(8), 139.8 C(Ar(Ph^{*})), 135.7 C(Ar(Ph^{*})), 133.2 $2 \times$ C(Ar(Ph^{*})), 128.3 $2 \times$ C(Ar(Ph^{*})), 71.9 C(12), 69.0 C(11), 62.0 C(13), 45.2 C(9), 31.6 C(10), 18.0 $2 \times$ C(Me(Ph^{*})), 16.9 C(Me(Ph^{*})), 16.2 $2 \times$ C(Me(Ph^{*})), 15.8 C(14);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3438, 2940, 2875, 1693, 1459, 1125, 1067, 921;

HRMS (ESI⁺) $\text{C}_{18}\text{H}_{29}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 293.2111; found 293.2108, Δ 1.06 ppm.

165y 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-1-(2,3,5,6-tetramethylphenyl)ethan-1-one



Hydroxy ketone **164** (83 mg, 0.30 mmol), Ph^x methyl ketone **119** (106 mg, 0.600 mmol), Ir(cod)acac (4.8 mg, 4.0 mol%), cataCXium® A (17.2 mg, 16.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and ^tBuOH (1.2 mL) was added. The reaction was heated at 115 °C for 16 h, cooled to RT, filtered through a silica pad ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 98:2 → 95:5) gave an inseparable mixture of diastereomers of the *title compound* as a white solid (107 mg, 83%, [95:5] d.r.)*

* Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification. The relative stereochemistry was assigned by nOe analysis.

m.p. = 147 – 150 °C;

Major (1SR, 2RS) diastereomer (from the mixture):

^1H NMR (600 MHz, CDCl_3) δ 6.95 (s, 1H, C(20)H), 3.05 (dd, J = 19.2, 1.7 Hz, 1H, C(15) H_AH_B), 2.81 – 2.73 (m, 1H, C(13)H), 2.61 (dd, J = 19.1, 11.3 Hz, 1H, C(15) H_AH_B), 2.38 – 2.28 (m, 1H, C(12) H_AH_B), 2.23 (s, 3H, C(Ph^{*}) H_3), 2.21 (s, 6H, $2 \times$ C(Ph^x) H_3), 2.19 (s, 3H, C(Ph^{*}) H_3), 2.16 (s, 3H, C(Ph^{*}) H_3), 2.08 (s, 3H, C(Ph^{*}) H_3), 2.06 (s, 3H, C(Ph^{*}) H_3), 2.02 (s, 6H, $2 \times$ C(Ph^x) H_3), 1.99 – 1.91

(m, 1H, C(10) H_AH_B), 1.74 – 1.61 (m, 3H, C(10) H_AH_B , C(11) H_2), 1.39 – 1.30 (m, 1H, C(12) H_AH_B), 1.14 (s, 3H, C(14) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 217.9 C(8), 210.5 C(16), 143.0 C(17), 138.9 C(Ar(Ph*)), 135.1 C(Ar(Ph*)), 134.5 2 $\times$ C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 132.8 C(Ar(Ph*)), 131.6 C(20), 128.5 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.9 2 $\times$ C(Ar(Ph*)), 58.3 C(9), 46.7 C(15), 39.6 C(13), 37.2 C(10), 30.4 C(12), 22.0 C(11), 19.6 2 $\times$ C(Ar(Ph*)), 19.3 C(Me(Ph*)), 18.5 C(Me(Ph*)), 18.1 C(14), 16.7 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.0 C(Me(Ph*)), 15.9 2 $\times$ C(Ar(Ph*));

Selected characteristic peaks of the minor (1*RS*, 2*RS*) diastereomer (from the mixture):

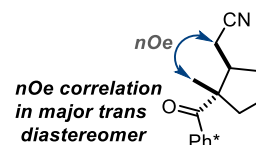
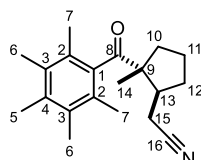
^1H NMR (600 MHz, CDCl_3) δ 3.08 – 3.07 (m, 1H, C(15) H_AH_B), 1.17 (s, 3H, C(14) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 218.6, 211.5, 143.0, 140.5, 134.9, 133.4, 132.8, 128.0, 127.4, 58.7, 47.4, 45.4, 39.2, 31.8, 29.8, 24.7, 21.7, 18.3, 18.2, 16.2, 16.0;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2941, 1703, 1674, 1469, 1378, 1303, 1260, 1219, 1109, 980;

HRMS (ESI^+) $\text{C}_{30}\text{H}_{40}\text{NaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 455.2913; found 455.2921, Δ 1.61 ppm.

165z 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)acetonitrile



Hydroxy ketone **164** (83 mg, 0.30 mmol), **Mn Cat01** (3.0 mg, 2.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and $^t\text{BuOH}$ (1.2 mL) and MeCN (78 μL , 1.5 mmol) were added. The reaction was heated at 115 $^\circ\text{C}$ for 16 h, cooled to RT, filtered through a silica pad ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 96:4 $\rightarrow$ 92:8) gave separable diastereomers of the *title compound* as a white solid (14 mg, 15%, [96:4] d.r.)*

* Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification.

The relative stereochemistry was assigned by nOe analysis.

Major (1*RS*, 2*SR*) diastereomer:

m.p. = 97 – 99 °C;

¹H NMR (600 MHz, CDCl₃) δ 2.69 (dd, *J* = 16.7, 3.6 Hz, 1H, C(15)*H_AH_B*), 2.47 (tdd, *J* = 10.5, 8.2, 3.5 Hz, 1H, C(13)*H*), 2.30 – 2.24 (m, 1H, C(15)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.21 – 2.17 (m, 4H, C(12)*H_AH_B*, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.08 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 3H, C(Ph*)*H₃*), 2.03 – 1.93 (m, 1H, C(10)*H_AH_B*), 1.78 – 1.62 (m, 3H, C(10)*H_AH_B*, C(11)*H₂*), 1.61 – 1.51 (m, 1H, C(12)*H_AH_B*), 1.14 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 217.4 C(8), 138.6 C(Ar(Ph*)), 135.5 C(Ar(Ph*)), 133.6 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 119.5 C(16), 58.0 C(9), 42.1 C(13), 38.1 C(10), 30.1 C(12), 21.6 C(11), 19.2 C(Me(Ph*)), 18.6 C(Me(Ph*)), 18.5 C(15), 17.9 C(14), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2952, 2248, 1680, 1473, 1385, 1303, 1264, 1218, 1114, 924;

HRMS (ESI⁺) C₂₀H₂₈NO⁺ ([M+H]⁺) requires 298.2165; found 298.2163, Δ 0.79 ppm.

Minor (1*SR*, 2*SR*) diastereomer:

m.p. = 90 – 92 °C;

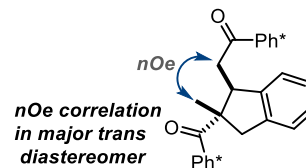
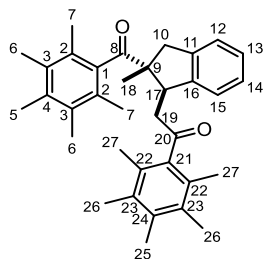
¹H NMR (600 MHz, CDCl₃) δ 2.70 – 2.58 (m, 2H, C(15)*H₂*), 2.28 (ddd, *J* = 13.2, 9.5, 6.8 Hz, 1H, C(12)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.22 – 2.15 (m, 8H, C(13)*H*, C(10)*H_AH_B*, 2 × C(Ph*)*H₃*), 2.05 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 3H, C(Ph*)*H₃*), 1.97 (td, *J* = 9.1, 4.6 Hz, 1H, C(10)*H_AH_B*), 1.92 – 1.83 (m, 1H, C(11)*H_AH_B*), 1.83 – 1.75 (m, 1H, C(11)*H_AH_B*), 1.69 (ddd, *J* = 13.7, 8.8, 5.3 Hz, 1H, C(12)*H_AH_B*), 1.11 (s, 3H, C(14)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 218.2 C(8), 139.9 C(Ar(Ph*)), 135.3 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 127.1 C(Ar(Ph*)), 120.2 C(16), 58.1 C(9), 47.5 C(13), 39.2 C(12), 31.1 C(10), 24.6 C(14), 21.1 C(11), 20.2 C(15), 18.3 C(Me(Ph*)), 18.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2937, 2244, 1680, 1460, 1263, 1221, 1079, 1023, 920;

HRMS (ESI⁺) C₂₀H₂₇NNaO⁺ ([M+Na]⁺) requires 320.1985; found 320.1283, Δ 0.49 ppm.

165aa 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



Hydroxy ketone **223a** (97 mg, 0.30 mmol), Ph* methyl ketone **31** (114 mg, 0.600 mmol), [Ir(cod)acac] (4.8 mg, 4.0 mol%), cataCXium® A (17.2 mg, 16.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and ^tBuOH (1.2 mL) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98:2 → 95:5) gave separable diastereomers of the *title compound* as a white solid (44 mg, 34%, [94:6] d.r.,* isolated in conjunction with 66 mg, 44% **S51**).

* Due to overlapping peaks in the crude ¹H NMR, the d.r. was calculated post-purification. The relative stereochemistry was assigned by nOe analysis.

Major (1*RS*, 2*RS*) diastereomer:

m.p. = 201 – 203 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.29 (d, *J* = 7.5 Hz, 1H, C(15)*H*), 7.21 – 7.16 (m, 1H, C(14)*H*), 7.16 – 7.12 (m, 1H, C(13)*H*), 7.10 (d, *J* = 7.3 Hz, 1H, C(12)*H*), 4.28 (d, *J* = 10.1 Hz, 1H, C(17)*H*), 3.61 (dd, *J* = 19.8, 1.5 Hz, 1H, C(19)*H_AH_B*), 3.28 (d, *J* = 15.3 Hz, 1H, C(10)*H_AH_B*), 2.97 (dd, *J* = 19.7, 10.3 Hz, 1H, C(19)*H_AH_B*), 2.78 (d, *J* = 15.3 Hz, 1H, C(10)*H_AH_B*), 2.27 (s, 3H, C(Ph*)*H₃*), 2.25 – 2.20 (m, 15H, 5 × C(Ph*)*H₃*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.14 (s, 3H, C(Ph*)*H₃*), 2.12 (s, 3H, C(Ph*)*H₃*), 1.25 (s, 3H, C(18)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 216.9 C(8), 210.6 C(20), 143.8 C(16), 141.2 C(11), 140.5 C(Ar(Ph*)), 139.3 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.7 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 127.7 2 × C(Ar(Ph*)), 126.9 C(14), 126.8

C(13), 124.9 C(15), 124.4 C(12), 60.5 C(9), 46.4 C(19), 44.4 C(17), 43.4 C(10), 20.0 C(18), 19.2 C(Me(Ph*)), 19.0 C(Me(Ph*)), 17.4 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3016, 2928, 1699, 1451, 1218, 1116, 932, 760;

HRMS (ESI⁺) C₃₅H₄₃O₂⁺ ([M+H]⁺) requires 495.3258; found 495.3254, Δ 0.65 ppm.

Minor (1*SR*, 2*RS*) diastereomer:

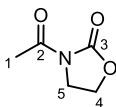
m.p. = 212 – 214 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.53 – 7.46 (m, 1H, C(15)H), 7.18 – 7.10 (m, 3H, C(12)H, C(13)H, C(14)H), 3.97 (dd, J = 10.8, 2.0 Hz, 1H, C(17)H), 3.61 (d, J = 15.2 Hz, 1H, C(10)H_AH_B), 3.35 (dd, J = 20.2, 2.1 Hz, 1H, C(19)H_AH_B), 3.09 (dd, J = 20.2, 10.8 Hz, 1H, C(19)H_AH_B), 2.80 (d, J = 15.2 Hz, 1H, C(10)H_AH_B), 2.22 (s, 3H, C(Ph*)H₃), 2.21 (s, 3H C(Ph*)H₃), 2.19 (s, 3H, C(Ph*)H₃), 2.15 – 2.10 (m, 12H, 4 × C(Ph*)H₃), 2.05 – 1.76 (m, 9H, 3 × C(Ph*)H₃), 1.22 (s, 3H, C(18)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 218.4 C(8), 210.7 C(20), 146.4 C(16), 141.0 C(Ar(Ph*)), 140.7 C(11), 140.6 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.6 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 127.8 2 × C(Ar(Ph*)), 127.2 C(13), 127.2 C(Ar(Ph*)), 126.9 C(14), 126.3 C(15), 125.1 C(12), 59.4 C(9), 50.4 C(17), 49.1 C(19), 45.8 C(10), 25.7 C(18), 18.1 C(Me(Ph*)), 18.1 C(Me(Ph*)), 17.1 2 × C(Me(Ph*)), 17.0 C(Me(Ph*)), 17.0 C(Me(Ph*)), 16.4 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2950, 1703, 1677, 1309, 924, 762;

HRMS (ESI⁺) C₃₅H₄₃O₂⁺ ([M+H]⁺) requires 495.3258; found 495.3266, Δ 1.70 ppm.

210 3-Acetyloxazolidin-2-one

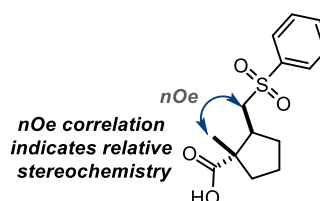
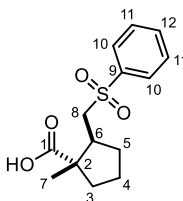
n-BuLi (2.5 M, 0.88 mL, 2.20 mmol) was added dropwise to a solution of 2-oxazolidinone (175 mg, 2.00 mmol) in THF (7 mL) at -78°C . The mixture was stirred for 30 min and acetyl chloride (0.16 mL, 2.20 mmol) was added dropwise. The reaction was stirred at -78°C for 30 min, quenched with the addition of sat. aq. NH_4Cl (5 mL) and warmed to RT. The layers were separated and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 80:20 $\rightarrow$ 70:30) gave the *title compound* as a white solid (159 mg, 62%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 4.48 – 4.30 (m, 2H, C(4) H_2), 4.10 – 3.90 (m, 2H, C(5) H_2), 2.53 (s, 3H, C(1) H_3);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.6 C(2), 153.9 C(3), 62.1 C(4), 42.5 C(5), 23.4 C(1);

m/z (ESI $^+$) Found ($[\text{M}+\text{H}]^+$) = 130, $\text{C}_5\text{H}_7\text{NO}_3$ requires 130.

The spectroscopic data matched that previously reported in the literature.¹⁶²

213 (1*SR*,2*SR*)-1-Methyl-2-((phenylsulfonyl)methyl)cyclopentane-1-carboxylic acid

A 2 – 5 mL microwave vial was charged with ketone **165h** (62 mg, 0.15 mmol, $>[95:5]$ d.r.) and 1,1,1,3,3,3-hexafluoroisopropanol (1.5 mL) and 37% aq. HCl (12 M, 0.3 mL) were added. The resulting mixture was stirred at 65°C for 16 h, cooled to RT and diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

Purification *via* flash column chromatography (eluent CH₂Cl₂/EtOAc/HCO₂H 89.95:10:0.05) gave the *title compound* as a white solid (39 mg, 93%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

m.p. = 112 – 114 °C;

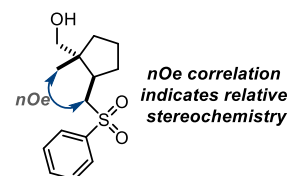
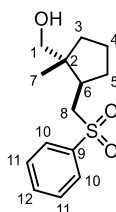
¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.80 (m, 2H, 2 × C(10)H), 7.73 – 7.61 (m, 1H, C(12)H), 7.57 (t, *J* = 7.6 Hz, 2H, 2 × C(11)H), 3.43 (dd, *J* = 13.8, 2.8 Hz, 1H, C(8)H_AH_B), 2.99 (dd, *J* = 13.8, 10.9 Hz, 1H, C(8)H_AH_B), 2.64 (tdd, *J* = 10.9, 7.9, 2.8 Hz, 1H, C(6)H), 2.31 – 2.17 (m, 1H, C(5)H_AH_B), 2.17 – 1.97 (m, 1H, C(3)H_AH_B), 1.83 – 1.70 (m, 2H, C(4)H₂), 1.70 – 1.58 (m, 1H, C(3)H_AH_B), 1.58 – 1.41 (m, 1H, C(5)H_AH_B), 1.08 (s, 3H, C(7)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 182.3 C(1), 139.8 C(9), 133.8 C(12), 129.4 2 × C(11), 128.1 2 × C(10), 58.1 C(8), 51.4 C(2), 40.7 C(6), 37.4 C(3), 30.1 C(5), 22.2 C(4), 18.0 C(7);

IR (film) ν_{max} /cm⁻¹ 3067, 2917, 1698, 1472, 1448, 1408, 1304, 1260, 1146, 1086, 1000, 913, 831;

HRMS (ESI⁻) C₁₄H₁₇O₄S⁻ ([M-H]⁻) requires 281.0853; found 281.0853, Δ 0.16 ppm.

214 ((1*RS*,2*RS*)-1-Methyl-2-((phenylsulfonyl)methyl)cyclopentyl)methanol



Ketone **165h** (62 mg, 0.15 mmol, >[95:5 d.r.]) was dissolved in CH₂Cl₂ (0.75 mL) and the solution was cooled to –17 °C (ice/salt bath). Br₂ (21 μL, 0.40 mmol) was added dropwise and the resulting solution was stirred at –17 °C for 40 min. The reaction mixture was then warmed to RT, 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 sec. The residue was dissolved in THF (1.5 mL) and the resulting stirred solution was cooled to 0 °C. LiAlH₄ (29 mg, 0.75 mmol) was added in a single portion and the reaction was stirred for 3 h at 0 °C. The resulting mixture was diluted with Et₂O (1.5 mL) and quenched by sequential dropwise addition of H₂O (30 μL), aq. NaOH (15% w/v, 30 μL) and H₂O (150 μL). MgSO₄ was added and the resulting suspension was stirred vigorously

for 15 min and then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (pentane/ $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$, 60:5:35) gave the *title compound* as a colourless oil (34 mg, 86%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe analysis.

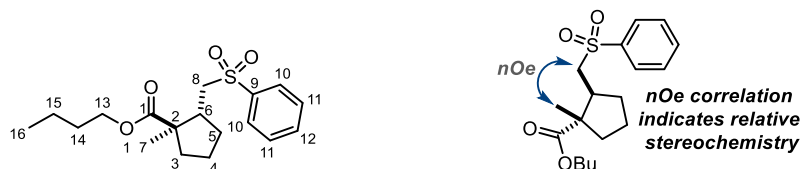
^1H NMR (400 MHz, CDCl_3) δ 7.96 – 7.87 (m, 2H, $2 \times \text{C}(10)\text{H}$), 7.68 – 7.61 (m, 1H, $\text{C}(12)\text{H}$), 7.60 – 7.50 (m, 2H, $2 \times \text{C}(11)\text{H}$), 3.57 – 3.31 (m, 3H, $\text{C}(1)\text{H}_2$, $\text{C}(8)\text{H}_\text{A}\text{H}_\text{B}$), 2.94 (dd, $J = 14.0, 9.7$ Hz, 1H, $\text{C}(8)\text{H}_\text{A}\text{H}_\text{B}$), 2.20 (tdd, $J = 10.5, 8.0, 2.9$ Hz, 1H, $\text{C}(6)\text{H}$), 2.11 – 1.94 (m, 1H, $\text{C}(5)\text{H}_\text{A}\text{H}_\text{B}$), 1.77 – 1.61 (m, 1H, $\text{C}(4)\text{H}_\text{A}\text{H}_\text{B}$), 1.62 – 1.48 (m, 2H, $\text{C}(3)\text{H}_\text{A}\text{H}_\text{B}$, $\text{C}(4)\text{H}_\text{A}\text{H}_\text{B}$), 1.47 – 1.35 (m, 1H, $\text{C}(5)\text{H}_\text{A}\text{H}_\text{B}$), 1.35 – 1.23 (m, 1H, $\text{C}(3)\text{H}_\text{A}\text{H}_\text{B}$), 0.79 (s, 3H, $\text{C}(7)\text{H}_3$);

^{13}C NMR (101 MHz, CDCl_3) δ 140.0 $\text{C}(9)$, 133.7 $\text{C}(12)$, 129.4 $2 \times \text{C}(11)$, 128.0 $2 \times \text{C}(10)$, 70.1 $\text{C}(1)$, 58.4 $\text{C}(8)$, 46.2 $\text{C}(2)$, 39.1 $\text{C}(6)$, 35.8 $\text{C}(3)$, 31.5 $\text{C}(5)$, 21.8 $\text{C}(4)$, 18.1 $\text{C}(7)$;

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3539, 2954, 2873, 1448, 1304, 1146, 1086, 745, 689;

HRMS (ESI^+) $\text{C}_{14}\text{H}_{20}\text{NaO}_3\text{S}^+$ ($[\text{M}+\text{Na}]^+$) requires 291.1025; found 291.1019, Δ 2.21 ppm.

215 (1*RS*,2*RS*)-1-Methyl-2-((phenylsulfonyl)methyl)cyclopentane-1-carboxylate



Ph* ketone **165h** (32 mg, 0.10 mmol, >[95:5] d.r.) was dissolved in CH_2Cl_2 (0.5 mL) and the solution was cooled to -17°C (ice/salt bath). Br_2 (10 μL , 0.20 mmol) was added dropwise and the resulting solution was stirred at -17°C for 20 min. $n\text{BuOH}$ (28 μL , 0.30 mmol) was added and the reaction was allowed to warm to RT overnight. The reaction was diluted with CH_2Cl_2 (10 mL) and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (pentane/ $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 80:5:15) gave the *title compound* as a colourless oil (30.4 mg, 90%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe analysis.

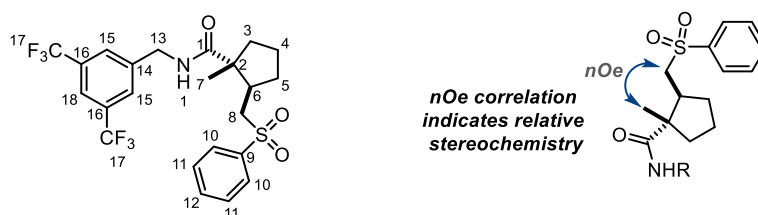
^1H NMR (500 MHz, CDCl_3) δ 8.02 – 7.77 (m, 2H, 2 $\times$ C(10)H), 7.70 – 7.61 (m, 1H, C(12)H), 7.61 – 7.50 (m, 2H, 2 $\times$ C(11)H), 4.06 – 3.88 (m, 2H, C(13)H₂), 3.42 (dd, J = 13.8, 2.6 Hz, 1H, C(8)H_AH_B), 2.97 (dd, J = 13.8, 11.1 Hz, 1H, C(8)H_AH_B), 2.57 (tdd, J = 10.9, 8.0, 2.6 Hz, 1H, C(6)H), 2.28 – 2.13 (m, 1H, C(5)H_AH_B), 2.04 (ddd, J = 12.9, 10.0, 8.1 Hz, 1H, C(3)H_AH_B), 1.71 (m, 2H, C(4)H₂), 1.63 – 1.43 (m, 4H, C(3)H_AH_B, C(5)H_AH_B, C(14)H₂), 1.38 – 1.27 (m, 2H, C(15)H₂), 1.03 (s, 3H, C(7)H₃), 0.91 (t, J = 7.4 Hz, 3H, C(16)H₃);

^{13}C NMR (126 MHz, CDCl_3) δ 176.6 C(1), 139.9 C(9), 133.7 C(12), 129.4 2 $\times$ C(11), 128.1 2 $\times$ C(10), 64.7 C(13), 58.3 C(8), 51.7 C(2), 40.7 C(6), 37.2 C(3), 30.7 C(14), 29.9 C(5), 22.1 C(4), 19.3 C(15), 18.1 C(7), 13.9 C(16);

IR (film) ν_{max} /cm⁻¹ 2964, 2876, 1723, 1653, 1554, 1448, 1308, 1196, 1148, 1117, 1087;

HRMS (ESI⁺) C₁₈H₂₇O₄S⁺ ([M+H]⁺) requires 339.1625; found 339.1620, Δ 1.40 ppm.

216 (1*RS*,2*RS*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-1-methyl-2-((phenylsulfonyl)methyl)cyclopentane-1-carboxamide



Ph* ketone **165h** (32 mg, 0.10 mmol, >[95:5] d.r.) was dissolved in CH_2Cl_2 (0.5 mL) and the solution was cooled to -17°C (ice/salt bath). Br_2 (10 μL , 0.20 mmol) was added dropwise and the resulting solution was stirred at -17°C for 20 min. DIPEA (70 μL , 0.40 mmol) and (3,5-bis(trifluoromethyl)phenyl)methanamine (73 mg, 0.30 mmol) were added sequentially and the reaction was allowed to warm to RT overnight. The reaction was diluted with CH_2Cl_2 (10 mL) and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), the layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 $\times$ 10 mL). The combined organic phases were washed with 1 M HCl and brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (pentane/ CH_2Cl_2 /EtOAc 70:5:25) gave the *title compound* as a tan solid (50 mg, 99%, >[95:5] d.r.) The relative stereochemistry was assigned by nOe and X-ray crystallography analysis.

m.p. = 122 – 124 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.91 – 7.84 (m, 2H, 2 × C(10)H), 7.76 (s, 1H, C(18)H), 7.69 (s, 2H, 2 × C(15)H), 7.67 – 7.59 (m, 1H, C(12)H), 7.54 (t, *J* = 7.7 Hz, 2H, 2 × C(11)H), 6.50 – 6.39 (m, 1H, NH), 4.56 – 4.45 (m, 2H, C(13)H₂), 3.53 (dd, *J* = 13.9, 3.4 Hz, 1H, C(8)H_AH_B), 2.98 (dd, *J* = 13.9, 9.8 Hz, 1H, C(8)H_AH_B), 2.68 (tdd, *J* = 10.5, 8.1, 3.4 Hz, 1H, C(6)H), 2.16 (dtd, *J* = 13.0, 8.3, 4.4 Hz, 1H, C(5)H_AH_B), 1.99 – 1.88 (m, 1H, C(3)H_AH_B), 1.82 – 1.67 (m, 2H, C(4)H₂), 1.67 – 1.59 (m, 1H, C(3)H_AH_B), 1.56 – 1.45 (m, 1H, C(5)H_AH_B), 1.11 (s, 3H, C(7)H₃);

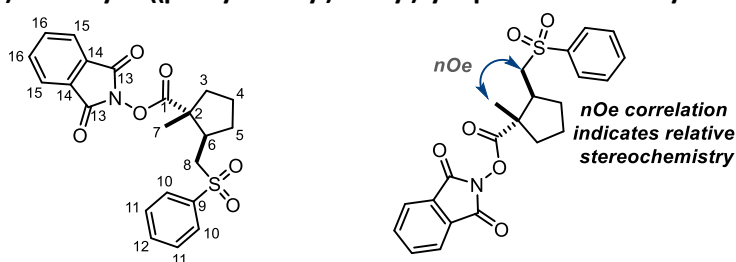
¹³C NMR (151 MHz, CDCl₃) δ 177.0 C(1), 141.5 C(14), 139.6 C(9), 133.9 C(12), 132.0 (q, *J*²_{C-F} = 33.4 Hz, 2 × C(16)), 129.4 2 × C(11), 128.0 2 × C(10), 127.8 (q, *J*³_{C-F} = 3.8 Hz, 2 × C(15)), 123.4 (q, *J*¹_{C-F} = 273.0 Hz, 2 × C(17)), 121.4 (hept, *J*³_{C-F} = 3.8 Hz, C(18)), 58.2 C(8), 51.7 C(2), 42.8 C(13), 40.1 C(6), 38.1 C(3), 30.2 C(5), 22.0 C(4), 18.7 C(7);

¹⁹F NMR (565 MHz, CDCl₃) δ –62.9;

IR (film) *ν*_{max}/cm^{–1} 3380, 2967, 1637, 1510, 1386, 1362, 1280, 1170, 1143, 1127, 1100;

HRMS (ESI⁺) C₂₃H₂₄F₆NO₃S⁺ ([M+H]⁺) requires 508.1376; found 508.1373, Δ 0.46 ppm.

217 1,3-Dioxoisindolin-2-yl (1*RS*,2*RS*)-1-methyl-2-((phenylsulfonyl)methyl)cyclopentane-1-carboxylate



Ketone **165h** (41 mg, 0.10 mmol, >[95:5] d.r.) was dissolved in CH₂Cl₂ (0.5 mL) and the solution was cooled to –17 °C (ice/salt bath). Br₂ (21 μL, 0.40 mmol) was added dropwise and the mixture was stirred at –17 °C for 20 min. *N*-hydroxyphthalimide (65 mg, 0.40 mmol) and *i*Pr₂NEt (70 μL, 0.40 mmol) were added sequentially and the reaction was allowed to warm to RT and stirred for 16 h. The mixture was diluted with CH₂Cl₂ (10 mL) and sat. aq. Na₂S₂O₃ (10 mL), the layers separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. Purification *via*

flash column chromatography (eluent pentane/CH₂Cl₂/EtOAc, 75:5:20) gave the *title compound* as a colourless oil (42 mg, 99%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe analysis.

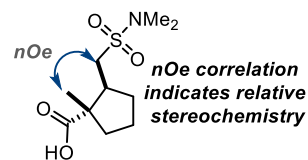
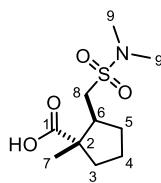
¹H NMR (600 MHz, CDCl₃) δ 8.02 – 7.95 (m, 2H, 2 × C(10)H), 7.92 – 7.84 (m, 2H, 2 × C(15)H), 7.83 – 7.78 (m, 2H, C(16)H), 7.65 – 7.59 (m, 1H, C(12)H), 7.58 – 7.53 (m, 2H, 2 × C(11)H), 3.62 (dd, *J* = 13.7, 2.5 Hz, 1H, C(8)H_AH_B), 3.04 (dd, *J* = 13.7, 11.6 Hz, 1H, C(8)H_AH_B), 2.79 (tdd, *J* = 11.1, 7.9, 2.5 Hz, 1H, C(6)H), 2.44 – 2.35 (m, 1H, C(5)H_AH_B) 2.35 – 2.26 (m, 1H, C(3)H_AH_B), 1.92 – 1.79 (m, 3H, C(3)H_AH_B, C(4)H₂), 1.65 (dddd, *J* = 18.2, 11.2, 9.2, 5.0 Hz, 1H, C(5)H_AH_B), 1.27 (s, 3H, C(7)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 172.9 C(1), 161.9 2 × C(13), 139.7 C(9), 134.9 2 × C(16), 133.8 C(12), 129.4 2 × C(11), 129.1 2 × C(14), 128.2 2 × C(10), 124.1 2 × C(15), 57.6 C(8), 51.1 C(2), 41.5 C(6), 37.4 C(3), 29.3 C(5), 22.2 C(4), 17.7 C(7);

IR (film) ν_{max} /cm⁻¹ 2934, 1783, 1745, 1370, 1307, 1149, 1085, 1025, 911, 878, 738, 698;

HRMS (ESI⁺) C₂₂H₂₂NO₆S⁺ ([M+H]⁺) requires 428.1162; found 428.1158, Δ 0.93 ppm.

218 (1*RS*,2*RS*)-2-((*N,N*-Dimethylsulfamoyl)methyl)-1-methylcyclopentane-1-carboxylic acid



Ketone **165i** (38 mg, 0.10 mmol, >[95:5] d.r.) was dissolved in CH₂Cl₂ (0.5 mL) and the solution was cooled to –17 °C (ice/salt bath). Br₂ (21 μL, 0.40 mmol) was added dropwise and the resulting solution was stirred at –17 °C for 40 min. The reaction mixture was then warmed to RT, 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 sec. The residue was dissolved in THF (1.0 mL), sat. aq. NaHCO₃ (1.0 mL) was added and the mixture was stirred at RT for 3 h. The reaction was diluted with CH₂Cl₂ (5 mL) and 3 M HCl (5 mL), the layers were separated and the aqueous phase extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phases were washed with brine, dried

over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{HCO}_2\text{H}$, 99.15:0.8:0.05) gave the *title compound* as a white solid (24.2 mg, 97%, >[95:5] d.r.)

The relative stereochemistry was assigned by nOe analysis.

m.p. = 93 – 95 °C;

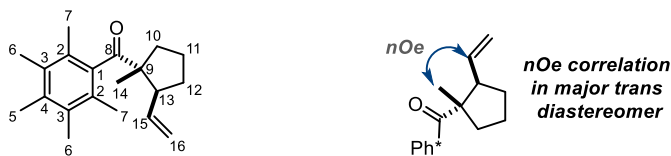
^1H NMR (400 MHz, CDCl_3) δ 3.35 – 3.19 (m, 1H, C(8) H_AH_B), 2.88 (s, 6H, 2 $\times$ C(9) H_3), 2.83 – 2.63 (m, 2H, C(6) H , C(8) H_AH_B), 2.32 (dtd, J = 12.7, 7.5, 5.0 Hz, 1H, C(5) H_AH_B), 2.21 – 2.06 (m, 1H, C(3) H_AH_B), 1.87 – 1.72 (m, 2H, C(4) H_2), 1.72 – 1.63 (m, 1H, C(3) H_AH_B), 1.61 – 1.49 (m, 1H, C(5) H_AH_B), 1.12 (s, 3H, C(7) H_3);

^{13}C NMR (101 MHz, CDCl_3) δ 183.3 C(1), 51.4 C(2), 49.6 C(8), 41.1 C(6), 37.7 C(3), 37.6 2 $\times$ C(9), 30.2 C(5), 22.1 C(4), 17.8 C(7);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2973, 2925, 1693, 1329, 1281, 1144, 957, 776, 713;

HRMS (ESI $^-$) $\text{C}_{10}\text{H}_{18}\text{NO}_4\text{S}^-$ ($[\text{M}-\text{H}]^-$) requires 248.0962; found 248.0959, Δ 1.02 ppm.

219 (1-Methyl-2-vinylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone



Sulfone **165r** (36 mg, 0.10 mmol, >[95:5] d.r.) was dissolved in $t\text{BuOH}$ (0.4 mL) and Alumina-supported KOH^* (200 mg) was added. The reaction was heated to 80 °C and CBr_2F_2 (40 μL , 0.44 mmol) was added. The reaction was stirred at 80 °C for 2 h and four portions of CBr_2F_2 (each 40 μL , 0.44 mmol) were added at 20 min intervals. The reaction was cooled to RT and filtered through a silica plug (elution with CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99:1) gave the *title compound* as a solid glass (8.2 mg, 29%, [93:7] d.r. *, isolated in conjunction with 6.4 mg **220**, 23%).

