Development of Cation-Directed Acylation Reactions

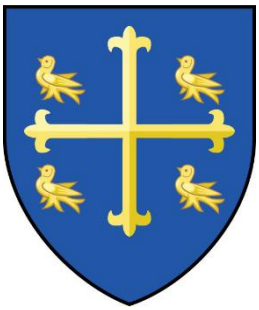
Benjamin Faraz Rahemtulla

A dissertation presented in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

University of Oxford



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Dedication

This thesis is dedicated to my father, Dr Amin Rahemtulla. Thank you for providing me with countless opportunities, support and encouragement throughout my life.

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford and in API Chemistry at GSK between October 2014 and February 2018. The dissertation is a product of my own work and includes no results obtained through collaboration, except where specifically indicated in the text.

Benjamin Faraz Rahemtulla

Acknowledgements

Firstly, I would like to thank the person without whom I wouldn't have had the opportunity to conduct this work and that is Professor Martin Smith. Tea breaks filled with (the love of) Marmite, videos of Nathaniel doing something comical (in some excellent outfits) and personal insight into various eminent chemists interspaced between conversations about autocatalysis and thermodynamics are no rarity and they will be sorely missed. I am incredibly grateful for the time spent working under your supervision over the last 4 and a half years, and all the advice, knowledge, skills and experience imparted over this time.

I would also like to thank my industrial supervisor Hugh Clark for support from afar and being extremely welcoming at GSK for my placement (the tea break timings certainly made it easy to adapt). I'm sure the process chemistry lingo will come in useful later in life!

I am especially grateful to Roly who supervised me when I joined the group as a Part II student and without whom I am certain I would not be nearly so competent. I wish you and Emily all the best together and you will both accomplish wonderful things.

Recently I've been involved in collaborating with Kat on a kinetics project – thanks for teaching me the difference between kinetics and *kinetics*! I hope you enjoyed our time working together and that you keep trying not to get injured every time you play sport!

My thanks must also go to the many people I have had the pleasure of working alongside throughout my time at Oxford, starting with the excellent (senior) Postdocs (man!) Craig, Jamie, Bryony and Niels for being the voices of reason and experience throughout my time in the group. Emily, you set an example for efficiency, accomplishing more than most before encouraging Roly to leave well before 8 pm – I guess not sleeping does help! Alex, you introduced me to the real F4 playlist and for that I will always be mentally scarred… The year above me was comprised of some "very talented" chemists Shuyu, John and Phil. I think Antti was there too maybe? Shuyu, I'm sure you will go on to create many more natural products (in the lab, and the distillery). John, I hope to see you on a cricket tour sometime soon – hopefully with the correct ratio of beers:cricket! Antti,

I know your time here has been “very nice” but you’ve been here nearly as long as I have (I still have that week on you!) so I think its time for us both to move on. Hopefully there won’t be any Canadians in Rob Phipps’ lab to keep trash talking you about ice hockey. And Phil, I look forwards to our reunion in San Francisco very soon, I guess I can’t say too many thanks here as I will certainly owe you more favours in the next months – I’ll have to get you a copy of the Arnie workout DVD!

To Al and Minh, you both rock – thanks for being my cinema, crossword and tea buddies. I have too much to say to fit in this space so I’ll just leave it at that. Arsienij, keep silently doing what you’re doing! Thanks Nick for filling in all those crossword answers that no normal person would know and Tudor, for being technically correct more times than most, and not tooooo smug… Owen, you were an exceptional Part II student who required no supervision and had all your own ideas; you made my life very easy and that’s the only reason you make it onto this as you’re really a third of a group member now!! Ricky, I hope you continue to enjoy teatime biscuits (though not too many or you’ll feel doughy) and “the other Ben” I’m glad we came up with a much better nickname for you, BAJer. Thanks also to the sub-group… I mean DMH group… members who shared the lab with us: Aubert for being so French, Younes for teaching me “street” language (and how to get detained at an airport), Hasan for some barely believable stories (not quite like Russell’s though) and Pascal for not being as French as Aubert (and the token white guy for the last year).

To the other members who I shared the lab with for shorter periods of time: Russel, Craig J, Alan, Krishna, Elliot, Danielle, Keishi, Liz, Hugo, Seb, Niamh, Liz, Pearse, Jack, Annie, Harry and Terry it’s been a blast.

There’s also the people outside chemistry who’ve kept me sane: the Univ people: Jamie; Lizzie; Todd; Franco; Paul; Amy; Max, and sailing people: Phil; Lottie; Ali and BG.

Finally, I would thank my family for their support, M&S supplies and rent-free accommodation, and Kathryn for being super supportive throughout, even when I’m writing until late while you’re asleep - I’m really excited to see where life will take us (hopefully to the South) and what our Pomsky(ies?) is(are) like.

List of Abbreviations

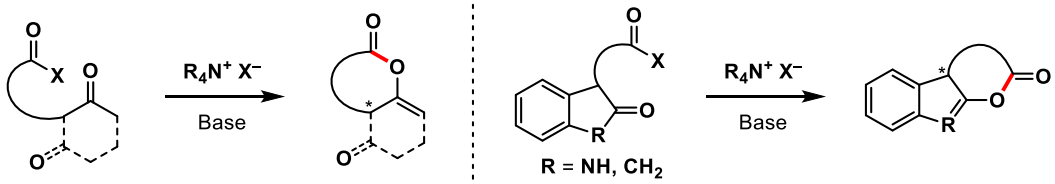
Å	Ångström(s)
Ac	acetyl
ACI	ammonia chemical ionization
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl (generic)
BINOL	1,1'-bi-2-napthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
°C	degrees Celsius
conc	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBALH	diisobutylaluminium hydride
DIPEA	diisopropylethylamine (Hünig's base)
DMF	*N,N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
dr	diastereoisomeric ratio
E	electrophile (generic)
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EI	electron-impact ionization
eq	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
FI	field ionization
FTIR	fourier-transform infra-red spectroscopy
g	gram(s)
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry

Hz	Hertz
i	*iso*
IBX	2-iodoxybenzoic acid
Im	imidazolide
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant (NMR)
k	rate constant
k_{rac}	rate constant of racemization
L	litre(s)
λ	wavelength
LDA	lithium diisopropylamide
LRMS	low-resolution mass spectrometry
µ	micro-
m	milli-
M	moles per litre
m	multiplet (NMR)
m-	meta-
MCI	methane chemical ionization
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mol	moles
mp	melting point
NBS	*N*-bromosuccinimide
NHS	*N*-hydroxysuccinimidyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o-	ortho-
p-	para-
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl
PPTS	pyridinium *para*-toluenesulfonate
PTC	phase-transfer catalyst

PTSA	*para*-toluenesulfonic acid
quant	quantitative
Quat	quaternary
R	substituent (generic)
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
rt	room temperature
s	*sec*-
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
SOMO	singly-occupied molecular orbital
t	*tert*-
T	temperature
TBAB	tetrabutylammonium bromide
Tf	trifluoromethylsulfonate
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
τ_R	retention time (for HPLC)
wt%	weight percent
X	leaving group (generic)

Abstract

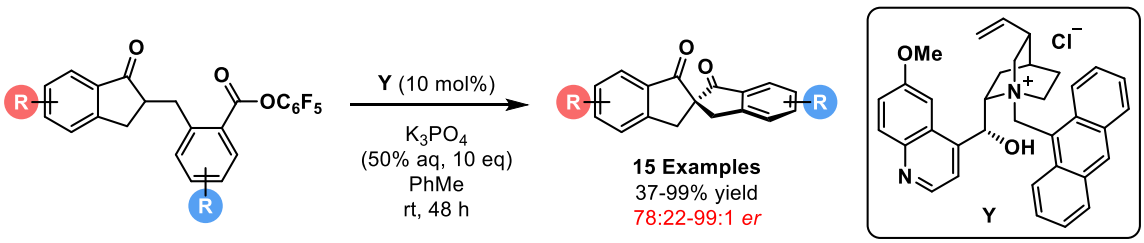
This thesis describes work conducted towards the enantioselective acylation of ketones using phase-transfer catalysis. Chapter 1 introduces the field of ketone acylation, with a focus on catalytic methods accompanied by the generation of axes, planes or points of chirality during these transformations. Chapters 2 describes the synthesis and evaluation of a variety of different frameworks for enantioselective ketone *O*-acylation; we highlight the selectivity and reactivity challenges faced when attempting this transformation (Scheme I).



Scheme I: Reaction Manifolds Investigated for Enantioselective *O*-Acylation

Chapter 3 focuses on the intramolecular *O*-acylation of enolates to generate axially chiral lactones. The development of these systems led to the discovery that the *C*/*O*-selectivity of this reaction was dependent on the steric hindrance about the axis of rotation, and *C*-acylation could be favoured under the correct conditions.

Chapter 4 describes the conception and development of an enantioselective *C*-acylation reaction, culminating in the first reported catalytic enantioselective direct *C*-acylation of a ketone (Scheme II). The scope and limitations of this methodology were investigated and the products were successfully elaborated to afford a range of spirocyclic architectures.



Scheme II: The First Direct Enantioselective *C*-Acylation of a Ketone

Finally, chapter 5 focuses on the kinetic analysis of the enantioselective *C*-acylation reaction in order to increase our understanding of the mechanisms behind phase-transfer catalysis and the mode of activation of the catalyst.

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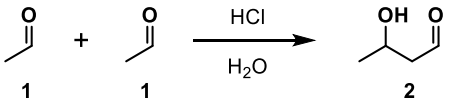
1. Introduction

1.1 Stereoselective α-Functionalization of Ketone Derivatives

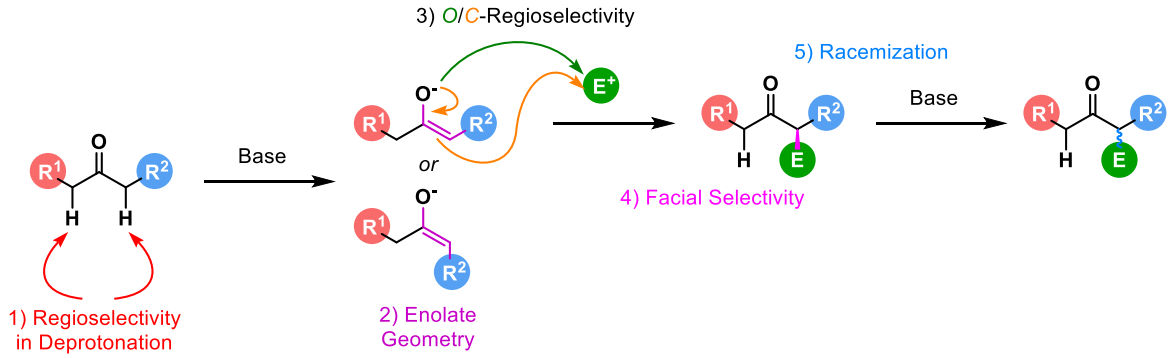
Reports of α-functionalizations of carbonyl derivatives are ubiquitous in Organic Chemistry, and were first disclosed in 1838 by Kane with the self-condensation of acetone,[1] followed by the first examples of an aldol reaction in 1869 by Borodin, and 1872 by Wurtz (Scheme 1).[2]



Scheme 1: Wurtz's Aldol Reaction

Since then, carbonyl α-functionalization has remained an extremely powerful method of forming carbon-carbon bonds and has been utilized extensively due to many factors, such as the availability of starting materials, predictability/reliability of reaction and practical simplicity. In addition, these reactions often lead to the formation of stereogenic centres, and this approach has featured heavily in the synthesis of chiral compounds using both diastereoselective and enantioselective methodologies.[3]

The α-functionalization of carbonyl compounds appears to be a simple transformation given its wide use, although in practice it is hindered by several complications (Scheme 2).

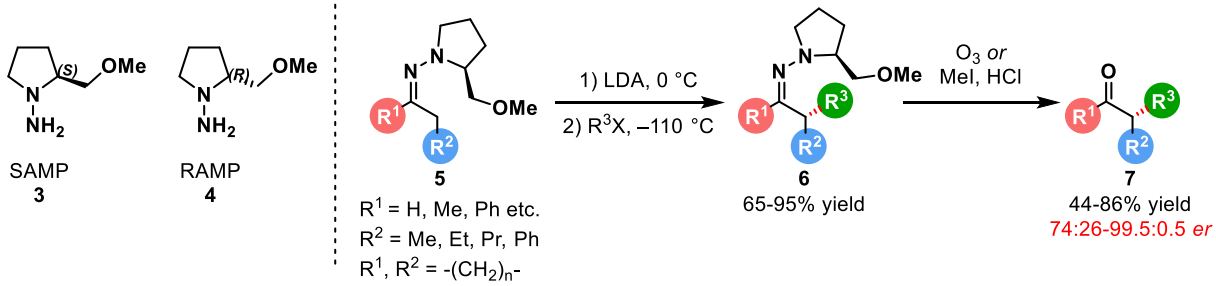


Scheme 2: Potential Difficulties with Asymmetric Enolate Functionalizations

Firstly, the presence of a mixture of *E*/*Z*-enolates could lead to a racemic product even with a high level of facial selectivity in the enolate addition step. This is often overcome by kinetic deprotonation with an appropriate base, such as LDA or LiHMDS.[4] Other factors such as the regioselectivity of enolization for non-symmetrical ketones, and whether the product is also

enolizable under the reaction conditions (and thus racemizable) must also be considered. The issue of *O*- vs *C*-selectivity of the reaction will be discussed on page 16.

Developments of the asymmetric aldol reaction based upon the studies of azaenolates[5] led to the discovery of an applicable chiral auxiliary in 1976 by Enders (Scheme 3).[6]



Scheme 3: Asymmetric Alkylation of SAMP/RAMP-Derived Hydrazones

In this methodology, Enders utilized chiral hydrazones (synthesized from proline-derived hydrazines **3** and **4**) to generate azaenolates which can control the selectivity of the alkylation reaction. Upon deprotonation with LDA, the enolate geometry of **5** has been shown to be $E_{C1\text{-}C4}Z_{N2\text{-}C5}$,[7] and this conformation allows chelation of the methoxy group on the prolinol derivative to the lithium azaenolate. The facial selectivity of the reaction is thus a result of the top face being blocked by the axial methylene groups of the auxiliary (Figure 1).

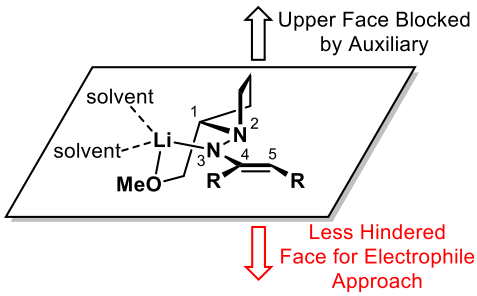
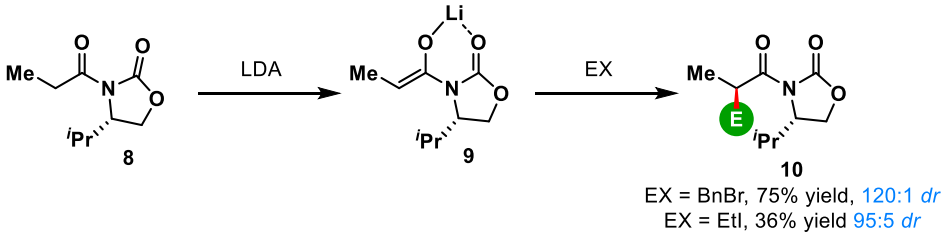


Figure 1: Enders' Proposed Stereochemical Model for SAMP-Controlled Alkylation

These azaenolates showed greater reactivity and regioselectivity than the corresponding enolate, as well as being simple to prepare and stable. In addition, and somewhat rarely, this auxiliary was also applicable to aldehydes. Most importantly, the range of electrophiles was extremely wide: epoxides, disulfides, Davis's oxaziridines and silyl triflates have been utilized with similar yield and diastereoselectivity compared to simple alkyl halides.[7] Further developments have introduced different hydrazones derived from *N*-amino cyclic carbamates which do not require extremely low

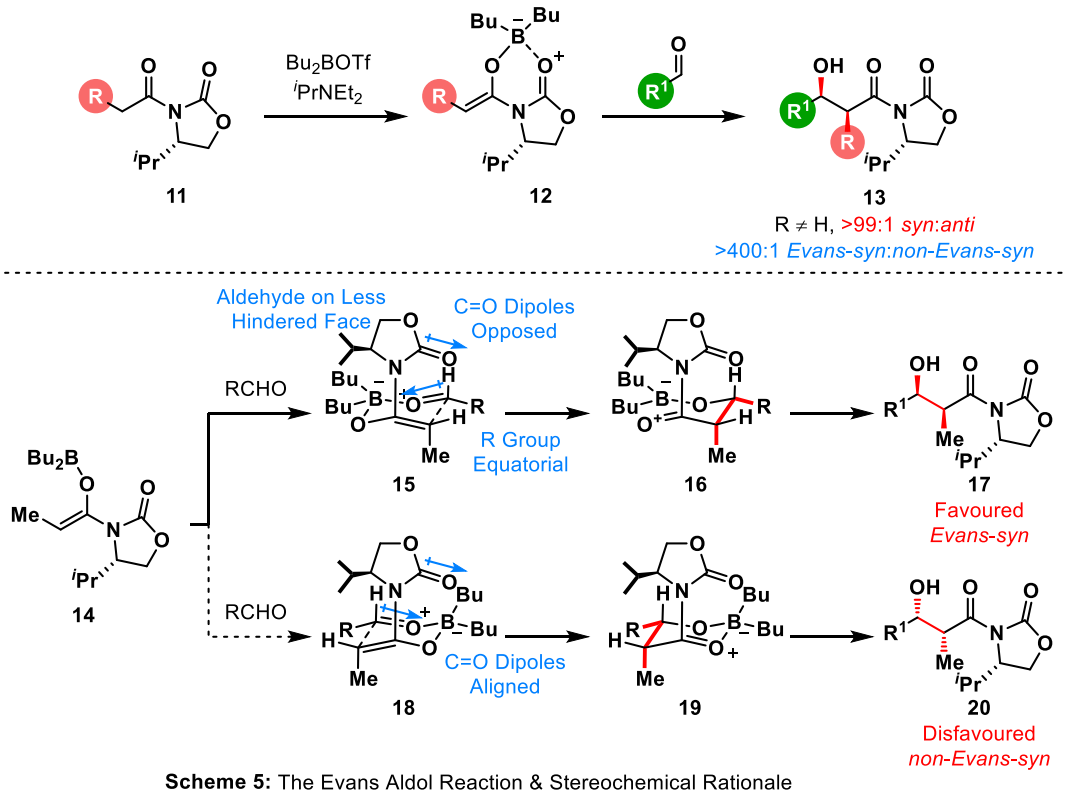
temperatures for stereoinduction, whilst offering greater ease of auxiliary cleavage.[8] Recently, McGlacken reported the enantioselective α-alkylation of an achiral hydrazone, using (−)-sparteine and *sec*-butyllithium with the products isolated in modest enantioenrichment.[9]

In 1981, Evans reported the development of a chiral auxiliary for the α-functionalization of carboxylic acid derivatives using oxazolidinones such as **8** (Scheme 4).[10]



Scheme 4: Evans' Oxazolidinone Auxiliary Approach

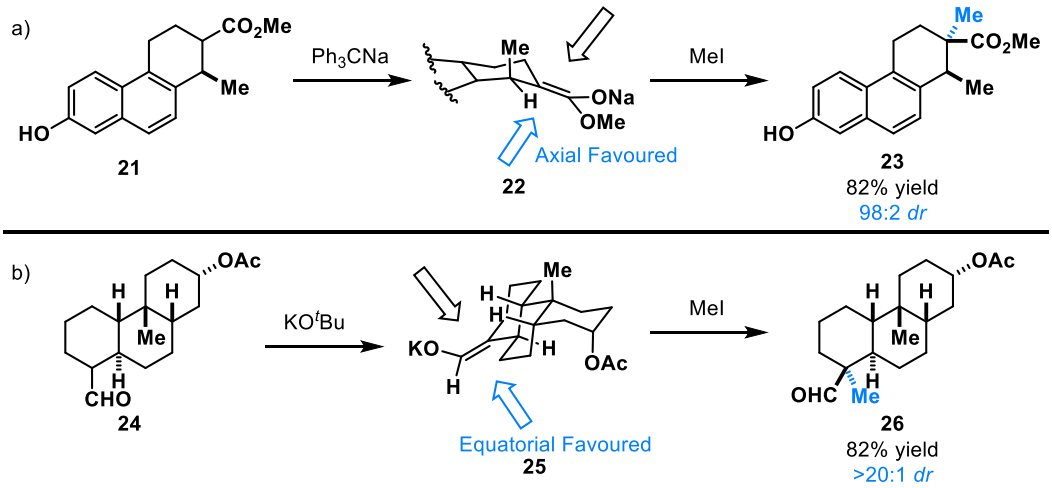
In this case, the oxazolidinone directs the attack onto the electrophile on the opposite face to the bulky group in **8**. As expected, enolate geometry has been demonstrated to be directly related to the level of stereoinduction of the reaction.[11] These auxiliaries take advantage of two-point binding to the lithium/sodium counterion to fix the enolate in a constrained conformation, favouring the *Z*- enolate. Furthermore, the use of bulky strong bases such as LDA and LiHMDS, as well as the intrinsic *Z*-selectivity of amide enolates, strongly favour the formation of the *Z*-enolate **9**, leading to excellent diastereoselection. Similarly, high levels of stereoinduction can also be obtained with titanium enolates under "soft" enolization conditions, presumably through pre-coordination of the titanium (IV) cation to the acyl carbonyl and auxiliary prior to deprotonation.[12] The nature of the electrophile can also influence the levels of selectivity, with bulkier electrophiles interacting more strongly with the steric bulk on the oxazolidinone, resulting in higher levels of stereoinduction. The corresponding aldol reaction proceeds through a different transition state, due to the loss in binding to the carbamate carbonyl group (Scheme 5).



Scheme 5: The Evans Aldol Reaction & Stereochemical Rationale

In this system, the stereochemistry is a result of two possible Zimmerman-Traxler transition states. In both transition states, the aldehyde is on the less-hindered face of the enolate and the R group is equatorial. However, they differ in the alignment of the dipoles: the disfavoured alignment of the carbonyl and auxiliary dipoles in **18** *versus* the favoured transition state **15** where the dipoles are opposed gives rise to the observed selectivity in the production of **17**. Further development of this method to tolerate other electrophiles has led to diastereoselective acylation,[13] hydroxylation,[14] and halogenation[15] reactions.

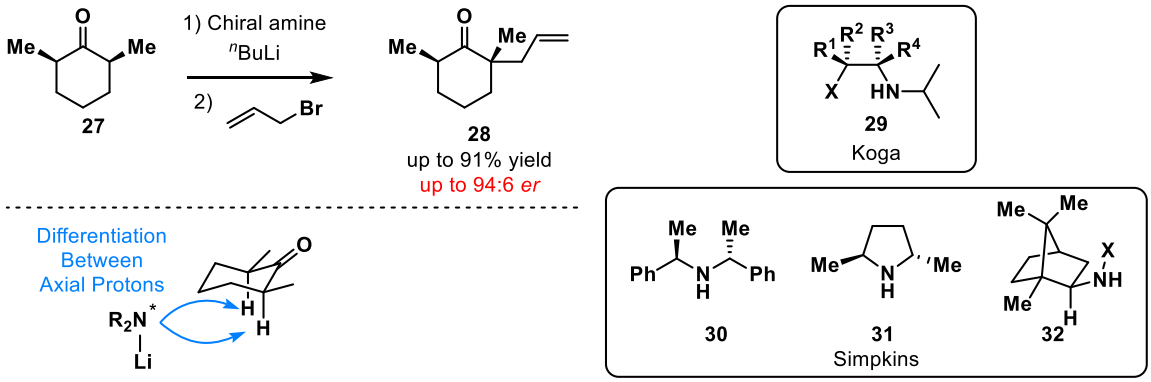
In addition to the aforementioned auxiliary-based approaches, there are also numerous examples of using substrate control to direct the facial selectivity of enolate alkylations, such as early examples from Hogg and Ireland in the synthesis of steroids **23** and **26**, respectively (Scheme 6).[16]



Scheme 6: Hogg's (a) and Ireland's (b) Substrate Stereocontrolled Alkylations

Other methods that take advantage of substrate control have been demonstrated by Matthews and Stork,[17] through interception of enone reduction, as well as the use of fused lactones by Marshall.[18] Diastereoselective functionalization of heteroatom-substituted enolates has also been disclosed by Seebach and Frater, where the enolate chelates to a metal.[19]

Another approach to the enantioselective α-functionalization of carbonyl compounds is *via* the use of a chiral base. Koga and Simpkins pioneered the enantioselective desymmetrization of *meso*-ketones with chiral lithium amides (Scheme 7).[20]

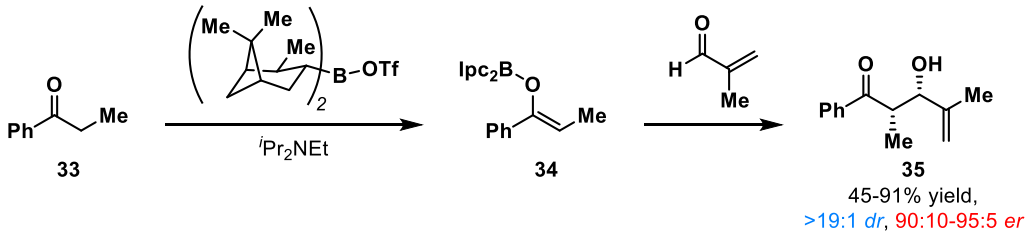


Scheme 7: Chiral Amide Bases for Desymmetrization of Cyclic *meso*-Ketones

The amide base can discriminate between the enantiotopic axial protons in the rigid cyclic system, although this methodology is limited by the requirement of a conformationally locked system.[21]

There has been widespread investigation into using chiral Lewis acids for stereoselective aldol reactions.[22] One successful method was to use chiral boron reagents which had previously been utilized in the asymmetric allylation of aldehydes.[23] The enantioselective boron-mediated aldol

reaction was developed independently in 1996 by Paterson, using Ipc_2B-enolates **34** (Scheme 8),[24] Masamune, with C_2-symmetric borolanes,[25] and Corey, with C_2-symmetric diazaborolidines.[26]

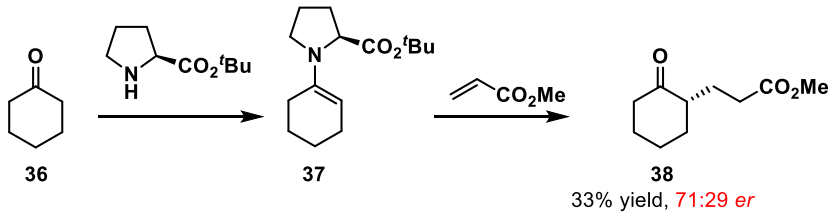


Scheme 8: Paterson's Isopinocampheyl-Substituted Boron Aldol Reaction

The group of Evans also reported an asymmetric boron-mediated aldol reaction, through formation of the boron enolate of an oxazolidinone amide.[27]

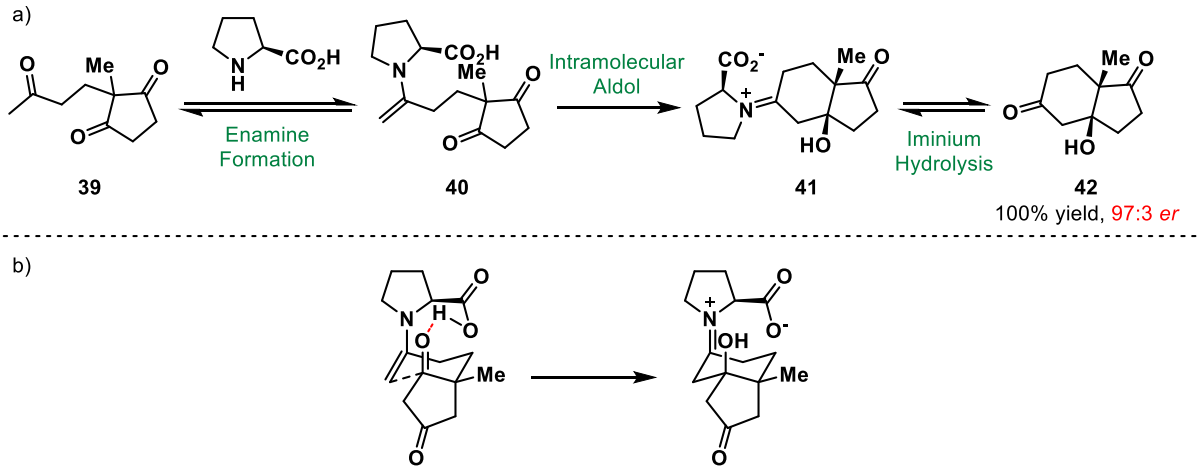
1.2 Catalytic Enantioselective α-Functionalization of Ketone Derivatives

More recently, enantioselective functionalizations of aldehydes have become prevalent, particularly in the field of organocatalysis and transition metal catalysis. The discovery of the proline ester-catalyzed Michael addition of **37** with methyl acrylate to give **38** in moderate enantioenrichment (71:29 *er*) sparked further developments (Scheme 9).[28]



Scheme 9: Yamada's Proline Enamine-Catalyzed Michael Addition

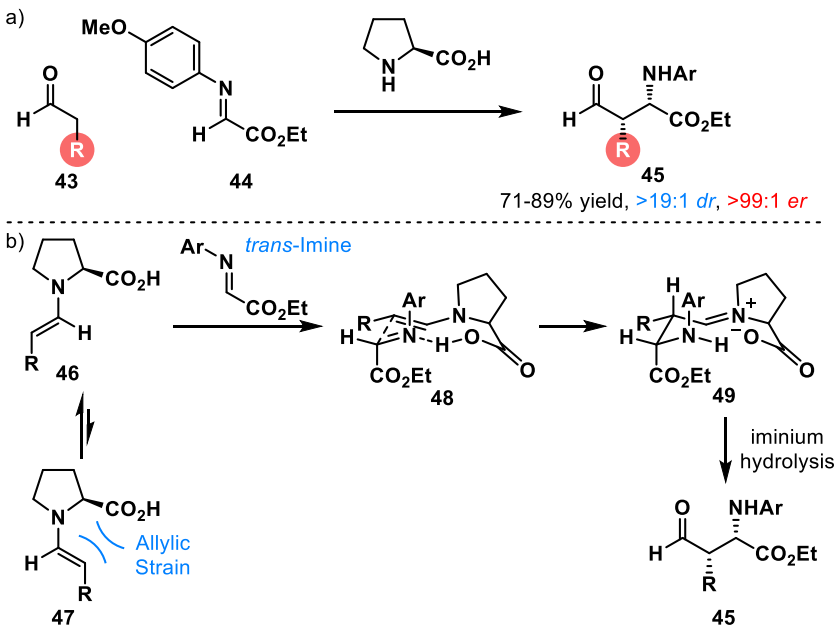
This methodology was then popularized after the use of proline in the aldol condensation for the synthesis of the Hajos-Parrish ketone (a specific case of a Robinson annulation) (Scheme 10a).[29] The much-debated mechanism is believed to proceed through the condensation of proline with the ketone to afford enamine **40** which then reacts with the ketone. In order to form cyclized product **42**, the enantiodetermining step is directed by the hydrogen bond from the proline enamine to the ketone on the electrophile in a Zimmerman-Traxler-like transition state (Scheme 10b).[30]



Scheme 10: a) The Hajos-Parrish-Wiechert Reaction; b) Transition State for the Intramolecular Aldol Reaction

An intermolecular variant of this reaction with acetone as the nucleophile and aldehydes as electrophiles was developed by Barbas and List.[31] MacMillan then extended this to the cross aldol reaction of aldehydes with the more enolizable aldehyde forming the enamine with proline, and thus the aldehyde in the product.[32] The aldehyde acceptor is also added slowly over the course of the reaction to minimize homodimerization.

This process is applicable to a wide range of X=Y type electrophiles to afford α-functionalized aldehydes in excellent levels of enantioenrichment,[33] with a particular focus on the Mannich reaction which was first reported by List (Scheme 11).[34]

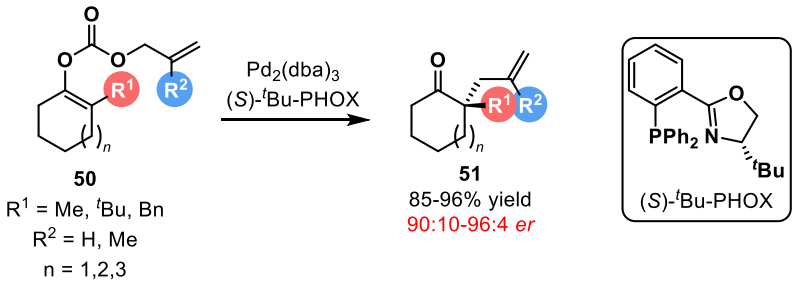


Scheme 11: a) List's Enantioselective Direct Mannich Reaction; b) Proposed Mechanism

Interestingly, due to the *trans*-imine **46** being favoured for steric reasons, the reaction is *syn*-selective. The a*nti*-selective catalytic enantioselective Mannich reaction was disclosed using a β-amino acid proline mimic to alter the enamine conformation, resulting in *anti*-selectivity.[35]

Other chiral amines have been developed, beginning with prolinamides[36] and dimethylthiazolidinium[34a] as proline surrogates for the asymmetric aldol reaction. The scope of reaction type has been extended to include Michael additions,[37] arylation,[38] α-oxidation[39] and α-halogenation[40] reactions, though most of these examples use specialized catalyst architectures that take advantage of specific substrate features.[33]

The use of transition metals to form α-allylated ketones has been widely documented since the Tsuji allylation was disclosed in 1980,[41] however, the asymmetric variant was not disclosed until over 20 years later by Stoltz for carbamates **50** derived from cyclohexanones (Scheme 12).[42]

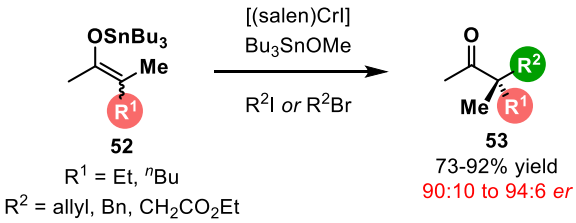


Scheme 12: Stoltz's Enantioselective Tsuji Allylation

Further developments were reported by Trost and Stoltz,[43] although they also suffer from limited scope due to the requirement of symmetrical substrates, or those bearing only one site for allylation. Rhodium and iridium catalyses have also been used in the enantioselective allylation of cyclic enolates,[44] acyl silanes,[45] and β-ketoesters.[46]

One particularly interesting advance was disclosed by List where enantioselective allylation of cyclic ketones was performed under both chiral phosphoric acid and palladium catalysis *via* activation of allylic alcohols with CO_2.[47]

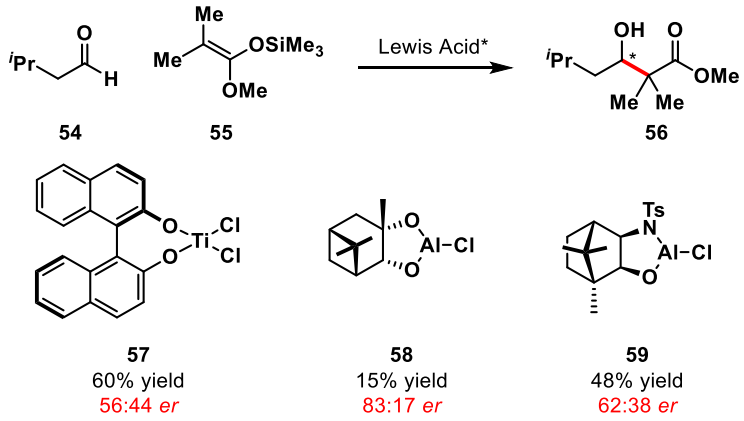
The intermolecular variant was developed by Trost in 1999,[48] allowing the allylation of tetralones with high levels of selectivity. Jacobsen also introduced an intermolecular alkylation of tributyltin enolates **52** using a Cr/salen complex to access highly enantioenriched ketones **53** (Scheme 13).[49]



Scheme 13: Jacobsen's Enantioselective Alkylation of Acyclic Enolates

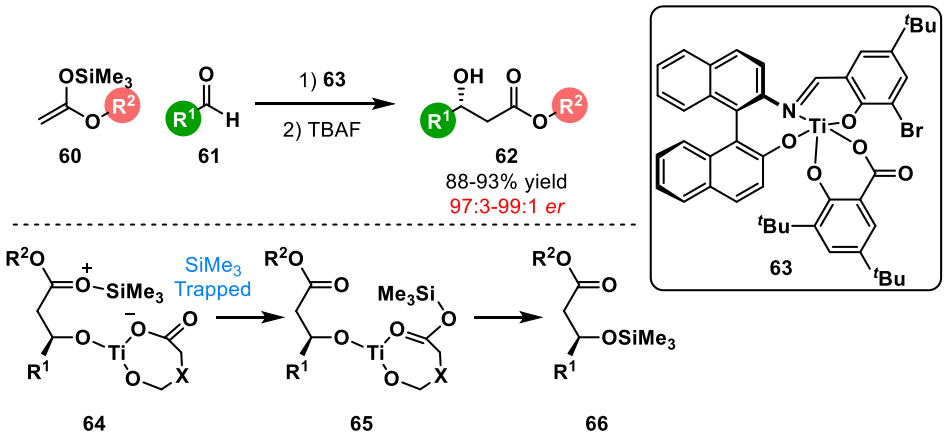
This methodology yields a broader substrate scope, with alkylating agents such as simple alkyl and propargyl halides being tolerated, as well as acyclic enolates (although these require relatively activated electrophiles such as benzyl/allyl halides).

The corresponding silyl enol ethers (rather than the stannyl enol ethers employed in Jacobsen's work),[50] can undergo an enantioselective aldol reaction in the presence of chiral Lewis acids. The first example was disclosed by Reetz in 1986 (Scheme 14),[51] and while the enantioselectivities were low, these results paved the way for further exploration of catalyst scaffolds.



Scheme 14: Reetz's Pioneering Enantioselective Mukaiyama Aldol Reaction

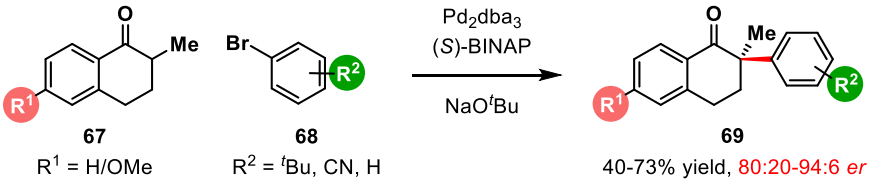
Since then, there has been a plethora of catalysts developed for this reaction, whether for stannyl enol ethers,[52] thioester silyl ketene acetals,[53] silyl ketene acetals,[54] or silyl enol ethers[55].[22, 56] Perhaps one of the more general methods was disclosed by Carreira in 1994 (Scheme 15),[57] where the titanium-centred catalyst **63** is derived from a tridentate Schiff base ligand and di-*tert*-butylsalicylic acid. This particular scaffold allows higher reaction temperatures (up to room temperature) a fast rate of reaction (2-8 hours) and low catalyst loadings (0.5-5 mol%) with excellent stereoselectivity in the products **62**.



Scheme 15: Carreira's Enantioselective Mukaiyama Aldol Reaction

The catalyst is readily customizable, with variation of the Schiff base allowing fine-tuning for particular substrates. The salicylate was shown to be crucial to catalyst turnover and overall selectivity, with the carboxylate in **64** trapping the electrophilic silyl group (**65**, preventing any racemic background reaction catalyzed by $SiMe_3^+$), followed by intramolecular silyl transfer to furnish the siloxy product **66**.

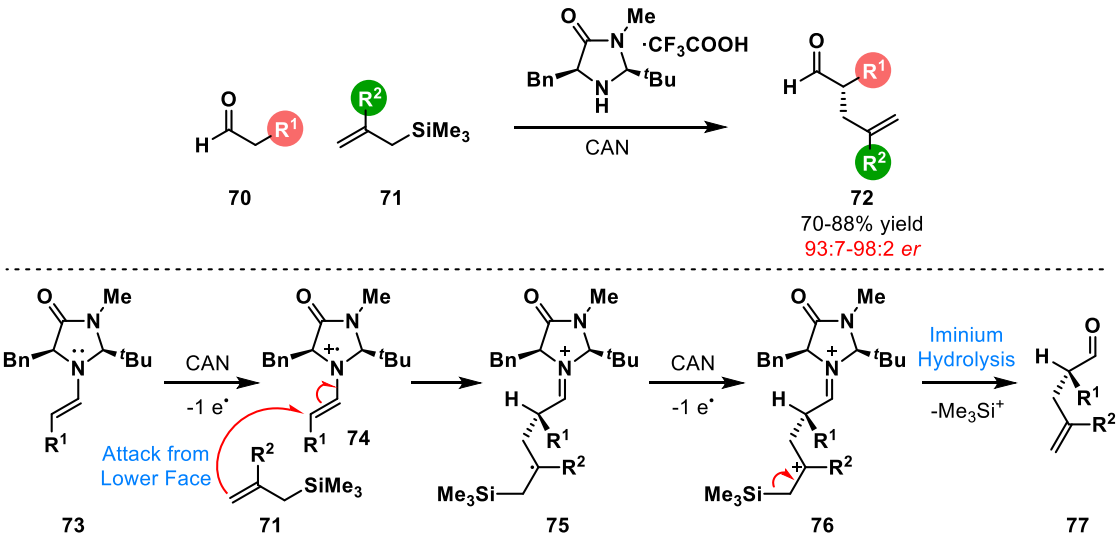
Transition metal enolate chemistry has not been limited to alkylation reactions, with the first (racemic) enolate arylation being reported by Buchwald in 1997.[58] The first asymmetric example was disclosed in 1998 (Scheme 16), by the same group using chiral BINAP ligands to impart asymmetry upon the arylation in the reductive elimination step, synthesizing 2-aryl-1-tetralones **69** with good to excellent enantioenrichment.[59]



Scheme 16: Buchwald's Enantioselective Enolate Arylation

The reaction requires the formation of quaternary stereocentres to avoid racemization under the basic conditions, and shows a strong dependence on ring size: 6-membered rings such as **67** result in higher selectivity than the corresponding 5-membered rings. Further advances were made by the same group, demonstrating that the use of nickel(0) results in much higher selectivity (up to 99:1 *er*) when the carbonyl system is an α-substituted-γ-butyrolactone.[60]

In 2007, the first report of enantioselective SOMO catalysis was made by MacMillan (Scheme 17).[61] This work opened up a different mode of ketone activation to enamine and iminium catalysis.

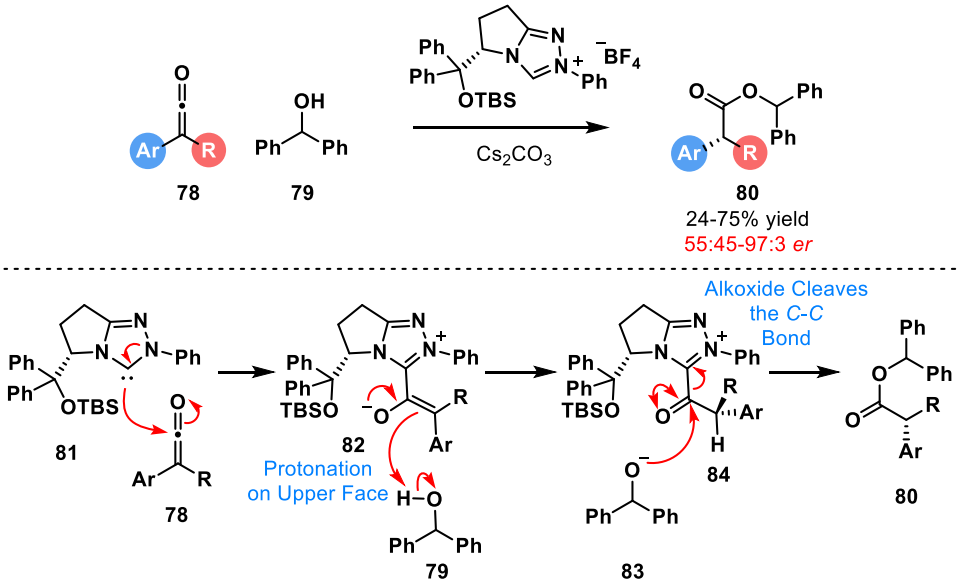


Scheme 17: Macmillan's SOMO Catalyzed Aldehyde Allylation and Mechanism

SOMO catalysis functions through removal of an electron from enamine **73** and then radical reaction with a nucleophile (**71**), followed by another oxidation to (iminium **75**) and hydrolysis. This requires a precise set of conditions, such as the ionization potential of the enamine **73** being lower than that of the ketone **70** or the amine catalyst, as well as the catalyst controlling the stereochemistry in the radical reaction. The carbonyl is generally an aldehyde, though the use of cyclohexanone has also been reported,[62] and nucleophiles such as silyl enol ethers,[63] vinyl potassium trifluoroborate salts,[64] and styrenes[65] have been utilized. Furthermore, radical nucleophiles can be generated *via* photoredox catalysis through cleavage of a C-X bond.[66]

Another method of α-functionalization of ketone derivatives is *via* *N*-heterocyclic carbene (NHC) organocatalysis.[67] While commonly used in umpolung processes to turn aldehydes into carbon nucleophiles, examples of azolium enolates undergoing cycloaddition processes have been disclosed.[68] Somewhat more rarely, it is possible to perform enolate-type electrophilic trapping using azolium enolates, as long as the reaction involves a nucleophilic attack to cleave the azolium ester, releasing the NHC catalyst and generating the oxidized product.[69] The first examples were

enantioselective esterifications of ketenes, independently reported by Ye and Smith (Scheme 18).[70]



Scheme 18: Ye's Enantioselective Esterification of Ketenes and Possible Mechanism

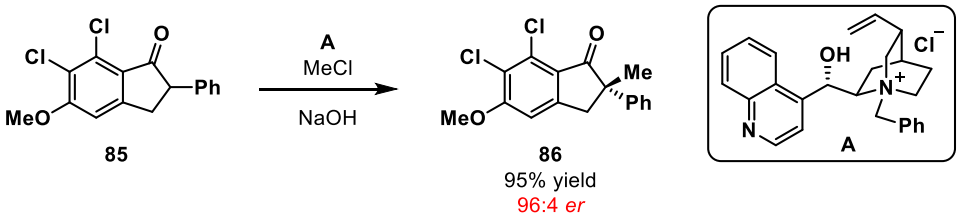
In this example, the azolium enolate **82** is protonated by the diphenylmethanol **79**, with the facial selectivity determined by the bulky diphenylsiloxy group on the lower face of the azolium enolate **81** directing the proton to the upper face. The released diphenylmethoxide **83** then displaces the NHC, generating the enantioenriched ester **80**. In this manner, reaction such as asymmetric protodehalogenation and fluorination of α-dichloroaldehydes[71] and halogenation of ketenes[72] are possible.

Other methods have been developed for selected reactions, for example the use of hydrogen-bonding catalysts such as thioureas[73] and chiral phosphoric acids[74] for the Mannich reaction and conjugate addition reactions; Lewis bases for the formation of chiral enolates;[75] and photochemical transformations.[76] However, despite the many advances in the field, few methods are available for the direct catalytic enantioselective α-functionalization of a ketone, which highlights the challenges faced when attempting such reactions.[3c]

1.3 Phase-Transfer Catalysis

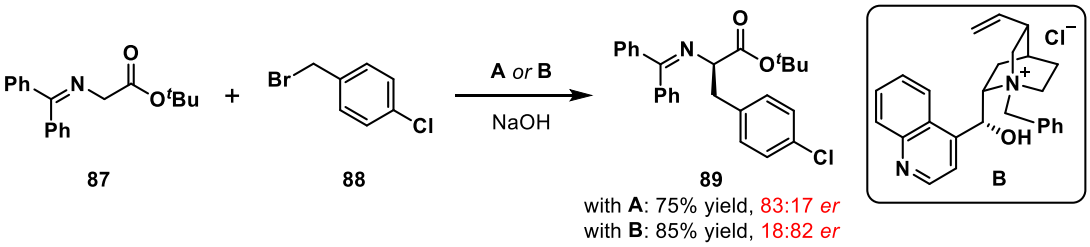
One area of organocatalysis that has provided consistent access to α-functionalized ketone derivatives is phase-transfer catalysis.[77] The first example of an enantioselective phase-transfer

catalyzed reaction to afford an α-functionalized ketone, **86**, was reported in 1984 by Dolling (Scheme 19).[78]



Scheme 19: Dolling's Enantioselective Alkylation of Indanone Derivative **85**

Here, Dolling utilized a benzylated natural product, *N*-benzyl cinchoninium chloride **A**, as the catalyst to direct the electrophile, methyl chloride, to one face of the enolate of **85**. The authors hypothesized that this selectivity is due to π-π stacking and hydrogen bonding of the catalyst hydroxyl group to the enolate, with the electrophile approaching from the outer face. Recent studies by Pliego[79] and Houk[80] suggest that, in fact, the electrophile is bound between the catalyst and enolate, with the benzylic protons acting as anion-binders. The most frequent use of this methodology has been the synthesis of amino acid derivatives, first reported by O'Donnell,[81] with the glycine imine **87** being a privileged substrate for enantioselective alkylation (Scheme 20).



Scheme 20: O'Donnell's Glycine Imine Alkylation

The opposite absolute stereochemistry was observed in the product, with similar levels of enantioinduction, when a pseudoenantiomer of the catalyst derived from cinchonidine (**B**) was employed. This reaction has been the standard for the development of new phase-transfer catalysts, with BINOL-derived scaffolds (**90**)[82] shown to be extremely efficient (Figure 2).[83]

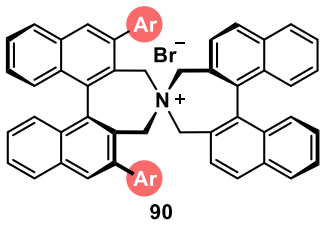


Figure 2: Maruoka's BINOL-Derived Phase-Transfer Catalysts

The mechanism by which phase-transfer catalysts, especially cinchona alkaloid-derived catalysts, function is still not fully understood, and of particular interest to our research group.[84] A general mechanism, suggested by Makosza,[85] is shown below using the benzylation of glycine imine **87** as an example (Figure 23.

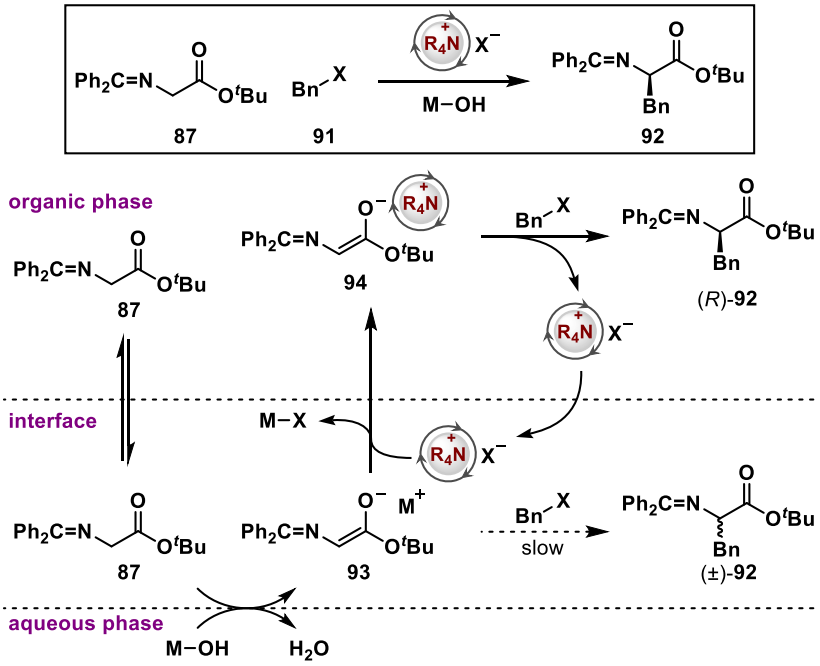
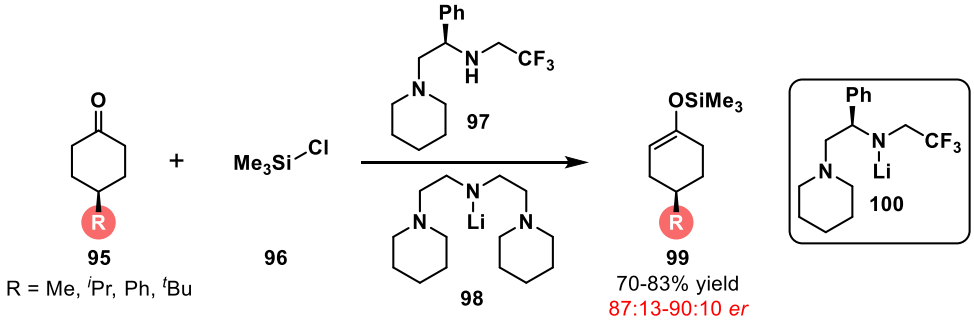


Figure 3: Generalized Mechanism of Phase-Transfer Catalysis

In the above example, the hydrophobic glycine imine **87** is deprotonated by the inorganic base at the liquid-liquid interface, and then undergoes counterion metathesis with the ammonium salt. The lipophilic ion pair **94** is then extracted into the organic phase and reacts with the electrophile, generating enantioenriched product **92**. Depending on the nature of the phase-transfer catalyst it may not enter the aqueous phase at all, despite its ionic nature, which means that the deprotonation event and counterion exchange all happen at the interface.

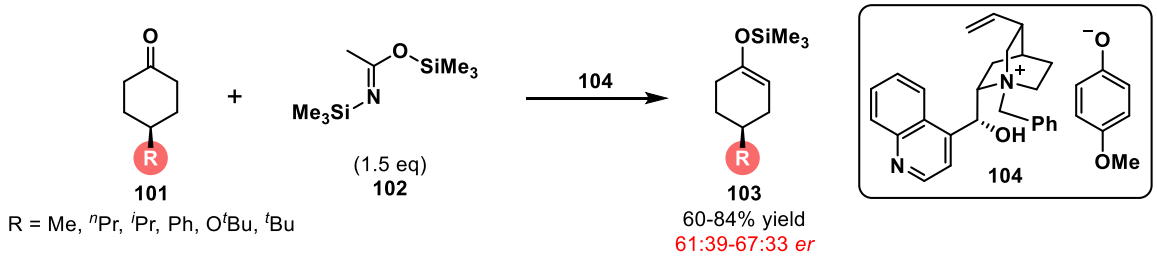
1.4 Catalytic Enantioselective *O*-Functionalization of Ketones

In addition to limited reports of direct α-functionalization of ketones, enantioselective *O*-functionalization remains a largely unexplored area of organic chemistry. This is in part due to lack of formation of a stereocentre in the reaction, as opposed to for *C*-functionalization. While there is a plethora of methods for desymmetrizing a *meso*-diketone by nucleophilic attack into the carbonyl,[86] very few utilize the nucleophilicity of an enolate. The first desymmetrization of a ketone *via O*-functionalization was reported by Koga in 1997 (Scheme 21).[87]



Scheme 21: Koga's Enantioselective Desymmetrization of a Ketone

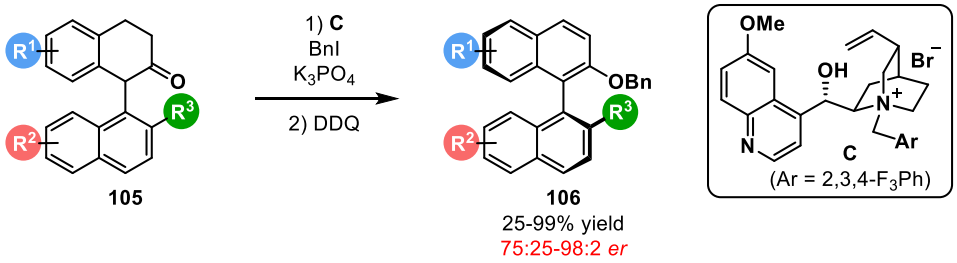
In this example, an asymmetric deprotonation was achieved through the use of **97** and **98** to generate the chiral lithium amide **100**, which deprotonates the symmetrical ketone **95** with subsequent quenching with chlorotrimethylsilane **96** to afford the product **99** in high yield and enantioenrichment. A similar functionalization was more recently achieved with chiral ammonium phenolates as the base (**104**), but with reduced enantioselectivity (Scheme 22, 61:39 to 67:33 *er*).[88]



Scheme 22: Levacher's Enantioselective Desymmetrization of a Ketone

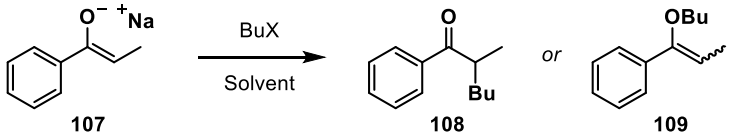
The most recent example, disclosed by our research group in 2017, showed that this approach could be used in the construction of enantioenriched biaryls. Point-chiral racemic ketone **101** is deprotonated to generate an axially chiral enolate that is then alkylated in a dynamic kinetic

resolution. The axially chiral benzyl enol ether formed in the reaction is then subsequently oxidized to afford the corresponding BINOL derivative **106** (Scheme 23).[89] The choice of electrophile is somewhat limiting, with only allyl or benzyl iodide giving the highest levels of enantioenrichment. Acyl or silyl electrophiles were found to afford only racemic enol ethers.[90]



Scheme 23: Smith's Enantioselective Ketone Benzylation to Afford BINOL Derivatives

This reaction shows remarkable levels of *O*-selectivity which is unusual for carbon electrophiles. There have been numerous reports that a there is a lower intrinsic barrier to *O*-alkylation than *C*-alkylation,[91] though *C*-alkylation is often observed. The reasons for this observation are complex, and many variables are involved, however some general trends can be seen: the solvent,[92] electrophile,[92] counterion[93] and electronics/steric bulk of the nucleophile[94] are all important in governing the regioselectivity. One example of such studies is that of Wagner, who examined the effect of the leaving group and solvent, in the butylation of propiophenone (Table 1).[92]



% *O*-butylation

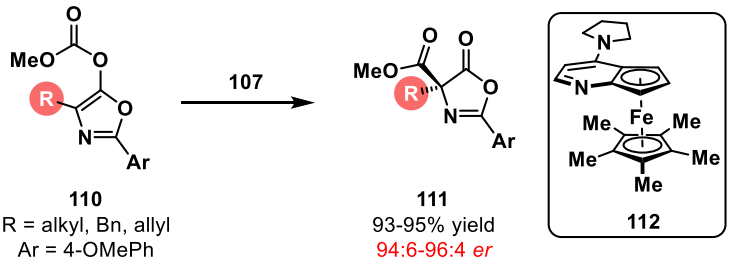
X	HMPA	DMSO	Et_2O
I	15	10	1
Br	40	23	5
Cl	67	46	18
OMs	83	N/A	11
OTs	85	44	20
F	96	N/A	N/A

Table 1: Wagner's Experiment on Leaving Group/Solvent Effects

Wagner's results show that, in this system, as the leaving group becomes more electronegative the ratio of *O*-alkylation (**109**) increases relative to *C*-alkylation (**108**). In addition, the strength of binding to the cation affects this ratio: a greater proportion of *O*-alkylation is observed in solvents which might compete with the enolate for binding to the sodium ion, resulting in weaker ion-pairing. A similar effect based on counterion size was observed by Dehmlow in the phase-transfer catalyzed alkylation of deoxybenzoin.[93]

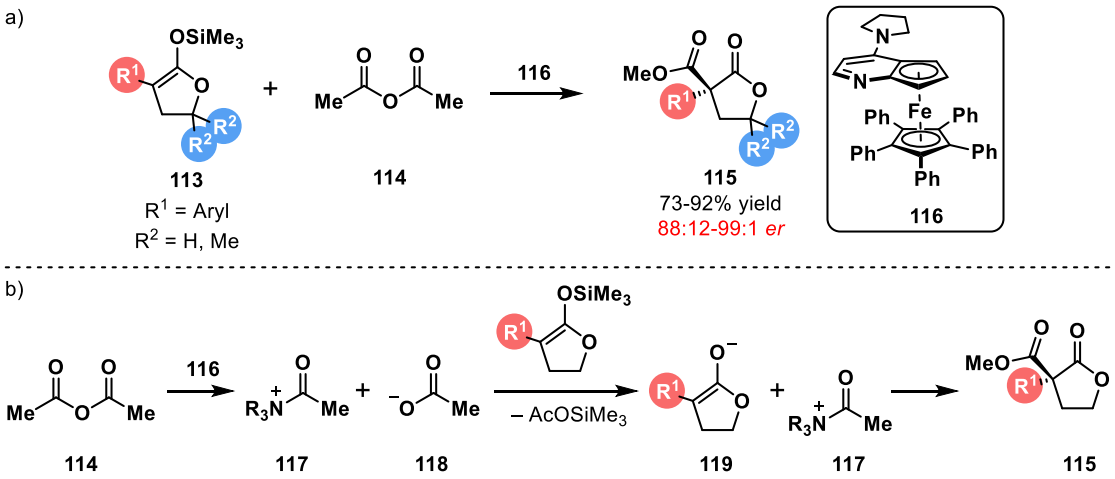
1.5 Catalytic Enantioselective Acylation of Ketone Derivatives

The racemic *C*-acylation of ketones has been extensively utilized as a method for synthesizing 1,3-dicarbonyls, especially β-ketoesters, since the first reports of the Claisen condensation in 1887.[95] An enantioselective variant, however, is more challenging due to the reversibility of the process without a final, thermodynamically favourable, deprotonation of the 1,3-dicarbonyl which would racemize the stereocentre. As such formation of a quaternary stereocentre is essential for this methodology to succeed. A method to provide enantioenriched 1,3-dicarbonyls **111** through Steglich rearrangement of **111**[96] was disclosed by Fu in 1998 (Scheme 24).[97]



Scheme 24: Fu's Enantioselective Steglich Rearrangement

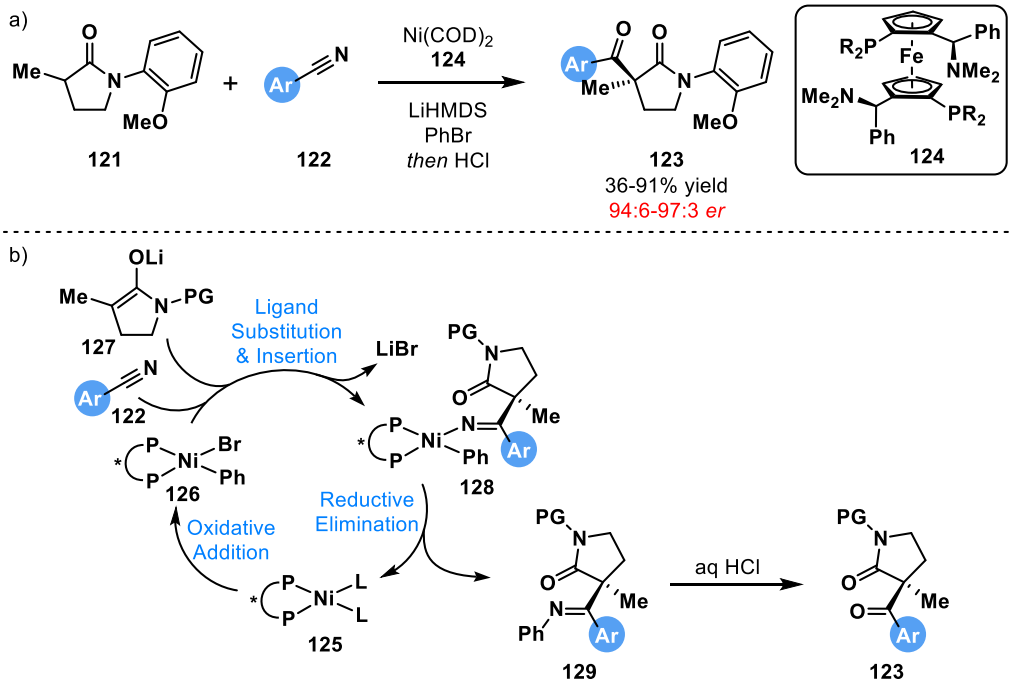
Further developments have shown that different types of Lewis bases can be employed as catalysts, such as isothioureas,[98] phosphines,[99] and betaines.[100] A significant advancement of this methodology was the use of silyl ketene acetals **113** to allow for intermolecular acylation, with total selectivity for the *C*-acylated product **115** (Scheme 25).[101] An acyclic example with a 2:1 ratio of *E*/*Z*- isomers also showed surprising levels of selectivity and yield (94:6 *er* and 82% yield). The levels of *C*-selectivity observed could be a consequence of any *O*-acylated product undergoing Steglich rearrangement to afford the *C*-acylated product **115**.



Scheme 25: a) Fu's Intermolecular *C*-Acylation of Silyl Ketene Acetals; b) Fu's Proposed Mechanism

Smith[102] and Jacobsen[103] have both recently demonstrated similar reactions under the influence of isothiourea and anion-binding catalysis, respectively.

The most recent report in the field was disclosed in 2016 by Stoltz, who demonstrated that lithium enolates derived from lactams could couple with aryl cyanides under nickel catalysis. The imine products **129** (which could be isolated) could then be converted into the corresponding "acylated" lactam **123** (Scheme 26).[104]



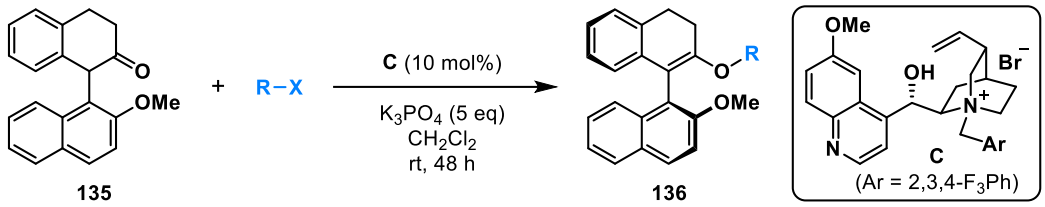
Scheme 26: a) Stoltz's Nickel-Catalyzed Lactam Enolate-Cyanide Coupling Reaction; b) Stoltz's Proposed Mechanism

Despite the success of various groups with α-functionalization of ketone derivatives, it is worth noting that, to the best of our knowledge, to date, there have been no reported examples of enantioselective direct *C*- or *O*-acylation of a ketone.

2. Ketone and Indole *O*-Acylation

2.1 Precedent for Enantioselective *O*-Acylation

Enantioselective *O*-acylation of a ketone, a previously unknown transformation, has recently been investigated by John Jolliffe in our research group during the work on enantioselective synthesis of BINOL derivatives **136** (Scheme 26).[90]



Entry	R–X	*er*
1	Ac_2O	50:50
2	AcCl	N/A[a]
3	TBDPSCl	50:50
4	Methyl iodide	58:42
5	Allyl iodide	88:12
6	Benzyl iodide	91:9

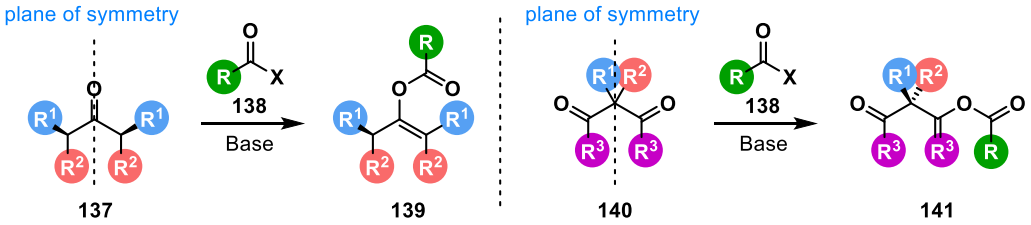
[a] No Conversion

Table 2: Effect of Electrophile on Enantioselective *O*-Functionalization of **135**

In this case however, only alkyl electrophiles were found to be effective, resulting in either poor yield or selectivity (Table 2), so we pursued other ideas for enantioselective ketone functionalization with acyl electrophiles. As mentioned earlier (Scheme 22, page 15), the desymmetrization of 4-substituted cyclohexanone was disclosed under phase-transfer conditions by Levacher.[88] This provided the inspiration for us to consider desymmetrization of a ketone as a viable strategy for enantioselective *O*-acylation.

2.2 Desymmetrization as a Strategy for *O*-Acylation

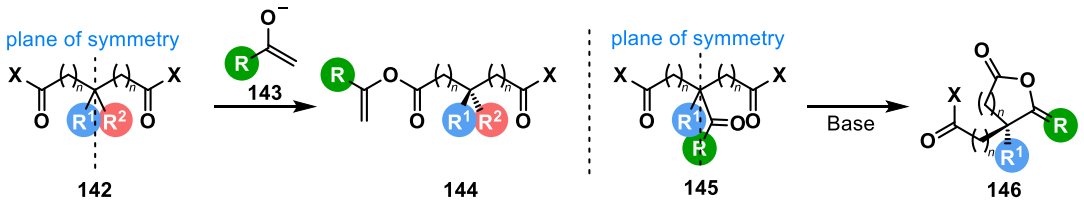
A desymmetrization of a ketone would require one of two attributes: either a ketone with a plane of symmetry running along the C-O bond, **137**, or a diketone with a plane of symmetry between the two ketones, **140** (Scheme 27).



Scheme 27: Possible Methods of Ketone Desymmetrization

The enolate geometry, a potential cause for low selectivity or multiple products, could be controlled through the use of cyclic ketones, and reactivity could potentially be increased through intramolecular reaction (and double-acylation of diketone derivatives, such as **141**, could be minimized).

Another possibility could be using a ketone to desymmetrize a diester such as **142** (Scheme 28).

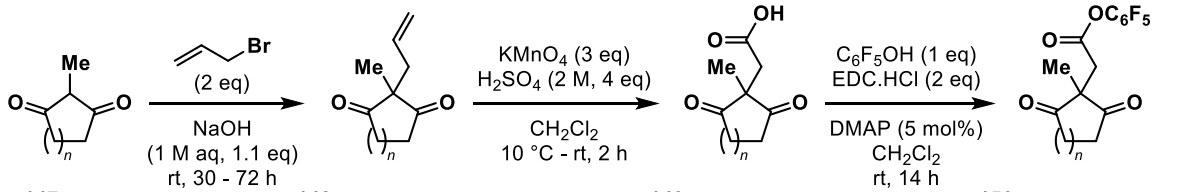


Scheme 28: Possible Methods of Ester Desymmetrization with a Ketone

One advantage of this approach could be the avoidance of double acylation, again through intramolecular reaction of relatively unactivated ketones (**145**).

2.2.1 Desymmetrization of a *meso*-Diketone

There are many cyclic diketones available commercially, and we identified target substrates **150** and **154** that could be synthesized in 3 steps in analogy to literature methods (Scheme 29).[105]



147, n = 1
151, n = 2

148, n = 1, 50% yield
152, n = 2, 84% yield

149, n = 1, 90% yield
153, n = 2, 74% yield

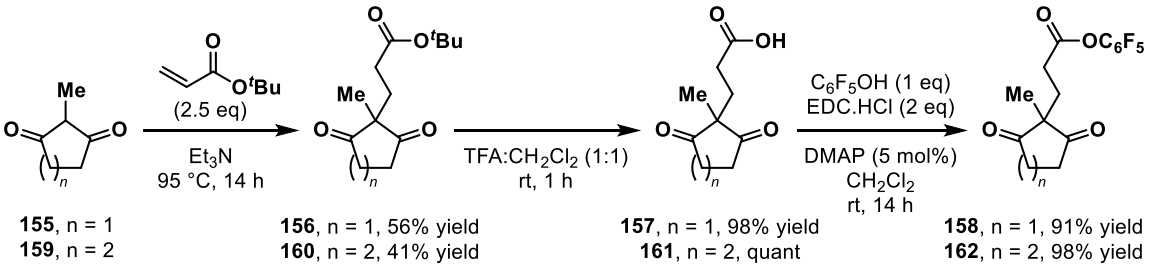
150, n = 1, 84% yield
154, n = 2, 80% yield

Scheme 29: Synthesis of *meso*-Diketoesters **150** and **154**

The allylation of 2-methylcyclopentane-1,3-dione **147** proceeded smoothly to afford **148** in 50% yield, which then underwent oxidative dihydroxylation/cleavage/oxidation with $KMnO_4$ in CH_2Cl_2 to afford **149** in 90% yield after recrystallization. We reasoned that we could convert carboxylic

acid **149** into a variety of activated esters to screen for reactivity. Pentafluorophenol had previously been demonstrated to be effective in ketone acylation reactions,[106] so was chosen as our leaving group for testing the viability of the desired *O*-acylation. Esterification of **149** with pentafluorophenol using *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide (EDC) as the coupling agent afforded **150** in 84% yield. The same methodology was applied to 2-methylcyclohexane-1,3-dione **151** successfully, affording **154** in 50% yield over three steps.

Substrates with a homologated acyl tether could be synthesized through the conjugate addition of diketones **155** and **159** into *tert*-butyl acrylate in triethylamine, followed by TFA-catalyzed acid hydrolysis to provide carboxylic acids **157** and **161** in 45% and 41% yields, respectively, over both steps (Scheme 30). Again, the pentafluorophenyl esters **158** and **162** were synthesized through coupling of the acid with pentafluorophenol with EDC in excellent yields.



155, n = 1
159, n = 2

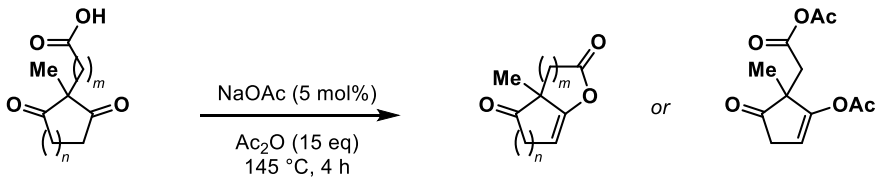
156, n = 1, 56% yield
160, n = 2, 41% yield

157, n = 1, 98% yield
161, n = 2, quant

158, n = 1, 91% yield
162, n = 2, 98% yield

Scheme 30: Synthesis of *meso*-Diketoesters **158** and **162**

We wanted to transform our substrates **149**, **153**, **157** & **161** to the racemic products **163**-**166** using established literature procedures (Scheme 31),[107] which would allow us to follow product formation by reverse-phase HPLC in our subsequent *O*-acylation reactions.



149, m = 1, n = 1
153, m = 1, n = 2
157, m = 2, n = 1
161, m = 2, n = 2

163, m = 1, n = 1, 0% yield
164, m = 1, n = 2, 62% yield
165, m = 2, n = 1, 72% yield
166, m = 2, n = 2, 51% yield

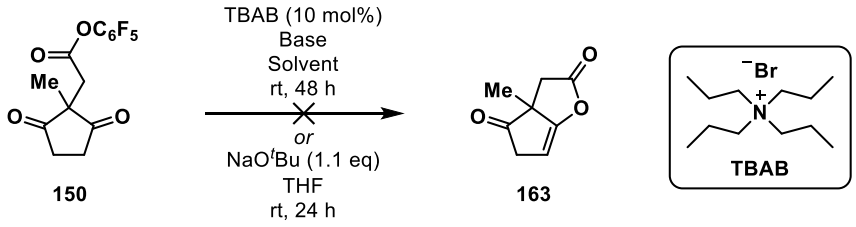
167, 61% yield

Scheme 31: Cyclization of Diketoacids with Acetic Anhdride

While the cyclization of **153**, **157** and **161** proceeded smoothly in moderate to good yields (51–72%), we were surprised to observe formation of **167** instead of **163** in 61% yield. We hypothesized that after *in situ* formation of the mixed anhydride, intramolecular attack by an enolate would lead to formation of the cyclized products **163**-**166**. For acid **149**, we postulated that the tether was too short to allow for the good orbital overlap required for formation of the strained 5,5 ring system. Another possible mechanism for the formation of **167** is that the cyclization was reversible and the product was ring-opened by acetate. The fused 5,5 ring system with an *exo*-internal double bond appears to be very strained, and likely to be an unsuitable target, despite its similarity to various intermediates in the synthesis of prostaglandins.[108]

With successful thermodynamic cyclizations of three substrates, we first attempted cyclization of **150** under phase-transfer conditions which we assumed to be challenging, given its lack of reactivity under thermodynamic cyclization conditions (Scheme 32).

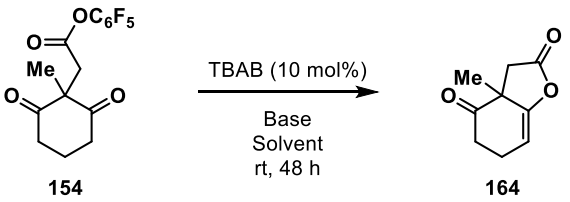
We utilized "standard" phase-transfer conditions, with two solvents (toluene and CH_2Cl_2) and various bases (solid KO^{t}Bu, solid KOH, solid and aqueous K_3PO_4, solid and aqueous K_2CO_3, solid and aqueous KF). For these initial experiments, we used the achiral catalyst tetrabutylammonium bromide (TBAB). TBAB has been observed in our group to show higher reactivity than the cinchona-derived catalysts and thus was used as a test for reactivity.



Scheme 32: Attempted Cyclization of **150**

Unsurprisingly, diketoester **150** showed absolutely no reactivity under phase-transfer conditions or even more forcing conditions of sodium *tert*-butoxide in THF, so we decided to focus on the substrates that had cyclized under thermodynamic conditions. We began by screening substrates **154** and **158** which, upon cyclization, would both give less strained 5,6 ring systems.

The tables shown below are not an exhaustive account of all conditions utilized but include selected examples to demonstrate trends. For a full account of all the conditions utilized see **Appendix A**.



154 **164**

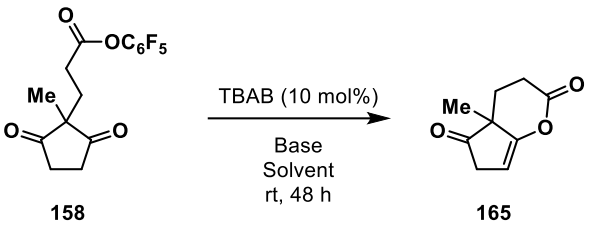
Entry	Solvent	Base	**154**:**164**:hydrolysis[a]
1	PhMe	KOH	22:78:0
2	PhMe	K_2CO_3	32:68:0
3	PhMe	K_3PO_4	50:50:0
4	CH_2Cl_2	KOH	7:93:0
5	CH_2Cl_2	K_2CO_3	17:83:0
6	CH_2Cl_2	K_3PO_4	70:30:0
7	PhMe	K_3PO_4	20:80:0[b]
8	CH_2Cl_2	K_3PO_4	32:68:0[b]

[a] Conversion by uncalibrated HPLC Analysis
[b] Conversion by ^{1}H NMR Analysis

Table 3: Attempted Cyclization of **154**

We hoped that a relatively strong base such as potassium hydroxide would give us good conversions with the achiral catalyst TBAB, but were disappointed to find that, in both toluene and CH_2Cl_2, it afforded lower conversions than potassium carbonate (Table 3, entries 1–2 & 4–5). No bases gave higher conversions than potassium carbonate other than potassium phosphate which gave far superior conversions in both toluene and CH_2Cl_2 (Table 3, entries 3 & 6). We reason that this is due to the highly basic nature of anhydrous phosphate, which has been observed to be a stronger base than hydroxide in organic solvents.[109] Comparison of our HPLC conversions to those obtained from ^{1}H NMR analysis of the crude reaction mixture demonstrated that the HPLC conversions were significantly overestimated (Table 3, entries 7–8 compared to entries 3 & 6).

Cyclization of ester **158** was then screened in the same manner (Table 4).



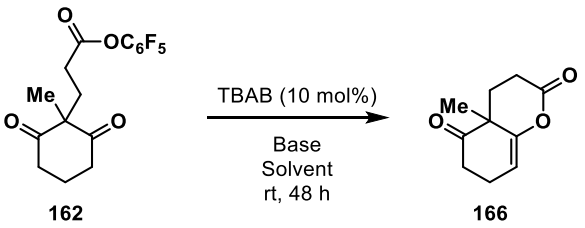
158 **165**

Entry	Solvent	Base	**158**:**165**:hydrolysis[a]
1	PhMe	KOH	20:80:0
2	PhMe	K_2CO_3	40:60:0
3	PhMe	K_3PO_4	45:55:0
4	CH_2Cl_2	KOH	22:78:0
5	CH_2Cl_2	K_2CO_3	30:55:15
6	CH_2Cl_2	K_3PO_4	58:42:0
7	PhMe	K_3PO_4	24:73:3[b]
8	CH_2Cl_2	K_3PO_4	32:68:0[b]

[a] Conversion by HPLC Analysis
[b] Conversion by ^{1}H NMR Analysis

Table 4: Attempted Cyclization of **158**

For substrate **158**, we observed very similar trends to the previously investigated substrate **154**. Hydroxide bases once again gave very low conversions (Table 4, Entries 1 & 4), though this time the conversion with potassium carbonate was much closer to that observed with phosphate (Table 4, entries 2–3 & 5–6). We saw no significant improvement in yield for this system over the previous, so substrate **162** was screened against the same series of reaction conditions, expecting that this would show higher conversion due to the more stable 6,6 ring system being formed (Table 5).



162 **166**

Entry	Solvent	Base	**162**:**166**:hydrolysis[a]
1	PhMe	KOH	9:78:13
2	PhMe	K_2CO_3	38:62:0
3	PhMe	K_3PO_4	41:59:0
4	CH_2Cl_2	KOH	14:86:0
5	CH_2Cl_2	K_2CO_3	38:55:7
6	CH_2Cl_2	K_3PO_4	50:45:5
7	PhMe	K_3PO_4	29:71:0[b]
8	CH_2Cl_2	K_3PO_4	40:60:0[b]

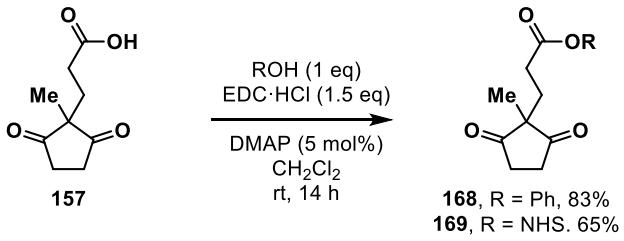
[a] Conversion by HPLC Analysis
[b] Conversion by ^{1}H NMR Analysis

Table 5: Attempted Cyclization of **162**

Again, similar levels of conversion and effect of base were observed compared to the previous systems (Table 5 *versus* Tables 3 & 4).

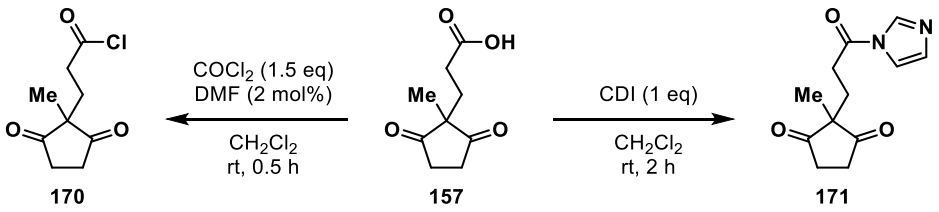
In summary of this screen, we can see that while there was some reactivity for each substrate: **154**, **158** and **162**; the levels of conversion were disappointingly low. The conversion could not be increased through prolonged reaction time, as our chiral catalysts tend to lose effectiveness after ~48 hours under basic conditions.[110] From our comparisons of the HPLC conversions compared to ^{1}H NMR analysis, we could see the absolute values from the HPLC would need calibration to determine accurate conversions, however they were shown to be a moderate approximation and proportional to the actual conversions determined by ^{1}H NMR spectroscopy.

With a lack of success with cyclization using pentafluorophenyl esters, we synthesized a variety of other activated ester derivatives of acid **157**. Esters **168** and **169** were formed in good yield (83% & 65% yield, respectively) *via* esterification of **157** with EDC and the corresponding alcohol (Scheme 33).



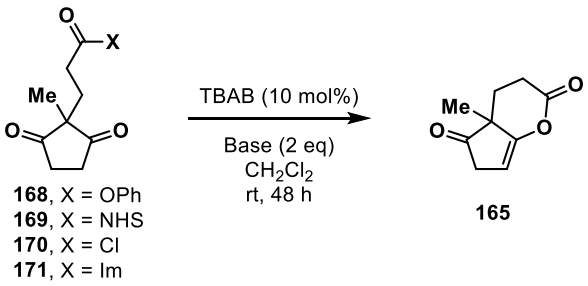
Scheme 33: Synthesis of Activated Ester Derivatives of **157**

Due to the difficulty of purification of the acid chloride **170** and acid imidazolide **171**, these were formed *in situ* and tested for consumption of acid **157** by HPLC, then added to the reaction mixture without any further purification (Scheme 34).



Scheme 34: Synthesis of Activated Ester Derivatives of **157**

A screen of these activated esters in CH_2Cl_2 with a variety of bases (KOH, K_3PO_4, K_2CO_3, KF, KOAc) and TBAB as the catalyst showed variable reactivity (Table 6, for full results see **Appendix B**).



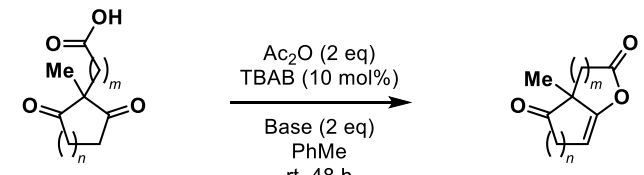
Entry	X	Base	P:SM:hydrolysis
1	OPh	K_3PO_4	0:63:37
2	OPh	KF	0:100:0
3	NHS	K_3PO_4	21:18:61
4	NHS	KF	7:53:40
5	NHS	K_2CO_3	29:22:49
6	Cl	KF	23:12:0[a]
7	Cl	KOH	0:0:0[a]
8	Im	KOH	0:0:0[a]

[a] The Remaining Material was Converted to an Unidentified Side-Product

Table 6: Selected Results from Cyclization of Active Esters **168–171**

Disappointingly, we failed to see any increase in conversion compared to **158**, Phenyl ester **168** proved unreactive under the reaction conditions (Table 6, entries 1–2) despite some reactivity being observed for pentafluorophenyl ester **158**. *N*-Hydroxysuccinimidyl ester **169** showed some reactivity, though lower conversions than for **158**, with a maximum conversion to product of 19% with K_2CO_3 (Table 6, entries 3–5). For both these esters we saw significant levels of hydrolysis, which was not observed for pentafluorophenyl ester **158**. For the acid chloride **170** and acid imidazolide **171**, we started to see an unidentified by-product being formed, possibly due to the lack of purification prior to subjection to the reaction conditions (Table 6, entries 6–8). The acid chloride should have proved most reactive so it was particularly surprising that we observed low levels of desired product **165**, only up to 23% (Table 6, entry 6).

One final method of cyclization for these substrates could be to perform the *O*-acylation under similar conditions to that of the acetic anhydride cyclization, although under kinetic control with a phase-transfer catalyst, rather than thermodynamic control. In this case we subjected the acids to standard phase-transfer conditions in the presence of acetic anhydride. The hypothesis was that we could form the mixed anhydride *in situ* and deprotonation of the ketone could then cause cyclization in the presence of a phase-transfer catalyst (Table 7, for full results see **Appendix C**).



153, m = 1, n = 1
157, m = 2, n = 2
161, m = 2, n = 2

164, m = 1, n = 2
165, m = 2, n = 1
166, m = 2, n = 2

Entry	Substrate	Base	P:SM[a]
1	**153**	KOH	34:66
2	**153**	K_3PO_4	46:54
3	**153**	KOAc	50:50
4	**157**	KOH	65:35
5	**157**	K_3PO_4	42:58
6	**157**	KOAc	52:48
7	**161**	KOH	58:42
8	**161**	K_3PO_4	50:50
9	**161**	KOAc	65:35
10	**153**	KOAc	15:85[b]
11	**157**	KOAc	27:73[b]
12	**161**	KOAc	48:52[b]

[a] Conversion by HPLC Analysis
[b] Conversion by ^{1}H NMR Analysis

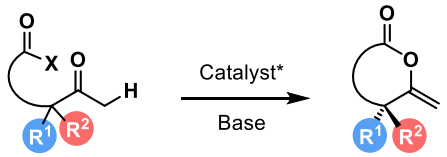
Table 7: Attempted Cyclization with *in situ* Activation of Acids **153**, **157**, **161**

The results from this reaction show that some reactivity can occur within this system providing proof of concept, although again, moderate conversions at best were observed. For all three substrates, **153**, **157** and **161**, conversions with each base used gave very similar conversions (Table 7, entries 1–9) The best HPLC conversions at 48 hours were with potassium acetate as a base (Table 7, entries 3, 6, 9), and we took these crude reaction mixtures and compared them to the ^{1}H NMR spectra. The HPLC conversions had variable agreement with the ^{1}H NMR conversion (Table 7, entries 10–12), presumably due to the change in chromophore (in this case there is no pentafluorophenyl ester in the starting material). We did however observe the same overall trend across the substrate series, with the highest conversions seen in formation of the 6,6 ring system. At this point we reasoned that while electrophile activation plays a part in the reaction, the lack of acidity in the ketone was limiting reactivity. While a simple method to acidify the ketone would be

to synthesize the α,α'-aryl derivative, this substitution pattern was not disclosed in the literature and would possess *meso*/C_2-symmetric diastereoisomers, further complicating the system. As such, we decided to modify our system by synthesizing an α-aryl ketone which could undergo cyclization in a kinetic resolution.

2.3 (Dynamic) Kinetic Resolution as a Strategy for *O*-Acylation

Another method of enantioselective *O*-acylation of a ketone would involve a kinetic resolution of an α-substituted ketone in an *enolexo*-manner to afford the corresponding enol lactone (Scheme 35).



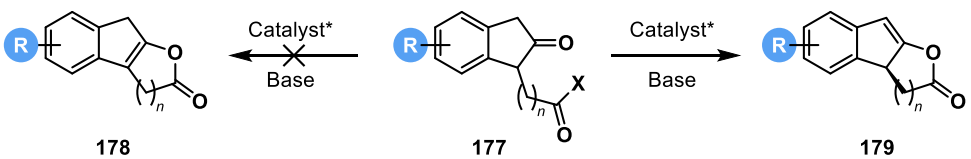
175 **176**

Scheme 35: Reaction Design for (Dynamic) Kinetic Resolution

Kinetic resolutions have a maximum theoretical yield of 50%, however, by virtue of the stereocentre being in an acidic position α- to the ketone, we hypothesized that, if R^1 = H in **175**, we could racemize the stereocentre through reversible deprotonation/reprotonation under the reaction conditions which would increase the maximum theoretical yield to 100% (a dynamic kinetic resolution).

2.3.1 A 2-Indanone-Derived System

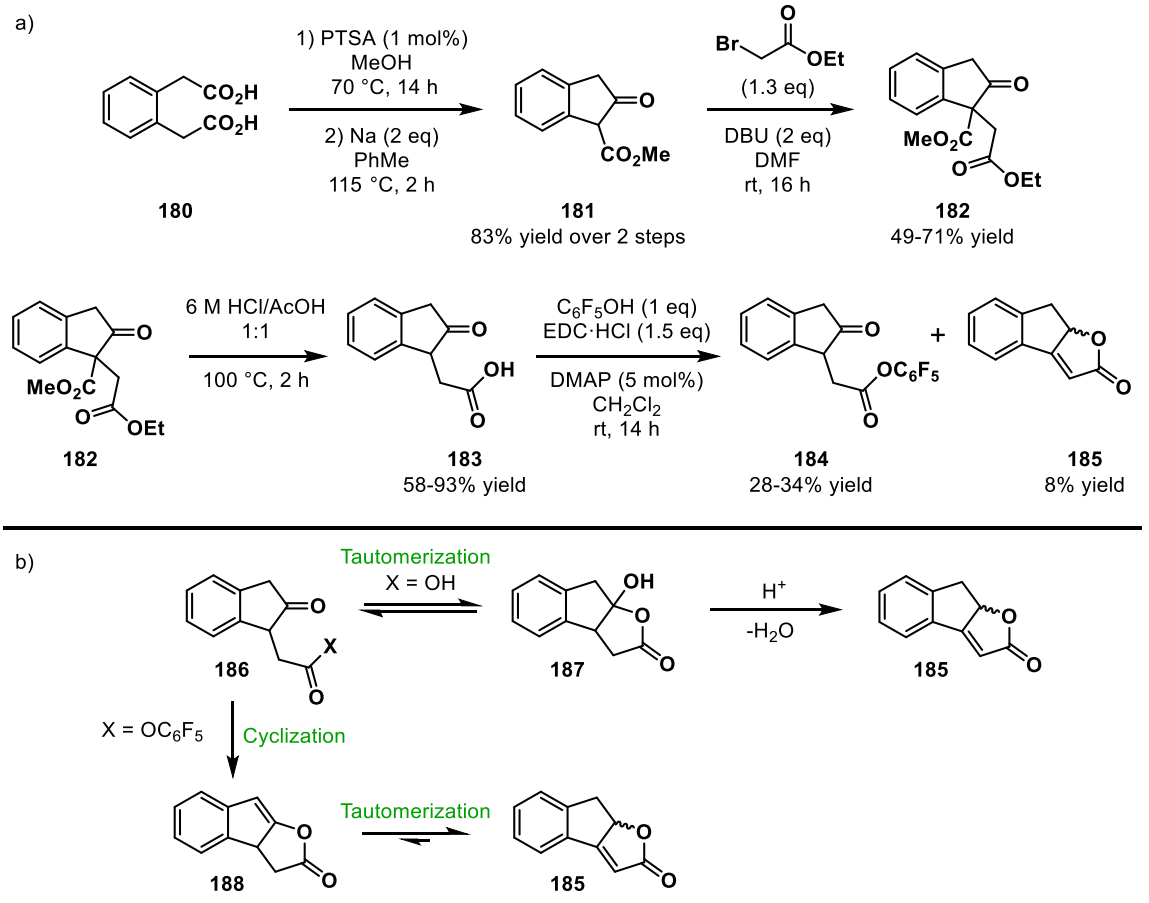
A substrate derived from 2-indanone bearing an acyl group tethered to the 1-position could be a viable substrate and several species of the type **177** have been described in the literature.[111] We postulated that under phase-transfer conditions, we could favour formation of the kinetic *enolexo*-product over the thermodynamically favoured *enolendo*-cyclization, which would afford the more-highly substituted double bond (Scheme 36).[112]



178 **177** **179**

Scheme 36: Desired Cyclization of Substrate **177** Based on 2-Indanone

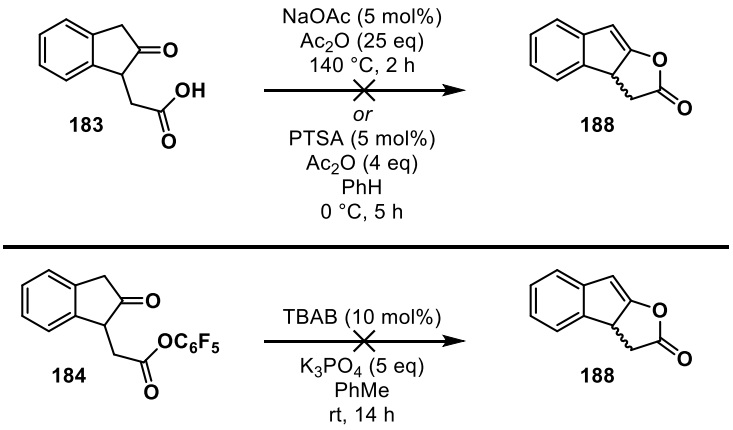
Synthesis of **184** began with esterification of 1,2-phenylenediacetic acid, followed by sodium-mediated cyclization to afford **181** in 83% yield over 2 steps (Scheme 37a). Subsequent regioselective monoalkylation of **181** with ethyl bromoacetate under mild reaction conditions (DBU as the base) afforded **182** in good yield. Hydrolysis/decarboxylation was achieved by reflux of **182** in 1:1 AcOH/6 M HCl, affording the desired acid **183** in good to excellent yield. Again, esterification with pentafluorophenol afforded **184**, although in poor yield.



Scheme 37: a) Synthesis of 2-Indanone Derivative **184**; b) Possible Mechanisms of Formation of **185**

A minor by-product isolated from this reaction was identified as furanone **185**, which appeared to be a product of cyclization under the esterification conditions, followed by isomerism of the double bond. It could, however, also have been generated from elimination of water from a cyclic tautomer of the ketoacid (Scheme 37b). Isomerization of **188** might have been predicted to occur given our formation of a monohydrofuranone ring (a structure rarely disclosed in the literature) in our desired product, and could be a method of racemization of the desired product in our

O-acylation reaction. Nevertheless, we subjected **183** to our previous thermodynamic cyclization conditions and also subjected **184** to our standard phase-transfer conditions (Scheme 38).

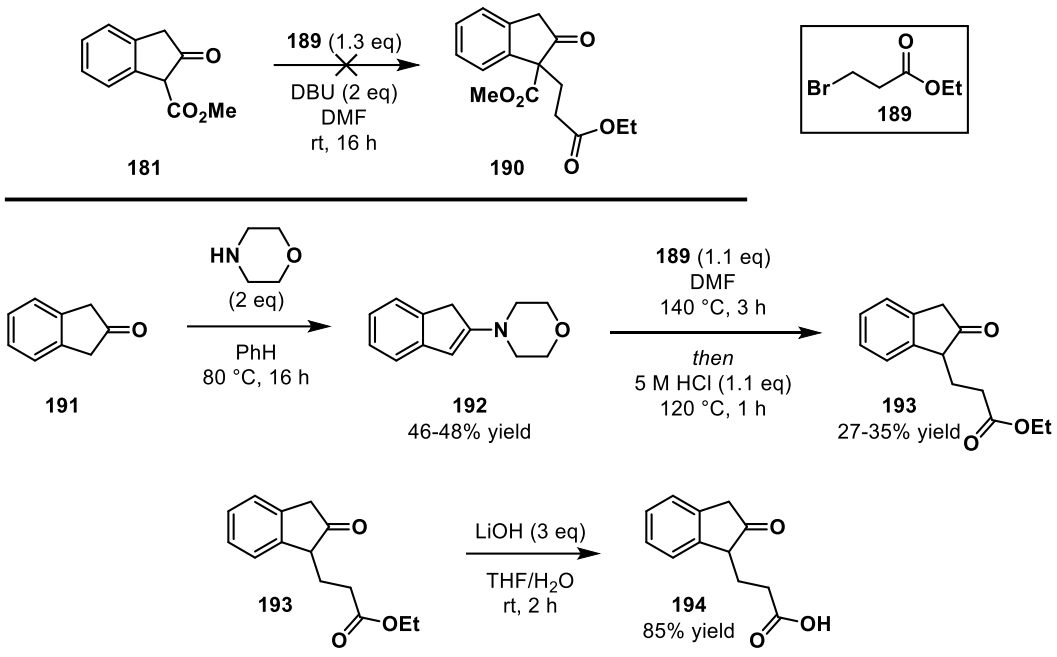


Scheme 38: Attempted Cyclization of 2-Indanone-Derived Substrates **183** and **184**

Surprisingly, despite the appearance of **188** in our esterification reaction, we saw no conversion to **188**, or any regioisomer, under a variety of conditions tested, presumably due to the angular strain associated with the double bond at a ring junction (see page 22).

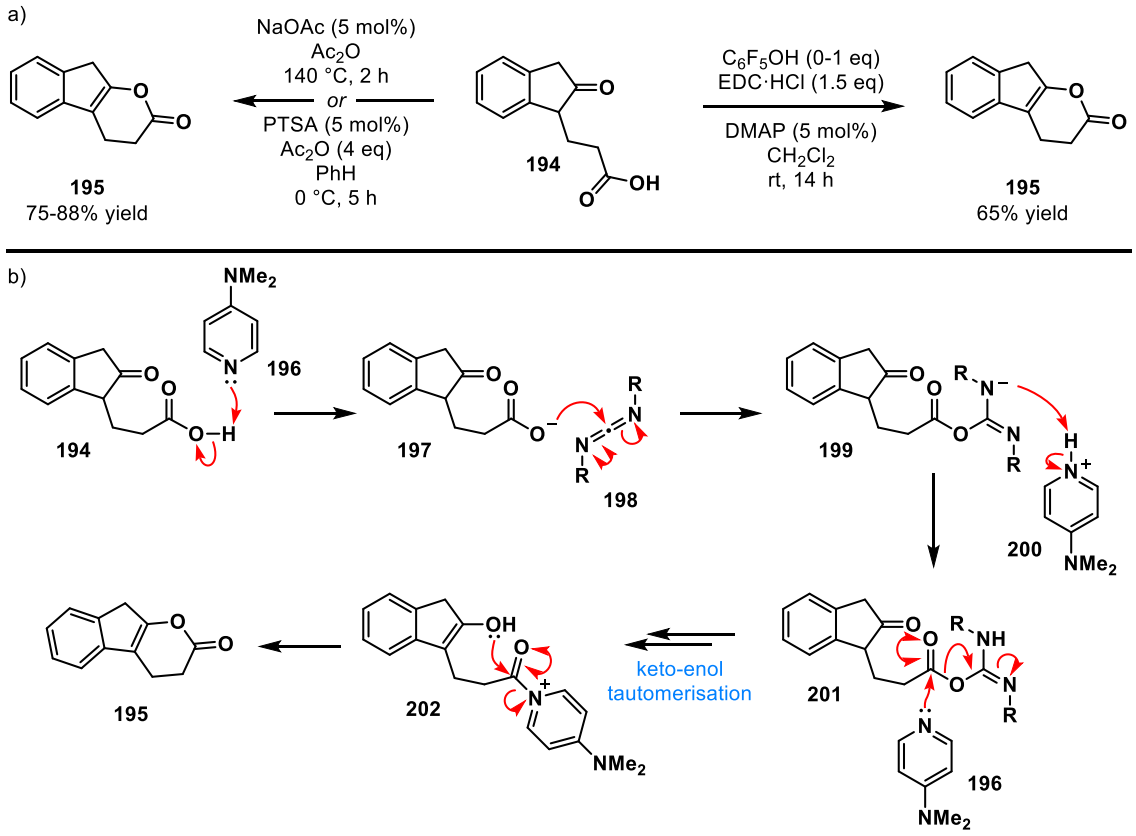
To overcome this problem, we decided to lengthen the acyl tether which would lead to formation of a trihydropyranone rather than the isomerizable furanone. In addition, it would avoid the strained 5,5 ring system in the product, though could enable undesired 6-*enolendo*-cyclization.

Ethyl 3-bromopropionate proved an unsuitable electrophile for **181**, due to the lack of α-carbonyl to activate the halogen towards substitution, with no reaction observed under our previously utilized conditions. Reports in the literature of 1-alkyl-2-indanones describe their synthesis from the morpholine enamine **192**, derived from 2-indanone.[113]



Scheme 39: Synthesis of Homologated 2-Indanone Derivative **194**

The morpholine enamine **192** was synthesized according to the method described by Moriconi (Scheme 39),[114] by refluxing 2-indanone **191** with 2 equivalents of morpholine in benzene with a Dean-Stark apparatus. Upon cooling to room temperature, the product crystallized out of the reaction mixture, although it required a further 2–3 recrystallizations from benzene before use in the next step (46–48% yield). This enamine proved more reactive to alkyl electrophiles than **181**, and the desired product **193** was isolated in 27–35% yield. Finally, saponification of **193** afforded **194** as an oil in good crude yield, although it proved extremely difficult to purify *via* flash column chromatography in our hands, and was used without any further purification. Acetic anhydride-mediated cyclization, and esterification of **194** with pentafluorophenol, afforded only one product: the *enolendo*-cyclized product **195** (Scheme 40a).

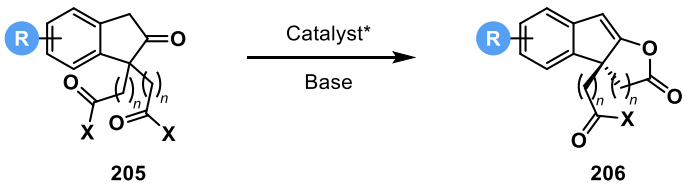


Scheme 40: a) Attempted Esterification of Acid **194**;
b) Possible Mechanism for Formation of **195**

Repeating this reaction in the absence of pentafluorophenol also afforded **195**, implying that the ketone was cyclizing onto the *O*-acylisourea intermediate **201** (Scheme 40b), rather than the esterified product, which would make the synthesis of any esters of **194** extremely challenging. Milder reaction conditions could not be found, and the *enolendo*-geometry appeared to be favoured under all conditions investigated, so attempts at cyclization of this substrate were discontinued.

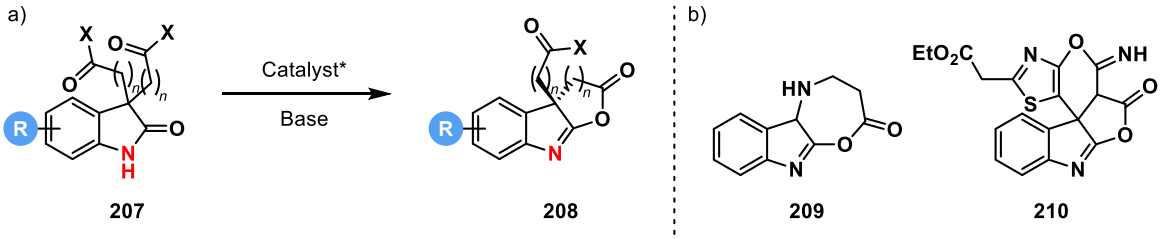
2.3.2 Desymmetrization of a Diester

Due to the problems encountered in the previous sections, we thought that desymmetrization of a diester may prove a more achievable goal. Our target substrates would continue to be 2-indanone-derived, however, rather than featuring a tertiary centre at the 1-position, it would incorporate a quaternary centre with symmetrical acyl-tethered chains (Scheme 41).



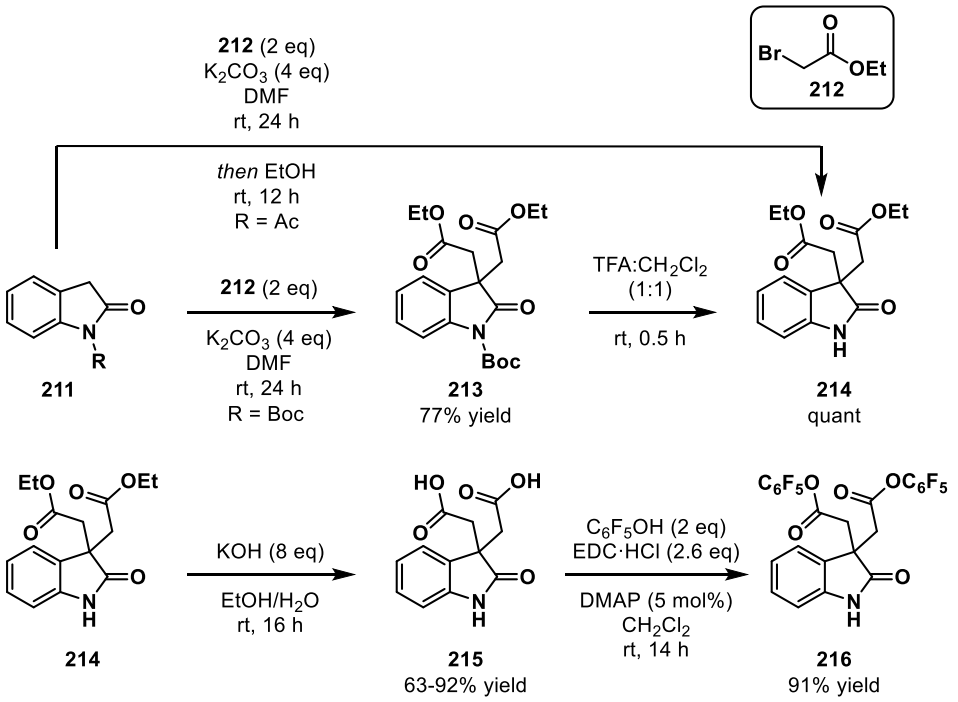
Scheme 41: Ideal Substrate **205** for Enantioselective Desymmetrization

Unfortunately, no compounds featuring our desired 1,1-disubstituted-2-indanone backbone have been disclosed in the literature (perhaps due to the synthetic challenge in incorporating the 1,1'-dialkyl groups) so we adjusted our aims. Our ideal substrate **205** could be altered to the corresponding oxindole **207**, featuring an acidic secondary amide (Scheme 42a). Several examples that feature the *O*-acyl indolenine motif that would be found in the cyclization product **208** have previously been described in the literature, such as **209** and **210** (Scheme 42b).[115]



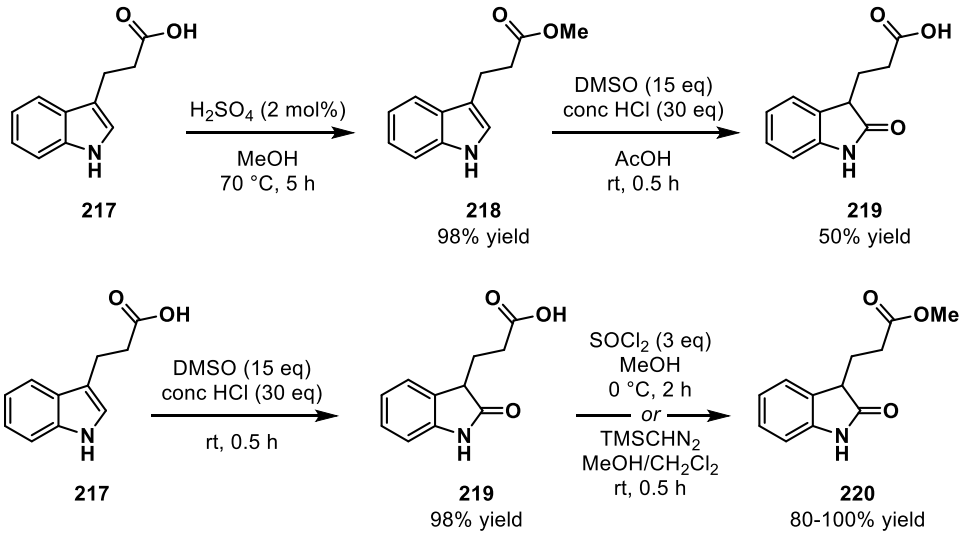
Scheme 42: a) Indole Substrate **207** for Enantioselective Desymmetrization;
b) Selected Examples with Similar Substitution

We proceeded with the synthesis of **216** and **223** with conditions analogous to those found in the literature (Scheme 43).[116] For **216**, the synthesis commenced from *N*-Boc oxindole **211**: double alkylation with ethyl bromoacetate afforded **213** in 77% yield, and subsequent deprotection afforded **214** in quantitative yield. Oxindole **214** could also be synthesized from *N*-acetyl oxindole, again alkylating with ethyl bromoacetate, with *in situ* deprotection reducing the step count of the synthesis. Saponification of the ethyl esters afforded **215** in good to excellent yield, which was used without any further purification, followed by esterification, furnishing desired diester **216**.



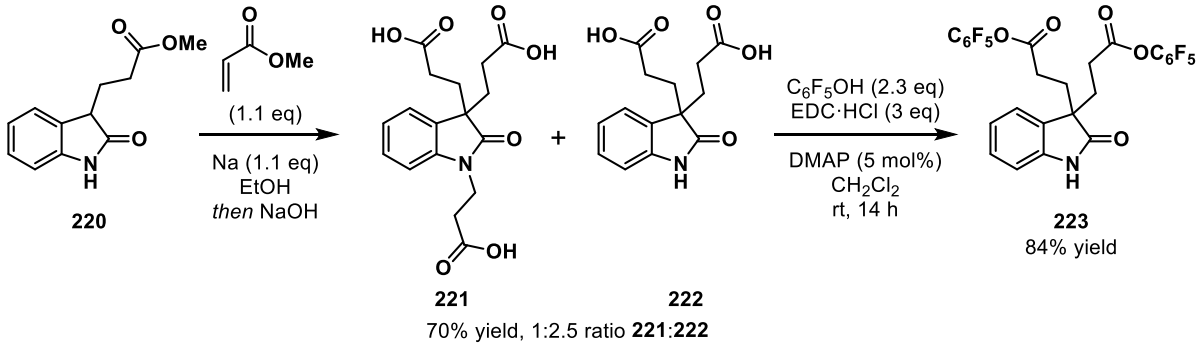
Scheme 43: Synthesis of Oxindole Diester **216**

The synthesis of **223** commenced with synthesis of the intermediate **220** *via* oxidation. The oxidation of indoles to oxindoles is known to proceed in DMSO with HCl,[117] and we planned to incorporate the oxindole moiety from the corresponding indole to access **220**. Initially we attempted to esterify commercial indole **218** with methanol, followed by oxidation to the corresponding oxindole **220** (Scheme 44).



Scheme 44: Synthesis of Oxindole Intermediate **220**

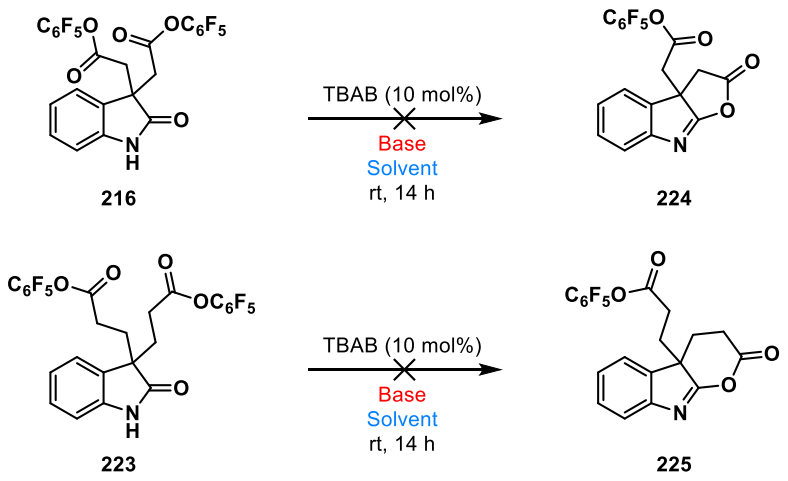
In practice, the esterification proceeded in excellent yield (98%) although the ester was then hydrolysed under the oxidation conditions to yield **219**, which required reesterification. Conditions for the esterification were examined, with both $TMSCHN_2$ or $SOCl_2$ in MeOH found to be efficient. Oxidation of indole **217** to oxindole **219**, under the same conditions as those used for the oxidation of **218**, followed by esterification afforded a more direct route to intermediate **220** in 85% yield over two steps. Reaction of **220** with methyl acrylate under previously-reported conditions[118] followed by *in situ* saponification with sodium hydroxide afforded a 2.5:1 mixture of di- and tri-alkylated acids **221** and **222** (Scheme 45).



Scheme 45: Synthesis of Oxindole Diester **223**

These acids could not be separated at this point, however were easily separable after esterification to the corresponding esters with pentafluorophenol, affording desired diester **223**.

Cyclization of these substrates was then attempted under a variety of phase-transfer conditions (Scheme 46).



Bases screened: KOH, K_3PO_4 (s/aq), K_2CO_3 (s/aq)
Solvents screened: PhMe, CH_2Cl_2, $^iPr_2O$

Scheme 46: Phase-Transfer Cyclization of *meso*-Indole Diesters **216** & **223**

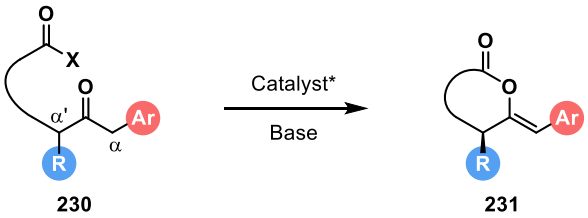
In each case, we isolated one or more products that were extremely polar, far more than would be expected for the desired product, and insoluble in organic solvents commonly used for NMR analysis ($CDCl_3$, CD_3OD, $(CD_3)_2SO$). From these observations, it seems likely that the amide has reacted intermolecularly, rather than intramolecularly, forming unidentifiable polymers.

One possible explanation of this phenomenon would be that intramolecular cyclization of this substrate *via* oxygen might not be as favourable as originally expected. In Mayr's recent review article,[91c] he summarizes research into the ambident reactivity of various functional groups, including ketones and amides. He discloses that whilst reaction through oxygen is very favourable for neutral amides (c.f. protonation of amides) to the order of 20 kJ mol^{-1}, when the amide is deprotonated the ambident selectivity is reversed to favour reaction through nitrogen to the order of 70 kJ mol^{-1}. This huge swing in selectivity could be one reason why we failed to see the expected reactivity from our oxindole systems.

2.3.3 Dynamic Kinetic Resolution of an α-Aryl Cyclopentanone

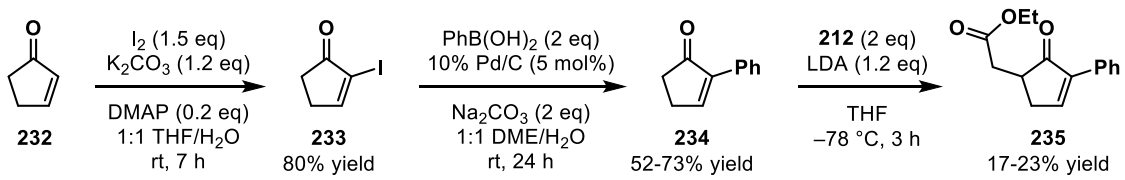
With amides proving ineffective for *O*-acylation under basic conditions, we returned to investigating ketones, although with an adjustment in strategy. We hypothesized that we could bias the regioselectivity and activate ketone **230** with an α-aryl group, and an acyl chain at the α'-position. This would hopefully allow for dynamic racemization of the α- and α'-stereocentres

before cyclization to afford an enantioenriched enol lactone **231**, although would potentially increase reaction scaffold complexity due to the presence of two reactive diastereoisomers (Scheme 47).



Scheme 47: Scaffold Design for Dynamic Kinetic Resolution *O*-Acylation

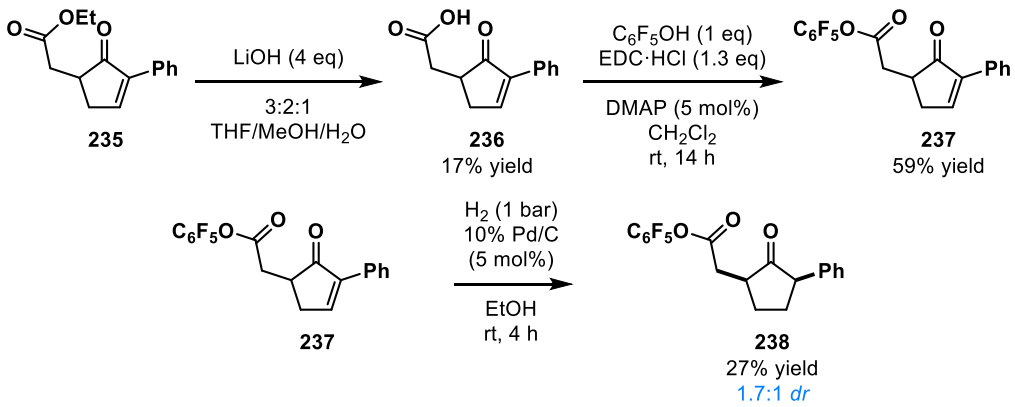
Fortunately, in a recent report on asymmetric hydrogenation, the Zhou group disclosed the synthesis of ethyl esters similar to those we would require for our reaction.[119] We could access several different ring sizes and acyl tether lengths according to their procedures. Our synthesis commenced with the iodination of enone **232** under Morita-Baylis-Hillman-type conditions with iodine, DMAP and K_2CO_3 (Scheme 48). Consumption of starting material was important for this step due to the similarity in polarity between **232** and **233**, and the product of the following reaction, **234**, making purification by flash column chromatography extremely challenging.



Scheme 48: Synthesis of Unsaturated Ester **235**

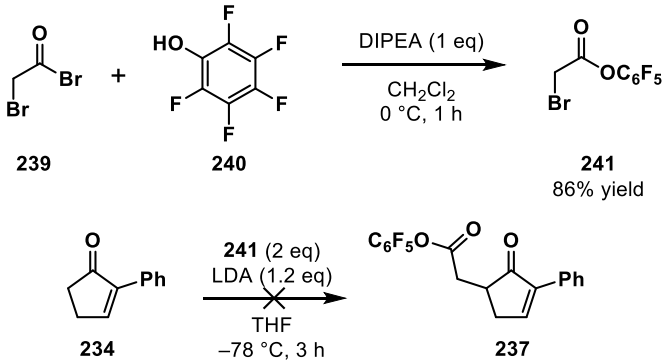
Suzuki coupling of **233** with phenylboronic acid using Pd/C afforded **234** in good yield (52–73%) after recrystallization which was necessary to ensure high levels of purity by removal of any residual **232** and **233** which might have presented difficulties with separation later on. Deprotonation of **234** with LDA, followed by alkylation with ethyl bromoacetate **212** afforded **235** in poor yield (17–23%), although similar to that disclosed in the literature (25%).[119]

It was originally thought that the desired activated esters could be synthesized *via* saponification of the enoneester, esterification and then hydrogenation, however in our hands this route proved challenging (Scheme 49).



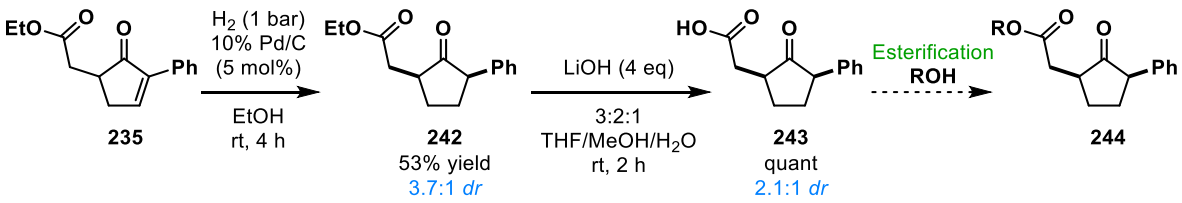
Scheme 49: Synthesis of Saturated Pentafluorophenyl Ester **238**

Saponification of **235** to afford **236** (a known compound the Moretó group had previously synthesized through Nickel-mediated cyclocarbonylation)[120] was only moderately successful, with the product isolated in very poor yield (17%) from a complex reaction mixture (Scheme 49). This was attributed to competitive deprotonation of the enone **235** (perhaps to the extended enolate) and subsequent polymerization under the reaction conditions. Nevertheless, the acid **236** was esterified in 59% yield, although the subsequent hydrogenation afforded a poor yield of **238** (27%). Attempted alkylation of enone **234** with pentafluorophenyl bromoacetate **241** under analogous conditions (LDA, THF, −78 °C) failed to furnish us with our desired substrate (Scheme 50).



Scheme 50: Attempted Synthesis of Unsaturated Ester **237**

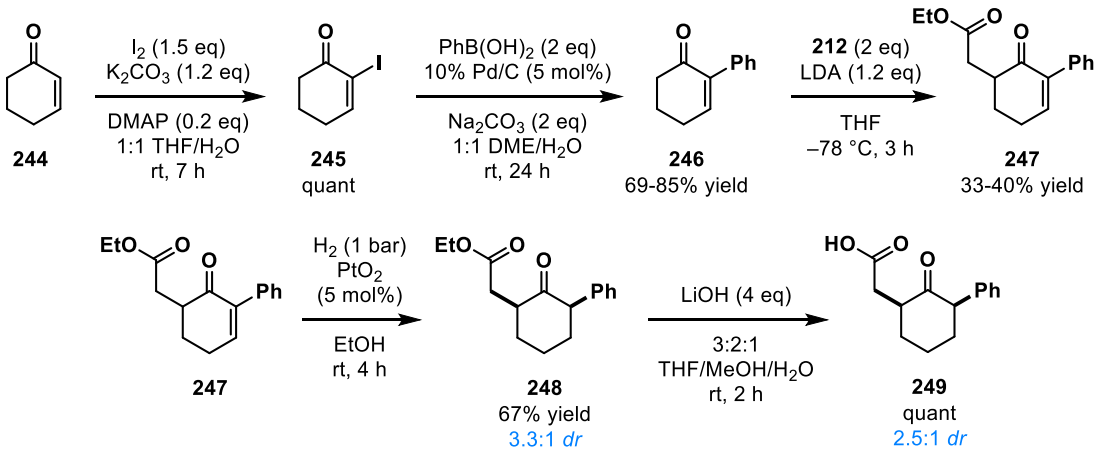
We hypothesized that we could reorder this synthesis to increase the yields and the esters could instead be accessed *via* hydrogenation followed by saponification, with esterification the last step (Scheme 51).



Scheme 51: Synthesis of Saturated Esters **244**

With our revised route, the hydrogenation proceeded smoothly to afford both diastereoisomers of **242** in a 3.7:1 ratio which were inseparable and carried on to the next step. The saponification proceeded smoothly to afford crude **243** which was not purified prior to use in subsequent reactions.

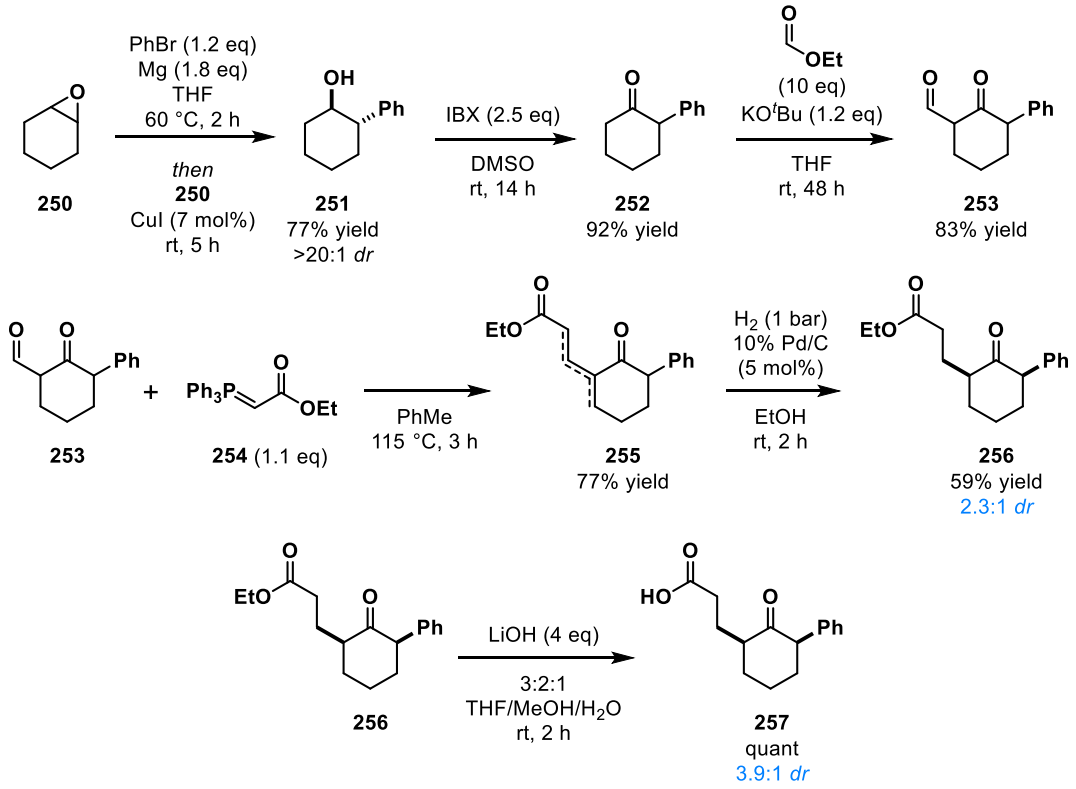
At this point we started to synthesize the cyclohexanone-based substrate (Scheme 52) and a compound with a homologated acyl tether (Scheme 53).



Scheme 52: Synthesis of Saturated Acid **249**

The synthesis of the cyclohexanone substrate with the same length acyl tether proceeded as above although starting with cyclohexanone. Iodination followed by Suzuki coupling afforded 2-phenylcyclohexenone **246** in good yield (63–85% over two steps). This time, upon deprotonation with LDA and alkylation under the same conditions as for **234**, we isolated **247** in improved yield (33–40%). Hydrogenation afforded **248** in a 3.3:1 ratio of diastereoisomers which could be separated by careful flash column chromatography. Hydrolysis of the separated diastereoisomers each afforded crude acid **249** as a 2.5:1 ratio of diastereoisomers, regardless of which diastereomer was hydrolysed demonstrating that at least one stereocentre is epimerizable under basic

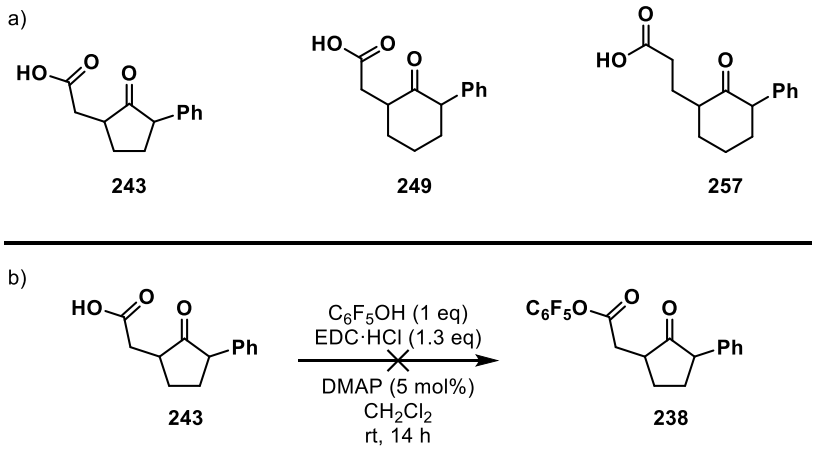
conditions, and thus that the presence of both diastereomers would not be problematic in our desired reaction. The synthesis of a compound with a homologated tether was not possible through the route described above due to the lack of reactivity of ethyl bromopropionate with the lithium enolate of **246**. Therefore, a route which incorporated the tether by Wittig reaction with an aldehyde was utilized (Scheme 53).



Scheme 53: Synthesis of Homologated Ketoacid **257**

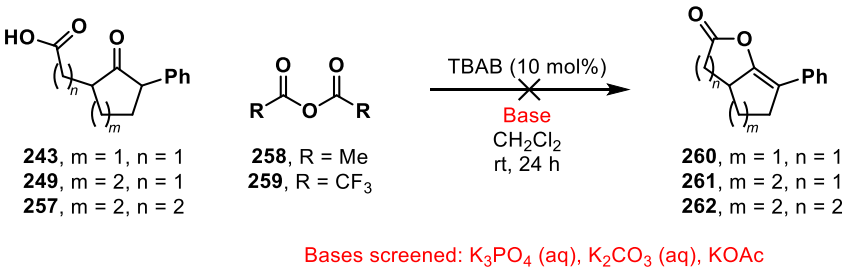
The copper-catalyzed ring opening of cyclohexene oxide with phenylmagnesium bromide proceed in good yield and excellent diastereoselectivity on a 5 g scale to afford **251** (77%, >20:1 *dr*). This was oxidised to 2-phenylcyclohexanone **252** with IBX in excellent yield (92%) and then subsequently formylated at the 6-position with ethyl formate to isolate **253** in 83% yield. Wittig reaction of **253** with **254** in toluene afforded **255** as a mixture of several isomers, in 77% total yield, which could all be converted to **256** by hydrogenation with Pd/C, giving **256** in 59% yield (2.3:1 *dr*). Finally, hydrolysis with lithium hydroxide afforded the crude ketoacid **257** in quantitative yield.

Esterification of the synthesized acids **243**, **249** and **257** proved a poor route to the desired activated esters, with no trace of the desired products found under our standard reaction conditions (Scheme 54).



Scheme 54: a) Synthesized Ketoacids **243**, **249** and **257**; b) Attempted Esterfication

While only a few conditions were attempted, we were disappointed to find that we could not even identify any cyclized products by mass spectrometry or ^{1}H NMR analysis. Polar decomposition products were the only components of the crude reaction mixtures. We do, however, know that cyclization is possible through *in situ* activation of the carboxylic acid (Chapter 2.2.1), so we postulated that this could be a possibility for our more activated system (Scheme 55).

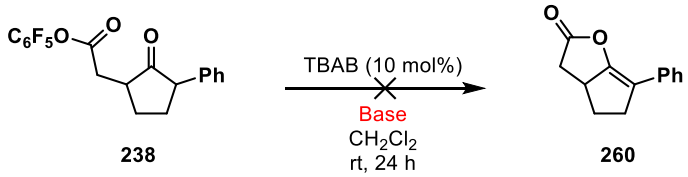


Scheme 55: Attempted Phase-Transfer Catalyzed Cyclization of Ketoacids **243**, **249** and **257**

We subjected acids **243**, **249** and **257** to conditions similar to those utilized previously: TBAB as the phase-transfer catalyst, acetic anhydride or trifluoroacetic anhydride as the activating agent, various inorganic bases (K_3PO_4, K_2CO_3, KOAc), in CH_2Cl_2 (the ketoacids **243**, **249** and **257** were insoluble in toluene and $^{i}Pr_2O$). Interestingly, TLC analysis of the crude reactions with substrate **243** showed different products depending on the choice of anhydride but upon workup showed only

starting material. We attribute this to formation of the mixed anhydride *in situ* which was detected by TLC analysis, however no cyclization occured (for steric reasons, see page 22), and the mixed anhydride hydrolysed back to the acid upon workup. For substrates **249** and **257**, we did see formation of the same products with both anhydrides. However, once again upon workup the ^{1}H NMR spectrum of the crude material was mainly composed of starting material after 48 hours. This appeared to be an unsuitable method for cyclization of the ketoacids **249** and **257**.

Finally, the cyclization of the preformed activated ester **238** was attempted (Scheme 56).



Scheme 56: Attempted Phase-Transfer Catalyzed Cyclization of Ketoester **238**

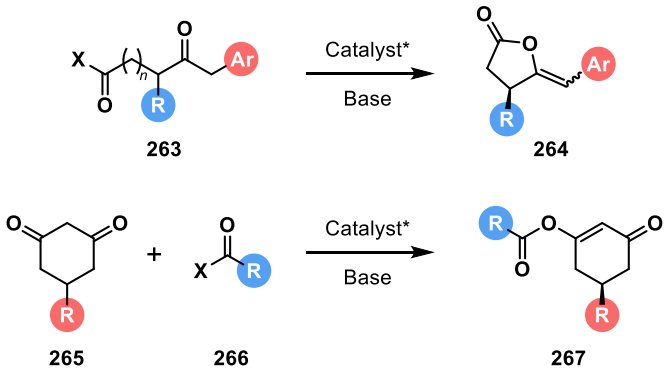
Once again, we found that formation of the fused 5,5 ring system with the internal *exo* double bond was not observed under the reaction conditions, and only a mixture of starting material and decomposition was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Unfortunately, due to time constraints, we did not synthesize the pentafluorophenyl ester of **249** through the route described for **238**, although it would likely prove to be a superior substrate.

2.4 Conclusion and Future Work

To conclude this chapter on the *O*-acylation of ketones and indoles, we have found that substrate design is a huge challenge. The substrates we utilized had been engineered to overcome some expected challenges such as enolate geometry, but were found to unreactive under our standard racemic phase-transfer conditions. Additionally, excessive strain in the desired products hindered our efforts.

Despite these challenges, the desired *O*-acylation reaction does appear to be possible, and irrespective of the poor conversions observed, substrates such as **154**, **158** and **162** did cyclize under phase-transfer conditions.

Future work would be directed towards the synthesis of substrates such as **263** and **265** (Scheme 57), avoiding the strained 5,5 ring system product which has plagued our early investigations into this reaction.

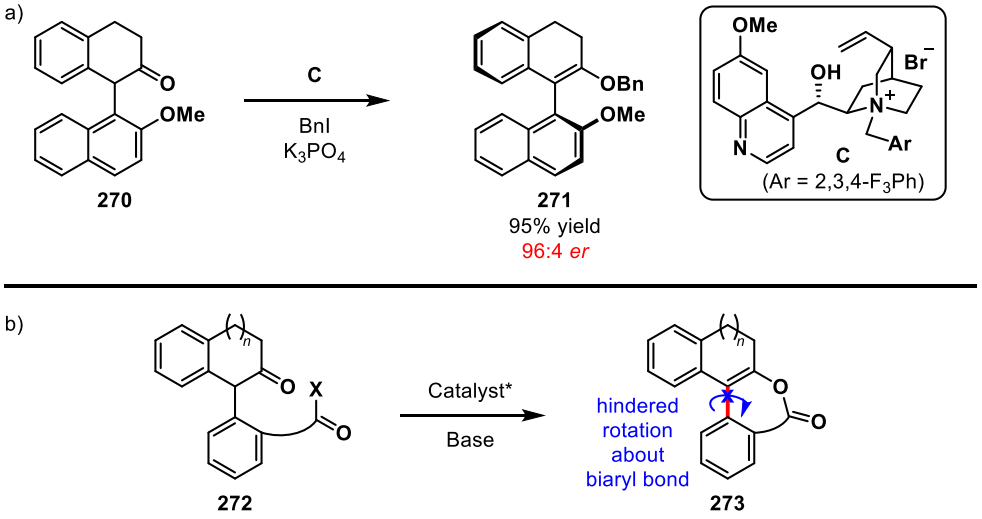


Scheme 57: Other Potential Substrates for Enantioselective *C*-Acylation

3. Dynamic Kinetic Resolution of Axially Chiral Enolates

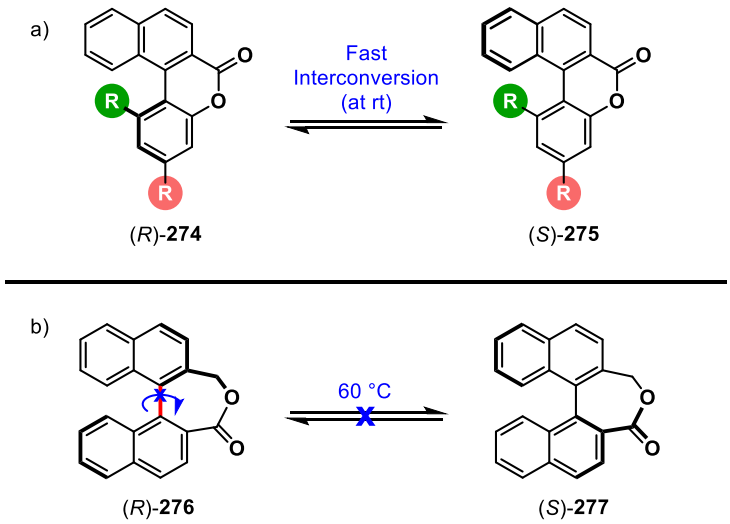
3.1 Enantioselective Functionalization of Benzhydrylic Ketones

Revisiting the earlier work in the group on enantioselective *O*-alkylation (Scheme 58), we knew that selective functionalization on oxygen in a benzhydrylic system was feasible under phase-transfer conditions, and good levels of reactivity were observed (the reaction was complete in 36–48 hours).