* Alumina-supported KOH was prepared by addition of neutral alumina (15.0 g, 147 mmol) to a solution of KOH (5.00 g, 89.1 mmol) in MeOH (25 mL) and stirring at RT for 1 h. The solvent was removed under reduced pressure to give $\text{KOH}-\text{Al}_2\text{O}_3$ as a free-flowing white powder, which was stored under air at RT.

* Due to overlapping peaks in the crude ^1H NMR, the d.r. was calculated post-purification. The relative stereochemistry was assigned by nOe analysis.

Major (1*RS*, 2*SR*) diastereomer (from the mixture):

^1H NMR (600 MHz, CDCl_3) δ 5.87 (ddd, $J = 17.1, 10.5, 7.7$ Hz, 1H, C(15)*H*), 5.11 – 4.98 (m, 2H, C(16)*H*₂), 3.16 – 3.01 (m, 1H, C(13)*H*), 2.24 (s, 3H, C(Ph*)*H*₃), 2.20 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 3H, C(Ph*)*H*₃), 2.11 (s, 4H, C(10)*H*_A*H*_B, C(Ph*)*H*₃), 2.06 (s, 3H, C(Ph*)*H*₃), 1.92 (dddd, $J = 13.2, 12.0, 8.5, 6.2$ Hz, 1H, C(12)*H*_A*H*_B), 1.82 – 1.70 (m, 3H, C(10)*H*_A*H*_B, C(11)*H*₂), 1.70 – 1.61 (m, 1H, C(12)*H*_A*H*_B), 1.08 (s, 3H, C(14)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 219.2 C(8), 139.8 C(Ar(Ph*)), 138.4 C(15), 134.9 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 132.9 C(Ar(Ph*)), 128.4 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 116.1 C(16), 58.9 C(9), 50.7 C(13), 40.8 C(10), 30.5 C(12), 22.7 C(11), 19.0 C(Me(Ph*)), 18.9 C(14), 18.7 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*));

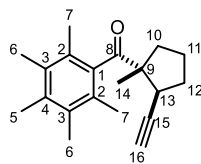
Selected characteristic peaks for the minor (1*RS*, 2*RS*) diastereomer (from the mixture):

^1H NMR (600 MHz, CDCl_3) δ 6.16 (dd, $J = 13.5, 9.1$ Hz, 1H, C(15)*H*), 3.16 – 3.08 (m, 1H, C(13)*H*), 2.25 (s, 3H, C(Ph*)*H*₃), 1.84 – 1.77 (m, 4H, C(10)*H*_A*H*_B, C(11)*H*₂, C(12)*H*_A*H*_B), 1.19 (s, 3H, C(14)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 218.9 C(8), 139.7 C(Ar(Ph*)), 137.9 C(15), 135.1 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 127.6 C(Ar(Ph*)), 106.2 C(16), 59.0 C(9), 50.4 C(13), 40.9 C(10), 32.3 C(12), 23.3 C(11), 22.6 C(Me(Ph*)), 19.7 C(14), 19.1 C(Me(Ph*)), 18.6 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2872, 1684, 1638, 1461, 1303, 1263, 1218, 1172, 1123, 1099, 1002, 919;

HRMS (ESI⁺) $\text{C}_{20}\text{H}_{29}\text{O}^+$ ([M+H]⁺) requires 285.2213; found 285.2207, Δ 1.97 ppm.

220 (2-Ethynyl-1-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

Sulfone **165r** (36 mg, 0.10 mmol, >[95:5] d.r.) was dissolved in ^tBuOH (0.4 mL) and Alumina-supported KOH* (200 mg) was added. The reaction was heated to 80 °C and CBr₂F₂ (40 μL, 0.44 mmol) was added. The reaction was stirred at 80 °C for 2 h and four portions of CBr₂F₂ (each 40 μL, 0.44 mmol) were added at 20 min intervals. The reaction was cooled to RT and filtered through a silica plug (elution with CH₂Cl₂) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1) gave the *title compound* as a white solid (6.4 mg, 23%, >[95:5] d.r.), isolated in conjunction with 8.2 mg, 29% **219**).

The relative stereochemistry was assigned by X-ray crystallography analysis.

m.p. = 110 – 112 °C;

¹H NMR (500 MHz, CDCl₃) δ 3.29 – 3.22 (m, 1H, C(13)*H*), 2.25 – 2.19 (m, 4H, C(12)*H_AH_B*, C(Ph*)*H₃*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.15 (d, *J* = 2.4 Hz, 1H, C(16)*H*), 2.12 – 2.09 (m, 7H, C(10)*H_AH_B*, 2 × C(Ph*)*H₃*), 1.89 – 1.67 (m, 4H, C(10)*H_AH_B*, C(11)*H₂*, C(12)*H_AH_B*), 1.20 (s, 3H, C(14)*H₃*);

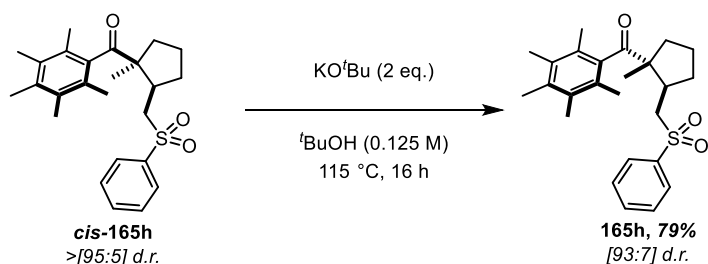
¹³C NMR (126 MHz, CDCl₃) δ 218.5 C(8), 139.3 C(Ar(Ph*)), 135.0 C(Ar(Ph*)), 133.1 2 × C(Ar(Ph*)), 128.6 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 84.9 C(15), 71.8 C(16), 58.7 C(9), 40.7 C(10), 39.6 C(13), 32.8 C(12), 23.4 C(11), 19.6 C(14), 19.1 C(Me(Ph*)), 18.7 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3275, 2940, 1684, 1453, 1384, 1302, 1232, 1096, 988, 918, 738;

HRMS (ESI⁺) C₂₀H₂₇O⁺ ([M+H]⁺) requires 283.2056; found 283.2050, Δ 2.22 ppm.

* Alumina-supported KOH was prepared by addition of neutral alumina (15.0 g, 147 mmol) to a solution of KOH (5.00 g, 89.1 mmol) in MeOH (25 mL) and stirring at RT for 1 h. The solvent was removed under reduced pressure to give KOH–Al₂O₃ as a free-flowing white powder, which was stored under air at RT.

6.3.3 Mechanistic Experiments

Resubjection of *cis*-**165h** with base

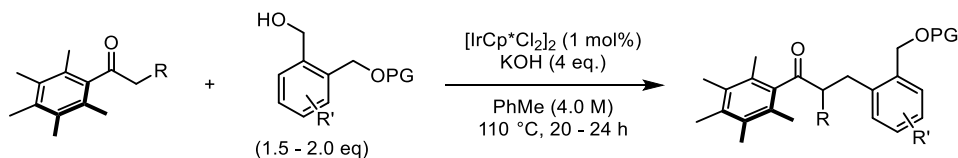
Ketone ***cis*-165h** (12.1 mg, 0.029 mmol) and KO^tBu (6.5 mg, 0.058 mmol) were added to a 1.75 mL vial. The vial was evacuated and back-filled with Ar (5 times). ^tBuOH (230 μL, 0.125 M) was added, the vial was sealed under Ar and the reaction was heated at 115 °C for 16 h. The mixture was cooled to RT, filtered through a silica plug (elution with Et₂O/CH₂Cl₂) and concentrated *in vacuo*. Purification *via* preparative thin layer chromatography (eluent pentane/CH₂Cl₂/Et₂O, 70:5:25) gave ketone **165h** as a white solid (9.6 mg, 79%, [93:7] d.r.)

The spectroscopic data were consistent with that reported above for **165h**.

6.4 Experimental for Chapter 4

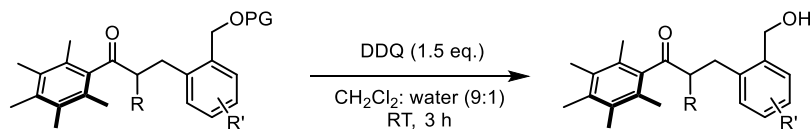
6.4.1 General Procedures

General Procedure H: Hydrogen Borrowing Alkylation with mono-protected benzylic diols

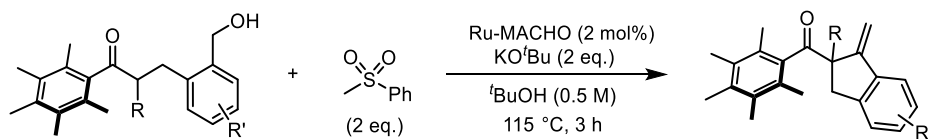


Ph* ketone (1.00 eq.), mono-protected diol (1.50 – 2.00 eq.), [IrCp*Cl₂]₂ (1.0 mol%) and KOH (4.00 eq.) were added to a 10 – 20 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (five times), and PhMe (4.0 M, degassed with Ar (balloon)) was added. The reaction was heated at 110 °C for 20 – 24 h, cooled to RT, filtered through a silica plug (Et₂O elution) and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

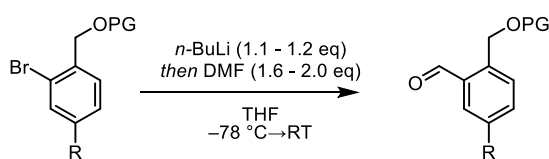
General Procedure I: Deprotection of PMB ethers using DDQ



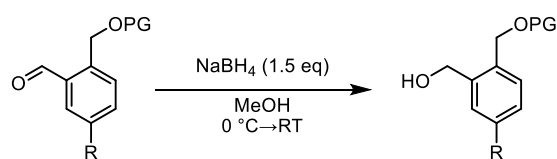
2,3-Dichloro-5,6-dicyano-*p*-benzoquinone, DDQ (1.50 – 1.60 eq.) was added to a stirred solution of PMB ether (1.00 eq.) in a 9:1 mixture of CH₂Cl₂:water (total concentration 0.10 M). The reaction was stirred at RT for 3 h and quenched by the addition of sat. aq. NaHCO₃. The layers were separated and the aqueous layer was extracted three times with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

General Procedure J: Acceptorless dehydrogenation to access exocyclic alkenes

Ph* hydroxy ketone substrate (1.00 eq.), methyl phenyl sulfone (2.00 eq.), Ru-MACHO® (1.0 mol%), and KO^tBu (2.00 eq.) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and ^tBuOH (0.50 M, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 3 h, cooled to RT, filtered through a silica pad (Et₂O/CH₂Cl₂/EtOAc elution as appropriate), and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

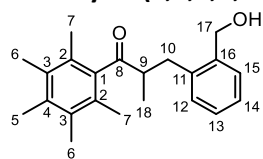
General Procedure K: Lithium–Halogen Exchange of Benzyl Ethers

n-BuLi (2.5 M in hexanes, 1.10 – 1.20 eq.) was added slowly to a solution of aryl bromide (1.00 eq.) in THF (0.30 M) at –78 °C. The mixture was stirred at –78 °C for 40 min and *N,N*-dimethylformamide (1.60 – 2.00 eq.) was added. The reaction was warmed to RT, stirred for 2 h, and quenched with the addition of sat. aq. NH₄Cl. The mixture was diluted with EtOAc and water, the layers separated, and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification was accomplished *via* flash column chromatography as indicated.

General Procedure L: Reduction of aryl aldehydes

Aryl aldehyde (1.00 eq.) was dissolved in MeOH (0.30 M) and the solution was cooled to 0 °C. NaBH₄ (1.50 eq.) was added and the reaction was allowed to warm to RT and stirred for 2 h. The reaction was quenched by addition of sat. aq. NH₄Cl and the mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and water, the layers separated, and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification, when required, was accomplished as indicated.

6.4.2 Preparation and Characterisation of Compounds

223a 3-(2-(Hydroxymethyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one

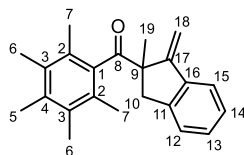
Ether **237a** (1.41 g, 3.17 mmol) and DDQ (1.08 g, 4.76 mmol) in a mixture of CH_2Cl_2 :water (28.8 mL: 3.2 mL) were subjected to **General Procedure I**. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 75:25 $\rightarrow$ 70:30) gave the *title compound* as a colourless oil (996 mg, 97%).

^1H NMR (600 MHz, CDCl_3) δ 7.44 – 7.32 (m, 1H, C(15)*H*), 7.25 – 7.19 (m, 3H, C(12)*H*, C(13)*H*, C(14)*H*), 4.76 (d, J = 12.3 Hz, 1H, C(17)*H*_A*H*_B), 4.65 (d, J = 12.3 Hz, 1H, C(17)*H*_A*H*_B), 3.36 (dd, J = 14.0, 5.6 Hz, 1H, C(10)*H*_A*H*_B), 3.18 (dq, J = 8.7, 7.2, 5.6 Hz, 1H, C(9)*H*), 2.68 (dd, J = 14.0, 8.7 Hz, 1H, C(10)*H*_A*H*_B), 2.23 (s, 3H, C(Ph*)*H*₃), 2.19 – 2.11 (m, 6H, 2 $\times$ C(Ph*)*H*₃), 2.03 (br. s, 6H, 2 $\times$ C(Ph*)*H*₃), 1.11 (d, J = 7.2 Hz, 3H, C(18)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 214.5 C(8), 139.5 C(Ar(Ph*)), 139.0 C(16), 138.3 C(11), 135.8 C(Ar(Ph*)), 133.3 2 $\times$ C(Ar(Ph*)), 130.7 C(12), 129.1 C(15), 128.4 2 $\times$ C(Ar(Ph*)), 128.0 C(13), 126.8 C(14), 63.3 C(17), 50.2 C(9), 34.1 C(10), 18.0 2 $\times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 2 $\times$ C(Me(Ph*)), 16.1 C(18);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3420, 2937, 2875, 1692, 1455, 1384, 1307, 1084, 1043, 1014, 925, 747;

HRMS (ESI^+) $\text{C}_{22}\text{H}_{28}\text{NaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 347.1982; found 347.1984, Δ 0.70 ppm.

224a (2-Methyl-1-methylene-2,3-dihydro-1*H*-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Alcohol **223a** (97 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.6 mmol) and $^t\text{BuOH}$ (0.6 mL) were subjected to **General Procedure J** at 115 °C for 3 h. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99.2:0.8 $\rightarrow$ 99:1) gave the *title compound* as a white solid (81 mg, 85%).

m.p. = 71 – 73 °C;

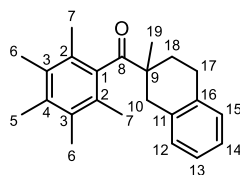
¹H NMR (500 MHz, CDCl₃) δ 7.50 – 7.40 (m, 1H, C(15)H), 7.22 – 7.13 (m, 2H, C(13)H, C(14)H), 7.10 (m, 1H, C(12)H), 5.67 (s, 1H, C(18)H_AH_B), 5.33 (s, 1H, C(18)H_AH_B), 3.50 (d, *J* = 16.9 Hz, 1H, C(10)H_AH_B), 2.89 (d, *J* = 16.9 Hz, 1H, C(10)H_AH_B), 2.19 (s, 3H, C(Ph*)H₃), 2.17 (s, 3H, C(Ph*)H₃), 2.05 (s, 6H, 2 × C(Ph*)H₃), 1.85 (s, 3H, C(Ph*)H₃), 1.65 (s, 3H, C(19)H₃);

¹³C NMR (126 MHz, CDCl₃) δ 215.7 C(8), 153.8 C(16), 143.3 C(11), 139.7 C(Ar(Ph*)), 139.5 C(17), 135.1 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.7 C(Ar(Ph*)), 128.9 C(13), 128.1 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 126.9 C(14), 125.2 C(12), 121.1 C(15), 106.2 C(18), 59.6 C(9), 42.9 C(10), 29.0 C(19), 18.7 C(Me(Ph*)) 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2932, 1691, 1476, 1438, 1262, 1217, 1101, 932, 896, 780, 762;

HRMS (ESI⁺) C₂₃H₂₆NaO⁺ ([M+Na]⁺) requires 341.1876; found 341.1874, Δ 0.56 ppm.

225a (2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone



Alcohol **223a** (97 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), [IrCp*Cl₂]₂ (2.4 mg, 1.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and PhMe (0.6 mL, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8 → 99:1) gave the *title compound* as a white solid (67 mg, 70%).

m.p. = 110 – 111 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.14 – 7.07 (m, 3H, C(13)H, C(14)H, C(15)H), 7.07 – 7.03 (m, 1H, C(12)H), 3.20 (d, *J* = 16.2 Hz, 1H, C(10)H_AH_B), 2.84 (dd, *J* = 9.1, 4.3 Hz, 2H, C(17)H₂), 2.74 (dd, *J* = 16.2, 2.4 Hz, 1H, C(10)H_AH_B), 2.24 (s, 3H, C(Ph*)H₃), 2.19 (s, 3H, C(Ph*)H₃), 2.19 (s, 3H,

$C(Ph^*)H_3$), 2.13 (s, 6H, $2 \times C(Ph^*)H_3$), 2.05 (dt, $J = 13.0, 9.2$ Hz, 1H, $C(18)H_AH_B$), 1.93 – 1.84 (m, 1H, $C(18)H_AH_B$), 1.19 (s, 3H, $C(19)H_3$);

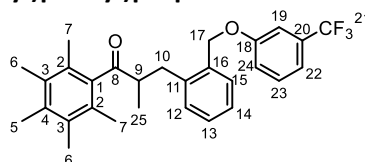
^{13}C NMR (151 MHz, $CDCl_3$) δ 219.8 $C(8)$, 139.8 $C(Ar(Ph^*))$, 135.0 $C(11)$, 135.0 $C(Ar(Ph^*))$, 135.0 $C(16)$, 133.3 $C(Ar(Ph^*))$, 133.2 $C(Ar(Ph^*))$, 129.9 $C(12)$, 128.8 $C(15)$, 127.6 $C(Ar(Ph^*))$, 126.0 $C(13)$, 125.9 $C(14)$, 47.9 $C(9)$, 39.0 $C(10)$, 31.5 $C(18)$, 25.8 $C(17)$, 20.9 $C(19)$, 19.2 $C(Me(Ph^*))$, 19.1 $C(Me(Ph^*))$, 16.8 $C(Me(Ph^*))$, 16.3, $C(Me(Ph^*))$, 16.3 $C(Me(Ph^*))$);

N.B.: Fewer ^{13}C signals were observed than expected due to overlapping aromatic signals.

IR (film) ν_{max}/cm^{-1} 2927, 1686, 1583, 1496, 1453, 1382, 1303, 1260, 1080, 990, 908, 752;

HRMS (ESI⁺) $C_{23}H_{28}NaO^+$ ($[M+Na]^+$) requires 343.2032; found 343.2035, Δ 0.76 ppm.

230 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-3-(2-((3-(trifluoromethyl)phenoxy)methyl)phenyl)propan-1-one



Alcohol **223a** (97 mg, 0.30 mmol), sulfone **228** (134 mg, 0.60 mmol), $[IrCp^*Cl_2]_2$ (2.4 mg, 1.0 mol% and KOH (66 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and PhMe (0.6 mL, degassed with Ar) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99.3:0.7 $\rightarrow$ 95:5) gave the *title compound* as a colourless solid (26 mg, 18%).

m.p. = 70 – 72 °C;

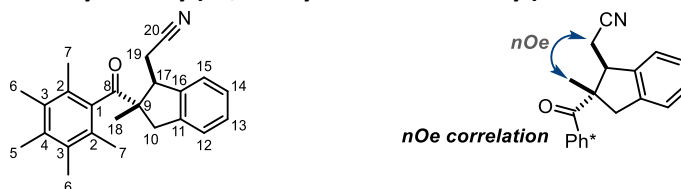
^1H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H, $C(15)H$, $C(23)H$), 7.34 – 7.30 (m, 1H, $C(14)H$), 7.30 – 7.23 (m, 3H, $C(12)H$, $C(13)H$, $C(22)H$), 7.15 (t, $J = 2.1$ Hz, 1H, $C(19)H$), 7.03 (dd, $J = 8.3, 2.6$ Hz, 1H, $C(24)H$), 5.03 (d, $J = 10.8$ Hz, 1H, $C(17)H_AH_B$), 4.99 (d, $J = 10.8$ Hz, 1H, $C(17)H_AH_B$), 3.40 (dd, $J = 14.0, 4.7$ Hz, 1H, $C(10)H_AH_B$), 3.14 (dq, $J = 9.5, 7.0, 4.6$ Hz, 1H, $C(9)H$), 2.67 (dd, $J = 14.0, 9.7$ Hz, 1H, $C(10)H_AH_B$), 2.19 (s, 3H, $C(Ph^*)H_3$), 2.10 (s, 6H, $2 \times C(Ph^*)H_3$), 2.00 (s, 6H, $2 \times C(Ph^*)H_3$), 1.12 (d, $J = 7.0$ Hz, 3H, $C(25)H_3$);

^{13}C NMR (151 MHz, CDCl_3) δ 213.9 C(8), 159.0 C(18), 139.5 C(Ar(Ph*)), 138.9 C(11), 135.7 C(Ar(Ph*)), 134.2 C(16), 133.3 $2 \times$ C(Ar(Ph*)), 132.0 (q, $J^2_{\text{C-F}} = 32.3$ Hz, C(20)), 131.2 C(12), 130.1 C(23), 130.1 C(15), 128.8 C(14), 128.3 $2 \times$ C(Ar(Ph*)), 126.9 C(13), 124.1 (q, $J^1_{\text{C-F}} = 272.4$ Hz, C(21)), 118.1 C(24), 117.8 (q, $J^3_{\text{C-F}} = 3.8$ Hz, C(22)), 111.6 (q, $J^3_{\text{C-F}} = 3.8$ Hz, C(19)), 68.5 C(17), 50.0 C(9), 34.5 C(10), 17.9 $2 \times$ C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.0 $2 \times$ C(Me(Ph*)), 15.5 C(25);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2978, 1697, 1493, 1450, 1329, 1233, 1170, 1129, 1067, 1014;

HRMS (ESI^+) $\text{C}_{29}\text{H}_{32}\text{F}_3\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) requires 469.2349; found 469.2342, Δ 1.50 ppm.

231 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)-2,3-dihydro-1H-inden-1-yl)acetonitrile



Alcohol **223a** (97 mg, 0.30 mmol), Ru-MACHO[®] (3.6 mg, 1.0 mol%) and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and ^tBuOH (0.6 mL, degassed with Ar (balloon)) and MeCN (32 μL , 0.60 mmol) were added. The reaction was heated at 115 $^{\circ}\text{C}$ for 3 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 96:4 $\rightarrow$ 94:6) gave the *title compound* as a colourless oil (21 mg, 20%, >[95:5] d.r.)

m.p. = 108 – 110 $^{\circ}\text{C}$;

^1H NMR (400 MHz, CDCl_3) δ 7.52 – 7.41 (m, 1H, C(12)*H*), 7.25 – 7.17 (m, 2H, C(13)*H*, C(14)*H*), 7.17 – 7.07 (m, 1H, C(15)*H*), 3.82 (dd, $J = 9.5, 3.5$ Hz, 1H, C(17)*H*), 3.32 (d, $J = 15.6$ Hz, 1H, C(10)*H*_A*H*_B), 2.99 (dd, $J = 17.0, 3.6$ Hz, 1H, C(19)*H*_A*H*_B), 2.82 (d, $J = 15.7$ Hz, 1H, C(10)*H*_A*H*_B), 2.59 (dd, $J = 16.9, 9.5$ Hz, 1H, C(19)*H*_A*H*_B), 2.23 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 2.09 (s, 3H, C(Ph*)*H*₃), 2.07 (s, 3H, C(Ph*)*H*₃), 1.29 (s, 3H, C(18)*H*₃);

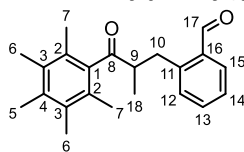
^{13}C NMR (101 MHz, CDCl_3) δ 216.3 C(8), 141.1 C(16), 140.9 C(11), 138.4 C(Ar(Ph*)), 135.8 C(Ar(Ph*)), 133.7 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 127.9 C(14), 127.8 C(Ar(Ph*)),

127.3 C(13), 124.8 C(15), 123.9 C(12), 119.4 C(20), 60.9 C(9), 46.3 C(17), 43.4 C(10), 19.3 C(Me(Ph*)), 19.2 C(18), 18.9 C(Me(Ph*)), 17.5 C(19), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2929, 2251, 1685, 1460, 1383, 1306, 1259, 1145, 1073, 914;

HRMS (ESI⁺) C₂₄H₂₈NO⁺ ([M+H]⁺) requires 368.1985; found 368.1980, Δ 1.03 ppm.

233 2-(2-Methyl-3-oxo-3-(2,3,4,5,6-pentamethylphenyl)propyl)benzaldehyde



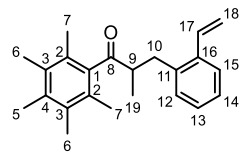
Dess-Martin periodinane (1.27 g, 3.00 mmol) was added to a solution of alcohol **223a** (810 mg, 2.50 mmol) in CH₂Cl₂ (12.5 mL) at 0 °C. The mixture was warmed to RT, stirred for 4 h and then quenched with Na₂S₂O₃ (10 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 90:10) gave the *title compound* as a colourless oil (800 mg, 99%).

¹H NMR (600 MHz, CDCl₃) δ 10.21 (s, 1H, C(17)H), 7.82 (dd, J = 7.6, 1.5 Hz, 1H, C(15)H), 7.50 (td, J = 7.5, 1.5 Hz, 1H, C(13)H), 7.42 – 7.35 (m, 2H, C(12)H, C(14)H), 3.66 (dd, J = 12.9, 5.7 Hz, 1H, C(10)H_AH_B), 3.17 – 3.10 (m, 1H, C(9)H), 3.08 (dd, J = 12.9, 8.1 Hz, 1H, C(10)H_AH_B), 2.22 (s, 3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.12 – 1.84 (br. s, 6H, 2 × C(Ph*)H₃), 1.09 (d, J = 7.1 Hz, 3H, C(18)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 213.6 C(8), 192.6 C(17), 142.8 C(11), 139.4 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 134.4 C(16), 133.7 C(13), 133.2 2 × C(Ar(Ph*)), 132.9 C(12) & C(15), 128.5 (br.) 2 × C(Ar(Ph*)), 127.1 C(14), 50.4 C(9), 34.4 C(10), 17.9 (br.) 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(18), 16.1 (br.) 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2932, 1697, 1600, 1574, 1453, 1383, 1292, 1211, 1163, 1085, 925, 758, 667 ;

HRMS (ESI⁺) C₂₂H₂₇O₂⁺ ([M+H]⁺) requires 323.2006; found 323.2004, Δ 0.56 ppm.

235 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-3-(2-vinylphenyl)propan-1-one

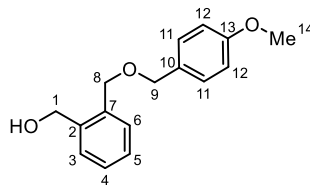
Methyltriphenylphosphonium bromide (446 mg, 1.25 mmol) was suspended in THF (2.5 mL) and the suspension was cooled to -78°C . *n*-BuLi (2.5 M in hexanes, 0.5 mL, 1.25 mmol) was added dropwise, the mixture was allowed to warm to 0°C and stirred for 1 h. The mixture was cooled to -78°C and a solution of aldehyde **233** (322 mg, 1.00 mmol) in THF (2.5 mL) was added slowly. The mixture was allowed to warm to RT, stirred for 3 h, quenched with sat. aq. NH_4Cl (5 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99.2:0.8 $\rightarrow$ 98:2) gave the *title compound* as a colourless oil (123 mg, 38%).

^1H NMR (600 MHz, CDCl_3) δ 7.50 – 7.44 (m, 1H, C(15)*H*), 7.23 – 7.18 (m, 2H, C(13)*H*, C(14)*H*), 7.16 (dt, $J = 5.5, 3.5$ Hz, 1H, C(12)*H*), 6.83 (dd, $J = 17.3, 10.9$ Hz, 1H, C(17)*H*), 5.61 (dd, $J = 17.3, 1.4$ Hz, 1H, C(18)*H*_A*H*_B), 5.21 (dd, $J = 10.9, 1.4$ Hz, 1H, C(18)*H*_A*H*_B), 3.35 (dd, $J = 13.8, 4.5$ Hz, 1H, C(10)*H*_A*H*_B), 3.04 (dq, $J = 9.5, 7.1, 4.5$ Hz, 1H, C(9)*H*), 2.63 (dd, $J = 13.8, 9.6$ Hz, 1H, C(10)*H*_A*H*_B), 2.24 (s, 3H, C(Ph*)*H*₃), 2.18 (s, 6H, $2 \times$ C(Ph*)*H*₃), 2.05 (s, 6H, $2 \times$ C(Ph*)*H*₃), 1.04 (d, $J = 7.1$ Hz, 3H, C(19)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 214.1 C(8), 139.6 C(Ar(Ph*)), 137.6 C(11), 137.0 C(16), 135.7 C(Ar(Ph*)), 134.7 C(17), 133.2 $2 \times$ C(Ar(Ph*)), 131.1 C(12), 128.5 (br.) $2 \times$ C(Ar(Ph*)), 127.8 C(13), 26.8 C(14), 126.1 C(15), 115.7 C(18), 49.8 C(9), 35.2 C(10), 17.9 $2 \times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 $2 \times$ C(Me(Ph*)), 15.3 C(19);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2982, 2934, 1694, 1449, 1384, 1318, 1259, 1151, 1086, 1050, 910;

HRMS (ESI⁺) $\text{C}_{23}\text{H}_{29}\text{O}^+$ ($[\text{M}+\text{H}]^+$) requires 321.2213; found 321.2213, Δ 0.15 ppm.

236a (2-(((4-Methoxybenzyl)oxy)methyl)phenyl)methanol

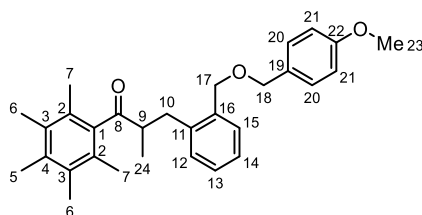
NaH (1.45 g, 36.2 mmol, 60% dispersed in mineral oil) was added portion-wise to a stirred solution of 1,2-benzenedimethanol (5.00 g, 36.2 mmol) and KI (2.72 g, 16.4 mmol) in *N,N*-dimethylformamide (55 mL) at $-20\text{ }^{\circ}\text{C}$ and the mixture was stirred for 1 h. 4-Methoxybenzyl chloride (4.44 mL, 32.8 mmol) was added, the reaction was allowed to warm to RT and stirred for 2 h. The mixture was cooled to $0\text{ }^{\circ}\text{C}$, quenched with sat. aq. NH_4Cl (20 mL) and diluted with Et_2O (100 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O ($2 \times 150\text{ mL}$). The combined organic phases were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ EtOAc , 85:15 $\rightarrow$ 82:18) gave the *title compound* as a colourless oil (6.18 g, 73%).

^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.39 (m, 1H, C(3)*H*), 7.37 – 7.32 (m, 1H, C(4)*H*), 7.32 – 7.25 (m, 4H, C(5)*H*, C(6)*H*, $2 \times$ C(11)*H*), 6.93 – 6.83 (m, 2H, $2 \times$ C(12)*H*), 4.65 (s, 2H, C(1)*H*₂), 4.62 (s, 2H, C(8)*H*₂), 4.52 (s, 2H, C(9)*H*₂), 3.81 (s, 3H, C(14)*H*₃);

^{13}C NMR (101 MHz, CDCl_3) δ 159.6 C(13), 140.8 C(2), 136.1 C(7), 130.3 C(6), 129.9 C(3), 129.9 $2 \times$ C(11), 129.5 C(10), 129.1 C(4), 128.1 C(5), 114.1 $2 \times$ C(12), 72.3 C(9), 71.2 C(8), 64.0 C(1), 55.4 C(14);

m/z (ESI⁺) Found ($[\text{M}+\text{Na}]^+$) = 281, $\text{C}_{16}\text{H}_{18}\text{NaO}$ requires 281.

The spectroscopic data matched that previously reported in the literature.¹⁶³

237a 3-(2-(((4-Methoxybenzyl)oxy)methyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one

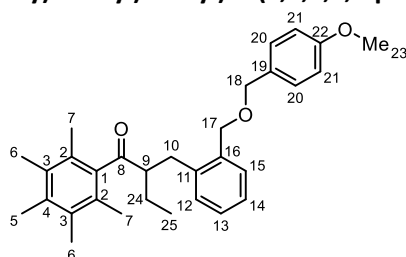
Ph* ethyl ketone **98** (722 mg, 3.54 mmol), alcohol **236a** (1.83 g, 7.08 mmol), [IrCp*Cl₂]₂ (28 mg, 1.0 mol%), KOH (794 mg, 14.6 mmol) and PhMe (0.90 mL) were subjected to **General Procedure H** at 110 °C for 20 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 93:7 → 90:10) gave the *title compound* as a colourless oil (1.41 g, 90%).

¹H NMR (600 MHz, CDCl₃) δ 7.35 (dd, *J* = 7.5, 2.0 Hz, 1H, C(15)*H*), 7.24 – 7.14 (m, 5H, C(12)*H*, C(13)*H*, C(14)*H*, 2 × C(20)*H*), 6.89 – 6.80 (m, 2H, 2 × C(21)*H*), 4.49 – 4.40 (m, 2H, C(17)*H*₂), 4.38 (s, 2H, C(18)*H*₂), 3.80 (s, 3H, C(23)*H*₃), 3.31 (dd, *J* = 13.8, 4.5 Hz, 1H, C(10)*H*_A*H*_B), 3.09 (dq, *J* = 9.7, 7.0, 4.5 Hz, 1H, C(9)*H*), 2.63 (dd, *J* = 13.8, 9.8 Hz, 1H, C(10)*H*_A*H*_B), 2.23 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 6H, 2 × C(Ph*)*H*₃), 2.13 – 1.88 (m, 6H, 2 × C(Ph*)*H*₃), 1.06 (d, *J* = 7.0 Hz, 3H, C(24)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.1 C(8), 159.4 C(22), 139.7 C(Ar(Ph*)), 138.7 C(11), 136.5 C(16), 135.7 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 130.8 C(14), 130.4 C(12), 129.7 C(15), 129.5 2 × C(20), 128.5 2 × C(Ar(Ph*)), 127.9 C(13), 126.5 C(19), 113.9 2 × C(21), 72.2 C(18), 69.9 C(17), 55.4 C(23), 50.0 C(9), 34.3 C(10), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.4 C(24);

IR (film) ν_{max} /cm⁻¹ 2905, 2872, 1695, 1657, 1514, 1454, 1302, 1249, 1082, 1038, 925;

HRMS (ESI⁺) C₃₀H₃₆NaO₃⁺ ([M+Na]⁺) requires 467.2557; found 467.2564, Δ 1.56 ppm.