Scheme 58: a) Previously Reported Ketone *O*-Alkylation; b) Proposed Intramolecular Ketone *O*-Acylation

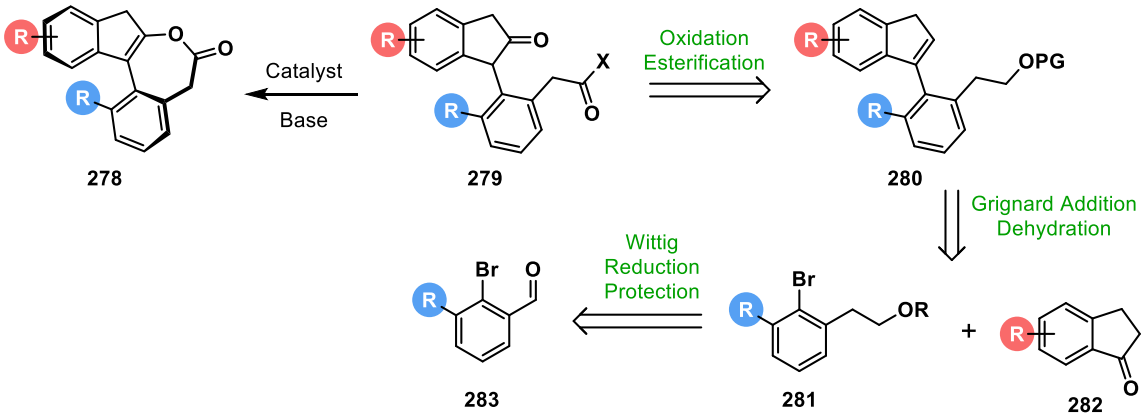
While intermolecular acyl electrophiles were tolerated but afforded only racemic products in the above system, we anticipated that an intramolecular tether might afford an atropisomeric enol lactone **273**. Bringmann first demonstrated that 6-membered biaryl lactones of type **274** (**R** = H/Me/^{i}Pr interconvert on the second timescale) (Scheme 59)[121] and has since demonstrated several examples of dynamic kinetic resolution of these substrates.[122]



Scheme 59: a) 6-Membered Lactones; b) Configurationally Stable 7-Membered Lactones

As has been reported, increasing the ring size of the lactone to a 7-membered ring affords conformationally stable lactones **277**,[123] with a much greater barrier to rotation than the corresponding 6-membered rings.

We considered that we could synthesize our desired starting material of type **278** (Scheme 60) through a similar strategy as that utilized in the group's work on the synthesis of BINOL derivatives (Scheme 60).

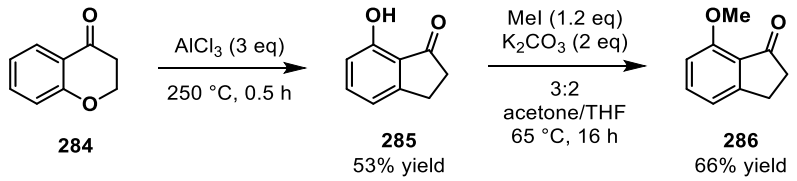


Scheme 60: Strategy for Synthesis of **279** for Enantioselective Intramolecular *O*-Acylation

Addition of the Grignard derived from **281** into 1-indanone **282** and subsequent dehydration would afford alkene **280**. Alkene **280** could then be oxidised to the corresponding 2-indanone and subsequent oxidation/esterification could afford desired starting material **279**.

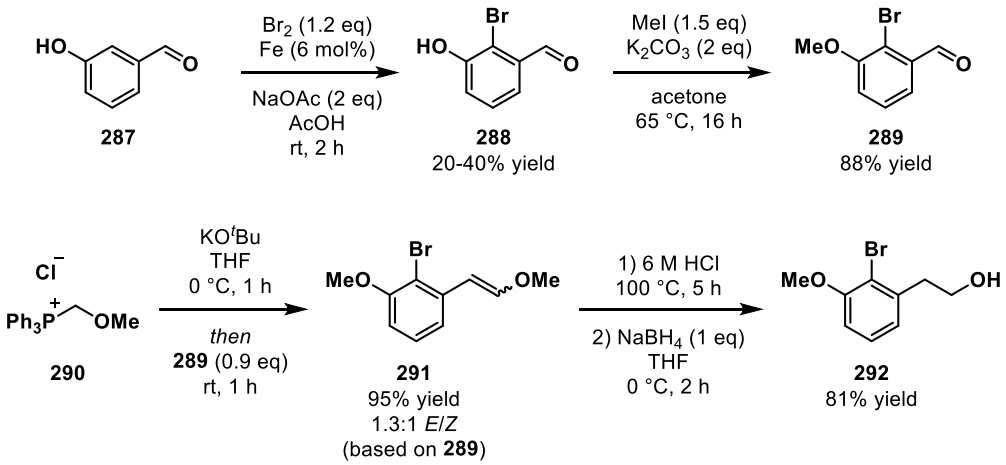
3.2 Substrate Synthesis and Results

The 1-indanone fragment was synthesized through the thermal rearrangement of 4-chromanone **284** with aluminium(III) chloride, and subsequent treatment of **285** with methyl iodide afforded the desired product, 7-methoxy-1-indanone **286**, in 35% yield over 2 steps (Scheme 61).



Scheme 61: Synthesis of 7-Methoxy-1-indanone **286**

Synthesis of the bromobenzene derivatives **289** and **292** have been described in the literature (Scheme 62).[124] In our hands, commercial 3-hydroxybenzaldehyde (**287**) underwent regioselective Friedel-Crafts bromination in the presence of Fe(III) to afford benzaldehyde **288** in moderate yield (20–40%) and was then methylated with methyl iodide to afford **289** (88% yield). According to the reported synthesis, we subjected aldehyde **289** to Wittig reaction conditions with **290** in the presence of KO^{t}Bu, which was then hydrolyzed with 6 M HCl at reflux.

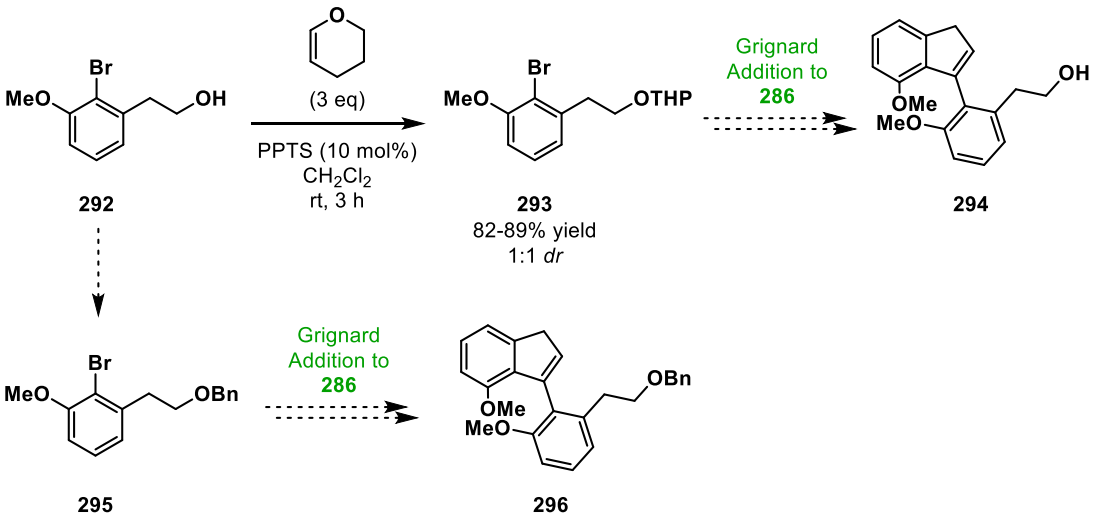


Scheme 62: Synthesis of Bromobenzene Derivative **292**

The homobenzaldehyde proved difficult to purify in our hands so we instead purified enol ether **291**, and, after hydrolysis, would then carry through the crude aldehyde to the next step. Upon repetition of the Wittig reaction of **289** with **290**, enol ether **291** proved simple to purify *via* flash column chromatography, and was isolated in 95% yield and as a 1.3:1 mixture of *E*/*Z*-isomers.

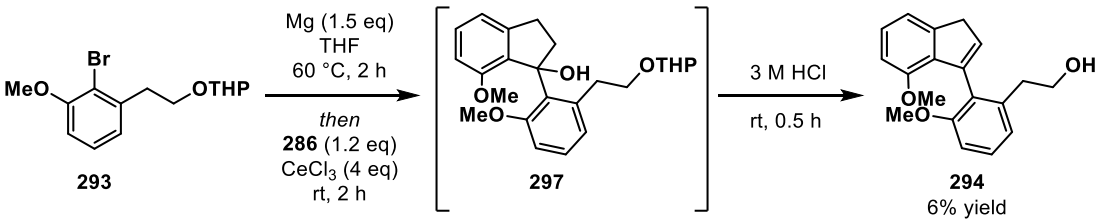
Hydrolysis of the enol ether revealed the homologated aldehyde, which was reduced to the corresponding alcohol **292** with sodium borohydride in 81% yield over 2 steps.

Due to the significant number of alcohol protecting groups, we could select a functional group that fitted our criteria: we thought that a protecting group that would be stable to Grignard formation and reaction (with a Lewis acid, such as $CeCl_3$, present) but would be cleaved during the acidic workup would be ideal as it would remove one step form the synthesis (Scheme 63). Alternatively, the protecting group could also be stable to acid, such as a benzyl group, and removed in a later step. As such we synthesized the THP-protected alcohol **293** which would be labile under the acid workup conditions.



Scheme 63: Choice of Protecting Group and Implications After Grignard Addition

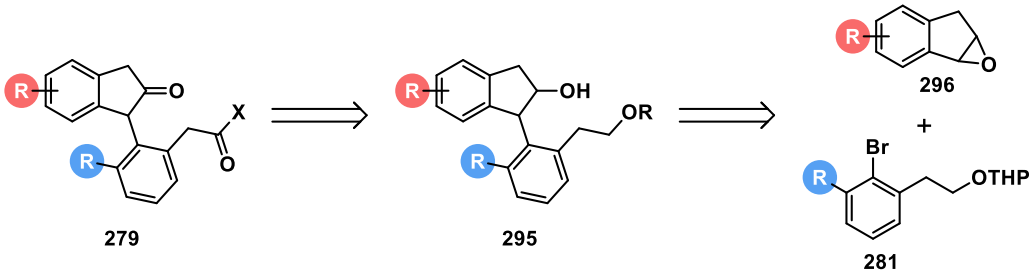
With the THP-protected alcohol **293** in hand, we attempted the addition of the Grignard reagent derived from **293** into the carbonyl group of **286**. We envisaged that an acidic workup would dehydrate the alcohol **297** and cleave the protecting group to reveal **294** (Scheme 64).



Scheme 64: Cerium-Mediated Grignard Addition of Bromobenzene Derivative **293** to 7-Methoxy-1-Indanone **286**

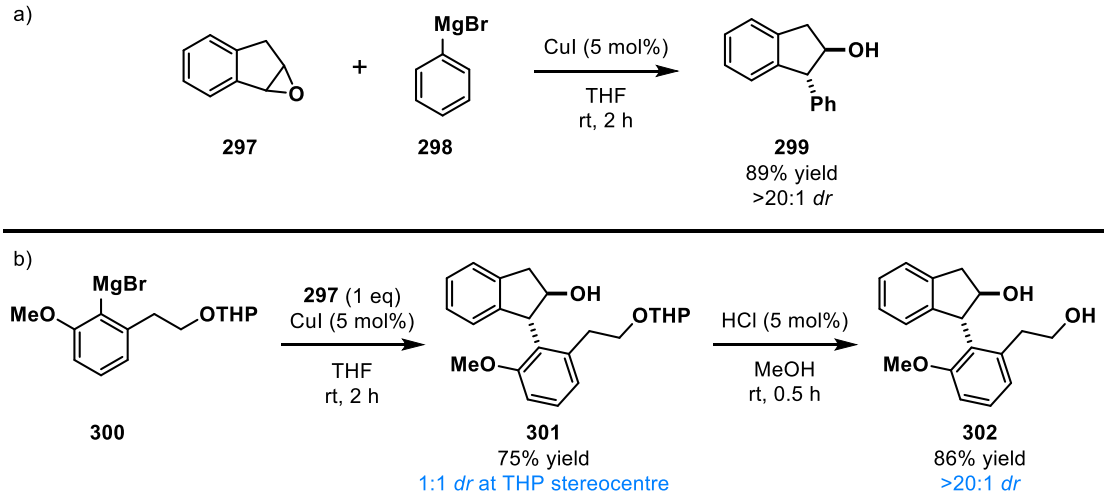
Formation of the Grignard reagent from **293** proceeded smoothly, and after addition of the Grignard reagent to **286** with $CeCl_3$ and subsequent quenching with 3 M HCl, after 30 minutes we obtained a 43% yield of a mixture of **294** and the corresponding THP-protected alcohol 1:3.5 ratio. Resubjecting this material to 3 M HCl for a further 5 hours led to complete conversion to **294**, however, we only obtained a 6% overall yield of the desired product. **294** was subsequently found to be unstable to acidic conditions (through subjecting the purified material to the same conditions).

At the same time, we investigated an alternative disconnection: nucleophilic attack of an organometallic species (which we knew we could generate from **281**) into an epoxide (an indene oxide derivative such as **296**) (Scheme 65).



Scheme 65: Alternate Strategy to Access *O*-Acylation Precursor **295**

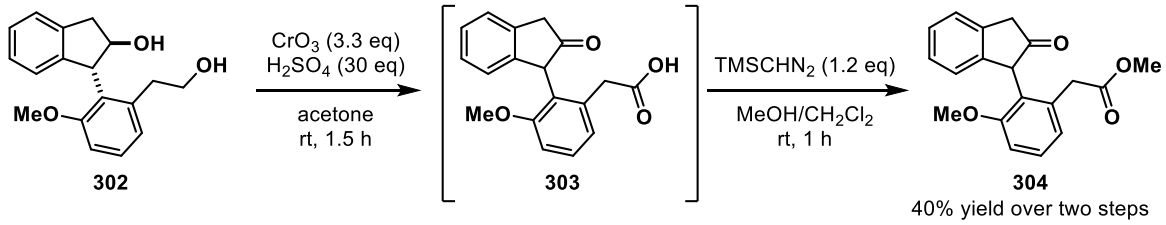
A test reaction was performed where commercial phenylmagnesium bromide was added to indene oxide **297**. This reaction showed production of benzhydryl alcohol **299**, although many other products were observed. Performing these reactions in the presence of CuI (5 mol%) showed significantly cleaner conversion to **299**, and it was isolated as a single diastereoisomer in 89% yield (Scheme 66a).



Scheme 66: a) Test Copper Catalyzed Epoxide Ring Opening; b) Epoxide Ring Opening with **300** Followed by Deprotection

We saw indene oxide **297** as a suitable test substrate for the reaction with a more hindered Grignard reagent and for testing our subsequent deprotection/oxidation conditions. The reaction of the Grignard reagent derived from **293** with indene oxide under copper(I) catalysis pleasingly afforded desired product **301** in 75% yield as a 1:1 mixture of diastereoisomers (with 15% protodebromination of **300** also isolated, Scheme 66b). The deprotection of **301** could be achieved under standard conditions with either sub-stoichiometric quantities of concentrated HCl in methanol, or PPTS in methanol both shown to be efficient on a small scale (95% and 86% yield, respectively), and an 86% yield with sub-stoichiometric HCl/methanol on a larger scale.

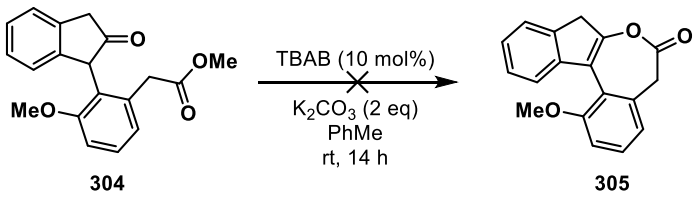
A one-pot oxidation of the secondary alcohol to the ketone and the primary alcohol to the carboxylic acid would be the shortest route to desired acid **303** and could be achieved using Jones reagent (Scheme 67). Mass spectrometry analysis of the crude reaction mixture showed the presence of ketoacid **303**.



Scheme 67: Oxidation of **302** to Ketoacid **33** followed by Trapping as Methyl Ester

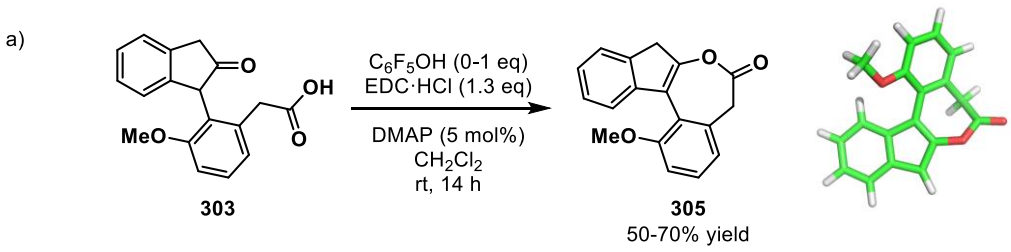
Acid **303** proved extremely challenging to purify in our hands, and various 2-indanones and 2-tetralones have been observed to be unstable by our research group in other pieces of work. As such, we decided to prove that the desired ketoacid **303** was present by trapping the acid with $TMSCHN_2$ and purifying the methyl ester. By subjecting the crude reaction mixture from the oxidation to $TMSCHN_2$ in methanol/CH_2Cl_2 we obtained ketoester **304** which could be purified by flash column chromatography in 40% yield over 2 steps.

We then subjected the methyl ester to standard phase-transfer conditions to see if cyclization occurred. Unfortunately, no reaction was observed and the starting material was recovered unchanged (Scheme 68).



Scheme 68: Attempted Cyclization of Methy Ester **304**

We thus decided to synthesize a more activated ester to see if the electron-rich methyl ester was prohibiting reaction. Crude acid **303** was esterified with pentafluorophenol with EDC as the coupling agent, and surprisingly we did not observe our desired ester but instead isolated cyclized product **305** in 50–70% yield (Scheme 69).



Scheme 69: Attempted Esterification of **303**, Yielding Cyclized Product **305**;

Similarly, the same product was obtained by subjecting **303** to identical reaction conditions but in the absence of pentafluorophenol, demonstrating that the ketone was cyclizing onto the *O*-acylisourea intermediate **308** formed by reaction of the carboxylic acid **303** with carbodiimide **198**.

Upon closer analysis, product **305** did not appear to be chiral on the HPLC timescale (no columns we tried separated the enantiomers of **305**), although it did appear chiral by ^{1}H NMR, suggesting the half-life to rotation was in the order of 10-100 seconds and thus unsuitable for the attempted asymmetric reaction.

We decided to increase the energetic barrier to rotation by introducing a group at the 7-position of the indanone fragment (Figure 4).

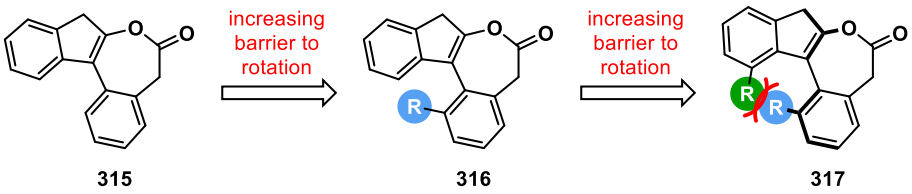
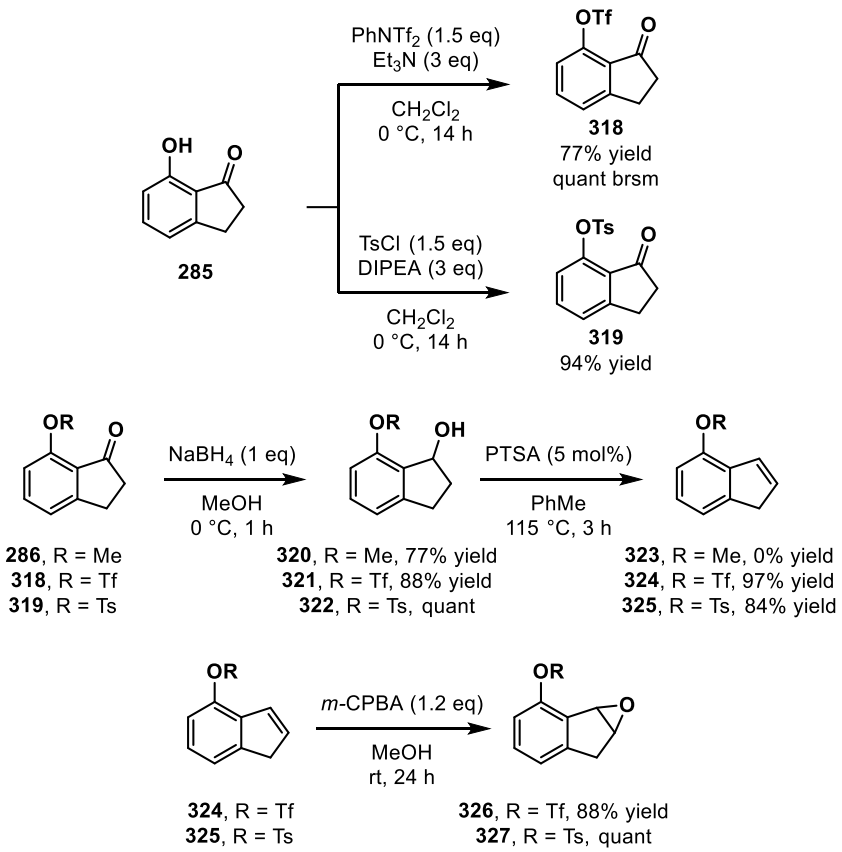


Figure 4: Increasing Barrier to Rotation by Increasing Steric Hindrance About Biaryl Axis

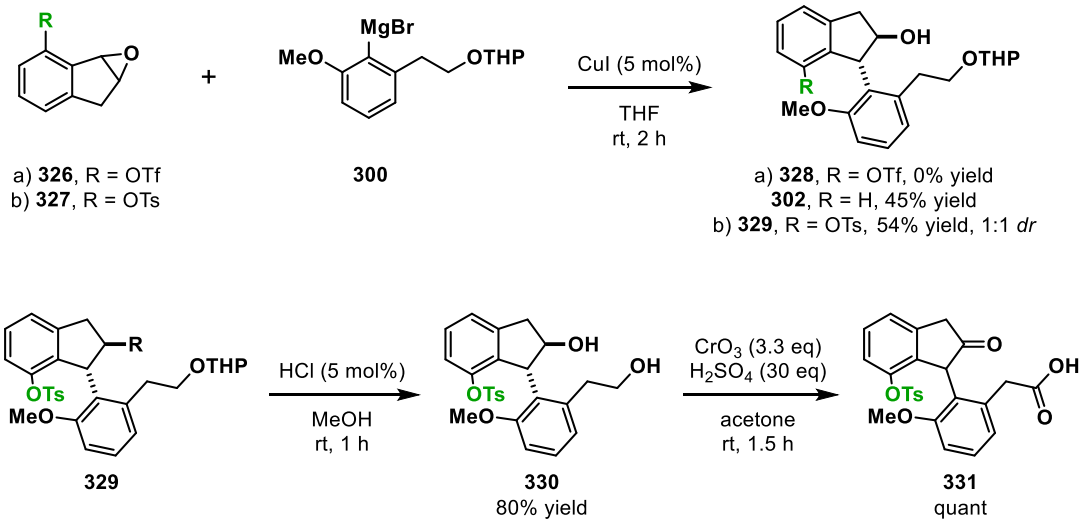
The synthesis of 7-substituted indene oxides was expected to be simple, despite requiring several steps (Scheme 70). With 7-methoxy-1-indanone **286** in hand (Scheme 61, Page 48), we also decided to synthesise the bulkier 7-triflyl-1-indanone **318** and 7-tosyl-1-indanone **319**. All three of these 1-indanones could be reduced and then dehydrated to afford the corresponding indenes. Epoxidation with *m*-CPBA was expected to afford the desired 7-substituted indene oxides.



Scheme 70: Synthesis of Indene Oxides **326** and **327**

The route to access the substituted indenes furnished substrates **324** & **325** bearing electron-withdrawing substituents with no issues with reduction/dehydration (84–85% yield over both steps). Epoxidation with *m*-CPBA afforded clean conversion to **326** and **327** in very good yields. For the dehydration of 7-methoxy-1-indanol **320**, with an electron-donating substituent, polymerization/decomposition was the only result. This phenomenon has also been disclosed in the literature in a paper titled "*Cationic Polymerisation and Copolymerisation of Methoxyindenes*".[125]

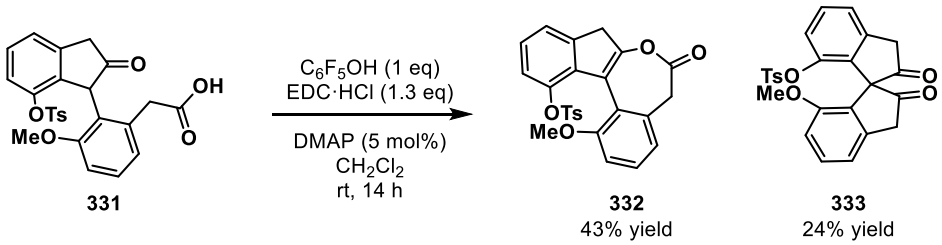
With 7-substituted indene oxides **326** and **327** in hand, we subjected them to the same copper-catalyzed Grignard addition conditions as before, followed by deprotection and oxidation (Scheme 71).



Scheme 71: Copper Catalyzed Grignard Addtion to a) **326**; b) **327** and Subsequent Deprotection and Oxidation of **329**

For the Grignard reagent addition to compound **326**, bearing an OTf group, the only product isolated was **302**, presumably due to insertion of the Cu(I) species into the C-O bond and subsequent protonation. Pleasingly, with tosyl-substituted indene oxide **327**, the reaction proceeded cleanly with desired product **329** isolated in 54% yield, again as a 1:1 mixture of diastereoisomers (Scheme 71b). Subsequent deprotection of the THP group afforded diol **330**, which was treated with Jones reagent and used without any further purification after aqueous workup.

When subjected to esterification conditions, we observed conversion to lactone **332**, but also observed formation of the *C*-acylated product **333** in a 1.8:1 ratio (Scheme 72).



Scheme 72: Esterification/Cyclization of **331**

While it is likely that *O*-acylated product **322** has a high enough barrier to rotation for an asymmetric process to be viable it was accompanied by a decrease in *O*-selectivity under these conditions. We postulate that, with the incorporation of a substituent in the 7-position of the

indanone fragment of **331**, the increase in steric clash between the methoxy- and tosyl-substituents also causes a bias away from the more sterically hindered *O*-acylated product. The formation of the *C*-acylated product **333** is expected to be less strained due to the quaternary centre geometry causing the aryl substituents to point away from each other.

3.3 Conclusions and Outlook

The formation of the cyclized product under our esterification conditions demonstrated that we needed to redesign our starting material synthesis to include a milder transformation as the final step. One additional problem was that the unsubstituted indanone-derived ester did not have a high enough energy barrier to rotation to be conformationally stable, requiring substitution in the 7-position that then hampered regioselectivity in the cyclization step. A solution to this would be to use a tetralone derivative rather than an indanone derivative, or, even better, a naphthol derivative as the increase in ring size would alter the geometry of the groups around the biaryls axis (Figure 5).

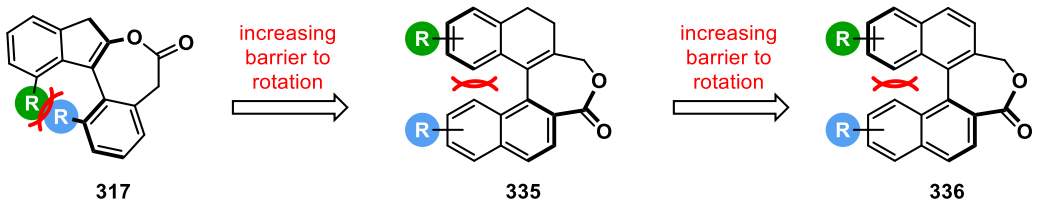


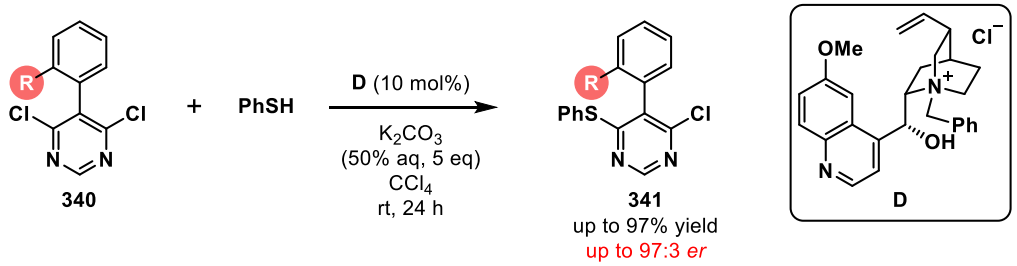
Figure 5: Possible Increase to the Barrier to Rotation by Altering Ring Size

The formation of the *C*-acylated product with more hindered ketoacid **331** also opened a new avenue of research as we formed a spiro-stereocentre and we hoped we could exploit this in an enantioselective manner. Our research focus thus turned to searching for a system that showed high *C*-selectivity for ketone acylation, affording spiro diketones.

4. Ketone *C*-Acylation

4.1 Project Aims

With our previous results indicating that *C*-acylation of a ketone was possible even when the substrate was biased towards *O*-acylation, we took inspiration from earlier investigations into axially chiral molecules from our research group (Scheme 73)[89, 126] and considered that a symmetrical spiro diketone would also be axially chiral.



Scheme 73: Previous Smith Group Investigation into the Synthesis of Axially Chiral Molecules

While the ketone carbonyl group could be removed after acylation to give access to axially chiral spiro compounds (e.g. hydrogenolysis of the ketones in **342** would afford a chiral product), we considered that the diketone could be a handle for otherwise achiral spiro systems (Figure 6).

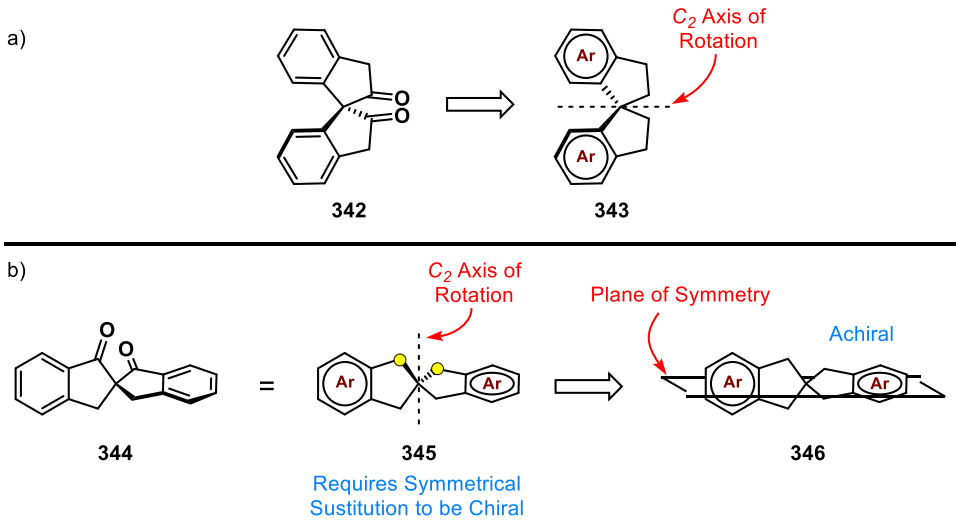
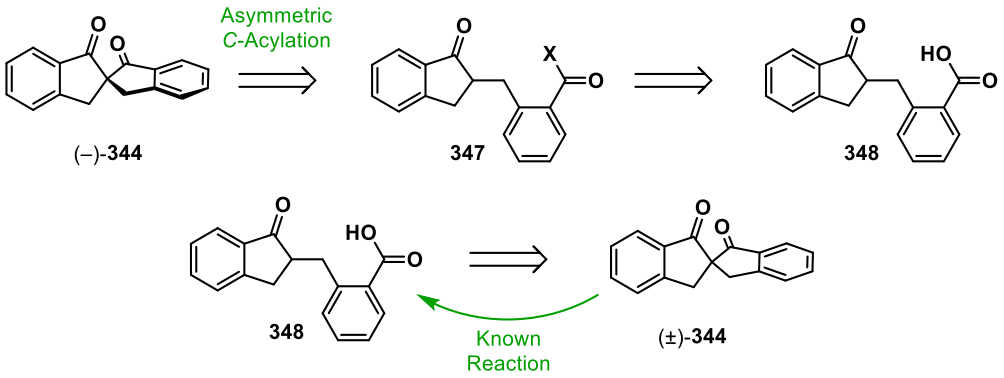


Figure 6: a) *C*-Acylation Substrates that are Axially Chiral without Ketone Functional Groups
b) C-Acylation Substrates Requiring Diketone for Asymmetry

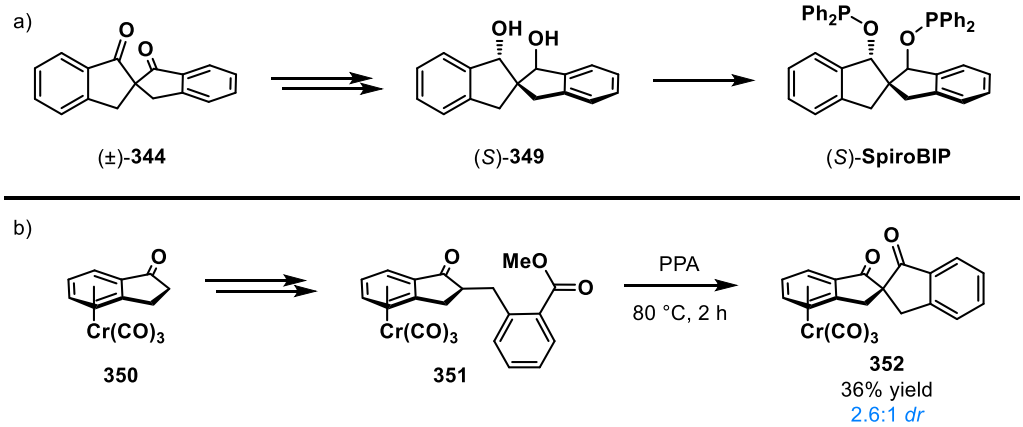
One diketone system that satisfied the properties we were interested in was 2,2′-spirobiindanedione **344**, which, from our *C*-acylation disconnection, could be accessed from acid **348** (Scheme 1). The reaction would be expected to favour the 5-*enolexo-exo-trig* over the

7-*enolexo-endo-trig* cyclization without the bias of the benzhydrylic ketone.[127] The synthesis of acid **348** has been reported in the literature, although only from ring opening of our desired product **344** with sodium hydroxide.[128] This would require us to synthesise **344** as a racemate, open with hydroxide, activate the carboxylic acid and then enantioselectively *C*-acylate - not an efficient process, although suitable for testing the viability of the reaction (Scheme 74).



Scheme 74: Retrosynthesis of *C*-Acylation Precursors

Spirobiindanone **344** has been used in the synthesis of chiral diol **349**, the diol source for the ligand SpiroBIP (Scheme 75a),[129] although enantioenriched **344** has only been accessed from the resolution of diol **349**[130] or cleavage of a planar chiral chromium complex **352** as reported by Schlögl in 1976 (Scheme 75b).[131]



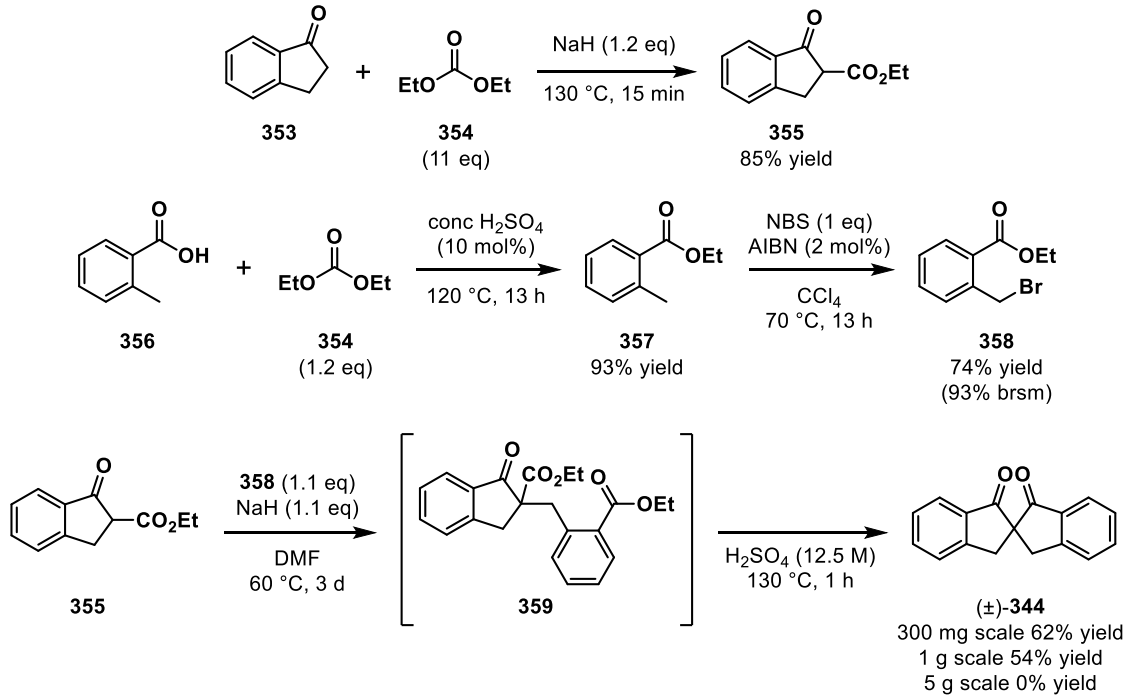
Scheme 75: a) Use of Spirobiindanone in Synthesis of Diol **349**;
b) Schlögl's Diastereoselective *C*-Acylation of Planar Chiral 1-Indanone Derivative **352**

In this report, they disclosed a diastereoselective *C*-acylation of a planar chiral chromium complex, **351**, a methyl ester synthesized from **350**. The diastereoselectivity of this reaction is due to cyclization occurring on the opposite face the planar chiral chromium complex to reduce the steric

interaction with the tricarbonylchromium group. Although their selectivity was low (2.6:1 *dr*), the two diastereoisomers were separable allowing access to enantioenriched spirobiindanone **344**.

4.2 Synthesis of Activated Ester 360 for the *C*-Acylation Reaction

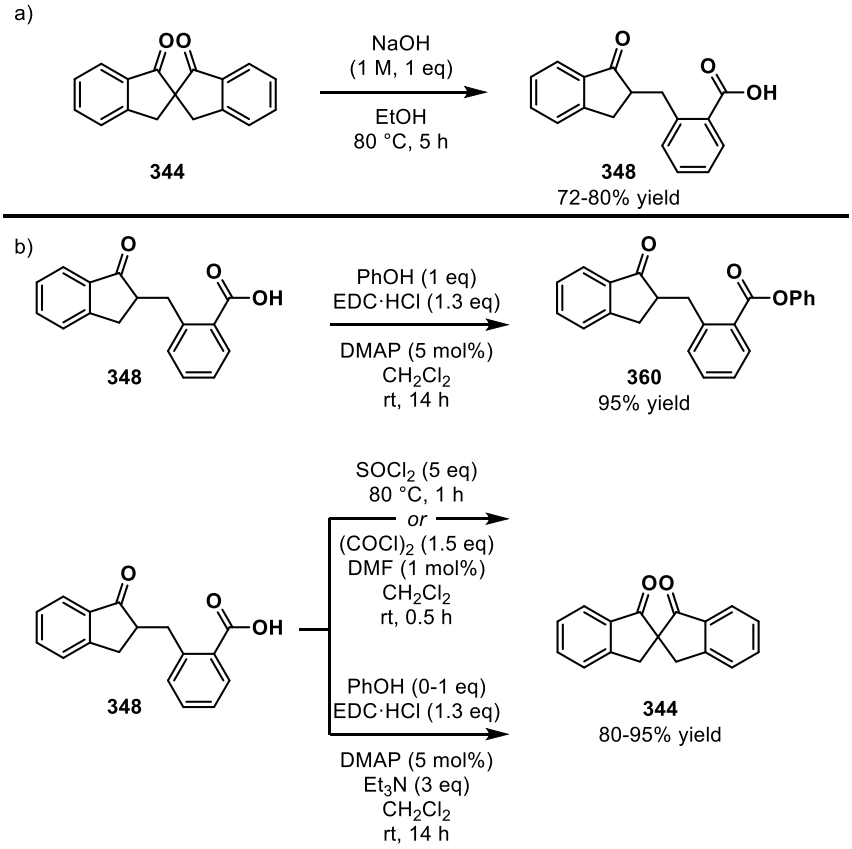
With a target substrate in mind, we commenced with the synthesis of **344**. The most efficient reported route to racemic spirobiindanone was reported in 1995 by Keay, and we followed their synthesis (Scheme 76).[130]



Scheme 76: Literature Synthesis of Spirobiindanone **344**

This route commenced with α-carboxylation of 1-indanone **353** *via* deprotonation with sodium hydride followed by quenching with diethyl carbonate **354** to afford **355** in 85% yield. Concomitantly, *o*-toluic acid was esterified with diethyl carbonate and catalytic sulfuric acid, and then underwent radical bromination using NBS and benzoyl peroxide as an initiator. This afforded substituted benzyl bromide **358** in 69% yield over 2 steps. β-Ketoester **355** was then deprotonated with sodium hydride, followed by dropwise addition of benzyl bromide **358** which afforded **359** upon workup. This crude β-ketoester, **359**, was then subjected to the literature ester hydrolysis/decarboxylation/cyclization conditions of reflux in 12.5 M H_2SO_4 for 1 hour. On a small scale (≈ 300 mg) this two-step sequence afforded a good yield of **344** (62%); however on larger

scales the procedure proved unreliable with no desired product isolated on a 5 g scale and raised safety concerns over the heating of sodium hydride in DMF.[132] As such, the reaction was repeated on a smaller scale multiple times (1 g scale, 54% yield) in order to synthesize sufficient quantities of material for investigating the desired cyclization. With racemic spirobiindanone **344** in hand, we then needed to open one 5-membered ring with hydroxide to reveal acid **348**, which could then be turned into a variety of activated esters (Scheme 77).

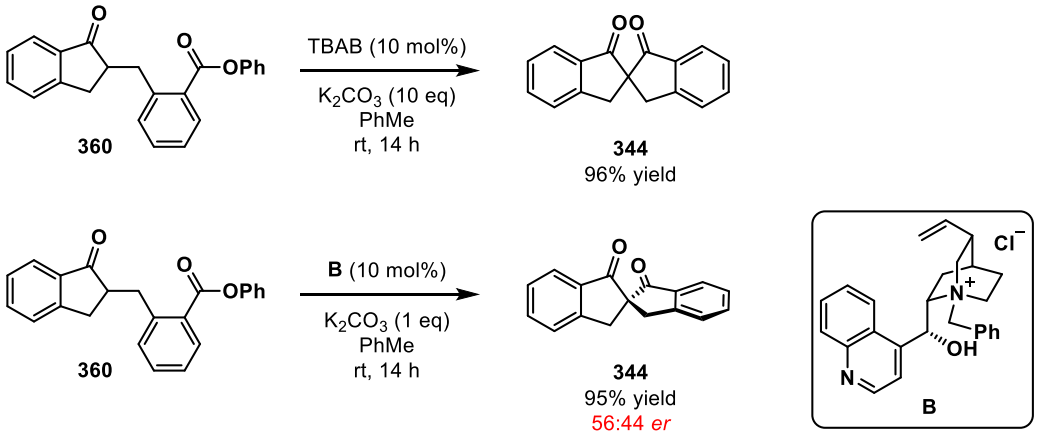


Scheme 77: a) Synthesis and b) Activation of Carboxylic Acid **348**

The hydrolysis of **344** proceeded smoothly, with ketoacid **348** isolated in consistently good yields after recrystallization of the crude reaction mixture (72–80%, Scheme 77a). Esterification with phenol using EDC as the coupling agent afforded **360** in 95% yield, although this was contaminated with a small amount (2–5 mol%) of phenol which coeluted with the product. When triethylamine was added to the coupling, spirobiindanone **344** was isolated in 80% yield, demonstrating that cyclization of this ketone into an activated intermediate was feasible. Cyclized product **344** was also obtained without phenol present, implying cyclization onto O-acylisourea was occurring.

When the esterification was attempted through activation of the carboxylic acid as the acid chloride, only cyclized spirobiindanone **344** was isolated (Scheme 77b).

A test reaction with phenyl ester **360** under mild phase-transfer conditions using TBAB as the catalyst and aqueous K_2CO_3 as the base showed good reactivity, with complete conversion to **344** in just 10 hours (96% yield) (Scheme 78).



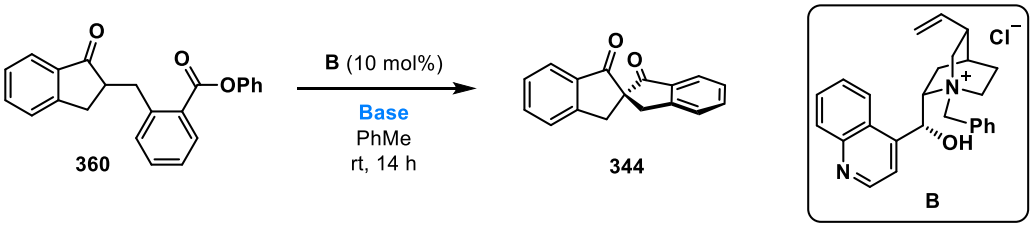
Scheme 78: Cyclization of **360** under Phase-Transfer Conditions

Pleasingly, when we used a non-racemic chiral catalyst, we observed some enantioinduction in the reaction (95% yield, 56:44 *er* with **B**), indicating that the system was suitable for further investigation.

4.3 Optimization of Cyclization of Phenyl Ester 360

With a racemic reaction in hand, we needed to develop the reaction to afford spirobiindanone **344** in high enantioenrichment and yield. This chapter will only highlight key results – for a full account of optimization, see **Appendix D**.

To begin with, we quickly investigated the effect of a few bases on the reaction with cinchonidine-derived catalyst **B** (Table 8).

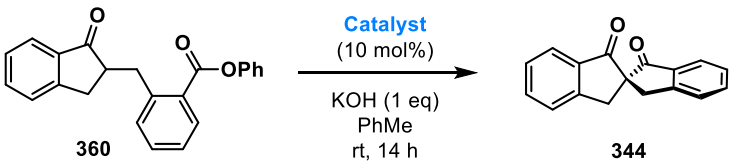


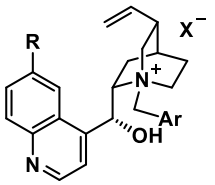
Entry	Base	*er*
1	K_2CO_3 (1 eq)	56:44
2	K_2CO_3 (50% aq, 10 eq)	50:50
3	KOH (50% aq, 10 eq)	N/A [a]
4	KOH (1 eq)	59:41
5	NaOH (1 eq)	52:48
6	$CsOH{\cdot}H_2O$ (1 eq)	56:44

[a] hydrolysis of ester

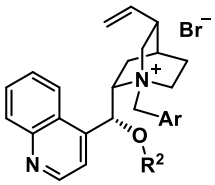
Table 8: Initial Base Screen

Pleasingly, we observed full consumption of **360** in all cases in just 14 hours. The use of aqueous potassium carbonate rather than solid potassium carbonate gave us racemic spirobiindanone **344** (50:50 *er*, Table 8, entries 1 & 2). Aqueous hydroxide bases showed complete hydrolysis of the ester to afford acid **348** and so were discounted from any further optimization (Table 8, entry 3). Pleasingly, solid hydroxide bases did not show hydrolysis of the ester and resulted in higher enantioselectivities than carbonate bases (up to 59:41 *er*, Table 8, entries 4–6). We were confident that having increased the enantioselectivity of the reaction to 59:41 *er* with potassium hydroxide, we would be able to evaluate the selectivity afforded by various catalysts (Table 9).

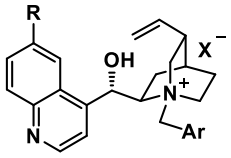




B R = H, Ar = Ph, X = Cl
F R = H, Ar = Ph, X = Br
J R = H, Ar = 2-Naphth, X = H
K R = H, Ar = 9-Anthr, X = H
D R = OMe, Ar = Ph, X = Cl
G R = OMe, Ar = Ph, X = Br
L R = OMe, Ar = 9-Anthr, X = Br



H R^2 = allyl, Ar = Ph
I R^2 = Me, Ar = 9-anthr

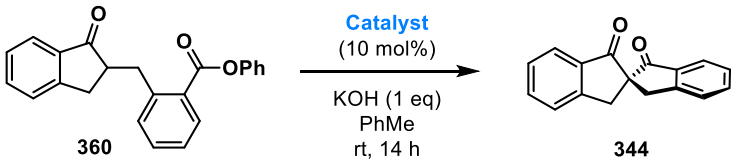


A R = H, Ar = Ph, X = Cl
M R = H, Ar = 3,5-$(CF_3)_2$Ph, X = Br
E R = OMe, Ar = Ph, X = Cl

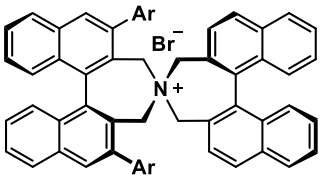
Entry	Catalyst	*er*
1	A	48:52
2	B	59:41
3	D	54:46
4	E	43:57
5	F	58:42
6	G	55:45
7	H	50:50
8	I	50:50
9	J	60:40
10	K	65:35
11	L	58:42
12	M	62:38

Table 9: Initial Catalyst Screen

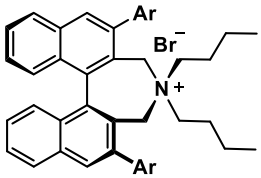
We possess a large variety of cinchona-derived catalysts, and this was our next port of call for optimization. A screen of the 4 commercially available cinchona-derived catalysts **A**, **B**, **D**, **E** demonstrated that the catalyst architecture did not have a significant effect, although cinchonidine-derived catalyst **B** gave the highest selectivity (Table 9, entries 1–4). Exchange of the counterion from chloride to bromide showed a small increase in selectivity (Table 9, entries 5 & 6). The hydroxyl group in the catalyst was shown to be important for high levels of selectivity, with *O*-capped catalysts such as **H** and **I** showing no enantioselectivity (Table 9, entries 7–8). The size of the aryl substituent on the catalyst influenced the enantioselectivity of the reaction, with bulkier catalysts showing higher levels of selectivity, up to a maximum of 65:35 *er* (Table 9, entries 9–12). With no significant increase in enantioenrichment observed, we tried a few different catalyst architectures that were not based on benzylated cinchona alkaloids (Table 10).



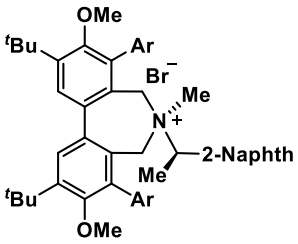
Entry	Catalyst	*er*
1	**N**	51:49
2	**O**	49:51
3	**P**	63:37
4	**Q**	69:31
5	**R**	67:33



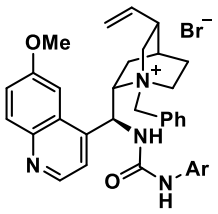
N Ar = 3,4,5-F_3Ph



O Ar = 3,4,5-F_3Ph



P Ar = 3,5-$(CF_3)_2$Ph

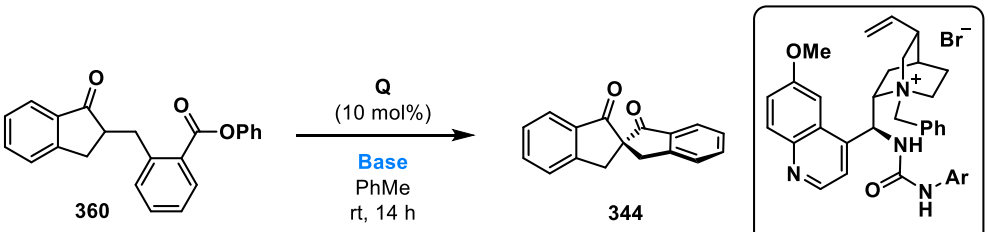


Q Ar = 4-NO_2Ph
R Ar = 3,5-$(CF_3)_2$Ph

Table 10: Extended Catalyst Screen

BINOL derived catalysts **N** and **O**, of the type pioneered by Maruoka, were largely ineffective in this transformation with **344** isolated with negligible enantioenrichment (51:49 *er*, Table 10, entries 1-2). Catalyst **P**, developed by Lygo, showed decent levels of enantioinduction (63:37 *er*, Table 10, entry 3), but the best enantioinduction was observed with bifunctional catalysts bearing a hydrogen bond donor: **Q** & **R** (Table 10, entries 4–5). Interestingly, despite inverting the benzylic stereocentre of quinine to synthesize the urea, **340** was isolated with the same sense of chirality (*S*) as it was when using catalyst **D**. We do not have an explanation for this other than a change in transition state due to the presence of the strong hydrogen bond donor.

In trying to rationalise the low levels of enantioselectivity we observed, we hypothesized that the reaction might be catalytic in base as a result of the leaving group being mildly basic (PhOH has a pK_a of 27.4 in MeCN, 18.0 in DMSO).[133]



Entry	Base	*er*
1	KOH (1 eq)	69:31
2	KOH (10 eq)	N/A[a]
3	KOH (0.1 eq)	63:37
4	$NaOPh{\cdot}H_2O$ (0.1 eq)	62:38
5	$NaOPh{\cdot}H_2O$ (1 eq)	51:49
6	$NaOPh{\cdot}H_2O$ (1 eq)	50:50[b]

[a] Hydrolysis of Ester
[b] No Catalyst

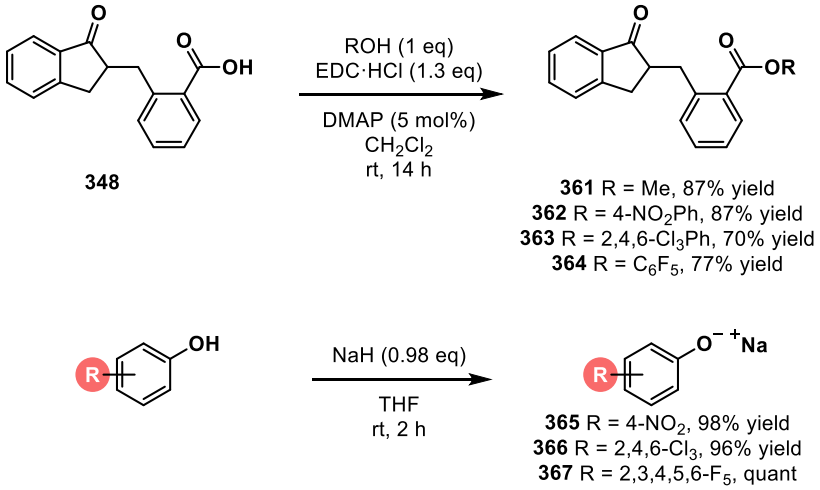
Table 11: Effect of Phenolate on Cyclization of **360**

As shown in Table 11, the stoichiometry of the base has a significant effect on the reaction - our previous results were obtained with 1 equivalent of potassium hydroxide (Table 11, entry 1). Increasing the quantity of hydroxide present in the reaction mixture showed hydrolysis of the ester, as previously observed for aqueous hydroxide (Table 11, entry 2). Decreasing the quantities of base to 0.1 equivalents still gave complete conversion, demonstrating that the released phenolate was acting as a base, however the enantioselectivity of the reaction decreased to 63:37 *er* (Table 11, entry 3). Use of sodium phenolate as the base in catalytic quantities gave a very similar result of 62:38 *er* (Table 11, entry 4). A stoichiometric quantity of sodium phenolate further decreased the enantioselectivity of the reaction, with **344** obtained in 51:49 *er* (Table 11, entry 5). We suggested that the phenolate leaving group was acting as an organosoluble base, causing the reaction to occur racemically without involvement of the catalyst. We tested this by performing the reaction with stoichiometric sodium phenolate in the absence of catalyst **Q** and saw complete conversion to racemic **344** in just 7 hours (Table 11, entry 6) which agrees with our hypothesis.

4.4 Leaving Group Optimization

To overcome this problem, we thus needed to ensure the reaction only proceeded with involvement of the catalyst. This could be achieved by deactivating the background reaction,

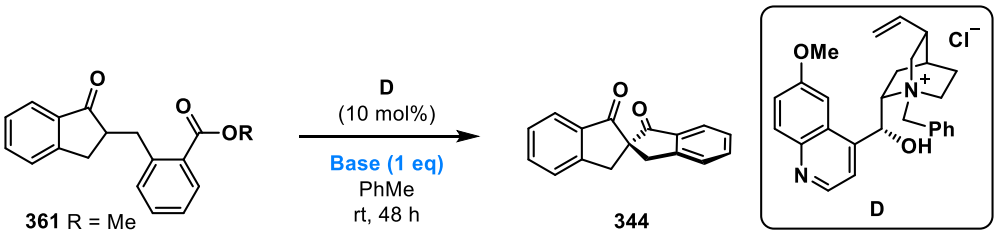
through the use of a less activated ester, or ensuring the leaving group was sufficiently acidic so as not to act as a base. We synthesized several different esters from acid **348** through EDC-mediated esterification in good yields (Scheme H). We also synthesized the corresponding sodium phenolate in each case to test if it could act as a base for the cyclization. We chose to synthesize methyl ester **361** to see if the reaction would proceed with an inferior leaving group, whilst electron-withdrawn phenyl esters **362**–**364** were synthesized to determine how acidifying the leaving group affects the reaction (Scheme 79).



Scheme 79: Synthesis of a Variety of Activated Esters and Corresponding Phenolates

Ideally, we also wanted to synthesize the acid chloride, however we had previously observed complete conversion to the cyclized product under our chlorination conditions (Scheme 77b, page 61).

With our substrates with varied leaving groups in hand, we subjected them all to phase-transfer conditions with commercial catalyst **D** and a base: either 1 equivalent KOH or 1 equivalent NaOR (Table 12).



361 R = Me
360 R = Ph
362 R = 4-NO_2Ph
363 R = 2,4,6-Cl_3Ph
364 R = C_6F_5

Entry	Substrate	Base	*er*
1	**361**	KOH	N/A[a]
2	**360**	KOH	51:49
3	**360**	NaOPh·H_2O	50:50
4	**362**	KOH	73:27
5	**362**	**365**	64:34[b]
6	**363**	KOH	79:21[c]
7	**363**	**366**	N/A[a]
8	**364**	KOH	79:21
9	**364**	**367**	N/A[a]

[a] No Conversion
[b] 35% Conversion
[c] 60% Conversion

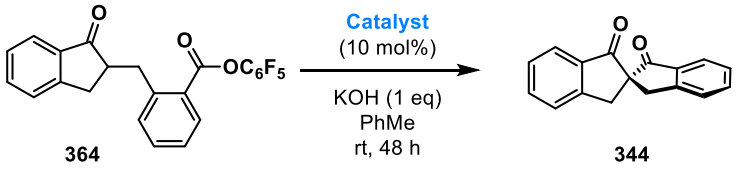
Table 12: Optimization of Leaving Group

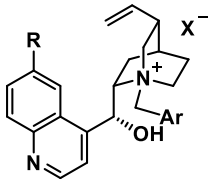
As can be seen above, methyl ester **361** proved unsuitable with no cyclization observed under phase-transfer conditions (Table 12, entry 1), demonstrating the need for a more activated leaving group. The phenolic derivatives all cyclized under the reaction conditions with 1 equivalent of potassium hydroxide (>90% conversion; any incomplete conversion observed was likely due to the challenges associated with the handling of 1 equivalent of a hygroscopic material on a 2–3 mg scale). We found that as the pK_a of the phenolate decreased (pK_a (DMSO) PhOH: 18.0; 4-NO_2Ph: 10.8; 1,3,5-Cl_3Ph: 10.2; C_6F_5OH: 8.9),[134] we obtained the product in increasing levels of enantioenrichment, with **344** obtained in 79:21 *er* for substrates **363** and **364** – significantly higher than the 51:49 *er* with substrate **360** (Table 12, entries 2, 4, 6, 8). Substrate **363** showed a significantly decreased conversion to the product, which we attribute to the increased steric hindrance about the ester carbonyl with the two *ortho*-chlorine atoms (Table 12, entry 6). In addition, we found that when using the leaving group as the base in the reaction we observed decreased conversion to the product, with substrates **363** and **364** showing no reactivity at all

(Table 12, entries 7 and 9). This suggested that 1,3,5-Cl_3PhO^- and $C_6F_5O^-$ were not sufficiently basic to carry out the background reaction. We thus selected pentafluorophenol as our optimal leaving group. It should be noted that pentafluorophenyl ester **364** showed a significantly longer reaction time (48 h) than substrate **360** bearing a phenyl leaving group.

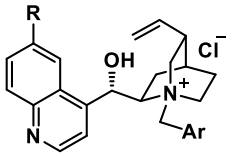
4.5 Optimization of the Cyclization Conditions for Ketoester 364

With a superior leaving group in hand for enantioselective cyclization, we needed to reoptimize our reaction conditions as we anticipated that we could now access **344** in very high enantioenrichment without the racemic background reaction. We started by re-examining the catalyst (Table 6, selected examples only – for a full account see **Appendix E**).

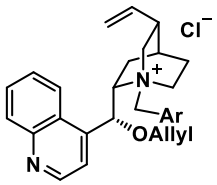




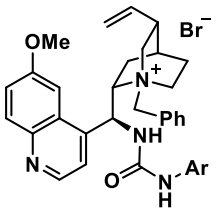
B R = H, Ar = Ph, X = Cl
K R = H, Ar = 9-Anthr, X = Cl
D R = OMe, Ar = Ph, X = Cl
L R = OMe, Ar = 9-Anthr, X = Br
T R = OMe, Ar = 3,5-$(CF_3)_2$Ph, X = Br
U R = OMe, Ar = 2-MePh, X = Br
V R = OMe, Ar = 3-MePh, X = Br
W R = OMe, Ar = 4-FPh, X = Br
X R = OMe, Ar = 2-Naphth, X = Br
Y R = OMe, Ar = 9-Anthr, X = Cl



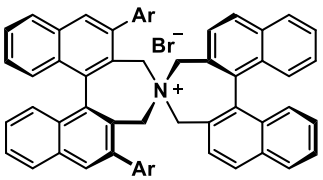
A R = H, Ar = Ph
E R = OMe, Ar = Ph



S Ar = 9-Anthr



Q Ar = 4-NO_2Ph



N Ar = 3,4,5-F_3Ph

Entry	Catalyst	*er*
1	**A**	23:75
2	**B**	75:25
3	**D**	79:21
4	**E**	25:75
5	**Q**	42:58
6	**S**	N/A[a]
7	**T**	N/A[b]
8	**U**	75:25
9	**V**	80:20
10	**W**	75:25
11	**X**	80:20
12	**L**	87:13
13	**K**	85:15
14	**Y**	88:12
15	**N**	N/A[b]
16	**Y** (0 °C)	80:20
17	**Y** (–20 °C)	N/A[a]

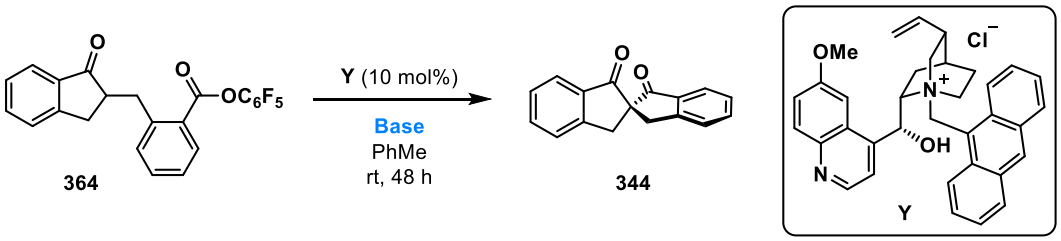
[a] No Reaction
[b] Decomposition of **364**

Table 13: Catalyst Optimization for Substrate **364**

Once again, we first evaluated the commercially available benzylated cinchona alkaloids **A**, **B**, **D**, **E**. We saw similar levels of enantioenrichment in **344** (Table 13, entries 1–4) although **D** showed the greatest selectivity (79:21 *er*) so we focused most of our optimization on quinine-derived catalysts. The most effective catalyst for the phenyl ester, **360**, was found to give very low levels of selectivity (42:58 *er*, Table 13, entry 5) and *O*-capped catalysts afforded no desired product (Table 13, entry 6). Electron-withdrawing substituents on the ring led to no retrieval of desired product (Table 13, entry 7), while weakly electron donating substituents (catalysts **U**–**W**) had only a minor effect on the reaction (Table 13, entries 8–10). As before, increasing the steric bulk on the benzyl group had a significant impact on enantioselectivity: increasing the size of the group to a naphthyl increased enantioenrichment to 80:20 *er* (Table 13, entry 11), whilst a further increase in enantioenrichment was observed with a 9-anthracenylmethyl group quaternizing the catalyst (Table 13, entry 12). The quinine-based catalyst was confirmed to afford higher enantioselectivity with the 9-anthracenylmethyl group than the cinchonidine scaffold which lacked the methoxy- group on the quinoline ring (Table 13, entries 12–13). One final increase in enantioenrichment could be gained by using a chloride counterion rather than a bromide counterion in the catalyst (catalyst **Y**, Table 13, entry 14). Other catalyst scaffolds, such as the BINOL-derived catalysts pioneered by Maruoka were found to be ineffective in this cyclization (Table 13, entry 15).

Decreasing the temperature of the reaction had previously been observed to increase selectivity while decreasing rate of reaction,[135] and we were disappointed to find that when conducting the reaction at 0 °C we saw a decrease in enantioselectivity (Table 13, entry 16). Further decreasing the temperature (to −20 °C) led to no reaction (Table 13, entry 17). The reasons for this observation are likely due to the conclusions we reach in Chapter 5 regarding the mechanism of this reaction.

These results identified quinine-derived **Y** as our optimal catalyst, giving us high levels of selectivity, and we next investigated the effect of the base on reaction. A variety of common inorganic bases were explored with a selection of counterions (Table 14).



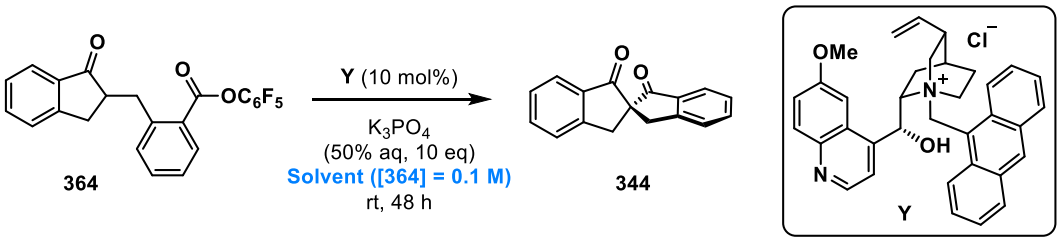
Entry	Base	*er*	Conversion[a]
1	KOH (1 eq)	89:11	62%
2	KOH (5 eq)	N/A[b]	-
3	NaOH (2 eq)	75:25	63%
4	$CsOH{\cdot}H_2O$ (2 eq)	N/A[b]	-
5	$RbOH{\cdot}H_2O$ (2 eq)	88:12	73%
6	Li_2CO_3 (5 eq)	N/A	0%
7	K_2CO_3 (5 eq)	95:5	56%
8	Cs_2CO_3 (5 eq)	91:9	100%
9	K_2CO_3 (50% aq, 10 eq)	96:4	95%
10	K_2CO_3 (50% aq, 5 eq)	95:5	88%
11	K_2CO_3 (33% aq, 10 eq)	96:4	80%
12	Cs_2CO_3 (50% aq, 10 eq)	93:7	70%
13	K_3PO_4 (2 eq)	89:11	47%
14	K_3PO_4 (50% aq, 10 eq)	97:3	100%
15	K_3PO_4 (sat aq, 10 eq)	96:4	100%

[a] Conversion Calculated by ^{1}H NMR Analysis of Crude Reaction Mixture
[b] Hydrolysis of **364**

Table 14: Catalyst Optimization for Substrate **364**

Aqueous hydroxide bases were not investigated due to the propensity for hydrolysis of the ester **364**, but we also found that greater excesses of solid hydroxide bases, as well as low loadings of cesium hydroxide, showed hydrolysis of the ester **364** (Table 14, entries 2 & 4). Changing the counterion to sodium or rubidium had some effect on enantioselectivity, although neither gave superior selectivity to potassium (Table 14, entries 1, 3, 5). For the solid carbonates, we observed a clear trend of increased reactivity with a higher atomic number counterion although with a corresponding decreased enantioselectivity. Lithium carbonate showed no reaction, potassium carbonate gave 56% conversion with the highest enantioenrichment of the metal carbonates (95:5 *er*), and caesium carbonate afforded full conversion, although at 91:9 *er* (Table 14, entries

6–9). The same selectivity trend was observed when using aqueous carbonates, with potassium carbonate showing higher selectivity than caesium carbonate, although this time accompanied by higher conversion (Table 14, entries 9 & 12). The concentration of aqueous potassium carbonate also had an effect, with lower conversions observed with lower base loading or lower concentration, although the difference in enantioselectivity was negligible (Table 14, entries 10–11). Solid potassium phosphate disappointingly showed lower enantioselectivity and conversion than potassium carbonate despite being the stronger base (pK_a 12.3 vs 10.3 in H_2O) (Table 14, entry 13).[136] Pleasingly, 50% aqueous potassium phosphate gave us complete conversion and the highest enantioselectivity observed so far (97:3 *er*, Table 14, entry 14). Saturated aqueous potassium phosphate also gave complete conversion, as expected, although with a small decrease in enantioselectivity to 96:4 *er* (Table 14, entry 15). With an optimized catalyst (**Y**) and base (50% aqueous potassium phosphate) in hand we proceeded to investigate the effect of solvent on the reaction (Table 15).