237b 2-(2-(((4-Methoxybenzyl)oxy)methyl)benzyl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one

Ph* ketone **S14** (654 mg, 3.00 mmol), alcohol **236a** (1.55 g, 6.00 mmol), [IrCp*Cl₂]₂ (36 mg, 1.5 mol%), KOH (673 mg, 12.0 mmol) and PhMe (0.75 mL) were subjected to

General Procedure H at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 94:6) gave the *title compound* as a colourless oil (1.06 g, 77%).

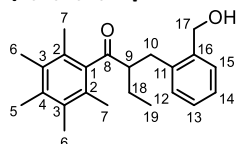
¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.32 (m, 1H, C(15)*H*), 7.25 – 7.20 (m, 3H, C(12)*H*, 2 × C(20)*H*), 7.20 – 7.16 (m, 2H, C(13)*H*, C(14)*H*), 6.88 – 6.84 (m, 2H, 2 × C(21)*H*), 4.45 (d, *J* = 11.4 Hz, 1H, C(17)*H_AH_B*), 4.42 (d, *J* = 11.4 Hz, 1H, C(17)*H_AH_B*), 4.37 (s, 2H, C(18)*H₂*), 3.80 (s, 3H, C(23)*H₃*), 3.21 (dd, *J* = 13.9, 6.5 Hz, 1H, C(10)*H_AH_B*), 3.08 – 2.97 (m, 1H, C(9)*H*), 2.71 (dd, *J* = 13.9, 7.3 Hz, 1H, C(10)*H_AH_B*), 2.22 (s, 3H, C(Ph*)*H₃*), 2.21 – 1.68 (m, 13H, C(24)*H_AH_B*, 4 × C(Ph*)*H₃*), 1.48 – 1.39 (m, 1H, C(24)*H_AH_B*), 0.93 (t, *J* = 7.4 Hz, 3H, C(25)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 212.5 C(8), 159.3 C(22), 139.6 C(Ar(Ph*)), 139.0 C(11), 136.5 C(16), 135.7 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 131.0 C(12), 130.5 C(19), 129.6 C(15), 129.4 2 × C(20), 129.0 2 × C(Ar(Ph*)), 127.9 C(13), 126.5 C(14), 113.9 2 × C(21), 72.2 C(18), 69.9 C(17), 56.8 C(9), 55.4 C(23), 31.9 C(10), 22.9 C(24), 17.7 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 12.2 C(25);

IR (film) ν_{max} /cm⁻¹ 2934, 1692, 1613, 1514, 1464, 1302, 1249, 1075, 1037, 822, 755;

HRMS (ESI⁺) C₃₁H₃₉O₃⁺ ([M+H]⁺) requires 458.2894; found 458.2886, Δ 1.61 ppm.

223b 2-(2-(Hydroxymethyl)benzyl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



PMB ether **237b** (243 mg, 0.531 mmol) and DDQ (182 mg, 0.800 mmol) were subjected to **General Procedure I** in a mixture of CH₂Cl₂:water (5.4 mL: 0.6 mL). Purification *via* flash column chromatography (eluent pentane/Et₂O, 82:18 → 70:30) gave the *title compound* as a colourless oil (167 mg, 93%).

¹H NMR (600 MHz, CDCl₃) δ 7.39 – 7.33 (m, 1H, C(15)*H*), 7.26 – 7.16 (m, 3H, C(12)*H*, C(13)*H*, C(14)*H*), 4.80 (d, *J* = 12.3 Hz, 1H, C(17)*H_AH_B*), 4.62 (d, *J* = 12.3 Hz, 1H, C(17)*H_AH_B*), 3.28 (dd, *J* = 14.0, 8.0 Hz, 1H, C(10)*H_AH_B*), 3.11 (tt, *J* = 8.0, 5.7 Hz, 1H, C(9)*H*), 2.79 (dd, *J* = 14.0, 5.7 Hz, 1H,

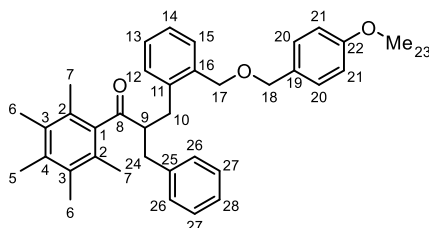
$C(10)H_AH_B$), 2.22 (s, 3H, $C(Ph^*)H_3$), 2.14 (br. s, 6H, $2 \times C(Ph^*)H_3$), 2.03 – 1.58 (m, 7H, $C(18)H_AH_B$, $2 \times C(Ph^*)H_3$), 1.51 – 1.40 (m, 1H, $C(18)H_AH_B$), 1.01 (t, $J = 7.4$ Hz, 3H, $C(19)H_3$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 213.2 $C(8)$, 139.3 $C(Ar(Ph^*))$, 139.1 $C(16)$, 138.6 $C(11)$, 135.8 $C(Ar(Ph^*))$, 133.2 $2 \times C(Ar(Ph^*))$, 130.8 $C(12)$, 129.3 $C(15)$, 128.9 $2 \times C(Ar(Ph^*))$, 127.9 $C(13)$, 126.7 $C(14)$, 63.3 $C(17)$, 57.3 $C(9)$, 30.9 $C(10)$, 23.5 $C(18)$, 17.7 $2 \times C(Me(Ph^*))$, 16.9 $C(Me(Ph^*))$, 16.1 $2 \times C(Me(Ph^*))$, 12.4 $C(19)$;

IR (film) ν_{max}/cm^{-1} 3446, 2932, 1691, 1456, 1384, 1301, 1260, 1139, 1090, 1042, 945;

HRMS (ESI⁺) $C_{23}H_{30}NaO_2^+$ ($[M+Na]^+$) requires 361.2138; found 361.2131, Δ 2.03 ppm.

237c 2-Benzyl-3-(2-(((4-methoxybenzyl)oxy)methyl)phenyl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Ph^{*} ketone **102** (840 mg, 3.00 mmol), alcohol **236a** (1.55 g, 6.00 mmol), $[IrCp^*Cl_2]_2$ (36 mg, 1.5 mol%), KOH (673 mg, 12.0 mmol) and PhMe (0.75 mL) were subjected to **General Procedure H** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 96:4 → 95:5) gave the *title compound* as a colourless oil (831 mg, 53%).

^1H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 1H, $C(15)H$), 7.24 – 7.14 (m, 8H, $C(12)H$, $C(13)H$, $C(14)H$, $2 \times C(20)H$, $2 \times C(27)H$, $C(28)H$), 7.09 – 7.03 (m, 2H, $2 \times C(26)H$), 6.89 – 6.83 (m, 2H, $2 \times C(21)H$), 4.24 – 4.13 (m, 4H, $C(17)H_2$, $C(18)H_2$), 3.81 (s, 3H, $C(23)H_3$), 3.36 (p, $J = 6.9$ Hz, 1H, $C(9)H$), 3.26 (dd, $J = 13.8$, 6.8 Hz, 1H, $C(10)H_AH_B$), 3.17 (dd, $J = 13.3$, 6.7 Hz, 1H, $C(24)H_AH_B$), 2.64 (dd, $J = 13.8$, 7.0 Hz, 1H, $C(10)H_AH_B$), 2.55 (dd, $J = 13.3$, 6.9 Hz, 1H, $C(24)H_AH_B$), 2.21 (s, 3H, $C(Ph^*)H_3$), 2.11 (s, 6H, $2 \times C(Ph^*)H_3$), 1.78 (br. s, 6H, $2 \times C(Ph^*)H_3$);

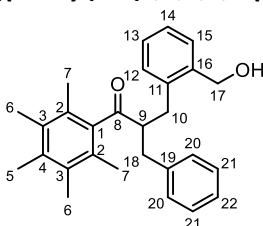
^{13}C NMR (151 MHz, $CDCl_3$) δ 211.4 $C(8)$, 159.3 $C(22)$, 140.1 $C(25)$, 139.0 $C(Ar(Ph^*))$, 138.4 $C(11)$, 136.6 $C(16)$, 135.9 $C(Ar(Ph^*))$, 133.2 $2 \times C(Ar(Ph^*))$, 131.1 $C(12)$, 130.6 $C(19)$, 129.7 $2 \times C(26)$, 129.5 $C(15)$, 129.3 $2 \times C(20)$, 129.1 $2 \times C(Ar(Ph^*))$, 128.4 $2 \times C(27)$, 127.8 $C(13)$, 126.6 $C(14)$,

126.3 C(28), 113.9 2 × C(21), 72.1 C(18), 69.7 C(17), 58.3 C(9), 55.4 C(23), 35.8 C(24), 32.2 C(10), 17.5 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2929, 1694, 1613, 1514, 1455, 1302, 1249, 1174, 1077, 1037, 902, 822;

HRMS (ESI⁺) C₃₆H₄₀NaO₃⁺ ([M+Na]⁺) requires 543.2870; found 543.2861, Δ 1.65 ppm.

223c 2-Benzyl-3-(2-(hydroxymethyl)phenyl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



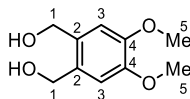
PMB ether **237c** (818 mg, 1.57 mmol) and DDQ (571 mg, 2.52 mmol) were subjected to **General Procedure I** in a mixture of CH₂Cl₂:water (13.5 mL: 1.5 mL). Purification *via* flash column chromatography (eluent pentane/Et₂O, 82:18 → 70:30) gave the *title compound* as a solid glass (464 mg, 74%).

¹H NMR (600 MHz, CDCl₃) δ 7.33 – 7.28 (m, 1H, C(15)H), 7.28 – 7.23 (m, 2H, 2 × C(21)H), 7.22 – 7.14 (m, 4H, C(12)H, C(13)H, C(14)H, C(22)H), 7.14 – 7.09 (m, 2H, 2 × C(20)H), 4.55 (d, J = 12.3 Hz, 1H, C(17)H_AH_B), 4.39 (d, J = 12.3 Hz, 1H, C(17)H_AH_B), 3.46 (tt, J = 8.4, 5.3 Hz, 1H, C(9)H), 3.30 (dd, J = 14.0, 8.4 Hz, 1H, C(18)H_AH_B), 3.20 (dd, J = 13.4, 5.3 Hz, 1H, C(10)H_AH_B), 2.65 (dd, J = 14.0, 5.3 Hz, 1H, C(18)H_AH_B), 2.53 (dd, J = 13.4, 8.4 Hz, 1H, C(10)H_AH_B), 2.22 (s, 3H, C(Ph*)H₃), 2.14 (s, 6H, 2 × C(Ph*)H₃), 1.85 (br. s, 6H, 2 × C(Ph*)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 212.2 C(8), 139.8 C(19), 139.0 C(16), 138.8 C(Ar(Ph*)), 138.2 C(11), 136.0 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 130.7 C(12), 129.4 2 × C(20), 129.2 C(15), 128.9 2 × C(Ar(Ph*)), 128.5 2 × C(21), 127.8 C(13), 126.7 C(14), 126.5 C(22), 63.1 C(17), 58.4 C(9), 36.6 C(10), 31.0 C(18), 17.7 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3443, 3025, 2926, 1692, 1454, 1301, 1260, 1217, 1125, 1008, 904;

HRMS (ESI⁺) C₂₈H₃₃O₂⁺ ([M+H]⁺) requires 401.2475; found 401.2465, Δ 2.47 ppm.

239 (4,5-Dimethoxy-1,2-phenylene)dimethanol

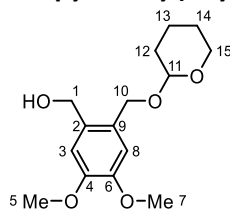
LiAlH_4 (854 mg, 22.5 mmol) was added portion-wise to a solution of 5,6-dimethoxyisobenzofuran-1(3H)-one (1.46 g, 7.50 mmol) in THF (25 mL). The mixture was heated to reflux for 4 h, cooled to 0 °C, and quenched with sequential dropwise addition of water (0.85 mL), NaOH (15% w/v, 0.85 mL) and water (2.6 mL). The mixture was diluted with CHCl_3 (25 mL), Na_2SO_4 was added and the mixture was stirred vigorously for 15 min. The mixture was filtered and concentrated *in vacuo* to give the *title compound* as a pale pink solid, which was used without further purification (990 mg, 66%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.90 (s, 2H, 2 $\times$ C(3)H), 4.69 (s, 4H, 2 $\times$ C(1)H₂), 3.90 (s, 6H, 2 $\times$ C(5)H₃), 2.47 – 2.22 (m, 2H, 2 $\times$ OH);

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 148.7 2 $\times$ C(4), 132.1 2 $\times$ C(2), 113.4 2 $\times$ C(3), 64.1 2 $\times$ C(1), 56.2 2 $\times$ C(5);

m/z (ESI⁺) Found ($[\text{M}+\text{Na}]^+$) = 221, $\text{C}_{10}\text{H}_{14}\text{NaO}_4$ requires 221;

The spectroscopic data matched that previously reported in the literature.¹⁶⁴

236d (4,5-Dimethoxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanol

Diol **239** (990 mg, 5.00 mmol) was suspended in CH_2Cl_2 (10 mL) and 3,4-dihydro-2H-pyran (0.22 mL, 2.41 mmol) and pyridinium *p*-toluenesulfonate (61 mg, 0.24 mmol) were added. The mixture was heated at 45 °C for 4 h, cooled to RT and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 60:40) gave the *title compound* as a colourless oil (345 mg, 51%).

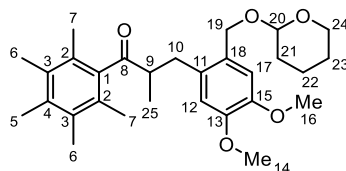
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.94 (s, 1H, C(8)H), 6.88 (s, 1H, C(3)H), 4.84 (d, J = 11.5 Hz, 1H, C(10)H_AH_B), 4.73 (t, J = 3.4 Hz, 1H, C(11)H), 4.68 – 4.58 (m, 2H, C(1)H₂), 4.55 (d, J = 11.5 Hz, 1H,

C(10) H_AH_B), 3.93 – 3.84 (m, 7H, C(5) H_3 , C(7) H_3 , C(15) H_AH_B), 3.62 – 3.52 (m, 1H, C(15) H_AH_B), 1.87 – 1.67 (m, 2H, C(12) H_AH_B , C(13) H_AH_B), 1.67 – 1.48 (m, 4H, C(12) H_AH_B , C(13) H_AH_B , C(14) H_2); ^{13}C NMR (101 MHz, CDCl_3) δ 148.9 C(6), 148.4 C(4), 133.4 C(9), 128.3 C(2), 113.8 C(3), 113.3 C(8), 97.8 C(11), 67.7 C(10), 63.6 C(1), 62.5 C(15), 56.2 C(5/7), 56.1 C(5/7), 30.6 C(12), 25.4 C(13), 19.4 C(14);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3449, 2943, 1610, 1519, 1466, 1346, 1283, 1210, 1109, 1026, 907;

HRMS (ESI^+) $\text{C}_{15}\text{H}_{22}\text{NaO}_5^+$ ($[\text{M}+\text{Na}]^+$) requires 305.1360; found 305.1352, Δ 2.18 ppm.

237d 3-(4,5-Dimethoxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Ph* ethyl ketone **98** (161 mg, 0.79 mmol), alcohol **236d** (335 mg, 1.19 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (6.3 mg, 1.0 mol%), KOH (177 mg, 3.16 mmol), and PhMe (0.2 mL) were subjected to **General Procedure H** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 80:20 $\rightarrow$ 70:30) gave the *title compound* as a colourless oil (352 mg, 95%, [49:51] d.r.)

The spectroscopic data were collected on the diastereomeric mixture and the relative stereochemistry is unassigned.

^1H NMR (400 MHz, CDCl_3) δ 6.90 (s, 1H, C(17') H), 6.88 (s, 1H, C(17'') H), 6.77 – 6.69 (m, 2H, C(12') H , C(12'') H), 4.67 (dd, J = 18.3, 11.6 Hz, 2H, C(19') H_AH_B , C(19'') H_AH_B), 4.61 – 4.56 (m, 1H, C(20') H), 4.49 (t, J = 3.6 Hz, 1H, C(20'') H), 4.40 (dd, J = 13.1, 11.6 Hz, 2H, C(19') H_AH_B , C(19'') H_AH_B), 3.93 – 3.80 (m, 14H, C(24') H_AH_B , C(24'') H_AH_B , C(14') H_3 , C(14'') H_3 , C(16') H_3 , C(16'') H_3), 3.55 – 3.45 (m, 2H, C(24') H_AH_B , C(24'') H_AH_B), 3.27 (dd, J = 13.8, 5.5 Hz, 2H, C(10') H_AH_B , C(10'') H_AH_B), 3.16 – 3.04 (m, 2H, C(9') H , C(9'') H), 2.71 – 2.57 (m, 2H, C(10') H_AH_B , C(10'') H_AH_B), 2.23 (2 $\times$ s, 6H, 2 $\times$ C(Ph*) H_3), 2.17 (s, 12H, 4 $\times$ C(Ph*) H_3), 2.03 (s, 12H, 4 $\times$ C(Ph*) H_3), 1.86 – 1.73 (m, 2H,

$C(23')H_AH_B$, $C(23'')H_AH_B$, 1.72 – 1.43 (m, 10H, $C(21')H_2$, $C(21'')H_2$, $C(22')H_2$, $C(22'')H_2$, $C(23')H_AH_B$, $C(23'')H_AH_B$), 1.09 (2 × d, $J = 7.1$ Hz, 6H, $C(25')H_3$, $C(25'')H_3$);*

^{13}C NMR (101 MHz, CDCl_3) δ 214.3 $C(8')$, 214.2 $C(8'')$, 148.4 $C(13')$, 148.3 $C(13'')$, 147.4 $C(15')$, 147.4 $C(15'')$, 139.8 $C(\text{Ar}(\text{Ph}^*))$, 139.7 $C(\text{Ar}(\text{Ph}^*))$, 135.7 2 × $C(\text{Ar}(\text{Ph}^*))$, 133.3 2 × $C(\text{Ar}(\text{Ph}^*))$, 131.4 $C(11')$, 131.2 $C(11'')$, 128.6 $C(18')$, 128.5 $C(18'')$ and 2 × $C(\text{Ar}(\text{Ph}^*))$, 128.4 2 × $C(\text{Ar}(\text{Ph}^*))$, 114.3 $C(12')$, 114.1 $C(12'')$, 113.3 $C(17')$, 113.0 $C(17'')$, 98.1 $C(20')$, 98.0 $C(20'')$, 66.7 $C(19')$, 66.6 $C(19'')$, 62.5 $C(24')$, 62.5 $C(24'')$, 56.1 $C(14')$, 56.1 $C(14'')$, 50.3 $C(9')$, 50.3 $C(9'')$, 34.2 $C(10')$, 34.1 $C(10'')$, 30.8 $C(21')$ & $C(21'')$, 25.6 $C(23')$ & $C(23'')$, 19.7 $C(22')$, $C(22'')$, 17.9 4 × $C(\text{Me}(\text{Ph}^*))$, 16.9 2 × $C(\text{Me}(\text{Ph}^*))$, 16.2 2 × $C(\text{Me}(\text{Ph}^*))$, 16.1 $C(25')$, 15.7 $C(25'')$);*

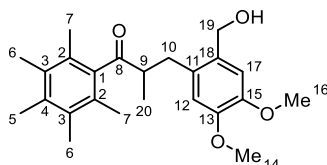
Fewer ^{13}C signals than expected due to overlapping peaks.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2945, 1694, 1519, 1465, 1350, 1277, 1203, 1111, 1037, 1022, 870, 815;

HRMS (ESI⁺) $\text{C}_{29}\text{H}_{40}\text{NaO}_5^+$ ($[\text{M}+\text{Na}]^+$) requires 491.2768; found 491.2755, Δ 2.62 ppm.

* N.B. The labels ' and '' are assigned arbitrarily and indicate peaks belonging to different diastereomers.

223d 3-(2-(Hydroxymethyl)-4,5-dimethoxyphenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



THP-protected alcohol **237d** (330 mg, 0.700 mmol) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (13 mg, 0.07 mmol) were dissolved in MeOH (7 mL) and the reaction mixture was stirred at RT for 4 h. The mixture was diluted with EtOAc (20 mL) and water (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 90:10 → 70:30) gave the *title compound* as a white solid (126 mg, 47%, isolated in conjunction with 91 mg, 33%, **240**).

m.p. = 138 – 140 °C;

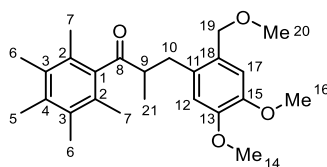
¹H NMR (600 MHz, CDCl₃) δ 6.94 (s, 1H, C(17)H), 6.76 (s, 1H, C(12)H), 4.75 (d, *J* = 12.1 Hz, 1H, C(19)H_AH_B), 4.59 (d, *J* = 12.1 Hz, 1H, C(19)H_AH_B), 3.91 (s, 3H, C(16)H₃), 3.88 (s, 3H, C(14)H₃), 3.34 (dd, *J* = 14.0, 6.6 Hz, 1H, C(10)H_AH_B), 3.19 (h, *J* = 7.2 Hz, 1H, C(9)H), 2.66 (dd, *J* = 14.0, 7.5 Hz, 1H, C(10)H_AH_B), 2.25 (s, 3H, C(Ph*)H₃), 2.19 (s, 6H, 2 × C(Ph*)H₃), 2.11 (br. s, 3H, C(Ph*)H₃), 1.96 (br. s, 3H, C(Ph*)H₃), 1.16 (d, *J* = 7.2 Hz, 3H, 13, C(20)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.5 C(8), 148.4 C(13), 147.6 C(15), 139.4 C(Ar(Ph*)), 135.9 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 131.3 C(18), 130.6 C(11), 128.4 (br.) 2 × C(Ar(Ph*)), 113.9 C(12), 112.4 C(17), 63.0 C(19), 56.1 C(14), 56.1 C(16), 50.6 C(9), 33.9 C(10), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.6 C(20), 16.1 2 × C(Me(Ph*));

IR (film) $\nu_{\max}$ /cm⁻¹ 3519, 2939, 1693, 1611, 1518, 1466, 1333, 1273, 1127, 1105, 911;

HRMS (ESI⁺) C₂₄H₃₂O₄Na⁺ ([M+Na]⁺) requires 407.2193; found 407.2180, Δ 3.11 ppm.

240 3-(4,5-Dimethoxy-2-(methoxymethyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



THP-protected alcohol **237d** (330 mg, 0.700 mmol) and TsOH·H₂O (13 mg, 0.07 mmol) were dissolved in MeOH (7 mL) and the reaction was stirred at RT for 4 h. The mixture was diluted with EtOAc (20 mL) and water (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 90:10 → 70:30) gave the *title compound* as a white solid (91 mg, 33% isolated in conjunction with 126 mg, 47%, **223d**).

m.p. = 85 – 87 °C;

¹H NMR (600 MHz, CDCl₃) δ 6.86 (s, 1H, C(17)H), 6.73 (s, 1H, C(12)H), 4.31 (dd, *J* = 11.0, 1.9 Hz, 2H, C(19)H₂), 3.87 (s, 3H, C(16)H₃), 3.85 (s, 3H, C(14)H₃), 3.30 (s, 3H, C(20)H₃), 3.29 – 3.24 (m, 1H, C(10)H_AH_B), 3.08 (dq, *J* = 8.9, 7.0, 5.2 Hz, 1H, C(9)H), 2.56 (dd, *J* = 13.9, 8.8 Hz, 1H,

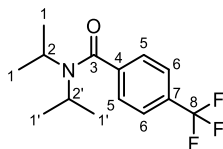
$C(10)H_AH_B$), 2.23 (s, 3H, $C(Ph^*)H_3$), 2.17 (s, 6H, $2 \times C(Ph^*)H_3$), 2.11 (br. s, 3H, $C(Ph^*)H_3$), 2.00 (br. s, 3H, $C(Ph^*)H_3$), 1.10 (d, $J = 7.1$ Hz, 3H, $C(21)H_3$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 214.3 $C(8)$, 148.3 $C(13)$, 147.4 $C(15)$, 139.7 $C(Ar(Ph^*))$, 135.8 $C(Ar(Ph^*))$, 133.3 $2 \times C(Ar(Ph^*))$, 131.2 $C(11)$, 128.5 $C(18)$ and $2 \times C(Ar(Ph^*))$ overlapped, 114.1 $C(12)$, 112.7 $C(17)$, 72.5 $C(19)$, 58.3 $C(20)$, 56.1 $C(14/16)$, 56.1 $C(14/16)$, 50.5 $C(9)$, 34.2 $C(10)$, 18.0 (br.) $2 \times C(Me(Ph^*))$, 16.9 $C(Me(Ph^*))$, 16.2 $2 \times C(Me(Ph^*))$, 15.8 $C(21)$;

IR (film) ν_{max}/cm^{-1} 2997, 2932, 1693, 1519, 1462, 1276, 1225, 1192, 1114, 1088, 917;

HRMS (ESI⁺) $C_{25}H_{35}O_4^+$ ($[M+H]^+$) requires 399.2530; found 399.2525, Δ 1.30 ppm.

242 *N,N*-Diisopropyl-4-(trifluoromethyl)benzamide



Triethylamine (4.3 mL, 30 mmol) was added slowly to a solution of diisopropylamine (4.3 mL, 30 mmol) and 4-(trifluoromethyl)benzoyl chloride (3.0 mL, 20 mmol) in PhMe (60 mL) at RT. The reaction was stirred at RT for 4 h and then diluted with water (100 mL) and PhMe (100 mL). The layers were separated and the aqueous layer was extracted with PhMe (2×100 mL). The combined organic phases were washed sequentially with 3 M aq. HCl and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 95:5 $\rightarrow$ 90:10) gave the *title compound* as a colourless oil (5.10 g, 93%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, $J = 7.9$ Hz, 2H, $2 \times C(6)H$), 7.41 (d, $J = 7.9$ Hz, 2H, $2 \times C(5)H$), 3.71 (s, 1H, $C(2)H$), 3.53 (s, 1H, $C(2')H$), 1.53 (s, 6H, $2 \times C(1)H_3$), 1.14 (s, 6H, $2 \times C(1')H_3$);*

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 $C(3)$, 142.3 $C(4)$, 130.7 (q, $J^2_{C-F} = 32.6$ Hz, $C(7)$), 125.9 $2 \times C(5)$, 125.6 (q, $J^3_{C-F} = 3.8$ Hz, $2 \times C(6)$), 124.2 (q, $J^1_{C-F} = 272.2$ Hz, $C(8)$), 51.0 $C(2)$, 46.0 $C(2')$, 20.6 $2 \times C(1)$, $2 \times C(1')$;*

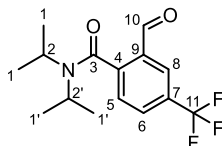
^{19}F NMR (471 MHz, $CDCl_3$) δ -62.8;

m/z (ESI⁺) Found ($[M+H]^+$) = 274, $C_{14}H_{19}F_3NO$ requires 274.

*N.B. The ' and '' labels refer to peaks which are split due to restricted rotation about the amide bond.

The spectroscopic data were consistent with that present in the literature.¹²⁶

243 2-Formyl-*N,N*-diisopropyl-4-(trifluoromethyl)benzamide



Amide **242** (2.50 g, 9.16 mmol) was dissolved in THF (20 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol) was added dropwise and the resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. *N,N*-dimethylformamide (1.5 mL, 22 mmol) was added dropwise then the mixture was allowed to warm to RT over 3 h. The reaction was quenched by addition of sat. aq. NH_4Cl and diluted with water (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc ($2 \times 50\text{ mL}$). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 92:8 $\rightarrow$ 80:20) gave the *title compound* as a white solid (2.54 g, 92%).

^1H NMR (600 MHz, CDCl_3) δ 10.12 (s, 1H, C(10)H), 8.28 – 8.15 (m, 1H, C(8)H), 7.87 (dd, $J = 8.0$, 1.9 Hz, 1H, C(6)H), 7.43 (d, $J = 8.0$ Hz, 1H, C(5)H), 3.59 (hept, $J = 6.8$ Hz, 1H, C(2)H), 3.52 (hept, $J = 6.7$ Hz, 1H, C(2')H), 1.61 (d, $J = 6.8$ Hz, 6H, $2 \times \text{C}(1)\text{H}_3$), 1.13 (d, $J = 6.7$ Hz, 6H, $2 \times \text{C}(1')\text{H}_3$);*

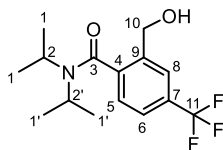
^{13}C NMR (151 MHz, CDCl_3) δ 189.2 C(10), 167.0 C(3), 144.2 C(4), 132.9 C(9), 131.4 (q, $J^2_{\text{C-F}} = 33.8$ Hz, C(7)), 130.8 (q, $J^3_{\text{C-F}} = 3.4$ Hz, C(6)), 126.9 C(5), 126.8 (q, $J^3_{\text{C-F}} = 3.7$ Hz, C(8)), 124.3 (q, $J^1_{\text{C-F}} = 273.4$ Hz, C(11)), 51.6 C(2'), 46.6 C(2), 20.7 C(1), 20.5 C(1');*

^{19}F NMR (565 MHz, CDCl_3) δ -63.0 ;

m/z (ESI⁺) Found ($[\text{M}+\text{H}]^+$) = 302, $\text{C}_{15}\text{H}_{19}\text{F}_3\text{NO}_2$ requires 302.

* N.B. The ' and '' labels refer to peaks which are split due to restricted rotation about the amide bond.

The spectroscopic data were consistent with that present in the literature.¹²⁶

244 2-(Hydroxymethyl)-N,N-diisopropyl-4-(trifluoromethyl)benzamide

Aldehyde **243** (2.52 g, 8.34 mmol) was dissolved in dry MeOH (21 mL) and cooled to 0 °C. NaBH₄ (473 mg, 12.5 mmol) was added, the reaction was allowed to warm to RT and stirred for 3 h. The reaction was quenched with water (10 mL) and concentrated *in vacuo*. The residue was diluted with water (40 mL) and Et₂O (50 mL), the layers separated and the aqueous phase was extracted with Et₂O (2 × 50 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give the *title compound* as a white solid, which required no further purification (2.50 g, 96%).

¹H NMR (600 MHz, DMSO) δ 7.87 – 7.81 (m, 1H, C(8)H), 7.65 (dd, *J* = 7.9, 1.9 Hz, 1H, C(6)H), 7.37 (d, *J* = 7.9 Hz, 1H, C(5)H), 5.47 (t, *J* = 5.6 Hz, 1H, OH), 4.58 (dd, *J* = 14.2, 5.6 Hz, 1H, C(10)H_AH_B), 4.48 (dd, *J* = 14.2, 5.6 Hz, 1H, C(10)H_AH_B), 3.59 (hept, *J* = 6.8 Hz, 1H, C(2)H), 3.45 (hept, *J* = 6.6 Hz, 1H, C(2')H), 1.47 (d, *J* = 6.8 Hz, 6H, 2 × C(1)H₃), 1.08 (dd, *J* = 6.7, 3.7 Hz, 6H, 2 × C(1')H₃);*

¹³C NMR (151 MHz, DMSO) δ 167.5 C(3), 140.2 C(9), 139.7 C(4), 128.5 (q, *J*²_{C-F} = 31.7 Hz, C(7)), 125.3 C(5), 124.1 (q, *J*¹_{C-F} = 272.3 Hz, C(11)), 123.7 (q, *J*³_{C-F} = 3.8 Hz, C(6)), 123.6 (q, *J*³_{C-F} = 4.4 Hz, C(8)), 59.4 C(10), 50.6 C(2), 44.9 C(2'), 20.3 C(1), 20.2 C(1), 20.1 C(1'), 20.0 C(1');*

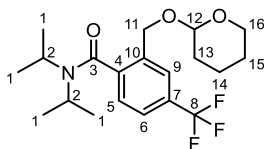
¹⁹F NMR (565 MHz, DMSO) δ –61.2;

m/z (ESI⁺) Found ([M+H]⁺) = 304, C₁₅H₂₁F₃NO₂ requires 304.

* N.B. The ' and '' labels refer to peaks which are split due to restricted rotation about the amide bond.

The spectroscopic data were consistent with that present in the literature.¹²⁶

247 *N,N*-Diisopropyl-2-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-4-(trifluoromethyl)benzamide



Alcohol **244** (2.30 g, 7.58 mmol) was dissolved in CH_2Cl_2 (25 mL) and 3,4-dihydro-2*H*-pyran (1.73 mL, 19.2 mmol) was added. Pyridinium *p*-toluenesulfonate (190 mg, 0.758 mmol) was added and the reaction was then stirred at RT for 18 h. The reaction mixture was diluted with pentane (20 mL), filtered through a plug of silica (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 90:10 $\rightarrow$ 80:20) gave the *title compound* as a viscous colourless oil that solidified on standing (2.73 g, 93%).

m.p. = 50 – 52 °C;

^1H NMR (500 MHz, CDCl_3) δ 7.82 (s, 1H, C(9')*H*), 7.78 (s, 1H, C(9'')*H*), 7.57 – 7.50 (m, 2H, C(6')*H*, C(6'')*H*), 7.24 (dd, J = 7.9, 4.7 Hz, 2H, C(5')*H*, C(5'')*H*), 4.81 (dd, J = 12.8, 10.3 Hz, 2H, C(11')*H*_A*H*_B, C(11'')*H*_A*H*_B), 4.70 (dd, J = 4.4, 2.9 Hz, 2H, C(12')*H*, C(12'')*H*), 4.57 (dd, J = 24.2, 12.8 Hz, 2H, C(11')*H*_A*H*_B, C(11'')*H*_A*H*_B), 3.98 – 3.80 (m, 2H, C(16')*H*_A*H*_B, C(16'')*H*_A*H*_B), 3.70 – 3.57 (m, 2H, C(2')*H*, C(2'')*H*), 3.57 – 3.44 (m, 4H, C(2⁺)*H*, C(2[‡])*H*, C(16')*H*_A*H*_B, C(16'')*H*_A*H*_B), 1.92 – 1.80 (m, 2H, C(14')*H*_A*H*_B, C(14'')*H*_A*H*_B), 1.80 – 1.69 (m, 2H, C(13')*H*_A*H*_B, C(13'')*H*_A*H*_B), 1.69 – 1.63 (m, 2H, C(13')*H*_A*H*_B, C(13'')*H*_A*H*_B), 1.63 – 1.50 (m, 18H, 2 $\times$ C(1')*H*₃, 2 $\times$ C(1'')*H*₃, C(15')*H*₂, C(15'')*H*₂, C(14')*H*_A*H*_B, C(14'')*H*_A*H*_B), 1.17 – 1.03 (m, 12H, 2 $\times$ C(1⁺)*H*₃, 2 $\times$ C(1[‡])*H*₃);*

^{13}C NMR (126 MHz, CDCl_3 { ^{19}F }) δ 168.6 C(3'), 168.5 C(3''), 141.0 C(4'), 140.6 C(4''), 136.1 C(10') & C(10''), 130.7 C(7'), 130.6 C(7''), 126.1 C(9'), 125.6 C(9''), 125.4 C(5'), 125.2 C(5''), 124.5 C(6'), 124.4 C(6''), 124.1 C(8'), 124.0 C(8''), 99.1 C(12'), 98.4 C(12''), 65.7 C(11'), 65.4 C(11''), 62.9 C(16'), 62.2 C(16''), 51.1 C(2') & C(2''), 46.1 C(2⁺), 46.1 C(2[‡]), 30.7 C(13'), 30.6 C(13''), 25.5 C(15'), 25.5 C(15''), 20.8 – 20.6 C(1)**, 19.9 C(14'), 19.4 C(14'');*

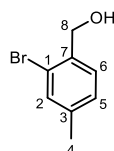
^{19}F NMR (471 MHz, CDCl_3) δ –62.67, –62.68;

HRMS (ESI⁺) $\text{C}_{20}\text{H}_{29}\text{F}_3\text{NO}_3$ ⁺ ([*M*+*H*]⁺) requires 388.2094; found 388.2085, Δ 2.35 ppm.

*N.B. The ' and '' labels represent different diastereomers and the † and ‡ labels refer to peaks which are split due to restricted rotation about the amide bond. These labels are assigned arbitrarily.

** Multiple Resonances in this region as a result of diastereomers (due to amide rotamers).

250e (2-Bromo-4-methylphenyl)methanol



2-Bromo-4-methylbenzaldehyde (5.00 g, 25.1 mmol) was subjected to **General Procedure L** with NaBH_4 (1.42 g, 37.7 mmol) in MeOH (80 mL). The *title compound* was formed as a colourless oil which required no further purification (5.05 g, 100%).

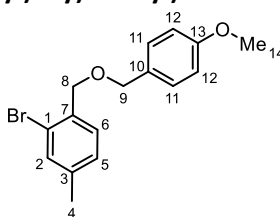
^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 1H, C(2)H), 7.33 (d, J = 7.7 Hz, 1H, C(6)H), 7.13 (d, J = 7.6 Hz, 1H, C(5)H), 4.71 (s, 2H, C(8)H₂), 2.33 (s, 3H, C(4)H₃), 1.93 (s, 1H, OH);

^{13}C NMR (101 MHz, CDCl_3) δ 139.6 C(3), 136.8 C(7), 133.2 C(2), 129.1 C(6), 128.5 C(5), 122.7 C(1), 65.1 C(8), 20.9 C(4);

m/z (ESI⁺) $\text{C}_8\text{H}_{10}^{79}\text{BrO}$, $[(\text{M}+\text{H})]^+$ requires 200; mass not found.

The spectroscopic data matched that previously reported in the literature.¹⁶⁵

251e 2-Bromo-1-(((4-methoxybenzyl)oxy)methyl)-4-methylbenzene



Alcohol **250e** (5.05 g, 25.1 mmol) was dissolved in *N,N*-dimethylformamide (50 mL) and cooled to 0 °C. NaH (60%, dispersed in mineral oil, 1.11 g, 27.6 mmol) was added and the reaction was stirred for 30 min at 0 °C. 4-Methoxybenzyl chloride (3.75 mL, 27.6 mmol) was added, the mixture was warmed to RT and stirred for 16 h. The reaction was quenched with the addition of NH_4Cl (20 mL) and diluted with Et_2O (200 mL) and water (200 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 × 150 mL). The combined organic phases

were washed with brine (3 × 200 mL) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99:1 → 98:2) gave the *title compound* as a colourless oil (6.93 g, 86%).

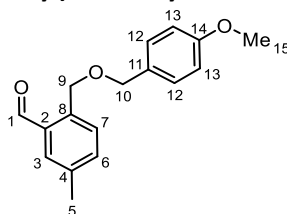
¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.35 (m, 2H, C(2)*H*, C(5)*H*), 7.35 – 7.29 (m, 2H, 2 × C(11)*H*), 7.11 (dd, *J* = 8.1, 1.7 Hz, 1H, C(6)*H*), 6.94 – 6.85 (m, 2H, 2 × C(12)*H*), 4.57 (s, 2H, C(8)*H*₂), 4.55 (s, 2H, C(9)*H*₂), 3.81 (s, 3H, C(14)*H*₃), 2.32 (s, 3H, C(4)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 159.4 C(13), 139.2 C(3), 134.7 C(7), 133.1 C(5), 130.4 C(10), 129.6 2 × C(11), 129.4 C(2), 128.3 C(6), 123.0 C(1), 114.0 2 × C(12), 72.4 C(9), 71.3 C(8), 55.4 C(14), 20.9 C(4);

IR (film) ν_{max} /cm⁻¹ 2836, 1612, 1514, 1456, 1356, 1249, 1174, 1093, 1039, 822;

HRMS (ESI⁺) C₁₆H₁₇⁷⁹BrNaO₂⁺ ([M+Na]⁺) requires 343.0304; found 343.0302, Δ 0.51 ppm.

252e 2-(((4-Methoxybenzyl)oxy)methyl)-5-methylbenzaldehyde



Aryl Bromide **251e** (5.14 g, 16.0 mmol) was subjected to **General Procedure K** with *n*-BuLi (2.5 M in hexanes, 7.7 mL, 19.2 mmol) and *N,N*-dimethylformamide (2.5 mL, 32.0 mmol) in THF (53 mL). Purification *via* flash column chromatography (eluent pentane/Et₂O, 5:95 → 85:15) gave the *title compound* as a colourless oil (4.07 g, 94%).

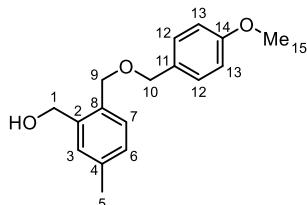
¹H NMR (400 MHz, CDCl₃) δ 10.20 (s, 1H, C(1)*H*), 7.67 (d, *J* = 2.0 Hz, 1H, C(3)*H*), 7.51 (d, *J* = 7.8 Hz, 1H, C(7)*H*), 7.39 (ddd, *J* = 7.7, 2.0, 0.8 Hz, 1H, C(6)*H*), 7.35 – 7.27 (m, 2H, 2 × C(12)*H*), 6.97 – 6.75 (m, 2H, 2 × C(13)*H*), 4.89 (s, 2H, C(9)*H*₂), 4.56 (s, 2H, C(10)*H*₂), 3.81 (s, 3H, C(15)*H*₃), 2.42 (s, 3H, C(5)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 193.0 C(1), 159.5 C(14), 138.1 C(8), 137.9 C(4), 134.7 C(6), 133.7 C(2), 132.5 C(3), 130.3 C(11), 129.6 2 × C(12), 128.9 C(7), 114.0 2 × C(13), 72.6 C(10), 69.2 C(9), 55.4 C(15), 21.0 C(5);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2838, 1688, 1613, 1571, 1514, 1359, 1302, 1248, 1084, 1036, 826, 774, 758;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{19}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 271.1329; found 271.1323, Δ 2.26 ppm.

236e (2-(((4-Methoxybenzyl)oxy)methyl)-5-methylphenyl)methanol



Aldehyde **252e** (4.06 g, 15.0 mmol) was subjected to **General Procedure L** with NaBH_4 (1.42 g, 37.7 mmol) in MeOH (80 mL). The *title compound* was formed as a colourless oil, which required no further purification (3.59 g, 88%).

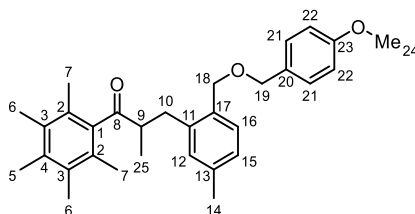
¹H NMR (400 MHz, CDCl_3) δ 7.27 (dd, J = 8.7, 2.0 Hz, 2H, 2 $\times$ C(12)H), 7.22 (d, J = 1.8 Hz, 1H, C(3)H), 7.19 (d, J = 7.6 Hz, 1H, C(7)H), 7.10 (dd, J = 7.6, 1.9 Hz, 1H, C(6)H), 6.92 – 6.84 (m, 2H, 2 $\times$ C(13)H), 4.61 (s, 2H, C(1)H₂), 4.59 (s, 2H, C(9)H₂), 4.50 (s, 2H, C(10)H₂), 3.81 (s, 3H, C(15)H₃), 2.70 (s, 1H, OH), 2.36 (s, 3H, C(5)H₃);

¹³C NMR (101 MHz, CDCl_3) δ 159.5 C(14), 140.6 C(2), 138.8 C(4), 133.0 C(8), 130.7 C(3), 130.3 C(7), 129.8 2 $\times$ C(12), 129.5 C(11), 128.5 C(6), 114.0 2 $\times$ C(13), 72.0 C(10), 70.9 C(9), 63.9 C(1), 55.3 C(15), 21.1 C(5);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3395, 2862, 1613, 1586, 1514, 1360, 1302, 1249, 1175, 1035, 822, 760;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{21}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$) requires 273.1485; found 273.1484, Δ 0.55 ppm.

237e 3-(2-(((4-Methoxybenzyl)oxy)methyl)-5-methylphenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Ph* ethyl ketone **98** (816 mg, 4.00 mmol), alcohol **236e** (2.18 g, 8.00 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (32 mg, 1.0 mol%), KOH (898 mg, 16.0 mmol) and PhMe (1.0 mL) were subjected to

General Procedure H at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 90:10) gave the *title compound* as a colourless oil (1.41 g, 69%).

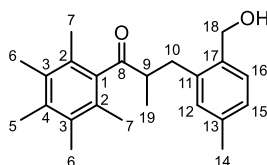
¹H NMR (600 MHz, CDCl₃) δ 7.24 – 7.19 (m, 3H, C(16)*H*, 2 × C(21)*H*), 7.02 – 6.97 (m, 2H, C(12)*H*, C(15)*H*), 6.88 – 6.82 (m, 2H, 2 × C(22)*H*), 4.43 – 4.36 (m, 2H, C(18)*H*₂), 4.35 (s, 2H, C(19)*H*₂), 3.80 (s, 3H, C(24)*H*₃), 3.27 (dd, *J* = 13.8, 4.5 Hz, 1H, C(10)*H*_A*H*_B), 3.15 – 3.05 (m, 1H, C(9)*H*), 2.59 (dd, *J* = 13.8, 9.7 Hz, 1H, C(10)*H*_A*H*_B), 2.30 (s, 3H, C(14)*H*₃), 2.23 (s, 3H, C(Ph*)*H*₃), 2.16 (br. s, 6H, 2 × C(Ph*)*H*₃), 2.09 (br. s, 6H, 2 × C(Ph*)*H*₃), 1.05 (d, *J* = 7.0 Hz, 3H, C(25)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.3 C(8), 159.3 C(23), 139.8 C(Ar(Ph*)), 138.7 C(11), 137.6 C(13), 135.6 C(Ar(Ph*)), 133.5 C(17), 133.2 2 × C(Ar(Ph*)), 131.6 C(12), 130.5 C(20), 129.9 C(16), 129.4 2 × C(21), 128.5 2 × C(Ar(Ph*)), 127.2 C(15), 113.9 2 × C(22), 72.0 C(19), 69.8 C(18), 55.4 C(24), 50.0 C(9), 34.3 C(10), 21.3 C(14), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.4 C(25);

IR (film) ν_{max} /cm⁻¹ 2931, 1694, 1614, 1514, 1456, 1248, 1173, 1076, 1037, 825, 763;

HRMS (ESI⁺) C₃₁H₃₉O₃⁺ ([M+H]⁺) requires 459.2894; found 459.2892, Δ 0.28 ppm.

223e 3-(2-(Hydroxymethyl)-5-methylphenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Ketone **237e** (1.75 g, 3.82 mmol) and DDQ (1.30 g, 5.73 mmol) were subjected to

General Procedure I in a mixture of CH₂Cl₂:water (36 mL: 4 mL). Purification *via* flash column chromatography (eluent pentane/Et₂O 95:5 → 70:30) gave the *title compound* as a white solid (643 mg, 50%).

N.B. This compound was isolated in combination with an inseparable mixture of the corresponding aldehyde and anisaldehyde.

m.p. = 91 – 93 °C;

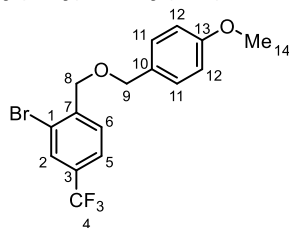
^1H NMR (600 MHz, CDCl_3) δ 7.25 (d, $J = 7.5$ Hz, 1H, C(16) H), 7.05 – 7.00 (m, 2H, C(12) H , C(15) H), 4.71 (d, $J = 12.1$ Hz, 1H, C(18) H_AH_B), 4.59 (d, $J = 12.1$ Hz, 1H, C(18) H_AH_B), 3.32 (dd, $J = 13.9, 5.6$ Hz, 1H, C(10) H_AH_B), 3.24 – 3.12 (m, 1H, C(9) H), 2.65 (dd, $J = 13.9, 8.6$ Hz, 1H, C(10) H_AH_B), 2.31 (s, 3H, C(14) H_3), 2.23 (s, 3H, C(Ph*) H_3), 2.17 (br. s, 6H, $2 \times$ C(Ph*) H_3), 2.05 (br. s, 6H, $2 \times$ C(Ph*) H_3), 1.11 (d, $J = 7.1$ Hz, 3H, C(19) H_3);

^{13}C NMR (151 MHz, CDCl_3) δ 214.6 C(8), 139.6 C(Ar(Ph*)), 138.2 C(11), 137.6 C(13), 136.1 C(17), 135.7 C(Ar(Ph*)), 133.3 $2 \times$ C(Ar(Ph*)), 131.4 C(12), 129.2 C(16), 128.4 $2 \times$ C(Ar(Ph*)), 127.4 C(15), 63.1 C(18), 50.2 C(9), 34.1 C(10), 21.2 C(14), 18.0 $2 \times$ C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 $2 \times$ C(Me(Ph*)), 16.1 C(19);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3348, 2934, 1783, 1746, 1456, 1385, 1306, 1219, 1085, 999, 923;

HRMS (ESI^+) $\text{C}_{23}\text{H}_{30}\text{NaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 361.2138; found 361.2133, Δ 1.52 ppm.

251f 2-Bromo-1-(((4-methoxybenzyl)oxy)methyl)-4-(trifluoromethyl)benzene



NaH (60% in mineral oil, 864 mg, 21.6 mmol) was added portion-wise to a solution of (2-bromo-4-(trifluoromethyl)phenyl)methanol (5.00 g, 19.6 mmol) in DMF (20 mL) at 0 °C and the mixture was stirred for 30 min. 4-Methoxybenzyl chloride (2.9 mL, 21 mmol) was added, the mixture was warmed to RT and stirred for 2 h. The reaction was quenched with the addition of sat. aq. NH_4Cl (15 mL) and the mixture was diluted with Et_2O (150 mL) and water (150 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2×150 mL). The combined organic phases were washed with brine (3×100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane $\rightarrow$ pentane/ Et_2O , 95:5) gave the *title compound* as a colourless oil (6.54 g, 89%).

¹H NMR (600 MHz, CDCl₃) δ 7.82 – 7.78 (m, 1H, C(2)H), 7.67 (dd, *J* = 8.0, 1.3 Hz, 1H, C(6)H), 7.58 (dd, *J* = 8.0, 1.8 Hz, 1H, C(5)H), 7.36 – 7.29 (m, 2H, 2 × C(11)H₂), 6.97 – 6.83 (m, 2H, 2 × C(12)H₂), 4.62 (s, 2H, C(8)H₂), 4.60 (s, 2H, C(9)H₂), 3.82 (s, 3H, C(14)H₃);

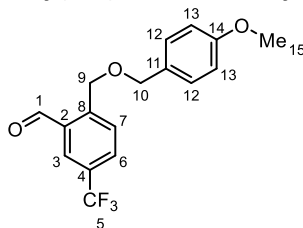
¹³C NMR (151 MHz, CDCl₃) δ 159.6 C(13), 142.2 C(7), 131.1 (q, *J*_{C-F} = 32.9 Hz, C(3)), 129.9 C(10), 129.6 2 × C(11), 129.4 (q, *J*_{C-F} = 3.8 Hz, C(2)), 129.1 C(6), 124.4 (q, *J*_{C-F} = 3.7 Hz, C(5)), 123.4 (q, *J*_{C-F} = 272.5 Hz, C(4)), 122.4 C(1), 114.1 2 × C(12), 72.9 C(9), 70.9 C(8), 55.4 C(14);

¹⁹F NMR (565 MHz, CDCl₃) δ –62.6;

IR (film) *ν*_{max}/cm⁻¹ 2838, 1614, 1515, 1323, 1251, 1173, 1132, 1078, 1040, 833;

HRMS (ESI⁺) C₁₆H₁₄⁷⁹BrF₃NaO₂⁺ ([M+Na]⁺) requires 397.0022; found 397.0014, Δ 1.88 ppm.

252f 2-(((4-Methoxybenzyl)oxy)methyl)-5-(trifluoromethyl)benzaldehyde



Aryl bromide **251f** (5.00 g, 13.3 mmol) was subjected to **General Procedure K** using *n*-BuLi (2.5 M in hexanes, 6.4 mL, 16.0 mmol) and *N,N*-dimethylformamide (1.65 mL, 21.3 mmol) in THF (45 mL). Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 90:10) gave the *title compound* as a colourless oil (3.13 g, 73%).

¹H NMR (600 MHz, CDCl₃) δ 10.22 (s, 1H, C(1)H), 8.11 (d, *J* = 1.8 Hz, 1H, C(3)H), 7.91 – 7.70 (m, 2H, C(6)H, C(7)H), 7.35 – 7.28 (m, 2H, 2 × C(12)H), 6.95 – 6.84 (m, 2H, 2 × C(13)H), 4.98 (s, 2H, C(9)H₂), 4.61 (s, 2H, C(10)H₂), 3.82 (s, 3H, C(15)H₃);

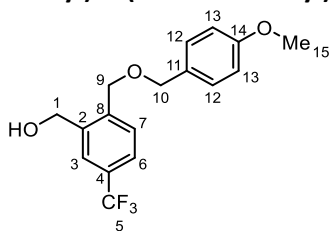
¹³C NMR (151 MHz, CDCl₃) δ 191.5 C(1), 159.6 C(14), 145.1 C(8), 133.7 C(2), 130.5 (q, *J*_{C-F} = 33.5 Hz, C(4)), 130.3 (q, *J*_{C-F} = 3.6 Hz, C(6)), 129.8 C(11), 129.6 2 × C(12), 129.2 (q, *J*_{C-F} = 3.8 Hz, C(3)), 129.0 C(7), 123.7 (q, *J*_{C-F} = 272.3 Hz, C(5)), 114.1 2 × C(13), 73.0 C(10), 68.9 C(9), 55.4 C(15);

¹⁹F NMR (565 MHz, CDCl₃) δ –62.8;

IR (film) *ν*_{max}/cm⁻¹ 2839, 1707, 1615, 1515, 1333, 1250, 1179, 1132, 1082, 1036, 846;

HRMS (ESI⁺) C₁₇H₁₅F₃NaO₃⁺ ([M+Na]⁺) requires 347.0866; found 347.0860, Δ 1.69 ppm.

236f (2-(((4-Methoxybenzyl)oxy)methyl)-5-(trifluoromethyl)phenyl)methanol



Aldehyde **252f** (3.13 g, 9.65 mmol) was subjected to **General Procedure L** with NaBH₄ (548 mg, 14.5 mmol) in MeOH (28 mL). The *title compound* was formed as a colourless oil that required no further purification (3.12 g, 99%).

¹H NMR (600 MHz, CDCl₃) δ 7.70 – 7.67 (m, 1H, C(3)H), 7.55 (dd, *J* = 7.3, 1.6 Hz, 1H, C(6)H), 7.45 (d, *J* = 7.9 Hz, 1H, C(7)H), 7.31 – 7.25 (m, 2H, 2 × C(12)H), 6.93 – 6.87 (m, 2H, 2 × C(13)H), 4.69 (s, 2H, C(1)H₂), 4.63 (s, 2H, C(9)H₂), 4.53 (s, 2H, C(10)H₂), 3.81 (s, 3H, C(15)H₃);

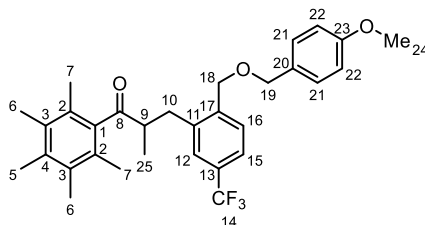
¹³C NMR (151 MHz, CDCl₃) δ 159.7 C(14), 141.1 C(2), 139.9 C(8), 130.9 (q, *J*²_{C-F} = 32.4 Hz, C(4)), 130.1 C(7), 129.9 2 × C(12), 129.2 C(11), 126.1 (q, *J*³_{C-F} = 3.8 Hz, C(3)), 124.8 (q, *J*³_{C-F} = 3.8 Hz, C(6)), 124.5 (q, *J*¹_{C-F} = 272.5 Hz, C(5)), 114.2 2 × C(13), 72.7 C(10), 70.2 C(9), 63.2 C(1), 55.4 C(15);

¹⁹F NMR (565 MHz, CDCl₃) δ -62.6;

IR (film) ν_{max}/cm⁻¹ 3446, 2839, 1614, 1515, 1332, 1251, 1167, 1127, 1081, 1037, 837;

HRMS (ESI⁺) C₁₇H₁₇NaF₃O₃⁺ ([M+Na]⁺) requires 349.1022; found 349.1017, Δ 1.31 ppm.

237f 3-(2-(((4-Methoxybenzyl)oxy)methyl)-5-(trifluoromethyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Ph* ethyl ketone **98** (816 mg, 4.00 mmol), alcohol **236f** (2.61 g, 8.00 mmol), [IrCp*Cl₂]₂ (32 mg, 1.0 mol%), KOH (898 mg, 16.0 mmol) and PhMe (1.0 mL) were subjected to **General Procedure H** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 94:6 → 85:15) gave the *title compound* as a pale-yellow oil (1.41 g, 69%).

¹H NMR (600 MHz, CDCl₃) δ 7.51 (d, *J* = 8.0 Hz, 1H, C(16)*H*), 7.47 – 7.42 (m, 2H, C(12)*H*, C(15)*H*), 7.26 – 7.23 (m, 2H, 2 × C(21)*H*), 6.91 – 6.85 (m, 2H, 2 × C(22)*H*), 4.52 (s, 2H, C(18)*H*₂), 4.45 (s, 2H, C(19)*H*₂), 3.81 (s, 3H, C(24)*H*₃), 3.32 (dd, *J* = 14.0, 5.1 Hz, 1H, C(10)*H*_A*H*_B), 3.16 – 2.96 (m, 1H, C(9)*H*), 2.68 (dd, *J* = 14.0, 9.1 Hz, 1H, C(10)*H*_A*H*_B), 2.23 (s, 3H, C(Ph*)*H*₃), 2.17 (br. s, 6H, 2 × C(Ph*)*H*₃), 1.95 (br. s, 6H, 2 × C(Ph*)*H*₃), 1.07 (d, *J* = 7.1 Hz, 3H, C(25)*H*₃);

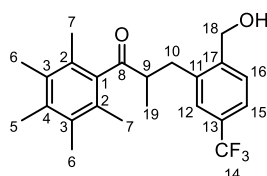
¹³C NMR (151 MHz, CDCl₃) δ 213.5 C(8), 159.5 C(23), 140.6 C(17), 139.4 C(11), 139.3 C(Ar(Ph*)), 135.9 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 130.0 C(20), 129.9 (q, *J*_{C-F} = 32.2 Hz, C(13)), 129.5 2 × C(21), 129.5 C(16), 128.4 br. 2 × C(Ar(Ph*)), 127.2 (q, *J*_{C-F} = 3.7 Hz, C(12)), 126.1 (q, *J*_{C-F} = 273.1 Hz, C(14)), 123.3 (q, *J*_{C-F} = 3.5 Hz, C(15)), 114.0 2 × C(22), 72.6 C(19), 69.1 C(18), 55.4 C(24), 49.7 C(9), 34.1 C(10), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)) 15.7 C(25);

¹⁹F NMR (565 MHz, CDCl₃) δ -62.5;

IR (film) *ν*_{max}/cm⁻¹ 2910, 1696, 1614, 1514, 1333, 1250, 1165, 1126, 1084, 1038, 911, 834;

HRMS (ESI⁺) C₃₁H₃₅F₃NaO₃⁺ ([M+Na]⁺) requires 535.2431; found 535.2419, Δ 2.19 ppm.

223f 3-(2-(Hydroxymethyl)-5-(trifluoromethyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Ketone **237f** (1.40 g, 2.73 mmol) and DDQ (931 mg, 4.10 mmol) were subjected to **General Procedure I** in a mixture of CH₂Cl₂:water (24 mL: 3 mL). Purification *via* flash column chromatography (eluent pentane/Et₂O 80:20 → 65:35) gave the *title compound* as a white solid (674 mg, 63%).

m.p. = 101 – 103 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.55 (d, *J* = 7.9 Hz, 1H, C(16)*H*), 7.51 – 7.43 (m, 2H, C(12)*H*, C(15)*H*), 4.88 (d, *J* = 12.9 Hz, 1H, C(18)*H*_A*H*_B), 4.72 (d, *J* = 12.9 Hz, 1H, C(18)*H*_A*H*_B), 3.39 (dd, *J* = 14.1, 6.6 Hz, 1H, C(10)*H*_A*H*_B), 3.29 – 3.14 (m, 1H, C(9)*H*), 2.71 (dd, *J* = 14.1, 7.7 Hz, 1H, C(10)*H*_A*H*_B), 2.23 (s,

3H, C(Ph*)H₃), 2.16 (s, 6H, 2 × C(Ph*)H₃), 2.12 – 1.74 (br. s, 6H, 2 × C(Ph*)H₃), 1.14 (d, *J* = 7.2 Hz, 3H, C(19)H₃);

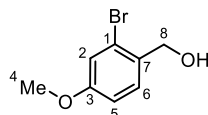
¹³C NMR (151 MHz, CDCl₃) δ 214.1 C(8), 142.9 C(17), 139.1 C(Ar(Ph*)), 138.8 C(11), 136.0 C(Ar(Ph*)), 133.4 2 × C(Ar(Ph*)), 129.9 (q, *J*²_{C-F} = 32.2 Hz, C(13)), 129.1 C(16), 128.4 (br.) 2 × C(Ar(Ph*)), 127.1 (q, *J*³_{C-F} = 3.6 Hz, C(12)), 124.3 (q, *J*¹_{C-F} = 271.8 Hz, C(14)), 123.5 (q, *J*³_{C-F} = 3.4 Hz, C(15)), 62.6 C(18), 50.0 C(9), 33.8 C(10), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.5 C(19), 16.1 2 × C(Me(Ph*));

¹⁹F NMR (471 MHz, CDCl₃) δ -62.6;

IR (film) ν_{max}/cm⁻¹ 3446, 2936, 1694, 1457, 1421, 1333, 1164, 1126, 1082, 913;

HRMS (ESI⁺) C₂₃H₂₈F₃O₂⁺ ([M+H]⁺) requires 393.2036; found 393.2027, Δ 2.20 ppm.

250g (2-Bromo-4-methoxyphenyl)methanol



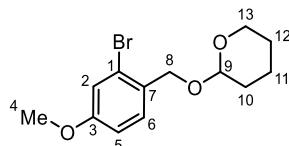
2-Bromo-4-methoxybenzaldehyde (5.38 g, 25.0 mmol) and NaBH₄ (1.42 g, 37.5 mmol) were subjected to **General Procedure L** in MeOH (80 mL) to give the *title compound* as a colourless oil that required no further purification (5.29 g, 97%).

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.30 (m, 1H, C(6)H), 7.11 (d, *J* = 2.6 Hz, 1H, C(2)H), 6.86 (dd, *J* = 8.5, 2.6 Hz, 1H, C(5)H), 4.68 (s, 2H, C(8)H₂), 3.80 (s, 3H, C(4)H₃);

¹³C NMR (101 MHz, CDCl₃) δ 159.7 C(3), 131.9 C(7), 130.1 C(6), 123.4 C(1), 118.1 C(2), 113.5 C(5), 64.8 C(8), 55.6 C(4);

m/z (ESI⁺) C₈H₁₀⁷⁹BrO₂ ([M+H]⁺) requires 217; mass not found.

The spectroscopic data matched that previously reported in the literature.¹⁶⁶

251g 2-((2-Bromo-4-methoxybenzyl)oxy)tetrahydro-2H-pyran

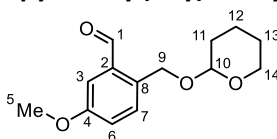
Alcohol **250g** (5.27 g, 24.3 mmol) was dissolved in CH_2Cl_2 (80 mL) and 3,4-dihydro-2H-pyran (3.3 mL, 37 mmol) and pyridinium *p*-toluenesulfonate (611 mg, 2.43 mmol) were added. The mixture was stirred overnight at RT and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99:1 $\rightarrow$ 94:6) gave the *title compound* as a colourless oil (6.25 g, 85%).

^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.34 (m, 1H, C(6)*H*), 7.11 (d, J = 2.6 Hz, 1H, C(2)*H*), 6.85 (dd, J = 8.5, 2.6 Hz, 1H, C(5)*H*), 4.80 – 4.71 (m, 2H, C(8)*H*_A*H*_B, C(9)*H*), 4.52 (d, J = 12.4 Hz, 1H, C(8)*H*_A*H*_B), 3.98 – 3.89 (m, 1H, C(13)*H*_A*H*_B), 3.79 (s, 3H, C(4)*H*₃), 3.60 – 3.52 (m, 1H, C(13)*H*_A*H*_B), 1.95 – 1.81 (m, 1H, C(11)*H*_A*H*_B), 1.81 – 1.46 (m, 5H, C(10)*H*₂, C(11)*H*_A*H*_B, C(12)*H*₂);

^{13}C NMR (101 MHz, CDCl_3) δ 159.6 C(3), 130.5 C(6), 129.9 C(7), 123.8 C(1), 118.1 C(2), 113.5 C(5), 98.4 C(9), 68.5 C(8), 62.3 C(13), 55.7 C(4), 30.7 C(10), 25.6 C(12), 19.5 C(11);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2944, 1606, 1570, 1496, 1440, 1241, 1135, 1038, 975, 907, 869;

HRMS (ESI^+) $\text{C}_{13}\text{H}_{17}^{79}\text{BrNaO}_3^+$ ($[\text{M}+\text{Na}]^+$) requires 323.0253; found 323.0251, Δ 0.67 ppm.

252g 5-Methoxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzaldehyde

Aryl bromide **251g** (4.22 g, 14.0 mmol) was subjected to **General Procedure K** using *n*-BuLi (2.5 M in hexanes, 6.8 mL, 16.8 mmol) and *N,N*-dimethylformamide (1.75 mL, 22.6 mmol) in THF (50 mL). Purification *via* flash column chromatography (eluent pentane/ Et_2O , 92:8 $\rightarrow$ 80:20) gave the *title compound* as a colourless oil (3.21 g, 92%).

^1H NMR (400 MHz, CDCl_3) δ 10.31 (s, 1H, C(1)*H*), 7.47 (d, J = 8.4 Hz, 1H, C(7)*H*), 7.41 (d, J = 2.8 Hz, 1H, C(3)*H*), 7.11 (dd, J = 8.4, 2.8 Hz, 1H, C(6)*H*), 5.13 – 5.05 (m, 1H, C(9)*H*_A*H*_B), 4.82 (d, J = 12.8 Hz, 1H, C(9)*H*_A*H*_B), 4.73 (dd, J = 4.2, 2.9 Hz, 1H, C(10)*H*), 3.86 (s, 4H, C(5)*H*₃, C(14)*H*_A*H*_B), 3.60 – 3.50

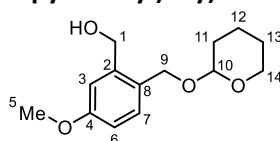
(m, 1H, C(14) H_AH_B), 1.92 – 1.77 (m, 1H, C(12) H_AH_B), 1.73 (tdd, $J = 9.2, 4.0, 2.9$ Hz, 1H, C(11) H_AH_B), 1.67 – 1.49 (m, 4H, C(11) H_AH_B , C(12) H_AH_B , C(13) H_2);

^{13}C NMR (101 MHz, CDCl_3) δ 192.1 C(1), 159.6 C(4), 135.2 C(8), 133.1 C(2), 131.2 C(7), 120.4 C(6), 114.2 C(3), 98.3 C(10), 65.8 C(9), 62.6 C(14), 55.7 C(5), 30.7 C(11), 25.5 C(13), 19.6 C(12);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2945, 1693, 1610, 1575, 1503, 1318, 1282, 1258, 1027;

HRMS (ESI $^+$) $\text{C}_{14}\text{H}_{18}\text{O}_4\text{Na}^+$ ($[\text{M}+\text{Na}]^+$) requires 273.1079; found 273.1089, Δ 2.88 ppm.

236g (5-Methoxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanol



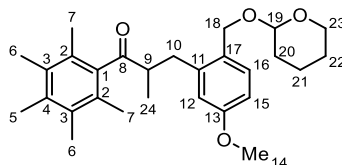
Aldehyde **252g** (3.10 g, 12.4 mmol) was subjected to **General Procedure L** with NaBH_4 (703 mg, 18.6 mmol) in MeOH (40 mL). The *title compound* was formed as a colourless oil that required no further purification (3.13 g, 100%).