Entry	Solvent	*er*
1	CH_2Cl_2	89:11[a]
2	$CHCl_3$	92:8
3	CCl_4	96:4
4	$(CHCl_2)_2$	50:50[a]
5	PhH	95:5
6	PhMe	97:3
7	*m*-xylene	90:10
8	*p*-xylene	94:6
9	Et_2O	78:22[a]
10	^{t}BuOMe	80:20[a]
11	$^{i}Pr_2O$	81:19[b]
12	1,4-dioxane	73:27
13	$CHCl_3$/PhMe 1:9	96:4[a]
14	PhMe ([**364**] = 1 M)	89:11

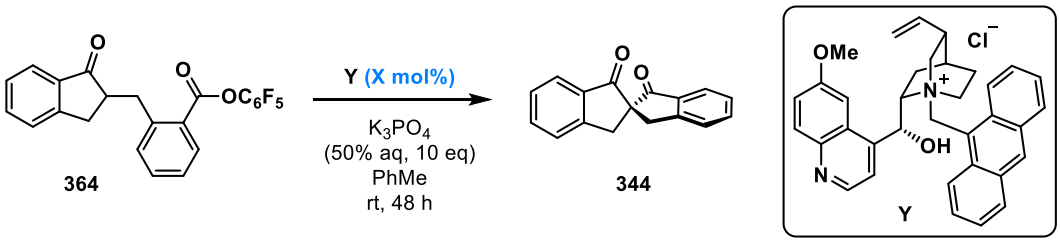
[a] Reaction Complete in 24 Hours
[b] <30% Conversion

Table 15: Solvent Optimization for Substrate **364**

We tested a variety of different types of solvent: chlorinated, aromatic and ethereal. We noticed that chlorinated solvents were generally well-tolerated (Table 15, entries 1-3), with the highest selectivities seen when using the least polar chlorinated solvents (chloroform and carbon tetrachloride). Aromatic solvents proved the best, with benzene and toluene both affording extremely high selectivity (Table 15, entries 5 & 6). Poorer selectivity was observed with ethereal solvents along with decreased conversion in the case of $^{i}Pr_2O$ (Table 15, entries 9–12). A general trend was observed: less polar solvents gave higher enantioselectivity, although with a lower rate of reaction (Table 15, entries 1–4 & 9–11). We reason that this is due to looser ion-pairing in more polar solvents, resulting in lower enantioselectivities. Our highest selectivity was still with toluene (97:3 *er*, Table 15, entry 6), although increasing the concentration of substrate in toluene to

increase the rate of reaction had a negative effect on selectivity (Table 15, entry 14). A mixed solvent of toluene/chloroform in a 9:1 ratio had previously been used in the research group,[137] and while we found a rate enhancement (complete conversion at 24 hours) we saw a slight decrease in enantioselectivity (Table 15, entry 13) so we continued with toluene as our optimal solvent.

One final optimization that we carried out was that of the catalyst loading; until now all our results had been with a 10 mol% loading and we hoped that a lower loading might prove beneficial (Table 16).



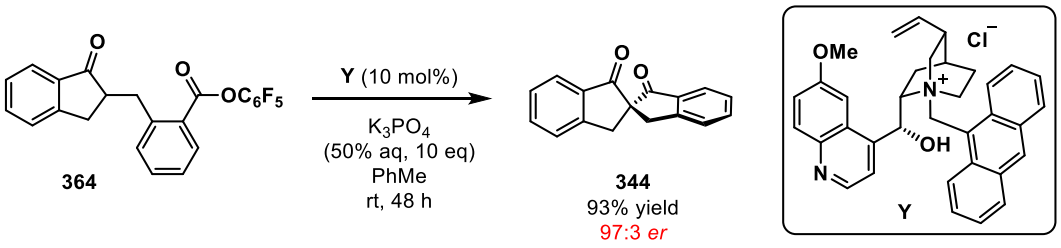
Entry	Catalyst Loading	*er*	Conversion[a]
1	10 mol%	97:3	100%
2	5 mol%	86:14	70%
3	2 mol%	83:17	50%

[a] Conversions Calculated by ^{1}H NMR Analysis of Crude Reaction Mixture

Table 16: Catalyst Loading Optimization for Substrate **364**

We found that the catalyst loading had a large influence on the reaction, affecting both the enantioenrichment of the product and the rate of reaction (Table 16, entries 1–3), an unusual result that is explained in Chapter 5.

We were confident we had reached the optimal conditions for the *C*-acylation reaction, so carried out the reaction on a 50 mg scale to verify our results on a preparative scale and isolate the enantioenriched spirobiindanone **344** as we had been using ^{1}H NMR conversions until this point (Scheme 80).



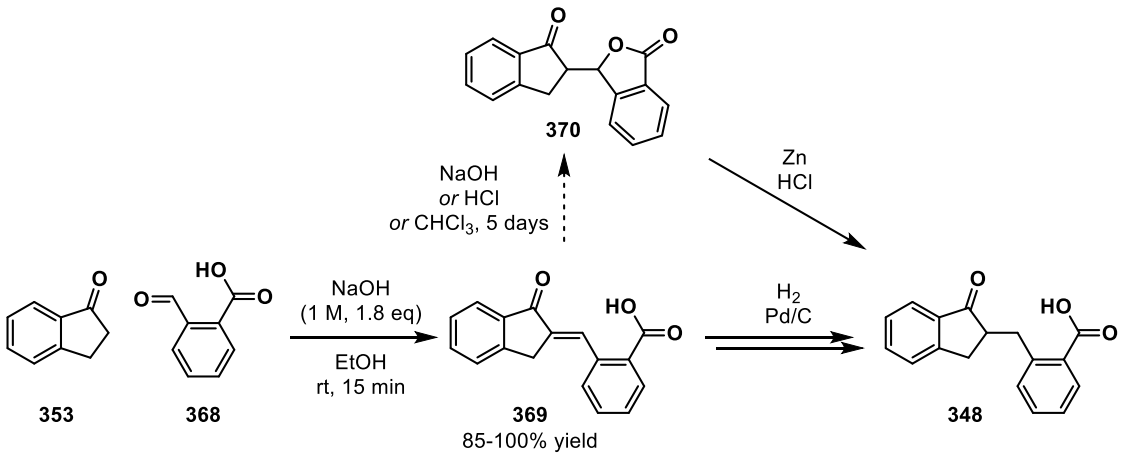
Scheme 80: Optimized *C*-Acylation Conditions

The reaction proceeded with the same level of stereocontrol as we had seen in our screening (97:3 *er*) and we isolated **344** in excellent yield (93%). We then performed this reaction on a 1.4 g scale and isolated the product **344** without any loss in yield or selectivity (92% yield, 97:3 *er*).

4.6 Redevelopment of Starting Material 364 Synthesis

We still had problems with the starting material synthesis to solve: the simplest substrate (**364**) was prepared *via* a largely linear process in a total of 7 steps with a non-scalable sodium hydride reaction in the middle of the synthesis. For more highly substituted substrates necessary to investigate the scope of the reaction, we would need to significantly alter the synthesis to rapidly construct our spirocycles.

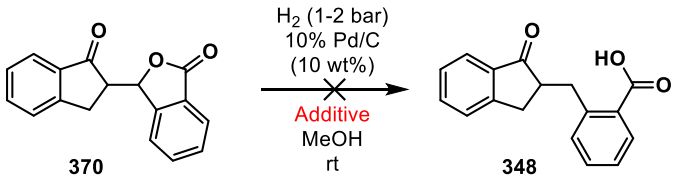
Studies by Luche-Ronteix in 1970 disclosed formation of **369** through the aldol reaction of 1-indanone **353** with 2-carboxybenzaldehyde **368**.[138] Although the reaction is extremely quick, the authors note that the product is highly unstable. The product from 1,4-addition of the carboxylic acid into the enone (**370**) was generated rapidly in acidic or basic conditions, and slowly when dissolved in solution (we observed complete conversion to **370** after 5 days in $CDCl_3$). We also observed formation of the 1,4-addition product **370** when crude compound **369** was left on the bench for weeks. Nevertheless, unsaturated acid **369** could be hydrogenated to afford our desired ketoacid **348**. The authors reported that the 1,4-addition product **370** could be reduced to form **340** with zinc in acetic acid; however the yield of this reaction was at most 30%, so avoiding the formation of **370** would be paramount to accessing large quantities of **348**.



Scheme 81: Luche-Ronteix's Aldol Condensation and Proposed Hydrogenation to Ketoacid **348**

Following Luche-Ronteix's procedure we obtained unsaturated acid **369** in excellent yields (85–100%, Scheme 81), although prolonged reaction time afforded significant quantities of **370**.

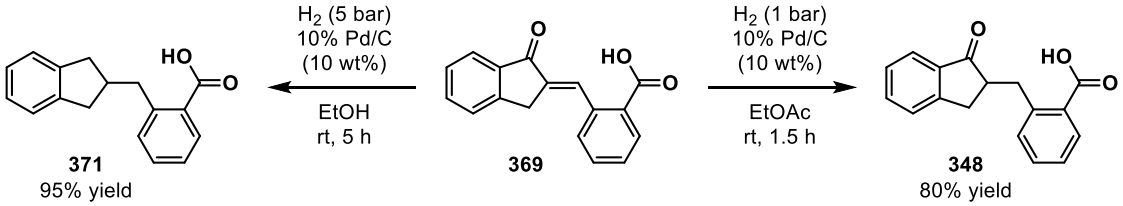
We first thought that we could perhaps hydrogenate cyclized adduct **370** by performing the hydrogenation under acidic or basic conditions. This should promote the $E1_{CB}$ reaction that extrudes the acid, allowing for hydrogenation of this enone (Scheme 82).



Additives: None, AcOH (2 eq), AcOH (as Solvent), NaOH (1 eq), NaOH (aq, 1.1 eq)

Scheme 82: Attempted Hydrogenated of Oxy-Michael Product **370**

Disappointingly, no conversion to desired product **348** was detected by ^{1}H NMR or mass spectrometry so we abandoned attempts at this reaction and instead focused on the hydrogenation of **369** (Scheme 83).

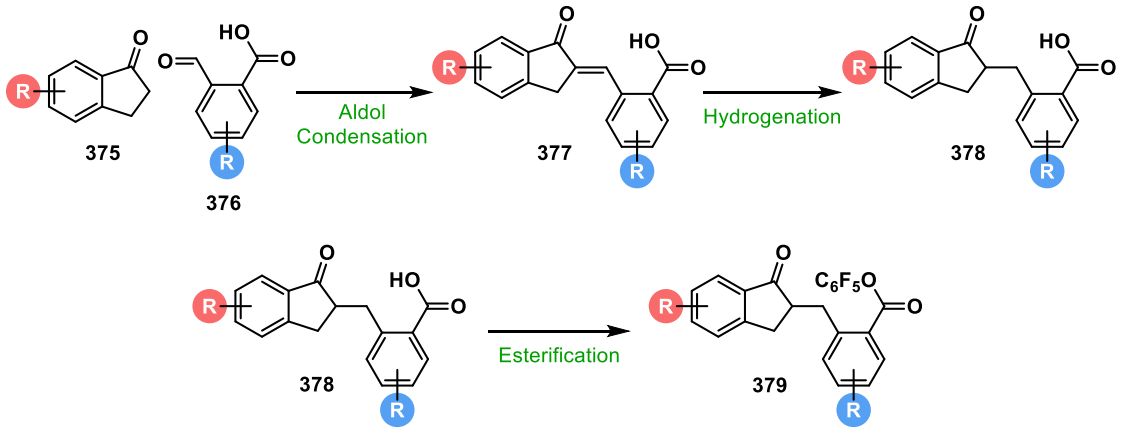


Scheme 83: Hydrogenation of Unsaturated Ketoacid **369**

We found that the hydrogenation conditions affected the product distribution between **348** and **371**. Firstly, overreduction of **369** to indane **371** was observed with 10 wt% Pd/C at 5 bar H_2 for

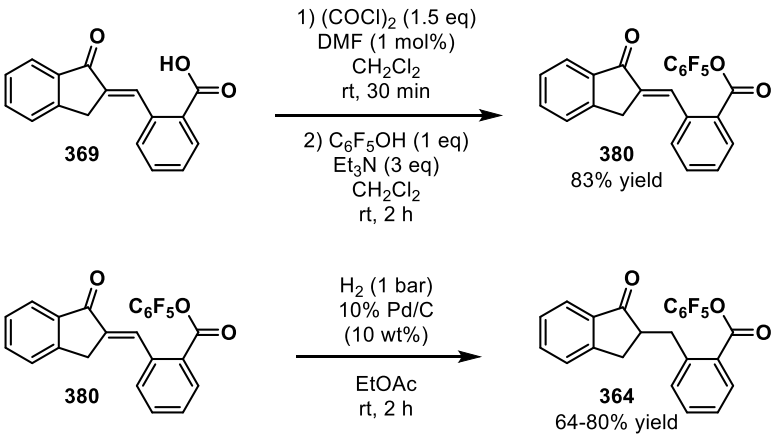
5 hours. A reduction in pressure to 1 bar afforded a mixture of overreduced products, a diastereoisomeric indanol, and indane **371**, although this could be suppressed by using a less active hydrogenation solvent, such as ethyl acetate. Careful monitoring of the reaction time was also essential as, even in ethyl acetate, overreduction was observed after 2 hours. The desired product **348** was then isolated with a basic aqueous extraction of the crude reaction mixture (to remove any cyclized product **370** that was present), followed by acidification, extraction into an organic solvent and then recrystallization from benzene, affording **348** in 80% yield.

Attempted formation of acid chloride of **348** resulted only in cyclization to spirobiindanone **344** (see Scheme 77b, page 61). In contrast, as before, a mild esterification with EDC as the coupling agent completed the synthesis of **364**. The total step count for unsubstituted ketoesters was reduced to 3 steps and allowed rapid access to derivatives **369** by starting with substituted 1-indanones **375** and 2-carboxybenzldehydes **376** (Scheme 84).



Scheme 84: Strategy to Access Ketoesters **379** for *C*-Acylation

Despite designing a successful route to **379**, we believed that the requirement to recrystallize **378** and the variable stability of substituted unsaturated acids **377** may cause problems. As such, we reordered the synthesis, performing first the esterification and then hydrogenation (Scheme 85).



Scheme 85: Reordered Route to Ketoester **364**

Esterification under the conditions that we previously found for **348** proved to be ineffective, with the long reaction time favouring conversion to the oxy-Michael product **370**. Instead, we generated the acid chloride with oxalyl chloride with catalytic DMF, which was stable as it could no longer undergo oxy-Michael addition. This was then esterified with pentafluorophenol in the presence of triethylamine in 83% yield. Hydrogenation was carried out under the same conditions as for **369**, again with small quantities of overreduction observed with protracted reaction times. This redesigned synthesis requires the same number of steps, but minimizes the time that reactive unsaturated acid **369** is in solution and avoids recrystallization.

4.7 Substrate Synthesis and Scope

To investigate the functional group tolerance of our *C*-acylation reaction, we required various substituted ketoesters. Our key building blocks for our substrate synthesis were therefore 1-indanones and 2-carboxybenzaldehydes (Figure 7).

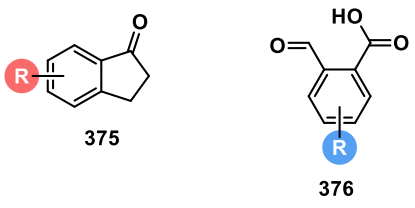


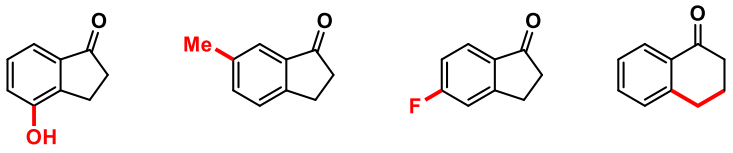
Figure 7: Key Building Blocks for *C*-Acylation Substrates

Whilst there were a huge number of possible substrates that could be synthesized due to the convergent nature of the synthesis, we targeted substrates that had identical substitution on the

1-indanone and 2-carboxybenzaldehyde as this would allow us to synthesize a variety of axially chiral molecules.

4.7.1 Synthesis of 1-Indanones

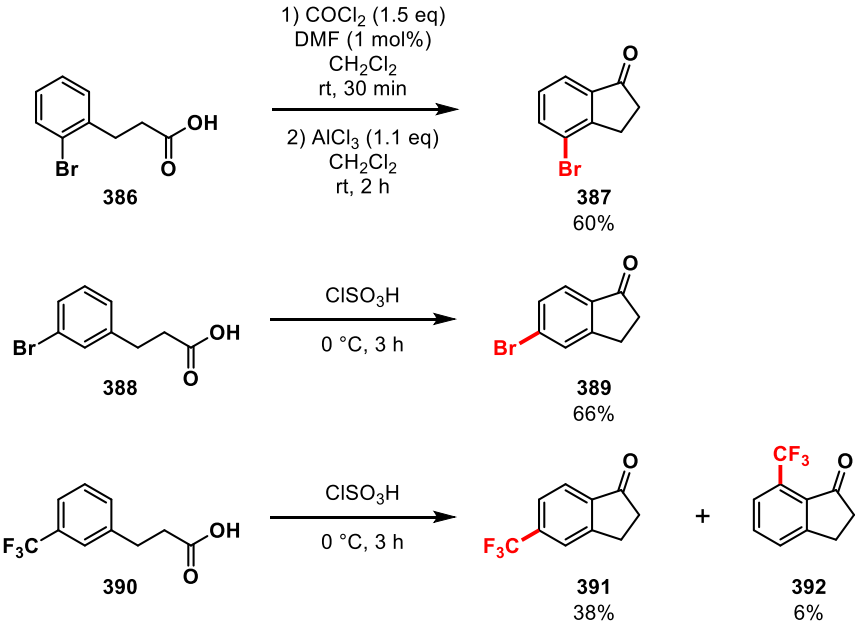
Fortunately, several 1-indanones are commercially available (**382**–**385**, Figure 8), while others can be accessed extremely rapidly (1–2 steps) from commercially available starting materials.



382 **383** **384** **385**

Figure 8: Commercially Available 1-Indanone Derivatives

A simple method of accessing substituted 1-indanones is through intramolecular Friedel-Crafts acylation of hydrocinnamic acids (Scheme 86).



386 → **387** 60%

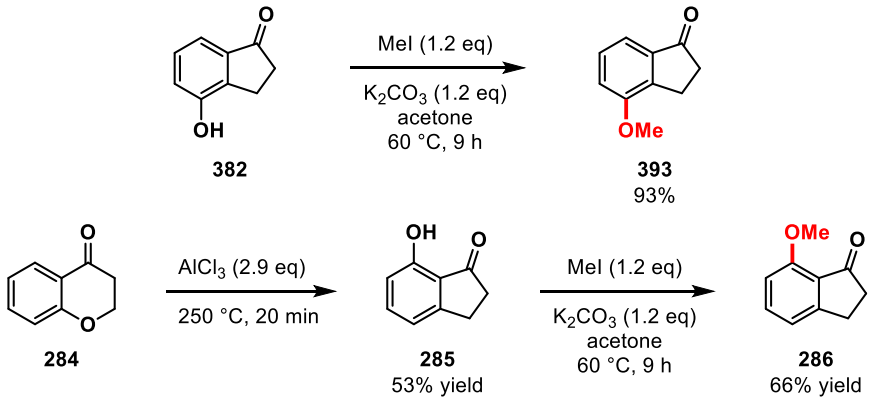
388 → **389** 66%

390 → **391** 38% + **392** 6%

Scheme 86: Synthesis of 1-Indanones Through Friedel-Crafts Acylation

Activation of 3-(2-bromophenyl)propionic acid **386** with oxalyl chloride generated the corresponding acid chloride, which then underwent Friedel-Crafts acylation in the presence of aluminium(III) chloride to afford **387** in 60% yield.[139] **388**, with bromine at the 5-position, could be accessed from regioselective intramolecular Friedel-Crafts acylation with chlorosulfonic acid in 63% yield.[140] Trifluoromethyl-substituted indanones **391** and **392** could be accessed through the

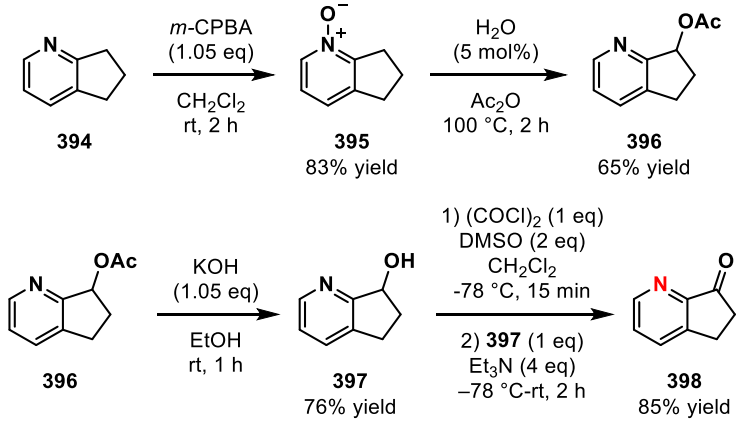
same strategy, with the poorer regioselectivity allowing access to two separable compounds in 38% and 6% yields, respectively.



Scheme 87: Synthesis of Methoxy-Substituted 1-Indanones

Commercially available 4-hydroxyindanone **382** was methylated to afford 4-methoxy-1-indanone **393** in excellent yield (Scheme 87), while its regioisomer 7-methoxy-1-indanone was accessed from aluminium(III) chloride mediated thermal rearrangement of 7-chromanone **284**,[141] followed by treatment with methyl iodide to afford **286** in 35% yield over two steps.

A pyridine derivative was also synthesized *via* a literature method (Scheme 88).

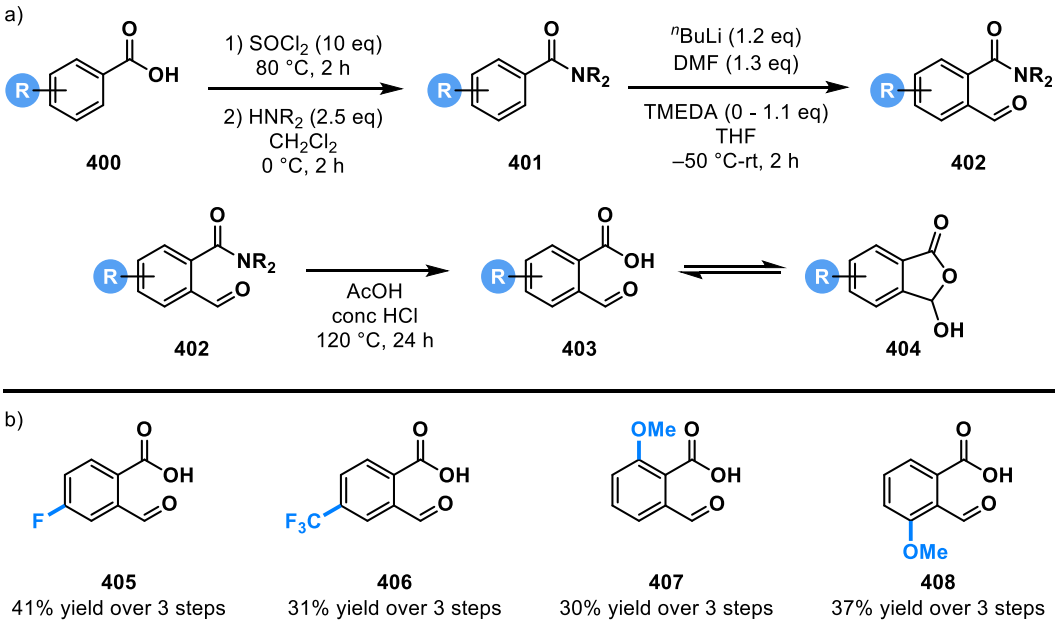


Scheme 88: Synthesis of Pyridine Derivative **398**

The 4-step sequence started with 2,3-cyclopentenopyridine **394** which was oxidised to the corresponding pyridine *N*-oxide **395** with *m*-CPBA in 83% yield.[142] Subsequent activation with acetic anhydride and [3,3]-rearrangement afforded the 1-acetoxy product **396** in 65% yield, which was then hydrolysed with potassium hydroxide in 76% yield. A final Swern oxidation afforded the desired pyridine derivative **398** (85% yield).

4.7.2 Synthesis of 2-Carboxybenzaldehydes

Some of the substituted 2-carboxybenzaldehydes could be accessed through a general strategy according to literature protocols (Scheme 89).[143] In this methodology, a substituted benzoic acid **400** is converted into a diethyl or diisopropyl amide **401**, and this motif directs lithiation with ^{n}BuLi/TMEDA *ortho*- to the amide. This organolithium species is then trapped with DMF to incorporate the aldehyde present in the desired products **402**. Hydrolysis of this benzamide with acetic and hydrochloric acids under reflux reveals the substituted 2-carboxybenaldehyde **403** which exists in equilibrium with the hydroxyisobenzofuranone form **404**. These carboxylic acids were difficult to purify by flash column chromatography due to the equilibrium of tautomers, so were purified by recrystallization or used as crude reactions mixtures from the acid catalyzed hydrolysis.



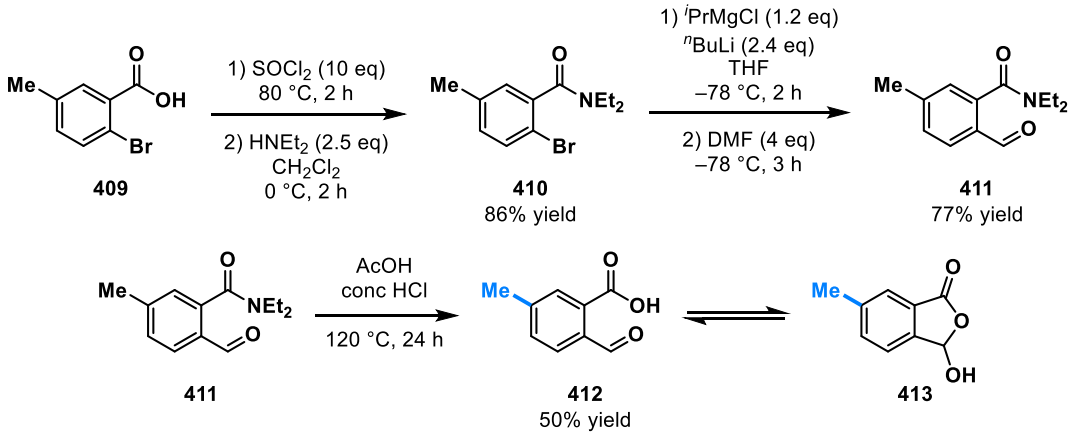
Scheme 89: a) Synthetic Strategy to Access Substituted 2-Carboxybenzaldehydes **403**
b) Substrates Synthesized Using This Route

This strategy allowed us to access **405** and **406** from the corresponding 4-substituted benzoic acid in moderate overall yields (41% and 31%, respectively).

The same strategy was applied to non-symmetrically substituted benzoic acids as well, with 2-methoxybenzoic acid showing good selectivity for lithiation *ortho* to the amide group compared

to the methoxy group, allowing synthesis of **407** in 30% yield over 3 steps. When applied to 3-methoxybenzoic acid, the lithiation was directed to the 2-position, in between the methoxy and amide groups. 3-Methoxy-2-carboxybenzaldehyde **407** was thus synthesized in 37% overall yield.

4-Methyl-2-carboxybezaldehyde **412** required a modification of this route due to a lack of regioselectivity in the lithiation step; the methyl substituent could not act as a directing group, in contrast to the methoxy-substituent in **408** (Scheme 90).



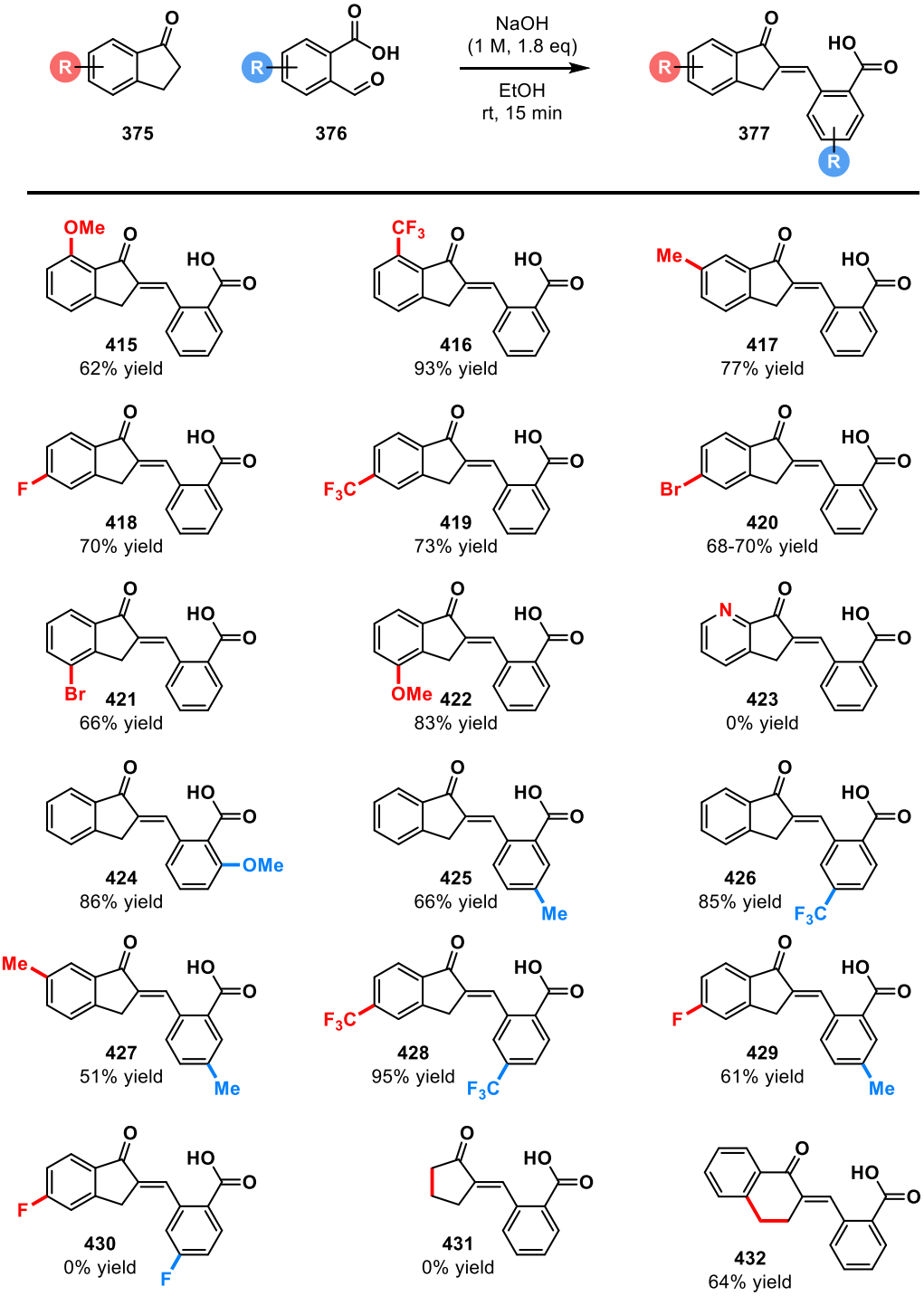
Scheme 90: Synthetic Strategy to Access Substituted 2-Carboxybenzaldehydes **412** Substrates Synthesized Using This Route

Commercial 2-bromo-5-methylbenzoic acid **409** could be amidated with diethylamine in 86% yield, and then undergo metal-halogen exchange, rather than directed *ortho*-lithiation, to generate the desired regioisomer of the organometallic species. Trapping with DMF followed by hydrolysis, as before, furnished us with our desired product **412** in 50% yield.

4.7.3 Synthesis of Substituted Ketoesters

With an array of functionalized 1-indanones and 2-carboxybenzaldehydes for the synthesis of substituted ketoesters, we proceeded to assemble the fragments *via* the same process we developed earlier (see Chapter 3.6). None of the reactions were optimized for individual substrates unless otherwise specified.

First, 1-indanones underwent aldol condensation with 2-carboxybenzaldehydes to furnish us with the unsaturated acids **377** (Scheme 91).

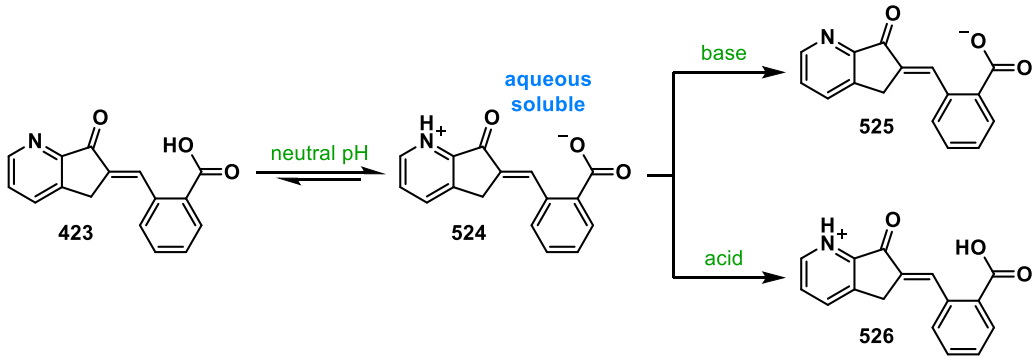


Scheme 91: Assembly of Unsaturated Ketoacids **377**

Good yields were obtained from this reaction with substituents on the indanone ring (**415**–**422**), with functional groups such as trifluoromethyl- and methoxy-groups tolerated at multiple positions (**415**, **416**, **419** & **422**). Substitution on the 2-carboxybenzaldehyde was also tolerated, again with products acquired in generally good yields (**424**–**426**). Ketoacids with substitution on both aromatic rings could also be prepared *via* the same method (**427**–**429**).

Addition of **384** to **405** unfortunately furnished no product **430** upon acidification to pH 2, an unexpected complication that resulted in our inability to synthesize the desired acid **430**. While cyclopentanone was ineffective as a nucleophile in this reaction to synthesize **431**, 1-tetralone was found to be reactive under these conditions, furnishing us with homologated cyclic ketone **432**.

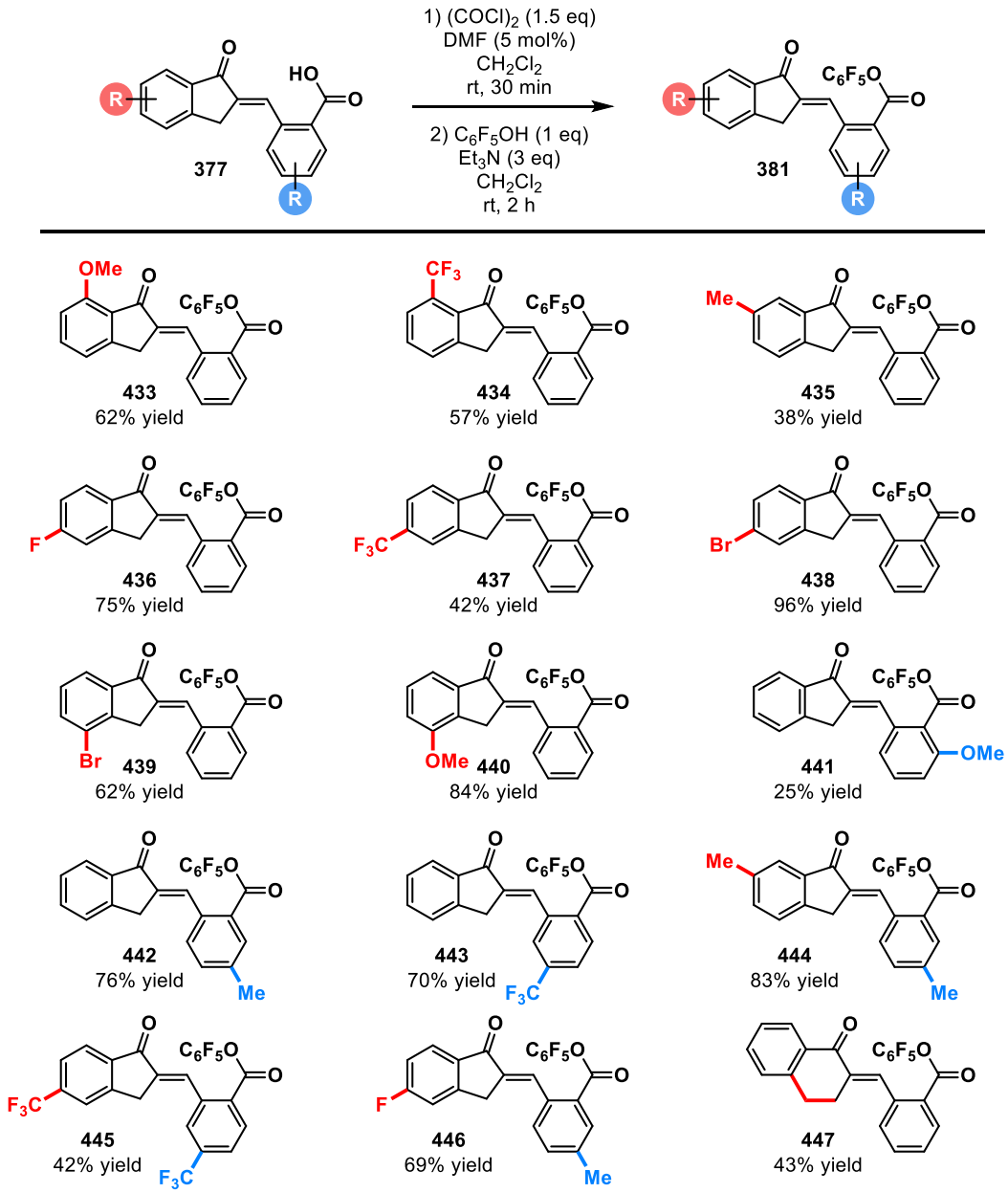
Disappointingly, we failed to isolate any unsaturated acid **423** from the reaction using pyridine derivative **398** despite complete starting material consumption. We hypothesize that the product bearing a pyridine and an acid would in fact be zwitterionic, and both acid soluble (due to the basic pyridine group) and base soluble (due to the carboxylic acid functional group).



Scheme 92: Potential Reasons for Lack of Product Retrieval in Synthesis of **423**

It would thus be extremely challenging to isolate and, in addition to our (future) observations that conversion to the oxy-Michael adduct is more significant with indanones substituted with an electron withdrawing group, we decided not to proceed with this substrate.

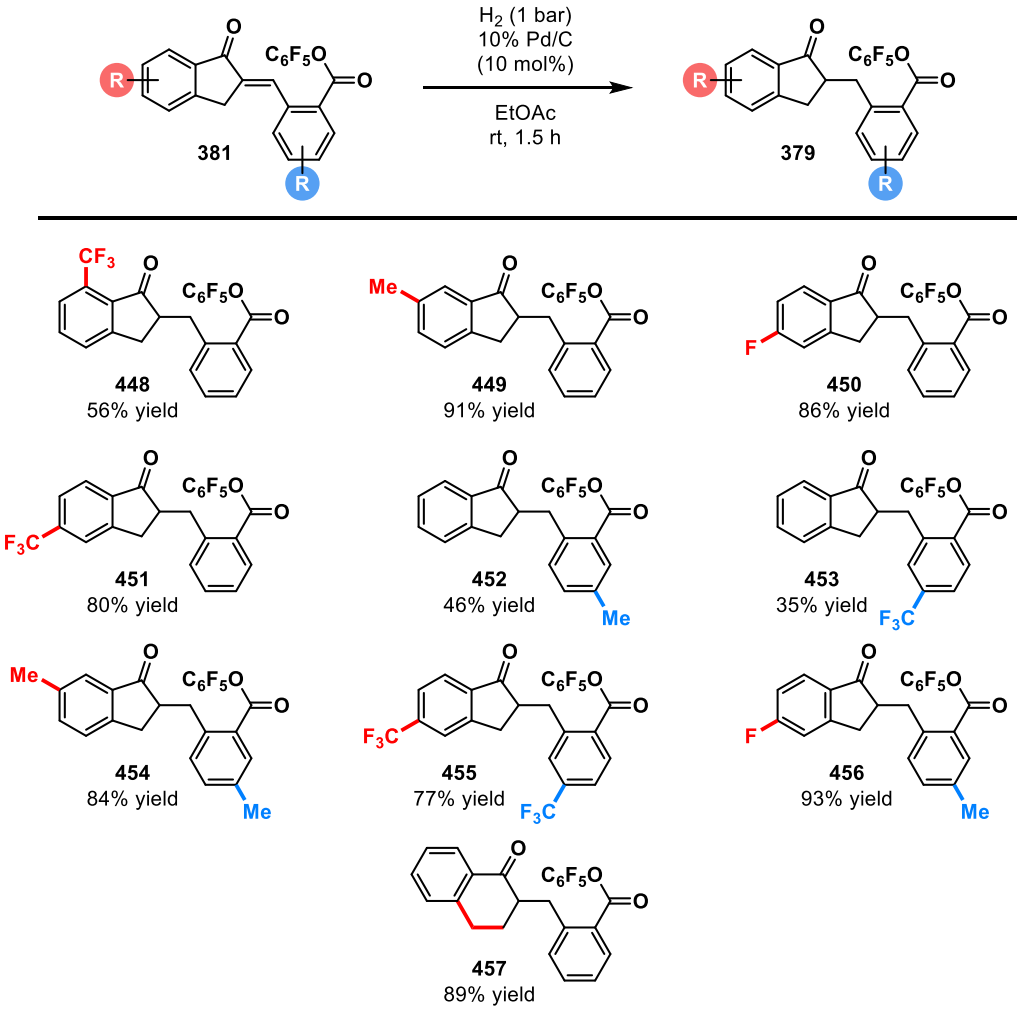
We were pleased to find that our library of unsaturated ketoacids **377** could all be converted to the corresponding ketoester **381** using our previously developed protocol (Scheme 93).



Scheme 93: Esterification of Unsaturated Ketoacids **377**

Substitution such as a methyl group at *C*-6 (**435**, 38% yield), fluorine at *C*-5 (**436**, 75% yield), and bromine at *C*-4 (**438**, 62% yield) and *C*-5 (**439**, 96% yield) were all tolerated on the 1-indanone moiety. Electron donating groups (OMe, **433**, 62% and **440,** 84% yield) were well tolerated, with good yields observed for both regioisomers synthesized. Electron-withdrawing groups (CF_3: **434**, 57% and **437**, 42%) were also tolerated on the indanone moiety, although with reduced yields. We postulate this reduced yield is due to more of the competing ketoacid cyclization with an electron withdrawing group conjugated with the ketone, further activating the enone to intramolecular

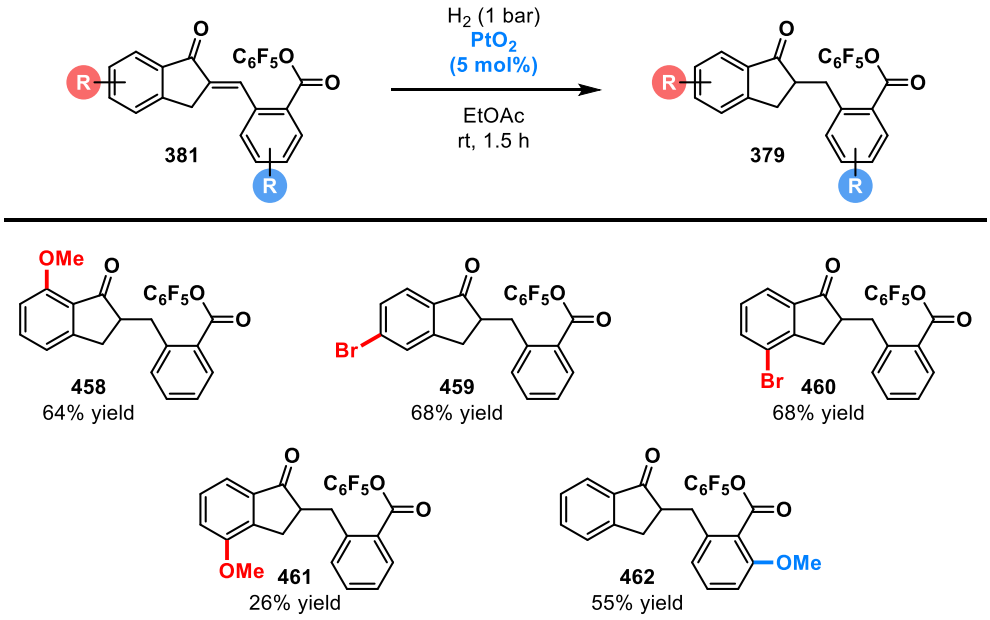
attack by the carboxylic acid. Similarly, substrates with a substituted benzoic acid moiety were also esterified to afford **441**–**443**. The low yield for methoxy-substituted **441** is likely again due to increased reactivity in the oxy-Michael cyclization with a more electron-rich carboxylic acid. Compounds with substitution on both aromatic rings could be also synthesized (**444**, 82% yield & **446**, 69% yield), again with a reduced yield for CF_3-bearing **445** (42 %). We were pleased to see that esterification of tetralone derivative **437** also proved to be successful in moderate yield (**447**, 43%). The unsaturated esters were then hydrogenated under our previously successful conditions in the synthesis of **364** to afford the substrates for the *C*-acylation reaction (Scheme 94).



Scheme 94: Hydrogenation of Unsaturated Ketoesters **381** with Pd/C

Pleasingly, these conditions led to successful reduction for many compounds. Substrates bearing electron withdrawing groups (**448**, **451**, **453**, **455**) were all reduced under these conditions in good to excellent yield, although **448** was isolated in only 56% yield. Compounds with electronically

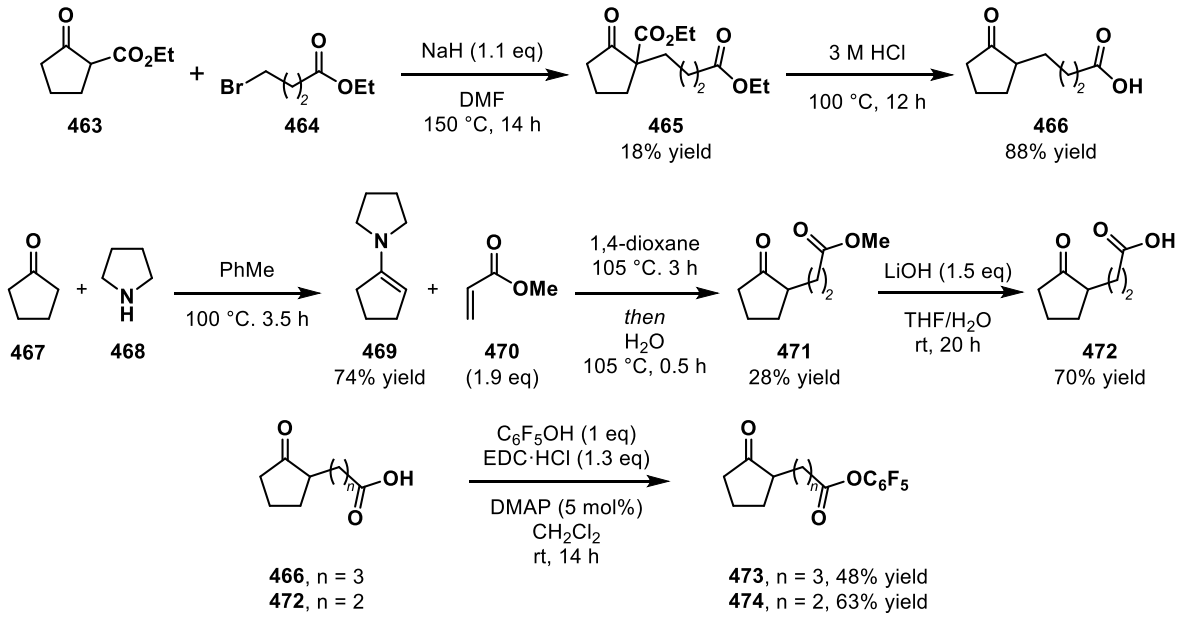
neutral groups (Me, F, Br) could also be reduced; the bromine-substituted compound **438** afforded only protodebrominated saturated ester **364**. Electron donating groups however (OMe) were not tolerated under these conditions and alternate conditions had to be found. Pleasingly, PtO_2 was found to be effective: reducing more electron-rich substrates with minimal amounts of overreduction that hampers the reduction with Pd/C at higher pressures/extended reaction times (Scheme 95).



Scheme 95: Hydrogenation of Unsaturated Ketoesters **381** with PtO_2

Substrates that were bromine-substituted or featured electron donating groups were thus subjected to hydrogenation conditions with PtO_2 as the catalyst. We could now isolate compounds **458**–**462**, with no protodebromination observed for **459**. The very low yield (26%) for **461** was due to the limited conversion after the 1.5 hour reaction time (53% of the starting material **440** was recovered from the reaction mixture).

We were also interested in whether the *C*-acylation reaction could proceed without an aromatic ring present in the backbone, so we synthesized the equivalent spirobicyclopentanone precursor **473** and a substrate featuring a shortened, less flexible, acyl tether, **474** (Scheme 96).



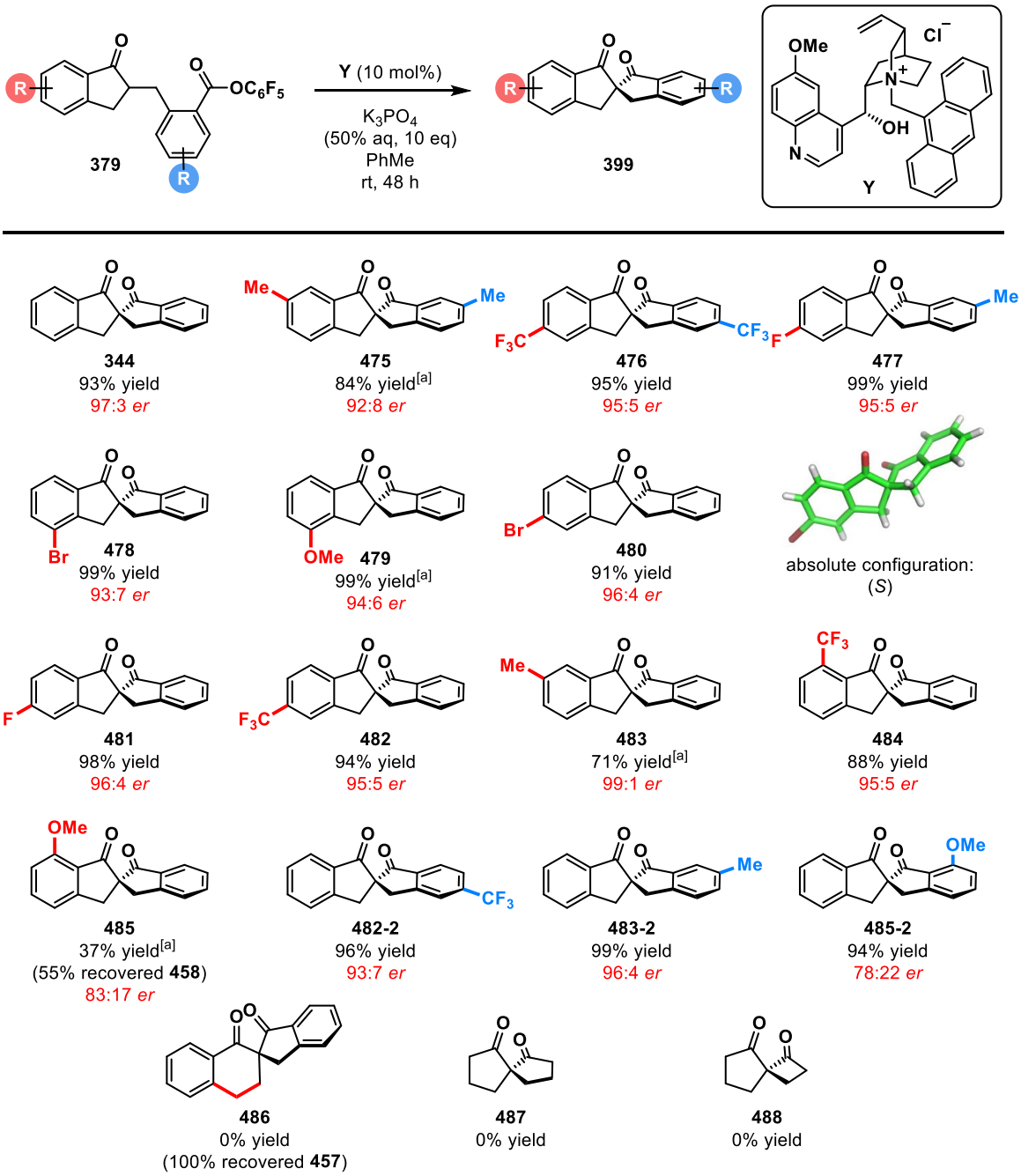
Scheme 96: Synthesis of Fully Saturated Ketoesters **473** and **474**

Our synthesis of **473** proceeded from β-ketoester **463** and ethyl 4-bromobutyrate **464**, allowing us access to **465** in 18% yield. Acid hydrolysis of both esters with *in situ* decarboxylation afforded acid **466** in 88% yield, which was followed by esterification with pentafluorophenol to give ketoester **473** in 48% yield.

Our synthesis of **474** commenced with the formation of Stork enamine **469**, through condensation of pyrrolidine with cyclopentanone in 74% yield. This was then alkylated with methyl acrylate to afford **471** in 28% yield. Hydrolysis of **471** followed by esterification of the crude carboxylic acid **472** afforded cyclization precursor **474** in 34% yield over two steps.

4.7.4 Enantioselective *C*-Acylation of Substituted Ketoesters

With substituted ketoester starting materials in hand, we could now subject them to our optimized *C*-acylation conditions to investigate the effect the substitution has on the reaction (Scheme 97).



Scheme 97: Substrate Scope of *C*-Acylation; [a] Reaction Performed for 120 Hours

Firstly, we cyclized compounds **475** and **476** which would afford us axially chiral spirobiindanones: **455** was fully consumed in 48 hours, and the product **476** was isolated in 95% yield and 95:5 *er*. Substrate **475** bearing a weakly electron donating methyl-group was found to cyclize much slower than unsubstituted compound **364**, and so the reaction conditions were altered to allow 5 days for cyclization for substrates with an electron-rich indanone moiety. This increase in reaction time allowed us to isolate **475** in 84% yield after 5 days in 92:8 *er*. Non-symmetrically doubly substituted

substrates also cyclized effectively, with point-chiral spirobiindanone **476** produced in 99% yield and 95:5 *er*.

Next, we investigated the cyclization on substrates that were substituted on the indanone moiety. Gratifyingly, we saw consistently high selectivities and yields across a range of substituents and regioisomers. *C*-4 Substitution was successful with bromo- and methoxy-substituted spirobiindanones (**478** and **479**) produced in 99% yield in both cases, in 93:7 and 94:6 *er*, respectively. Substitution at the 5-position was well tolerated with bromo-(**480**, 91% yield, 96:4 *er*), fluoro-(**481**, 98% yield, 96:4 er), and trifluoromethyl-(**482**, 94% yield, 95:5 er) substituents. A crystal structure of **480** confirmed the absolute configuration at the spiro-stereocentre as (*S*), the same as that suggested, by comparison of the literature values for optical rotation to our own, for unsubstituted spirobiindanone **344**. *S*ubstitution at *C*-6 and *C*-7 proved successful with methyl-(**483**, 71% yield, 99:1 *er*) and trifluoromethyl-(**484**, 88% yield, 95:5 *er*) substituents. A methoxy group at the *C*-7 position led to low conversion (55% recovered starting material **458** after 5 days) with **485** showing the lowest yield and enantioselectivity of any substrate with a substituted indanone moiety (37% yield, 83:17 *er*).

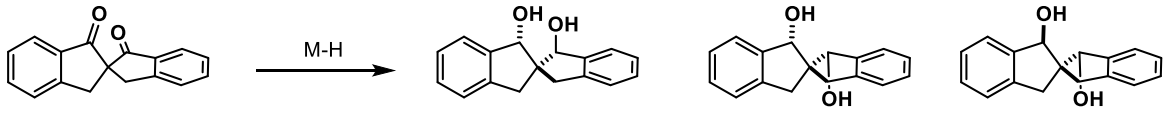
C-Acylation of substrates bearing substituents on the benzoate ring proceeded cleanly with high levels of yield and selectivity. Spirobiindanones **482-2** (96% yield, 93:7 er) and **483-2** (99% yield, 96:4 er) were both obtained in excellent yield and enantioenrichment and, pleasingly, **485-2** was obtained in 94% yield and 78:22 *er* after just two days. These yields are higher than those for the corresponding indanone-substituted products (**482**, **483** and **485**), although show lower enantioselectivity in the cyclization. This effectively gives us two routes to the same molecule, where we could choose between higher yield or higher enantioenrichment of the product.

We did however find that the reaction was not suitable for systems not derived from 1-indanone. Spirotetralone **486** was not formed at all under our reaction conditions, with starting material **457** unmodified under the reaction conditions after 2 days. This is likely due to a specific requirement of the reaction, with the pK_a of the 1-tetralone being higher than that of 1-indanone and thus not

sufficiently deprotonated by our phosphate base to react, allowing retrieval of the starting material (1-tetralone's pKa is 24.7 in DMSO; no pK_a data is available for indanone, although cyclopentanone has a lower pK_a than cyclohexanone (25.8 vs 26.7 in DMSO), so the pK_a of 1-indanone would be expected to be in the region of 23.0-24.0 in DMSO). The fully saturated ring systems performed poorly, with decomposition of both **473** and **474** starting materials furnishing none of desired products **487** or **488**, respectively. We expect this decomposition could be due to alternate sites of deprotonation leading to polymerization in the more flexible saturated systems.

4.8 Derivatization of Spirobiindanones

We next investigated how we could chemoselectively derivatize the cyclized products. The only previously disclosed functionalization of spirobiindanone was the reduction of racemic material, where an investigation into the diastereoselectivity of this transformation was examined (Table 17).[130]



(±)-**344** (*cis*,*cis*)-**349** (*cis*,*trans*)-**492** (*trans*,*trans*)-**493**

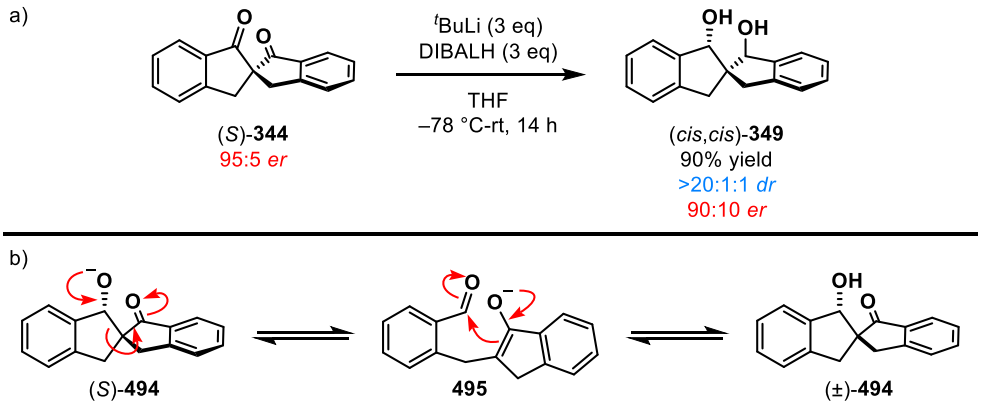
Entry	M-H	Conditions[a]	Ratio of Diols **349**:**492**:**493**	Isolated Yield
1	$LiAlH_4$	Et_2O, 0 °C	9:75:16	94%
2	DIBALH	THF, –78 °C	35:46:19	96%
3	Li^{t}Bu(^{i}Bu)$_2$AlH	THF, –78 °C	100:0:0	97%

[a] Calculated by ^{1}H NMR Spectroscopy

Table 17: Keay's Research into the Diastereoselective Reduction of (±)-**344**

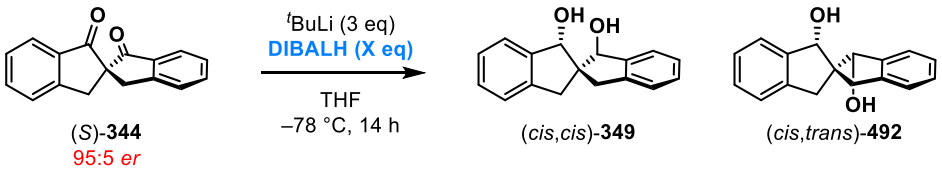
In this report, Keay's group disclosed that racemic spirobiindanedione **344** could be reduced with varying levels of diastereoselectivity depending on the choice of reducing agent. Chelating reducing agents favoured formation of the (*cis*,*trans*)-diastereoisomer **492**, while bulkier, less chelating, metal hydrides favoured the (*cis*,*cis*)-diastereomer **349**, which was then resolved to give access to enantioenriched spirodiol **349**. Formation of the (*trans*,*trans*) diastereoisomer **493** was not favoured under any conditions they investigated.

In our hands we found that this reduction was more interesting than it first appeared (Scheme 98a). Firstly, under the previously reported conditions, we observed a decrease in enantioenrichment in the product (95:5 *er* to 90:10 *er*). It occurred to us that this decrease in enantioenrichment could be due to a retro-aldol reaction of the mono-reduced species (Scheme 98b).



Scheme 98: a) Reduction of Enantioenriched **344** Under Keay's Conditions; b) Racemization by Reversible Retro-Aldol Reaction of Monoreduced **494**

Keeping the reaction at −78 °C for the duration of the reaction halted this process, with the product now isolated in the same enantioenrichment as the starting material (>20:1:1 *dr*, 95:5 *er*). During the course of this investigation into the diastereoselective reduction, we found that the stoichiometry of DIBALH to ^{t}BuLi was crucial. A decreased yield with some unidentified decomposition products was observed with a slight excess of ^{t}BuLi and a decrease in diastereoselectivity was observed with an excess of DIBALH. Fortuitously, we found that this decrease in diastereoselectivity was accompanied by an increase in enantioenrichment (Table 18, entries 1–4).



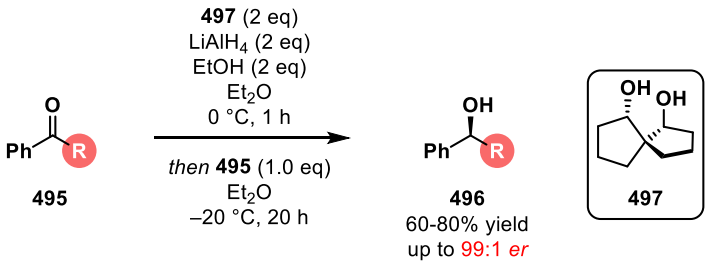
Entry	DIBAL eq	Ratio of Diols 349:492[a]	*er* (349)
1	3.0	>20:1	95:5
2	3.15	16:1	95.5:4.5
3	3.3	7.5:1	96:4
4	3.6	4.5:1	97:3

[a] Calculated by ^{1}H NMR Spectroscopy

Table 18: Effect of Excess DIBALH on Stereoinduction of the Reduction of **344**

For the purposes of this investigation we used starting material that was not as enantioenriched as possible to better monitor small changes in enantioenrichment. The increase in enantioenrichment observed was low relative to the decrease in diastereoselectivity, although, since we produced highly enantioenriched starting material **344** from our *C*-acylation reaction (97:3 *er*), we expected to be able to increase the enantioenrichment from 97:3 to >99:1 *er* without too great a loss in diastereoselection.

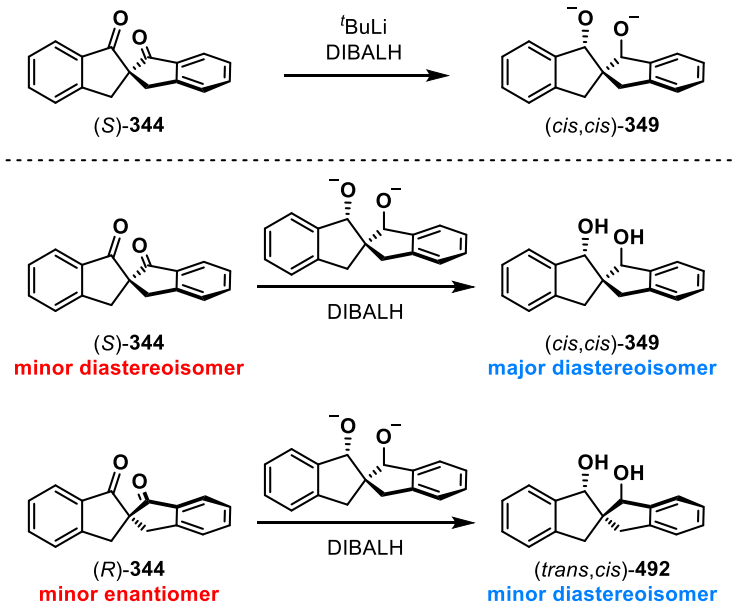
The reasons behind the enantioenrichment observed in this transformation have not been fully investigated although there are some suggestions as to how this transformation works in the literature. Firstly, many chiral alcohols (usually diols) have been shown to modify reducing agents derived from metal hydrides to effect enantioselective reductions. One example disclosed by Kumar shows that the related diol (derived from spirobicyclopentanone) **497** could modify $LiAlH_4$ to allow for asymmetric reduction of simple ketones (Scheme 99).[144]



Scheme 99: Use of Related Diol **497** in Asymmetric Reduction

In this example, 1 equivalent of the chiral diol **497** is added to 1 equivalent of $LiAlH_4$, followed by 1 equivalent of ethanol. This affords the chiral reducing agent to which ketones were added. The highest yields and selectivities for acetophenone were observed at very low temperatures (−80 °C), although the authors carried out the substrate scope at −20 °C.

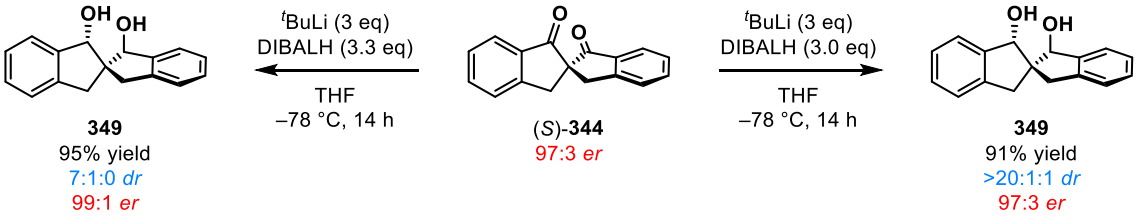
Based on the observation that chiral diols can generate chiral reducing agents with metal hydrides, our hypothesis is that, under our reaction conditions, we are generating chiral diol **349** in an enantioenriched form, which can then modify the excess DIBALH to cause a kinetic resolution to take place (Scheme 100). There are no previous reports of a chiral alcohol modifying DIBALH,[145] although we see no other possibilities under our reaction conditions.



Scheme 100: Possible Rationale for Kinetic Resolution under Reduction Conditions

We propose that a highly enantioenriched diol **349**, generated from the diastereoselective reduction with the precomplexed DIBALH/^{t}BuLi, in combination with the excess DIBALH forms a chiral reducing agent. This complex then performs a kinetic resolution on the enantioenriched spirobiindanone **344**, with the minor enantiomer converted to the minor diastereoisomer. Unfortunately, the enantiomers of the minor diastereomer were not separable by chiral HPLC and we could not investigate the enantioenrichment of the minor diastereomer to verify this hypothesis.

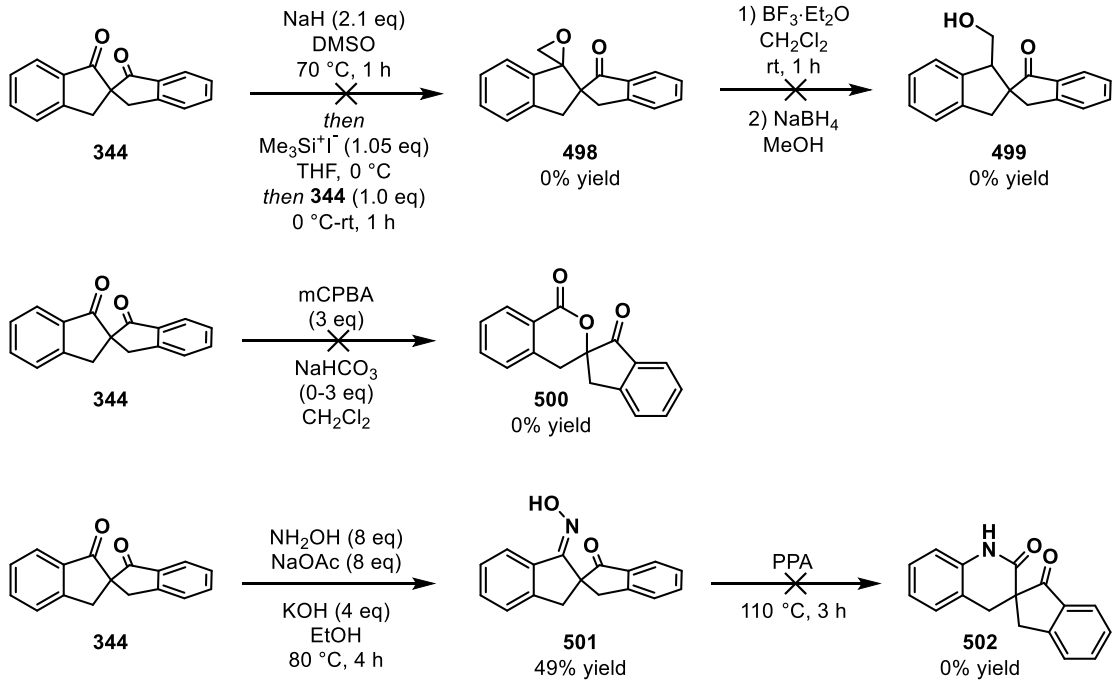
Taking advantage of this effect, we could therefore, using 97:3 *er* starting material from our optimized *C*-acylation reaction, access spirodiol **349** in either excellent yield and diastereoselection with retention of enantioenrichment (91% yield, >20:1:1 *dr*, 97:3 *er*), or in an enantioenriched form at the cost of diastereoselectivity (95% yield, 7:1:0 *dr*, 99:1 *er*) (Scheme 101).