^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, $J = 8.3$ Hz, 1H, C(7) H), 6.97 (d, $J = 2.8$ Hz, 1H, C(3) H), 6.81 (dd, $J = 8.3, 2.7$ Hz, 1H, C(6) H), 4.85 (d, $J = 11.4$ Hz, 1H, C(9) H_AH_B), 4.72 (t, $J = 3.4$ Hz, 1H, C(10) H), 4.71 – 4.61 (m, 2H, C(1) H_2), 4.54 (d, $J = 11.4$ Hz, 1H, C(9) H_AH_B), 3.89 (ddd, $J = 11.5, 8.2, 3.1$ Hz, 1H, C(14) H_AH_B), 3.82 (s, 3H, C(5) H_3), 3.62 – 3.53 (m, 1H, C(14) H_AH_B), 1.86 – 1.67 (m, 2H, C(11) H_AH_B , C(12) H_AH_B), 1.67 – 1.45 (m, 4H, C(11) H_AH_B , C(12) H_AH_B , C(13) H_2);

^{13}C NMR (101 MHz, CDCl_3) δ 160.0 C(4), 142.2 C(2), 132.0 C(7), 128.0 C(8), 115.4 C(3), 113.1 C(6), 97.8 C(10), 67.6 C(9), 64.0 C(1), 62.5 C(14), 55.5 C(5), 30.6 C(11), 25.4 C(13), 19.4 C(12);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3453, 2945, 2870, 1613, 1582, 1265, 1120, 1035;

HRMS (ESI $^+$) $\text{C}_{14}\text{H}_{20}\text{O}_4\text{Na}^+$ ($[\text{M}+\text{Na}]^+$) requires 275.1254; found 275.1250, Δ 1.29 ppm.

237g 3-(5-Methoxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one

Ph* ethyl ketone **98** (714 mg, 3.50 mmol), alcohol **236g** (1.76 g, 7.00 mmol), [IrCp*Cl₂]₂ (32 mg, 1.0 mol%), KOH (898 mg, 16.0 mmol) and PhMe (1.0 mL) were subjected to **General Procedure H** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/Et₂O, 95:5 → 75:25) gave the *title compound* as a pale-yellow oil (1.12 g, 73%, [45:55] d.r.)

The spectroscopic data were collected on the diastereomeric mixture and the relative stereochemistry is unassigned.

¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.16 (m, 2H, C(16')H, C(16'')H), 6.76 – 6.60 (m, 4H, C(12')H, C(12'')H, C(15')H, C(15'')H), 4.71 – 4.59 (m, 2H, C(18')H_AH_B, C(18'')H_AH_B), 4.57 (t, *J* = 3.6 Hz, 1H, C(19')H), 4.42 (t, *J* = 3.5 Hz, 1H, C(19'')H), 4.40 – 4.29 (m, 2H, C(18')H_AH_B, C(18'')H_AH_B), 3.91 – 3.79 (m, 2H, C(23')H_AH_B, C(23'')H_AH_B), 3.75 (s, 6H, C(14')H₃, C(14'')H₃), 3.51 – 3.41 (m, 2H, C(23')H_AH_B, C(23'')H_AH_B), 3.33 – 3.20 (m, 2H, C(10')H_AH_B, C(10'')H_AH_B), 3.18 – 3.04 (m, 2H, C(9')H, C(9'')H), 2.73 – 2.48 (m, 2H, C(10')H_AH_B, C(10'')H_AH_B), 2.20 (2 × s, 6H, 2 × C(Ph*)H₃), 2.15 (br. s, 12H, 4 × C(Ph*)H₃), 2.11 – 1.92 (m, 12H, 4 × C(Ph*)H₃), 1.83 – 1.72 (m, 2H, C(21')H_AH_B, C(21'')H_AH_B), 1.72 – 1.34 (m, 10H, C(20')H₂, C(20'')H₂, C(21')H_AH_B, C(21'')H_AH_B, C(22')H₂, C(22'')H₂), 1.06 (d, *J* = 7.0 Hz, 6H, C(24')H₃, C(24'')H₃);*

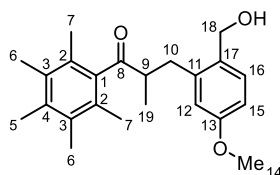
¹³C NMR (101 MHz, CDCl₃) δ 214.3 C(8'), 214.2 C(8''), 159.3 C(13'), 159.2 C(13''), 140.6 C(11'), 140.4 C(11''), 139.8 C(Ar(Ph*)), 139.7 C(Ar(Ph*)), 135.7 2 × C(Ar(Ph*)), 133.2 4 × C(Ar(Ph*)), 131.5 C(16'), 131.3 C(16''), 128.8 C(17'), 128.6 C(17''), 128.5 4 × C(Ar(Ph*)), 116.7 C(12'), 116.4 C(12''), 111.5 C(15'), 111.5 C(15''), 97.9 C(19'), 97.7 C(19''), 66.6 C(18'), 66.5 C(18''), 62.3 C(23'), 62.3 C(23''), 55.4 C(14') & C(14''), 49.9 C(9'), 49.8 C(9''), 34.7 C(10'), 34.5 C(10''), 30.7 C(20') & C(20''), 25.6 C(22') & C(22''), 19.6 C(21') & C(21''), 18.0 4 × C(Me(Ph*)), 16.9 2 × C(Me(Ph*)), 16.2 4 × C(Me(Ph*)), 15.7 C(24'), 15.3 C(24'');*

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2936, 1695, 1613, 1579, 1504, 1464, 1262, 1114, 1011, 902;

HRMS (ESI⁺) $\text{C}_{28}\text{H}_{39}\text{O}_4^+$ ([M+H]⁺) requires 439.2843; found 439.2843, Δ 0.10 ppm.

* N.B. The labels ' and '' are assigned arbitrarily and indicate peaks belonging to different diastereomers.

223g 3-(2-(Hydroxymethyl)-5-methoxyphenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



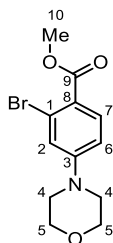
THP-protected alcohol **237g** (1.11 g, 2.53 mmol) was dissolved in THF (20 mL) and aqueous HCl (3 M, 5 mL) was added. The mixture was stirred at RT for 16 h and then diluted with water (20 mL) and EtOAc (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 70:30 → 60:40) gave the *title compound* as a colourless oil (231 mg, 26%).

¹H NMR (600 MHz, CDCl_3) δ 7.27 (d, J = 8.2 Hz, 1H, C(16)*H*), 6.78 – 6.71 (m, 2H, C(12)*H*, C(15)*H*), 4.68 (d, J = 12.0 Hz, 1H, C(18)*H_AH_B*), 4.57 (d, J = 12.0 Hz, 1H, C(18)*H_AH_B*), 3.79 (s, 3H, C(14)*H₃*), 3.34 (dd, J = 13.9, 5.7 Hz, 1H, C(10)*H_AH_B*), 3.24 – 3.15 (m, 1H, C(9)*H*), 2.67 (dd, J = 13.9, 8.5 Hz, 1H, C(10)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 6H, 2 × C(Ph*)*H₃*), 2.13 – 1.93 (m, 6H, 2 × C(Ph*)*H₃*), 1.12 (d, J = 7.2 Hz, 3H, C(19)*H₃*);

¹³C NMR (151 MHz, CDCl_3) δ 214.4 C(8), 159.3 C(13), 140.1 C(11), 139.5 C(Ar(Ph*)), 135.8 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 131.5 C(17), 130.8 C(16), 128.4 2 × C(Ar(Ph*)), 116.5 C(12), 111.7 C(15), 62.9 C(18), 55.4 C(14), 50.2 C(9), 34.3 C(10), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.1 2 × C(Me(Ph*)) & C(19);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3438, 2944, 1689, 1611, 1579, 1502, 1309, 1260, 1162, 1051, 921;

HRMS (ESI⁺) $\text{C}_{23}\text{H}_{30}\text{NaO}_3^+$ ([M+Na]⁺) requires 377.2087; found 377.2078, Δ 2.37 ppm.

S52 Methyl 2-Bromo-4-morpholinobenzoate

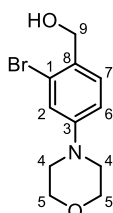
Methyl 2-bromo-4-fluorobenzoate (5.00 g, 21.4 mmol) and morpholine (9.4 mL, 110 mmol) were dissolved in DMSO (20 mL) and the mixture was heated to 120 °C for 2 h. The mixture was cooled to RT, diluted with water (100 mL) and EtOAc (100 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 85:15 → 80:20) gave the *title compound* as a colourless oil (5.23 g, 78%).

¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.8 Hz, 1H, C(7)*H*), 7.10 (d, *J* = 2.6 Hz, 1H, C(2)*H*), 6.78 (dd, *J* = 8.9, 2.6 Hz, 1H, C(6)*H*), 3.87 (s, 3H, C(10)*H*₃), 3.86 – 3.80 (m, 4H, 2 × C(5)*H*₂), 3.32 – 3.22 (m, 4H, 2 × C(4)*H*₂);

¹³C NMR (101 MHz, CDCl₃) δ 166.0 C(9), 153.8 C(3), 133.3 C(7), 124.4 C(8), 120.5 C(1), 119.8 C(2), 112.4 C(6), 66.6 2 × C(5), 52.1 C(10), 47.6 2 × C(4);

m/z (ESI⁺) Found ([M+H]⁺) = 300, C₁₂H₁₅⁷⁹BrNO₃ requires 300.

The spectroscopic data were consistent with that reported in the literature.¹⁶⁷

250h (2-Bromo-4-morpholinophenyl)methanol

Methyl Ester **S52** (5.20 g, 17.3 mmol) was dissolved in THF (80 mL) and cooled to 0 °C. LiAlH₄ (657 mg, 17.3 mmol) was added, the mixture was warmed to RT and stirred for 1 h. The reaction was cooled to 0 °C and quenched by sequential dropwise addition of H₂O (0.66 mL), aq. NaOH (15% w/v, 0.66 mL), and H₂O (2.0 mL). MgSO₄ was added and the resulting suspension was

stirred vigorously for 15 min and then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (pentane/EtOAc, 80:20 → 75:25) gave the *title compound* as a colourless oil (3.80 g, 81%).

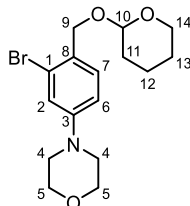
¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J* = 8.4 Hz, 1H, C(7)*H*), 7.08 (d, *J* = 2.4 Hz, 1H, C(2)*H*), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H, C(6)*H*), 4.66 (s, 2H, C(9)*H*₂), 3.97 – 3.74 (m, 4H, 2 × C(5)*H*₂), 3.23 – 3.02 (m, 4H, 2 × C(4)*H*₂), 1.97 (s, 1H, OH);

¹³C NMR (101 MHz, CDCl₃) δ 151.9 C(3), 130.9 C(8), 130.2 C(7), 124.1 C(1), 119.5 C(2), 114.7 C(6), 66.8 2 × C(5), 64.9 C(9), 49.0 2 × C(4);

IR (film) ν_{max} /cm⁻¹ 3431, 2829, 1605, 1552, 1498, 1450, 1380, 1232, 1121, 942, 761;

HRMS (ESI⁺) C₁₁H₁₅⁷⁹BrNO₂⁺ ([M+H]⁺) requires 272.0281; found 272.0277, Δ 1.33 ppm.

251h 4-(3-Bromo-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)morpholine



Alcohol **250h** (3.78 g, 13.9 mmol) was dissolved in CH₂Cl₂ (50 mL) and 3,4-dihydro-2H-pyran (1.9 mL, 21 mmol) and pyridinium *p*-toluenesulfonate (349 mg, 1.39 mmol) were added. The reaction was stirred at RT for 16 h, filtered through a SiO₂ plug (CH₂Cl₂/Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 95:5 → 90:10) gave the *title compound* as a colourless oil (2.30 g, 46%).

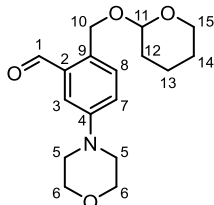
¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 8.5 Hz, 1H, C(7)*H*), 7.08 (d, *J* = 2.5 Hz, 1H, C(2)*H*), 6.84 (dd, *J* = 8.5, 2.5 Hz, 1H, C(6)*H*), 4.80 – 4.72 (m, 2H, C(9)*H*_A*H*_B, C(10)*H*), 4.51 (d, *J* = 12.3 Hz, 1H, C(9)*H*_A*H*_B), 3.98 – 3.89 (m, 1H, C(14)*H*_A*H*_B), 3.89 – 3.80 (m, 4H, 2 × C(5)*H*₂), 3.63 – 3.51 (m, 1H, C(14)*H*_A*H*_B), 3.18 – 3.07 (m, 4H, 2 × C(4)*H*₂), 1.95 – 1.81 (m, 1H, C(12)*H*_A*H*_B), 1.80 – 1.46 (m, 5H, C(11)*H*₂, C(12)*H*_A*H*_B, C(13)*H*₂);

¹³C NMR (101 MHz, CDCl₃) δ 151.8 C(3), 130.5 C(7), 128.7 C(8), 124.4 C(1), 119.5 C(2), 114.6 C(6), 98.3 C(10), 68.5 C(9), 66.8 2 × C(5), 62.3 C(14), 49.1 2 × C(4), 30.7 C(11), 25.6 C(13), 19.5 C(12);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2947, 2856, 1605, 1553, 1500, 1450, 1230, 1122, 1035, 943, 907, 869, 812;

HRMS (ESI⁺) $\text{C}_{16}\text{H}_{22}^{79}\text{BrNaNO}_3^+$ ([M+Na]⁺) requires 378.0675; found 378.0674, Δ 0.31 ppm.

252h 5-Morpholino-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzaldehyde



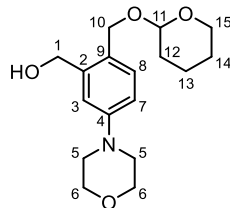
Aryl bromide **251h** (2.28 g, 6.39 mmol) was subjected to **General Procedure K** using *n*-BuLi (2.5 M in hexanes, 3.1 mL, 7.7 mmol) and *N,N*-dimethylformamide (1.0 mL, 13 mmol) in THF (21 mL). Purification *via* flash column chromatography (eluent pentane/EtOAc, 88:12 → 80:20) gave the *title compound* as a yellow oil (1.37 g, 70%).

¹H NMR (600 MHz, CDCl₃) δ 10.32 (s, 1H, C(1)*H*), 7.54 – 7.33 (m, 2H, C(7)*H*, C(8)*H*), 7.19 – 7.02 (m, 1H, C(3)*H*), 5.08 (d, *J* = 12.8 Hz, 1H, C(10)*H_AH_B*), 4.81 (d, *J* = 12.8 Hz, 1H, C(10)*H_AH_B*), 4.73 (t, *J* = 3.6 Hz, 1H, C(11)*H*), 4.00 – 3.77 (m, 5H, 2 × C(6)*H₂*, C(15)*H_AH_B*), 3.63 – 3.51 (m, 1H, C(15)*H_AH_B*), 3.29 – 3.14 (m, 4H, 2 × C(5)*H₂*), 1.90 – 1.78 (m, 1H, C(13)*H_AH_B*), 1.78 – 1.68 (m, 1H, C(12)*H_AH_B*), 1.66 – 1.44 (m, 4H, C(12)*H_AH_B*, C(13)*H_AH_B*, C(14)*H₂*);

¹³C NMR (151 MHz, CDCl₃) δ 192.5 C(1), 150.8 C(4), 134.9 C(2), 132.2 C(9), 131.0 C(8), 120.9 C(7), 116.8 C(3), 98.3 C(11), 66.7 2 × C(6), 65.9 C(10), 62.6 C(15), 49.3 2 × C(5), 30.7 C(12), 25.6 C(14), 19.6 C(13);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2948, 2855, 1693, 1606, 1508, 1348, 1245, 1123, 1034, 969, 886, 765;

HRMS (ESI⁺) $\text{C}_{17}\text{H}_{24}\text{NO}_4^+$ ([M+H]⁺) requires 306.1700; found 306.1700, Δ 0.12 ppm.

236h (5-Morpholino-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanol

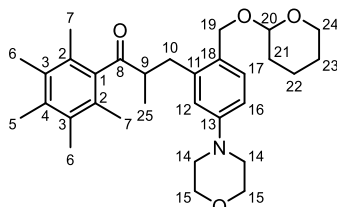
Aldehyde **252h** (1.36 g, 4.45 mmol) was subjected to **General Procedure L** with NaBH₄ (252 mg, 6.67 mmol) in MeOH (15 mL). The *title compound* was formed as a colourless oil that required no further purification (1.36 g, 99%).

¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 8.4 Hz, 1H, C(8)*H*), 6.97 (d, *J* = 2.7 Hz, 1H, C(3)*H*), 6.81 (dd, *J* = 8.4, 2.6 Hz, 1H, C(7)*H*), 4.84 (d, *J* = 11.4 Hz, 1H, C(10)*H_AH_B*), 4.73 (t, *J* = 3.5 Hz, 1H, C(11)*H*), 4.68 (dd, *J* = 12.2, 6.1 Hz, 1H, C(1)*H_AH_B*), 4.62 (dd, *J* = 12.2, 6.6 Hz, 1H, C(1)*H_AH_B*), 4.52 (d, *J* = 11.4 Hz, 1H, C(10)*H_AH_B*), 3.94 – 3.81 (m, 5H, 2 × C(6)*H₂*, C(15)*H_AH_B*), 3.63 – 3.50 (m, 1H, C(15)*H_AH_B*), 3.24 (t, *J* = 6.5 Hz, 1H, OH), 3.21 – 3.13 (m, 4H, 2 × C(5)*H₂*), 1.85 – 1.66 (m, 2H, C(12)*H_AH_B*, C(13)*H_AH_B*), 1.66 – 1.47 (m, 4H, C(12)*H_AH_B*, C(13)*H_AH_B*, C(14)*H₂*);

¹³C NMR (126 MHz, CDCl₃) δ 151.7 C(4), 141.7 C(2), 131.8 C(8), 127.0 C(9), 117.0 C(3), 114.5 C(7), 97.7 C(11), 67.7 C(10), 67.0 2 × C(6), 64.4 C(1), 62.4 C(15), 49.2 2 × C(5), 30.6 C(12), 25.4 C(14), 19.4 C(13);

IR (film) ν_{max} /cm⁻¹ 3408, 2943, 2858, 1725, 1613, 1506, 1451, 1240, 1118, 1023, 759;

HRMS (ESI⁺) C₁₇H₂₆NO₄⁺ ([M+H]⁺) requires 308.1856; found 308.1852, Δ 1.39 ppm.

237h 2-Methyl-3-(5-morpholino-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one

Ph* ethyl ketone **98** (592 mg, 2.90 mmol), alcohol **236h** (1.34 g, 4.36 mmol), [IrCp*Cl₂]₂ (23 mg, 1.0 mol%), KOH (651 mg, 11.6 mmol) and PhMe (0.73 mL) were subjected to **General Procedure H** at 110 °C for 24 h. Purification *via* flash column chromatography (eluent

pentane/Et₂O, 85:15 → 70:30) gave the *title compound* as a pale yellow oil (952 mg, 66%, [46:54] d.r.)

The spectroscopic data were collected on the diastereomeric mixture and the relative stereochemistry is unassigned.

¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.23 (m, 2H, C(17')H, C(17'')H), 6.88 – 6.73 (m, 4H, C(12')H, C(12'')H, C(16')H, C(16'')H), 4.71 (d, *J* = 11.6 Hz, 1H, C(19')H_AH_B), 4.66 (d, *J* = 11.4 Hz, 1H, C(19'')H_AH_B), 4.62 (t, *J* = 3.6 Hz, 1H, C(20')H), 4.47 (t, *J* = 3.5 Hz, 1H, C(20'')H), 4.41 (d, *J* = 11.6 Hz, 1H, C(19')H_AH_B), 4.36 (d, *J* = 11.4 Hz, 1H, C(19'')H_AH_B), 3.95 – 3.78 (m, 10H, 2 × C(15')H₂, 2 × C(15'')H₂, C(24')H_AH_B, C(24'')H_AH_B), 3.59 – 3.49 (m, 2H, C(24')H_AH_B, C(24'')H_AH_B), 3.43 – 3.30 (m, 2H, C(10')H_AH_B, C(10'')H_AH_B), 3.23 – 3.06 (m, 10H, C(9')H, C(9'')H, 2 × C(14')H₂, 2 × C(14'')H₂), 2.76 – 2.59 (m, 2H, C(10')H_AH_B, C(10'')H_AH_B), 2.26 (s, 3H, C(Ph*)H₃), 2.25 (s, 3H, C(Ph*)H₃), 2.23 – 2.16 (m, 12H, 4 × C(Ph*)H₃), 2.01 (br. s, 12H, 4 × C(Ph*)H₃), 1.87 – 1.78 (m, 2H, C(22')H_AH_B, C(22'')H_AH_B), 1.72 – 1.44 (m, 10H, C(21')H₂, C(21'')H₂, C(22')H_AH_B, C(22'')H_AH_B, C(23')H₂, C(23'')H₂), 1.12 (2 × d, *J* = 7.0 Hz, 6H, C(25')H₃, C(25'')H₃);*

¹³C NMR (126 MHz, CDCl₃) δ 214.3 C(8'), 214.2 C(8''), 151.0 C(13), 151.0 C(13'), 140.1 C(11'), 139.9 C(11''), 139.8 C(Ar(Ph*)), 139.7 C(Ar(Ph*)), 135.7 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 131.3 C(17'), 131.1 C(17''), 128.5 2 × C(Ar(Ph*)), 128.0 C(18'), 127.8 C(18''), 118.6 C(12'), 118.3 C(12''), 113.6 C(16'), 113.6 C(16''), 97.8 C(20'), 97.7 C(20''), 67.0 2 × C(15'), 2 × C(15''), 66.7 C(19'), 66.6 C(19''), 62.3 C(24'), 62.2 C(24''), 50.0 C(9'), 49.9 C(9''), 49.5 2 × C(14'), 2 × C(14''), 35.0 C(10'), 34.8 C(10''), 30.7 C(21') & C(21''), 25.6 C(23') & C(23''), 19.6 C(22') & C(22''), 19.6 4 × C(Me(Ph*)), 17.9 C(Me(Ph*)), 16.9 2 × C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 16.1 C(Me(Ph*)), 15.7 C(25') & C(25'');*

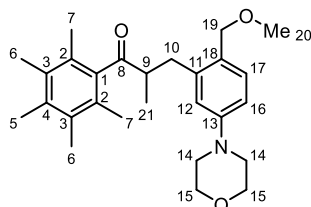
Fewer peaks were observed than expected in the ¹³C spectrum (for Ph* Ar) due to overlapping peaks.

IR (film) ν_{max} /cm⁻¹ 2948, 1693, 1612, 1452, 1237, 1122, 1022, 975;

HRMS (ESI⁺) C₃₁H₄₄NO₄⁺ ([M+H]⁺) requires 494.3265; found 494.3250, Δ 3.05 ppm.

* N.B. The labels ' and '' are assigned arbitrarily and indicate peaks belonging to different diastereomers.

253 3-(2-(Methoxymethyl)-5-morpholinophenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



THP-protected alcohol **237h** (927 mg, 1.88 mmol) was dissolved in MeOH:water (18 mL: 2 mL) and *p*-toluenesulfonic acid monohydrate (393 mg, 2.07 mmol) was added. The mixture was stirred at RT for 16 h and then heated to 65 °C for 2 h. The mixture was cooled to RT, quenched with the addition of NaHCO₃ (10 mL) and diluted with EtOAc (50 mL) and water (40 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 80:20 → 70:30) gave the *title compound* as a white solid (583 mg, 73%).

m.p. = 114 – 116 °C;

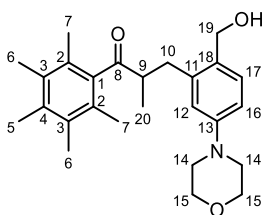
¹H NMR (600 MHz, CDCl₃) δ 7.20 (d, *J* = 8.4 Hz, 1H, C(17)*H*), 6.78 (s, 1H, C(12)*H*), 6.74 (d, *J* = 8.4 Hz, 1H, C(16)*H*), 4.34 – 4.20 (m, 2H, C(19)*H*₂), 3.85 (t, *J* = 4.7 Hz, 4H, 2 × C(15)*H*₂), 3.32 (dd, *J* = 13.4, 5.0 Hz, 1H, C(10)*H*_A*H*_B), 3.25 (s, 3H, C(20)*H*₃), 3.20 – 3.07 (m, 5H, C(9)*H*, 2 × C(14)*H*₂), 2.59 (dd, *J* = 13.6, 8.9 Hz, 1H, C(10)*H*_A*H*_B), 2.23 (s, 3H, C(Ph*)*H*₃), 2.17 (br. s, 6H, 2 × C(Ph*)*H*₃), 2.05 (br. s, 6H, 2 × C(Ph*)*H*₃), 1.11 (d, *J* = 7.1 Hz, 3H, C(21)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.3 C(8), 151.1 C(13), 140.1 C(Ar(Ph*)), 139.8 C(11), 135.7 C(Ar(Ph*)), 133.2 2 × C(Ar(Ph*)), 131.1 C(17), 128.5 2 × C(Ar(Ph*)), 127.9 C(18), 118.5 C(16), 113.6 C(12), 72.6 C(19), 67.0 2 × C(15), 58.0 C(20), 50.2 C(9), 49.5 2 × C(14), 35.0 C(10), 17.9 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.9 C(21);

IR (film) ν_{max} /cm⁻¹ 2859, 1693, 1610, 1509, 1452, 1380, 1242, 1123, 1088, 971, 925, 890;

HRMS (ESI⁺) C₂₇H₃₇NNaO₃⁺ ([M+Na]⁺) requires 446.2666; found 446.2662, Δ 0.82 ppm.

223h 3-(2-(Hydroxymethyl)-5-morpholinophenyl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one



Methyl ether **253** (500 mg, 1.18 mmol) was dissolved in a mixture of THF (15 mL):water (10 mL) and *p*-toluenesulfonic acid monohydrate (449 mg, 2.36 mmol) was added. The mixture was stirred at RT for 24 h. The reaction was quenched with the addition of sat. aq. NaHCO₃ (20 mL), and diluted with EtOAc (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined aqueous phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 80:20 → 60:40) gave the *title compound* as a white solid (256 mg, 53%).

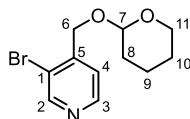
m.p. = 55 – 57 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, *J* = 8.3 Hz, 1H, C(17)*H*), 6.79 (s, 2H, C(12)*H*, C(16)*H*), 4.67 (dd, *J* = 12.0, 4.0 Hz, 1H, C(19)*H_AH_B*), 4.56 (dd, *J* = 12.0, 5.1 Hz, 1H, C(19)*H_AH_B*), 3.86 (t, *J* = 4.8 Hz, 4H, 2 × C(15)*H₂*), 3.36 (dd, *J* = 13.7, 6.1 Hz, 1H, C(10)*H_AH_B*), 3.24 – 3.16 (m, 1H, C(9)*H*), 3.16 – 3.10 (m, 4H, 2 × C(14)*H₂*), 2.67 (dd, *J* = 13.7, 7.9 Hz, 1H, C(10)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 6H, 2 × C(Ph*)*H₃*), 2.01 (s, 6H, 2 × C(Ph*)*H₃*), 1.13 (d, *J* = 7.2 Hz, 3H, C(20)*H₃*);

¹³C NMR (126 MHz, CDCl₃) δ 214.4 C(8), 151.0 C(13), 139.5 C(Ar(Ph*)), 139.5 C(11), 135.8 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 130.8 C(18), 130.5 C(17), 128.4 2 × C(Ar(Ph*)), 118.2 C(12), 113.9 C(16), 67.0 2 × C(15), 62.9 C(19), 50.2 C(9), 49.5 2 × C(14), 34.6 C(10), 17.9 2 × C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.4 C(20), 16.1 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3458, 2979, 1692, 1610, 1507, 1452, 1267, 1240, 1122, 912;

HRMS (ESI⁺) C₂₆H₃₅NNaO₃⁺ ([M+Na]⁺) requires 432.2509; found 432.2503, Δ 1.35 ppm.

251i 3-Bromo-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine

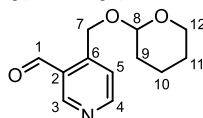
3-Bromopyridine-4-methanol (3.76 g, 20.0 mmol) was dissolved in CH_2Cl_2 (70 mL). 3,4-dihydro-2H-pyran (2.73 mL, 30.0 mmol) and pyridinium *p*-toluenesulfonate (503 mg, 2.00 mmol) were added, the reaction was heated to 40 °C and stirred for 16 h. The mixture was cooled to RT and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 92:8 → 88:12) gave the *title compound* as a colourless (2.08 g, 38%).

¹H NMR (400 MHz, CDCl_3) δ 8.64 (s, 1H, C(2)*H*), 8.51 (d, *J* = 5.0 Hz, 1H, C(3)*H*), 7.51 (d, *J* = 4.8 Hz, 1H, C(4)*H*), 4.86 – 4.71 (m, 2H, C(6)*H_AH_B*, C(7)*H*), 4.55 (dd, *J* = 15.3, 0.9 Hz, 1H, C(6)*H_AH_B*), 3.94 – 3.82 (m, 1H, C(11)*H_AH_B*), 3.69 – 3.47 (m, 1H, C(11)*H_AH_B*), 1.99 – 1.86 (m, 1H, C(9)*H_AH_B*), 1.86 – 1.70 (m, 2H, C(8)*H₂*), 1.70 – 1.43 (m, 3H, C(9)*H_AH_B*, C(10)*H₂*);

¹³C NMR (101 MHz, CDCl_3) δ 151.3 C(2), 148.4 C(3), 147.5 C(5), 122.8 C(4), 120.2 C(1), 98.8 C(7), 67.3 C(6), 62.4 C(11), 30.5 C(8), 25.5 C(10), 19.4 C(9);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2943, 1587, 1398, 1349, 1202, 1130, 1075, 1038, 972, 908;

HRMS (ESI⁺) $\text{C}_{11}\text{H}_{14}^{79}\text{BrNNaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 294.0100; found 294.0094, Δ 2.20 ppm.

252h 4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)nicotinaldehyde

Pyridyl bromide **251h** (1.63 g, 6.00 mmol) was subjected to **General Procedure K** using *n*-BuLi (2.5 M in hexane, 2.64 mL, 6.60 mmol) and *N,N*-dimethylformamide (0.93 mL, 12.0 mmol) in THF (20 mL). Purification *via* flash column chromatography (eluent pentane/EtOAc, 85:15 → 80:20) gave the *title compound* as a yellow oil (501 mg, 38%).

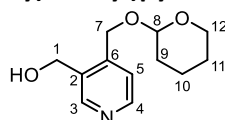
¹H NMR (400 MHz, CDCl_3) δ 10.22 (s, 1H, C(1)*H*), 8.99 (s, 1H, C(3)*H*), 8.79 (d, *J* = 5.2 Hz, 1H, C(4)*H*), 7.76 (d, *J* = 4.9 Hz, 1H, C(5)*H*), 5.22 (dd, *J* = 16.9, 1.1 Hz, 1H, C(7)*H_AH_B*), 4.99 (dd, *J* = 17.1, 1.0 Hz, 1H, C(7)*H_AH_B*), 4.81 – 4.77 (m, 1H, C(8)*H*), 3.97 – 3.72 (m, 1H, C(12)*H_AH_B*), 3.69 – 3.38 (m, 1H, C(12)*H_AH_B*), 1.98 – 1.67 (m, 3H, C(9)*H₂*, C(10)*H_AH_B*), 1.67 – 1.51 (m, 3H, C(10)*H_AH_B*, C(11)*H₂*);

¹³C NMR (101 MHz, CDCl₃) δ 192.0 C(1), 154.6 C(3), 154.4 C(4), 150.6 C(6), 128.3 C(2), 121.8 C(5), 99.0 C(8), 65.7 C(7), 62.7 C(12), 30.7 C(9), 25.5 C(11), 19.6 C(10);

IR (film) $\nu_{\max}$ /cm⁻¹ 2949, 1701, 1594, 1557, 1418, 1347, 1202, 1125, 1069, 1037, 976, 869;

HRMS (ESI⁺) C₁₂H₁₅NNaO₃⁺ ([M+Na]⁺) requires 244.0944; found 244.0942, Δ 0.74 ppm.

236i (4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-3-yl)methanol



Aldehyde **252i** (495 mg, 2.24 mmol) was subjected to **General Procedure L** with NaBH₄ (127 mg, 3.36 mmol) in MeOH (11 mL). Purification *via* flash column chromatography (eluent pentane/EtOAc/EtOH, 10:90:0 → 0:99:1) gave the *title compound* as a colourless oil (398 mg, 79%).

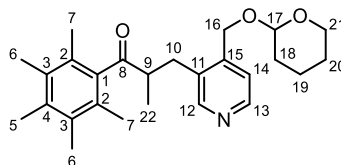
¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 1H, C(3)H), 8.55 (d, *J* = 5.0 Hz, 1H, C(4)H), 7.38 (d, *J* = 5.0 Hz, 1H, C(5)H), 4.93 (d, *J* = 13.1 Hz, 1H, C(7)H_AH_B), 4.81 – 4.68 (m, 3H, C(1)H₂, C(8)H), 4.63 (d, *J* = 13.1 Hz, 1H, C(7)H_AH_B), 3.93 – 3.78 (m, 1H, C(12)H_AH_B), 3.64 – 3.48 (m, 1H, C(12)H_AH_B), 2.34 (br. s, 1H, OH), 1.93 – 1.71 (m, 2H, C(9)H_AH_B, C(10)H_AH_B), 1.71 – 1.29 (m, 4H, C(9)H_AH_B, C(10)H_AH_B, C(11)H₂);

¹³C NMR (101 MHz, CDCl₃) δ 149.7 C(4), 149.5 C(3), 145.9 C(6), 134.5 C(2), 123.3 C(5), 98.8 C(8), 66.3 C(7), 62.7 C(12), 61.1 C(1), 30.6 C(9), 25.3 C(11), 19.5 C(10);

IR (film) $\nu_{\max}$ /cm⁻¹ 3248, 2947, 1604, 1417, 1352, 1202, 1123, 1070, 1035, 975, 906;

HRMS (ESI⁺) C₁₂H₁₇NNaO₃⁺ ([M+Na]⁺) requires 246.1101; found 246.1098, Δ 1.02 ppm.

237i 2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-3-yl)propan-1-one



Ph* ethyl ketone **98** (241 mg, 1.18 mmol), alcohol **236i** (396 mg, 1.77 mmol), [IrCp*Cl₂]₂ (9.4 mg, 1.0 mol%), KOH (265 mg, 4.72 mmol) and PhMe (0.3 mL) were subjected to **General Procedure H**

at 110 °C for 24 h. Purification *via* flash column chromatography (eluent pentane/EtOAc, 80:20 → 70:30) gave the *title compound* as a yellow oil (416 mg, 86%, [49:51] d.r.)