Scheme 101: Stereoselective Reductions of **344**

When using the protocol with a slight excess of DIBALH, the minor diastereoisomer was separable by careful flash column chromatography to afford **349** as a single diastereoisomer in 78% yield.

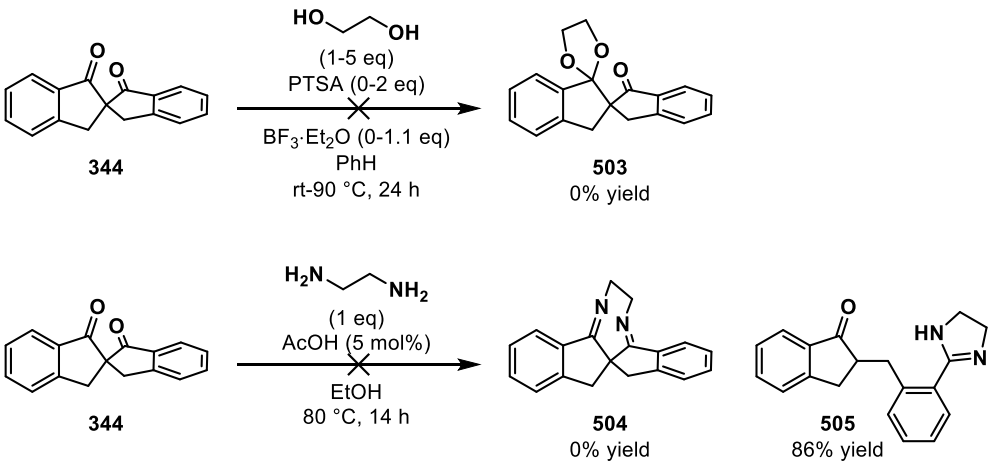
Other functionalizations of the ketone proved more challenging than expected, with the spiro stereocentre adjacent to the ketone acting as a large steric block (Scheme 102). We used racemic spirobiindanone in these investigations unless otherwise specified.



Scheme 102: Attempted Monofunctionalization at Ketone

Functionalizations at the carbonyl centre proved unachievable in our hands. Corey-Chaykovsky reactions using spirobiindanone **344** resulted in complete consumption of starting material

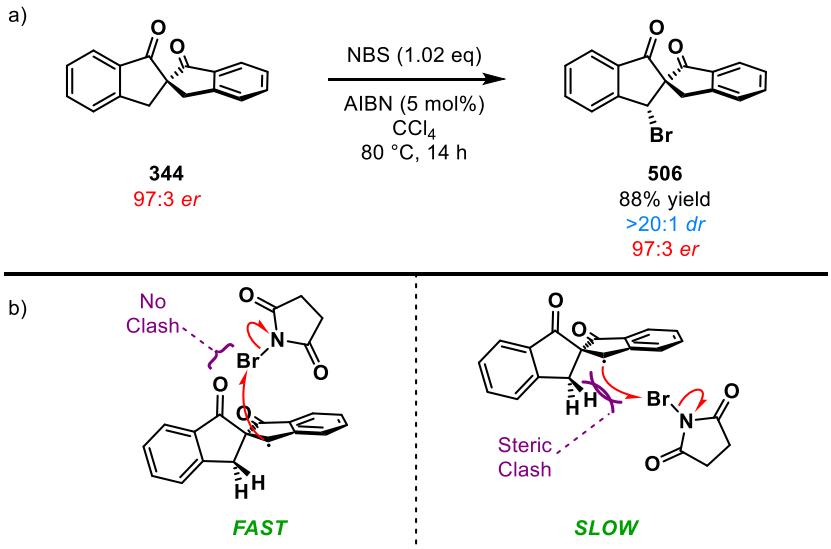
although no desired product **498** could be isolated. We thought that the epoxide **498** might be unstable, so we took the crude reaction mixture and attempted a Meerwein rearrangement with $BF_3.Et_2O$ to the corresponding aldehyde which we hoped could be reduced to reveal the homologated alcohol **499**. Unfortunately, we isolated no desired product from this sequence and the idea was deferred in favour of attempting other reactions to demonstrate the utility of **344**. We reasoned that ring expansion of **344** through either Baeyer-Villiger rearrangement or oxime formation followed by Beckmann rearrangement might be feasible, although again the carbonyl group proved too sterically hindered and only starting materials **344** and **501** were isolated. Another class of functionalization that would be useful would be to synthesize the monoketal **503**, which would allow for monofunctionalization (Scheme 103). Despite reports in the literature of ketalization of similarly sterically hindered pivalophenone with ethylene glycol,[146] we saw no reaction under those conditions (or with a dithiol) with spirobiindanone **344**.



Scheme 103: Attempted Monoprotection of **344**

Condensation with an amine would lead to imine formation, and we could take this further by attempting to generate an extra ring through double imine formation with a diamine. While attempted condensation with hydrazine gave a complex mixture of products, we did see some reactivity with ethylene diamine. Unfortunately, rather than giving our desired diamine, we isolated ring-opened product **505**, which was predicted to be racemic even with enantioenriched starting material due to the reaction presumably proceeding through an achiral enol.

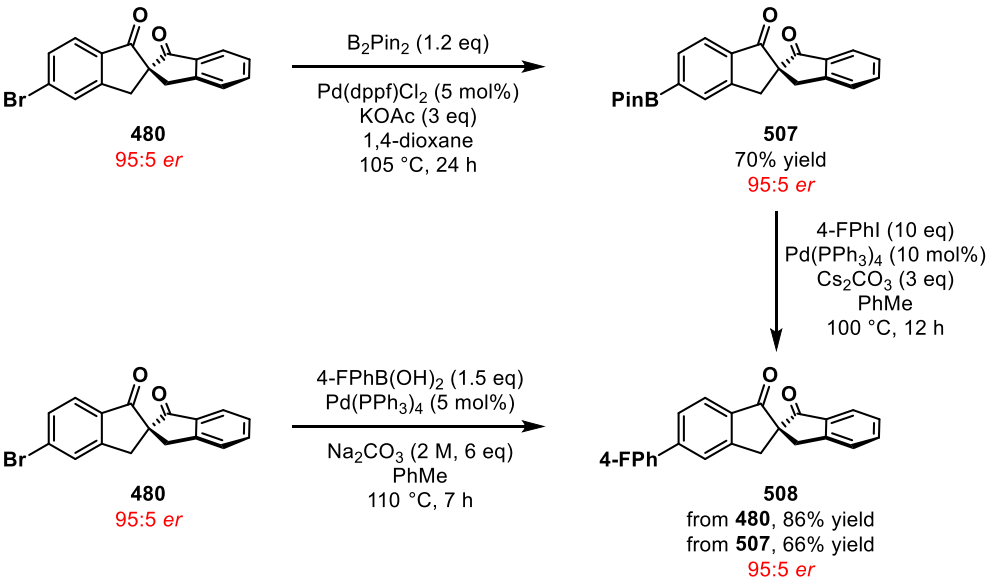
When functionalization at the carbonyl position proved to be challenging, we moved on to investigate derivatizations of **344** at other positions. We found that radical bromination at the benzylic position was possible, with a mono-brominated product **506** isolated in 90% yield and most importantly as a single diastereoisomer. Pleasingly, with enantioenriched starting material this reaction proceeded in similar yield and no degradation in enantioenrichment (Scheme 104a, 88% yield, >20:1 *dr*, 97:3 *er*).



Scheme 104: a) Radical Bromination of **344**; b) Proposed Setereochemical Rationale of Radical Bromination

nOe ^{1}H NMR Spectroscopy allowed us to assign the configuration at the *C*-3 position with the bromine atom on the same face as the carbonyl. This is presumably due to addition of the bromine past the carbonyl rather than the sterically bulkier CH_2 group (Scheme 104b).

With a novel diastereoselective functionalization of spirobiindanone **344** discovered, we focused on further transformations to further elaborate the spirocyclic scaffold we had (Scheme 105).

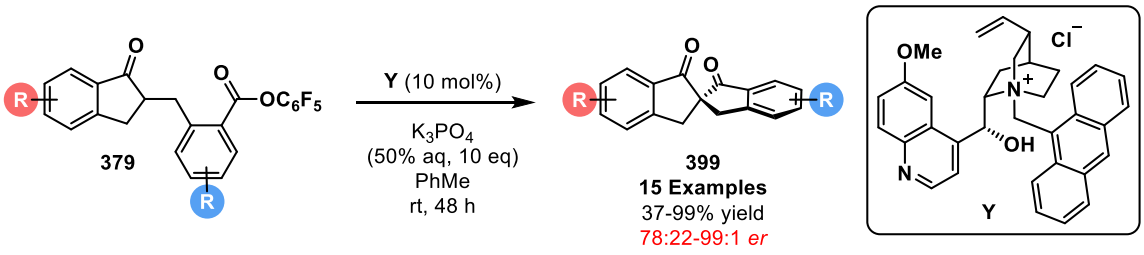


Scheme 105: Cross-Coupling Reactions Usings Bromine-Substituted Spirobiindanone **478**

Bromine-substituted spirobiindanone **478** could be functionalized through Miyaura coupling with B_2Pin_2 to the corresponding boronic ester **507** (70% yield). Unfortunately, the enantiomers of this boronic ester could not be separated on our chiral HPLC, so we then subjected it to Suzuki-Miyaura cross-coupling conditions with 1-fluoro-4-iodobenzene. The desired product **508** was isolated in 66% yield with no degradation in enantioenrichment over either step (95:5 *er*); this biaryl was also accessed from cross-coupling of our bromine-substituted spirobiindanone **408** with 4-fluorophenylboronic acid in 86% yield and 95:5 *er*.

4.9 Conclusions and Outlook

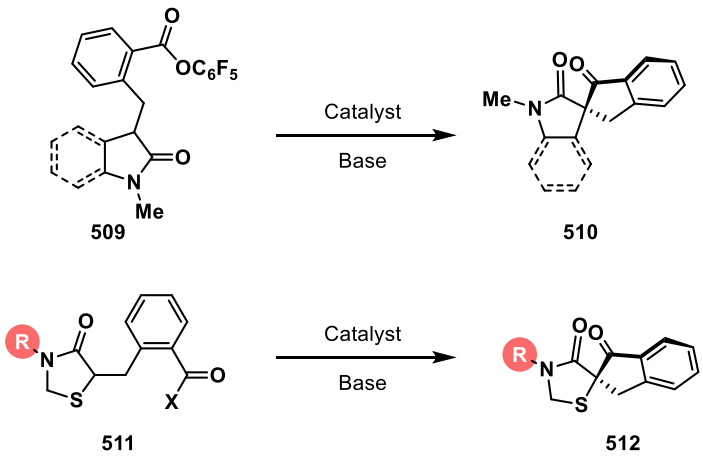
In this chapter we have described the conception and development of the first reported direct enantioselective *C*-acylation of a ketone. We found that pentafluorophenyl ester **364** was a superior substrate to phenyl ester **360** due to the increased leaving group acidity, with the cyclized product **344** obtained in high yields and enantioenrichment. The starting material synthesis was redesigned to allow for rapid access to saturated esters from 1-indanone and 2-carboxybenzaldehyde building blocks. The reaction scope tolerated a wide variety of substituents on both the indanone and benzoic acid moieties, with excellent levels of yield (up to 99% yield) and stereoselectivity (up to 99:1 *er*) (Scheme 106).



Scheme 106: The First Direct Enantioselective *C*-Acylation of a Ketone

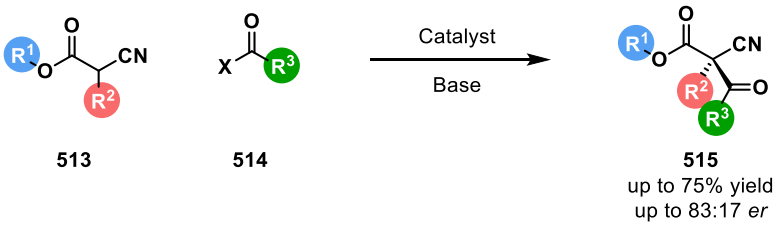
The scope however, was limited to indanone-based ketones, with tetralone- and cyclopentanone-derived ketones found to be ineffective in the *C*-acylation reaction. Derivatization of the enantioenriched spirobiindanone **344** proved more challenging than expected, with the ketone surprisingly unreactive towards ketone functionalizations other than reduction. The outcomes of this reduction were dependent on the reducing agent used, with an excess of DIBALH allowing for an *in situ* generated chiral reducing agent to cause a kinetic resolution of spirobiindanone **344** to occur. From this, we could choose to access spirobiindanediol **349** in either high diastereoselectivity or increased enantioenrichment. Other derivatizations were possible, with successful diastereoselective monobromination in excellent yield and no degradation in enantioenrichment.

Future work would be directed towards expanding the scope of the reaction, by moving away from the indanone-derived systems. Incorporation of a heterocycle instead of the indanone moiety would give rise to a variety of different spirocycles (Scheme 107), with the potential for them to be used as 3-D fragments: small molecules frequently used in drug discovery.[147]



Scheme 107: Possible Hetereocycle-Containing Spirocyclic Fragments

Furthermore, it would be interesting to extend this disconnection of 1,3-dicarbonyls to other systems, specifically, intermolecular reactions with common acylating agents such as acid chlorides. Provisional results by a Part II student under my supervision, Owen Smith, demonstrated we could impart some enantioselectivity on the reaction (Scheme 108).



Scheme 108: Preliminary *C*-Acylation of Cyanoesters **513**

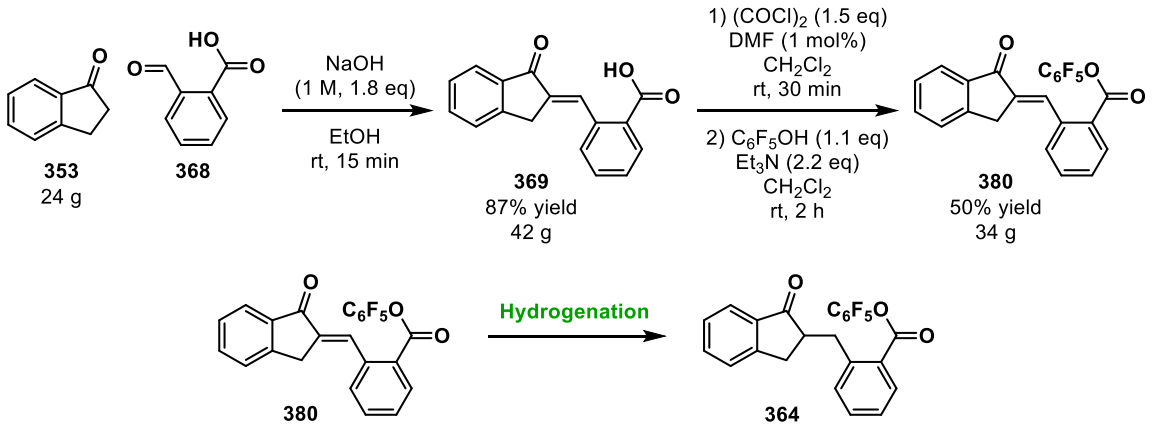
While the highest yields did not correspond to the highest enantioenrichments in **515**, the moderate selectivities were extremely promising.

5. Kinetic Analysis of the Enantioselective *C*-Acylation of Ketone 364

5.1 Starting Material Synthesis

To gain some insight into the mechanism of asymmetric phase-transfer catalysis, we decided to analyse the kinetic profile of the enantioselective *C*-acylation reaction (Chapter 4). The experimental work performed in this chapter was done in collaboration with Katrina Badiola, and all data processing and analysis was performed by her.

To embark on a kinetic analysis of this reaction, we needed large quantities of starting material **364**. Previous studies in the group have shown that the reproducibility of results is often dependant on the quality of the starting materials. Thus, we decided to synthesize a large quantity (≈ 20 g) of the starting material **364**, and recrystallize the product in bulk to ensure homogeneity between experiments (Scheme 109). We also planned to perform the same process (batch synthesis followed by recrystallization) for the catalyst **Y**, however, following batch synthesis we were unable to crystallize the ammonium salt and it was used without further purification.



Scheme 109: Batch Synthesis of Ketoester **364**

Fortunately, we could utilize the scale-up equipment and expertise of the process chemists in the API Chemistry department at GSK, Stevenage. The three-step small-scale synthesis of the desired starting material **364** was followed with minor adaptations in experimental procedure to cater for the increased scale (see Experimental Methods Chapter for details), and the first two steps proceeded smoothly to afford 34 g of **380** after crystallization of the crude mixture from isopropyl

acetate. We postulated that we could optimize the hydrogenation to avoid overreduction, so screens of available hydrogenation catalysts were performed (Figure 9).

In the first screen, a wide variety of hydrogenation catalysts were evaluated on a 10 mg scale with THF, ethanol or ethyl acetate as the solvent. The catalysts were all palladium, platinum and rhodium metals, mostly as a dispersion on carbon, with a 1% metal loading. The reactions were conducted at 2 bar pressure for 2.5 hours, analysed (Figure A) and then, to check for overreduction, resubjected to hydrogenation conditions for a further 2 hours at 4 bar pressure (Figure 10). For analysis, the crude reaction mixtures were diluted in methanol in filter-equipped HPLC vials, subjected to HPLC and compared to an authentic sample of the product **364** and overreduction products **371** and **372**.

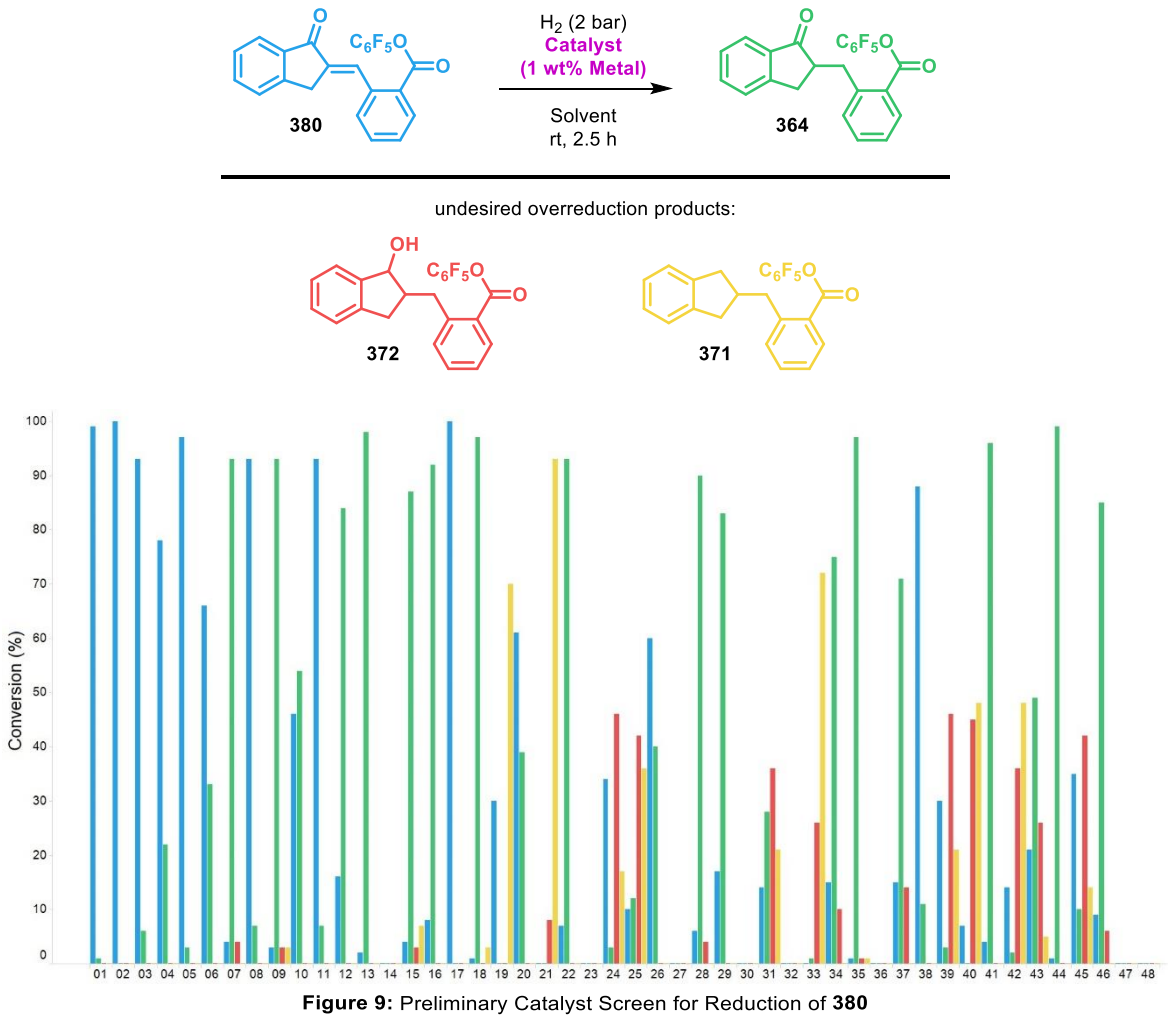


Figure 9: Preliminary Catalyst Screen for Reduction of **380**

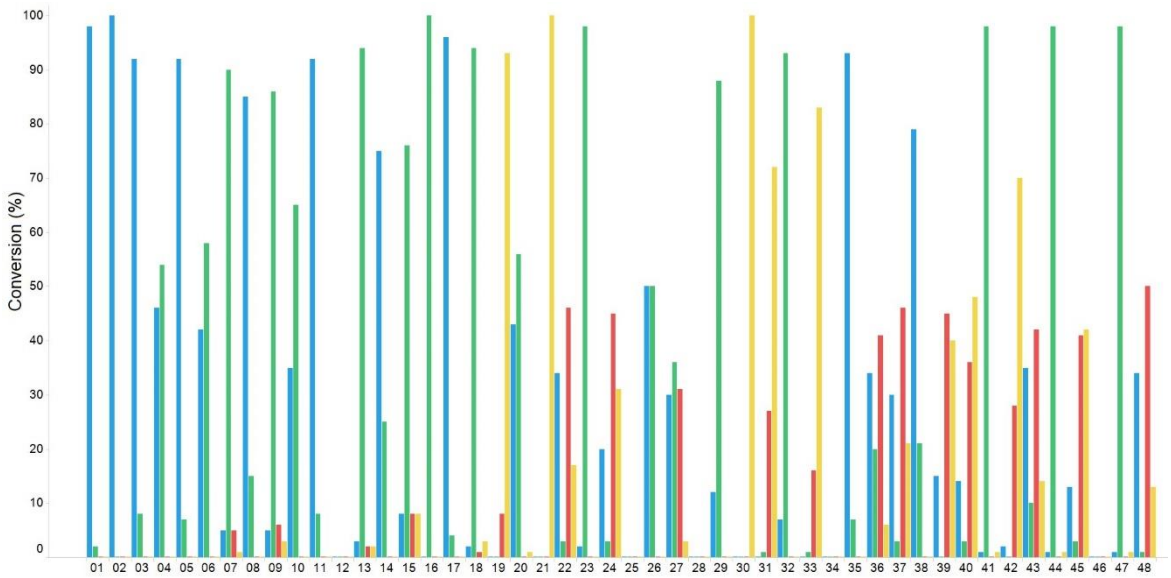


Figure 10: Catalyst Screen for Reduction of **380** after 2 Additional Hours at 4 Bar Pressure

As can be seen from the above figures, overreduction (to afford **372** (red lines) and **371** (yellow lines)) was a problem for many catalysts, and due to the significant number of hits with good conversion to **364** (green lines), these were discarded without any optimization of conditions.

The best eight of these results were then taken forward to be slightly scaled up and evaluated in vessels like that in which the large-scale reaction would be performed. These reactions were carried out on a 150 mg scale, under 2 bar pressure for 2 hours and are summarised in Figure 11.

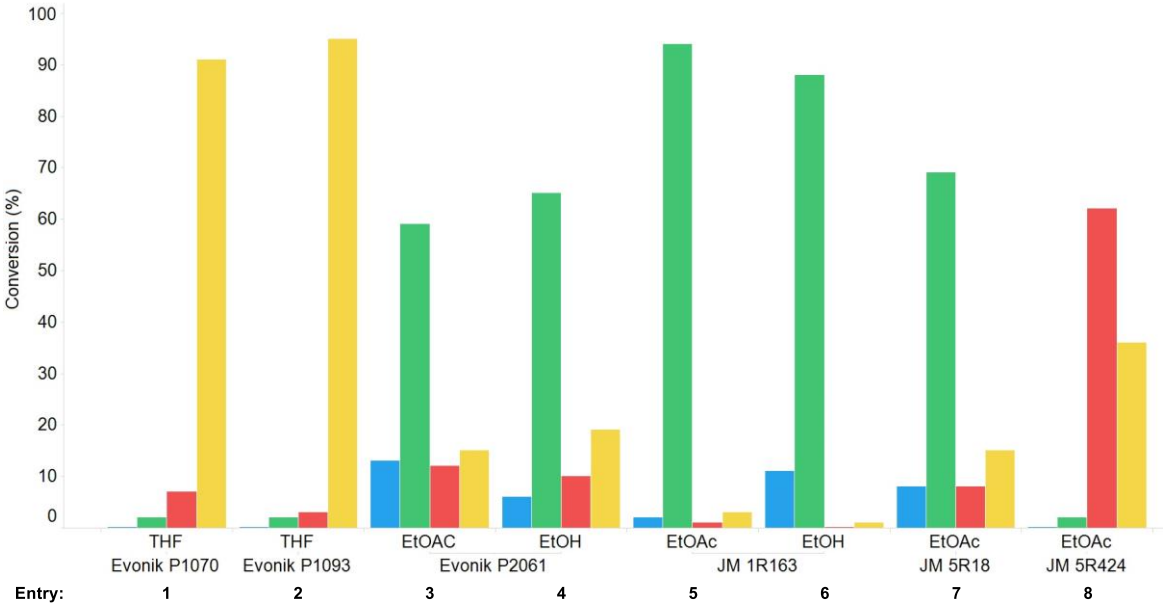


Figure 11: Evaluation of Catalyst Screen Best Hits

Catalyst JM 1R163 in either ethanol or ethyl acetate was optimal (Figure 11, Entries 5, 6), with the greatest conversion to the desired product **364** and with minimal overreduction observed. One problem with this catalyst was that the reactions had been screened on a 1% metal loading, and the optimal catalyst was a 1% dispersion on carbon, requiring a 100 wt% loading of catalyst. One final screen was therefore carried out to see if a reduced loading could be tolerated by the reaction, again on a 150 mg scale (Figure 12).

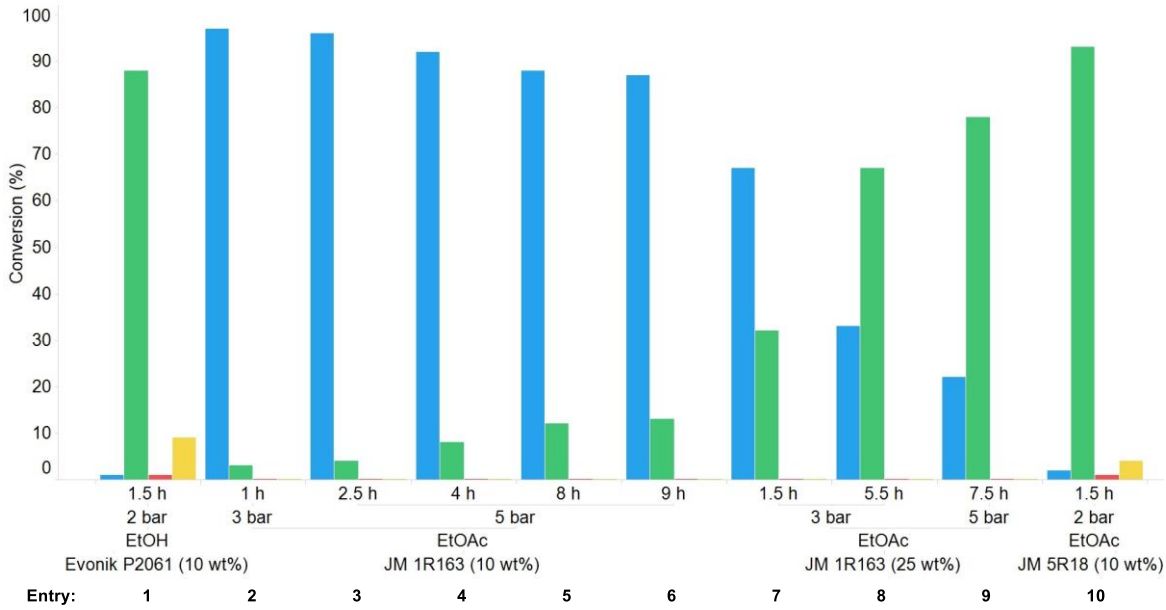
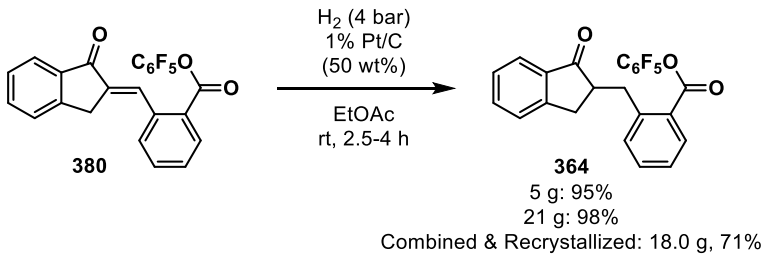


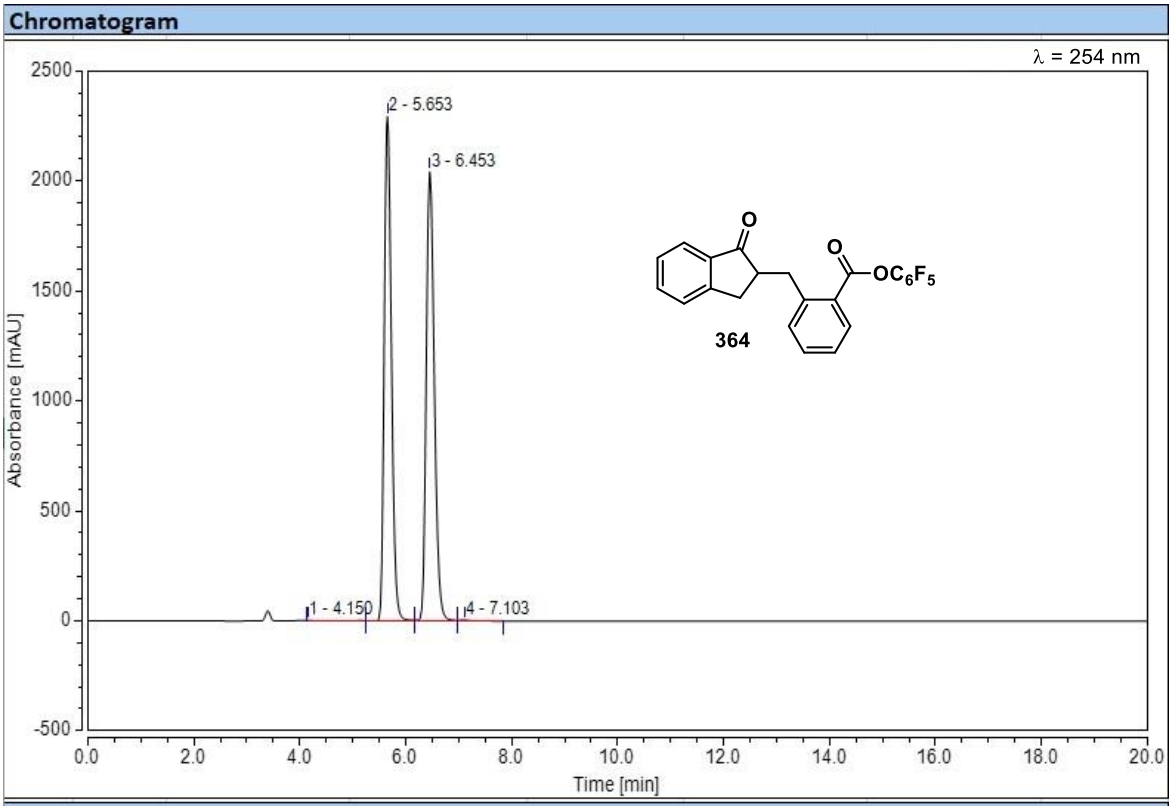
Figure 12: Evaluation of Catalysts at Reduced Catalysts Loadings

With a reduced loading of catalyst JM 1R163, the rate of hydrogenation decreased (Figure 12, entries 2–6 and 7–9), as shown by the results with 10 wt% (13% conversion after 9 hours of reaction at 5 bar, entry 6). Nevertheless, we proceeded with use of JM 1R163 as the catalyst as we were pleased with the results with 25 wt% loading (78% conversion after 7.5 hours) that showed no overreduction, unlike for catalysts Evonik P2061 (Figure 12, entry 1) and JM 5R18 (Figure 12, entry 10). Fortunately, we had sufficient quantities of catalyst JM 1R163 to perform the large-scale reaction with a 50 wt% loading to increase conversion (Scheme 110).



Scheme 110: Large-Scale Hydrogenation of Unsaturated Ketoester **380**

Before the final 21 g scale-up of the hydrogenation of **380** to **364** was performed, a 5 g scale scale-up was carried out (Scheme 110). Pleasingly, after just 2.5 hours at 4 bar pressure, there was a 95% conversion to **364**, 1% remaining **380**, and 4% overreduction to **371** and **372**. This result gave us confidence that the 21 g reaction would proceed smoothly, and from this final large-scale reaction there was a 98% conversion to **364** after 4 h (Scheme 110). The 5 g and 21 g reactions were then combined and recrystallized. A variety of solvents were investigated for recrystallization of **364** and hexane and isopropanol were both found to be effective, with isopropanol showing superior dissolving power at reflux (≈$^{1}/_{7}$ g mL^{-1} **364** in isopropanol and $^{1}/_{14}$ g mL^{-1} **364** in hexane) and cleaner crystallization. Unfortunately, the recrystallization failed to remove the minor by-products, so the mixture of **380**, **370**, **371** and **264** was purified by flash column chromatography followed by crystallization from isopropanol to afford pure **364** (18.0 g, 71% from **380**, >99.9% by HPLC, Figure 13).



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %
1		4.150	0.472	0.163	0.07
2		5.653	357.746	2293.281	49.94
3		6.453	357.842	2039.634	49.96
4		7.103	0.233	1.368	0.03
Total:			**716.293**	**4334.447**	**100.00**

Figure 13: HPLC Trace of Purified **364**

5.2 Development of Kinetic Method

With sufficient starting material, **364**, in hand, we needed to develop an analytical method that would allow rapid and accurate calculation of the concentration of all species (the solvent, internal standard **520**, both enantiomers of starting material **364** and both enantiomers of the product **344**). We used chiral HPLC for this and a chromatograph of the optimized chiral HPLC method using an IA column that separates all the components of the reaction, including our chosen internal standard, 9-methylanthracene **520**, is shown below (Figure 14).

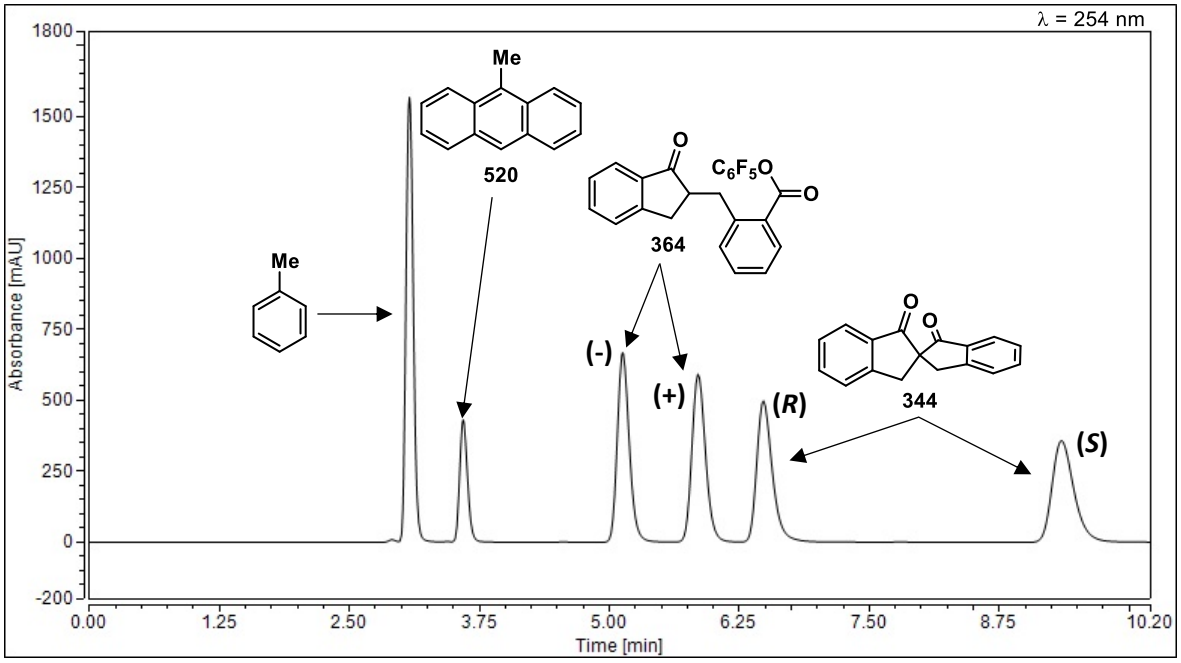


Figure 14: HPLC Trace of Optimized Method for Kinetic Analysis

This method clearly separated all the species present in the reaction mixture (after filtering through a silica plug with 50:50 hexane:IPA to remove the catalyst). We then noticed the formation of by-product 9-anthracenemethanol as a result of catalyst decomposition under the reaction conditions, which coelutes with (*R*)-enantiomer of **344**. Fortunately, this peak did not absorb at higher wavelengths, so by extracting the peaks at 292 and 240 nm, we could avoid this peak affecting our calculations for the concentration of all analytes.

A standard curve for each analyte was generated through aliquoting known amounts of standard **520**, substrate **364**, and product **344** at different concentrations across the conversion space, and comparing the HPLC integrations to the known amount of internal standard **520** to get ratios of substrate/product to standard, and thus the concentration of all the species in solution (Figure 15).

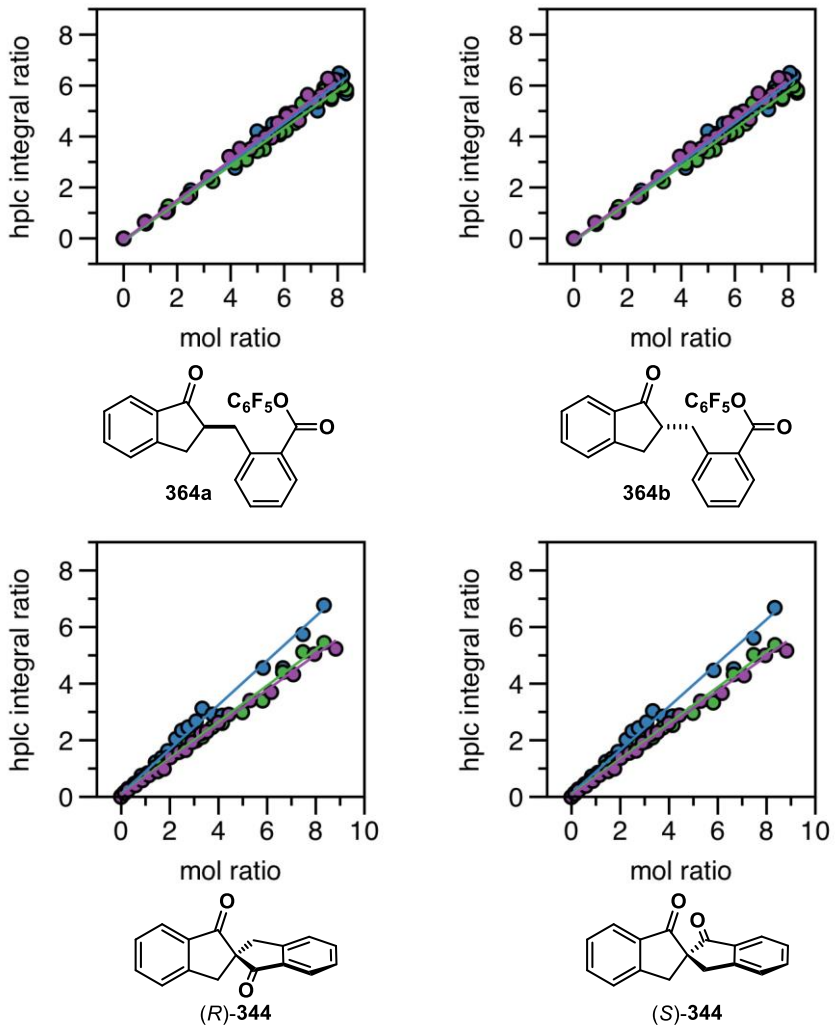


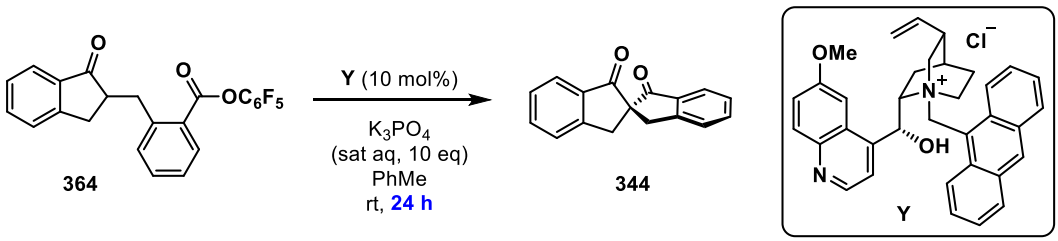
Figure 15: Standard Curves for Each Analyte

Our standard curve for each analyte gave a linear dependence of peak area relative (to the internal standard) to concentration, allowing us to calculate the molar concentration of each analyte by using Equation 1.

$$mol_x = \frac{int_x * mol_s}{slope_x * int_s} \qquad \text{(Equation 1)}$$

This equation calculates the molar concentration of the analyte (mol_x) by comparison of the HPLC signal integral of the analyte (int_x) to the integral of the standard (int_s) multiplied by the slope of the standard curve ($slope_x$). This ratio is multiplied by the molar concentration of internal standard added at the beginning of the reaction (mol_s) to give the analyte concentration at a given time point.

We then used the standard curve to test the HPLC readout: we performed an experiment where a test reaction was aliquoted to be analysed using our kinetics protocol, and then immediately quenched with ammonium chloride and worked up in the usual way. The starting material **364** and product **344** were both isolated, and compared against the values calculated from the HPLC trace and our standard curves (Scheme 111). The HPLC data was in good agreement with the experimental data, verifying our calibration curve and allowing us to be confident in our method.



calculated: **364** 27.5 mg, **344** 8.5 mg
isolated: **364** 29.8 mg, **344** 9.2 mg

Scheme 111: Calculated *versus* Isolated Yields

The practical method for setting up these experiments has previously been shown to be crucial to reproducibility within the group,[148] so all reactions were done in triplicate, on separate stirrer plates in custom moulds to provide the most accurate data possible. A prestirring protocol was utilized based on these previous studies where the catalyst was stirred with the base and a small quantity of toluene before the substrate was added as a solution in toluene to initiate the reaction. This prestirring protocol was done to minimize the effect of any catalyst activation steps on the initial rate so we could focus on the reaction rather than precatalyst activation. To reduce variability between reactions we used saturated aqueous potassium phosphate (calculated to be 4.77 M by titration with 5 M HCl), instead of 50% aqueous potassium phosphate that was found to be optimal for enantioselectivity in Chapter 4.

5.3 Kinetic Investigation Results

Our initial hypothesis was that the reaction proceeded *via* an interfacial mechanism, shown in Figure 16. In this case, the substrate would be deprotonated at the interface, undergo counterion metathesis to form an ion pair with the chiral ammonium salt, then cyclize enantioselectively. We set out to probe this hypothesis with a series of experiments.

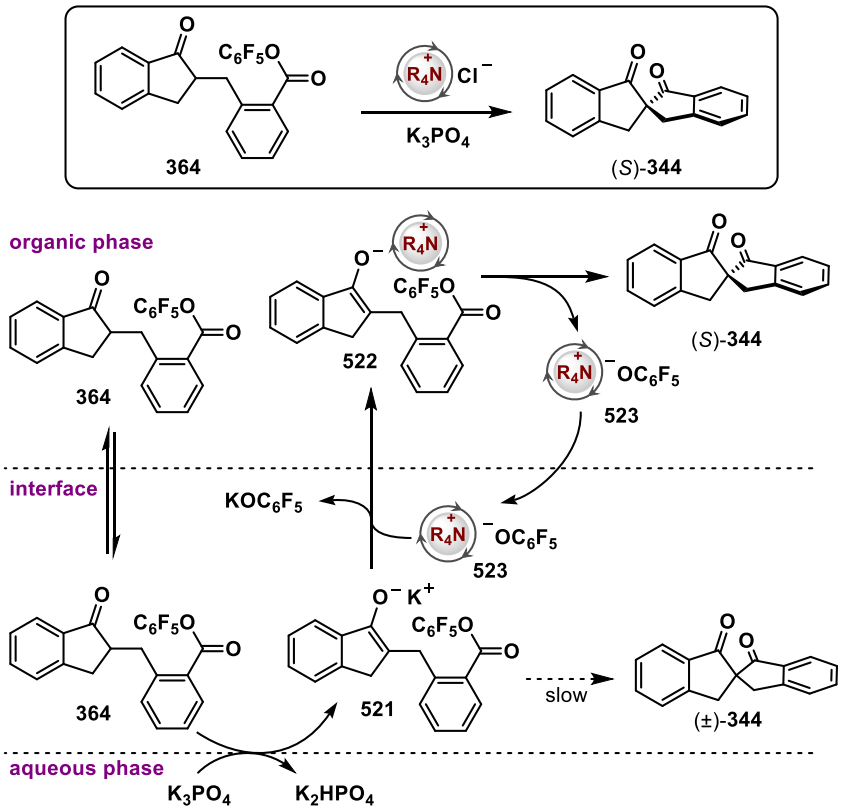


Figure 16: Hypothesized Mechanism of *C*-Acylation of **364**

Firstly, the reaction was first monitored in triplicate under our modified conditions described above for 48 hours, sampling the reaction mixture every hour (Figure 17, **364** in **red**, **344** in **blue**).

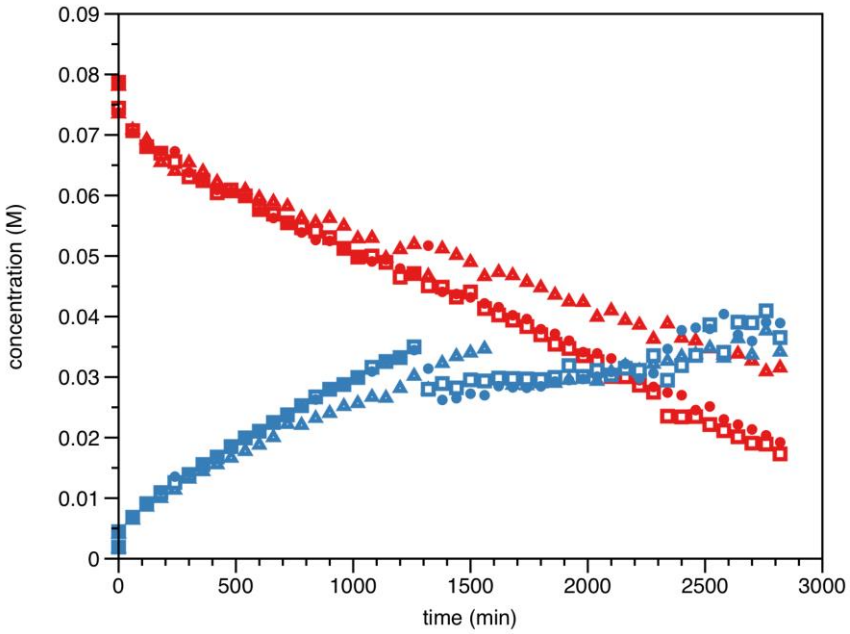


Figure 17: Reaction Profile over 48 Hours

As can be seen, the data are similar between runs for the first 6–8 hours, although we experience significant variance later in the reaction (after 800 minutes). We attribute this to insoluble catalyst

species and product **344** crystallizing out of the reaction mixture (Figure 18). This made the reaction difficult to analyse as we could not fit the graph to determine the overall kinetic order of the reaction. The starting material does appear to be consumed in a largely linear fashion though, assuming it does not also crystallize out, suggesting that the reaction may be 0^{th} order in **364**.

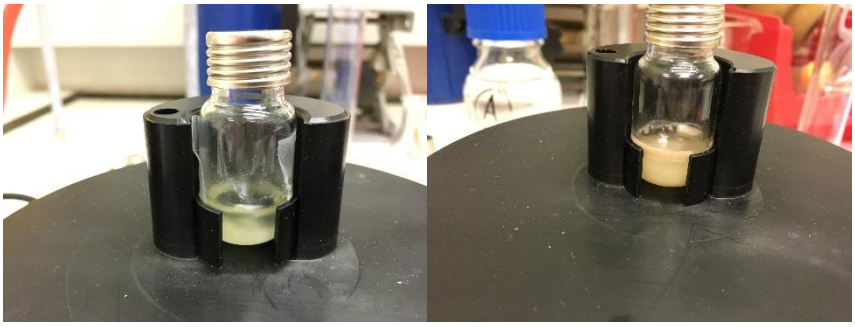


Figure 18: Picture of Reaction Vessels After 3 Minutes (Left) and 54 Hours (Right) of Reaction

When we isolated the solids from the flask, we found that the product had crystallized as enantiopure crystals (>99.5:0.5 *er*), which corresponds with the observed decrease in product enantioenrichment throughout the reaction (Figure 19a).

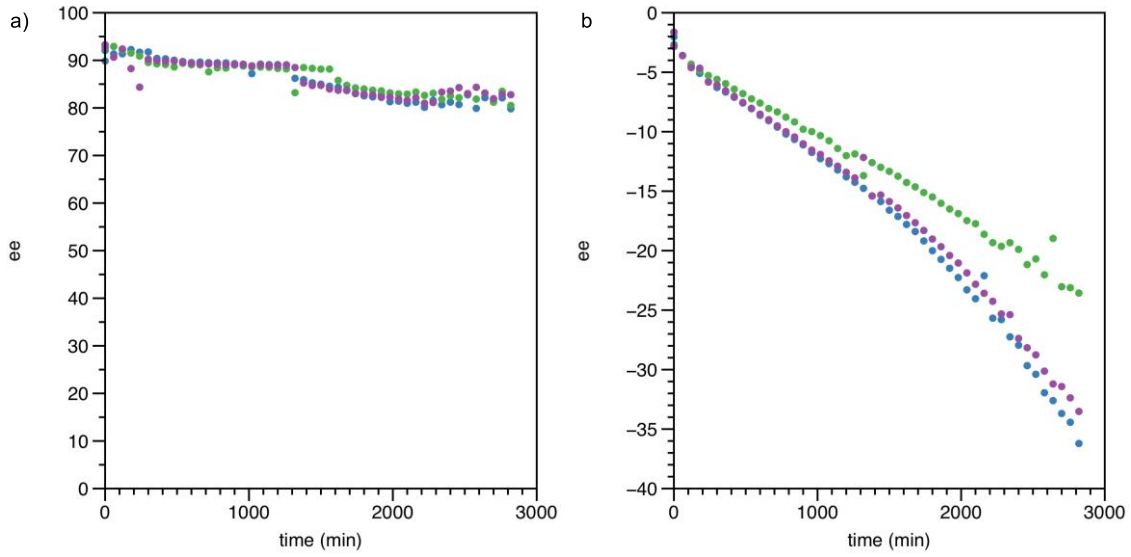


Figure 19: a) Product **344** Enantioenrichment (*ee*) *versus* Time in 48 Hour Reaction;
b) Substrate **364** Enantioenrichment *versus* Time in 48 Hour Reaction

Throughout the course of the reaction, the starting material becomes enantioenriched (Figure 19b), so there must be a kinetic resolution occurring. This implies the chiral catalyst is involved in deprotonation of the starting material, not as was suggested for the mechanism in our initial hypothesis (Figure 16).

The above difficulties with precipitation highlight that investigating the reaction in its entirety would not be possible in a reproducible manner and no alternate solvent was found that avoided product crystallization.[148] As such, we turned to initial rate kinetics to investigate the reaction before the conversion became high enough to cause crystallization. The reaction profile indicated there was an initial period of up to 8 hours which would prove suitable to analyse.

We then tested the viability of this approach by sampling the reaction mixture every 20 minutes for 5 hours (Figure 20). The data showed a straight line from 0 to 5 hours and as our data analysis suggested that the straight line was identical from 0 to 1 hour, to minimize the length of experiment and avoid excessive quantities of data, we sampled the reaction every 5 minutes for 1 hour.

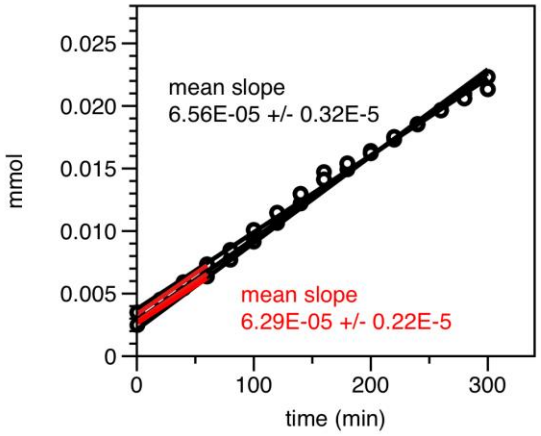


Figure 20: Comparison of Product Formation over **1** and **5** Hours

Given that we observed a kinetic resolution, we amended our hypothesis to involve the catalyst in the deprotonation of substrate **364** (Figure 21). Our second hypothesis was that the active catalyst species is generated by the base through either counterion metathesis or deprotonation – **Y** is insoluble in toluene without any base present, suggesting it is a precatalyst. This active species (possibly **524**) then deprotonates the substrate, forming an ion pair that then undergoes cyclization. The rate-determining step could be any of: deprotonation, cyclization or regeneration of the active species.

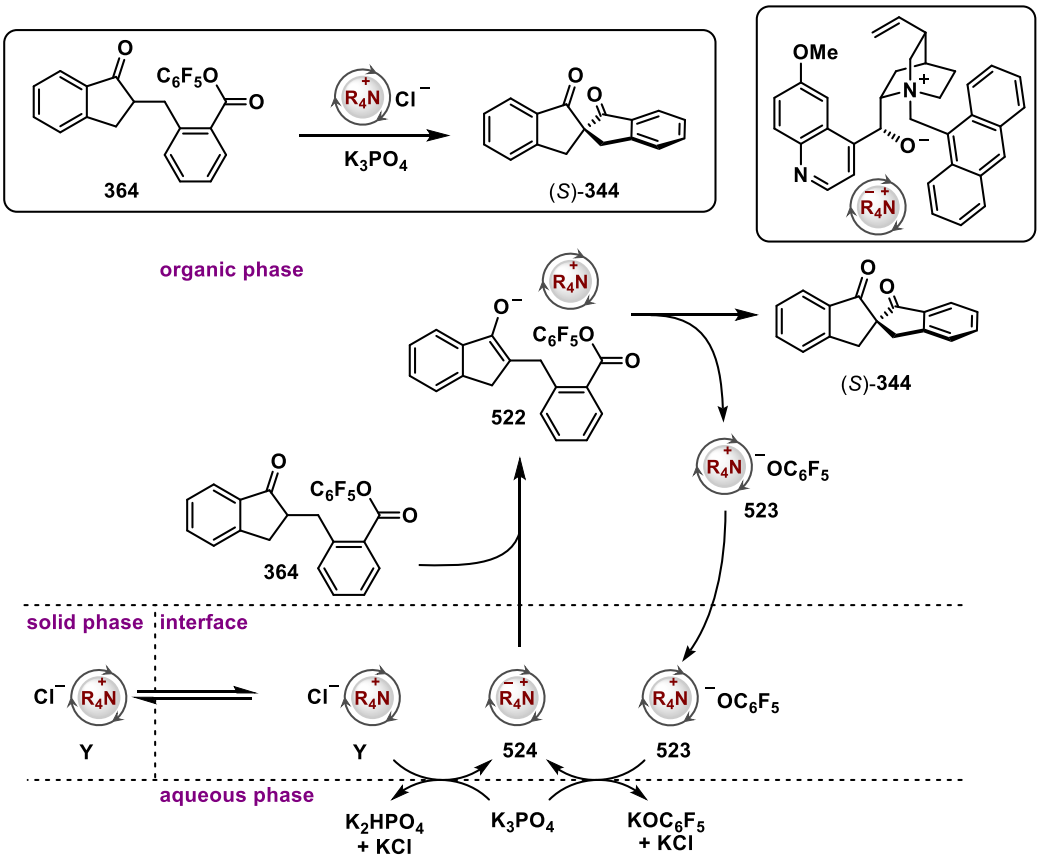


Figure 21: Second Hypothesized Mechanism of *C*-Acylation of **364**

We next sought to establish the order of reaction with respect to the variables: catalyst, substrate, and base. By varying the catalyst loading (and thus concentration) between 2 and 30 mol% and monitoring total product formation, we could measure the initial rates. A double logarithmic plot of rate against concentration of catalyst **Y** afforded the data shown below (Figure 22) and a kinetic order with respect to catalyst of 0.84.

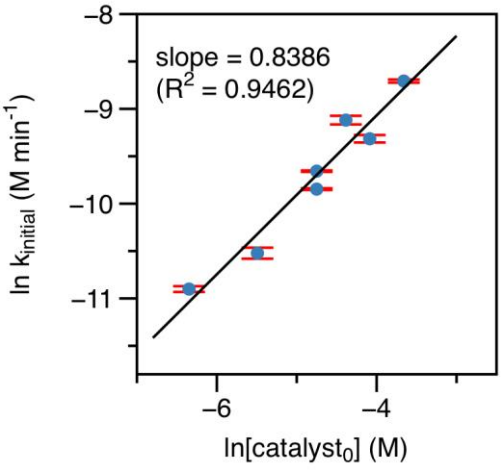


Figure 22: Double Logarithmic Plot to Determine Kinetic Order in Catalyst

We then used the same method to investigate the order in substrate **364** (Figure 23). Surprisingly, we found that the order was −0.07 in substrate, an observation that fits with the linear shape of the consumption of substrate **364** over 48 hours in Figure C. This 0th order dependence suggests that either the substrate is not involved in the rate-determining step or is exhibiting saturation kinetics. Unfortunately, as it is a unimolecular cyclization, we couldn't investigate whether it showed saturation kinetics by varying its concentration, as the relative catalyst concentration also changes significantly at very low substrate loadings.

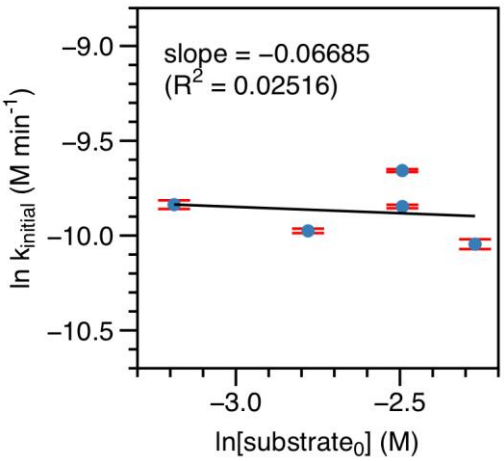


Figure 23: Double Logarithmic Plot to Determine Kinetic Order in Substrate

We also investigated the effect that the base has on the reaction using two methods. First, we varied the equivalents (and thus concentration) of saturated potassium phosphate (Figure 24).

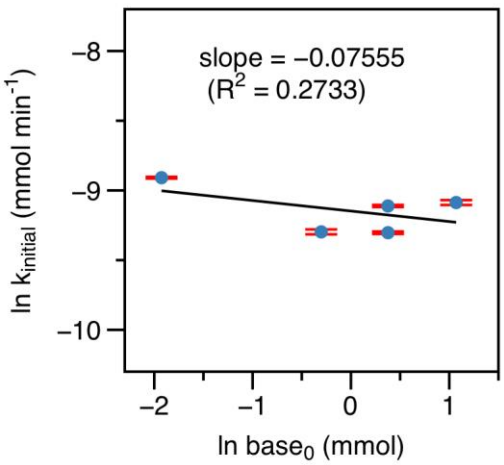


Figure 24: Double Logarithmic Plot to Determine Kinetic Order in Base

Our results with varying the base equivalents show a −0.07 gradient, roughly 0, with a R^2 value of 0.27, which signifies that our data points did not correlate very well with that straight line. This does however alter the overall concentration of the reaction mixture, so we instead varied the concentration of the aqueous base. This might have perturbed the extraction of the base into the interface as the extractability of aqueous bases depends on the concentration.[149] We thus prepared different concentrations of base, between 1.23 M and 4.77 M (saturated) solutions in water (w/v), to vary the base concentration without affecting the overall ratio of organic:aqueous (Figure 25).

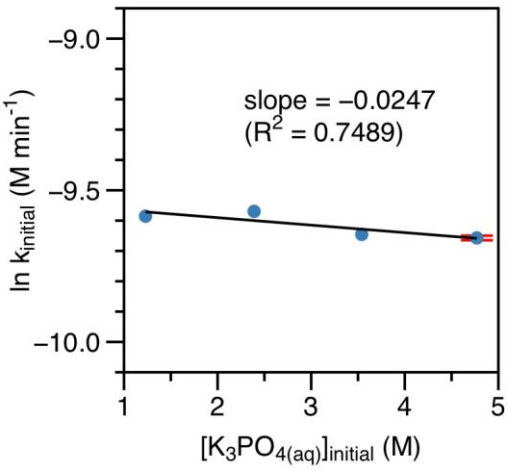


Figure 25: Double Logarithmic Plot to Determine Kinetic Order in Base

Similarly to the previous data set, this showed a near-zeroth order rate dependence on the base and thus we were confident that the base was having no effect on the rate of reaction in the range that we investigated.

One final effect that often has an influence on phase-transfer catalysis is that of stirring speed. In the literature, two predominant scenarios are proposed: firstly, an interfacial process[85] that shows strong dependence upon stirring speed, and secondly, an extractive process[150] that shows no dependence upon stirring speed *above a threshold critical for mass transport*. We expect, given the pK_a of indanone is relatively high for a phase-transfer reaction (~23 in DMSO) for the mechanism to be interfacial, and thus to see a strong dependence on stirring speed. As such, we

varied the stirring speed between 500 and 1400 rpm (Figure 26) and monitored the initial rate of reaction.

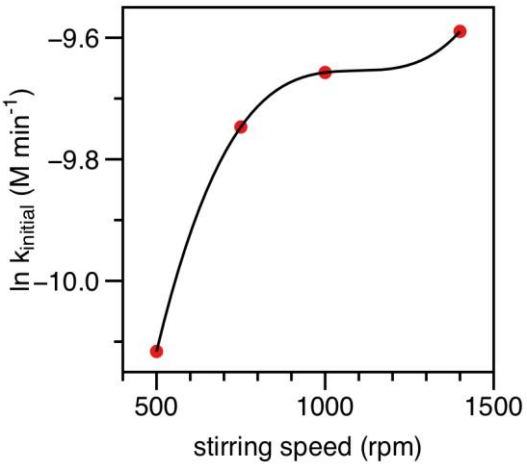


Figure 26: Plot of Rate Against Stirring Speed

As expected, the rate showed a strong dependence on stirring speed and as such we interpret this as good evidence of interfacial kinetics.

We also separated the two enantiomers of **364** by chiral semi-prep HPLC, with the aim of crystallizing them to find out which enantiomer is consumed fastest. Unfortunately, despite the racemic mixture of (*S*) and (*R*)-**364** being crystalline, the enantiopure compounds were oils at room temperature. We then subjected the separate enantiomers to our reaction conditions (on a decreased scale, with a control experiment using racemic **364**) to investigate the deprotonation event (Scheme 28). The result from this reaction would indicate reversible deprotonation if we saw formation of the opposite enantiomer from enantiopure starting material **364** (and *vice versa*).

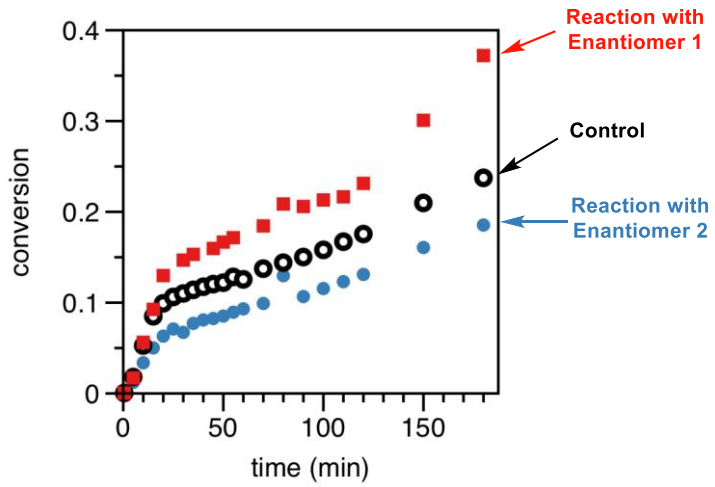


Figure 27: Reaction Profile with Different Enantiomers of Starting Material

We found that there was no appreciable racemization of the two enantiomers (the starting material was not 100% enantiopure (99.5:0.5 *er* for enantiomer 1 and 96.5:3.5 *er* for enantiomer 2) so some kinetic resolution would be expected), and the rate of consumption of one enantiomer was faster than that of the other, implying that the deprotonation of **364** is effectively irreversible (it may be reversible but slow compared to cyclization).

5.4 Summary

From our kinetic investigation, we can determine that the rate equation for the *C*-acylation reaction is as follows (Equation 2):

$$\frac{d[P]}{dt} = k[substrate]^{Sat}[catalyst]^{0.84}[base]^{Sat} \qquad \text{(Equation 2)}$$

The effectively 0th order in substrate suggests that, due to the low loadings of catalyst, it exhibits saturation kinetics and that its concentration would have a significant effect on the rate of reaction with stoichiometric quantities of catalyst. It is also likely that the base exhibits saturation kinetics as the order has been shown to be close to 0 although the concentrations investigated have been far in excess of catalyst concentration. The partial order in phase-transfer catalyst is unexpected, with a first order dependence on catalyst the predicted result of our hypothesis. We have previously observed in other systems that the order of catalyst is often close to 0.5 which corresponds to the catalyst resting state being dimeric, with a fast but unfavourable equilibrium to the active monomeric species.[84c, 151]

5.5 Conclusions

Our experiments have shown that the intramolecular *C*-acylation reaction is not as simple as first expected. From our investigations, we suggest that the rate-determining step is substrate deprotonation or catalyst regeneration. We propose that the mechanism is a modified form of the interfacial mechanism (Figure 28).[84b, 149]

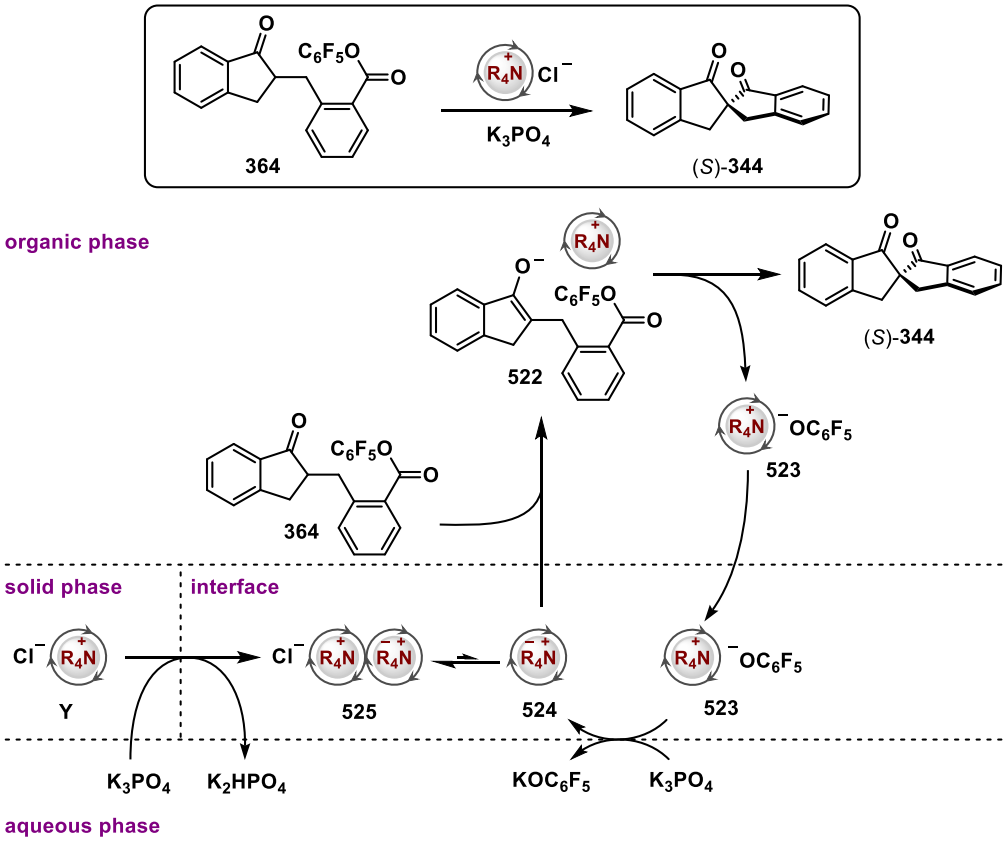


Figure 28: Final Hypothesized Mechanism of *C*-Acylation of **364**

We propose that the insoluble precatalyst is activated by prestirring with base. The catalytically active species **524** is in a rapid reversible unfavourable equilibrium with a resting state **525** that we propose to be dimeric in nature based on other investigations. The catalytically active species is then extracted into the organic phase where reaction takes place as it is saturated in substrate **364**. The substrate is then deprotonated (with one enantiomer being preferentially deprotonated by the chiral species **524**) and then rapidly cyclizes to generate catalyst species **344** which undergoes counterion metathesis to regenerate the active catalyst.