The spectroscopic data were collected on the diastereomeric mixture and the relative stereochemistry is unassigned.

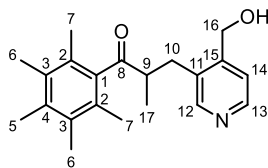
¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, *J* = 5.0 Hz, 2H, C(13')H, C(13'')H), 8.41 (s, 2H, C(12')H, C(12'')H), 7.44 – 7.35 (m, 1H, C(14')H, C(14'')H), 4.78 (dd, *J* = 13.6, 9.4 Hz, 2H, C(16')H_AH_B, C(16'')H_AH_B), 4.66 (t, *J* = 3.5 Hz, 1H, C(17')H), 4.60 (t, *J* = 3.5 Hz, 1H, C(17'')H), 4.50 (dd, *J* = 15.0, 13.6 Hz, 2H, C(16')H_AH_B, C(16'')H_AH_B), 3.91 – 3.77 (m, 2H, C(21')H_AH_B, C(21'')H_AH_B), 3.57 – 3.48 (m, 2H, C(21')H_AH_B, C(21'')H_AH_B), 3.26 (dd, *J* = 14.1, 4.8 Hz, 2H, C(10')H_AH_B, C(10'')H_AH_B), 3.14 – 3.00 (m, 2H, C(9')H, C(9'')H), 2.64 (ddd, *J* = 14.1, 9.5, 1.7 Hz, 2H, C(10')H_AH_B, C(10'')H_AH_B), 2.23 (s, 6H, 2 × C(Ph*)H₃), 2.17 (s, 12H, 4 × C(Ph*)H₃), 2.10 (s, 12H, 4 × C(Ph*)H₃), 1.93 – 1.80 (m, 2H, C(19')H_AH_B, C(19'')H_AH_B), 1.80 – 1.48 (m, 10H, C(18')H₂, C(18'')H₂, C(19')H_AH_B, C(19'')H_AH_B, C(20')H₂, C(20'')H₂), 1.15 – 1.02 (m, 6H, C(22')H₃, C(22'')H₃);

¹³C NMR (101 MHz, CDCl₃) δ 213.4 C(8'), 213.3 C(8''), 151.1 C(12'), 151.0 C(12''), 148.0 C(13'), 148.0 C(13''), 146.1 C(15'), 145.9 C(15''), 139.3 C(Ar(Ph*)), 139.3 C(Ar(Ph*)), 135.9 2 × C(Ar(Ph*)), 133.3 4 × C(Ar(Ph*)), 133.0 C(11'), 132.9 C(11''), 128.3 br. 4 × C(Ar(Ph*)), 122.5 C(14'), 122.3 C(14''), 98.5 C(17'), 98.4 C(17''), 65.0 C(16'), 65.0 C(16''), 62.4 C(21'), 62.3 C(21''), 49.4 C(9'), 49.3 C(9''), 31.6 C(10'), 31.5 C(10''), 30.6 C(18'), 30.6 C(18''), 25.5 C(20') & C(20''), 19.4 C(19'), 19.4 C(19''), 18.0 4 × C(Me(Ph*)), 16.9 2 × C(Me(Ph*)), 16.2 4 × C(Me(Ph*)), 15.8 C(22'), 15.5 C(22'');

IR (film) ν_{max} /cm⁻¹ 2941, 1696, 1595, 1456, 1120, 1071, 1035, 976, 925, 907, 762;

HRMS (ESI⁺) C₂₆H₃₆NO₃⁺ ([M+H]⁺) requires 410.2690; found 410.2691, Δ 0.21 ppm.

* N.B. The labels ' and '' are assigned arbitrarily and indicate peaks belonging to different diastereomers.

223i 3-(4-(Hydroxymethyl)pyridin-3-yl)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one

THP-protected alcohol **237i** (397 mg, 0.971 mmol) was dissolved in a mixture of THF (9 mL):water (1 mL) and *p*-toluenesulfonic acid monohydrate (203 mg, 1.07 mmol) was added. The mixture was stirred at RT for 16 h, then heated at 60 °C for 2 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (5 mL) and the mixture was diluted with EtOAc (50 mL) and water (50 mL), the layers separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 50:50 → 30:70) gave the *title compound* as a white solid (259 mg, 82%).

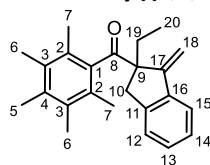
m.p. = 135 – 136 °C;

¹H NMR (600 MHz, CDCl₃) δ 8.45 (d, *J* = 5.0 Hz, 1H, C(13)*H*), 8.41 (s, 1H, C(12)*H*), 7.43 (d, *J* = 5.0 Hz, 1H, C(14)*H*), 4.83 (d, *J* = 13.9 Hz, 1H, C(16)*H_AH_B*), 4.72 (d, *J* = 14.0 Hz, 1H, C(16)*H_AH_B*), 3.28 (dd, *J* = 14.2, 5.8 Hz, 1H, C(10)*H_AH_B*), 3.17 – 3.05 (m, 1H, C(9)*H*), 2.64 (dd, *J* = 14.2, 8.4 Hz, 1H, C(10)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.16 (s, 6H, 2 × C(Ph*)*H*₃), 2.00 (br. s, 6H, 2 × C(Ph*)*H*₃), 1.11 (d, *J* = 7.2 Hz, 3H, C(17)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 213.8 C(8), 150.8 C(12), 148.4 C(15), 147.9 C(13), 139.0 C(Ar(Ph*)), 136.0 C(Ar(Ph*)), 133.4 2 × C(Ar(Ph*)), 132.8 C(11), 128.3 2 × C(Ar(Ph*)), 122.1 C(14), 61.5 C(16), 49.7 C(9), 31.4 C(10), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 C(17), 16.2 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3399, 2986, 2906, 1693, 1600, 1456, 1383, 1218, 1072, 927;

HRMS (ESI⁺) C₂₁H₂₇NO₂Na⁺ ([M+Na]⁺) requires 348.1934; found 348.1929, Δ 1.44 ppm.

224b (2-Ethyl-1-methylene-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Alcohol **223b** (101 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (0.6 mL) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8 → 99:1) gave the *title compound* as a white solid (76 mg, 76%).

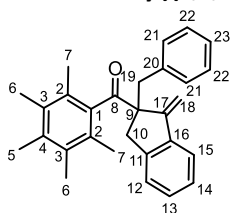
m.p. = 110 – 111 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.37 (m, 1H, C(15)*H*), 7.23 – 7.14 (m, 2H, C(13)*H*, C(14)*H*), 7.14 – 7.01 (m, 1H, C(12)*H*), 5.75 (s, 1H, C(18)*H_AH_B*), 5.27 (s, 1H, C(18)*H_AH_B*), 3.42 (d, *J* = 17.4 Hz, 1H, C(10)*H_AH_B*), 2.98 (d, *J* = 17.4 Hz, 1H, C(10)*H_AH_B*), 2.31 (dq, *J* = 13.4, 7.4 Hz, 1H, C(19)*H_AH_B*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.04 (s, 3H, C(Ph*)*H₃*), 2.02 (s, 3H, C(Ph*)*H₃*), 1.96 (dq, *J* = 13.4, 7.4 Hz, 1H, C(19)*H_AH_B*), 1.85 (s, 3H, C(Ph*)*H₃*), 0.76 (t, *J* = 7.4 Hz, 3H, C(20)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 215.8 C(8), 151.1 C(17), 144.0 C(11), 140.6 C(16), 139.9 C(Ar(Ph*)), 135.0 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.6 C(Ar(Ph*)), 128.8 C(13), 128.3 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 126.8 C(14), 124.9 C(12), 120.6 C(15), 106.5 C(18), 63.8 C(9), 39.1 C(10), 33.8 C(19), 18.6 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*)), 8.6 C(20);

IR (film) ν_{max} /cm⁻¹ 2938, 1687, 1635, 1476, 1462, 1302, 1260, 900, 779, 761, 730;

HRMS (ESI⁺) C₂₄H₂₉O⁺ ([M+H]⁺) requires 333.2213; found 333.2212, Δ 0.31 ppm.

224c (2-Benzyl-1-methylene-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223b** (120 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (1.2 mL, degassed with

Ar) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8 → 99:1) gave the *title compound* as a white solid (54 mg, 46%).

m.p. = 104 – 106 °C;

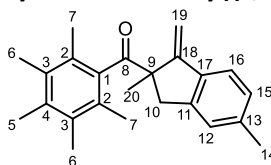
¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.33 (m, 1H, C(15)*H*), 7.24 – 7.19 (m, 2H, 2 × C(21)*H*), 7.14 – 6.99 (m, 5H, C(13)*H*, C(14)*H*, 2 × C(22)*H*, C(23)*H*), 6.92 – 6.82 (m, 1H, C(12)*H*), 5.86 (s, 1H, C(18)*H_AH_B*), 5.55 (s, 1H, C(18)*H_AH_B*), 3.43 (dd, *J* = 13.4, 1.7 Hz, 2H, C(19)*H₂*), 3.28 (d, *J* = 17.1 Hz, 1H, C(10)*H_AH_B*), 3.20 (d, *J* = 17.1 Hz, 1H, C(10)*H_AH_B*), 2.16 (s, 3H, C(Ph*)*H₃*), 2.13 (s, 3H, C(Ph*)*H₃*), 2.01 (s, 3H, C(Ph*)*H₃*), 1.89 (s, 3H, C(Ph*)*H₃*), 1.86 (s, 3H, C(Ph*)*H₃*);

¹³C NMR (101 MHz, CDCl₃) δ 214.1 C(8), 152.0 C(17), 143.8 C(11), 139.8 C(16), 139.4 C(Ar(Ph*)), 137.5 C(20), 135.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 132.5 C(Ar(Ph*)), 131.2 2 × C(21), 128.7 C(13), 128.3 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 127.8 2 × C(22), 126.6 C(14), 126.5 C(23), 124.7 C(12), 120.7 C(15), 107.3 C(18), 64.5 C(9), 46.1 C(19), 38.3 C(10), 18.4 C(Me(Ph*)), 18.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 3026, 2924, 1686, 1633, 1475, 1454, 1302, 1259, 1219, 1135, 903;

HRMS (ESI⁺) C₂₉H₃₀NaO⁺ ([M+Na]⁺) requires 417.2189; found 417.2181, Δ 1.87 ppm.

224e (2,5-Dimethyl-1-methylene-2,3-dihydro-1*H*-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **223e** (102 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (0.6 mL) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8) gave the *title compound* as a white solid (69 mg, 69%).

m.p. = 145 – 147 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, *J* = 7.8 Hz, 1H, C(16)*H*), 7.01 (d, *J* = 7.9 Hz, 1H, C(15)*H*), 6.92 (s, 1H, C(12)*H*), 5.59 (s, 1H, C(19)*H_AH_B*), 5.25 (s, 1H, C(19)*H_AH_B*), 3.47 (d, *J* = 16.9 Hz, 1H, C(10)*H_AH_B*), 2.83 (d, *J* = 16.9 Hz, 1H, C(10)*H_AH_B*), 2.31 (s, 3H, C(14)*H₃*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.17

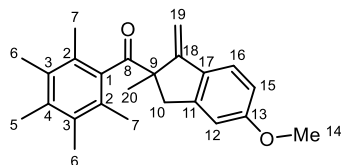
(s, 3H, C(Ph*)H₃), 2.06 (s, 3H, C(Ph*)H₃), 2.04 (s, 3H, C(Ph*)H₃), 1.87 (s, 3H, C(Ph*)H₃), 1.63 (s, 3H, C(20)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 215.8 C(8), 153.7 C(18), 143.5 C(11), 139.8 C(Ar(Ph*)), 138.9 C(13), 136.9 C(17), 135.0 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.6 C(Ar(Ph*)), 128.1 C(Ar(Ph*)), 128.0 C(15), 127.7 C(Ar(Ph*)), 125.7 C(12), 120.9 C(16), 105.2 C(19), 59.8 C(9), 42.8 C(10), 29.1 C(20), 21.6 C(14), 18.7 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max}/cm⁻¹ 3021, 1684, 1633, 1609, 1439, 1365, 1301, 1263, 1145, 913, 885, 815;

HRMS (ESI⁺) C₂₄H₂₈ONa⁺ ([M+Na]⁺) requires 355.2032; found 355.2023, Δ 0.15 ppm.

224g (5-Methoxy-2-methyl-1-methylene-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **223g** (53 mg, 0.15 mmol), methyl phenyl sulfone (47 mg, 0.30 mmol), Ru-MACHO® (1.8 mg, 1.0 mol%), KO^tBu (34 mg, 0.30 mmol) and ^tBuOH (0.3 mL) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 98.8:1.2 → 98.4:1.6) gave the *title compound* as a white solid (43 mg, 82%).

m.p. = 158 – 160 °C;

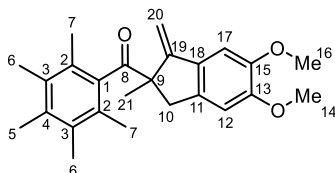
¹H NMR (400 MHz, C₆D₆) δ 7.24 (d, *J* = 8.5 Hz, 1H, C(16)H), 6.72 (dd, *J* = 8.5, 2.4 Hz, 1H, C(15)H), 6.43 – 6.35 (m, 1H, C(12)H), 5.55 (s, 1H, C(19)H_AH_B), 5.53 (s, 1H, C(19)H_AH_B), 3.61 (d, *J* = 17.0 Hz, 1H, C(10)H_AH_B), 3.20 (s, 3H, C(14)H₃), 2.69 (d, *J* = 17.0 Hz, 1H, C(10)H_AH_B), 2.03 (s, 3H, C(Ph*)H₃), 1.99 (s, 3H, C(Ph*)H₃), 1.96 (s, 3H, C(Ph*)H₃), 1.94 (s, 3H, C(Ph*)H₃), 1.78 (s, 3H, C(Ph*)H₃), 1.73 (s, 3H, C(20)H₃);

¹³C NMR (101 MHz, C₆D₆) δ 214.3 C(8), 161.3 C(13), 154.1 C(18), 145.4 C(11), 140.6 C(Ar(Ph*)), 134.7 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 132.8 C(17), 132.5 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 122.4 C(16), 114.7 C(15), 109.4 C(12), 103.7 C(19), 60.1 C(9), 54.8 C(14), 43.1 C(10), 29.3 C(20), 18.7 C(Me(Ph*)), 18.5 C(Me(Ph*)), 16.6 C(Me(Ph*)), 16.0 2 × C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3052, 1730, 1682, 1604, 1493, 1304, 1258, 1150, 908, 883, 838;

HRMS (ESI⁺) $\text{C}_{24}\text{H}_{28}\text{NaO}_2^+$ ([M+Na]⁺) requires 371.1982; found 371.1974, Δ 1.90 ppm.

224d (5,6-Dimethoxy-2-methyl-1-methylene-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone



Hydroxy ketone **223d** (58 mg, 0.15 mmol), methyl phenyl sulfone (47 mg, 0.30 mmol), Ru-MACHO[®] (1.8 mg, 1.0 mol%), KO^tBu (34 mg, 0.30 mmol) and ^tBuOH (0.3 mL) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 92:8 → 90:10) gave the *title compound* as a white solid (52 mg, 92%).

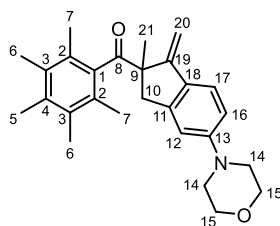
m.p. = 160 – 162 °C;

¹H NMR (400 MHz, CDCl₃) δ 6.91 (s, 1H, C(17)*H*), 6.60 (s, 1H, C(12)*H*), 5.45 (s, 1H, C(20)*H_AH_B*), 5.20 (s, 1H, C(20)*H_AH_B*), 3.90 (s, 3H, C(16)*H₃*), 3.83 (s, 3H, C(14)*H₃*), 3.44 (d, *J* = 16.6 Hz, 1H, C(10)*H_AH_B*), 2.82 (d, *J* = 16.6 Hz, 1H, C(10)*H_AH_B*), 2.20 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.06 (s, 3H, C(Ph*)*H₃*), 2.05 (s, 3H, C(Ph*)*H₃*), 1.87 (s, 3H, C(Ph*)*H₃*), 1.64 (s, 3H, C(21)*H₃*);

¹³C NMR (101 MHz, CDCl₃) δ 215.8 C(8), 154.1 C(19), 150.7 C(13), 149.0 C(15), 139.9 C(Ar(Ph*)), 135.9 C(11), 135.0 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.6 C(Ar(Ph*)), 131.8 C(18), 128.1 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 107.3 C(12), 103.5 C(20), 103.2 C(17), 60.1 C(9), 56.1 C(16), 56.1 C(14), 42.8 C(10), 29.1 C(21), 18.7 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2998, 1685, 1604, 1503, 1466, 1315, 1271, 1219, 1070, 987, 905;

HRMS (ESI⁺) $\text{C}_{25}\text{H}_{30}\text{NaO}_3^+$ ([M+Na]⁺) requires 401.2087; found 401.2082, Δ 1.24 ppm.

224h (2-Methyl-1-methylene-5-morpholino-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223h** (123 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (0.6 mL) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 90:10 → 88:12) gave the *title compound* as an off-white solid (51 mg, 42%).

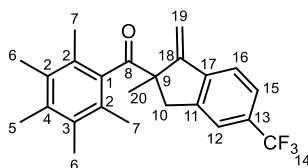
m.p. = 155 – 157 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.36 (d, *J* = 8.5 Hz, 1H, C(17)*H*), 6.79 (d, *J* = 8.5 Hz, 1H, C(16)*H*), 6.62 (s, 1H, C(12)*H*), 5.48 (s, 1H, C(20)*H_AH_B*), 5.16 (s, 1H, C(20)*H_AH_B*), 3.92 – 3.75 (m, 4H, 2 × C(15)*H₂*), 3.46 (d, *J* = 16.8 Hz, 1H, C(10)*H_AH_B*), 3.18 – 3.07 (m, 4H, 2 × C(14)*H₂*), 2.83 (d, *J* = 16.8 Hz, 1H, C(10)*H_AH_B*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.17 (s, 3H, C(Ph*)*H₃*), 2.06 (s, 3H, C(Ph*)*H₃*), 2.04 (s, 3H, C(Ph*)*H₃*), 1.88 (s, 3H, C(Ph*)*H₃*), 1.63 (s, 3H, C(21)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 215.7 C(8), 153.4 C(19), 152.3 C(13), 144.8 C(11), 139.8 C(Ar(Ph*)), 135.0 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.6 C(Ar(Ph*)), 131.8 C(18), 128.1 C(Ar(Ph*)), 127.7 C(Ar(Ph*)), 121.9 C(17), 115.1 C(16), 111.2 C(12), 103.5 C(20), 67.0 2 × C(15), 60.0 C(9), 49.5 2 × C(14), 43.1 C(10), 29.1 C(21), 18.7 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2852, 1689, 1608, 1499, 1450, 1243, 1123, 1041, 964, 883;

HRMS (ESI⁺) C₂₇H₃₃NNaO₂⁺ ([M+Na]⁺) requires 426.2404; found 426.2399, Δ 1.14 ppm.

224f (2-Methyl-1-methylene-5-(trifluoromethyl)-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223f** (118 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (0.6 mL) were subjected to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.3:0.7) gave the *title compound* as a white solid (50 mg, 43%).

m.p. = 126 – 128 °C;

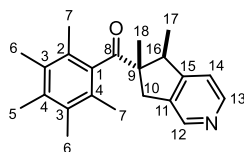
¹H NMR (600 MHz, CDCl₃) δ 7.54 (d, *J* = 8.1 Hz, 1H, C(16)*H*), 7.45 (d, *J* = 8.1 Hz, 1H, C(15)*H*), 7.36 (s, 1H, C(12)*H*), 5.78 (s, 1H, C(19)*H_AH_B*), 5.45 (s, 1H, C(19)*H_AH_B*), 3.54 (d, *J* = 17.1 Hz, 1H, C(10)*H_AH_B*), 2.92 (d, *J* = 17.1 Hz, 1H, C(10)*H_AH_B*), 2.20 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 2.05 (s, 3H, C(Ph*)*H*₃), 2.04 (s, 3H, C(Ph*)*H*₃), 1.83 (s, 3H, C(Ph*)*H*₃), 1.66 (s, 3H, C(20)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.9 C(8), 152.6 C(18), 143.7 C(11), 142.9 C(17), 139.2 C(Ar(Ph*)), 135.4 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 132.9 C(Ar(Ph*)), 130.8 (q, *J*²_{C-F} = 32.0 Hz, C(13)), 128.0 C(Ar(Ph*)), 127.5 C(Ar(Ph*)), 124.4 (q, *J*¹_{C-F} = 271.9 Hz, C(14)), 124.1 (q, *J*³_{C-F} = 3.8 Hz, C(15)), 122.2 (q, *J*³_{C-F} = 4.0 Hz, C(12)), 121.3 C(16), 109.0 C(19), 59.9 C(9), 42.6 C(10), 28.8 C(20), 18.8 C(Me(Ph*)), 18.4 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

¹⁹F NMR (471 MHz, CDCl₃) δ –62.2;

IR (film) *ν*_{max}/cm⁻¹ 2935, 1691, 1433, 1335, 1322, 1167, 1127, 1079, 990, 914, 842;

HRMS (ESI⁺) C₂₄H₂₅F₃NaO⁺ ([M+Na]⁺) requires 409.1750; found 409.1747, Δ 0.56 ppm.

224i (5,6-Dimethyl-6,7-dihydro-5H-cyclopenta[*c*]pyridin-6-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223i** (98 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), Ru-MACHO® (3.6 mg, 1.0 mol%), KO^tBu (68 mg, 0.60 mmol) and ^tBuOH (0.6 mL) were subjected

to **General Procedure J**. Purification *via* flash column chromatography (eluent pentane/EtOAc, 85:15 → 82:18) gave the *title compound* as a colourless oil (27 mg, 28%, [92:8] d.r.)

The relative stereochemistry for the major diastereomer (drawn) was tentatively assigned by analogy with the carbocyclic analogue **262**.

Major (5SR, 6SR) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 8.54 – 8.30 (m, 2H, C(12)*H*, C(13)*H*), 7.10 (d, *J* = 4.9 Hz, 1H, C(14)*H*), 3.64 (q, *J* = 7.0 Hz, 1H, C(16)*H*), 3.39 (d, *J* = 15.5 Hz, 1H, C(10)*H_AH_B*), 2.88 (d, *J* = 15.5 Hz, 1H, C(10)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H*₃), 2.21 (s, 3H, C(Ph*)*H*₃), 2.19 (s, 3H, C(Ph*)*H*₃), 2.14 (s, 3H, C(Ph*)*H*₃), 2.13 (s, 3H, C(Ph*)*H*₃), 1.34 (d, *J* = 7.1 Hz, 3H, C(17)*H*₃), 1.18 (s, 3H, C(18)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 216.4 C(8), 155.1 C(15), 148.1 C(13), 145.4 C(12), 138.9 C(Ar(Ph*)), 137.1 C(11), 135.5 C(Ar(Ph*)), 133.6 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 128.2 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 119.1 C(14), 61.8 C(9), 45.1 C(16), 42.4 C(10), 19.2 C(Me(Ph*)), 18.7 C(Me(Ph*)), 18.3 C(18), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*)), 12.1 C(17);

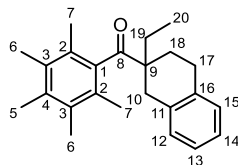
Selected characteristic peaks for the minor (5RS, 6SR) diastereomer (from the mixture):

¹H NMR (600 MHz, CDCl₃) δ 7.16 (d, *J* = 4.9 Hz, 1H, C(14)*H*), 3.18 (q, *J* = 7.3 Hz, 1H, C(16)*H*), 2.82 (d, *J* = 15.6 Hz, 3H, C(10)*H_AH_B*), 2.15 (s, 3H, C(Ph*)*H*₃), 2.14 (s, 3H, C(Ph*)*H*₃), 1.99 (s, 3H, C(Ph*)*H*₃), 1.38 (d, *J* = 7.2 Hz, 3H, C(17)*H*₃), 1.15 (s, 3H, C(18)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 216.6 C(8), 157.2 C(15), 148.1 C(13), 146.1 C(12), 140.5 C(Ar(Ph*)), 136.5 C(11), 135.3 C(Ar(Ph*)), 133.4 C(Ar(Ph*)), 132.9 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 127.1 C(Ar(Ph*)), 119.6 C(14), 58.5 C(9), 52.2 C(16), 42.8 C(10), 25.5 C(18), 18.3 C(17), 17.9 C(Me(Ph*)), 17.8 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.0 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2998, 1683, 1601, 1486, 1419, 1384, 1305, 1178, 1084, 834, 758;

HRMS (ESI⁺) C₂₂H₂₈NO⁺ ([M+H]⁺) requires 322.2165; found 322.2158, Δ 2.44 ppm.

225b (2-Ethyl-1,2,3,4-tetrahydronaphthalen-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223b** (101 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (4.8 mg, 2.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and PhMe (0.6 mL, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et_2O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99.2:0.8) and subsequent recrystallisation (vapour diffusion over three days using CHCl_3 as the solvent and MeOH as the precipitant) gave the *title compound* as a white solid (21 mg, 21%).

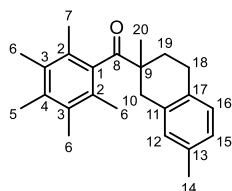
m.p. = 93 – 95 °C;

^1H NMR (500 MHz, CDCl_3) δ 7.14 – 7.04 (m, 3H, C(13)*H*, C(14)*H*, C(15)*H*), 7.04 – 6.99 (m, 1H, C(12)*H*), 3.07 (d, J = 16.2 Hz, 1H, C(10)*H_AH_B*), 2.84 – 2.77 (m, 2H, C(17)*H₂*), 2.74 (dd, J = 16.3, 2.3 Hz, 1H, C(10)*H_AH_B*), 2.24 (s, 3H, C(Ph*)*H₃*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.12 (s, 3H, C(Ph*)*H₃*), 2.09 (s, 4H, C(18)*H_AH_B*, C(Ph*)*H₃*), 2.00 – 1.89 (m, 1H, C(18)*H_AH_B*), 1.79 – 1.60 (m, 2H, C(19)*H₂*), 0.96 (t, J = 7.4 Hz, 3H, C(20)*H₃*);

^{13}C NMR (126 MHz, CDCl_3) δ 217.7 C(8), 139.5 C(Ar(Ph*)), 135.4 C(16), 135.1 C(11), 135.0 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 129.7 C(12), 128.6 C(15), 128.1 $2 \times$ C(Ar(Ph*)), 125.9 C(14), 125.9 C(13), 51.2 C(9), 36.9 C(10), 28.6 C(18), 25.9 C(17), 25.5 C(19), 19.1 C(Me(Ph*)), 19.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.2 C(Me(Ph*)), 8.9 C(20);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2934, 1682, 1495, 1452, 1383, 1302, 1258, 1158, 1083, 999, 888;

HRMS (ESI⁺) $\text{C}_{24}\text{H}_{30}\text{NaO}^+$ ($[\text{M}+\text{Na}]^+$) requires 357.2189; found 357.2180, Δ 2.36 ppm.

225e (2,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Alcohol **223e** (102 mg, 0.300 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), [IrCp*Cl₂]₂ (2.4 mg, 1.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and PhMe (0.6 mL) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8 → 99:1) gave the *title compound* as a white solid (67 mg, 67%).

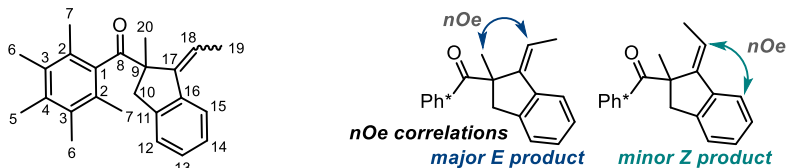
m.p. = 127 – 129 °C;

¹H NMR (600 MHz, CDCl₃) δ 6.98 (d, *J* = 7.7 Hz, 1H, C(16)*H*), 6.93 (dd, *J* = 7.8, 1.9 Hz, 1H, C(15)*H*), 6.87 (s, 1H, C(12)*H*), 3.16 (d, *J* = 16.2 Hz, 1H, C(10)*H_AH_B*), 2.80 (dd, *J* = 9.3, 4.2 Hz, 2H, C(18)*H₂*), 2.69 (dd, *J* = 16.3, 2.3 Hz, 1H, C(10)*H_AH_B*), 2.27 (s, 3H, C(14)*H₃*), 2.24 (s, 3H, C(Ph*)*H₃*), 2.19 (s, 3H, C(Ph*)*H₃*), 2.18 (s, 3H, C(Ph*)*H₃*), 2.13 (s, 3H, C(Ph*)*H₃*), 2.12 (s, 3H, C(Ph*)*H₃*), 2.06 – 1.97 (m, 1H, C(19)*H_AH_B*), 1.92 – 1.80 (m, 1H, C(19)*H_AH_B*), 1.19 (s, 3H, C(20)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 219.9 C(8), 139.9 C(Ar(Ph*)), 135.4 C(13), 135.0 C(Ar(Ph*)), 134.8 C(11), 133.2 C(Ar(Ph*)), 133.2 C(Ar(Ph*)), 131.9 C(17), 130.4 C(12), 128.7 C(16), 127.6 2 × C(Ar(Ph*)), 126.8 C(15), 47.9 C(9), 39.0 C(10), 31.6 C(19), 25.4 C(18), 21.1 C(14), 20.8 C(20), 19.2 C(Me(Ph*)), 19.1 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 2 × C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2980, 2931, 1684, 1506, 1455, 1384, 1301, 1113, 1076, 987, 911, 806;

HRMS (ESI⁺) C₂₄H₃₀NaO⁺ ([M+Na]⁺) requires 357.2189; found 357.2188, Δ 0.31 ppm.

254 (1-Ethylidene-2-methyl-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223a** (97 mg, 0.30 mmol), ethyl phenyl sulfone (102 mg, 0.600 mmol), [IrCp*Cl₂]₂ (2.4 mg, 1.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and PhMe (0.6 mL, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8) gave the *title compound* as a separable mixture of *E* and *Z* alkenes as white solids (25 mg, 25%, 89:11 [*E*:*Z*]*).

* Due to overlapping signals in the crude NMR spectrum, the *E*:*Z* ratio was determined post-purification.

Data for major E isomer:

m.p. = 99 – 101 °C;

¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 7.6 Hz, 1H, C(15)*H*), 7.23 – 7.17 (m, 1H, C(14)*H*), 7.17 – 7.06 (m, 2H, C(12)*H*, C(13)*H*), 5.87 (q, *J* = 7.4 Hz, 1H, C(18)*H*), 3.52 (d, *J* = 16.6 Hz, 1H, C(10)*H_AH_B*), 2.87 (d, *J* = 16.6 Hz, 1H, C(10)*H_AH_B*), 2.19 (s, 3H, C(Ph*)*H*₃), 2.16 (s, 3H, C(Ph*)*H*₃), 2.07 – 2.02 (m, 6H, C(19)*H*₃, C(Ph*)*H*₃), 2.00 (s, 3H, C(Ph*)*H*₃), 1.84 (s, 3H, C(Ph*)*H*₃), 1.60 (s, 3H, C(20)*H*₃);

¹³C NMR (101 MHz, CDCl₃) δ 215.6 C(8), 144.6 C(17), 144.2 C(11), 140.0 C(16), 139.3 C(Ar(Ph*)), 134.8 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 132.5 C(Ar(Ph*)), 128.3 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 127.6 C(13), 126.5 C(14), 125.0 C(15), 124.9 C(12), 121.4 C(18), 60.3 C(9), 42.6 C(10), 27.7 C(20), 18.8 C(Me(Ph*)), 18.4 C(Me(Ph*)), 16.7 C(Me(Ph*)), 16.1 C(Me(Ph*)), 16.1 C(Me(Ph*)), 15.0 C(19);

IR (film) ν_{max} /cm⁻¹ 2929, 1689, 1474, 1460, 1384, 1303, 1258, 1219, 989, 934, 902, 861, 838, 816;

HRMS (ESI⁺) C₂₄H₂₈NaO⁺ ([M+Na]⁺) requires 355.2032; found 355.2029, Δ 0.84 ppm.

Data for minor Z isomer:

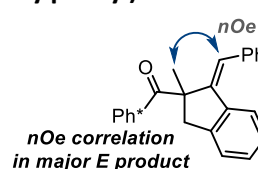
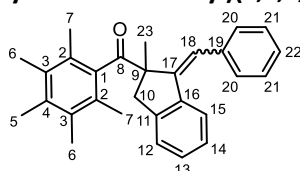
m.p. = 69 – 71 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.34 – 7.30 (m, 1H, C(15)H), 7.14 – 7.10 (m, 1H, C(14)H), 7.10 – 7.04 (m, 1H, C(13)H), 7.03 – 6.96 (m, 1H, C(12)H), 6.26 (q, *J* = 7.6 Hz, 1H, C(18)H), 3.59 (d, *J* = 16.8 Hz, 1H, C(10)H_AH_B), 2.89 (d, *J* = 16.8 Hz, 1H, C(10)H_AH_B), 2.17 (s, 3H, C(Ph*)H₃), 2.15 (s, 3H, C(Ph*)H₃), 2.01 (s, 3H, C(Ph*)H₃), 1.99 (s, 3H, C(Ph*)H₃), 1.92 (d, *J* = 7.6 Hz, 3H, C(19)H₃), 1.84 (s, 3H, C(Ph*)H₃), 1.77 (s, 3H, C(20)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 214.6 C(8), 144.2 C(17), 142.0 C(16), 141.9 C(11), 139.6 C(Ar(Ph*)), 134.9 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.5 C(Ar(Ph*)), 128.4 C(Ar(Ph*)), 127.8 C(Ar(Ph*)), 127.6 C(13), 126.7 C(14), 124.7 C(12), 120.2 C(18), 119.8 C(15), 60.6 C(9), 44.5 C(10), 25.9 C(20), 19.0 C(Me(Ph*)), 18.3 C(Me(Ph*)), 16.7 C(Me(Ph*)), 16.1 C(Me(Ph*)), 16.1 C(Me(Ph*)), 13.9 C(19);

IR (film) ν_{max} /cm⁻¹ 2927, 1689, 1650, 1461, 1383, 1302, 1260, 1074, 990, 838, 760, 738, 699;

HRMS (ESI⁺) C₂₄H₂₈NaO⁺ ([M+Na]⁺) requires 355.2032; found 355.2029, Δ 1.01 ppm.