5.6 Future Work

Work on the kinetic analysis of the *C*-acylation reaction is still ongoing, now wholly under the guidance of Katrina Badiola.

The current focus is on investigating the catalyst activation steps by initiating the reaction with the base rather than the substrate, and investigating the initial rate. In our studies with the enantioenriched forms of **364** we have seen that the initial rate is different when initiating with base compared to initiating with a solution of substrate (Figure 29).

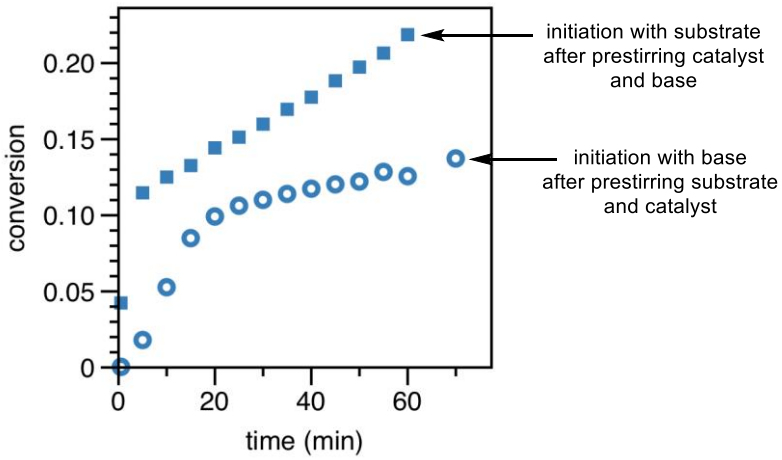


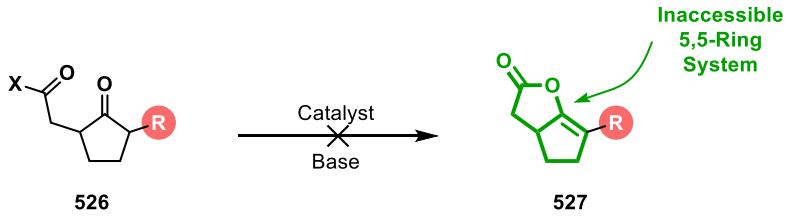
Figure 29: Reaction Profile with Differing Methods of Reaction Initiation

This will hopefully provide some insight into the identity and generation of the catalytically active species.

6. Summary

This thesis has described investigations into the enantioselective acylation of ketones.

In Chapter 2, we investigated various different substrates for enantioselective *O*-acylation of ketones, with two main strategies: desymmetrization and (dynamic) kinetic resolution. We found that reactivity was extremely limited for non-activated ketones and indoles. Our early investigations were also limited by the lack of reactivity to form 5,5-fused enol lactones such as **527** (Scheme 112)

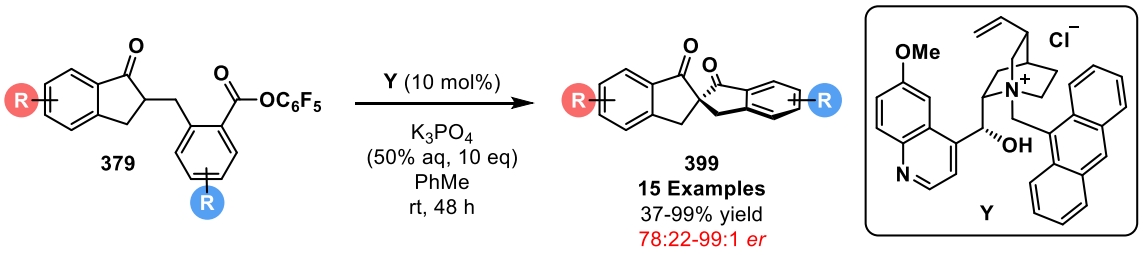


Scheme 112: Unreactive Intramolecular *O*-Acylation Systems

In Chapter 3 we returned to a system based upon one that had previously been investigated in the Smith group. We saw far greater reactivity with benzhydryl ketones, though could not increase the steric hindrance sufficiently to afford axially chiral products while maintaining selectivity for functionalization on the oxygen atom of the enolate.

In Chapter 4 we took advantage of this reversal in selectivity to investigate whether we could observe enantioinduction in a *C*-acylation reaction to afford spirocyclic products. A first-generation system was optimized to afford spirobiindanone **344** in up to 69:31 *er*. Optimization of the leaving group led to the discovery that the phenolate leaving group acidity was crucial to the enantioselectivity of the reaction, and that a pentafluorophenyl ester was optimal. The final, optimized, reaction condition, with **Y** as the catalyst, afforded substituted spirobiindanones **472** in excellent yields and enantioenrichment (Scheme 113).

The ketoesters used in the substrate scope were synthesized from the corresponding 1-indanones and 2-carboxybenzaldehydes. The 1-indanones were accessed from Friedel-Crafts Acylation, while the 2-carboxybenzaldehydes were accessed from *ortho*-lithiation of benzamides, trapping with DMF, and subsequent hydrolysis.



Scheme 113: The First Direct Enantioselective *C*-Acylation of a Ketone

We then demonstrated that the spirobiindanone scaffold could be expanded through derivatization of the unsubstituted compound **344** through reduction and radical bromination. The diol product **349** was found to cause a kinetic resolution *in situ* resulting in conditions whereby the enantioenrichment of the product could be increased at the cost of diastereoselection.

In Chapter 5 we describe work carried out to investigate the kinetic behaviour of the reaction, and inform our understanding of phase-transfer catalysis. We observed that, unlike for other systems previously investigated by our group and others, the catalyst was involved in the deprotonation of the substrate **364** and the reaction was limited by the rate of deprotonation or catalyst turnover. We have proposed a catalytic cycle that fits with our kinetic analysis (Figure 30) and preliminary modelling is underway.

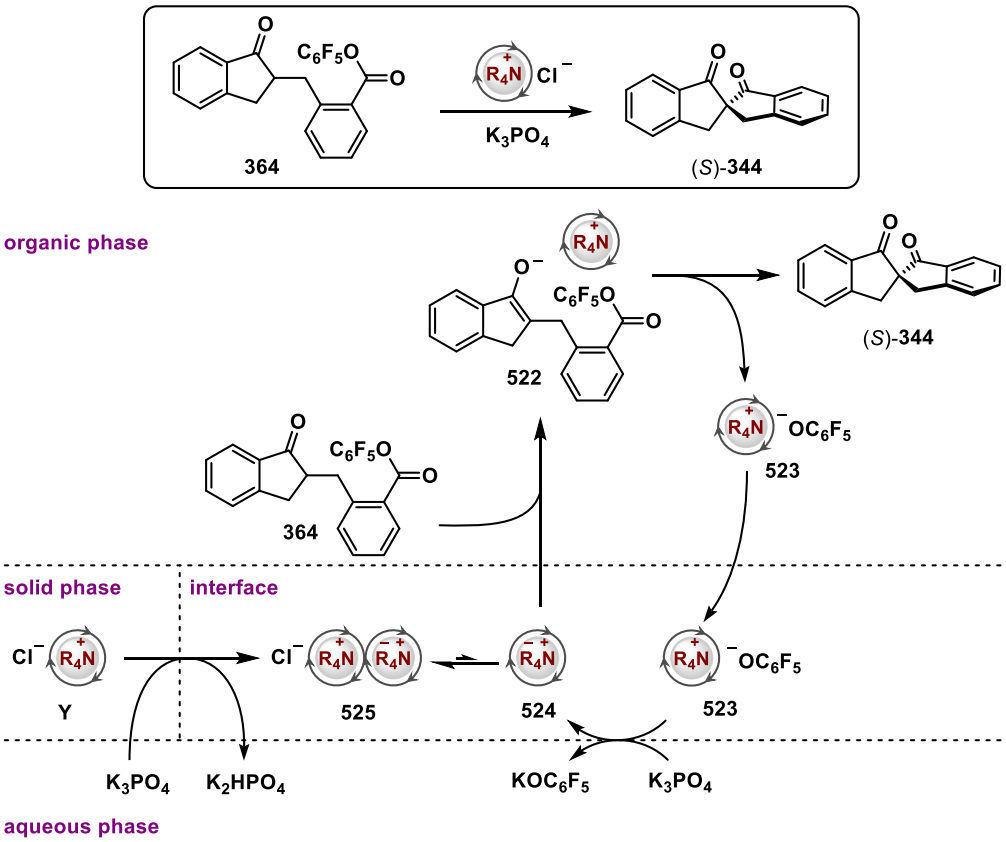


Figure 30: Final Hypothesized Mechanism of *C*-Acylation of **364**

7. Experimental

7.1 General Information

Naming and Numbering

Compounds have been named according to IUPAC recommendations or more commonly utilised names where appropriate. The atomic numbering system for compounds does not correspond to IUPAC names, but was chosen to allow for simple and consistent assignment of spectra.

Reaction Conditions

All reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen unless otherwise stated. Room temperature refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of −78 °C were obtained using a dry ice/acetone bath *or* a Julabo FT902 immersion cooler. Reflux conditions were obtained using a Drysyn® heating block equipped with a contact thermometer.

Solvents and Reagents

CH_2Cl_2, diethyl ether, methanol, tetrahydrofuran and toluene were purified by filtration through activated alumina columns, employing the method of Grubbs *et al*.[152] Et_3N was distilled from calcium hydride and stored over potassium hydroxide. Tetramethylethylenediamine was distilled from potassium hydroxide and stored over calcium hydride. Dimethyl sulfoxide was purchased as an anhydrous solvent in a Sure/Seal™ bottle from Sigma-Aldrich All other solvents and reagents were used as supplied without further purification. Petrol 40-60, corresponds to the fractions of petroleum ether boiling between 40 °C and 60 °C.

Chromatography

Thin layer chromatography was carried out on Merck Kieselgel 60, F_{254} 0.25mm precoated aluminium plates and visualisation was achieved by UV light (λ_{max} = 254 nm) and/or by staining with potassium permanganate solution or bromocresol green solution. Flash column chromatography was performed using silica gel 60 (0.043-0.063 nm, VWR) using head pressure provided by house nitrogen supply, employing the method of Still *et al*.[153]

Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were recorded on Bruker Avance spectrometers and referenced to residual non-deuterated solvent peaks. Chemical shifts are quoted in ppm with signal splitting recorded as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), triplet of doublets (td), quartet (q), septet (sept), and multiplet (m). The abbreviation br is to denote broad and app. to denote apparent. Coupling constants, *J*, are measured to the nearest 0.1 Hz and are presented as observed. ^{19}F NMR spectra were referenced externally to $CFCl_3$ = 0 ppm. Due to significant (C-F) coupling and unresolved fine structure, pentafluorophenyl ^{13}C peaks are reported only when clearly resolved. Assignment of spectra was assisted by the results of DEPT, COSY, HSQC, HMBC, and NOESY experiments.

Infrared Spectroscopy

Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer fitted with a diamond ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass Spectrometry

Low-resolution mass spectra were recorded on a Micro Mass LCT Premier spectrometer under conditions of electrospray ionization (ESI). High resolution mass spectra were recorded on a Bruker MicroTOF and Micromass GCT spectrometers under conditions of electrospray ionization (ESI), electron ionization (EI), field ionization (FI), ammonia chemical ionization (ACI), or methane chemical ionization (MCI).

Polarimetry

Optical rotations were recorded on a Schmidt-Haensch Unipol L2000 polarimeter and values are quoted [° mL g^{-1} dm^{-1}]. Concentrations are quoted in g/100 mL. Temperatures are recorded in °C.

HPLC

Analytical chiral HPLC was carried out on a Dionex UltiMate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler and TCC-3000SD column compartment, and an appropriate Daicel Chiralpak column (dimensions 0.46 cm ø × 25 cm) and corresponding guard

column (0.4 cm ø × 1 cm). Wavelengths are reported in nm, retention times (τ_R) are reported in minutes and solvent flow rates are reported in mL min^{-1}.

Melting Points

Melting points were determined by using Reichert melting point apparatus and are uncorrected.

X-ray Crystallography

Single Crystal X-ray diffraction experiments were carried out by Dr John Jolliffe and Dr Amber Thompson on Oxford Diffraction Supernova and Nonius KappaCCD diffractometers in the Oxford Chemical Crystallographical suite.

Catalyst Synthesis

Catalysts that were not commercially available were prepared following well established literature procedures of *N*-alkylation of cinchona alkaloids.[154]

7.2 General Experimental Procedures

General Procedure A: Carbodiimide-Mediated Esterification of Carboxylic Acids

The appropriate acid (1.0 eq), EDC·HCl (1.3-2 eq), and DMAP (0.05 eq) were added to a flame dried round-bottom flask, and dissolved in CH_2Cl_2 (2 mL/mmol acid). The mixture was stirred for 30 minutes and then a solution of *the appropriate alcohol* (1.0 eq) in CH_2Cl_2 (2 mL/mmol acid) was added to the solution. The reaction mixture was stirred at room temperature for 14 hours upon which it was quenched by addition of brine and diluted in CH_2Cl_2. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue *via* flash column chromatography (see experimental methods section for specific details) afforded the corresponding ester.

General Procedure B: Hydrogenation of Enones

A stirred suspension of *the corresponding unsaturated acid or activated ester* (1.0 eq) and 10% Pd/C (10 wt%) (0.1 mg/mg *unsaturated acid or ester*) *or* platinum(IV) oxide (10 wt% *unsaturated acid or ester*) in EtOAc (7.0 mL/mmol acid *or* ester) was purged with hydrogen (1 balloon). After 10 minutes, purging was stopped and the balloon was replaced with a new balloon of hydrogen. Once the starting material had been consumed (indicated by TLC analysis) the reaction flask was opened to air, the reaction mixture filtered through Celite® with CH_2Cl_2 and the resulting solution concentrated under reduced pressure. Purification of the residue *via* flash column chromatography *or* recrystallization (see experimental methods section for specific details) afforded the corresponding saturated acid/activated ester.

General procedure C: Screening the Cyclization of Phenyl Ester 360

A mixture of **360** (10 mg, 0.029 mmol) and phase-transfer catalyst (0.003 mmol, 0.1 eq) were dissolved in toluene (0.29 mL) and to this solution was added base (X eq). The reaction mixture was stirred until complete consumption of the starting material was observed, by TLC analysis, when the reaction was quenched with water (5 mL). The organic layer was extracted with CH_2Cl_2

(3 × 5 mL) and the combined organic extracted were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude residue.

General Procedure D: Screening the Cyclization of Pentafluorophenyl Ester 364

A mixture of **364** (10 mg, 0.023 mmol) and phase-transfer catalyst (0.002 mmol, 0.1 eq) were dissolved in solvent (X mL) and to this solution was added base (X eq). The reaction mixture was stirred until complete consumption of the starting material was observed, by TLC analysis, or 48 hours had passed, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The organic layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracted were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude residue.

General Procedure E: Aldol Condensation of 1-Indanones with *o*-Carboxybenzaldehydes[138]

To a stirred room temperature solution of *the appropriate 1-indanone* (1.0 eq) and *the appropriate o-carboxybenzaldehyde* (1.0 eq) in ethanol (2.4 mL/mmol indanone) was added aqueous sodium hydroxide (1 M, 1.8 eq). The reaction mixture was stirred for 15 minutes after which cold water was added and the resulting solution poured onto diethyl ether. The aqueous layer was separated and the organic layer extracted with water. The combined aqueous extracts were acidified with aqueous H_2SO_4 (2.5 M) and the precipitate isolated *via* filtration, then dried under high vacuum to afford the corresponding unsaturated acid.

General Procedure F: Esterification of Unsaturated Acids

To a stirred suspension of *the appropriate crude unsaturated acid* (1.0 eq) in CH_2Cl_2 (3.0 mL/mmol acid) was added oxalyl chloride (1.5 eq) followed by 1 drop of *N*,*N*-dimethylformamide. After evolution of gas had ceased (30 minutes), the mixture was concentrated under reduced pressure. The residue was subsequently dissolved in CH_2Cl_2 (3.0 mL/mmol acid) and to this solution was added pentafluorophenol (1.0 eq) and Et_3N (3.0 eq). The reaction mixture was stirred at room temperature for 2 hours upon which it was quenched by addition of water and diluted in CH_2Cl_2. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Purification of the residue *via* flash column chromatography (see experimental methods section for specific details) afforded the corresponding unsaturated activated ester.

General Procedure G: Asymmetric Phase-Transfer *C*-Acylation of Activated Esters

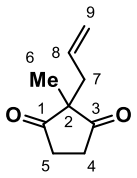
In a 7 mL screw-topped vial, *the appropriate saturated activated ester* (1.0 eq) and **Y** (0.10 eq) *or* TBAB (0.1 eq) were dissolved in toluene (10 mL/mmol ester) and 50% w/w aqueous potassium phosphate (10.0 eq) *or* potassium hydroxide (2.0 eq) was added. The biphasic reaction mixture was rapidly stirred at room temperature for *the appropriate time* and then water and CH_2Cl_2 were added. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue *via* flash column chromatography (see experimental methods section for specific details) afforded the corresponding enantioenriched spirobiindanone.

General Procedure H: Experimental Procedure for Kinetic Analysis of Asymmetric *C*-Acylation Reaction

To a 10 mL screw-capped vial (in a custom-made vial holder) was added *the appropriate amount of* phase-transfer catalyst **Y** and a 12 × 3 mm stirrer bar. Toluene (0.56 mL) was added and the suspension stirred at 1000 rpm. *The appropriate amount of* saturated (4.77 M) aqueous potassium phosphate was added and the resulting suspension stirred at room temperature for 30 minutes. During this prestirring time, the mixture was sonicated for 5 seconds after 5, 15 and 25 minutes post-addition of potassium phosphate. After exactly 30 minutes of stirring, the reaction was initiated by addition of a solution of 9-methylanthracene **520** (2.88 mg) and *the appropriate amount* of **364** in toluene (0.9 mL). At predetermined intervals, 2 μL aliquots were taken from the reaction mixture and filtered through a small silica plug (~0.2 cm in a glass Pasteur pipette), eluting with 1:1 ^{i}PrOH/hexane, into a HPLC vial. These samples were analysed by chiral HPLC (Chiralpak IA, 30% ^{i}PrOH, 70% hexane, 1.1 mLmin^{-1}, λ = 292 & 240 nm, 50 μL injection).

7.3 Experimental Procedures for Individual Compounds

2-Allyl-2-methylcyclopentane-1,3-dione, 148



According to a literature procedure,[155] 1 M aqueous NaOH (23 mL, 25 mmol, 1.1 eq) was added to 2-methyl-1,3-cyclopentanedione (2.50 g, 22.3 mmol, 1.0 eq) and the mixture stirred vigorously for 10 minutes. Allyl bromide (3.85 mL, 44.6 mmol, 2.0 eq) was then added to the biphasic mixture and stirred vigorously for 30 hours. The reaction mixture was diluted in EtOAc (30 mL) and the phases separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:7 EtOAc/heptane to afford **148** as a colourless oil (1.90 g, 56%).

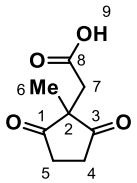
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H = 5.59 (ddt, *J* = 16.7, 10.4, 7.3 Hz, 1H, H_8), 5.15-4.85 (m, 2H, H_9) 2.72 (s, 4H, H_4 & H_5), 2.23 (dt, *J* = 7.3, 1.2 Hz, 2H, H_7), 0.98 (s, 3H, H_6);

^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C = 216.4 (Quat, C_1 & C_3), 132.6 (CH, C_8), 119.50 (CH, C_9), 56.2 (Quat, C_2), 39.5 (CH_2, C_7), 35.4 (CH_2, C_4 & C_5), 17.7 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 2979, 2932, 2361, 1720, 1641, 1453, 1419, 1371, 1319, 1208, 1068, 1030;

HRMS (ACI^+) calculated for $C_9H_{13}O_2^+$ = 153.0910, mass found = 153.0909.

2-(1-Methyl-2,5-dioxocyclopentyl)acetic acid, 149



Analogously to a literature procedure,[105] aqueous H_2SO_4 (2 M, 13.1 mL, 26.3 mmol, 4.0 eq) was added to a round-bottom flask, equipped with an internal thermometer, which contained a solution of **148** (1.0 g, 6.8 mmol, 1.0 eq) in CH_2Cl_2 (3.3 mL) and the mixture stirred rapidly. The

mixture was cooled to 10 °C, followed by slow addition of potassium permanganate (3.12 g, 19.7 mmol, 3.0 eq) whilst ensuring the temperature of the solution did not rise about 15 °C. Once all the potassium permanganate had been added, the solution was stirred for a further 2 hours before the solids were filtered off. The biphasic mixture was diluted in EtOAc (15 mL), separated, and the aqueous layer extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by recrystallization (H_2O) to afford **149** as a colourless solid (0.38 g, 34%).

mp = 165-167 °C;

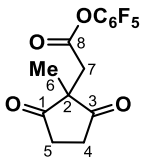
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H = 12.63 (s, 1H, H_9), 2.99-2.84 (m, 2H, H_4 & H_5), 2.76 (s, 2H, H_7), 2.70-2.59 (m, 2H, $H_{4'}$ & $H_{5'}$), 1.00 (s, 3H, H_6);

^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C = 216.7 (Quat, C_1 & C_3), 173.1 (Quat, C_8), 53.0 (Quat, C_2), 40.5 (CH_2, C_7), 35.0 (CH_2, C_4 & C_5), 19.8 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 2988, 1758, 1701, 1451, 1420, 1397, 1321, 1303, 1204, 1154, 1076;

HRMS (ESI$^+$) calculated for $C_8H_9O_4^-$ = 169.0506, mass found = 169.0503.

Pentafluorophenyl 2-(1-methyl-2,5-dioxocyclopentyl)acetate, 150



This compound was prepared according to **General Procedure A**.

Esterification with crude diketoacid **149** (100 mg, 0.587 mmol, 1.0 eq), EDC·HCl (225 mg, 1.17 mmol, 2.0 eq), DMAP (4 mg, 0.03 mmol 0.05 eq), and pentafluorophenol (109 mg, 0.587 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 3:17 EtOAc/heptane afforded title compound **150** as a colourless oil that solidified on standing to a white solid (165 mg, 84%).

mp = 54-56 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.27 (d, *J* = 1.8 Hz, 2H, H_7), 3.07-2.69 (m, 4H, H_4 & H_5), 1.27-1.12 (m, 3H, H_6);

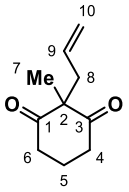
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 214.5 (Quat, C & C_3), 168.1 (Quat, C_8), 53.0 (Quat, C_2), 38.3 (CH_2, C_7), 34.7 (CH_2, C_4 & C_5), 20.4 (CH_3, C_6);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.0, −157.1, −161.8;

FTIR (film) ν_{max}/cm^{-1} = 2927, 1773, 1725, 1521, 1455, 1400, 1347, 1168, 1119, 1074;

HRMS (EI/ACI) sample was unfortunately lost by the Mass Spectrometry staff.

2-Allyl-2-methylcyclohexane-1,3-dione, 152



According to a literature procedure,[156] 1 M aqueous NaOH (20 mL, 20 mmol, 1.0 eq) was added to 2-methyl-1,3-cyclohexanedione (2.50 g, 19.8 mmol, 1.0 eq) and the mixture stirred vigorously for 10 minutes. Allyl bromide (3.42 mL, 39.6 mmol, 2.0 eq) was then added to the biphasic mixture and stirred vigorously for 72 hours. The reaction mixture was diluted in EtOAc (30 mL) and the phases separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:4 EtOAc/heptane to afford **152** as a colourless oil (2.84 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.74-5.44 (m, 1H, H_9), 5.14-4.94 (m, 2H, H_{10}), 2.75-2.58 (m, 4H, H_4 & H_6), 2.53 (d, *J* = 7.3 Hz, 2H, H_8), 2.08-1.80 (m, 2H, H_5), 1.25 (d, *J* = 1.5 Hz, 3H, H_7);

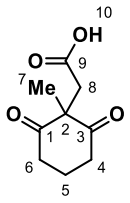
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 209.8 (Quat, C_1 & C_3), 132.2 (CH, C_9), 119.2 (CH_2, C_{10}), 65.2 (Quat, C_2), 41.3 (CH_2, C_8), 38.2 (CH_2, C_4 & C_6), 19.5 (CH_3, C_7), 17.5 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2968, 1724, 1693, 1640, 1455, 1427, 1373, 1320, 1210, 1129, 1069, 1025;

HRMS (ACI^+) calculated for $C_{10}H_{15}O_2^+$ = 167.1067, mass found = 167.1067.

The data matched those of the literature.[157]

2-(1-Methyl-2,5-dioxocyclohexyl)acetic acid, 153



Analogously to a literature procedure,[105] aqueous H_2SO_4 (2 M, 30.1 mL, 60.2 mmol, 4.0 eq) was added to a round-bottom flask, equipped with an internal thermometer, which contained a solution of **152** (2.50 g, 15.0 mmol, 1.0 eq) in CH_2Cl_2 (7.6 mL) and the mixture stirred rapidly. The mixture was cooled to 10 °C, followed by slow addition of potassium permanganate (7.13 g, 45.0 mmol, 3.0 eq) whilst ensuring the temperature of the solution did not rise about 15 °C. Once all the potassium permanganate had been added, the solution was stirred for a further 2 hours before the solids were filtered off. The biphasic mixture was diluted in EtOAc (30 mL), separated, and the aqueous layer extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by recrystallization (H_2O) to afford **153** as an orange crystalline solid (1.37 g, 50%).

mp = 156-158 °C;

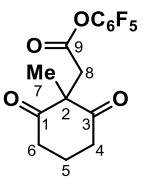
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H = 12.28 (s, 1H, H_{10}), 2.94-2.74 (m, 4H, H_4, H_6, H_8), 2.45 (m, 2H, $H_{4'}$ & $H_{6'}$), 2.11-1.71 (m, 2H, H_5), 1.16 (d, J = 1.9 Hz, 3H, H_7);

^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C = 210.8 (Quat, C_1 & C_3), 173.2 (Quat, C_9), 60.7 (Quat, C_2), 39.6 (CH_2, C_8), 37.6 (CH_2, C_4 & C_6), 23.2 (CH_3, C_7), 17.5 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2961, 1692 (br), 1458, 1392, 1320, 1289, 1200, 1140, 1075, 1026;

LRMS (ESI^-) calculated for $C_9H_{11}O_4^-$ = 183, mass found = 183.

Pentafluorophenyl 2-(1-methyl-2,5-dioxocyclohexyl)acetate, 154



This compound was prepared according to **General Procedure A**.

Esterification with diketoacid **153** (300 mg, 1.63 mmol, 1.0 eq), EDC·HCl (612 mg, 3.19 mmol, 2.0 eq), DMAP (10 mg, 0.08 mmol, 0.05 eq), and pentafluorophenol (295 mg, 1.63 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/heptane afforded title compound **154** as a white solid (450 mg, 80%).

mp = 67-69 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.35 (d, *J* = 2.0 Hz, 2H, H_8), 2.85-2.59 (m, 4H, H_4 & H_6), 2.21-1.88 (m, 2H, H_5), 1.38 (d, *J* = 2.0 Hz, 3H, H_7);

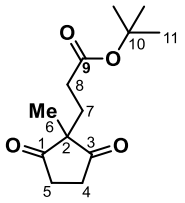
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 209.0 (Quat, C_1 & C_3), 168.4 (Quat, C_9), 61.6 (Quat, C_2), 37.5 (CH_2, C_8), 37.4 (CH_2, C_4 & C_6), C, 23.7 (CH_3, C_7), 17.3 (CH_2, C_5);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −151.9, −157.9, −162.3;

FTIR (film) ν_{max}/cm^{-1} = 2967, 1782, 1731, 1699, 1518, 1459, 1397, 1380, 1344, 1316, 1288, 1112, 1073, 1023;

Compound **154** was not detected by ACI, EI or ESI mass spectrometry;

tert-Butyl 3-(1-methyl-2,5-dioxocyclopentyl)propanoate, 156



Analogously to a literature procedure,[158] 2-methyl-1,3-cyclopentanedione (1.22 g, 10.9 mmol, 1.0 eq), *tert*-butyl acrylate (4.0 mL, 27.2 mmol, 2.5 eq) and Et_3N (20 mL) were added to a round-bottom flask and heated to reflux for 14 hours. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude reaction mixture was purified *via* flash column chromatography, eluting with 1:4 EtOAc/heptane afforded **156** as an orange oil (1.35 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.94-2.67 (m, 4H, H_4 & H_5), 2.20 (t, *J* = 7.5 Hz, 2H, H_8), 1.92 (t, *J* = 7.6 Hz, 2H, H_7), 1.40 (d, *J* = 1.3 Hz, 9H, H_{11}), 1.12 (s, 3H, H_6);

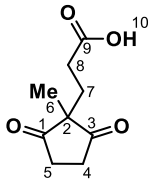
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 215.7 (Quat, C_1 & C_3), 172.1 (Quat, C_9), 80.9 (Quat, C_{10}), 55.3 (Quat C_2), 34.8 (CH_2, C_4 & C_5), 29.9 (CH_2, C_8), 29.2 (CH_2, C_7), 28.0 (CH_3, C_{11}), 19.7 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 2978, 2932, 1719 (br), 1455, 1420, 1368, 1300, 1256, 1154, 1075;

LRMS (ESI^+) calculated for $C_{13}H_{21}O_4^+$ = 241, mass found = 241.

The data matched those of the literature.[158]

3-(1-Methyl-2,5-dioxocyclopentyl)propanoic acid, 157

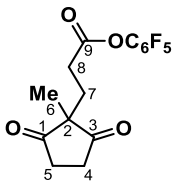


Analogously to a literature procedure,[158] a 1:1 mixture of TFA/CH_2Cl_2 (30 mL) was added slowly to a round-bottom flask containing **156** (1.2 g, 1.0 eq). The solution was stirred for 2 hours at which point the starting material had been fully consumed by HPLC analysis. The solution was diluted with toluene (20 mL), and concentrated under reduced pressure. The residue was further azeotroped with toluene (2 × 20 mL) to afford crude acid **157** as a pale yellow solid (0.90 g, 98%), which was used without further purification.

^1H NMR (400 MHz, $CDCl_3$) δ_H = 2.80 (s, 4H, H_4 & H_5), 2.34 (t, *J* = 7.5 Hz, 2H, H_8), 1.97 (t, *J* = 7.5 Hz, 2H, H_7), 1.14 (s, 3H, H_6);

LRMS (ESI^-) calculated for $C_9H_{11}O_4^-$ = 183, mass found = 183.

Pentafluorophenyl 3-(1-methyl-2,5-dioxocyclopentyl)propanoate, 158



This compound was prepared according to **General Procedure A**.

Esterification with crude diketoacid **157** (300 mg, 1.63 mmol, 1.0 eq), EDC·HCl (612 mg, 3.19 mmol, 2.0 eq), DMAP (10 mg, 0.08 mmol, 0.05 eq), and pentafluorophenol (295 mg, 1.63 mmol, 1.0 eq).

Purification *via* flash column chromatography, eluting with 3:17 EtOAc/heptane afforded title compound **158** as a colourless oil that solidified on standing to a white solid (518 mg, 91%).

mp = 54-56 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.91-2.74 (m, 4H, H_4 & H_5), 2.70 (dd, *J* = 8.4, 7.1 Hz, 2H, H_8), 2.08 (dd, *J* = 8.4, 7.1 Hz, 2H, H_7), 1.20 (s, 3H, H_6);

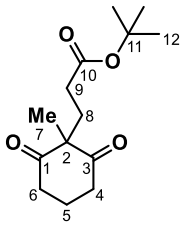
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 215.1 (Quat, C_1 & C_3), 168.8 (Quat, C_9), 54.9 (Quat, C_2), 34.7 (CH_2, C_4 & C_5), 27.9 (CH_2, C_8), 27.9 (CH_2, C_7), 19.8 (CH_3, C_6);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.5, −157.8, −162.2;

FTIR (film) ν_{max}/cm^{-1} = 2933, 1787, 1721, 1518, 1455, 1421, 1377, 1299, 1145, 1101, 1042;

Compound **158** was not detected by ACI, EI or ESI mass spectrometry;

tert-Butyl 3-(1-methyl-2,5-dioxocyclohexyl)propanoate, 160



Analogously to a literature procedure,[158] 2-methyl-1,3-cyclohexanedione (1.5 g, 11.9 mmol, 1.0 eq), *tert*-butyl acrylate (4.31 mL, 29.7 mmol, 2.5 eq) and Et_3N (20 mL) were added to a round-bottom flask and heated to reflux for 14 hours. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude reaction mixture was purified *via* flash column chromatography, eluting with 1:4 EtOAc/heptane afforded **160** as a colourless oil (1.24 g, 41%).

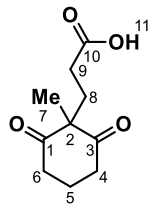
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.80-2.57 (m, 4H, H_4 & H_6), 2.19-1.82 (m, 6H, H_5, H_8 & H_9), 1.48-1.37 (m, 9H, H_{12}), 1.24 (d, *J* = 1.8 Hz, 3H, H_7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 209.8 (Quat, C_1 & C_3), 172.0 (Quat, C_{10}), 80.7 (Quat, C_{11}), 64.4 (Quat, C_2), 37.8 (Quat, C_4 & C_6), 31.0 (CH_2, C_8), 30.5 (CH_2, C_9), 28.0 (CH_3, C_{12}), 20.0 (CH_3, C_7), 17.6 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2978, 1725, 1695, 1458, 1368, 1318, 1298, 1257, 1227, 1155, 1103, 1027;

HRMS (ESI$^+$) calculated for $C_{14}H_{22}O_4Na^+$ = 277.1410, mass found = 277.1410.

3-(1-Methyl-2,5-dioxocyclohexyl)propanoic acid, 161

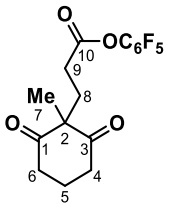


Analogously to a literature procedure,[158] a 1:1 mixture of TFA/CH_2Cl_2 (28 mL) was added slowly to a round-bottom flask containing **160** (1.15 g, 1.0 eq). The solution was stirred for 2 hours at which point the starting material had been fully consumed by HPLC analysis. The solution was diluted with toluene (15 mL), and concentrated under reduced pressure. The residue was further azeotroped with toluene (2 × 15 mL) to afford crude acid **161** as a pale yellow solid (0.95 g, quant), which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.67 (td, *J* = 6.8, 1.1 Hz, 4H, H_4 & H_6), 2.26 (dd, *J* = 9.2, 6.8 Hz, 2H, H_9), 2.14 (dd, *J* = 8.5, 6.2 Hz, 2H, H_8), 1.98 (p, *J* = 6.7 Hz, 2H, H_5), 1.29 (s, 3H, H_7);

LRMS (ESI$^-$) calculated for $C_{10}H_{13}O_4^-$ = 197, mass found = 197.

Pentafluorophenyl 3-(1-methyl-2,5-dioxocyclohexyl)propanoate, 162



This compound was prepared according to **General Procedure A**.

Esterification with crude diketoacid **161** (300 mg, 1.51 mmol, 1.0 eq), EDC·HCl (569 mg, 2.97 mmol, 2.0 eq), DMAP (9 mg, 0.07 mmol, 0.05 eq), and pentafluorophenol (281 mg, 1.51 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/heptane afforded title compound **162** as a colourless oil that solidified on standing to a white solid (532 mg, 98%).

mp = 54-56 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.84-2.61 (m, 4H, C_4 & C_6), 2.57 (td, *J* = 7.8, 1.4 Hz, 2H, H_9), 2.24 (td, *J* = 7.8, 1.4 Hz, 2H, H_8), 2.14-1.82 (m, 2H, H_5), 1.37 (d, *J* = 1.5 Hz, 3H, H_7);

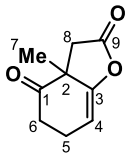
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 209.4 (Quat, C_1 & C_3), 168.8 (Quat, C_{10}, 64.2 (Quat, C_2, 37.8 (CH_2, C_4 & C_5), 28.8 (CH_2, C_9), 28.8 (CH_2, C_8), 22.8 (CH_3, C_7), 17.5 (CH_2, C_5);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.5, −158.1, −162.4;

FTIR (film) ν_{max}/cm^{-1} = 2968, 1788, 1728, 1697, 1520, 1460, 1378, 1319, 1294, 1102, 1026;

Compound **162** was not detected by ACI, EI or ESI mass spectrometry;

3a-Methyl-3,3a,5,6-tetrahydrobenzofuran-2,4-dione, 164



Analogously to a literature procedure,[107] acetic anhydride (1.3 mL, 14.1 mmol, 13 eq) was added to **153** (200 mg, 1.09 mmol, 1.0 eq) and the mixture heated to reflux for 75 minutes. NaOAc (5 mg, 0.05 mmol, 0.05 eq) was added and the mixture heated for a further 150 minutes. The mixture was concentrated, and the residue purified by flash column chromatography, eluting with 3:17 EtOAc/heptane, to afford **164** as an orange oil (111 mg, 61%).

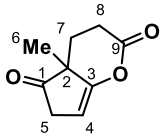
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.49 (dd, *J* = 6.4, 2.8 Hz, 1H, H_4), 3.00 (d, *J* = 18.1 Hz, 1H, H_8), 2.82-2.69 (m, 1H, H_6), 2.69-2.54 (m, 1H, H_5), 2.54-2.36 (m, 2H, $H_{5'}$ & $H_{6'}$), 2.44 (d, *J* = 18.0 Hz, 1H, $H_{8'}$), 1.46 (s, 3H, H_7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 208.7 (Quat, C_1), 171.7 (Quat, C_9), 152.4 (Quat, C_3), 100.0 (CH, C_4), 50.7 (Quat, C_2), 36.8 (CH_2, C_8), 34.1 (CH_2, C_6), 22.9 (CH_3, C_7), 19.5 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2490, 1807, 1698, 1457, 1392, 1320, 1288, 1199, 1140, 1091, 1035;

HRMS (ESI^+) calculated for $C_9H_{11}O_3^+$ = 167.0703, mass found = 167.0703.

4a-Methyl-3,4,4a,6-tetrahydrocyclopenta[*b*]pyran-2,5-dione, 165



Analogously to a literature procedure,[107] acetic anhydride (1.3 mL, 14.1 mmol, 13 eq) was added to **157** (200 mg, 1.09 mmol, 1.0 eq) and the mixture heated to reflux for 75 minutes. NaOAc (5 mg, 0.05 mmol, 0.05 eq) was added and the mixture heated for a further 150 minutes. The mixture was concentrated, and the residue purified by flash column chromatography, eluting with 3:17 EtOAc/heptane, to afford **165** as a pale yellow solid (130 mg, 72%).

mp = 66-68 °C;

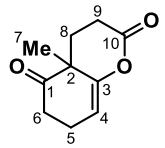
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.41 (dd, *J* = 2.9, 1.8 Hz, 1H, H_4), 3.20 (dd, *J* = 22.3, 1.9 Hz, 1H, H_5), 2.95 (dd, *J* = 22.3, 2.8 Hz, 1H, $H_{5'}$), 2.85-2.66 (m, 2H, H_8), 1.94-1.83 (m, 2H, H_7), 1.31 (s, 3H, H_6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 213.2 (Quat, C_1), 166.6 (Quat, C_9), 154.4 (Quat, C_3), 100.1 (CH, C_4), 45.4 (Quat, C_2), 39.7 (CH_2, C_5), 27.1 (CH_2, C_8), 25.4 (CH_2, C_7), 19.5 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 3111, 1752, 1729, 1703, 1408, 1328, 1288, 1195, 1084, 1043;

HRMS (EI^+) calculated for $C_9H_{10}O_3$ = 166.0624, mass found = 166.0623.

4a-Methyl-4,4a,6,7-tetrahydro-2*H*-chromene-2,5(3*H*)-dione, 166



Analogously to a literature procedure,[107] acetic anhydride (1.3 mL, 14.1 mmol, 13 eq) was added to **161** (217 mg, 1.09 mmol, 1.0 eq) and the mixture heated to reflux for 75 minutes. NaOAc (5 mg, 0.05 mmol, 0.05 eq) was added and the mixture heated for a further 150 minutes. The mixture was concentrated, and the residue purified by flash column chromatography, eluting with 3:17 EtOAc/heptane, to afford **166** as a pale yellow solid (130 mg, 51%).

mp = 45-47 °C;

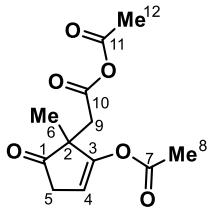
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.57 (t, *J* = 4.1 Hz, 1H, H_4), 2.84-2.72 (m, 1H, H_6), 2.72-2.59 (m, 2H, H_9), 2.57-2.31 (m, 3H, H_5 & H_6), 2.10 (ddd, *J* = 13.9, 9.5, 7.6 Hz, 1H, C_8), 1.92 (ddd, *J* = 13.9, 6.7, 5.1 Hz, 1H, $C_{8'}$), 1.40 (s, 3H, H_7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 210.2 (Quat, C_1), 167.5 (Quat, C_{10}), 151.2 (Quat, C_3), 106.3 (CH, C_4), 45.0 (Quat, C_2), 34.7 (CH_2, C_6), 27.5 (CH_2, C_9), 26.5 (CH_2, C_8), 22.3 (CH_3, C_7), 20.0 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2972, 1758, 1717, 1691, 1454, 1420, 1378, 1329, 1273, 1254, 1191, 1155, 1131, 1096, 1045, 1026;

HRMS (ACI^+) calculated for $C_{10}H_{13}O_3^+$ = 181.0859, mass found = 181.0858.

Acetic 2-(2-acetoxy-1-methyl-5-oxocyclopent-2-en-1-yl)acetic anhydride, 167



Analogously to a literature procedure,[107] acetic anhydride (0.7 mL, 7.6 mmol, 13 eq) was added to **149** (100 mg, 0.59 mmol, 1.0 eq) and the mixture heated to reflux for 75 minutes. NaOAc (3 mg, 0.03 mmol, 0.05 eq) was added and the mixture heated for a further 150 minutes. The mixture was concentrated, and the residue purified by flash column chromatography, eluting with 1:4 EtOAc/heptane, to afford **167** as a colourless oil (91 mg, 61%).

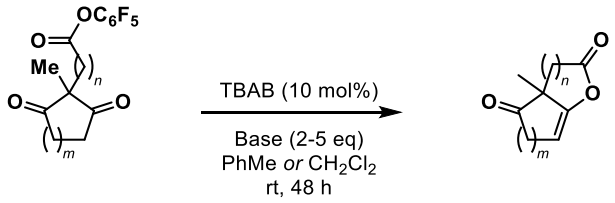
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.62 (dd, *J* = 3.1, 2.0 Hz, 1H, H_4), 3.15 (dd, *J* = 17.3, 3.1 Hz, 1H, H_5), 2.90 (dd, *J* = 17.3, 2.0 Hz, 1H, $H_{5'}$), 2.73 (d, *J* = 26.3 Hz, 1H, H_9), 2.69 (d, *J* = 26.3 Hz, 1H, $H_{9'}$), 2.20 (s, 3H, H_{12}), 2.13 (s, 3H, H_8), 1.26 (d, *J* = 3.3 Hz, 3H, H_6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 215.1 (Quat, C_1), 173.9 (Quat, C_{10}), 169.1 (Quat, C_7), 167.9 (Quat, C_{11}), 148.2 (Quat, C_3), 107.7 (CH, C_4), 53.1 (Quat, C_2), 39.7 (CH_2, C_5), 37.4 (CH_2, C_9), 21.4 (CH_3, C_8), 21.4 (CH_3, C_{12}), 17.8 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 2931, 2852, 1805, 1748 (br), 1472, 1385, 1191, 1157, 1131, 1062, 1027;

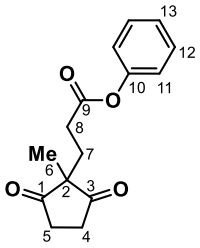
HRMS (ACI^-) calculated for $C_{12}H_{13}O_6^-$ = 253.0718, mass found = 253.0715.

Cyclization Screen of Pentafluorophenyl Esters 154, 158 & 162



A mixture of *the appropriate pentafluorophenyl ester* (1.0 eq) and TBAB (0.1 eq) were dissolved in *the appropriate solvent* ([acid] = 0.1 M) and to this solution was added *the appropriate base* (2.0-5.0 eq). The reaction mixture was stirred for 48 hours and aliquots of the organic phase were analysed directly by reverse-phase HPLC analysis.

Phenyl 3-(1-methyl-2,5-dioxocyclopentyl)propanoate, 168



This compound was prepared according to **General Procedure A**.

Esterification with crude diketoacid **157** (250 mg, 1.36 mmol), EDC·HCl (521 mg, 2.71 mmol), DMAP (8 mg, 0.07 mmol), and phenol (127 mg, 1.36 mmol). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/heptane afforded title compound **168** as a white solid (291 mg, 83%).

mp = 58-60 °C;

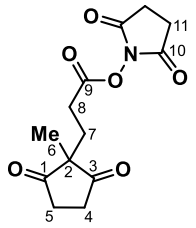
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.32 (m, 2H, H_{12}), 7.24-7.17 (m, 1H, H_{13}), 7.07-7.00 (m, 2H, H_{11}), 2.79 (s, 4H, H_4 & H_5), 2.56 (t, *J* = 7.4 Hz, 2H, H_8), 2.09 (t, *J* = 7.4 Hz, 2H, H_7), 1.17 (s, 3H, H_6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 215.6 (Quat, C_1), 171.5 (Quat, C_9), 150.4 (Quat, C_{10}), 129.5 (CH, C_{12}), 126.0 (CH, C_{13}), 121.5 (CH, C_{11}), 55.3 (Quat, C_2), 34.8 (CH_2, C_4 & C_5), 29.0 (CH_2, C_8), 28.6 (CH_2, C_7), 20.3 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 2930, 1754, 1719, 1593, 1493, 1455, 1419, 1375, 1299, 1192, 1163, 1135, 1072;

HRMS (ESI^+) calculated for $C_{15}H_{17}O_4^+$ = 261.1122, mass found = 261.1121.

_N_-Hydroxysuccinimidyl 3-(1-methyl-2,5-dioxocyclopentyl)propanoate, 169



This compound was prepared according to **General Procedure A**.

Esterification with crude diketoacid **157** (250 mg, 1.36 mmol), EDC·HCl (521 mg, 2.72 mmol), DMAP (8 mg, 0.07 mmol), and *N*-hydroxysuccinimide (156 mg, 1.36 mmol). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/heptane afforded title compound **169** as a white solid (265 mg, 76%).

mp = 120-122 °C;

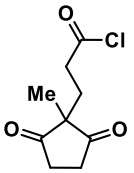
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.82 (dd, *J* = 5.4, 1.8 Hz, 8H, H_4, H_5, H_{11}), 2.64 (dd, *J* = 8.9, 6.9 Hz, 2H, H_8), 2.04 (dd, *J* = 8.9, 6.9 Hz, 2H, H_7), 1.17 (s, 3H, H_6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 214.9 (Quat, C_1 & C_3), 168.9 (Quat, C_9), 167.9 (Quat, C_{10}), 54.8 (Quat, C_2), 34.8 (CH_2, C_4 & C_5), 27.8 (CH_2, C_7), 25.7 (CH_2, C_8), 25.6 (CH_2, C_{11}), 19.3 (CH_3, C_6);

FTIR (film) ν_{max}/cm^{-1} = 2938, 1814, 1783, 1718, 1454, 1420, 1372, 1298, 1205, 1070;

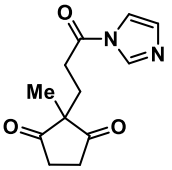
HRMS (ESI^+) calculated for $C_{13}H_{16}O_6N^+$ = 282.0972, mass found = 282.0972.

3-(1-Methyl-2,5-dioxocyclopentyl)propanoyl chloride, 170



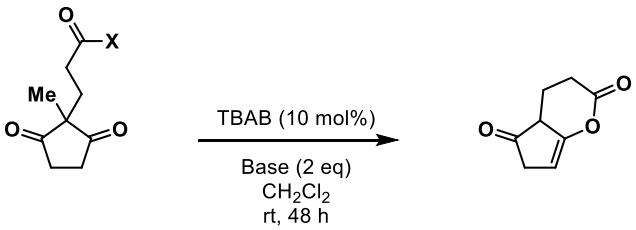
To a stirred solution of **157** (80 mg, 0.43 mmol, 1.0 eq) in CH_2Cl_2 (1.2 mL) was added oxalyl chloride (55 µL, 0.65 mmol, 1.5 eq) followed by 1 drop of *N*,*N*-dimethylformamide. After evolution of gas had ceased (30 minutes), the mixture was concentrated under reduced pressure. The residue was subsequently dissolved in CH_2Cl_2 (4.3 mL) and this 0.1 M solution of **170** in CH_2Cl_2 was used without any further purification.

2-(3-(1*H*-Imidazol-1-yl)-3-oxopropyl)-2-methylcyclopentane-1,3-dione, 171



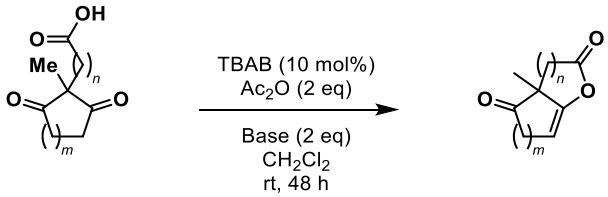
To a solution of **157** (80 mg, 0.43 mmol, 1.0 eq) in CH_2Cl_2 (4.3 mL) was added CDI (70 mg, 0.43 mmol, 1.0 eq), and the mixture was stirred for 2 hours. This 0.1 M solution of **171** in CH_2Cl_2 was used without any further purification.

Cyclization Screen of Activated Esters 168–171



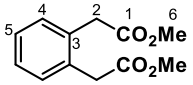
A mixture of *the appropriate pentafluorophenyl ester* (1.0 eq) and TBAB (0.1 eq) were dissolved in *the appropriate solvent* ([acid] = 0.1 M) and to this solution was added *the appropriate base* (2.0 eq). The reaction mixture was stirred for 48 hours and aliquots of the organic phase were analysed directly by reverse-phase HPLC analysis.

Cyclization Screen of Diketoacids 149, 153, 157 & 161



A mixture of *the appropriate diketocarboxylic acid* (1.0 eq) and TBAB (0.1 eq) were dissolved in *the appropriate solvent* ([acid] = 0.1 M) and to this solution was added acetic anhydride (2.0 eq) and *the appropriate base* (2 eq). The reaction mixture was stirred for 48 hours and aliquots of the organic phase were analysed directly by reverse-phase HPLC analysis.

Dimethyl 2,2'-(1,2-phenylene)diacetate, 530



According to a literature procedure,[159] PTSA (20 mg, 0.10 mmol, 0.01 eq) was added to a stirred solution of 1,2-benzenediacetic acid (2.0 g, 10.3 mmol, 1.0 eq) in methanol (20 mL). The solution was heated to reflux for 14 hours and then concentrated under reduced pressure. The crude residue was dissolved in EtOAc (30 mL) and washed with aqueous saturated $NaHCO_3$ (30 mL) and then brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, to afford **530** as a colourless oil (2.18 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.19 (m, 4H, H_4 & H_5), 3.65 (d, *J* = 1.2 Hz, 4H, H_2), 3.61 (d, *J* = 1.2 Hz, 6H, H_6);

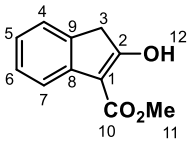
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 171.7 (Quat, C_1), 133.1 (Quat, C_3), 130.9 (CH, C_4), 127.7 (CH, C_5), 52.1 (CH_3, C_6), 38.8 (CH_2, C_2);

FTIR (film) ν_{max}/cm^{-1} = 3025, 2954, 1731, 1435, 1338, 1255, 1194, 1156, 1091, 1009;

LRMS (ESI$^+$) calculated for $C_{12}H_{14}O_4Na^+$ = 245, mass found = 245.

The data matched those of the literature.[159]

Methyl 2-oxo-1-indanecarboxylate, 181



According to a literature procedure,[159] sodium (413 mg, 18.0 mmol, 2.0 eq) was added portionwise to a stirred solution of **530** (2.00 g, 9.0 mmol, 2.0 eq) in benzene (20 mL). The mixture was heated to reflux for 15 hours and then cooled to room temperature before being quenched by slow addition of 2 M HCl (10 mL). The biphasic mixture was extracted with EtOAc (3 × 30mL) and the combined organic extracts washed with brine (20 mL). The organic layer was dried over

Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **181** as a pale yellow solid (1.48 g, 87%).

mp = 65-67 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H (enol) = 10.94 (s, 1H, H_{12}), 7.51 (d, *J* = 7.6 Hz, 1H, H_7), 7.31-7.14 (m, 2H, H_4 & H_6), 7.03 (td, *J* = 7.5, 1.4 Hz, 1H, H_5), 3.88 (d, *J* = 1.3 Hz, 3H, H_{11}), 3.50 (s, 2H, H_3);

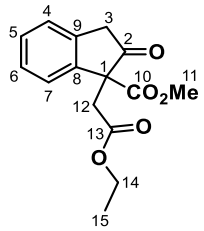
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 180.7 (Quat, C_2), 169.4 (Quat, C_{10}), 139.5 (Quat, C_8), 133.1 (Quat, C_9), 127.1 (CH, C_4), 123.8 (CH, C_5), 123.7 (CH, C_6), 120.2 (CH, C_7), 105.2 (Quat, C_1), 51.6 (CH_3, C_{11}), 37.7 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3047, 2954, 1653, 1589, 1475, 1444, 1384, 1356, 1339, 1305, 1230, 1196, 1052, 1025;

LRMS (ESI^-) calculated for $C_{11}H_9O_3^-$ = 189, mass found = 189.

The data matched those of the literature.[159]

Methyl 1-(2-ethoxy-2-oxoethyl)-2-oxo-2,3-dihydro-1*H*-indene-1-carboxylate, 182



According to a literature procedure,[111] to a solution of **181** (4.00 mg, 21.0 mmol, 1.0 eq) in DMF (16.7 mL) was added ethyl bromoacetate (4.66 mL, 42.0 mmol, 2.0 eq) followed by DBU (6.26 mL, 42.0 mmol, 2.0 eq). The reaction mixture was stirred for 17 hours, quenched by addition of water (150 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (50 mL), 1 M aqueous HCl (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **182** as a pale yellow solid (4.10 g, 71%).

mp = 60-62 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.41-7.15 (m, 4H, H_4, H_5, H_6 & H_7), 3.98-3.84 (m, 2H, H_{14}), 3.78 (dd, *J* = 41.2, 22.3 Hz, 2H, H_3), 3.62 (d, *J* = 1.4 Hz, 3H, H_{11}), 3.40 (dd, *J* = 47.6, 17.6 Hz, 2H, H_{12}), 1.04 (td, *J* = 7.2, 1.4 Hz, 3H, H_{15});

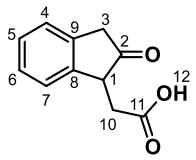
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 211.0 (Quat, C_2), 169.8 (Quat, C_{10}), 169.7 (Quat, C_{13}), 139.8 (Quat, C_8), 138.5 (Quat, C_9), 128.8 (CH, C_{Ar}), 127.8 (CH, C_{Ar}), 125.1 (CH, C_{Ar}), 123.3 (CH, C_{Ar}), 61.9 (Quat, C_1), 60.9 (CH_2, C_{14}), 53.1 (CH_3, C_{11}), 43.3 (CH_2, C_3), 39.1 (CH_2, C_{12}), 13.8 (CH_3, C_{15});

FTIR (film) ν_{max}/cm^{-1} = 2983, 1764, 1731, 1479, 1462, 1435, 1391, 1373, 1344, 1247, 1226, 1142, 1071, 1030;

HRMS (ESI^+) calculated for $C_{15}H_{16}O_5Na^+$ = 299.0890, mass found = 299.0888.

The data matched those of the literature.[111]

2-(2-Oxo-2,3-dihydro-1*H*-inden-1-yl)acetic acid, 183



According to a literature procedure,[111] a solution of **182** (300 mg, 1.09 mmol, 1.0 eq) was refluxed in 1:1 6 M HCl/AcOH (2.56 mL) for 2 hours. The resulting mixture was cooled to room temperature, diluted in water (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and azeotroped with toluene (3 × 5 mL). The residue was purified by flash column chromatography, eluting with 30:70:1 EtOAc/petrol 40-60/AcOH to afford **183** as an orange oil (193 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.28-7.13 (m, 4H, H_4, H_5, H_6, H_7), 3.70 (t, *J* = 5.5 Hz, 1H, H_1), 3.53 (s, 2H, H_3), 3.03-2.86 (m, 2H, H_{10});

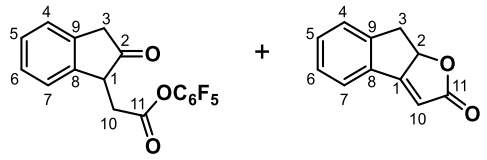
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 176.9 (Quat, C_{11}), 140.2 (Quat, C_8), 137.2 (Quat, C_9), 127.9 (CH, C_{Ar}), 127.7 (CH, C_{Ar}), 125.0 (CH, C_{Ar}), 124.0 (CH, C_{Ar}), 48.7 (CH, C_1), 43.1 (CH_2, C_3), 35.0 (CH_2, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 3027, 2922, 1744, 1709, 1481, 1402, 1306, 1281, 1196, 1172, 1145;

HRMS (ESI^-) calculated for $C_{11}H_9O_3^-$ = 189.0557, mass found = 189.0557.

N.B. *C*-2 not observed in ^{13}C NMR spectrum, presumably due to rapid interconversion with lactone. The data matched those of the literature.[111]

Pentafluorophenyl 2-(2-oxo-2,3-dihydro-1*H*-inden-1-yl)acetate, 184 & 8,8a-dihydro-2*H*-indeno[2,1-*b*]furan-2-one, 185



Prepared according to **General Procedure A**.

Esterification with crude diketoacid **183** (150 mg, 0.79 mmol, 1.0 eq), EDC·HCl (228 mg, 1.19 mmol, 1.5 eq), DMAP (5 mg, 0.04 mmol, 0.05 eq), and pentafluorophenol (144 mg, 0.78 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **184** as a yellow solid (60 mg, 28%) and **185** as an orange oil (34 mg, 8%).

184:

mp = 56-58 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.37-7.30 (m, 4H, H_4, H_5, H_6 & H_7), 3.95 (t, *J* = 5.7 Hz, 1H, H_1), 3.80-3.51 (m, 2H, H_3), 3.45-3.10 (m, 2H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 214.8 (Quat, C_2), 167.7 (Quat, C_{11}), 139.4 (Quat, C_8), 137.0 (Quat, C_9), 128.3 (CH, C_{Ar}), 127.9 (Quat, C_{Ar}), 125.1 (Quat, C_{Ar}), 123.9 (Quat, C_{Ar}), 48.7 (CH, C_1), 43.0 (CH_2, C_3), 34.3 (CH_2, C_{10});

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.3, −157.6, −162.1;

FTIR (film) ν_{max}/cm^{-1} = 2917, 1789, 1756, 1519, 1481, 1361, 1103;

HRMS (ACI^+) calculated for $C_{17}H_{10}F_5O_3^+$ = 357.0545, mass found = 357.0537.

185:

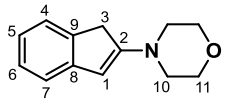
^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.65 (d, *J* = 7.4 Hz, 1H, H_7), 7.48 (dd, *J* = 7.5, 1.4 Hz, 1H, H_4), 7.45-7.37 (m, 2H, H_5 & H_6), 6.04 (d, *J* = 2.2 Hz, 1H, H_{10}), 5.50 (td, *J* = 7.4, 2.3 Hz, 1H, H_2), 3.48 (dd, *J* = 14.5, 7.5 Hz, 1H, H_3), 2.90 (dd, *J* = 14.5, 7.2 Hz, 1H, $H_{3'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 175.3 (Quat, C_{11}), 174.0 (Quat, C_1), 145.7 (Quat, C_9), 132.2 (CH, C_4), 131.9 (Quat, C_8), 128.4 (CH, H_5 *or* H_6), 126.8 (CH, H_5 *or* H_6), 124.5 (CH, C_7), 108.9 (CH, C_{10}), 86.0 (CH, C_2), 36.5 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2918, 1764, 1737, 1651, 1521, 1461, 1331, 1154, 1132, 1099, 1072, 1050;

HRMS (ACI$^+$) calculated for $C_{11}H_9O_2^+$ = 173.0597, mass found = 173.0596.

4-(1*H*-Inden-2-yl)morpholine, 192



According to a literature procedure,[114] morpholine (3.92 mL, 45.3 mmol, 2.0 eq) was dried by refluxing in benzene (23 mL) with a Dean-Stark apparatus for 2 hours. 2-Indanone (3.00 g, 22.7 mmol, 1.0 eq) was added and the mixture refluxed for a further 14 hours. The solution was allowed to cool at which point the product crystallized from the reaction mixture and was filtered and washed with benzene (5 mL). The solid was then recrystallized from benzene a further two times to afford **192** as an off-white solid (2.19 g, 48%).

mp = 188-190 °C;

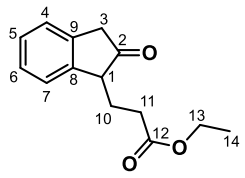
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.16 (d, *J* = 7.2 Hz, 1H, H_4), 7.07 (td, *J* = 7.5, 1.1 Hz, 1H, H_6), 7.00 (d, *J* = 7.4 Hz, 1H, H_7), 6.84 (td, *J* = 7.4, 1.3 Hz, 1H, H_5), 5.50 (s, 1H, H_1), 3.80-3.66 (m, 4H, H_{11}), 3.31 (s, 2H, H_3), 3.13 2.93 (m, 4H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.6 (Quat, C_2), 146.6 (Quat, C_8), 137.1 (Quat, C_9), 126.7 (CH, C_6), 122.9 (CH, C_5), 121.1 (CH, C_4), 117.8 (CH, C_7), 100.5 (CH, C_1), 66.4 (CH_2, C_{11}), 48.4 (CH_2, C_{10}), 37.0 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3079, 2961, 2888, 2845, 1581, 1566, 1462, 1447, 1388, 1277, 1261, 1232, 1190, 1120, 1016;

LRMS (ESI$^+$) calculated for $C_{13}H_{16}ON^+$ = 202, mass found = 202.

Ethyl 3-(2-oxo-2,3-dihydro-1*H*-inden-1-yl)propanoate, 193



According to a literature procedure,[113] to a solution of **192** (5.0 g, 24.8 mmol, 1.0 eq) in DMF (15 mL) was added ethyl 3-bromopropionate **189** (3.50 mL, 27.3 mmol, 1.1 eq) in DMF (5 mL) and the mixture heated to reflux for 3 hours. The solution was cooled to room temperature, 5 M HCl (5.47 mL, 27.3 mmol, 1.1 eq) was added and the mixture heated to reflux again for a further hour. The mixture was cooled to room temperature, adjusted to pH 4 with 1 M aqueous HCl (if needed) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with 1 M aqueous HCl (20 mL) and water (30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography, eluting with 3:47 to 1:9 EtOAc/petrol 40-60, to afford **193** as a yellow oil (2.06 g, 25%).

mp = 188-190 °C;

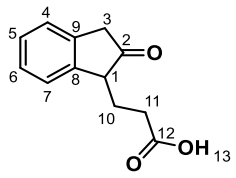
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.30 (m, 4H, H_4, H_5, H_6 & H_7), 4.08 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.54 (d, *J* = 4.6 Hz, 3H, H_1 & H_3), 2.39 (t, *J* = 7.5 Hz, 2H, H_{11}), 2.27 (m, 1H, H_{10}), 2.15 (m, 1H, $H_{10'}$), 1.22 (t, *J* = 7.1 Hz, 3H, C_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 217.2 (Quat, C_2), 173.0 (Quat, C_{12}), 141.1 (Quat, C_8) 136.9 (Quat, C_9), 127.7 (CH, C_{Ar}), 127.6 (CH, C_{Ar}), 124.9 (CH, C_{Ar}), 124.6 (CH, C_{Ar}), 60.5 (CH_2, C_{13}), 51.7 (CH, C_1), 43.4 (CH_2, C_3), 30.8 (CH_2, C_{11}), 26.3 (CH_2, C_{10}), 14.2 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 2981, 2933, 1730 (br), 1480, 1463, 1447, 1375, 1307, 1234, 1181, 1162, 1142, 1096, 1078, 1026;

HRMS (ESI$^+$) calculated for $C_{14}H_{16}O_3Na^+$ = 255.0992, mass found = 255.0991.

3-(2-Oxo-2,3-dihydro-1*H*-inden-1-yl)propanoic acid, 194

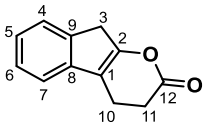


Lithium hydroxide monohydrate (853 mg, 20.3 mmol, 3.0 eq) was added to a stirred solution of **193** (1.58 g, 6.80 mmol, 1.0 eq) in 1:1 ethanol/water (16 mL). The solution was stirred for 2 hours and then extracted with Et_2O (2 × 15 mL) and the organic extracts discarded. The aqueous layer was acidified to pH 1 with 3 M HCl (6 mL) and extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford **194** as an orange oil that was used without any further purification (1.21 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.31 (m, 4H, H_4, H_5, H_6 & H_7), 3.55 (m, 2H, H_3), 2.87-2.70 (m, 1H, H_1), 2.57-2.40 (m, 2H, H_{11}), 2.29 (m, 1H, H_{10}), 2.15 (m, 1H, $H_{10'}$);

LRMS (ESI^-) calculated for $C_{12}H_{11}O_3^-$ = 203, mass found = 203.

4,9-Dihydroindeno[2,1-*b*]pyran-2(3*H*)-one, 195



Prepared according to **General Procedure A**.

Esterification with crude diketoacid **194** (150 mg, 0.734 mmol, 1.0 eq), EDC·HCl (211 mg, 1.10 mmol, 1.5 eq), DMAP (5 mg, 0.04 mmol, 0.05 eq), and pentafluorophenol (135 mg, 0.733 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **195** as an orange oil (89 mg, 65%).

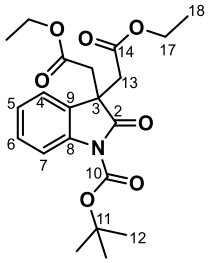
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 (dt, *J* = 7.2, 0.7 Hz, 1H, H_4), 7.32 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H, H_6), 7.19 (m, 2H, H_5 & H_7), 3.53 (t, *J* = 2.6 Hz, 2H, H_3), 2.91 (td, *J* = 7.5, 1.0 Hz, 2H, H_{11}), 2.83-2.77 (m, 2H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.5 (Quat, C_{12}), 155.4 (Quat, C_2), 141.7 (Quat, C_9), 136.6 (Quat, C_8), 126.9 (CH, C_6), 124.4 (CH, C_5), 123.9 (CH, C_4), 118.2 (CH, C_7), 114.8 (Quat, C_1), 35.4 (CH_2, C_3), 28.4 (CH_2, C_{11}), 17.2 (CH_2, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 2917, 2360, 1765, 1665, 1536, 1518, 1461, 1393, 1337, 1316, 1290, 1244, 1151, 1115, 1093;

HRMS (ACl^+) calculated for $C_{12}H_{11}O_2^+$ = 187.0753, mass found = 187.0753.