255 (1-Benzylidene-2-methyl-2,3-dihydro-1H-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Hydroxy ketone **223a** (97 mg, 0.30 mmol), benzyl phenyl sulfone (139 mg, 0.600 mmol), [IrCp*Cl₂]₂ (2.4 mg, 1.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and PhMe (0.6 mL, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8 → 99.1:0.9) gave the *title compound* as a separable mixture of *E* and *Z* alkenes as white solids (26 mg, 22%, 74:26 [*E*:*Z*]* (isolated in conjunction with 17 mg, 14% **256**)).

* Due to overlapping signals in the crude NMR spectrum, the *E*:*Z* ratio was determined post-purification. The stereochemistry was determined using *n*Oe analysis.

Data for *E* isomer:

m.p. = 130 – 132 °C;

¹H NMR (600 MHz, CDCl₃) δ 7.41 – 7.35 (m, 2H, 2 × C(21)*H*), 7.34 – 7.29 (m, 3H, 2 × C(20)*H*, C(22)*H*), 7.14 – 7.11 (m, 2H, C(13)*H*, C(15)*H*), 7.09 (d, *J* = 8.0 Hz, 1H, C(12)*H*), 6.96 – 6.87 (m, 1H, C(14)*H*), 6.74 (s, 1H, C(18)*H*), 3.63 (d, *J* = 16.5 Hz, 1H, C(10)*H_AH_B*), 2.97 (d, *J* = 16.5 Hz, 1H, C(10)*H_AH_B*), 2.24 (s, 3H, C(Ph*)*H*₃), 2.21 (s, 3H, C(Ph*)*H*₃), 2.10 (s, 3H, C(Ph*)*H*₃), 2.02 (2 × s, 6H, 2 × C(Ph*)*H*₃), 1.75 (s, 3H, C(23)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 215.6 C(8), 145.8 C(17), 144.9 C(11), 139.3 C(Ar(Ph*)), 138.5 C(16), 138.2 C(19), 135.1 C(Ar(Ph*)), 133.1 C(Ar(Ph*)), 132.6 C(Ar(Ph*)), 128.6 2 × C(21), 128.5 C(15), 128.5 C(Ar(Ph*)), 128.4 2 × C(20), 127.9 C(Ar(Ph*)), 127.1 C(22), 126.1 C(14), 125.8 C(18), 125.0 C(12), 124.6 C(13), 61.1 C(9), 42.6 C(10), 28.3 C(23), 18.9 C(Me(Ph*)), 18.7 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) ν_{max} /cm⁻¹ 2930, 1688, 1637, 1472, 1461, 1383, 1303, 1261, 1153, 1074, 991, 911, 841;

HRMS (ESI⁺) C₂₉H₃₀NaO⁺ ([M+Na]⁺) requires 417.2189; found 417.2182, Δ 1.58 ppm.

Data for *Z* isomer:

m.p. = 122 – 124 °C;

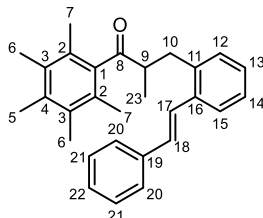
¹H NMR (600 MHz, CDCl₃) δ 7.53 – 7.48 (m, 1H, C(15)*H*), 7.42 – 7.38 (m, 2H, 2 × C(20)*H*), 7.34 – 7.30 (m, 2H, 2 × C(21)*H*), 7.29 – 7.27 (m, 1H, C(22)*H*), 7.26 (s, 1H, C(18)*H*), 7.20 (t, *J* = 7.5 Hz, 1H, C(14)*H*), 7.16 – 7.10 (m, 1H, C(13)*H*), 6.99 – 6.94 (m, 1H, C(12)*H*), 3.53 (d, *J* = 16.3 Hz, 1H, C(10)*H_AH_B*), 2.92 (dt, *J* = 16.2, 1.2 Hz, 1H, C(10)*H_AH_B*), 2.20 (s, 3H, C(Ph*)*H*₃), 2.17 (s, 3H, C(Ph*)*H*₃), 1.99 (s, 6H, 2 × C(Ph*)*H*₃), 1.74 (s, 3H, C(Ph*)*H*₃), 1.52 (s, 3H, C(23)*H*₃);

¹³C NMR (151 MHz, CDCl₃) δ 213.8 C(8), 145.0 C(17), 143.3 C(16), 142.8 C(11), 138.5 C(Ar(Ph*)), 136.9 C(19), 134.7 C(Ar(Ph*)), 132.9 C(Ar(Ph*)), 132.4 C(Ar(Ph*)), 129.4 2 × C(20), 128.6 C(Ar(Ph*)), 128.2 C(13) & C(Ar(Ph*)), 127.6 2 × C(21), 126.8 C(22), 126.8 C(14), 125.0 C(18), 124.1 C(12), 120.4 C(15), 63.6 C(9), 44.7 C(10), 24.1 C(23), 19.3 C(Me(Ph*)), 18.8 C(Me(Ph*)), 16.5 C(Me(Ph*)), 16.0 C(Me(Ph*)), 15.8 C(Me(Ph*));

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3022, 2923, 2349, 1690, 1493, 1462, 1444, 1302, 1259, 1076, 989, 891, 862;

HRMS (ESI⁺) C₂₉H₃₀NaO⁺ ([M+Na]⁺) requires 417.2189; found 417.2182, Δ 1.73 ppm.

256 (E)-2-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-3-(2-styrylphenyl)propan-1-one



Hydroxy ketone **223a** (97 mg, 0.30 mmol), benzyl phenyl sulfone (139 mg, 0.600 mmol), [IrCp*Cl₂]₂ (2.4 mg, 1.0 mol%) and KOH (67 mg, 1.2 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and PhMe (0.6 mL, degassed with Ar (balloon)) was added. The reaction was heated at 115 °C for 24 h, cooled to RT, filtered through a silica pad (Et₂O elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/Et₂O, 99.2:0.8 → 99.1:0.9) gave the *title compound* as a white solid (17 mg, 14%, isolated in conjunction with 26 mg, 22% **255**).

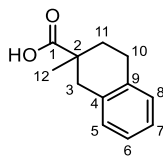
m.p. = 86 – 88 °C;

¹H NMR (700 MHz, CDCl₃) δ 7.58 – 7.51 (m, 1H, C(13)H), 7.31 – 7.23 (m, 4H, 2 × C(20)H, 2 × C(21)H), 7.23 – 7.19 (m, 1H, C(15)H), 7.19 – 7.12 (m, 4H, C(12)H, C(14)H, C(17)H, C(22)H), 6.91 (d, *J* = 16.0 Hz, 1H, C(18)H), 3.43 (dd, *J* = 13.8, 4.3 Hz, 1H, C(10)H_AH_B), 3.04 (dtd, *J* = 14.0, 7.0, 4.2 Hz, 1H, C(9)H), 2.61 (dd, *J* = 13.8, 10.1 Hz, 1H, C(10)H_AH_B), 2.18 (s, 3H, C(Ph*)H₃), 2.06 (s, 6H, 2 × C(Ph*)H₃), 1.96 (s, 6H, 2 × C(Ph*)H₃), 1.00 (d, *J* = 7.0 Hz, 3H, C(23)H₃);

¹³C NMR (176 MHz, CDCl₃) δ 214.1 C(8), 139.6 C(Ar(Ph*)), 137.8 C(11), 137.5 C(19), 136.4 C(16), 135.7 C(Ar(Ph*)), 133.3 2 × C(Ar(Ph*)), 131.5 C(17), 130.7 C(18), 128.8 2 × C(21), 128.4 2 × C(Ar(Ph*)), 127.8 C(12), 127.6 C(15), 127.0 C(22), 126.6 2 × C(20), 126.1 C(13), 126.0 C(14), 49.8 C(9), 35.7 C(10), 18.0 2 × C(Me(Ph*)), 16.9 C(Me(Ph*)), 16.2 2 × C(Me(Ph*)), 15.2 C(23);

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3015, 2921, 1687, 1576, 1496, 1453, 1436, 1216, 1083, 964, 923;

HRMS (ESI⁺) C₂₉H₃₃O⁺ ([M+H]⁺) requires 397.2526; found 397.2519, Δ 1.85 ppm.

257 2-Methyl-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid

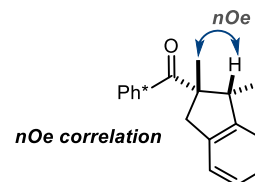
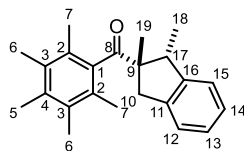
Ketone **225a** (64 mg, 0.20 mmol) was dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) (1.7 mL) and HCl (12 M, 0.34 mL) was added. The reaction was heated at 65 °C for 16 h, cooled to RT and then diluted with CH₂Cl₂ (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH₂Cl₂/EtOAc/HCO₂H 97.95:2:0.05) gave the *title compound* as an off-white solid (37.5 mg, 99%).

¹H NMR (600 MHz, CDCl₃) δ 7.15 – 6.95 (m, 4H, C(5)*H*, C(6)*H*, C(7)*H*, C(8)*H*), 3.24 (d, *J* = 16.4 Hz, 1H, C(3)*H_AH_B*), 2.97 – 2.86 (m, 1H, C(10)*H_AH_B*), 2.87 – 2.76 (m, 1H, C(10)*H_AH_B*), 2.67 (d, *J* = 16.4 Hz, 1H, C(3)*H_AH_B*), 2.20 – 2.10 (m, 1H C(11)*H_AH_B*), 1.82 – 1.68 (m, 1H, C(11)*H_AH_B*), 1.32 (s, 3H, C(12)*H₃*);

¹³C NMR (151 MHz, CDCl₃) δ 183.6 C(1), 135.1 C(9), 134.8 C(4), 129.4 C(5), 128.9 C(8), 126.0 C(7), 126.0 C(6), 41.7 C(2), 38.4 C(3), 31.7 C(11), 26.2 C(10), 24.3 C(12);

HRMS (ESI⁺) C₁₂H₁₃O₂⁺ ([M-H]⁺) requires 189.0921; found 189.0913, Δ 4.18 ppm.

The spectroscopic data were consistent with that present in the literature.¹⁶⁸

261 ((1*RS*, 2*SR*)-1,2-Dimethyl-2,3-dihydro-1*H*-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Alkene **224a** (64 mg, 0.20 mmol) was dissolved in MeOH (5 mL, degassed with N₂ (balloon)). Pd/C (13 mg, 10 wt%, (20 wt% loading w.r.t. alkene **224a**)) was added, a balloon of H₂ was attached and the gas was bubbled through the mixture for 15 min. The mixture was left under an atmosphere of H₂ for 2 h. The reaction mixture was filtered through a Celite® pad (washed

with CH_2Cl_2) and concentrated *in vacuo* to give the *title compound* as a white solid that required no further purification (64 mg, 99%, >[95:5] d.r.)

m.p. = 147 – 148 °C;

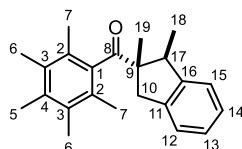
^1H NMR (500 MHz, CDCl_3) δ 7.21 – 7.17 (m, 2H, C(13)*H*, C(15)*H*), 7.17 – 7.11 (m, 2H, C(12)*H*, C(14)*H*), 3.66 (d, J = 15.2 Hz, 1H, C(10)*H_AH_B*), 3.17 (q, J = 7.1 Hz, 1H, C(17)*H*), 2.77 (d, J = 15.2 Hz, 1H, C(10)*H_AH_B*), 2.23 (s, 3H, C(Ph*)*H₃*), 2.20 (s, 3H, C(Ph*)*H₃*), 2.18 – 2.13 (m, 6H, 2 × C(Ph*)*H₃*), 2.00 (s, 3H, C(Ph*)*H₃*), 1.38 (d, J = 7.2 Hz, 3H, C(18)*H₃*), 1.15 (s, 3H, C(19)*H₃*);

^{13}C NMR (126 MHz, CDCl_3) δ 217.7 C(8), 147.9 C(16), 141.1 C(Ar(Ph*)), 140.3 C(11), 134.9 C(Ar(Ph*)), 133.3 C(Ar(Ph*)), 132.7 C(Ar(Ph*)), 127.9 C(Ar(Ph*)), 127.1 C(Ar(Ph*)), 126.8 C(13), 126.6 C(14), 125.0 C(12), 124.1 C(15), 58.5 C(9), 52.5 C(17), 45.3 C(10), 25.8 C(19), 19.4 C(18), 17.8 C(Me(Ph*)), 17.7 C(Me(Ph*)), 16.8 C(Me(Ph*)), 16.2 C(Me(Ph*)), 16.1 C(Me(Ph*));

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2931, 1683, 1479, 1453, 1381, 1260, 1178, 1153, 1085, 1071, 924, 911;

HRMS (ESI⁺) [$\text{C}_{23}\text{H}_{29}\text{O}$]⁺ ([M+H]⁺) requires 321.2213; found 321.2211, Δ 0.61 ppm.

262 ((1*RS*,2*RS*)-1,2-Dimethyl-2,3-dihydro-1*H*-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone



Alkene **223a** (64 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (6 mL, degassed with N_2) and a 1 mL aliquot of a solution of Crabtree's catalyst ($[\text{Ir}(\text{cod})(\text{py})(\text{PCy}_3)]^+\text{PF}_6^-$, 64 mg, 40 mol% in 4 mL CH_2Cl_2) was added. A balloon of H_2 was attached and bubbled through the solution for 2 min. The reaction was left under an atmosphere of H_2 and 3 × 1 mL aliquots of the catalyst solution were added every 10 min. The solution was left under an atmosphere of H_2 for 2 h, filtered through a Celite® pad (washed with CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99.2:0.8 → 99.1:0.9) gave the *title compound* as a white solid (44 mg, 68%, >[95:5] d.r.)

The relative stereochemistry was assigned by X-ray crystallography analysis.

m.p. = 105 – 106 °C;

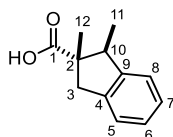
¹H NMR (600 MHz, CDCl₃) δ 7.19 – 7.15 (m, 1H, C(12)H), 7.14 – 7.09 (m, 3H, C(13)H, C(14)H, C(15)H), 3.60 (q, *J* = 7.1 Hz, 1H, C(17)H), 3.36 (d, *J* = 15.3 Hz, 1H, C(10)*H_AH_B*), 2.81 (d, *J* = 15.3 Hz, 1H, C(10)*H_AH_B*), 2.22 (s, 3H, C(Ph*)H₃), 2.19 (s, 3H, C(Ph*)H₃), 2.16 (s, 3H, C(Ph*)H₃), 2.12 (s, 3H, C(Ph*)H₃), 2.11 (s, 3H, C(Ph*)H₃), 1.32 (d, *J* = 7.1 Hz, 3H, C(18)H₃), 1.18 (s, 3H, C(19)H₃);

¹³C NMR (151 MHz, CDCl₃) δ 217.3 C(8), 145.4 C(16), 141.1 C(11), 139.3 C(Ar(Ph*)), 135.2 C(Ar(Ph*)), 133.5 C(Ar(Ph*)), 133.0 C(Ar(Ph*)), 128.3 C(Ar(Ph*)), 128.0 C(Ar(Ph*)), 126.7 C(12), 126.6 C(13/14), 124.3 C(13/14), 123.4 C(15), 61.8 C(9), 44.7 C(17), 44.6 C(10), 19.2 C(Me(Ph*)), 18.7 C(Me(Ph*)), 18.2 C(19), 16.7 C(Me(Ph*)), 16.3 C(Me(Ph*)), 16.1 C(Me(Ph*)), 12.7 C(18);

IR (film) ν_{max} /cm⁻¹ 2939, 1683, 1460, 1381, 1306, 1260, 1149, 1080, 989, 913;

HRMS (ESI⁺) C₂₃H₂₉O⁺ ([M+H]⁺) requires 321.2213; found 321.2211, Δ 0.70 ppm.

263 (1*RS*, 2*RS*)-1,2-Dimethyl-2,3-dihydro-1H-indene-2-carboxylic acid



Ketone **262** (32 mg, 0.10 mmol) was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (1.0 mL) and HCl (37% aq., 0.2 mL) was added. The reaction was heated at 65 °C for 18 h, cooled to RT and diluted with water (10 mL) and CH₂Cl₂ (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (CH₂Cl₂/EtOAc/HCO₂H, 97.95:2:0.05) gave the *title compound* as a colourless oil (19.0 mg, 99%, >[95:5] d.r.)

The relative stereochemistry was assigned by analogy with parent compound **262**.

m.p. = 70 – 72 °C;

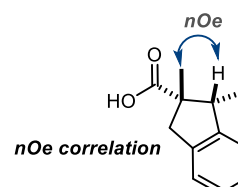
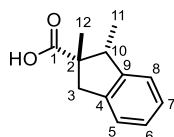
¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.03 (m, 4H, C(5)H, C(6)H, C(7)H, C(8)H), 3.64 (q, *J* = 7.1 Hz, 1H, C(10)H), 3.50 (d, *J* = 15.6 Hz, 1H, C(3)*H_AH_B*), 2.80 (d, *J* = 15.6 Hz, 1H, C(3)*H_AH_B*), 1.33 (d, *J* = 7.1 Hz, 3H, C(11)H₃), 1.18 (s, 3H, C(12)H₃);

^{13}C NMR (101 MHz, CDCl_3) δ 183.8 C(1), 145.6 C(9), 140.6 C(4), 126.8 C(6/7), 126.8 C(6/7), 124.5 C(5), 123.5 C(8), 53.5 C(2), 45.6 C(10), 43.6 C(3), 18.3 C(12), 13.3 C(11);

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2976, 1703, 1547, 1477, 1405, 1328, 1269, 1018, 942, 759, 734;

HRMS (ESI^-) $\text{C}_{12}\text{H}_{13}\text{O}_2^-$ ($[\text{M}-\text{H}]^-$) requires 189.0921; found 189.0915, Δ 2.97 ppm.

264 (1*RS*,2*SR*)-1,2-Dimethyl-2,3-dihydro-1*H*-indene-2-carboxylic acid



Ketone **261** (32 mg, 0.10 mmol) was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (1.0 mL) and HCl (37% aq., 0.2 mL) was added. The reaction was heated at 65 °C for 18 h, cooled to RT and diluted with water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{HCO}_2\text{H}$, 97:95:2:0.05) gave the *title compound* as a colourless oil (18.6 mg, 97%, >[95:5] d.r.)

The relative stereochemistry was assigned by analogy with parent compound **261**.

^1H NMR (600 MHz, CDCl_3) δ 11.43 (br. s, 1H, OH), 7.23 – 7.12 (m, 4H, C(5)*H*, C(6)*H*, C(7)*H*, C(8)*H*), 3.60 (d, J = 16.0 Hz, 1H, C(3)*H*_A*H*_B), 3.13 (q, J = 7.2 Hz, 1H, C(10)*H*), 2.72 (d, J = 16.0 Hz, 1H, C(3)*H*_A*H*_B), 1.40 (s, 3H, C(12)*H*₃), 1.23 (d, J = 7.1 Hz, 3H, C(11)*H*₃);

^{13}C NMR (151 MHz, CDCl_3) δ 182.2 C(1), 146.3 C(9), 140.8 C(4), 126.9 C(6), 126.8 C(7), 124.8 C(5), 124.0 C(8), 53.8 C(2), 50.1 C(10), 41.1 C(3), 24.9 C(12), 17.3 C(11);

m/z (ESI^-) Found ($[\text{M}-\text{H}]^-$) = 189, $\text{C}_{12}\text{H}_{13}\text{O}_2$ requires 189.

The spectroscopic data matched that already reported in the literature.¹³⁰

265 (1*RS*,2*SR*)-1,2-Dimethyl-*N*-(thiazol-2-yl)-2,3-dihydro-1*H*-indene-2-carboxamide

Carboxylic acid **265** (19 mg, 0.10 mmol) was dissolved in MeCN (1.0 mL) and added to a 2 – 5 mL microwave vial. 2-Aminothiazole (12 mg, 0.12 mmol), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (32 mg, 0.17 mmol), 1-hydroxybenzotriazole (16 mg, 0.12 mmol) and DIPEA (38 μ L, 0.22 mmol) were added. The microwave vial was sealed and the reaction was heated at 85 °C for 16 h. The reaction was cooled to RT and diluted with EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 $\times$ 15 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent PhMe/EtOAc, 96:4) gave the *title compound* as a white solid (17 mg, 63%, >[95:5] d.r.)

m.p. = 134 – 136 °C;

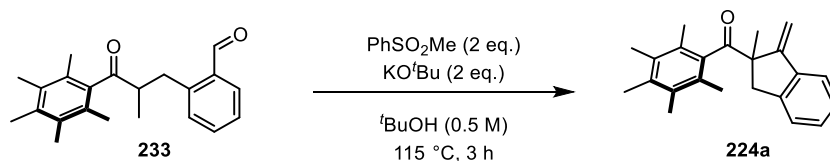
¹H NMR (500 MHz, CDCl₃) δ 8.89 (br. s, 1H, NH), 7.39 (d, *J* = 3.5 Hz, 1H, C(15)*H*), 7.33 – 7.27 (m, 1H, C(5)*H*), 7.27 – 7.22 (m, 2H, C(6)*H*, C(7)*H*), 7.22 – 7.15 (m, 1H, C(8)*H*), 6.95 (d, *J* = 3.5 Hz, 1H, C(14)*H*), 3.57 (d, *J* = 16.2 Hz, 1H, C(3)*H_AH_B*), 3.22 (q, *J* = 7.1 Hz, 1H, C(10)*H*), 2.95 (d, *J* = 16.1 Hz, 1H, C(3)*H_AH_B*), 1.51 (s, 3H, C(12)*H₃*), 1.21 (d, *J* = 7.2 Hz, 3H, C(11)*H₃*);

¹³C NMR (126 MHz, CDCl₃) δ 173.6 C(1), 158.2 C(13), 146.2 C(9), 140.1 C(4), 137.4 C(15), 127.8 C(7), 127.7 C(6), 125.1 C(5), 124.2 C(8), 113.8 C(14), 54.7 C(2), 50.0 C(10), 41.8 C(3), 24.1 C(12), 15.7 C(11);

IR (film) ν_{max} /cm⁻¹ 3188, 2965, 1679, 1536, 1480, 1320, 1273, 1161, 1011, 912;

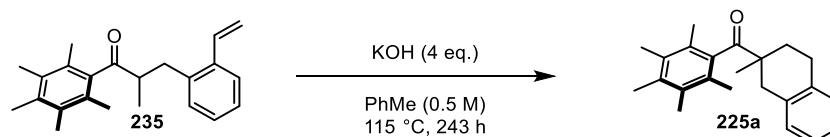
HRMS (ESI⁺) C₁₅H₁₇N₂OS⁺ ([M+H]⁺) requires 273.1056; found 273.1045, Δ 4.00 ppm.

6.4.3 Mechanistic Experiments

6.4.3.1 Metal-free experiment with aldehyde **233**

Aldehyde **223** (97 mg, 0.30 mmol), methyl phenyl sulfone (94 mg, 0.60 mmol), and KO^tBu (68 mg, 0.60 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times), and $^t\text{BuOH}$ (0.6 mL, degassed with Ar (balloon)) was added. The reaction was heated at $115\text{ }^\circ\text{C}$ for 3 h, cooled to RT, filtered through a silica pad ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99.1:0.9 $\rightarrow$ 99:1) gave the ketone **224a** as a white solid (92 mg, 96%).

The spectroscopic data were consistent with that reported above for **224a**.

5.4 Metal-free experiment with styrene **235**

Styrene **235** (40 mg, 0.125 mmol) and KOH (28 mg, 0.50 mmol) were added to a 2 – 5 mL microwave vial. The vial was sealed, evacuated and back-filled with Ar (3 times) and PhMe (0.25 mL, degassed with Ar (balloon)) was added. The reaction was heated at $115\text{ }^\circ\text{C}$ for 24 h, cooled to RT, filtered through a silica pad ($\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ elution) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/ Et_2O , 99:1) gave the ketone **225a** as a white solid (28 mg, 70%).

The spectroscopic data were consistent with that reported above for **225a**.

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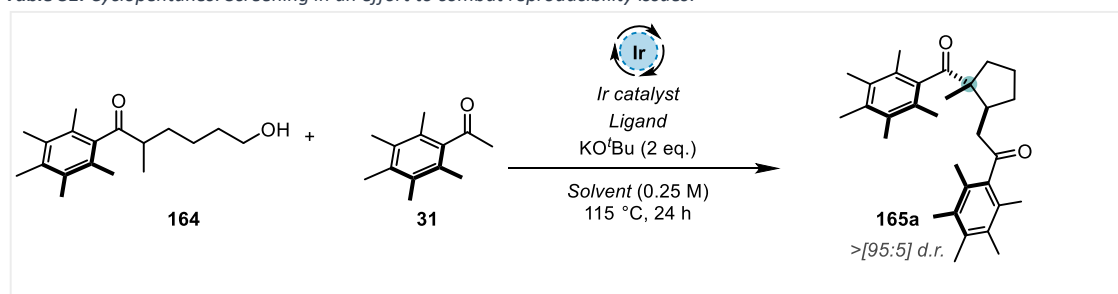
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Appendices

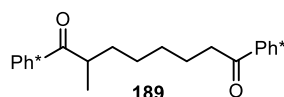
Appendix I: Full Optimisation Table for Cyclopentane Reproducibility Issues

Table S1: Cyclopentanes: Screening in an effort to combat reproducibility issues.



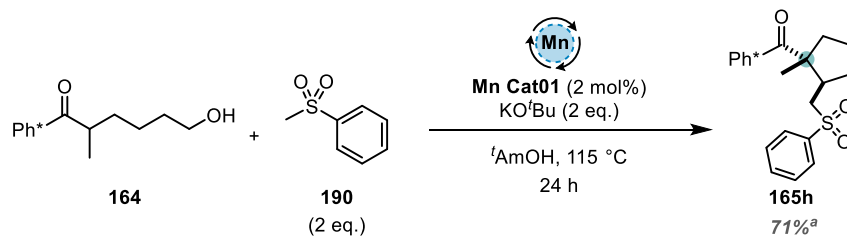
Entry	Eq. 31	Ir catalyst (mol%)	Ligand (mol%)	Solvent	Yield (%) ^a	
					164	165a
1	1.5	[Ir(cod)Cl] ₂ (1)	cataCXium® A (4)	^t BuOH	-	77 (83)
2a	1.5	Ir(cod)acac (2)	cataCXium® A (4)	^t BuOH	-	75 (69)
2b	1.5	Ir(cod)acac (2)	cataCXium® A (4)	^t BuOH	37	37
2c	1.5	Ir(cod)acac (2)	cataCXium® A (4)	^t BuOH	50	26
2d	1.5	Ir(cod)acac (2)	cataCXium® A (4)	^t BuOH	51	15
3a	2	[Ir(cod)Cl] ₂ (1)	cataCXium® A (4)	^t BuOH	-	72 (74)
3b	2	[Ir(cod)Cl] ₂ (1)	cataCXium® A (4)	^t BuOH	43	20
4	2	Ir(cod)acac (2)	cataCXium® A (4)	^t BuOH	61	23
5	2	Ir(cod)acac (2)	P ^t Bu ₃ (4)	^t BuOH	-	42 (38) ^{b(i)}
6	2	Ir(cod)acac (2)	HBF ₄ ·P ^t Bu ₃ (4)	^t BuOH	7	55
7	2	Ir(cod)acac (2)	cataCXium® A (4)	PhMe	7	40
8	2	Ir(cod)acac (2)	cataCXium® A (4)	^t BuOH ^c	61	27
9	2	Ir(cod)acac (2)	cataCXium® A (4)	^t AmOH ^c	15	33
10	2	Ir(cod)acac (4)	cataCXium® A (8)	^t BuOH	-	59 (59) ^{b(iii)}
11	2	Ir(cod)acac (4)	cataCXium® A (10)	^t BuOH	2	60
12a	2	Ir(cod)acac (4)	cataCXium® A (16)	^t BuOH	15	66 (64) ^{b(iii)}
12b	2	Ir(cod)acac (4)	cataCXium® A (16)	^t BuOH	10	70 (69) ^{b(iv)}

^a Yield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard, isolated yields are given in parentheses. ^b acyclic side product **189** isolated in (i) 48%, (ii) 40%, (iii) 12%, (iv) 10% yield ^c solvent dried over 3 Å molecular sieves. Entry 3a repeated from **Table 3** for comparison.



Appendix II: Data for Hydrogen Evolution Experiment

Table S2: Gas evolved from the acceptorless dehydrogenation–intramolecular conjugate addition reaction.



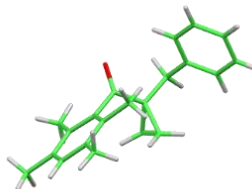
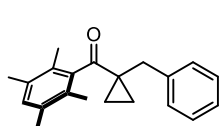
Time (h)	Volume of gas collected (cm ³)		
	Control (<i>t</i> AmOH only)	Experiment 1	Experiment 2
1	6.5	10.5	10.5
2	6.5	12.5	12.5
3	6.5	13.0	13.0
4	6.5	13.5	13.0
5	6.5	13.5	13.0
6	6.5	13.5	13.0
7	6.5	13.5	13.0
24	6.5	13.0	12.5

^aYield determined via ¹H quantitative NMR using 1,1,2,2-tetrachloroethane as an internal standard.

Appendix III: Single Crystal X-Ray Structure Data

115a (1-Benzylcyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

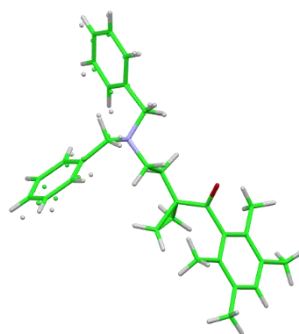
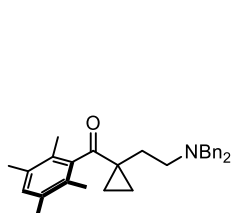
Crystals were grown over 1 – 2 weeks *via* vapour diffusion using CH₂Cl₂ as the solvent and *i*PrOH as the precipitant.



Empirical formula	C ₂₁ H ₂₄ O	M_r	292.42
Crystal Type	Monoclinic	Space group	P 2 ₁ /n
Unit cell dimensions			
a	= 12.6727(4) Å	α	= 90°
b	= 8.6802(3) Å	β	= 91.672(3)°
c	= 14.8889(4)	γ	= 90°
Volume	1637.11(9) Å ³	Z	4
Density (calculated)	1.186 Mg/m ³	Absorption Coeff.	0.071 mm ⁻¹
Crystal size	0.15 × 0.08 × 0.05 mm ³		
Crystal colour	clear pale colourless		
Crystal shape	lath		
Theta range for data collection	3.606 – 28.279°	Wavelength	0.71073 Å
Max. & min. transmission	1.00 & 0.78	Temperature	100 K
F(000)	632		
h_{min}, h_{max}	–16 ≤ h ≤ 16		
k_{min}, k_{max}	–11 ≤ k ≤ 10		
l_{min}, l_{max}	–19 ≤ l ≤ 19		
Δρ_{max}	0.36		
Δρ_{min}	–0.24		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	= 0.9956
Reflections collected	19645	Independent reflections	4056
R(int)	= 0.028	θ(max)	= 28.279°
Final R (I>2σ(I)) R1	= 0.0393	Completeness to θmax	99.8%
wR2	= 0.0924		
Number of parameters	199	Number of restraints	0

115m (1-(2-(Dibenzylamino)ethyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

Crystals were grown over 1 – 2 weeks *via* vapour diffusion using a mixture of MTBE and CH₂Cl₂ as the solvent and hexane as the precipitant.

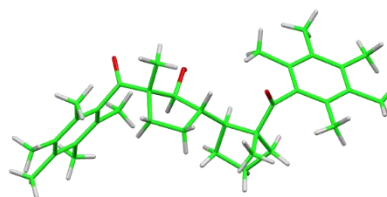
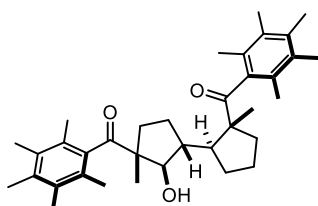


Empirical formula	C ₃₀ H ₃₅ NO	M_r	425.61
Crystal Type	Monoclinic	Space group	C 2/c
Unit cell dimensions			
a	= 19.4632(5) Å	α	= 90°
b	= 6.9774(2) Å	β	= 92.285(2)°
c	= 35.9129(8)	γ	= 90°
Volume	4873.2(2) Å ³	Z	8
Density (calculated)	1.160 Mg/m ³	Absorption Coeff.	0.069 mm ⁻¹
Crystal size	0.10 × 0.09 × 0.01 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	plate		
Theta range for data collection	3.289 – 28.281°	Wavelength	0.71073 Å
Max. & min. transmission	1.00 & 0.94	Temperature	100 K
F(000)	1840		
h_{min}, h_{max}	–25 ≤ h ≤ 25		
k_{min}, k_{max}	–9 ≤ k ≤ 9		
l_{min}, l_{max}	–46 ≤ l ≤ 47		
Δρ_{max}	0.36		
Δρ_{min}	–0.27		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9809
Reflections collected	47381	Independent reflections	6035
R(int)	0.050	θ(max)	= 28.281°
Final R (I>2σ(I)) R1	0.0418	Completeness to θmax	99.8%
wR2	0.0981		
Number of parameters	333	Number of restraints	584

N.B. Mercury visualisations of this data in this thesis have disorder omitted for clarity.

159 (1-(2-(Dibenzylamino)ethyl)cyclopropyl)(2,3,5,6-tetramethylphenyl)methanone

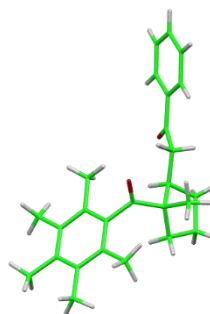
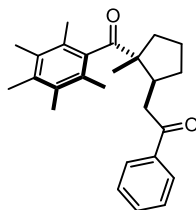
Crystals were recrystallised from hexane over 5 days



Empirical formula	C ₃₆ H ₅₀ O ₃	Mr	530.79
Crystal Type	Triclinic	Space group	P -1
Unit cell dimensions		α	=71.112(4)°
a	= 7.6969(3) Å	β	=86.060(4)°
b	= 11.9672(5) Å	γ	=82.635(3)°
c	= 17.2521(7) Å	Z	2
Volume	1490.50(11) Å ³	Absorption Coeff.	0.561 mm ⁻¹
Density (calculated)	1.183 Mg/m ³		
Crystal size	0.20 × 0.12 × 0.08 mm ³	Wavelength	1.54184 Å
Crystal colour	Clear pale colourless	Temperature	150 K
Crystal shape	block		
Theta range for data collection	3.929 – 76.176°		
Max. & min. transmission	0.96 & 0.92		
F(000)	580		
h_{min}, h_{max}	–9 ≤ h ≤ 9		
k_{min}, k_{max}	–15 ≤ k ≤ 15		
l_{min}, l_{max}	–21 ≤ l ≤ 21		
$\Delta\rho_{\text{max}}$	0.44		
$\Delta\rho_{\text{min}}$	–0.32		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9978
Reflections collected	13912	Independent reflections	6145
R(int)	0.033	$\theta(\text{max})$	= 76.176°
Final R (I>2σ(I)) R1	0.0485	Completeness to θ_{max}	99.7%
wR2	0.1210		
Number of parameters	352	Number of restraints	0

165b 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-1-phenylethan-1-one-methane

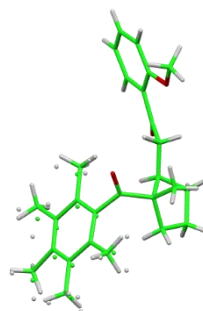
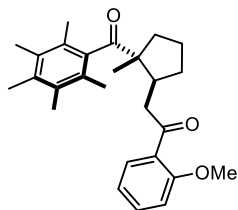
Crystals were grown over 1 – 2 weeks *via* vapour diffusion using a mixture of MTBE and CH₂Cl₂ as the solvent and hexane as the precipitant



Empirical formula	C ₂₆ H ₃₂ O ₂	Mr	376.54
Crystal Type	Orthorhombic	Space group	P 2 ₁ 2 ₁ 2 ₁
Unit cell dimensions			
a	= 6.4053(1) Å	α	90°
b	= 10.6579(1) Å	β	90°
c	= 30.1739(4) Å	γ	90°
Volume	2059.88(5) Å ³	Z	4
Density (calculated)	1.214 Mg/m ³	Absorption Coeff.	0.576 mm ⁻¹
Crystal size	0.05 × 0.20 × 0.20 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	plate		
Theta range for data collection	4.400 – 76.432	Wavelength	1.54184 Å
Max. & min. transmission	0.890 & 0.970	Temperature	150 K
F(000)	816		
h_{min}, h_{max}	–8 ≤ h ≤ 8		
k_{min}, k_{max}	–13 ≤ k ≤ 13		
l_{min}, l_{max}	–38 ≤ l ≤ 37		
Δρ_{max}	–0.11		
Δρ_{min}	0.14		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9945
Reflections collected	50395	Independent reflections	4293
R(int)	0.043	θ(max)	= 76.432°
Final R (I>2σ(I)) R1	0.0310	Completeness to θmax	99.5%
wR2	0.0868		
Number of parameters	382	Number of restraints	153

165d 1-(2-Methoxyphenyl)-2-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)ethan-1-one-methane

Crystals were grown over 1 – 2 weeks *via* vapour diffusion using a mixture of MTBE and CH₂Cl₂ as the solvent and hexane as the precipitant

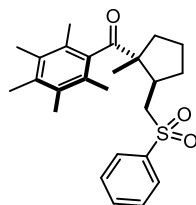


Empirical formula	C ₂₇ H ₃₄ O ₃	M_r	422.6
Crystal Type	Monoclinic	Space group	2/a
Unit cell dimensions			
a	= 18.7554(4) Å	α	90°
b	= 7.8146(1) Å	β	101.062(2)°
c	= 31.5067(6) Å	γ	90°
Volume	4532.01(15) Å ³	Z	8
Density (calculated)	1.19 Mg/m ³	Absorption Coeff.	0.593 mm ⁻¹
Crystal size	0.10 × 0.10 × 0.30 mm ³		
Crystal colour	clear pale colourless		
Crystal shape	block		
Theta range for data collection	5 – 76	Wavelength	1.541840 Å
Max. & min. transmission	0.85 & 0.94	Temperature	150 K
F(000)	1760		
h_{min}, h_{max}	–23 ≤ h ≤ 23		
k_{min}, k_{max}	–9 ≤ k ≤ 9		
l_{min}, l_{max}	–39 ≤ l ≤ 39		
Δρ_{max}	0.28		
Δρ_{min}	–0.22		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	1.001
Reflections collected	22559	Independent reflections	4725
R(int)	0.036	θ(max)	= 76.41°
Final R (I>2σ(I)) R1	0.0403	Completeness to θmax	0.993
wR2	0.1095		
Number of parameters	323	Number of restraints	396

N.B. Mercury visualisations of this data in this thesis have disorder omitted for clarity.

165h (1-Methyl-2-((phenylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

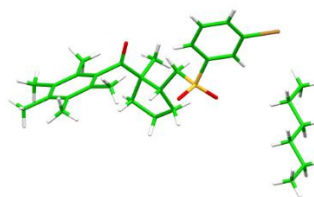
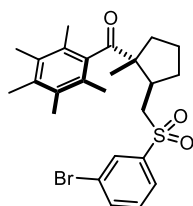
Crystals were grown over 1 – 2 weeks *via* vapour diffusion using a mixture of hexane and CH₂Cl₂ as the solvent and MeOH as the precipitant.



Empirical formula	C ₂₅ H ₃₂ O ₃ S	M_r	412.59
Crystal Type	Orthorhombic	Space group	P b c a
Unit cell dimensions			
a	= 8.9910(1) Å	α	= 90°
b	= 14.5710(1) Å	β	= 90°
c	= 32.8041(2) Å	γ	= 90°
Volume	4297.59(6) Å ³	Z	8
Density (calculated)	1.28 Mg/m ³	Absorption Coeff.	1.517 mm ⁻¹
Crystal size	0.01 × 0.10 × 0.30 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	lath		
Theta range for data collection	6 – 76	Wavelength	1.541840 Å
Max. & min. transmission	0.85 & 0.98	Temperature	150 K
F(000)	1776		
h_{min}, h_{max}	–11 ≤ h ≤ 11		
k_{min}, k_{max}	–18 ≤ k ≤ 17		
l_{min}, l_{max}	–41 ≤ l ≤ 41		
Δρ_{max}	0.30		
Δρ_{min}	–0.38		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.977
Reflections collected	106899	Independent reflections	4496
R(int)	0.053	θ(max)	= 76.13°
Final R (I>2σ(I)) R1	0.0341	Completeness to θmax	99.8%
wR2	0.0980		
Number of parameters	262	Number of restraints	0

165m (2-(((3-Bromophenyl)sulfonyl)methyl)-1-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

Crystals were grown over 4 days *via* vapour diffusion using a mixture of MTBE and CHCl₃ as the solvent and hexane as the precipitant.



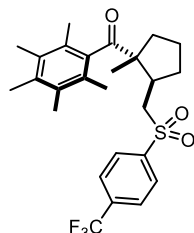
Empirical formula	C ₂₅ H ₃₁ BrO ₃ S·0.5(C ₆ H ₁₄)	Mr	534.58
Crystal Type	Monoclinic	Space group	P2 ₁ /c
Unit cell dimensions			
a	= 19.7734(2) Å	α	= 90°
b	= 8.9224(1) Å	β	= 105.1963°
c	= 15.2607(2) Å	γ	= 90°
Volume	2598.24(5) Å ³	Z	4
Density (calculated)	1.37 Mg/m ³	Absorption Coeff.	3.114 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.50 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	needle		
Theta range for data collection	5 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.20 & 0.54	Temperature	150 K
F(000)	1124		
h_{min}, h_{max}	–24 ≤ h ≤ 24		
k_{min}, k_{max}	–11 ≤ k ≤ 11		
l_{min}, l_{max}	–19 ≤ l ≤ 19		
Δρ_{max}	0.63		
Δρ_{min}	–0.56		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.996
Reflections collected	14898	Independent reflections	5386
R(int)	0.033	θ(max)	= 76.288°
Final R (I>2σ(I)) R1	0.0349	Completeness to θmax	98.9%
wR2	0.1004		
Number of parameters	298	Number of restraints	0

N.B. Mercury visualisations of this data in this thesis have hexane omitted for clarity.

165n

1-Methyl-2-(((4-(trifluoromethyl)phenyl)sulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

Crystals were grown over 4 days *via* vapour diffusion using CHCl_3 as the solvent and hexane as the precipitant.

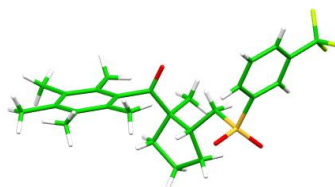
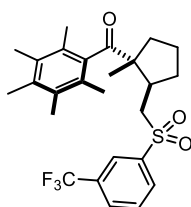


Empirical formula	$\text{C}_{26}\text{H}_{31}\text{F}_3\text{O}_3\text{S}$	M_r	480.59
Crystal Type	Triclinic	Space group	P -1
Unit cell dimensions			
a	= 7.4347(2) Å	α	=103.4840°
b	= 8.8266(2) Å	β	=92.5338°
c	= 18.8432(4) Å	γ	=98.6062°
Volume	1184.89(5) Å ³	Z	2
Density (calculated)	1.35 Mg/m ³	Absorption Coeff.	1.643 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.20 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	cube		
Theta range for data collection	5 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.65 & 0.72	Temperature	150 K
F(000)	508		
$h_{\min}, h_{\max}$	-8 ≤ h ≤ 9		
$k_{\min}, k_{\max}$	-11 ≤ k ≤ 11		
$l_{\min}, l_{\max}$	-23 ≤ l ≤ 23		
$\Delta\rho_{\max}$	0.34		
$\Delta\rho_{\min}$	-0.36		
Refinement method	Full-matrix least-squares on F^2	Goodness-of-fit on F^2	0.9841
Reflections collected	22626	Independent reflections	22626
R(int)	0.022	$\theta(\max)$	= 73.98°
Final R ($I > 2\sigma(I)$) R1	0.0365	Completeness to $\theta_{\max}$	98.4%
wR2	0.1024		
Number of parameters	298	Number of restraints	0

165o

1-Methyl-2-(((3-(trifluoromethyl)phenyl)sulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

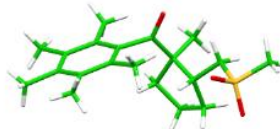
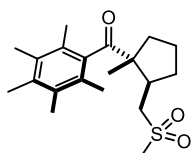
Crystals were grown over 4 days *via* vapour diffusion using CHCl_3 as the solvent and hexane as the precipitant.



Empirical formula	$\text{C}_{26}\text{H}_{31}\text{F}_3\text{O}_3\text{S}$	M_r	480.59
Crystal Type	Monoclinic	Space group	$P 2_1/c$
Unit cell dimensions			
a	= 17.8290 Å	α	= 90°
b	= 9.0231 Å	β	= 101.6620°
c	= 14.8418 Å	γ	= 90°
Volume	2338.36 Å ³	z	4
Density (calculated)	1.37 Mg/m ³	Absorption Coeff.	1.665 mm ⁻¹
Crystal size	0.05 × 0.30 × 0.30 mm ³		
Crystal colour	clear pale colourless		
Crystal shape	plate		
Theta range for data collection	3 – 75	Wavelength	1.54184 Å
Max. & min. transmission	0.51 & 0.92	Temperature	100 K
F(000)	1016		
$h_{\min}, h_{\max}$	-22 ≤ h ≤ 21		
$k_{\min}, k_{\max}$	-11 ≤ k ≤ 10		
$l_{\min}, l_{\max}$	-18 ≤ l ≤ 18		
$\Delta\rho_{\max}$	0.82		
$\Delta\rho_{\min}$	-0.51		
Refinement method	Full-matrix least-squares on F^2	Goodness-of-fit on F^2	0.985
Reflections collected	39759	Independent reflections	4811
R(int)	0.033	$\theta(\max)$	= 76.23°
Final R ($I > 2\sigma(I)$) R1	0.040	Completeness to $\theta_{\max}$	98.2%
wR2	0.106		
Number of parameters	298	Number of restraints	0

165r (1-Methyl-2-((methylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and hexane as the precipitant.

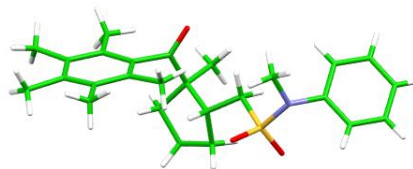
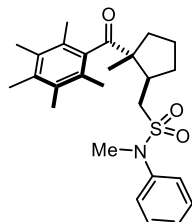


Empirical formula	C ₂₀ H ₃₀ O ₃ S	Mr	350.52
Crystal Type	Orthorhombic	Space group	P b c a
Unit cell dimensions			
a	= 7.8993(1) Å	α	= 90°
b	= 17.4094(1) Å	β	= 90°
c	= 26.6953(2) Å	γ	= 90°
Volume	3671.19(6) Å ³	Z	8
Density (calculated)	1.27 Mg/m ³	Absorption Coeff.	1.678
Crystal size	0.10 × 0.30 × 0.40 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	plate		
Theta range for data collection	5 – 75	Wavelength	1.54184 Å
Max. & min. transmission	0.47 & 0.85	Temperature	150 K
F(000)	1520		
h_{min}, h_{max}	–9 ≤ h ≤ 9		
k_{min}, k_{max}	–21 ≤ k ≤ 21		
l_{min}, l_{max}	–33 ≤ l ≤ 33		
Δρ_{max}	0.35		
Δρ_{min}	–0.45		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9691
Reflections collected	76451	Independent reflections	3821
R(int)	0.046	θ(max)	= 76.343°
Final R (I>2σ(I)) R1	0.1023	Completeness to θmax	99.6%
wR2	0.1071		
Number of parameters	217	Number of restraints	0

165s

***N*-Methyl-1-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)-*N*-phenylmethanesulfonamide**

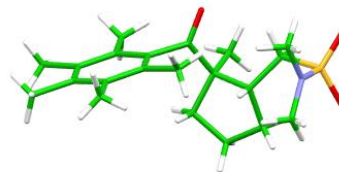
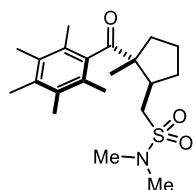
Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and hexane as the precipitant.



Empirical formula	C ₂₆ H ₃₅ NO ₃ S	Mr	441.63
Crystal Type	Triclinic	Space group	P -1
Unit cell dimensions			
a	= 8.8562(3) Å	α	=74.402(3)°
b	= 9.5977(3) Å	β	=78.995(3)°
c	= 14.4886(5) Å	γ	=80.383(2)°
Volume	1155.60(7) Å ³	Z	2
Density (calculated)	1.27 Mg/m ³	Absorption Coeff.	1.456 mm ⁻¹
Crystal size	0.40 × 0.40 × 0.40 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	cube		
Theta range for data collection	5 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.37 & 0.56	Temperature	150 K
F(000)	476		
h_{min}, h_{max}	–11 ≤ h ≤ 9		
k_{min}, k_{max}	–11 ≤ k ≤ 10		
l_{min}, l_{max}	–18 ≤ l ≤ 16		
Δρ_{max}	0.25		
Δρ_{min}	–0.46		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	1.0199
Reflections collected	15037	Independent reflections	4733
R(int)	0.021	θ(max)	= 73.128°
Final R (I>2σ(I)) R1	0.0383	Completeness to θmax	98.2%
wR2	0.1023		
Number of parameters	280	Number of restraints	0

165i *N,N*-Dimethyl-1-(2-methyl-2-(2,3,4,5,6-pentamethylbenzoyl)cyclopentyl)methanesulfonamide

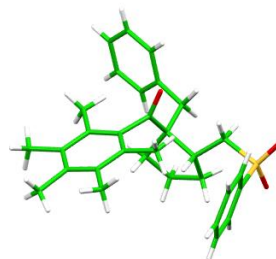
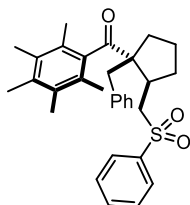
Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and hexane as the precipitant.



Empirical formula	C ₂₁ H ₃₃ NO ₃ S	Mr	379.56
Crystal Type	Triclinic	Space group	P -1
Unit cell dimensions			
a	= 6.5901(2) Å	α	=110.073(4)°
b	= 12.8809(6) Å	β	=97.579(3)°
c	= 12.9173(5) Å	γ	=100.566(3)°
Volume	989.64(8) Å ³	Z	2
Density (calculated)	1.27 Mg/m ³	Absorption Coeff.	1.610 mm ⁻¹
Crystal size	0.05 × 0.10 × 0.40 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	lath		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.57 & 0.92	Temperature	150 K
F(000)	412		
h_{min}, h_{max}	–7 ≤ h ≤ 8		
k_{min}, k_{max}	–15 ≤ k ≤ 16		
l_{min}, l_{max}	–16 ≤ l ≤ 15		
Δρ_{max}	0.39		
Δρ_{min}	–0.42		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9905
Reflections collected	11578	Independent reflections	4073
R(int)	0.031	θ(max)	= 73.587°
Final R (I>2σ(I)) R1	0.0416	Completeness to θmax	98.7%
wR2	0.1059		
Number of parameters	235	Number of restraints	0

165v 1-Benzyl-2-((phenylsulfonyl)methyl)cyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

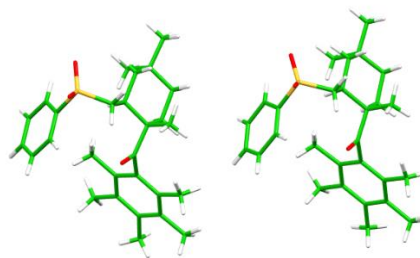
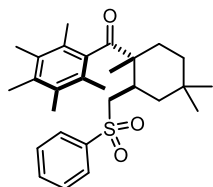
Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and hexane as the precipitant.



Empirical formula	C ₃₁ H ₃₆ O ₃ S	M_r	488.69
Crystal Type	Triclinic	Space group	P -1
Unit cell dimensions			
a	= 10.4881(5) Å	α	= 60.203(6)°
b	= 12.4032(7) Å	β	= 74.388(5)°
c	= 12.4500(7) Å	γ	= 68.482(5)°
Volume	1299.90(15) Å ³	Z	2
Density (calculated)	1.25 Mg/m ³	Absorption Coeff.	1.337 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.20 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	irregular		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.55 & 0.77	Temperature	150 K
F(000)	524		
h_{min}, h_{max}	–12 ≤ h ≤ 13		
k_{min}, k_{max}	–15 ≤ k ≤ 13		
l_{min}, l_{max}	–15 ≤ l ≤ 13		
Δρ_{max}	0.31		
Δρ_{min}	–0.40		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9851
Reflections collected	16552	Independent reflections	5353
R(int)	0.027	θ(max)	= 72.559°
Final R (I>2σ(I)) R1	0.0367	Completeness to θmax	97.9%
wR2	0.0997		
Number of parameters	316	Number of restraints	0

167d (2,3,4,5,6-Pentamethylphenyl)(1,4,4-trimethyl-2-(phenylsulfonyl)methyl)cyclohexyl)methanone

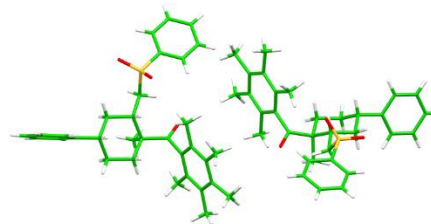
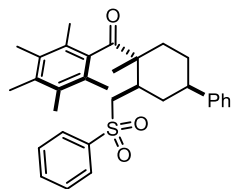
Crystals were grown over 4 days *via* vapour diffusion using a mixture of MTBE and CHCl_3 as the solvent and hexane as the precipitant.



Empirical formula	$\text{C}_{28}\text{H}_{38}\text{O}_3\text{S}$	M_r	454.67
Crystal Type	Monoclinic	Space group	$P 2_1/c$
Unit cell dimensions			
a	= 21.3312(2) Å	α	= 90°
b	= 12.6039(1) Å	β	= 115.7155°
c	= 20.5534(2) Å	γ	= 90°
Volume	4978.62(9) Å ³	Z	8
Density (calculated)	1.21 Mg/m ³	Absorption Coeff.	1.354 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.20 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	cube		
Theta range for data collection			
	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission			
	0.62 & 0.76	Temperature	150 K
F(000)	1968		
$h_{\min}, h_{\max}$	–26 ≤ h ≤ 26		
$k_{\min}, k_{\max}$	–15 ≤ k ≤ 15		
$l_{\min}, l_{\max}$	–25 ≤ l ≤ 25		
$\Delta\rho_{\max}$	0.34		
$\Delta\rho_{\min}$	–0.45		
Refinement method	Full-matrix least-squares on F^2	Goodness-of-fit on F^2	0.9766
Reflections collected	93581	Independent reflections	10329
R(int)	0.041	$\theta(\max)$	= 74.644°
Final R ($I > 2\sigma(I)$) R1	0.0442	Completeness to $\theta_{\max}$	99.3%
wR2	0.1168		
Number of parameters	577	Number of restraints	0

167e (1-Methyl-4-phenyl-2-((phenylsulfonyl)methyl)cyclohexyl)(2,3,4,5,6-pentamethylphenyl)methanone

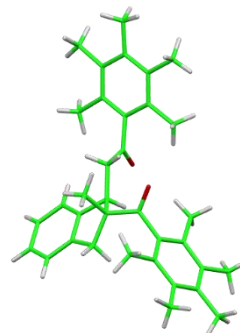
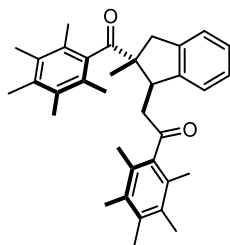
Crystals were grown over 4 days *via* vapour diffusion using a mixture of hexane and CHCl₃ as the solvent and MeOH as the precipitant.



Empirical formula	C ₃₂ H ₃₈ O ₃ S	M_r	502.72
Crystal Type	Triclinic	Space group	P-1
Unit cell dimensions			
a	= 8.7976(1) Å	α	=108.163(2)°
b	= 15.5963(4) Å	β	=98.2579(15)°
c	= 20.6782(4) Å	γ	=92.4685(16)°
Volume	2656.27(10) Å ³	Z	4
Density (calculated)	1.26 Mg/m ³	Absorption Coeff.	1.323 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.60 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	needle		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.48 & 0.77	Temperature	150 K
F(000)	1080		
h_{min}, h_{max}	–11 ≤ h ≤ 8		
k_{min}, k_{max}	–19 ≤ k ≤ 19		
l_{min}, l_{max}	–25 ≤ l ≤ 25		
Δρ_{max}	0.40		
Δρ_{min}	–0.41		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9868
Reflections collected	36853	Independent reflections	10940
R(int)	0.030	θ(max)	= 73.919°
Final R (I>2σ(I)) R1	0.0394	Completeness to θmax	98.6%
wR2	0.1036		
Number of parameters	649	Number of restraints	0

165aa 2-(2-Methyl-2-(2,3,4,5,6-pentamethylbenzoyl)-2,3-dihydro-1H-inden-1-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one

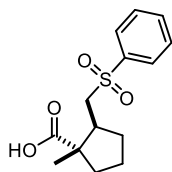
Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and MeOH as the precipitant.



Empirical formula	C ₃₅ H ₄₂ O ₂	Mr	494.72
Crystal Type	Triclinic	Space group	P -1
Unit cell dimensions			
a	= 8.7254(3) Å	α	= 70.039(3)°
b	= 12.3914(5) Å	β	= 83.589(3)°
c	= 14.0387(5) Å	γ	= 74.142(3)°
Volume	1372.10(9) Å ³	Z	2
Density (calculated)	1.197 Mg/m ³	Absorption Coeff.	0.551 mm ⁻¹
Crystal size	0.05 × 0.20 × 0.20 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	plate		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.630 & 0.970	Temperature	150 K
F(000)	536		
h_{min}, h_{max}	–10 ≤ h ≤ 10		
k_{min}, k_{max}	–15 ≤ k ≤ 15		
l_{min}, l_{max}	–17 ≤ l ≤ 17		
Δρ_{max}	0.34		
Δρ_{min}	–0.21		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9828
Reflections collected	26727	Independent reflections	5667
R(int)	0.027	θ(max)	= 76.282°
Final R (I>2σ(I)) R1	0.0432	Completeness to θmax	98.7%
wR2	0.1254		
Number of parameters	334	Number of restraints	0

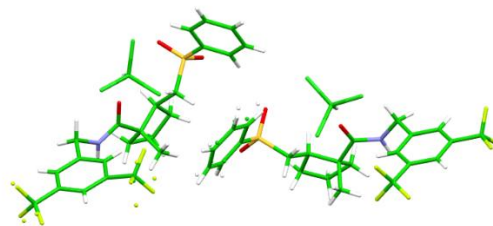
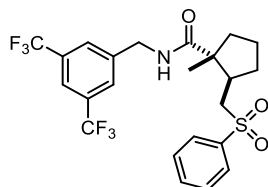
213 1-Methyl-2-((phenylsulfonyl)methyl)cyclopentane-1-carboxylic acid

Crystals were grown over 6 weeks from CDCl₃



Empirical formula	C ₁₄ H ₁₈ O ₄ S	Mr	282.36
Crystal Type	Monoclinic	Space group	P 21/c
Unit cell dimensions			
a	= 10.0128(1) Å	α	= 90°
b	= 13.9422(1) Å	β	= 114.9904°
c	= 10.8501(1) Å	γ	= 90°
Volume	1372.87(2) Å ³	Z	4
Density (calculated)	1.37 Mg/m ³	Absorption Coeff.	2.172 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.20 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	irregular		
Theta range for data collection	5 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.47 & 0.65	Temperature	150 K
F(000)	600		
h_{min}, h_{max}	–12 ≤ h ≤ 12		
k_{min}, k_{max}	–17 ≤ k ≤ 17		
l_{min}, l_{max}	–13 ≤ l ≤ 13		
Δρ_{max}	0.28		
Δρ_{min}	–0.36		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9772
Reflections collected	29135	Independent reflections	2871
R(int)	0.021	θ(max)	= 76.183°
Final R (I>2σ(I)) R1	0.0274	Completeness to θmax	99.6%
wR2	0.0765		
Number of parameters	176	Number of restraints	2

216

***N*-(3,5-Bis(trifluoromethyl)benzyl)-1-methyl-2-((phenylsulfonyl)methyl)cyclopentane-1-carboxamide**Crystals were grown over 6 weeks from CDCl₃

Empirical formula	C ₂₃ H ₂₃ F ₆ NO ₃ S · CHCl ₃	M_r	626.87
Crystal Type	Monoclinic	Space group	P 2 ₁ /c
Unit cell dimensions			
a	= 9.9278(1) Å	α	= 90°
b	= 27.1253(2) Å	β	= 90.7049(8)°
c	= 20.2583(2) Å	γ	= 90°
Volume	90.7049(8) Å ³	Z	8
Density (calculated)	1.53 Mg/m ³	Absorption Coeff.	4.390 mm ⁻¹
Crystal size	0.20 × 0.40 × 0.80 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	lath		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.04 & 0.42	Temperature	150 K
F(000)	2560		
h_{min}, h_{max}	–12 ≤ h ≤ 12		
k_{min}, k_{max}	–34 ≤ k ≤ 34		
l_{min}, l_{max}	–22 ≤ l ≤ 25		
Δρ_{max}	0.96		
Δρ_{min}	–0.88		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	1.0031
Reflections collected	128032	Independent reflections	11382
R(int)	0.070	θ(max)	= 74.751°
Final R (I > 2σ(I)) R1	0.0604	Completeness to θmax	99.4%
wR2	0.1449		
Number of parameters	814	Number of restraints	2265

N.B. Mercury visualisations of this data in this thesis have disorder omitted for clarity.

220 (2-Ethynyl-1-methylcyclopentyl)(2,3,4,5,6-pentamethylphenyl)methanone

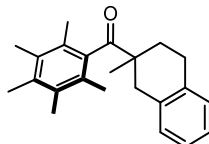
Crystals were grown over 4 days *via* vapour diffusion using CHCl_3 as the solvent and MeOH as the precipitant.



Empirical formula	$\text{C}_{20}\text{H}_{30}\text{NO}_3$	Mr	330.6
Crystal Type	Monoclinic	Space group	$P 2_1/n$
Unit cell dimensions		α	$= 90^\circ$
a	$= 12.1214(1) \text{ \AA}$	β	$= 100.9471(1)^\circ$
b	$= 6.1585(1) \text{ \AA}$	γ	$= 90^\circ$
c	$= 21.8361(2) \text{ \AA}$	Z	4
Volume	$1600.40(3) \text{ \AA}^3$	Absorption Coeff.	0.530 mm^{-1}
Density (calculated)	1.172 Mg/m^3		
Crystal size	$0.20 \times 0.40 \times 0.60 \text{ mm}^3$		
Crystal colour	Clear pale colourless		
Crystal shape	plate		
Theta range for data collection	$4 - 76$	Wavelength	$1.54180 \text{ \AA}$
Max. & min. transmission	$0.71 \text{ \& } 0.90$	Temperature	150 K
F(000)	616		
$h_{\text{min}}, h_{\text{max}}$	$-15 \leq h \leq 14$		
$k_{\text{min}}, k_{\text{max}}$	$-6 \leq k \leq 7$		
$l_{\text{min}}, l_{\text{max}}$	$-26 \leq l \leq 27$		
$\Delta\rho_{\text{max}}$	0.27		
$\Delta\rho_{\text{min}}$	-0.21		
Refinement method	Full-matrix least-squares on F^2	Goodness-of-fit on F^2	0.9561
Reflections collected	3317	Independent reflections	3154
R(int)	0.025	$\theta(\text{max})$	$= 76.002^\circ$
Final R ($I > 2\sigma(I)$) R1	0.0417	Completeness to θ_{max}	99.1%
wR2	0.1159		
Number of parameters	190	Number of restraints	0

225a (2-Methyl-1,2,3,4-tetrahydronaphthalen-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

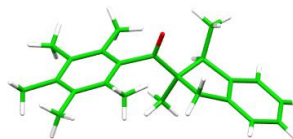
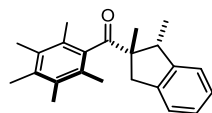
Recrystallised from MeOH



Empirical formula	C ₂₃ H ₂₈ O	M_r	320.47
Crystal Type	Monoclinic	Space group	P 2 ₁ /n
Unit cell dimensions			
a	= 6.2088(1) Å	α	= 90°
b	= 12.5108(3) Å	β	= 93.915(2)°
c	= 23.2538(5) Å	γ	= 90°
Volume	1802.07(7) Å ³	Z	4
Density (calculated)	1.18 Mg/m ³	Absorption Coeff.	0.531 mm ⁻¹
Crystal size	0.20 × 0.20 × 0.60 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	needle		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.49 & 0.90	Temperature	150 K
F(000)	696		
h_{min}, h_{max}	–7 ≤ h ≤ 7		
k_{min}, k_{max}	–15 ≤ k ≤ 13		
l_{min}, l_{max}	–29 ≤ l ≤ 26		
Δρ_{max}	0.27		
Δρ_{min}	–0.17		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9798
Reflections collected	11817	Independent reflections	3732
R(int)	0.027	θ(max)	= 73.883°
Final R (I > 2σ(I))	R1 0.0472	Completeness to θmax	99.0%
wR2	0.1219		
Number of parameters	217	Number of restraints	0

261 ((1*RS*,2*SR*)-1,2-Dimethyl-2,3-dihydro-1*H*-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

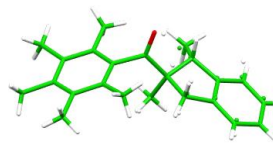
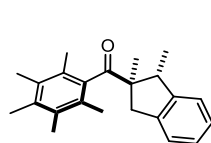
Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and hexane as the precipitant.



Empirical formula	C ₂₃ H ₂₈ O	M_r	320.47
Crystal Type	Monoclinic	Space group	P 2 ₁ /n
Unit cell dimensions			
a	= 6.9236(1)	α	= 90°
b	= 10.2877(1)	β	= 97.5344(5)°
c	= 25.5860(1)	γ	= 90°
Volume	1372.87(2) Å ³	Z	4
Density (calculated)	1.18 Mg/m ³	Absorption Coeff.	0.529 mm ⁻¹
Crystal size	0.10 × 0.10 × 0.30 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	needle		
Theta range for data collection	3 – 76	Wavelength	1.54184
Max. & min. transmission	0.84 & 0.95	Temperature	100 K
F(000)	696		
h_{min}, h_{max}	–8 ≤ h ≤ 8		
k_{min}, k_{max}	–10 ≤ k ≤ 12		
l_{min}, l_{max}	–31 ≤ l ≤ 32		
Δρ_{max}	0.25		
Δρ_{min}	–0.23		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9799
Reflections collected	43267	Independent reflections	3738
R(int)	0.020	θ(max)	= 73.824°
Final R (I>2σ(I)) R1	0.0438	Completeness to θmax	98.8%
wR2	0.1151		
Number of parameters	217	Number of restraints	0

262 ((1*RS*,2*RS*)-1,2-Dimethyl-2,3-dihydro-1*H*-inden-2-yl)(2,3,4,5,6-pentamethylphenyl)methanone

Crystals were grown over 4 days *via* vapour diffusion using CHCl₃ as the solvent and hexane as the precipitant



Empirical formula	C ₂₃ H ₂₈ O	Mr	320.47
Crystal Type	Monoclinic	Space group	P 1 2 ₁ /n 1
Unit cell dimensions			
a	= 6.4087(1) Å	α	= 90°
b	= 12.2607(2) Å	β	= 95.8532(14)°
c	= 23.2559(3) Å	γ	= 90°
Volume	1817.81(5) Å ³	Z	4
Density (calculated)	1.17 Mg/m ³	Absorption Coeff.	0.526 mm ⁻¹
Crystal size	0.10 × 0.20 × 0.50 mm ³		
Crystal colour	Clear pale colourless		
Crystal shape	lath		
Theta range for data collection	4 – 76	Wavelength	1.54184 Å
Max. & min. transmission	0.48 & 0.99	Temperature	150 K
F(000)	696		
h_{min}, h_{max}	–7 ≤ h ≤ 7		
k_{min}, k_{max}	–15 ≤ k ≤ 15		
l_{min}, l_{max}	–29 ≤ l ≤ 29		
Δρ_{max}	0.58		
Δρ_{min}	–0.27		
Refinement method	Full-matrix least-squares on F ²	Goodness-of-fit on F²	0.9677
Reflections collected	35895	Independent reflections	3775
R(int)	0.048	θ(max)	= 74.612°
Final R (I>2σ(I)) R1	0.0684	Completeness to θmax	99.5%
wR2	0.1775		
Number of parameters	244	Number of restraints	921

N.B. Mercury visualisations of this data in this thesis have disorder omitted for clarity.