Diethyl 2,2'-(1-(*tert*-butoxycarbonyl)-2-oxoindoline-3,3-diyl)diacetate, 213



A solution of *N*-Boc oxindole (1.00 g, 4.29 mmol, 1.0 eq), potassium carbonate (2.37 g, 17.1 mmol, 4.0 eq) and ethyl bromoacetate (0.95 mL, 8.57 mmol, 2.0 eq) in DMF (10 mL) was stirred for 24 hours. The solution was diluted in water (100 mL), neutralized with 1 M aqueous HCl (20 mL), and extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with 1:9 to 1:4 EtOAc/petrol 40-60, to afford **213** as a white solid (1.58 g, 77%).

mp = 92-94 °C;

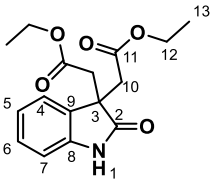
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.87 (d, *J* = 8.2 Hz, 1H, H_7), 7.35-7.27 (m, 1H, H_6), 7.27-7.20 (m, 1H, H_4), 7.11 (t, *J* = 7.5 Hz, 1H, H_5), 3.99-3.80 (m, 4H, H_{17}), 3.04-2.87 (m, 4H, H_{13}), 1.65 (s, 9H, H_{12}), 1.02 (td, *J* = 7.2, 1.5 Hz, 6H, H_{18});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 177.1 (Quat, C_2), 168.8 (Quat, C_{14}), 149.3 (Quat, C_{10}), 140.6 (Quat, C_8), 128.9 (CH, C_6), 128.6 (Quat, C_9), 124.3 (CH, C_5), 122.7 (CH, C_4), 115.2 (CH, C_7), 84.2 (Quat, C_{11}), 60.9 (CH_2, C_{17}), 47.5 (Quat, C_3), 42.3 (CH_2, C_{13}), 28.1 (CH_3, C_{12}), 13.7 (CH_3, C_{18});

FTIR (film) ν_{max}/cm^{-1} = 2982, 2936, 1795, 1772, 1727, 1609, 1480, 1466, 1394, 1354, 1299, 1251, 1150, 1118, 1088, 1052, 1026, 1007;

HRMS (ESI^+) calculated for $C_{21}H_{27}O_7NNa^+$ = 428.1680, mass found = 428.1675.

Diethyl 2,2'-(2-oxoindoline-3,3-diyl)diacetate, 214



213 (900 mg, 2.22 mmol, 1.0 eq) was dissolved in a 1:1 mixture of TFA/CH_2Cl_2 (10 mL) and stirred for 30 minutes. The solution was neutralized by addition of saturated aqueous $NaHCO_3$ (80 mL) and the biphasic mixture extracted with CH_2Cl_2 (3 × 40 mL) The combined extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with 1:2 EtOAc/petrol 40-60, to afford **214** as a white solid (734 mg, quant).

mp = 64-66 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.42 (s, 1H, H_1), 7.28 (d, *J* = 7.4 Hz, 1H, C_4), 7.21 (t, *J* = 7.7 Hz, 1H, H_6), 6.99 (t, *J* = 7.5 Hz, 1H, H_5), 6.89 (d, *J* = 7.7 Hz, 1H, H_7), 3.97 (dq, *J* = 6.9, 6.9 Hz, 4H, H_{12}), 2.96 (dd, *J* = 53.9, 15.9 Hz, 4H, H_{10}), 1.07 (td, *J* = 7.1, 1.4 Hz, 6H, H_{13});

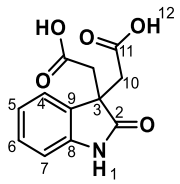
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 180.3 (Quat, C_2), 169.5 (Quat, C_{11}), 141.5 (Quat, C_8), 130.4 (Quat, C_9), 128.7 (CH, C_6), 123.9 (CH, C_4), 122.3 (CH, C_5), 109.9 (CH, C_7), 60.7 (CH_2, C_{12}), 47.6 (Quat, C_3), 40.8 (CH_2, C_{10}), 13.9 (CH_3, C_{13});

FTIR (film) ν_{max}/cm^{-1} = 3258, 2982, 1727, 1620, 1473, 1371, 1338, 1301, 1270, 1189, 115, 1025;

HRMS (ESI^+) calculated for $C_{16}H_{19}O_5NNa^+$ = 328.1155, mass found = 328.1158.

The data matched those of the literature.[160]

2,2′-(2-Oxoindoline-3,3-diyl)diacetic acid, 215



Potassium hydroxide (1.07 g, 19.1 mmol, 8.0 eq) was added to a solution of **214** (734 mg, 2.40 mmol, 1.0 eq) in ethanol (40.2 mL) and water (5.02 mL). The reaction mixture was stirred for 14 hours and then concentrated under reduced pressure. The residue was dissolved in water (20 mL), washed with chloroform (15 mL), and the organic extract discarded. The aqueous phase was acidified to pH 2 with 3 M HCl and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to afford **215** as a white solid that was used without any further purification (474 mg, 79%).

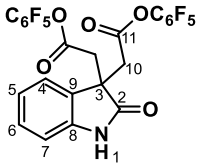
mp = 184-186 °C;

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H = 12.11 (s, 2H, H_{12}), 10.36 (s, 1H, H_1), 7.28 (dd, *J* = 7.4, 1.3 Hz, 1H, H_4), 7.14 (td, *J* = 7.7, 1.3 Hz, 1H, H_6), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H, H_5), 6.79 (dt, *J* = 7.5, 0.8 Hz, 1H, H_7), 2.89 (d, *J* = 15.9 Hz, 2H, H_{10}), 2.66 (d, *J* = 15.9 Hz, 2H, $H_{10'}$);

LRMS (ESI^-) calculated for $C_{12}H_{10}NO_6^-$ = 248, mass found = 248.

The data matched those of the literature.[160]

Dipentafluorophenyl 2,2′-(2-oxoindoline-3,3-diyl)diacetate, 216



Prepared according to **General Procedure A**.

Esterification with crude diacid **215** (250 mg, 1.00 mmol, 1.0 eq), EDC·HCl (500 mg, 2.60 mmol, 2.6 eq), DMAP (10 mg, 0.08 mmol, 0.08 eq), and pentafluorophenol (370 mg, 2.00 mmol, 2.0 eq). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded title compound **216** as a yellow solid (531 mg, 91%).

mp = 64-66 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.89 (s, 1H, H_1), 7.43 (dt, *J* = 7.5, 0.6 Hz, 1H, H_4), 7.33 (td, *J* = 7.8, 1.2 Hz, 1H, H_6), 7.13 (td, *J* = 7.6, 1.0 Hz, 1H, H_5), 6.96 (dt, *J* = 7.8, 0.8 Hz, 1H, H_7), 3.51 (d, *J* = 16.4 Hz, 2H, H_{10}), 3.34 (d, *J* = 16.4 Hz, 2H, $H_{10'}$);

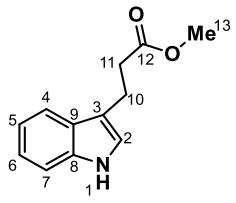
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 177.9 (Quat, C_2), 165.5 (Quat, C_{11}), 140.9 (Quat, C_8), 129.7 (CH, C_6), 128.4 (Quat, C_9), 124.0 (CH, C_4), 123.3 (CH, C_5), 110.4 (CH, C_7), 47.1 (Quat, C_3), 39.3 (CH_2, C_{10});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.1, −157.2, −161.9;

FTIR (film) ν_{max}/cm^{-1} = 3229, 2924, 2361, 2339, 1789, 1722, 1620, 1520, 1473, 1337, 1188, 1103;

HRMS (ESI^+) calculated for $C_{24}H_9O_5F_{10}N^+$ = 604.0213, mass found = 604.0211.

Methyl 3-(1*H*-indol-3-yl)propanoate, 218



According to a literature procedure,[161] indole-3-propionic acid (3.00 g, 15.9 mmol, 1.0 eq) and conc H_2SO_4 (0.30 mL, 0.3 eq) in methanol (48 mL) were heated to reflux for 5 hours. The reaction mixture was then concentrated under reduced pressure, diluted in water (50 mL), and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded title compound **218** as a white solid (3.17 g, 98%).

mp = 68-70 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.99 (s, 1H, H_1), 7.62 (d, *J* = 7.8 Hz, 1H, H_4), 7.36 (dd, *J* = 8.2, 1.3 Hz, 1H, H_7), 7.21 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H, H_6), 7.14 (td, *J* = 7.5, 6.9, 1.2 Hz, 1H, H_5), 7.01 (br s, 1H, H_2), 3.69 (d, *J* = 1.2 Hz, 3H, H_{13}), 3.12 (dd, *J* = 8.3, 7.1 Hz, 2H, H_{10}), 2.74 (dd, *J* = 8.3, 7.1 Hz, 2H, H_{11});

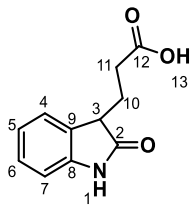
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.9 (Quat, C_{12}), 136.3 (Quat, C_8), 127.2 (Quat, C_9), 122.1 (CH, C_6), 121.4 (CH, C_2), 119.4 (CH, C_5), 118.7 (CH, C_4), 115.0 (Quat, C_3), 111.2 (CH, C_7), 51.6 (CH_3, C_{13}), 34.8 (CH_2, C_{11}), 20.7 (CH_2, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 3411, 2951, 1723, 1620, 1489, 1457, 1436, 1339, 1269, 1226, 1201, 1162, 1124, 1095, 1071, 1011;

HRMS (ACl^+) calculated for $C_{12}H_{14}O_2N^+$ = 204.1019, mass found = 204.1021.

The data matched those of the literature.[162]

3-(2-Oxoindolin-3-yl)propanoic acid, 219



Analogously to a literature procedure,[163] Acetic acid (3.0 mL, 52.5 mmol, 7.1 eq) and concentrated HCl (18.3 mL, 221 mmol, 30.0 eq) were added to a solution of **218** (1.50 g, 7.38 mmol, 1.0 eq) in DMSO (7.90 mL, 111 mmol, 15.0 eq). The reaction mixture was stirred for 2.5 hours at room temperature and then quenched by addition of water (80 mL), and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with 10% aqueous sodium chloride (30 mL), dried over $MgSO_4$ and concentrated. Purification *via* flash column chromatography, eluting with 1:1 to 1:0 EtOAc/petrol 40-60, afforded title compound **219** as a white solid (765 mg, 50%).

mp = 148-150 °C;

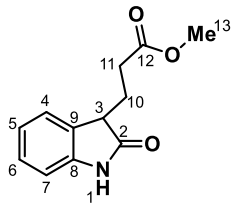
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H = 12.16 (s, 1H, H_{13}), 10.40 (s, 1H, H_1), 7.26 (d, *J* = 7.4 Hz, 1H, H_4), 7.18 (t, *J* = 7.6 Hz, 1H, H_6), 6.96 (t, *J* = 7.5 Hz, 1H, H_5), 6.83 (d, *J* = 7.7 Hz, 1H, H_7), 3.46 (t, *J* = 6.4 Hz, 1H, H_3), 2.38-2.14 (m, 2H, H_{11}), 2.03 (dtd, *J* = 9.1, 6.8, 4.6 Hz, 2H, H_{10});

^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ_C = 179.0 (Quat, C_2), 174.3 (Quat, C_{12}), 143.1 (Quat, C_8), 129.6 (Quat, C_9), 128.2 (CH, C_6), 124.5 (CH, C_4), 121.8 (CH, C_5), 109.7 (CH, C_7), 44.6 (CH, C_3), 30.5 (CH_2, C_{11}), 25.8 (CH_2, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 3217, 1704, 1621, 1486, 1471, 1409, 1341, 1222, 1104;

LRMS (ESI^-) calculated for $C_{11}H_{10}O_3N^-$ = 204, mass found = 204.

Methyl 3-(2-oxoindolin-3-yl)propanoate, 220



Concentrated aqueous HCl (4.23 mL, 47.1 mmol, 17.8 eq) was added to a solution of indole-3-propionic acid **217** (500 mg, 2.64 mmol, 1.0 eq) in DMSO (1.75 mL, 22.9 mmol, 8.65 eq) dropwise. The reaction mixture was stirred for 30 minutes upon which it was diluted in water (30 mL) and extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in methanol (12.3 mL) and cooled to 0 °C. Thionyl chloride (575 µL, 7.93 mmol, 3.0 eq) was added dropwise and the reaction mixture stirred for 2 hours. After 2 hours had elapsed, the solution was concentration and then dissolved in CH_2Cl_2 (20 mL). This solution was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried over Na_2SO_4 and concentrated. Purification *via* flash column chromatography, eluting with 2:3 EtOAc/petrol 40-60, afforded title compound **220** as a white solid (493 mg, 85%).

mp = 75-77 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.11 (s, 1H, H_1), 7.25-7.14 (m, 2H, H_4 & H_6), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H, H_5), 6.91 (d, *J* = 7.6 Hz, 1H, H_7), 3.62 (s, 3H, H_{13}), 3.57-3.51 (m, 1H, H_3), 2.57-2.43 (m, 1H, H_{11}), 2.43-2.18 (m, 3H, H_{10} & $H_{11'}$);

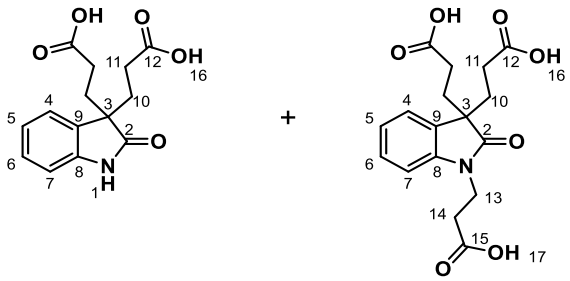
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 180.1 (Quat, C_2), 173.4 (Quat, C_{12}), 141.7 (Quat, C_8), 128.7 (Quat, C_9), 128.2 (CH, C_6), 124.2 (CH, C_4), 122.4 (CH, C_5), 109.9 (CH, C_7), 51.7 (CH_3, C_{13}), 44.9 (CH, C_3), 30.1 (CH_2, C_{11}), 25.5 (CH_2, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 3247, 2981, 1701 (br), 1620, 1486, 1471, 1437, 1376, 1332, 1212, 1173, 1103, 1016;

LRMS (ESI^+) calculated for $C_{12}H_{13}O_3NNa^+$ = 242, mass found = 242.

The data matched those of the literature.[164]

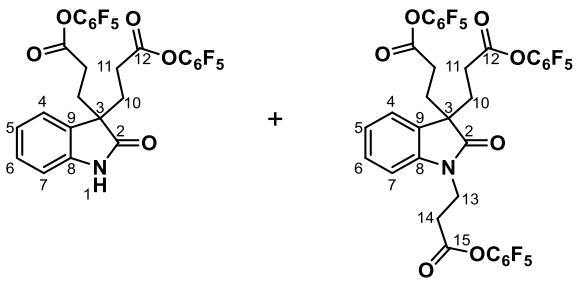
3,3′-(2-Oxoindoline-3,3-diyl)dipropionic acid, 221 and 3,3′,3″-(2-oxoindoline-1,3,3-triyl)tripropionic acid, 222



According to a literature procedure,[116b] sodium (73 mg, 3.15 mmol, 1.15 eq) was dissolved in ethanol (3.0 mL) and heated to reflux for 20 minutes. At this temperature, a solution of **220** (600 mg, 2.74 mmol, 1.0 eq) in ethanol (3 mL) was added, followed by methyl acrylate (273 µL, 3.01 mmol, 1.1 eq). The reaction mixture was heated to reflux for a further 3 hours before 3.75 M aqueous NaOH (620 µL, 2.33 mmol, 0.85 eq) was added and the resulting mixture stirred for a further 2.5 hours. The reaction mixture was cooled to room temperature, diluted in water (20 mL) and washed with Et_2O (10 mL). The aqueous layer was cooled to 0 °C, and acidified to pH 1 with 1 M aqueous HCl. The solution was extracted with EtOAc (3 × 10 mL), and the combined organic extracts dried over Na_2SO_4 and concentrated under reduced pressure to afford **221** and **222** in a 2.5:1 ratio (695 mg, 70%). This mixture was used without any purification for the next step.

LRMS (ESI^-) calculated for $C_{14}H_{15}O_5N^-$ = 276, mass found = 276; LRMS (ESI^-) calculated for $C_{17}H_{19}O_7N^-$ = 348, mass found = 348.

Tripentafluorophenyl 3,3′-(2-oxoindoline-3,3-diyl)dipropionate, 223 and tripentafluorophenyl 3,3′,3″-(2-oxoindoline-1,3,3-triyl)tripropionate, 531



Prepared according to **General Procedure A**.

Esterification with a 2.5:1 mixture of crude diacids **221** and **222** (695 mg, 1.0 eq), EDC·HCl (1.34 mg, 6.99 mmol), DMAP (10 mg, 0.09 mmol), and pentafluorophenol (1.09 g, 5.92 mmol). Purification *via* flash column chromatography, eluting with 3:17 to 1:4 EtOAc/petrol 40-60, afforded title compounds **223** as a yellow gum (740 mg, 84%) and **531** as a yellow gum (518 mg, 92%).

223:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.23 (s, 1H, H_1), 7.33 (dd, *J* = 8.4, 7.1 Hz, 1H, H_6), 7.26 (d, *J* = 7.4 Hz, 1H, H_4), 7.17 (t, *J* = 7.5 Hz, 1H, H_5), 7.00 (d, *J* = 7.7 Hz, 1H, H_7), 2.64-2.38 (m, 4H, H_{10} & H_{11}), 2.39-2.20 (m, 4H, $H_{10'}$ & $H_{11'}$)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 179.8 (Quat, C_2), 168.4 (Quat, C_{12}), 140.6 (Quat, C_8), 129.5 (Quat, C_9), 129.2 (CH, C_6), 123.6 (CH, C_4), 123.6 (CH, C_5), 110.4 (CH, C_7), 51.3 (Quat, C_3), 31.9 (CH_2, C_{11}), 28.4 (CH_2, C_{10});

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.6, −157.7, −162.1;

FTIR (film) ν_{max}/cm^{-1} = 3223, 2981, 1788, 1711, 1621, 1519, 1473, 1451, 1373, 1277, 1223, 1102;

HRMS (ESI^+) calculated for $C_{26}H_{13}O_5F_{10}Na^+$ = 632.0526, mass found = 632.0524.

531:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 (t, *J* = 7.7 Hz, 1H, H_6), 7.29 (d, *J* = 7.3 Hz, 1H, H_4), 7.20 (t, *J* = 7.5 Hz, 1H, H_5), 7.05 (d, *J* = 7.9 Hz, 1H, H_7), 4.19 (t, *J* = 6.8 Hz, 2H, H_{13}), 3.19 (t, *J* = 6.7 Hz, 2H, H_{14}), 2.45 (m, 4H, H_{10} & H_{11}), 2.28 (m, 4H, $H_{10'}$ & $H_{11'}$);

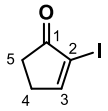
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 178.1 (Quat, C_2), 168.3 (Quat, C_{12}), 167.2 (Quat, C_{15}), 142.2 (Quat, C_8), 129.3 (CH, C_6), 129.1 (Quat, C_9), 123.9 (CH, C_5), 123.5 (CH, C_4), 108.9 (CH, C_7), 50.7 (Quat, C_3), 35.8 (CH_2, C_{14}), 31.9 (CH_2, C_{11}), 31.3 (CH_2, C_{13}), 28.2 (CH_2, C_{10});

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.7, −157.7, −162.2;

FTIR (film) ν_{max}/cm^{-1} = 2980, 1787, 1714, 1613, 1518, 1489, 1469, 1374, 1101;

HRMS (ESI^+) calculated for $C_{35}H_{17}O_7NF_{15}^+$ = 848.0760, mass found = 848.0761.

2-Iodocyclopent-2-enone, 233



According to a literature procedure,[165] potassium carbonate (10.1 g, 73.1 mmol, 1.2 eq), iodine (23.2 g, 91.4 mmol, 1.5 eq) and DMAP (1.40 g, 12.2 mmol, 0.2 eq) were added to a solution of cyclopentenone (5.1 mL, 60.9 mmol, 1.0 eq) in 1:1 THF/water (250 mL). The mixture was stirred for 5 hours, then diluted with EtOAc (300 mL) and ice-cooled saturated aqueous $Na_2S_2O_3$ (200 mL). The phases were separated and the aqueous phase was extract with EtOAc (2 × 100 mL). The combined organic phases were washed with 0.1 M aqueous HCl (150 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, to afford **233** as a white solid (10.1 g, 80%).

mp = 65-67 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.96 (t, *J* = 2.9 Hz, 1H, H_3), 2.84-2.65 (m, 2H, H_4), 2.54-2.35 (m, 2H, H_3);

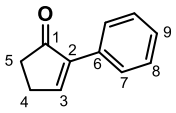
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 204.1 (Quat, C_1), 169.7 (CH, C_3), 102.9 (Quat, C_2), 31.3 (CH_2, C_4), 31.0 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2918, 1794, 1704, 1575, 1430, 1398, 1283, 1230, 1154;

LRMS (ESI^+) calculated for $C_5H_6IO^+$ = 209, mass found = 209.

The data matched those of the literature.[165]

2-Phenylcyclopent-2-enone, 234



According to a literature procedure,[166] to a solution of **233** (5.20 g, 25.0 mmol, 1.0 eq) in 1:1 DME/water (100 mL) were added Na_2CO_3 (5.30 g, 50.0 mmol, 2.0 eq), phenylboronic acid (6.10 g, 50.0 mmol, 2.0 eq) and 10% Pd/C (1.33 g, 1.25 mmol, 0.05 eq). The mixture was stirred for

20 hours before the Pd/C was filtered off and washed with Et_2O (the catalyst could be reused for future cross-coupling experiments). The remaining solution was extracted with Et_2O (2 × 50 mL) and the combined organic extracts washed with 1 M aqueous NaOH (25 mL), water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, afforded **234** as a white solid (2.88 g, 73%).

mp = 55-57 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.82 (t, *J* = 2.9 Hz, 1H, H_3), 7.74-7.63 (m, 2H, H_7), 7.42-7.29 (m, 3H, H_8 & H_9), 2.71 (tt, *J* = 4.6, 2.3 Hz, 2H, H_4), 2.60, (dd, *J* = 6.1, 2.8 Hz, 2H, H_5);

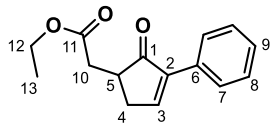
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 207.7 (Quat, C_1), 159.0 (CH, C_3), 143.5 (Quat, C_2), 131.7 (Quat, C_6), 128.5 (CH, C_8), 128.4 (CH, C_9), 127.1 (CH, C_7), 35.8 (CH_2, C_5), 26.2 (CH_2, C_4);

FTIR (film) ν_{max}/cm^{-1} = 3056, 2918, 1698, 1495, 1438, 1405, 1331, 1303, 1268, 1132, 1016;

HRMS (ACI$^+$) calculated for $C_{11}H_{11}O^+$ = 159.0804, mass found = 159.0803.

The data matched those of the literature.[166]

Ethyl 2-(2-oxo-3-phenylcyclopent-3-en-1-yl)acetate, 235



According to a literature procedure,[119] diisopropylamine (1.12 mL, 7.93 mmol, 1.25 eq) was dissolved in THF (12 mL) and cooled to −78 °C. To this solution was added ^{n}BuLi in hexanes (2.5 M, 3.03 mL, 7.58 mmol, 1.2 eq) and the solution stirred for 10 minutes at −78 °C, allowed to warm to 0 °C for 15 minutes and then cooled to −78 °C once again. To this solution, a solution of **234** (1.00 g, 6.32 mmol, 1.0 eq) in THF (2.0 mL) was added by syringe pump over 30 minutes, and the mixture stirred for a further 30 minutes at −78 °C once addition was complete. A solution of ethyl bromoacetate (1.40 mL, 12.6 mmol, 2.0 eq) in THF (2.0 mL) was then added and the reaction mixture stirred for 2.5 hours at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) at −78 °C and then allowed to warm to room temperature. The biphasic mixture was

extracted with Et_2O (3 × 20 mL) and the combined organic extracts washed with brine (30 mL), filtered over Na_2SO_4, and concentrated under reduced pressure. Purification *via* flash column chromatography, eluting with 1:3 to 3:7 EtOAc/petrol 40-60, afforded **235** as a yellow oil (340 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.81 (s, 1H, H_3), 7.72-7.65 (m, 2H, H_8), 7.44-7.28 (m, 3H, H_7 & H_9), 4.16 (q, *J* = 7.2 Hz, 2H, H_{12}), 3.08-2.96 (m, 1H, H_{10}), 2.95-2.87 (m, 2H, H_4 & H_5), 2.65-2.56 (m, 2H, $H_{4'}$ & $H_{10'}$), 1.23 (t, *J* = 7.3 Hz, 3H, H_{13});

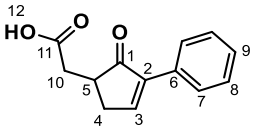
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 207.4 (Quat, C_1), 172.0 (Quat, C_{11}), 157.1 (CH, C_3), 143.5 (Quat, C_2), 131.7 (Quat, C_6), 128.5 (CH, C_9), 128.4 (CH, C_7), 127.0 (CH, C_8), 60.7 (CH_2, C_{12}), 42.9 (CH, C_5), 35.4 (CH_2, C_{10}), 33.3 (CH_2, C_4), 14.2 (CH_3, C_{13});

FTIR (film) ν_{max}/cm^{-1} = 3057, 2981, 2919, 1731, 1698, 1598, 1494, 1446, 1406, 1373, 1303, 1258, 1211, 1178, 1132, 1075, 1030, 1001;

LRMS (ESI$^+$) calculated for $C_{15}H_{16}O_3Na^+$ = 267, mass found = 267.

The data matched those of the literature.[119]

2-(2-Oxo-3-phenylcyclopent-3-en-1-yl)acetic acid, 236



To a solution of **235** (150 mg, 0.613 mmol, 1.0 eq) in 3:2:1 MeOH/THF/water (6.0 mL) was added lithium hydroxide monohydrate (103 mg, 2.45 mmol, 4.0 eq) and the mixture stirred for 2 hours. The reaction mixture was quenched with water (20 mL) and 3 M HCl (2 mL) and the solution extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and purified with flash column chromatography, eluting with 1:19 to 1:9 MeOH/CH_2Cl_2, to afford **236** as a yellow solid (23 mg, 17%).

mp = 105-107 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.03 (s, 1H, H_{12}), 7.81 (t, *J* = 3.0 Hz, 1H, H_3), 7.73-7.61 (m, 2H, H_8), 7.46-7.28 (m, 4H, H_7 & H_9), 3.10-2.99 (m, 1H, H_5), 2.98-2.80 (m, 2H, H_4 & H_{10}), 2.58 (dd, *J* = 16.6, 8.6 Hz, 1H, $H_{4'}$), 2.48 (dt, *J* = 19.3, 2.8 Hz, 1H, $H_{10'}$);

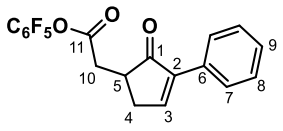
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 207.4 (Quat, C_1), 177.6 (Quat, C_{11}), 157.4 (CH, C_3), 142.5 (Quat, C_2), 131.4 (Quat, C_6), 128.6 (CH, C_9), 128.5 (CH, C_7), 127.0 (CH, C_8), 42.6 (CH, C_5), 35.1 (CH_2, C_{10}), 33.3 (CH_2, C_4);

FTIR (film) ν_{max}/cm^{-1} = 3059, 2918, 2850, 1701, 1597, 1494, 1447, 1406, 1305, 1260, 1231, 1176, 1133, 1075, 1035, 1002;

LRMS (ESI^-) calculated for $C_{13}H_{11}O_3^-$ = 215, mass found = 215.

The data matched those of the literature.[120]

Pentafluorophenyl 2-(2-oxo-3-phenylcyclopent-3-en-1-yl)acetate, 237



Prepared according to **General Procedure A**.

Esterification with crude diacid **236** (22 mg, 0.10 mmol, 1.0 eq), EDC·HCl (29 mg, 0.15 mmol, 1.5 eq), DMAP (0.6 mg, 0.005 mmol, 0.05 eq), and pentafluorophenol (19 mg, 0.10 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **237** as a yellow solid (23 mg, 59%).

mp = 68-70 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.84 (t, *J* = 3.0 Hz, 1H, H_3), 7.79-7.67 (m, 2H, H_8), 7.46-7.30 (m, 3H, H_7 & H_9), 3.39-3.26 (m, 1H, H_{10}), 3.20-2.97 (m, 2H, H_4 & H_5), 2.87 (dd, *J* = 16.8, 9.3 Hz, 1H, $H_{10'}$), 2.56 (dt, *J* = 19.0, 2.8 Hz, 1H, $H_{4'}$);

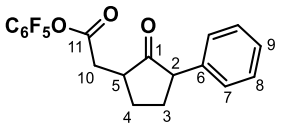
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 206.1 (Quat, C_1), 168.2 (Quat, C), 157.0 (CH, C_3), 142.6 (Quat, C_2), 131.2 (Quat, C_6), 128.7 (CH, C_9), 128.5 (CH, C_7), 127.0 (CH, C_8), 42.5 (CH, C_5), 34.5 (CH_2, C_{10}), 32.9 (CH_2, C_4);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.51, −157.6, −162.1;

FTIR (film) ν_{max}/cm^{-1} = 2917, 2849, 1787, 1707, 1519, 1471, 1448, 1364, 1307, 1205, 1098;

HRMS (ESI^+) calculated for $C_{19}H_{11}O_3F_5Na^+$ = 405.0520, mass found = 405.0518.

Pentafluorophenyl 2-(2-oxo-3-phenylcyclopentyl)acetate, 238



Prepared according to **General Procedure B**.

Hydrogenation with crude diacid **237** (22 mg, 0.10 mmol, 1.0 eq) and 10% Pd/C (3 mg, 10 wt%) in EtOH (0.2 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **238** as a yellow gum mixture of two diastereoisomers (6 mg, 27%, 1.7:1 *dr*).

mp = 68-70 °C;

Major diastereoisomer:

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.36 (m, 2H, H_8), 7.32-7.26 (m, 2H, H_7), 7.26-7.18 (m, 1H, H_9), 3.44 (dd, *J* = 12.4, 8.4 Hz, 1H, H_2), 3.24 (dd, *J* = 17.1, 4.1 Hz, 1H, H_{10}), 2.90 (dd, *J* = 17.1, 8.1 Hz, 1H, $H_{10'}$), 2.78 (ddt, *J* = 12.1, 8.1, 4.0 Hz, 1H, H_5), 2.64-2.56 (m, 1H, H_3), 2.56-2.47 (m, 1H, H_4), 2.14 (qd, *J* = 12.5, 6.1 Hz, 1H, $H_{3'}$), 1.80 (qd, *J* = 12.3, 6.2 Hz, 1H, $H_{4'}$);

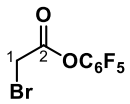
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 215.8 (Quat, C_1), 168.2 (Quat, C_{11}), 138.2 (Quat, C_6), 128.7 (CH, C_8), 128.0 (CH, C_7), 127.1 (CH, C_9), 54.7 (CH, C_2), 46.2 (CH, C_5), 33.5 (CH_2, C_{10}), 29.6 (CH_2, C_3), 27.0 (CH_2, C_4);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.4, −157.6, −162.1;

FTIR (film) ν_{max}/cm^{-1} = 2917, 2849, 1788, 1744, 1520, 1097, 1001;

HRMS (ESI^+) calculated for $C_{19}H_{13}O_3F_5Na^+$ = 407.0677, mass found = 407.0676.

Pentafluorophenyl bromoacetate, 241



According to a literature procedure,[167] a solution of pentafluorophenol (4.01 g, 21.8 mmol, 1.0 eq) and Hünig's base (3.80 mL, 21.8 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) was added to a solution of bromoacetyl bromide (1.90 mL, 21.8 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) and stirred for 1 hour. The mixture was diluted with water (50 mL) and the phases separated. The organic layer was washed with 1 M aqueous HCl (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by distillation to afford **241** as a colourless oil (5.40 g, 86%).

bp = 112 °C (18 mbar);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.14 (d, *J* = 1.3 Hz, 2H, H_1);

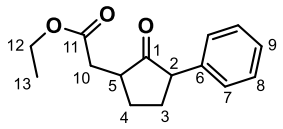
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 163.5 (Quat, C_2), 22.3 (CH_2, C_1);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.4, −156.7, −161.7;

FTIR (film) ν_{max}/cm^{-1} = 2970, 1788, 1655, 1517, 1473, 1425, 1403, 1269, 1240, 1206, 1145, 1088, 1042, 1023;

LRMS (ESI^+) calculated for $C_8H_3BrF_5O_2^+$ = 305, 307, mass found = 305, 307.

Ethyl 2-(2-oxo-3-phenylcyclopentyl)acetate, 242



Prepared according to **General Procedure B**.

Hydrogenation with crude diacid **235** (490 mg, 2.01 mmol, 1.0 eq) and 10% Pd/C (106 mg, 0.05 eq) in EtOH (6.0 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **242** as a yellow oil mixture of two diastereoisomers (258 mg, 53%, 3.7:1 *dr*).

***cis*-Isomer:**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.42-7.20 (m, 5H, H_7, H_8 & H_9), 4.15 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.42 (dd, *J* = 12.5, 8.4 Hz, 1H, H_2), 2.81 (qd, *J* = 9.9, 8.6, 4.4 Hz, 1H, H_{10}), 2.33 (m, 4H, H_3, H_4, H_5 & $H_{10'}$), 2.20-2.06 (m, 1H, $H_{3'}$), 1.74 (ddt, *J* = 18.1, 12.2, 5.9 Hz, 1H, $H_{4'}$), 1.27 (t, *J* = 7.1 Hz, 3H, H_{12})

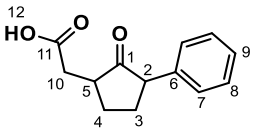
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 218.1 (Quat, C_1), 172.0 (Quat, C_{11}), 138.4 (Quat, C_6), 128.6 (CH, C_8), 128.2 (CH, C_7), 126.9 (CH, C_9), 60.7 (CH_2, C_{12}), 54.9 (CH, C_2), 46.3 (CH, C_5), 34.3 (CH_2, C_{10}), 29.8 (CH_2, C_3), 27.2 (CH_2, C_4), 14.2 (CH_3, C_{13});

FTIR (film) ν_{max}/cm^{-1} = 3028, 2963, 2875, 1735 (br), 1602, 1496, 1451, 1405, 1373, 1320, 1262, 1182, 1144, 1072, 1030;

LRMS (ESI^+) calculated for $C_{15}H_{18}O_3Na^+$ = 269, mass found = 269.

The data matched those of the literature.[119]

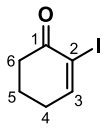
2-(2-Oxo-3-phenylcyclopent-3-en-1-yl)acetic acid, 243



According to a literature procedure,[119] to a solution of **242** (245 mg, 0.986 mmol, 1.0 eq) in 3:2:1 MeOH/THF/water (10 mL) was added lithium hydroxide monohydrate (167 mg, 3.95 mmol, 4.0 eq) and the mixture stirred for 2 hours. The reaction mixture was quenched with water (30 mL) and 3 M HCl (3 mL) and the solution extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure to afford **243** as a yellow solid that was used without any further purification (273 mg, quant, 2.1:1 *dr*).

LRMS (ESI^-) calculated for $C_{13}H_{13}O_3^-$ = 217, mass found = 217.

2-Iodocyclohex-2-enone, 245



According to a literature procedure,[168] potassium carbonate (8.63 g, 62.4 mmol, 1.2 mL), iodine (19.8 g, 78.0 mmol, 1.5 eq) and DMAP (1.27 g, 10.4 mmol, 0.2 eq) were added to a solution of cyclohexenone (5.0 mL, 52.0 mmol, 1.0 eq) in 1:1 THF/water (200 mL). The mixture was stirred for 5 hours, then diluted with EtOAc (300 mL) and ice-cooled saturated aqueous $Na_2S_2O_3$ (200 mL). The phases were separated and the aqueous phase was extract with EtOAc (2 × 100 mL). The combined

organic phases were washed with 0.1 M aqueous HCl (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with 0:1 to 1:10 EtOAc/petrol 40-60, to afford **245** as a white solid (11.5 g, quant).

mp = 46-48 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.76 (t, *J* = 4.4 Hz, 1H, H_3), 2.74-2.58 (m, 2H, H_6), 2.43 (td, *J* = 6.0, 4.5 Hz, 2H, H_4), 2.27-1.91 (m, 2H, H_5);

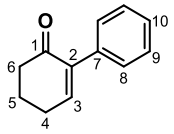
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 192.2 (Quat, C_1), 159.4 (CH, C_3), 103.9 (Quat, C_2), 37.3 (CH_2, C_6), 30.0 (CH_2, C_4), 22.9 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 2498, 2867, 1681, 1585, 1425, 1315, 1154, 1120;

HRMS (ACI$^+$) calculated for $C_6H_8IO^+$ = 222.9614, mass found = 222.9611.

The data matched those of the literature.[168]

2-Phenylcyclohex-2-enone, 246



According to a literature procedure,[166] to a solution of **245** (5.00 g, 22.5 mmol, 1.0 eq) in 1:1 DME/water (88 mL) were added Na_2CO_3 (4.77 g, 45.0 mmol, 2.0 eq), phenylboronic acid (5.50 g, 45.0 mmol, 2.0 eq) and 10% Pd/C (1.2 g, 1.13 mmol, 0.05 eq). The mixture was stirred for 23 hours before the Pd/C was filtered off and washed with Et_2O (the catalyst could be reused for future cross-coupling experiments). The remaining solution was extracted with Et_2O (2 × 50 mL) and the combined organic extracts washed with 1 M aqueous NaOH (25 mL), water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, afforded **246** as a white solid (3.29 g, 85%).

mp = 90-92 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40-7.27 (m, 5H, H_8, H_9 & H_{10}), 7.05 (t, *J* = 4.3 Hz, 1H, H_3), 2.62 (t, *J* = 6.7 Hz, 2H, H_6), 2.59-2.52 (m, 2H, H_4), 2.12 (m, 2H, H_5);

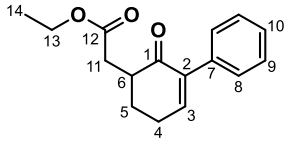
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 198.0 (Quat, C_1), 148.1 (CH, C_3), 140.4 (Quat), 136.6 (Quat), 128.6 (CH, C_8 *or* C_9), 128.0 (CH, C_8 *or* C_9), 127.6 (CH, C_{10}), 39.1 (CH_2, C_6), 26.6 (CH_2, C_4), 23.0 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 3022, 2946, 2867, 1679, 1586, 1493, 1445, 1426, 1357, 1316, 1209, 1154, 1121, 1071;

LRMS (ESI^+) calculated for $C_{12}H_{13}O^+$ = 173, mass found = 173.

The data matched those of the literature.[166]

Ethyl 2-(2-oxo-3-phenylcyclohex-3-en-1-yl)acetate, 247



According to a literature procedure,[119] diisopropylamine (1.17 mL, 8.27 mmol, 1.25 eq) was dissolved in THF (14 mL) and cooled to −78 °C. To this solution was added ^{n}BuLi in hexanes (2.5 M, 3.18 mL, 7.94 mmol, 1.2 eq) and the solution stirred for 10 minutes at −78 °C, allowed to warm to 0 °C for 15 minutes and then cooled to −78 °C once again. To this solution, a solution of **246** (1.14 g, 6.62 mmol, 1.0 eq) in THF (2.0 mL) was added by syringe pump over 30 minutes, and the mixture stirred for a further 30 minutes at −78 °C once addition was complete. A solution of ethyl bromoacetate (1.48 mL, 13.2 mmol, 2.0 eq) in THF (2.0 mL) was then added and the reaction mixture stirred for 2.5 hours at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) at −78 °C and then allowed to warm to room temperature. The biphasic mixture was extracted with Et_2O (3 × 20 mL) and the combined organic extracts washed with brine (30 mL), filtered over Na_2SO_4, and concentrated under reduced pressure. Purification *via* flash column chromatography, eluting with 1:3 to 3:10 EtOAc/petrol 40-60, afforded **247** as a yellow oil (520 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.37-7.27 (m, 5H, H_8, H_9 & H_{10}), 7.00 (ddd, *J* = 5.6, 2.7, 1.3 Hz, 1H, H_3), 4.17 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.05 (dddd, *J* = 13.6, 6.8, 6.0, 4.5 Hz, 1H, H_6), 2.94 (dd, *J* = 16.4,

6.0 Hz, 1H, H_{11}), 2.73-2.51 (m, 2H, H_4), 2.35 (dd, *J* = 16.3, 6.9 Hz, 1H, $H_{11'}$), 2.19 (dtdd, *J* = 12.0, 4.7, 2.5, 1.3 Hz, 1H, H_5), 1.96 (tdd, *J* = 13.3, 11.2, 5.2 Hz, 1H, $H_{5'}$), 1.28 (t, *J* = 7.1 Hz, 3H, H_{14});

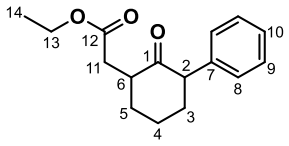
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 198.2 (Quat, C_1), 172.6 (Quat, C_{12}), 147.1 (CH, C_3), 139.9 (Quat, C_2), 136.4 (Quat, C_7), 128.6, 128.0, 127.6, 60.6 (CH_2, C_{13}), 44.3 (CH, C_6), 35.0 (CH_2, C_{11}), 28.8 (CH_2, C_5), 26.4 (CH_2, C_4), 14.2 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 2981, 2933, 1731, 1680, 1493, 1445, 1419, 1369, 1348, 1261, 1179, 1129, 1096, 1029;

LRMS (ESI^+) calculated for $C_{16}H_{18}O_3Na^+$ = 281, mass found = 281.

The data matched those of the literature.[119]

Ethyl 2-(2-oxo-3-phenylcyclohexyl)acetate, 248



Prepared according to **General Procedure B**.

Hydrogenation with crude diacid **247** (1.00 g, 3.87 mmol, 1.0 eq) and PtO_2 (100 mg, 0.11 eq) in EtOH (12.0 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **248** as a colourless oil, which was a mixture of two diastereoisomers that could be separated (674 mg, 67%, 3.3:1 *dr*).

***cis*-Isomer (major):**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.32 (t, *J* = 7.4 Hz, 2H, H_8), 7.29-7.20 (m, 1H, H_{10}), 7.16-7.07 (m, 2H, H_9), 4.10 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.73-3.62 (m, 1H, H_2), 3.08 (dq, *J* = 12.9, 6.3 Hz, 1H, H_6), 2.80 (dd, *J* = 16.6, 7.4 Hz, 1H, H_{11}), 2.30 (m, 2H, H_3 & H_5), 2.20 (dd, *J* = 16.7, 6.0 Hz, 1H, $H_{11'}$), 2.09-1.88 (m, 3H, $H_{3'}$, H_4 & $H_{5'}$), 1.58 (qd, *J* = 12.7, 3.2 Hz, 1H, $H_{4'}$), 1.23 (t, *J* = 7.2 Hz, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 209.4 (Quat, C_1), 172.6 (Quat, C_{12}), 138.4 (Quat, C_7), 128.7 (CH, C_9), 128.3 (CH, C_8), 127.0 (CH, C_7), 60.5 (CH_2, C_{13}), 57.5 (CH, C_2), 47.6 (CH, C_6), 36.3 (CH_2, C_{11}), 34.7 (CH_2, C_3), 34.6 (CH_2, C_5), 25.5 (CH_2, C_4), 14.2 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 2981, 2934, 2861, 1731, 1714, 1448, 1370, 1344, 1272, 1239, 1195, 1168, 1115, 1094, 1067, 1026;

HRMS (EI^+) calculated for $C_{16}H_{20}O_3^+$ = 260.1407, mass found = 260.1407.

***trans*-Isomer (minor):**

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.33-7.14 (m, 5H, H_8, H_9 & H_{10}), 4.05 (q, *J* = 7.1 Hz, 2H, H_{13}), 3.76 (t, *J* = 4.6 Hz, 1H, H_2), 2.93 (ddt, *J* = 12.3, 8.2, 5.8 Hz, 1H, H_6), 2.69 (dd, *J* = 16.5, 7.8 Hz, 1H, H_{11}), 2.53 (dt, *J* = 14.2, 3.4 Hz, 1H, H_5), 2.13 (dd, *J* = 16.5, 5.9 Hz, 1H, $H_{11'}$), 2.09-1.79 (m, 3H, H_3, H_4 & $H_{5'}$), 1.70 (dp, *J* = 12.9, 4.2 Hz, 1H, $H_{3'}$), 1.49 (ddt, *J* = 20.2, 12.2, 7.2 Hz, 1H, $H_{4'}$), 1.17 (q, *J* = 7.1 Hz, 3H, H_{14});

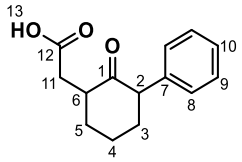
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 212.0 (Quat, C_1), 172.2 (Quat, C_{12}), 137.6 (Quat, C_7), 128.8 (CH, C_9), 127.3 (CH, C_8), 126.8 (CH, C_{10}), 60.5 (CH_2, C_{13}), 44.3 (CH, C_2), 34.8 (CH, C_6), 33.7 (CH_2, C_3), 30.7 (CH_2, C_5), 20.9 (CH_2, C_4), 14.2 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 2934, 2863, 1732, 1712, 1601, 1498, 1448, 1370, 1344, 1272, 1204, 1169, 1111, 1096, 1068, 1029;

HRMS (EI^+) calculated for $C_{16}H_{20}O_3^+$ = 260.1407, mass found = 260.1411.

The data matched those of the literature.[119]

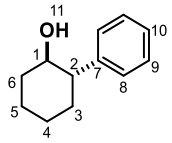
2-(2-Oxo-3-phenylcyclohexyl)acetic acid, 249



According to a literature procedure,[119] to a solution of **248** (100 mg, 0.384 mmol, 1.0 eq) in 3:2:1 MeOH/THF/water (3.8 mL) was added lithium hydroxide monohydrate (61 mg, 1.52 mmol, 4.0 eq) and the mixture stirred for 2 hours. The reaction mixture was quenched with water (15 mL) and 3 M HCl (1 mL) and the solution extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure to afford **249** as a yellow solid that was used without any further purification (99 mg, quant, 2.5:1 *dr*).

LRMS (ESI^-) calculated for $C_{14}H_{15}O_3^-$ = 231, mass found = 231.

trans-2-Phenylcyclohexan-1-ol, 251



Analogously to a literature procedure,[169] magnesium turnings (2.23 g, 91.7 mmol, 1.8 eq) were heated to 150 °C under vacuum and stirred vigorously for 1 hour. The flask was filled with nitrogen and allowed to cool to room temperature before THF (30 mL) was added, followed by the slow addition of bromobenzene (6.51 mL, 61.4 mmol, 1.2 eq). The solution was heated to reflux for 2 hours and then cooled to 30 °C. This Grignard solution was added to flask containing a suspension of copper(I) iodide (680 mg, 3.57 mmol, 0.07 eq) in THF (70 mL), stirred for 10 minutes, and then cooled to 0 °C. Cyclohexene oxide (5.15 mL, 51.0 mmol, 1.0 eq) was added dropwise, and the reaction mixture stirred for a further 5 hours at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) and then extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (50 mL), water (50 mL) and brine (50 mL), and then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **251** as a white solid (>20:1 *dr*, 6.95 g, 77%).

mp = 54-56 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.26 (t, *J* = 7.5 Hz, 2H, H_9), 7.22-7.10 (m, 3H, H_8 & H_{10}), 3.58 (td, *J* = 10.1, 4.3 Hz, 1H, H_1), 2.35 (ddd, *J* = 13.1, 9.9, 3.5 Hz, 1H, H_2), 2.10-1.96 (m, 1H, H_6), 1.78 (m, 2H, H_3 & H_5), 1.69 (dt, *J* = 13.0, 3.4 Hz, 1H, H_4), 1.54-1.13 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$ & $H_{6'}$);

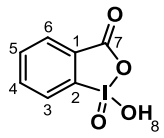
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 143.3 (Quat, C_7), 128.8 (CH, C_9), 127.9 (CH, C_8), 126.8 (CH, C_{10}), 74.4 (CH, C_1), 53.2 (CH, C_2), 34.4 (CH_2, C_6), 33.3 (CH_2, C_3), 26.1 (CH_2, C_4), 25.1 (CH_2, C_5);

FTIR (film) ν_{max}/cm^{-1} = 3398 (br), 3027, 2927, 2855, 1602, 1493, 1448, 1346, 1268, 1234, 1124, 1058;

LRMS (ACI$^+$) calculated for $C_{12}H_{16}ONH_4^+$ = 194.1939, mass found = 194.1938.

The data matched those of the literature.[169]

2-Iodoxybenzoic acid (IBX), 532

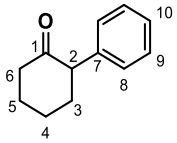


According to a literature procedure,[170] 2-iodobenzoic acid (25.0 g, 101 mmol, 1.0 eq) was added in one portion to a suspension of Oxone® (90.5 g, 131 mmol, 1.3 eq) in water (325 mL) in a 1 L round-bottom flask with an overhead stirrer. The mixture was heated to 70 °C over 20 minutes and stirred at that temperature for 3 hours and during this time, the mixture changed from a thick slurry to a fine dispersion of solid. The mixture was cooled to 5 °C, stirred slowly for 1.5 hours and then filtered. The filter cake was washed with water (6 × 50 mL) and acetone (2 × 50 mL) and then left to dry overnight to afford **532** as a white solid (20.1 g, 71%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H = 10.04-9.28 (br s, 1H, H_8), 8.15 (d, *J* = 7.9 Hz, 1H, H_3), 8.07-7.96 (m, 2H, H_5 & H_6), 7.84 (t, *J* = 7.3 Hz, 1H, H_4).

The data matched those of the literature.[170]

2-Phenylcyclohexan-1-one, 252



According to a literature procedure,[169] IBX (20.0 g, 70.9 mmol, 2.5 eq) was added slowly to a solution of **251** (5.00 g, 28.4 mmol, 1.0 eq) in DMSO (100 mL). The reaction mixture was stirred for 14 hours and then quenched with saturated aqueous $NaHCO_3$ (150 mL) and saturated aqueous $Na_2S_2O_3$ (150 mL), and extracted with 1:1 hexane/EtOAc (200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **252** as a white solid (4.54 g, 92%).

mp = 56-58 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.38-7.31 (ddd, *J* = 7.5, 7.0, 1.5 Hz, 2H, H_9), 7.26 (tt, *J* = 6.9, 1.4 Hz, 1H, H_{10}), 7.18-7.10 (dd, *J* =7.4, 1.4 Hz, m, 2H, H_8), 3.69-3.52 (m, 1H, H_2), 2.59-2.39 (m, 2H, H_6), 2.28 (dddd, *J* = 15.6, 7.6, 3.9, 2.0 Hz, 1H, H_3), 2.16 (dqt, *J* = 9.5, 3.7, 1.9 Hz, 1H, H_5), 2.11-1.93 (m, 2H, $H_{3'}$ & H_4), 1.82-1.73 (m, 2H, $H_{4'}$ & $H_{5'}$);

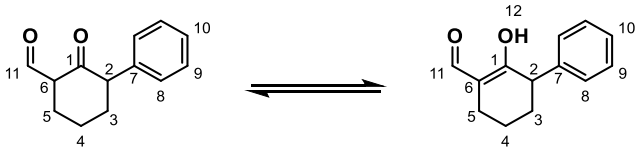
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 210.3 (Quat, C_1), 138.8 (Quat, C_7), 128.5 (CH, C_8), 128.4 (CH, C_9), 126.9 (CH, C_{10}), 57.4 (CH, C_2), 42.2 (CH, C_6), 35.1 (CH, C_3), 27.8 (CH, C_5), 25.3 (CH, C_4);

FTIR (film) ν_{max}/cm^{-1} = 3029, 2935, 2861, 1711, 1603, 1498, 1448, 1427, 1306, 1204, 1125, 1062, 1024;

LRMS (ESI^+) calculated for $C_{12}H_{14}ONa^+$ = 197, mass found = 197.

The data matched those of the literature.[169]

2-Oxo-3-phenylcyclohexane-1-carbaldehyde, 253



According to a literature procedure,[169] ethyl formate (4.0 mL, 74.1 mmol, 5.0 eq) was added to a suspension of KO^{t}Bu (1.34 g, 12.0 mmol, 1.2 eq) in THF (40 mL), stirred for 15 minutes, and then cooled to 0 °C. To this suspension was added dropwise a solution of **252** (1.74 g, 10.0 mmol, 1.0 eq) in ethyl formate (4.0 mL). The reaction mixture was stirred for 15 minutes and then allowed to warm to room temperature and stirred for 48 hours at which point the solution had turned into a viscous yellow suspension. The reaction mixture was quenched with slow addition of 1 M aqueous HCl (15 mL) and water (50 mL), and the biphasic mixture extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, to afford **253** as a brown oil (1.64 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 14.36 (d, *J* = 2.7 Hz, 1H, H_{12}), 8.88 (s, 1H, H_{11}), 7.36 (t, *J* = 7.4 Hz, 2H, H_9), 7.29 (d, *J* = 6.7 Hz, 1H, H_{10}), 7.21 (d, *J* = 7.4 Hz, 2H, H_8), 3.71 (t, *J* = 7.1 Hz, 1H, H_2), 2.63-2.38 (m, 2H, H_5), 2.24-2.05 (m, 1H, H_3), 1.83 (m, 2H, $H_{3'}$ & H_4), 1.76-1.55 (m, 1H, $H_{4'}$);

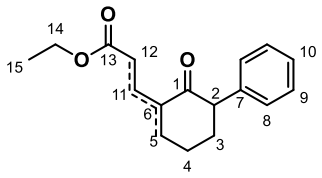
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 189.6 (Quat, C_{11}), 183.1 (Quat, C_1), 141.7 (Quat, C_7), 128.6 (CH, C_9), 128.4 (CH, C_8), 126.9 (CH, C_{10}), 109.8 (Quat, C_6), 47.5 (CH, C_2), 31.4 (CH_2, C_3), 23.6 (CH_2, C_5), 20.7 (CH_2, C_4);

FTIR (film) ν_{max}/cm^{-1} = 3062, 3028, 2938, 2860, 1725, 1637, 1582, 1495, 1451, 1364, 1338, 1237, 1182, 1152, 1071, 1030;

LRMS (ESI^-) calculated for $C_{13}H_{13}O_2^-$ = 201, mass found = 201.

The data matched those of the literature.[169]

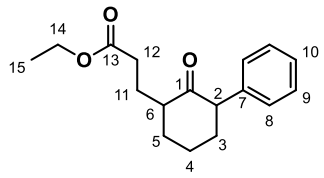
Ethyl 3-(2-oxo-3-phenylcyclohexyl)acrylate & isomers, 255



According to a literature procedure,[119] to a solution of **253** (1.50 g, 7.41 mmol, 1.0 eq) in anhydrous toluene (45 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (2.93 g, 8.16 mmol, 1.1 eq), and the resulting solution was heated to reflux for 3 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 6:1 petrol 40-60/EtOAc (26.5 mL), filtered and the filter cake washed with 6:1 petrol 40-60/EtOAc (2 × 10 mL). The filtrate was concentrated and then purified by flash column chromatography, eluting with 1:19 to 3:17 EtOAc/petrol 40-60, to afford **255** as a mixture of regioisomers (1.55 g, 77%). The mixture was used without separating the regioisomers.

LRMS (ESI^+) calculated for $C_{17}H_{20}O_3Na^+$ = 295, mass found = 295.

Ethyl 3-(2-oxo-3-phenylcyclohexyl)propanoate, 256



Prepared according to **General Procedure B**.

Hydrogenation with crude diacid **255** (586 mg, 2.20 mmol, 1.0 eq) and 10% Pd/C (117 mg, 0.22 mmol, 0.1 eq) in EtOH (20 mL). Purification *via* flash column chromatography, eluting with 1:9 to 1:19 EtOAc/petrol 40-60, afforded title compound **256** as a yellow oil mixture of two diastereoisomers (345 mg, 59%, 2.3:1 *dr*).

mp = 68-70 °C;

***cis*-Isomer (major):**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35-7.30 (m, 2H, H_9), 7.26 (dd, *J* = 7.8, 1.9 Hz, 1H, H_{10}), 7.16-7.08 (m, 2H, H_8), 4.10 (dq, *J* = 7.1 Hz, 2H, H_{14}), 3.62 (dd, *J* = 12.1, 5.3 Hz, 1H, H_2), 2.63-2.51 (m, 1H, H_6), 2.45-2.23 (m, 4H, H_3, H_5, $H_{5'}$ & H_{12}), 2.17-1.91 (m, 4H, H_4, H_{11}, $H_{11'}$ & H_{12}), 1.65-1.47 (m, 2H, $H_{3'}$ & $H_{4'}$), 1.23 (t, *J* = 7.2 Hz, 3H, H_{15});

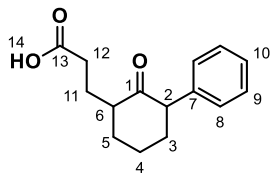
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 210.5 (Quat, C_1), 173.7 (Quat, C_{13}), 138.5 (Quat, C_7), 128.8 (CH, C_8), 128.2 (CH, C_9), 126.9 (CH, C_{10}), 60.2 (CH_2, C_{14}), 58.0 (CH, C_2), 50.2 (CH, C_6), 36.6 (CH_2, C_{12}), 35.3 (CH_2, C_3), 31.8 (CH_2, C_5), 25.7 (CH_2, C_{11}), 24.9 (CH_2, C_4), 14.2 (CH_3, C_{15});

FTIR (film) ν_{max}/cm^{-1} = 3029, 2933, 2861, 1731, 1712, 1603, 1498, 1448, 1374, 1304, 1260, 1164, 1097, 1068, 1034;

LRMS (ESI^+) calculated for $C_{17}H_{22}O_3Na^+$ = 297, mass found = 297.

The data matched those of the literature.[119]

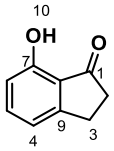
3-(2-Oxo-3-phenylcyclohexyl)propanoic acid, 257



According to a literature procedure,[119] to a solution of **256** (150 mg, 0.576 mmol, 1.0 eq) in 3:2:1 MeOH/THF/water (6.0 mL) was added lithium hydroxide monohydrate (97 mg, 2.31 mmol, 4.0 eq) and the mixture stirred for 2 hours. The reaction mixture was quenched with water (20 mL) and 3 M HCl (1 mL) and the solution extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure to afford **257** as a yellow solid that was used without any further purification (140 mg, quant, 3.9:1 *dr*).

LRMS (ESI^-) calculated for $C_{15}H_{17}O_3$ = 245, mass found = 245.

7-Hydroxy-1-indanone, 285



According to a literature procedure,[141] 4-chromanone (5.00 g, 33.7 mmol, 1.0 eq) and anhydrous $AlCl_3$ (13.0 g, 97.5 mmol, 2.9 eq) were fused together in a round-bottom flask under an atmosphere of N_2 at 250 °C for 20 minutes and then allowed to cool to room temperature. CH_2Cl_2 (100 mL) and cold HCl (50 mL conc HCl and 50 mL ice-water) were added to the solid reaction mixture. The black slurry was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, to afford indanone **285** as a yellow solid (2.67 g, 53%).

mp = 108-110 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 9.06 (s, 1H, H_{10}), 7.46 (dd, *J* = 7.9, 7.5 Hz, 1H, H_5), 6.94 (dd, *J* = 7.5, 0.8 Hz, 1H, H_6), 6.75 (dd, *J* = 7.9, 0.7 Hz, 1H, H_4), 3.13-3.08 (m, 2H, H_3), 2.73-2.68 (m, 2H, H_2);

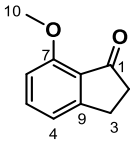
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 210.1 (Quat, C_1), 157.5 (Quat, C_7), 155.3 (Quat, C_9), 137.6 (CH, C_5), 122.7 (Quat, C_8), 117.4 (CH, C_6), 113.4 (CH, C_4), 26.0 (CH_2, C_3), 26.0 (CH_2, C_2);

FTIR (film) ν_{max}/cm^{-1} = 3363, 2924, 1675, 1617, 1598, 1466, 1435, 1408, 1327, 1293, 1246, 1201, 1175, 1160, 1060;

LRMS (ESI$^+$) calculated for $C_9H_8O_2Na^+$ = 171, mass found = 171.

The data matched those of the literature.[141]

7-Methoxy-1-indanone, 286



According to a literature procedure,[171] to a solution of 7-hydroxy-1-indanone **285** (1.00 g, 6.74 mmol) in acetone/THF (3:2, 160 mL) was added K_2CO_3 (1.86 g, 13.4 mmol, 2.0 eq) and iodomethane (0.50 mL, 8.10 mmol, 1.2 eq). The reaction mixture was stirred at reflux for 16 hours and then cooled to room temperature. Brine (80 mL) and CH_2Cl_2 (80 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with CH_2Cl_2 to afford **286** as a yellow crystalline solid (0.73 g, 66%).

mp = 98-100 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.50 (t, *J* = 7.9 Hz, 1H, H_5), 6.99 (d, *J* = 7.5 Hz, 1H, H_4), 6.76 (d, *J* = 8.2 Hz, 1H, H_6), 3.93 (s, 3H, H_{10}), 3.08-3.03 (m, 2H, H_3), 2.67-2.62 (m, 2H, H_2);

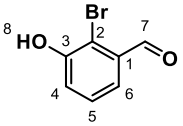
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 204.8 (Quat, C_1), 158.1 (Quat, C_7), 158.0 (Quat, C_9), 136.4 (CH, C_5), 125.2 (Quat, C_8), 118.5 (CH, C_6), 108.8 (CH, C_4), 55.8 (CH_3, C_{10}), 36.8 (CH_2, C_3), 25.6 (CH_2, C_2);

FTIR (film) ν_{max}/cm^{-1} = 2839, 1712, 1694, 1592, 1479, 1452, 1438, 1406, 1344, 1299, 1275, 1235, 1198, 1085, 1065, 1021;

LRMS (ESI$^+$) calculated for $C_{10}H_{11}O_2^+$ = 163, mass found = 163.

The data matched those of the literature.[171]

2-Bromo-3-hydroxybenzaldehyde, 288



According to a literature procedure,[172] 3-hydroxybenzaldehyde (16.1 g, 132 mmol, 1.0 eq), iron powder (560 mg, 10.0 mmol, 0.06 eq), and NaOAc (21.3 g, 260 mmol, 1.97 eq) were suspended in acetic acid (120 mL), and the suspension warmed until a clear solution was obtained. The mixture was allowed to cool to room temperature and to this was added dropwise, over 15 minutes, a solution of bromine (7.75 mL, 150 mmol, 1.14 eq) in acetic acid (25 mL) while ensuring the temperature of the mixture did not exceed room temperature. The reaction mixture was stirred for 2 hours, then poured onto ice water (800 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over $MgSO_4$, concentrated and purified by flash column chromatography, eluting with CH_2Cl_2 to afford clean **288** as a yellow solid (10.2 g). Additional **288** (5.6 g) could be obtained by recrystallization of the mixed fractions (~60 mL CH_2Cl_2) to afford a total of 15.8 g **288** (60%).

mp = 140-142 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.29 (d, *J* = 0.7 Hz, 1H, H_7), 7.51 (dd, *J* = 7.5, 1.7 Hz, 1H, H, C_6), 7.36 (t, *J* = 7.8 Hz, 1H, H_5), 7.29 (dd, *J* = 8.1, 1.7 Hz, 1H, C_4), 5.95 (s, 1H, H_8);

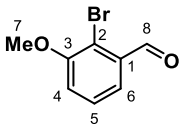
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 191.2 (CH, C_7), 153.0 (Quat, C_3), 133.8 (Quat, C_1), 128.9 (CH, C_5), 122.8 (CH, C_6), 121.7 (CH, C_4), 114.0 (Quat C_2);

FTIR (film) ν_{max}/cm^{-1} = 3179, 2981, 1661, 1566, 1462, 1399, 1347, 1296, 1220, 1167;

LRMS (ESI$^+$) calculated for $C_7H_6BrO_2^+$ = 201, 203, mass found = 201, 203.

The data matched those of the literature.[172]

2-Bromo-3-methoxybenzaldehyde, 289



According to a literature procedure,[173] potassium carbonate (11.7 g, 84.7 mmol, 2.0 eq) was added to a solution of **288** (8.50 g, 42.3 mmol, 1.0 eq) in acetone (115 mL) at 0 °C. Methyl iodide (3.95 mL, 64.5 mmol, 1.5 eq) was added dropwise, the reaction mixture allowed to warm to room temperature, and then stirred for 16 hours. The mixture was diluted in water (750 mL) and

extracted with EtOAc (3 × 350 mL). The combined organic extracts were washed with brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, to afford **289** as a white solid (8.01 g, 88%).

mp = 70-72 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.43 (d, *J* = 0.8 Hz, 1H, H_8), 7.51 (dd, *J* = 7.7, 1.5 Hz, 1H, H_6), 7.37 (td, *J* = 7.9, 0.8 Hz, 1H, H_5), 7.12 (dd, *J* = 8.1, 1.5 Hz, 1H, H_4), 3.95 (s, 3H, H_7);

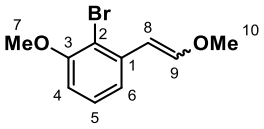
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 192.3 (CH, C_8), 156.3 (Quat, C_3), 134.8 (Quat, C_1), 128.4 (CH, C_5), 121.4 (CH, C_6), 117.1 (Quat, C_2), 116.9 (CH, C_4), 56.7 (CH_3, C_7);

FTIR (film) ν_{max}/cm^{-1} = 2925, 2842, 2358, 1696, 1570, 1468, 1432, 1382, 1303, 1273, 1239, 1063, 1032;

HRMS (ACI$^+$) calculated for $C_8H_7{}^{79}BrO_2{}^+$ = 214.9702, mass found = 214.9709.

The data matched those of the literature.[173]

2-Bromo-1-methoxy-3-(2-methoxyvinyl)benzene, 291



Analogously to a literature procedure,[124] KO^{t}Bu (1.56 g, 13.9 mmol, 1.3 eq) was added to a stirred solution of $MeOCH_2PPH_3Cl$ (4.77 g, 13.9 mmol, 1.3 eq) in THF (18 mL) at 0°C under N_2. The mixture was allowed to stir for 1 hour at 0 °C, before a solution of **289** (2.30 g, 1.07 mmol, 1.0 eq) in THF (8 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour before saturated NH_4Cl (40 mL) was added and the biphasic mixture stirred for 5 minutes. The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic extracts washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in Et_2O (15 mL) and stirred for 30 minutes. The insoluble triphenylphosphine oxide was filtered off and washed with Et_2O (2 × 15 mL), and the filtrate was concentrated under reduced pressure. Purification *via* flash column chromatography, eluting with

1:30 EtOAc/petrol 40-60, afforded **291** as a 1.3:1 mixture of *E*/*Z*-isomers as a colourless oil (2.30 g, 95%).

(*E*)-Isomer (major):

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.17 (t, *J* = 8.2 Hz, 1H, H_5), 7.01 (d, *J* = 12.9 Hz, 1H, H_9), 6.98 (dd, *J* = 7.9, 1.2 Hz, 1H, H_6), 6.72 (dd, *J* = 8.1, 1.3 Hz, 1H, H_4), 6.17 (d, *J* = 12.9 Hz, 1H, H_8), 3.89 (s, 3H, H_7), 3.74 (s, 3H, H_{10});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 156.2 (Quat, C_3), 150.7 (CH, C_9), 138.0 (Quat, C_1), 127.8 (CH, C_5), 117.9 (CH, C_6), 112.4 (Quat, C_2), 108.9 (CH, C_4), 104.7 (CH, C_8), 56.5 (CH_3, C_{10}), 56.3 (CH_3, C_7);

(*Z*)-Isomer (minor):

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.68 (dd, *J* = 7.9, 1.4 Hz, 1H, H_6), 7.22 (t, *J* = 8.2 Hz, 1H, H_5), 6.73 (dd, *J* = 8.1, 1.3 Hz, 1H, H_4), 6.27 (d, *J* = 7.2 Hz, 1H, H_9), 5.69 (d, *J* = 7.2 Hz, 1H, H_8), 3.89 (s, 3H, H_7), 3.79 (s, 3H, H_{10});

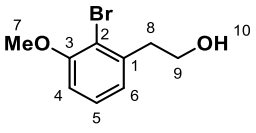
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 155.9 (Quat, C_3), 149.4 (CH, C_9), 136.6 (Quat, C_1), 127.4 (CH, C_5), 122.6 (CH, C_6), 112.2 (Quat, C_2), 109.2 (CH, C_4), 104.1 (CH, C_8), 60.9 (CH_3, C_{10}), 56.4 (CH_3, C_7);

Mixture of isomers:

FTIR (film) ν_{max}/cm^{-1} = 2936, 2836, 1636, 1589, 1562, 1468, 1420, 1310, 1265, 1212, 1160, 1103, 1062, 1023;

HRMS (EI^+) calculated for $C_{10}H_{11}{}^{79}BrO_2{}^+$ = 241.9934, mass found = 241.9937.

2-(2-Bromo-3-methoxyphenyl)ethan-1-ol, 292



Analogously to a literature procedure,[124] aqueous HCl (6 M, 4.6 mL, 3.4 eq) was added to a solution of **291** (2.00 g, 8.23 mmol, 1.0 eq) in THF (11.9 mL) and heated to reflux for 2 hours. The solution was allowed to cool to room temperature, diluted in water (5 mL) and the phases separated. The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic extracts washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated under reduced

pressure. The crude residue was dissolved in methanol (13.7 mL) and cooled to 0 °C. To this solution was added sodium borohydride (311 mg, 8.23 mmol, 1.0 eq) and the reaction mixture stirred for 2 hours at room temperature. The reaction mixture was concentrated and the residue was treated with 3 M HCl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:3 EtOAc/petrol 40-60, to afford **292** as a colourless oil (1.715 g, 81%).

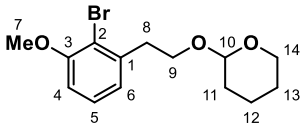
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.21 (t, *J* = 7.9 Hz, 1H, H_5), 6.90 (dd, *J* = 7.7, 1.4 Hz, 1H, H_6), 6.79 (dd, *J* = 8.2, 1.4 Hz, 1H, H_4), 3.89 (s, 3H, H_7), 3.88 (t, *J* = 6.7 Hz, 2H, H_9), 3.07 (t, *J* = 6.7 Hz, 2H, H_8), 1.58 (s, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.2 (Quat, C_3), 139.6 (Quat, C_1), 127.8 (CH, C_5), 123.3 (CH, C_6), 114.1 (Quat, C_2), 110.1 (CH, C_4), 62.1 (CH_2, C_9), 56.4 (CH_3, C_7), 39.6 (CH_2, C_8);

FTIR (film) ν_{max}/cm^{-1} = 3347, 2938, 2838, 1593, 1571, 1469, 1432, 1300, 1267, 1079, 1032;

HRMS (ACI^+) calculated for $C_9H_{11}{}^{79}BrO_2NH_4^+$ = 248.0286, mass found = 248.0281.

2-(2-Bromo-3-methoxyphenethoxy)tetrahydro-2*H*-pyran, 293



Dihydropyran (2.27 mL, 24.9 mmol, 3.0 eq) and PPTS (208 mg, 0.831 mmol, 1.0 eq) were added to a solution of **292** (1.92 g, 8.31 mmol, 1.0 eq) in CH_2Cl_2 (11.5 mL) and the resulting solution stirred for 4 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (15 mL), saturated aqueous $NaHCO_3$ (15 mL), water (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by flash column chromatography to afford **293** as a colourless oil (2.14 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.19 (t, *J* = 7.9 Hz, 1H, H_5), 6.91 (dd, *J* = 7.6, 1.4 Hz, 1H, H_6), 6.76 (dd, *J* = 8.2, 1.4 Hz, 1H, H_4), 4.61 (dd, *J* = 4.3, 2.8 Hz, 1H, H_{10}), 4.00-3.89 (m, 1H, H_9), 3.88 (s, 3H, H_7), 3.78

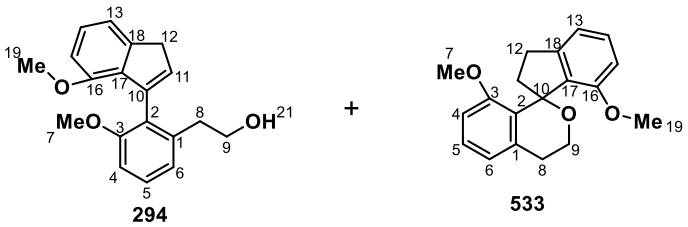
(ddd, *J* = 11.1, 8.3, 3.3 Hz, 1H, H_{14}), 3.65 (dt, *J* = 9.8, 7.2 Hz, 1H, H_9), 3.52-3.41 (m, 1H, H_{14}), 3.10 (t, *J* = 7.3 Hz, 2H, H_8), 1.99-1.65 (m, 2H, H_{11} & H_{13}), 1.65-1.42 (m, 4H, $H_{11'}$, H_{12}, $H_{12'}$ & $H_{13'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.0 (Quat, C_3), 140.1 (Quat, C_1), 127.6 (CH, C_5), 123.2 (CH, C_6), 114.2 (Quat, C_2), 109.8 (CH, C_4), 98.7 (CH, C_{10}), 66.4 (CH_2, C_9), 62.2 (CH_2, C_{14}), 56.3 (CH_3, C_7), 36.7 (CH, C_8), 30.7 (CH_2, C_{11}), 25.5 (CH_2, C_{13}), 19.5 (CH_2, C_{12});

FTIR (film) ν_{max}/cm^{-1} = 2939, 2870, 1571, 1469, 1432, 1267, 1134, 1120, 1075, 1030;

HRMS (ACI$^+$) calculated for $C_{14}H_{19}{}^{79}BrO_3NH_4^+$ = 332.0856, mass found = 332.0859.

2-(2-(1*H*-Inden-3-yl)-3-methoxyphenyl)ethan-1-ol, 294 & 8'-methoxy-2,3-dihydrospiro[indene-1,1'-isochromane], 533



Magnesium turnings (116 mg, 4.76 mmol, 1.5 eq) were heated to 150 °C under vacuum and stirred vigorously for 1 hour. The flask was filled with nitrogen and allowed to cool to room temperature before THF (15 mL) was added, followed by the slow addition of **203** (1.00 g, 3.17 mmol, 1.0 eq). The solution was heated to reflux, at which point 1,2-dibromoethane (0.1 mL) was added to initiate formation of the Grignard reagent and the bubbling mixture stirred at reflux for 2 hours and then cooled to 30 °C. Meanwhile, 7-methoxyindan-1-one **286** (618 mg, 3.81 mmol, 1.2 eq) and cerium trichloride (1.88 g, 7.62 mmol, 2.4 eq) were flame-dried and then suspended in THF (5 mL) and stirred for 2 hours. After 2 hours had elapsed, the Grignard solution (~15 mL) was added to the indanone solution with a cannula and stirred at room temperature for 2 hours. 3 M HCl (38 mL, 92.0 mmol, 36 eq) was added and the mixture stirred for a further 30 minutes. The mixture was concentrated under reduced pressure and then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts purified by flash column chromatography, eluting with 1:0 to 1:19 CH_2Cl_2/methanol, to afford the product as a mixture of **294**, **533** and THP-protected alcohol (35%).

This mixture was dissolved in THF (15 mL) and 3 M HCl (20 mL) was added and the mixture stirred for 3 hours, at which point all the THP-protected alcohol had been consumed. The mixture was concentrated under reduced pressure and then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts purified by flash column chromatography, eluting with CH_2Cl_2, to afford clean **294** as a yellow oil (36 mg, 6%) and **533** as a yellow solid (71 mg, 12%).

294:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.26 (t, *J* = 7.9 Hz, 1H, H_{14}), 7.18-7.14 (m, 2H, H_5 & H_6), 6.92 (dd, *J* = 7.7, 1.2 Hz, 1H, H_{13}), 6.82 (dd, *J* = 8.3, 1.2 Hz, 1H, H_{15}), 6.77-6.71 (m, 1H, H_4), 6.23 (t, *J* = 2.1 Hz, 1H, H_{11}), 3.69 (s, 3H, H_7), 3.67-3.60, (m, 2H, H_9), 3.55 (dd, *J* = 5.2, 2.0 Hz, 2H, H_{12}), 3.51 (s, 3H, H_{19}), 2.97 (dt, *J* = 13.3, 6.5 Hz, 1H, H_8), 2.72 (dtd, *J* = 13.1, 6.2, 3.3 Hz, 2H, $H_{8'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 158.1 (Quat, C_3), 154.2 (Quat, C_{16}), 146.3 (Quat, C_{18}), 139.1 (Quat, C_1), 137.7 (Quat, C_{10}), 134.0 (Quat, C_{17}), 131.1 (CH, C_{11}), 128.2 (CH, C_{14}), 127.9 (Quat, C_2), 126.0 (CH, C_5), 121.7 (CH, C_{13}), 117.3 (CH, C_6), 109.6 (CH, C_4), 108.5 (CH, C_{15}), 63.2 (CH_2, C_9), 55.8 (CH_3, C_7), 55.7 (CH_3, C_{19}), 38.8 (CH_2, C_{12}), 36.6 (CH_2, C_8);

FTIR (film) ν_{max}/cm^{-1} = 3436, 2937, 1701, 1598, 1480, 1467, 1438, 1342, 1263, 1198, 1169, 1152, 1081, 1067;

HRMS (ACI$^+$) calculated for $C_{19}H_{21}O_3^+$ = 297.1485, mass found = 297.1482.

533:

mp = 102-104 °C;

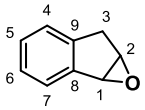
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.20 (dd, *J* = 8.0, 7.5 Hz, 1H, H_5), 7.15 (t, *J* = 7.8 Hz, 1H, H_{14}), 6.91 (dq, *J* = 7.5, 0.9 Hz, 1H, H_6), 6.82 (dq, *J* = 7.6, 0.9 Hz, 1H, H_{13}), 6.70-6.65 (m, 1H, H_{15}), 6.62 (dd, *J* = 8.0, 0.9 Hz, 1H, H_4), 4.13 (ddd, *J* = 11.1, 5.2, 3.3 Hz, 1H, H_9), 3.95 (ddd, *J* = 11.1, 10.0, 3.3 Hz, 1H, H_9), 3.47 (s, 3H, H_7), 3.37 (s, 3H, H_{19}), 3.32-3.21 (m, 1H, H_{12}), 3.19-3.09 (m, 1H, H_8), 3.09-2.99 (m, 1H, H_{12}), 2.76 (dt, *J* = 16.0, 3.2 Hz, 1H, H_8), 2.65 (ddd, *J* = 13.4, 9.5, 7.6 Hz, 1H, H_{11}), 2.44 (ddd, *J* = 13.4, 8.7, 2.7 Hz, 1H, H_{11});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.5 (Quat, C_3), 156.1 (Quat, C_{16}), 146.6 (Quat, C_{18}), 136.0 (Quat, C_1), 134.8 (CH, C_{17}), 130.1 (CH, C_2), 129.2 (CH, C_5), 126.6 (CH, C_{14}), 121.1 (CH, C_{13}), 117.3 (CH, C_6), 109.7 (CH, C_{15}), 109.3 (CH, C_4), 86.0 (Quat, C_{10}), 61.0 (CH_2, C_9), 55.6 (CH_3, C_7), 55.6 (CH_3, C_{19}), 38.4 (CH_2, C_{11}), 31.0 (CH_2, C_{12}), 29.6 (CH_2, C_8);

FTIR (film) ν_{max}/cm^{-1} = 2932, 2834, 2360, 2342, 1586, 1470, 1438, 1310, 1265, 1086, 1059, 1032;

HRMS (ESI^+) calculated for $C_{19}H_{21}O_3^+$ = 297.1485, mass found = 297.1463.

Indene oxide, 297



According to a literature procedure,[174] saturated $NaHCO_3$ (40 mL) and *m*-CPBA (70% w/w, 3.96 g, 25.8 mmol, 1.0 eq) were added to a solution of indene (2.00 g, 17.2 mmol, 1.0 eq) in chloroform (40 mL) at 0 °C. The solution was stirred for 5 hours at room temperature after which time a further portion of *m*-CPBA (70% w/w, 1.98 g, 12.9 mmol, 0.5 eq) was added and the solution stirred for a further two hours until the starting material had been fully consumed. The phases were separated and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ (30 mL) and water (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, to afford **297** as a white solid (1.36 g, 60%).

mp = 28-30 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.47 (dt, *J* = 7.3, 1.0 Hz, 1H, H_4), 7.29-7.11 (m, 3H, H_5, H_6 & H_7), 4.23 (dd, *J* = 2.9, 1.2 Hz, 1H, H_1), 4.10 (t, *J* = 2.9 Hz, 1H, H_2), 3.18 (dt, *J* = 17.9, 0.5 Hz, 1H, H_3), 2.94 (dd, *J* = 18.0, 2.9 Hz, 1H, $H_{3'}$);

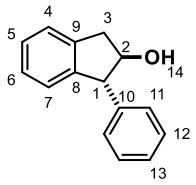
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 143.5 (Quat, C_9), 140.8 (Quat, C_8), 128.6 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 126.1 (CH, C_{Ar}), 125.2 (CH, C_4), 59.1 (CH, C_1), 57.7 (CH, C_2), 34.6 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3423, 3045, 2910, 2359, 2342, 1751, 1476, 1463, 1390, 1213, 1184, 1102, 1021;

HRMS (MCI$^+$) calculated for $C_9H_9O^+$ = 133.0648, mass found = 133.0646.

The data matched those of the literature.[175]

trans-1-Phenyl-2,3-dihydro-1_H_-inden-2-ol, 299



To a solution of phenylmagnesium bromide (3 M in Et_2O, 253 µL, 0.759 mmol, 1.0 eq) in THF (0.5 mL) was added a suspension of **297** (100 mg, 0.759 mmol, 1.0 eq) and copper(I) iodide (12 mg, 0.061 mmol, 0.08 eq) in THF (0.8 mL) and the resulting suspension stirred for 2 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **299** as a pale yellow oil (>20:1 *dr*, 141 mg, 89%).

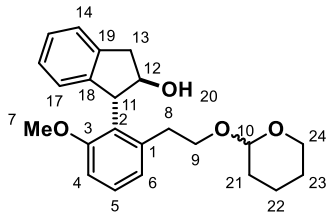
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.31-7.04 (m, 8H, H_{Ar}), 6.86 (d, *J* = 7.4 Hz, 1H, H_{Ar}), 4.33 (q, *J* = 7.1 Hz, 1H, H_1), 4.05 (d, *J* = 6.8 Hz, 1H, H_2), 3.17 (dd, *J* = 15.6, 6.9 Hz, 1H, H_3), 2.82 (dd, *J* = 15.6, 7.3 Hz, 1H, H_3), 2.69 (br s, 1H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 143.8 (Quat, C_8), 142.1 (Quat, C_{10}), 140.6 (Quat, C_9), 128.8 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 127.1 (CH, C_{Ar}), 127.0 (CH, C_{Ar}), 125.3 (CH, C_{Ar}), 124.7 (CH, C_{Ar}), 82.2 (CH, C_2), 60.2 (CH, C_1), 40.1 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3335, 3026, 2904, 1602, 1494, 1474, 1454, 1331, 1140, 1075, 1035;

HRMS (EI$^+$) calculated for $C_{15}H_{14}O^+$ = 210.1039, mass found = 210.1044.

***trans*-1-(2-Methoxy-6-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)phenyl)-2,3-dihydro-1*H*-inden-2-ol, 301**



Magnesium turnings (46.3 mg, 1.90 mmol, 1.5 eq) were heated to 150 °C under vacuum and stirred vigorously for 1 hour. The flask was filled with nitrogen and allowed to cool to room temperature before THF (5 mL) was added, followed by the slow addition of **293** (400 mg, 1.27 mmol, 1.0 eq). The solution was heated to reflux, at which point 1,2-dibromoethane (0.05 mL) was added to initiate formation of the Grignard reagent and the bubbling mixture stirred at reflux for 2 hours and then cooled to 30 °C. This solution was added to a suspension of **297** (167 mg, 1.27 mmol, 1.0 eq) and copper(I) iodide (12 mg, 0.063 mmol, 0.05 eq) in THF (2 mL) and the resulting suspension stirred for 2 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **301** as an orange oil (1:1 *dr*, 350 mg, 75%).

Both diastereoisomers:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.22-7.15 (m, 4H, H_5 & H_{14}), 7.11 (td, *J* = 7.4, 1.1 Hz, 2H, H_{16}), 7.03 (t, *J* = 7.4 Hz, 2H, H_{15}), 6.92 (ddd, *J* = 7.7, 3.2, 1.2 Hz, 2H, H_6), 6.70 (m, 4H, H_4 & H_{17}), 5.11-4.92 (m, 2H, H_{12}), 4.64-4.51 (m, 4H, H_{11} & H_{10}), 4.14-3.94 (m, 2H, H_9), 3.86 (br s, 2H, H_{20}), 3.82-3.68 (m, 2H, $H_{9'}$), 3.63 (ddd, *J* = 11.0, 7.8, 3.4 Hz, 2H, H_{24}), 3.53-3.37 (m, 4H, H_{13} & $H_{24'}$), 3.34 (s, 6H, H_7), 3.24-2.94 (m, 6H, $H_{13'}$ & H_8), 1.86-1.36 (m, 14H, H_{21}, H_{22} & H_{23});

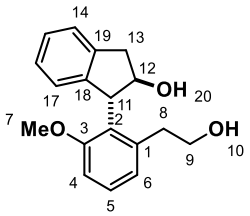
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 158.6 (Quat, C_3), 158.6 (Quat, C_3), 145.5 (Quat, C_{18}), 145.5 (Quat, C_{18}), 140.1 (Quat, C_1), 140.0 (Quat, C_1), 139.9 (Quat, C_{19}), 139.9 (Quat, C_{19}), 129.1 (Quat, C_2), 128.9

(Quat, C_2), 127.6 (CH, C_5), 127.5 (CH, C_5), 126.2 (CH, C_{16}), 126.2 (CH, C_{16}), 125.9 (CH, C_{15}), 125.9 (CH, C_{15}), 124.1 (CH, C_{14}), 124.1 (CH, C_{14}), 122.7 (CH, C_6), 122.7 (CH, C_6), 110.7 (CH, C_4), 110.6 (CH, C_4), 98.8 (CH, C_{10}), 98.7 (CH, C_{10}), 79.0 (CH, C_{12}), 78.8 (CH, C_{12}), 68.7 (CH_2, C_9), 68.6 (CH_2, C_9), 62.2 (CH_2, C_{24}), 62.1 (CH_2, C_{24}), 55.3 (CH_3, C_7), 55.3 (CH_3, C_7), 54.5 (CH, C_{11}), 54.4 (CH, C_{11}), 41.3 (CH_2, C_{13}), 41.3 (CH_2, C_{13}), 34.0 (CH_2, C_8), 34.0 (CH_2, C_8), 30.5 (CH_2, C_{21}), 30.4 (CH_2, C_{21}), 25.3 (CH_2, C_{23}), 25.3 (CH_2, C_{23}), 19.4 (CH_2, C_{22}), 19.4 (CH_2, C_{22});

FTIR (film) ν_{max}/cm^{-1} = 3436, 2941, 1580, 1469, 1438, 1352, 1254, 1200, 1182, 1135, 1119, 1078, 1026;

HRMS (ESI^+) calculated for $C_{23}H_{28}O_4Na^+$ = 391.1880, mass found = 391.1881.

trans-1-(2-(2-Hydroxyethyl)-6-methoxyphenyl)-2,3-dihydro-1_H_-inden-2-ol, 302



ConcHCl (0.05 mL, 0.701 mmol, 0.7 eq) was added to a solution of **301** (306 mg, 0.831 mmol, 1.0 eq) in methanol (2.3 mL) and the solution stirred for 30 minutes. The reaction mixture was diluted in water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:1 EtOAc/petrol 40-60, to afford **302** as a white solid (>20:1 *dr*, 350 mg, 75%).

mp = 98-100 °C;

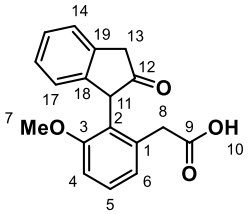
^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.24-7.15 (m, 2H, H_5 & H_{14}), 7.11 (tt, *J* = 7.4, 1.2 Hz, 1H, H_{15}), 7.03 (t, *J* = 7.4 Hz, 1H, H_{16}), 6.88 (dd, *J* = 7.7, 1.2 Hz, 1H, H_6), 6.72 (dd, *J* = 8.2, 1.2 Hz, 1H, H_4), 6.66 (d, *J* = 7.4 Hz, 1H, H_{17}), 5.02 (dt, *J* = 7.9, 7.0 Hz, 1H, H_{12}), 4.59 (d, *J* = 6.7 Hz, 1H, H_{11}), 3.97 (ddd, *J* = 10.8, 6.2, 4.9 Hz, 1H, H_9), 3.82 (ddd, *J* = 10.5, 8.6, 5.3 Hz, 1H, $H_{9'}$), 3.49-3.38 (m, 1H, H_{13}), 3.35 (s, 3H, H_7), 3.14 (ddd, *J* = 14.6, 8.8, 6.1 Hz, 1H, H_8), 3.01-2.89 (m, 2H, $H_{8'}$ & $H_{13'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 158.6 (Quat, C_3), 145.3 (Quat, C_{18}), 140.0 (Quat, C_1), 139.8 (Quat, C_{19}), 129.2 (Quat, C_2), 127.8 (CH, C_5), 126.2 (CH, C_{16}), 126.0 (CH, C_{15}), 124.1 (CH, C_{14}), 122.7 (CH, C_6), 122.6 (CH, C_{17}), 110.7 (CH, C_4), 78.8 (CH, C_{12}), 64.1 (CH_2, C_9), 55.3 (CH_3, C_7), 54.1 (CH, C_{11}), 41.3 (CH_2, C_{13}), 36.4 (CH_2, C_8);

FTIR (film) ν_{max}/cm^{-1} = 3324, 3067, 3019, 2937, 2836, 2361, 2342, 1599, 1580, 1469, 1437, 1337, 1281, 1253, 1212, 1163, 1078, 1042, 1024;

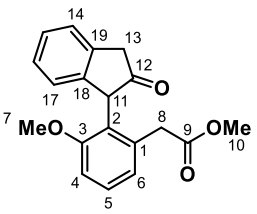
HRMS (ACI^+) calculated for $C_{18}H_{20}O_3NH_4^+$ = 302.1751, mass found = 302.1742.

2-(3-Methoxy-2-(2-oxo-2,3-dihydro-1*H*-inden-1-yl)phenyl)acetic acid, 303



Jones reagent (2 M, 406 µL, 0.812 mmol, 3.3 eq) was added to a solution of **302** (70 mg, 0.246 mmol, 1.0 eq) in acetone (2.47 mL). The reaction mixture was stirred for 1.75 hours, and then quenched with ^{i}PrOH (2 mL) at which point the orange solution turned green to signify consumption of the Cr(VI) species. Solvent was evaporated under a flow of N_2, and the residue diluted in water (5 mL), extracted with CH_2Cl_2 (3 × 5 mL) and concentrated to afford crude acid **303** as a brown gum (73 mg, quant) which was used without any further purification.

Methyl 2-(3-methoxy-2-(2-oxo-2,3-dihydro-1*H*-inden-1-yl)phenyl)acetate, 304



Crude acid **303** (73 mg, 0.246 mmol, 1.0 eq) was dissolved in a mixed solvent of 1:1 CH_2Cl_2/methanol (2.0 mL) and to this solution was added $TMSCHN_2$ (2 M in hexane, 123 µL, 246 mmol, 1.0 eq) and the reaction mixture stirred for 1 hour. The reaction mixture was quenched by the addition of acetic acid (2 mL) and then diluted in water (10 mL) and CH_2Cl_2 (10 ml). The

phases were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, to afford **304** as an orange solid (30 mg, 40%).

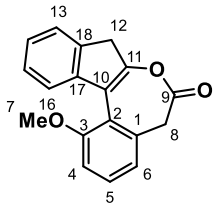
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.32 (d, *J* = 7.5 Hz, 1H, H_{14}), 7.23 (m, 2H, H_5 & H_{15}), 7.16 (t, *J* = 7.5 Hz, 1H, H_{16}), 6.97 (d, *J* = 7.7 Hz, 1H, H_6), 6.94 (d, *J* = 7.6 Hz, 1H, H_{17}), 6.74 (d, *J* = 8.2 Hz, 1H, H_4), 4.85 (s, 1H, H_{11}), 3.84 (dd, *J* = 41.3, 16.3 Hz, 2H, H_8), 3.74-3.64 (m, 5H, H_{10} & H_{13}), 3.42 (s, 3H, H_7);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 214.4 (Quat, C_{12}), 170.8 (Quat, C_9), 155.8 (Quat, C_3), 141.2 (Quat, C_{18}), 136.3 (Quat, C_{19}), 133.8 (Quat, C_1), 127.6 (CH, C_5), 127.4 (Quat, C_2), 126.2 (CH, C_{16}), 126.0 (CH, C_{15}), 123.2 (CH, C_{14}), 123.1 (CH, C_{17}), 122.5 (CH, C_6), 110.5 (CH, C_4), 54.7 (CH_3, C_7), 52.6 (CH, C_{11}), 51.4 (CH_3, C_{10}), 42.4 (CH_2, C_{13}), 38.6 (CH_2, C_8);

FTIR (film) ν_{max}/cm^{-1} = 2952, 2919, 2849, 2361, 2338, 1737 (br), 1585, 1469, 1437, 1319, 1260, 1143, 1069;

HRMS (ESI$^+$) calculated for $C_{19}H_{18}O_4Na^+$ = 331.1097, mass found = 331.1096.

1-Methoxy-5,8-dihydro-6*H*-benzo[*d*]indeno[2,1-*b*]oxepin-6-one, 305



Prepared according to **General Procedure A**.

Esterification with crude diacid **303** (30 mg, 0.10 mmol, 1.0 eq), EDC·HCl (30 mg, 0.16 mmol, 1.5 eq), DMAP (1.0 mg, 0.005 mmol, 0.05 eq), and pentafluorophenol (20 mg, 0.10 mmol, 1.0 eq). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **305** as an orange solid (20 mg, 70%).

mp = 184-186 °C (sublimation);

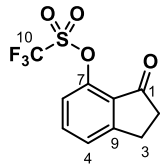
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.46-7.40 (m, 2H, H_5 & H_{13}), 7.32-7.28 (m, 2H, H_{15} & H_{16}), 7.23 (ddd, *J* = 7.4, 5.5, 3.1 Hz, 1H, H_{14}), 7.02 (m, 2H, H_4 & H_6), 3.92-3.81 (m, 5H, H_7, H_8 & H_{12}), 3.66-3.55 (m, 2H, $H_{8'}$ & $H_{12'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 166.1 (Quat, C_9), 155.7 (Quat, C_3), 153.7 (Quat, C_{11}), 141.0 (Quat, C_{17}), 135.3 (Quat, C_{18}), 131.8 (Quat, C_2), 129.5 (CH, C_5), 125.3 (CH, C_{15}), 123.7 (CH, C_{14}), 122.5 (CH, C_{13}), 122.3 (CH, C_{16}), 121.7 (Quat, C_{10}), 120.2 (CH, C_6), 118.5 (Quat, C_1), 109.5 (CH, C_4), 54.2 (CH_3, C_7), 40.3 (CH_2, C_8), 36.6 (CH_2, C_{12});

FTIR (film) ν_{max}/cm^{-1} = 2955, 2920, 2850, 2360, 2342, 1774, 1576, 1471, 1460, 1438, 1269, 1245, 1216, 1205, 1160, 1111, 1098, 1069;

HRMS (ESI^+) calculated for $C_{18}H_{15}O_3^+$ = 279.1016, mass found = 279.1017.

3-Oxo-2,3-dihydro-1*H*-inden-4-yl trifluoromethanesulfonate, 318



According to a literature procedure,[141] Et_3N (520 µL, 3.75 mmol, 1.11 eq) and *N*-phenyl triflimide (1.25 g, 3.51 mmol, 1.04 eq) was added to a solution of **285** (500 mg, 3.37 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) and the mixture stirred for 24 hours. The reaction mixture was washed with water (5 mL) and brine (5 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried over $MgSO_4$, concentrated and purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **318** as an orange solid (732 mg, 77%, quant based on recovered starting material) and recovered **285** (125 mg, 25%).

mp = 38-40 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.65 (t, *J* = 7.8 Hz, 1H, H_5), 7.51 (dq, *J* = 7.8, 1.0 Hz, 1H, H_6), 7.17 (d, *J* = 8.0 Hz, 1H, H_4), 3.24-3.14 (m, 2H, H_2), 2.82-2.69 (m, 2H, H_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 202.1 (Quat, C_1), 157.6 (Quat, C_9), 145.2 (Quat, C_7), 136.0 (CH, C_5), 129.1 (Quat, C_8), 127.0 (CH, C_6), 120.2 (CH, C_4), 118.8 (q, *J* = 320.0 Hz, C_{10}), 36.6 (CH_2, C_2), 25.7 (CH_2, C_3);

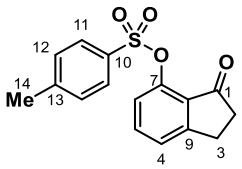
^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −73.5;

FTIR (film) ν_{max}/cm^{-1} = 2981, 1721, 1616, 1470, 1427, 1209, 1168, 1140;

LRMS (ESI^+) calculated for $C_{10}H_7O_4F_3SNa^+$ = 303, mass found = 303.

The data matched those of the literature.[141]

3-Oxo-2,3-dihydro-1*H*-inden-4-yl 4-methylbenzenesulfonate, 319



Hünig's base (3.02 mL, 20.2 mmol, 3.0 eq) and tosyl chloride (1.93 g, 10.1 mmol, 1.5 eq) were added to a solution of **285** (1.00 g, 6.75 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred for 24 hours and quenched by the addition of water (30 mL). The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic extracts washed with 1 M aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, concentrated and purified by flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, to afford **319** as a yellow solid (1.92 g, 94%).

mp = 94-96 °C;

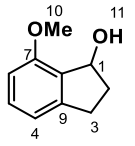
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.94-7.87 (m, 2H, H_{12}), 7.55 (t, *J* = 7.8 Hz, 1H, H_5), 7.40-7.35 (m, 1H, H_6), 7.32 (d, *J* = 8.2 Hz, 2H, H_{11}), 7.21 (dd, *J* = 8.0, 0.9 Hz, 1H, H_4), 3.15-3.03 (m, 2H, H_3), 2.64-2.56 (m, 2H, H_2), 2.44 (s, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 202.3 (Quat, C_1), 157.2 (Quat, C_9), 145.4 (Quat, H_7), 145.3 (Quat, C_{13}), 135.6 (CH, C_5), 132.6 (Quat, C_{10}), 129.6 (CH, C_{11}), 129.4 (Quat, C_8), 128.8 (CH, C_{12}), 125.6 (CH, C_6), 121.6 (CH, C_4), 36.7 (CH_2, C_2), 25.5 (CH_2, C_3), 21.8 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 3068, 2926, 1716, 1608, 1583, 1468, 1374, 1354, 1329, 1293, 1241, 1220, 1192, 1172, 1093;

HRMS (ESI^+) calculated for $C_{16}H_{15}O_4S^+$ = 303.0686, mass found = 303.0682.

7-Methoxy-2,3-dihydro-1*H*-inden-1-ol, 320



According to a literature procedure,[176] sodium borohydride (397 mg, 10.5 mmol, 1.0 eq) was added to a solution of **286** (1.70 g, 10.5 mmol, 1.0 eq) in 1:1 THF/methanol (42 mL) at 0 °C. The reaction mixture was stirred at this temperature for 10 minutes and then allowed to warm to room temperature and stirred for 1 additional hour. The reaction was diluted in water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with 1 M aqueous HCl (35 mL) and saturate aqueous $NaHCO_3$ (35 mL), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography, eluting with 2:3 EtOAc/petrol 40-60, to afford **320** as a white solid (1.33 g, 77%).

mp = 48-50 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.23 (t, *J* = 7.8 Hz, 1H, H_5), 6.95-6.77 (m, 1H, H_4), 6.71 (dd, *J* = 8.1, 0.8 Hz, 1H, H_6), 5.48 (dd, *J* = 7.2, 4.6 Hz, 1H, H_1), 3.87 (s, 3H, H_{10}), 3.14-3.02 (m, 1H, H_3), 2.88-2.75 (m, 1H, H_3), 2.45 (dddd, *J* = 13.7, 8.7, 7.2, 5.1 Hz, 1H, H_2), 2.03 (dddd, *J* = 13.5, 8.9, 6.1, 4.6 Hz, 1H, H_2);

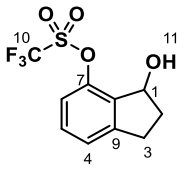
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 156.4 (Quat, C_7), 145.6 (Quat, C_9), 132.2 (Quat, C_8), 130.0 (CH, C_5), 117.5 (CH, C_4), 108.0 (CH, C_6), 74.5 (CH, C_1), 55.2 (CH_3, C_{10}), 33.9 (CH_2, C_2), 30.4 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3437, 2937, 2837, 1606, 1591, 1479, 1440, 1338, 1308, 1262, 1175, 1073, 1047, 1026;

HRMS (MCl^+) calculated for $C_{10}H_{13}O_2^+$ = 165.0910, mass found = 165.0904.

The data matched those of the literature.[176]

3-Hydroxy-2,3-dihydro-1*H*-inden-4-yl trifluoromethanesulfonate, 321



According to a literature procedure,[177] sodium borohydride (52 mg, 1.42 mmol, 1.0 eq) was added to a solution of **318** (383 mg, 1.42 mmol, 1.0 eq) in methanol (8 mL) at 0 °C and the solution stirred for 1 hour. The reaction mixture was poured onto water (40 mL) and CH_2Cl_2 (50 mL) and the phases separated. The organic phase was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, to afford **321** as a pale yellow solid (342 mg, 88%).

mp = 43-45 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 (t, *J* = 7.8 Hz, 1H, H_5), 7.31-7.27 (m, 1H, H_4), 7.09 (d, *J* = 8.0 Hz, 1H, H_6), 5.59-5.37 (m, 1H, H_1), 3.21 (dt, *J* = 15.5, 7.4 Hz, 1H, H_3), 2.89 (ddd, *J* = 16.4, 8.6, 4.9 Hz, 1H, H_3), 2.46 (ddt, *J* = 13.4, 8.5, 6.6 Hz, 1H, H_2), 2.21 (d, *J* = 5.1 Hz, 1H, H_{11}), 2.13 (dddd, *J* = 13.4, 8.4, 4.9, 3.8 Hz, 1H, H_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 148.1 (Quat, C_9), 146.1 (Quat, C_7), 137.0 (Quat, C_8), 130.6 (CH, C_5), 125.3 (CH, C_4), 119.2 (CH, C_6), 118.1 (q, *J* = 320.1 Hz, C_{10}), 73.9 (CH, C_1), 35.2 (CH_2, C_2), 30.5 (CH_2, C_3);

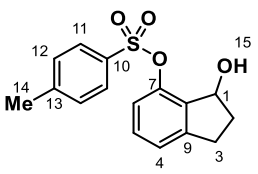
^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −73.6;

FTIR (film) ν_{max}/cm^{-1} = 3371, 2955, 2361, 2341, 1467, 1421, 1250, 1212, 1140;

HRMS (ESI$^+$) calculated for $C_{10}H_9O_4SNa^+$ = 305.0066, mass found = 305.0067.

The data matched those of the literature.[177]

3-Hydroxy-2,3-dihydro-1*H*-inden-4-yl 4-methylbenzenesulfonate, 322



Analogously to a literature procedure,[177] sodium borohydride (63 mg, 1.65 mmol, 1.0 eq) was added to a solution of **319** (500 mg, 1.65 mmol, 1.0 eq) in methanol (10 mL) at 0 °C and the solution stirred for 1 hour. The reaction mixture was poured onto water (50 mL) and CH_2Cl_2 (50 mL) and the phases separated. The organic phase was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, to afford **322** as a yellow solid (512 mg, quant).

mp = 46-48 °C;

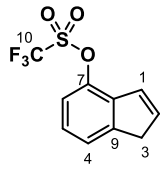
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.86-7.76 (m, 2H, H_{11}), 7.37 (d, *J* = 8.1 Hz, 2H, H_{12}), 7.23-7.08 (m, 2H, H_4 & H_5), 6.57 (dd, *J* = 7.8, 1.1 Hz, 1H, H_6), 5.30 (dt, *J* = 6.2, 2.2 Hz, 1H, H_1), 3.23 (dt, *J* = 16.1, 8.0 Hz, 1H, H_3), 3.01-2.88 (m, 1H, H_{15}), 2.82 (ddd, *J* = 16.2, 8.3, 3.2 Hz, 1H, H_3), 2.48 (s, 3H, H_{14}), 2.32-2.08 (m, 2H, H_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 148.0 (Quat, C_7), 145.9 (Quat, C_9), 145.7 (Quat, C_{13}), 138.4 (Quat, C_{10}), 132.2 (Quat, C_8), 130.0 (CH, C_{12}), 129.9 (CH, C_5), 128.7 (CH, C_{11}), 124.2 (CH, C_4), 120.2 (CH, C_6), 72.9 (CH, C_1), 34.7 (CH_2, C_2), 30.7 (CH_2, C_3), 21.8 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 3538, 2943, 2361, 1614, 1596, 1582, 1466, 1369, 1308, 1217, 1190, 1177, 1157, 1093, 1045, 1018;

HRMS (ESI^+) calculated for $C_{16}H_{16}O_4SNa^+$ = 327.0662, mass found = 327.0660.

1*H*-Inden-4-yl trifluoromethanesulfonate, 324



321 (340 mg, 1.20 mmol, 1.0 eq) and PTSA (12 mg, 0.06 mmol, 0.05 eq) were dissolved in toluene (4 mL) and heated to reflux for 3 hours with a Dean-Stark apparatus. The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **324** as an orange oil (310 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.48 (dt, *J* = 7.3, 0.9 Hz, 1H, H_4), 7.25 (dd, *J* = 8.3, 7.2 Hz, 1H, H_5), 7.19 (d, *J* = 8.2 Hz, 1H, H_6), 7.07-6.84 (m, 1H, H_1), 6.70 (dt, *J* = 5.6, 2.0 Hz, 1H, H_2), 3.51 (t, *J* = 2.0 Hz, 2H, H_3);

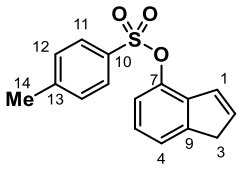
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 147.0 (Quat, C_7), 142.6 (Quat, C_9), 137.3 (Quat, C_8), 136.7 (CH, C_2), 127.0 (CH, C_1), 126.1 (CH, C_5), 123.7 (CH, C_4), 119.0 (CH, C_6), 118.7 (q, *J* = 320.5 Hz, C_{10}), 39.7 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −73.3;

FTIR (film) ν_{max}/cm^{-1} = 2970, 2361, 1583, 1467, 1422, 1315, 1250, 1208, 1169, 1140, 1100;

Compound **324** was not detected by ACI, MCI, EI or ESI mass spectrometry.

1*H*-Inden-4-yl 4-methylbenzenesulfonate, 325



322 (1.80 mg, 5.91 mmol, 1.0 eq) and PTSA (50.9 mg, 0.296 mmol, 0.05 eq) were dissolved in toluene (20 mL) and heated to reflux for 3 hours with a Dean-Stark apparatus. The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **325** as a white solid (1.50 mg, 89%).

mp = 88-90 °C;

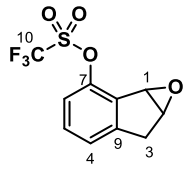
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.75-7.67 (m, 2H, H_{11}), 7.34 (dt, *J* = 7.3, 0.9 Hz, 1H, H_4), 7.32-7.27 (m, 2H, H_{12}), 7.13-7.02 (m, 1H, H_6), 6.83 (dd, *J* = 8.2, 0.8 Hz, 1H, H_6), 6.70 (dtd, *J* = 5.7, 2.0, 0.8 Hz, 1H, H_1), 6.48 (dt, *J* = 5.7, 2.0 Hz, 1H, H_2), 3.39 (t, *J* = 2.0 Hz, 2H, H_3), 2.44 (s, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 146.4 (Quat, C_7), 145.3 (Quat, C_{13}), 142.5 (Quat, C_9), 138.4 (Quat, C_{10}), 135.1 (CH, C_2), 132.7 (Quat, C_8), 129.8 (CH, C_{12}), 128.5 (CH, C_{11}), 127.9 (CH, C_1), 125.5 (CH, C_5), 122.6 (CH, C_4), 120.2 (CH, C_6), 39.5 (CH_2, C_3), 21.7 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 3067, 2922, 1598, 1585, 1465, 1372, 1313, 1220, 1204, 1190, 1180, 1167, 1158, 1091;

HRMS (ESI$^+$) calculated for $C_{16}H_{14}O_3SNa^+$ = 309.0556, mass found = 309.0556.

1a,6a-Dihydro-6*H*-indeno[1,2-*b*]oxiren-2-yl trifluoromethanesulfonate, 326



m-CPBA (70% w/w, 112 mg, 0.454 mmol, 1.2 eq) were added to a solution of **324** (100 mg, 0.378 mmol, 1.0 eq) in CH_2Cl_2 (2.0 mL) at 0 °C. The solution was stirred for 3 hours at room temperature and the reaction mixture quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL), saturated aqueous $Na_2S_2O_3$ (3 mL) and CH_2CL_2 (10 mL). The phases were separated and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and water (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:19 to 1:4 EtOAc/petrol 40-60, to afford **326** as a colourless oil (65 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.33 (dd, *J* = 8.2, 7.5 Hz, 1H, H_5), 7.25 (d, *J* = 7.4 Hz, 1H, H_4), 7.12 (dd, *J* = 8.2, 0.9 Hz, 1H, H_6), 4.47 (dd, *J* = 3.0, 1.2 Hz, 1H, H_1), 4.19 (t, *J* = 2.9 Hz, 1H, H_2), 3.30 (dq, *J* = 18.3, 0.9 Hz, 1H, H_3), 3.06 (ddt, *J* = 18.3, 3.0, 1.0 Hz, 1H, $H_{3'}$);

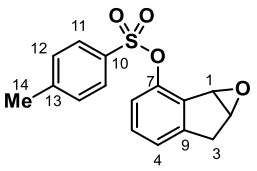
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 147.3 (Quat, C_7), 146.7 (Quat, C_9), 133.8 (Quat, C_8), 130.5 (CH, C_5), 126.2 (CH, C_4), 119.3 (CH, C_6), 118.8 (q, *J* = 321.1 Hz, C_{10}), 57.5 (CH, C_2), 55.7 (CH, C_1), 34.8 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −72.9;

FTIR (film) ν_{max}/cm^{-1} = 3046, 2919, 1471, 1421, 1250, 1208, 1174, 1157, 1137, 1011;

HRMS (ESI$^+$) calculated for $C_{10}H_8O_4F_3S^+$ = 281.0090, mass found = 281.0900.

1a,6a-Dihydro-6*H*-indeno[1,2-*b*]oxiren-2-yl 4-methylbenzenesulfonate, 327



m-CPBA (70% w/w, 1.55 g, 6.29 mmol, 1.2 eq) were added to a solution of **325** (1.50 mg, 5.24 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) at 0 °C. The solution was stirred for 3 hours at room temperature and the reaction mixture quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL), saturated aqueous $Na_2S_2O_3$ (15 mL) and CH_2Cl_2 (20 mL). The phases were separated and the organic phase was washed with saturated aqueous $Na_2S_2O_3$ (30 mL) and water (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:17 to 1:3 EtOAc/petrol 40-60, to afford **327** as a white solid (1.32 g, 85%).

mp = 118-120 °C;

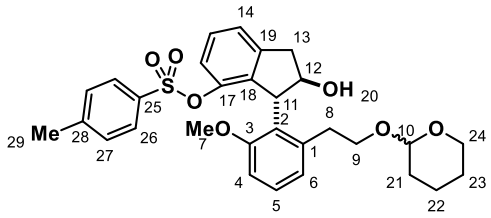
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.82-7.67 (m, 2H, H_{11}), 7.40-7.30 (m, 2H, H_{12}), 7.21-7.08 (m, 2H, H_4 & H_5), 6.75 (dq, *J* = 7.9, 0.9 Hz, 1H, H_6), 4.25 (dd, *J* = 2.9, 1.2 Hz, 1H, H_1), 4.04 (t, *J* = 2.9 Hz, 1H, H_2), 3.19 (dq, *J* = 18.1, 1.0 Hz, 1H, H_3), 2.96 (ddt, *J* = 18.2, 3.0, 1.0 Hz, 1H, $H_{3'}$), 2.46 (s, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 146.8 (Quat, C_7), 146.4 (Quat, C_{13}), 145.6 (Quat, C_9), 134.8 (Quat, C_{10}), 132.4 (Quat, C_8), 129.9 (CH, C_{12}), 129.8 (CH, C_5), 128.6 (CH, C_{11}), 124.9 (CH, C_6), 120.5 (CH, C_4), 57.3 (CH, C_2), 56.1 (CH, C_1), 34.8 (CH_2, C_3), 21.8 (CH_3, C_{14});

FTIR (film) ν_{max}/cm^{-1} = 3049, 2924, 1620, 1597, 1581, 1471, 1418, 1373, 1295, 1219, 1206, 1190, 1173, 1094, 1014;

HRMS (ESI$^+$) calculated for $C_{16}H_{14}O_4SNa^+$ = 325.0505, mass found = 325.0504.

trans-2-Hydroxy-3-(2-methoxy-6-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)phenyl)-2,3-dihydro-1*H*-inden-4-yl 4-methylbenzenesulfonate, 329



Magnesium turnings (62.0 mg, 2.11 mmol, 1.5 eq) were heated to 150 °C under vacuum and stirred vigorously for 1 hour. The flask was filled with nitrogen and allowed to cool to room temperature before THF (7 mL) was added, followed by the slow addition of **293** (531 mg, 1.41 mmol, 1.0 eq).

The solution was heated to reflux, at which point 1,2-dibromoethane (0.05 mL) was added to initiate formation of the Grignard reagent and the bubbling mixture stirred at reflux for 2 hours and then cooled to 30 °C. This solution was added to a suspension of **327** (425 mg, 1.41 mmol, 1.0 eq) and copper(I) iodide (16 mg, 0.070 mmol, 0.05 eq) in THF (2 mL) and the resulting suspension stirred for 2 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, to afford **329** as an orange oil (1:1 *dr*, 412 mg, 54%).

mp = 36-38 °C;

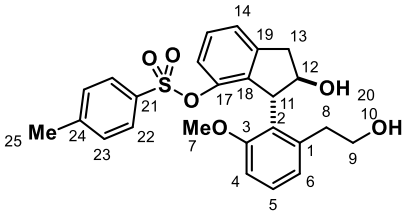
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.36-7.21 (m, 4H, H_{26}), 7.23-7.05 (m, 6H, H_5 & H_{27}), 7.02 (dd, *J* = 7.5, 2.3 Hz, 2H, H_{14}), 6.93 (td, *J* = 7.8, 4.3 Hz, 2H, H_{15}), 6.84 (d, *J* = 7.9 Hz, 2H, H_6), 6.56 (dd, *J* = 13.0, 8.1 Hz, 4H, H_4 & H_{16}), 4.77-4.60, (m, 4H, H_{11} & H_{12}), 4.49 (dt, *J* = 16.9, 3.6 Hz, 2H, H_{10}4.05 (dt, *J* = 9.9, 5.9 Hz, 1H, H_9), 3.90 (td, *J* = 9.2, 6.0 Hz, 1H, H_9), 3.80-3.48 (m, 4H, $H_{9'}$ & H_{24}), 3.48-3.22 (m, 6H, H_{13}, H_8 & H_{24}), 3.19 (s, 6H, H_7), 3.03-2.75 (m, 4H, $H_{8'}$ & $H_{13'}$), 2.30 (m, 6H, H_{29}), 1.85-1.24 (m, 6H, H_{21}, H_{22} & H_{23});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 158.5 (Quat, C_3), 158.4 (Quat, C_3), 145.5 (Quat, C_{17}), 145.4 (Quat, C_{17}), 144.7 (Quat, C_{28}), 144.7 (Quat, C_{28}), 144.5 (Quat, C_{19}), 144.1 (Quat, C_{19}), 139.6 (Quat, C_1), 139.5 (Quat, C_1), 137.9 (Quat, C_{18}), 137.8 (Quat, C_{18}), 133.2 (Quat, C_{25}), 133.2 (Quat, C_{25}), 129.5 (CH, C_{27}), 129.5 (CH, C_{27}), 128.9 (Quat, C_2), 128.6 (Quat, C_2), 128.3 (CH, C_{26}), 128.2 (CH, C_{26}), 127.5 (CH, C_5), 127.4 (CH, C_5), 127.1 (CH, C_{15}), 127.1 (CH, C_{15}), 122.9 (CH, C_{19}), 122.8 (CH, C_{19}), 122.8 (CH, C_6), 122.4 (CH, C_6), 118.9 (CH, C_{16}), 118.7 (CH, C_{16}), 109.9 (CH, C_4), 109.7 (CH, C_4), 99.0 (CH, C_{10}), 98.6 (CH, C_{10}), 79.4 (CH, C_{12}), 79.3 (CH, C_{12}), 69.0 (CH_2, C_9), 68.8 (CH_2, C_9), 62.4 (CH_2, C_{24}), 62.0 (CH_2, C_{24}), 55.3 (CH_3, C_7), 55.3 (CH_3, C_7), 53.3 (CH, C_{11}), 53.1 (CH, C_{11}), 41.8 (CH_2, C_{13}), 41.6 (CH_2, C_{13}), 33.3 (CH_2, C_8), 33.2 (CH_2, C_8), 30.3 (CH_2, C_{21}), 30.2 (CH_2, C_{21}), 25.3 (CH_2, C_{23}), 25.3 (CH_2, C_{23}), 21.7 (CH_3, C_{29}), 21.5 (CH_3, C_{29}), 19.5 (CH_2, C_{22}), 19.3 (CH_2, C_{22});

FTIR (film) ν_{max}/cm^{-1} = 3437, 2040, 2361, 2340, 1753, 1598, 1680, 1467, 1439, 1372, 1353, 1251, 1221, 1190, 1177, 1157, 1135, 1120, 1092, 1028;

HRMS (ESI^+) calculated for $C_{30}H_{34}O_7NaS^+$ = 561.1918, mass found = 561.1915.

trans-2-Hydroxy-3-(2-(2-hydroxyethyl)-6-methoxyphenyl)-2,3-dihydro-1*H*-inden-4-yl 4-methylbenzenesulfonate, 330



Conc HCl (0.3 mL, 0.39 mmol, 0.7 eq) was added to a solution of **329** (300 mg, 0.557 mmol, 1.0 eq) in methanol (1.3 mL) and the solution stirred for 30 minutes. The reaction mixture was diluted in water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:1 EtOAc/petrol 40-60, to afford **330** as a white solid (>20:1 *dr*, 224 mg, 88%).

mp = 70-72 °C;

^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.44-7.39 (m, 2H, H_{22}), 7.24-7.16 (m, 3H, H_5 & H_{23}), 7.08 (dd, *J* = 7.6, 1.1 Hz, 1H, H_{14}), 7.05-6.96 (m, 1H, H_{15}), 6.89 (dd, *J* = 7.8, 1.2 Hz, 1H, H_6), 6.66 (dd, *J* = 8.2, 1.1 Hz, 1H, H_4), 6.59 (d, *J* = 8.1 Hz, 1H, H_{16}), 4.77 (d, *J* = 5.5 Hz, 1H, H_{11}), 4.73 (dt, *J* = 7.7, 5.8 Hz, 1H, H_{12}), 4.07-3.99 (m, 1H, H_9), 3.86 (td, *J* = 10.2, 4.2 Hz, 1H, H_9), 3.81-3.58 (br s, 1H, H_{10}/H_{20}), 3.47 (dd, *J* = 16.3, 7.6 Hz, 1H, H_{13}), 3.34 (ddd, *J* = 14.9, 10.0, 5.3 Hz, 1H, H_8), 3.28 (s, 3H, H_7), 2.97 (dd, *J* = 16.3, 5.9 Hz, 1H, $H_{13'}$), 2.89 (dt, *J* = 14.6, 4.2 Hz, 1H, $H_{8'}$), 2.41 (s, 3H, H_{25});

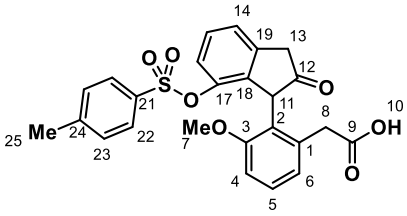
^{13}C NMR (12 MHz, $CDCl_3$) δ_C = 157.4 (Quat, C_3), 144.5 (Quat, C_{17}), 143.7 (Quat, C_{24}), 143.3 (Quat, C_{19}), 138.4 (Quat, C_1), 136.5 (Quat, C_{18}), 132.3 (Quat, C_{21}), 128.5 (CH_2, C_{23}), 128.1 (Quat, C_2), 127.1 (CH, C_{22}), 126.6 (CH, C_5), 126.1 (CH, C_{15}), 121.7 (CH, C_{14}), 121.7 (CH, C_6), 117.5 (CH, C_{16}), 108.8 (CH,

C_4), 78.3 (CH, C_{12}), 62.8 (CH_2, C_9), 54.1 (CH_3, C_7), 51.9 (CH, C_{11}), 40.7 (CH_2, C_{13}), 34.7 (CH_2, C_8), 20.6 (CH_3, C_{25});

FTIR (film) ν_{max}/cm^{-1} = 3559, 3350, 3063, 2963, 2955, 2924, 2835, 2360, 1615, 1598, 1580, 1495, 1467, 1437, 1402, 1371, 1349, 1293, 1270, 1249, 1222, 1192, 1177, 1155, 1094, 1080, 1043, 1020;

HRMS (ESI^+) calculated for $C_{25}H_{26}O_6NaS^+$ = 477.1342, mass found = 477.1339.

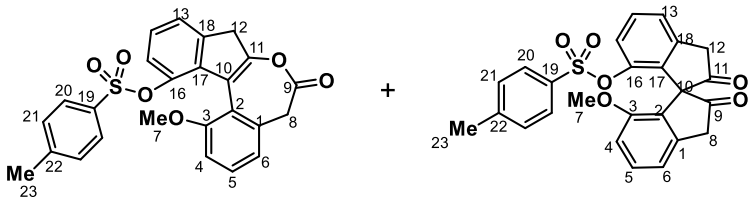
2-(3-methoxy-2-(2-oxo-7-(tosyloxy)-2,3-dihydro-1*H*-inden-1-yl)phenyl)acetic acid, 331



Jones reagent (2 M CrO_3 in H_2SO_4, 109 µL, 0.218 mmol, 3.3 eq) was added to a solution of **330** (30 mg, 0.067 mmol, 1.0 eq) in acetone (0.67 mL). The reaction mixture was stirred for 1.5 hours, and then quenched with ^{i}PrOH (2 mL) at which point the orange solution turned green to signify consumption of the Cr(VI) species. Solvent was evaporated under a flow of N_2, and the residue diluted in water (5 mL), extracted with CH_2Cl_2 (3 × 5 mL) and concentrated to afford crude acid **331** as a brown gum (33 mg, quant) which was used without any further purification.

LRMS (ESI^-) calculated for $C_{25}H_{22}O_7S^-$ = 465, mass found = 465.

1-methoxy-6-oxo-5,8-dihydro-6H-benzo[d]indeno[2,1-b]oxepin-12-yl 4-methylbenzenesulfonate, 332 & 7′-methoxy-2,2′-dioxo-2,2′,3,3′-tetrahydro-1,1′-spirobi[inden]-7-yl 4-methylbenzenesulfonate, 333



332 **333**

Prepared according to **General Procedure A**.

Esterification with crude diacid **331** (33 mg, 0.071 mmol, 1.0 eq), EDC·HCl (19 mg, 0.10 mmol, 1.5 eq), DMAP (3.0 mg, 0.004 mmol, 0.05 eq), and pentafluorophenol (13 mg, 0.071 mmol, 1.0 eq).

Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded **332** as a yellow oil (14 mg, 43%) and **333** as a yellow oil (8 mg, 24%)

332:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.48 (t, *J* = 8.0 Hz, 1H, H_5), 7.39 (td, *J* = 6.5, 5.9, 3.0 Hz, 1H, H_{14}), 7.30-7.23 (m, 2H, H_{13} & H_{15}), 7.12-6.91 (m, 6H, H_4, H_6, H_{20} & H_{21}), 3.89 (d, *J* = 22.8 Hz, 1H, H_{12}), 3.83 (s, 3H, H_7), 3.68 (d, *J* = 12.3 Hz, 1H, H_8), 3.59 (d, *J* = 22.9 Hz, 1H, $H_{12'}$), 3.12 (d, *J* = 12.3 Hz, 1H, $H_{8'}$), 2.44 (s, 3H, H_{23});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 166.7 (Quat, C_9), 157.4 (Quat, C_3), 155.0 (Quat, C_{11}), 144.5 (Quat, C_{22}), 143.1 (Quat, C_{16}), 138.5 (Quat, C_{18}), 135.0 (Quat, C_{17}), 132.2 (Quat, C_{19}), 132.1 (Quat, C_2), 130.5 (CH, C_5), 129.3 (CH, C_{21}), 128.0 (CH, C_{20}), 125.8 (CH, C_{13}), 122.6 (CH, C_{14}), 121.9 (CH, C_{15}), 120.1 (CH, C_6), 119.9 (Quat, C_{10}), 119.3 (Quat, C_1), 110.5 (CH, C_4), 55.5 (CH_3, C_7), 40.8 (CH_2, C_8), 37.5 (CH_2, C_{12}), 21.6 (CH_3, C_{23});

FTIR (film) ν_{max}/cm^{-1} = 2980, 2928, 1797, 1630, 1607, 1588, 1567, 1531, 1511, 1486, 1448, 1429, 1412, 1336, 1317, 1281, 1260, 1253, 1232, 1152, 1056, 1010;

HRMS (ESI^+) calculated for $C_{25}H_{26}O_6SNa^+$ = 481.0873, mass found = 481.0872.

333:

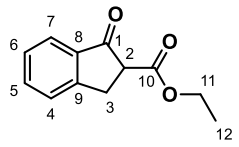
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.41-7.33 (m, 3H, H_5 & H_{20}), 7.27 (m, 2H, H_{13} & H_{14}), 7.22 (d, *J* = 8.1 Hz, 2H, H_{21}), 7.12 (q, *J* = 5.0, 4.3 Hz, 1H, H_{15}), 6.98 (d, *J* = 7.7 Hz, 1H, H_6), 6.75 (d, *J* = 8.3 Hz, 1H, H_4), 3.95-3.58 (m, 4H, H_8, $H_{8'}$, H_{12} & $H_{12'}$), 3.50 (s, 3H, H_7), 2.44 (s, 3H, H_{23});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 209.5 (Quat, C_9 *or* C_{11}), 209.4 (Quat, C_9 *or* C_{11}), 155.8 (Quat, C_3), 146.0 (Quat, C_{16}), 145.2 (C_{22}), 140.7 (Quat, C_{18}), 139.6 (Quat, C_1), 133.1 (Quat, C_{17}), 132.7 (Quat, C_{19}), 130.1 (CH, C_5), 129.7 (CH, C_{21}), 129.4 (CH, C_{14}), 128.5 (Quat, C_2), 128.2 (CH, C_{20}), 122.6 (CH, C_{13}), 118.6 (CH, C_{15}), 117.3 (CH, C_6), 109.8 (CH, C_4), 73.2 (Quat, C_2), 55.5 (CH_3, C_7), 44.1 (CH_2, C_8), 43.8 (CH_2, C_{12}), 21.7 (CH_3, C_{23});

FTIR (film) ν_{max}/cm^{-1} = 2918, 2850, 1359, 1769, 1740, 1590, 1521, 1484, 1470, 1373, 1296, 1268, 1227, 1192, 1177, 1126, 1092;

HRMS (ESI$^+$) calculated for $C_{25}H_{26}O_6SNa^+$ = 481.0873, mass found = 481.0871.

Ethyl 1-indanone-2-carboxylate, 354



According to a literature procedure,[178] NaH (60% dispersion in mineral oil (1.64 g, 41.0 mmol, 1.2 eq) was suspended in diethyl carbonate (120 mL) under a nitrogen atmosphere. To this suspension was added a solution of 1-indanone (4.50 g, 34.0 mmol, 1.0 eq) in diethyl carbonate (120 mL). The solution was heated to reflux for 10 minutes and a dark green solid was formed. A further 90 mL of diethyl carbonate was added and the mixture was further heated for 15 minutes and then allowed to cool to room temperature. The resultant solid was dissolved in aqueous HCl (2 M, 500 mL) and extracted with EtOAc (4 × 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a brown oil. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to yield **354** as orange oil (6.63 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.43 (br s, 1H, OH), 7.80-7.32 (m, 8H, H_{Ar}), 4.34-4.18 (m, 4H, keto and enol H_{11}), 3.70 (dd, *J* = 8.2, 4.0 Hz, 1H, H_2), 3.58-3.31 (m, 4H, keto and enol H_3), 1.39-1.20 (m, 6H, keto and enol H_{12});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 199.6 (keto, Quat, C_1), 169.1 (keto, Quat, C_{10}), 153.7 (enol, Quat, C_1), 143.2 (keto, Quat, C_8), 135.4 (keto, CH, C_7), 135.3 (keto, Quat, C_9) 129.3 (enol, CH, C_7), 127.8 (keto, CH, C_6), 126.8 (enol, CH, C_6), 126.6 (keto, CH, C_5), 124.7 (enol, CH, C_5), 124.6 (keto, CH, C_4), 120.7 (enol, CH, C_4), 102.5 (enol, Quat, C_2), 61.7 (keto, CH_2, C_{11}), 60.1 (enol, CH_2, C_{11}), 53.3 (keto, CH, C_2), 32.6 (enol, CH_2, C_3), 30.3 (keto, CH_2, C_3), 14.5 (enol, CH_3, C_{12}), 14.2 (keto, CH_3, C_{12});

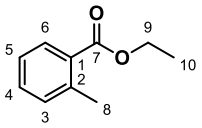
FTIR (film) ν_{max}/cm^{-1} = 2983, 2361, 1738, 1711, 1648, 1608, 1573, 1465, 1414, 1369, 1316, 1298, 1256, 1207, 1186, 1153, 1126, 1092, 1008;

LRMS (ESI$^+$) calculated for $C_{12}H_{12}O_3^+$ = 205, mass found = 205.

N.B. there were two fewer quaternary C_{Ar} peaks in the ^{13}C NMR spectrum than expected (as observed in the literature).

The data matched those of the literature.[178]

Ethyl 2-methylbenzoate, 357



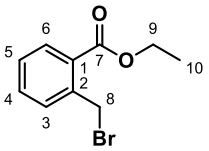
According to a literature procedure,[143] *o*-toluic acid (10.0 g, 73.5 mmol, 1.0 eq) was added to diethyl carbonate (16.0 mL, 132 mmol, 1.8 eq) and to this mixture was added conc H_2SO_4 (0.4 mL). The solution was heated to 120 °C and stirred for 13 hours. The solution was allowed to cool to room temperature and then pour onto 10 % aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford **357** as a pale yellow oil (11.23 g, 93%). The crude compound was used without any further purification.

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.94-7.89 (m, 1H, H_{Ar}), 7.45-7.36 (m, 1H, H_{Ar}), 7.28-7.21 (m, 2H, H_{Ar}), 4.36 (q, *J* = 7.1 Hz, 2H, H_9), 2.61 (s, 3H, H_8), 1.40 (t, *J* = 7.1 Hz, 3H, H_{10});

LRMS (ESI^+) calculated for $C_{10}H_{12}O_2Na^+$ = 187, mass found = 187.

The data matched those of the literature.[179]

Ethyl 2-(bromomethyl)benzoate, 358



Analogously to a literature procedure,[180] *N*-bromosuccinimide (6.23 g, 35.0 mmol, 1.1 eq) and AIBN (150 mg, 0.91 mmol, 0.03 eq) were added to a solution of **357** (5 g, 30.5 mmol, 1.0 eq) in CCl_4 (30 mL) and heated to reflux for 14 hours. The reaction mixture was allowed to cool to room temperature before being filtered and concentrated under reduced pressure. The residue was

purified by flash column chromatography, eluting with 1.5:98.5 Et_2O/petrol 40-60, to afford **358** as a colourless oil (5.55 g, 74%).

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.97 (dd, *J* = 7.7, 1.4 Hz, 1H, H_6), 7.53-7.43 (m, 2H, H_3 & H_4), 7.37 (ddd, *J* = 7.8, 6.9, 1.8 Hz, 1H, H_5), 4.96 (s, 2H, H_8), 4.41 (q, *J* = 7.1 Hz, 2H, H_9), 1.42 (t, *J* = 7.1 Hz, 3H, H_{10});

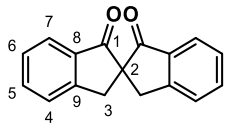
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 166.7 (Quat, C_7), 139.1 (Quat, C_2), 132.4 (CH, C_4), 131.6 (CH, C_6), 131.3 (CH, C_5), 129.6 (Quat, C_1), 128.5 (CH, C_3), 61.3 (CH_2, C_9), 31.6 (CH_2, C_8), 14.3 (CH_3, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 2981, 2360, 1715, 1600, 1577, 1448, 1366, 1295, 1262, 1226, 1112, 1075, 1046, 1018;

LRMS (ESI^+) calculated for $C_{10}H_{11}BrO_2Na^+$ = 265, 267, mass found = 265, 267.

The data matched those of the literature.[181]

2,2'-Spirobiindane-1,1'-dione, 344



According to a literature procedure,[130] NaH (60% dispersion in mineral oil, 66 mg, 1.65 mmol, 1.1 eq) was added portionwise to a stirred solution of **355** (308 mg, 1.51 mmol, 1.0 eq) in DMF (1 mL). After H_2 evolution had ceased the mixture was heated to 60 °C for 1 hour after which time a solution of **358** (400 mg, 1.65 mmol, 1.1 eq) in DMF (1 mL) was added and the reaction mixture stirred for 72 hours. After 72 hours had elapsed the mixture was cooled to room temperature and water was added (1 mL). The solution was extracted with Et_2O (3 × 3 mL) and the combined organic extracts washed with brine (5 mL), dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was then dissolved in aqueous H_2SO_4 (12.5 m, 50 mL) and heated to 130 °C. After 1 hour had elapsed, the solution was allowed to cool to room temperature and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (3 M, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by

flash column chromatography, eluting with 1:5 EtOAc/petrol 40-60, to afford **344** as a colourless solid (230 mg, 62%).

mp = 170-172 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.76 (d, *J* = 7.7Hz, 1H, H_7), 7.66 (ddd, *J* =7.9, 7.0, 0.8 Hz, 1H, H_5), 7.56 (d, *J* = 7.7 Hz, 1H, H_4), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H, H_6), 3.73 (d, *J* = 17.0 Hz, 1H, H_3), 3.20 (d, *J* = 17.0 Hz, 1H, $H_{3'}$);

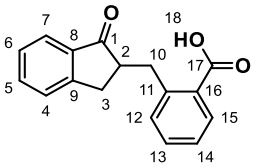
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 202.7 (Quat, C_1), 153.9 (Quat, C_9), 135.5 (Quat, C_8), 135.3 (CH, C_5), 127.8 (CH, C_6), 126.4 (CH, C_4), 124.9 (CH, C_7), 65.4 (Quat, C_2), 38.1 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2917, 1720, 1696, 1605, 1586, 1463, 1429, 1325, 1273, 1209, 1186, 1154, 1137, 1088, 1027;

LRMS (ESI^+) calculated for $C_{17}H_{13}O_2^+$ = 249, mass found = 249;

The data matched those of the literature.[130]

2-(1-Oxoindan-2-ylmethyl)benzoic acid, 348



According to a literature procedure,[128] to a stirred suspension of **344** (400 mg, 1.62 mmol, 1.0 eq) in EtOH (9 mL) was added aqueous NaOH (1 M, 1.62 mL, 1.0 eq). The reaction mixture was heated to 90 °C for 5 hours before being concentrated under reduced pressure. The residue was acidified with aqueous HCl (0.63 M) and the aqueous layer extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by recrystallization (PhH) to afford **348** as a colourless solid (341 mg, 80%).

mp = 144-146 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 11.30 (br s, 1H, H_{18}), 8.09 (dd, *J* = 7.8, 1.3 Hz, 1H, H_{15}), 7.78 (d, *J* = 7.6 Hz, 1H, H_7), 7.55 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, H_{13}), 7.50 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H, H_5),

7.43-7.30 (m, 4H, H_4, H_6, H_{12} & H_{14}), 3.87-3.75 (m, 1H, H_{10}), 3.23-3.10 (m, 3H, H_2, H_3, $H_{10'}$), 2.96-2.85 (m, 1H, $H_{3'}$);

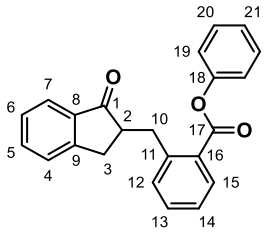
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 208.0 (Quat, C_1), 172.7 (Quat, C_{17}), 153.6 (Quat, C_9), 142.6 (Quat, C_{11}), 136.4 (Quat, C_8), 134.7 (CH, C_5), 133.0 (CH, C_{13}), 131.9 (CH, C_{15}), 131.7 (CH, C_4), 128.7 (Quat, C_{16}), 127.4 (CH, C_{12}), 126.6 (CH, C_{14}), 126.5 (CH, C_6), 124.0 (CH, C_7), 48.7 (CH, C_2), 35.0 (CH_2, C_{10}), 32.4 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3070, 1716, 1687, 1603, 1575, 1489, 1465, 1434, 1404, 1271, 1209, 1150, 1075;

LRMS (ESI^+) calculated for $C_{17}H_{14}O_3^+$ = 289, mass found = 289.

The data matched those of the literature.[128]

Phenyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 360



To a mixture of **348** (600 mg, 2.28 mmol), EDC·HCl (562 mg, 2.93 mmol, 1.3 eq), and DMAP (13 mg, 0.11 mmol, 0.05 eq) in flame dried round-bottom flask was added CH_2Cl_2 (3 mL) and the mixture was stirred for 30 minutes. A solution of PhOH (208 mg, 2.21 mmol, 0.98 eq) in CH_2Cl_2 (3 mL) was added and the solution stirred for 14 hours. The reaction mixture was concentrated under reduced pressure and then poured onto brine (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **360** as a colourless oil that solidified on standing (554 mg, 73%).

mp = 63-65 °C;

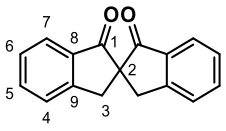
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.19 (dd, *J* = 7.8, 1.3 Hz, 1H, H_{15}), 7.76 (d, *J* = 7.6 Hz, 1H, H_7), 7.59-7.51 (m, 2H, H_5 & H_{13}), 7.49-7.32 (m, 6H, H_4, H_{12}, H_{14}, H_{20} & H_{21}), 7.30-7.20 (m, 3H, H_6 & H_{19}), 3.83-3.69 (m, 1H, H_{10}), 3.26-3.13 (m, 3H, H_2, H_3, $H_{10'}$), 3.00-2.88 (m, 1H, $H_{3'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 207.6 (Quat, C_1), 166.0 (Quat, C_{17}), 153.5 (Quat, C_9), 150.8 (Quat, C_{18}), 142.5 (Quat, C_{11}), 136.6 (Quat, C_8), 134.7 (CH, C_5), 132.7 (CH, C_{13}), 131.9 (CH, C_{12}), 131.4 (CH, C_{15}), 129.6 (CH, C_{20}), 127.4 (CH, C_{21}), 126.7 (CH, C_4), 126.6 (CH, C_{14}), 126.0 (CH, C_6), 124.0 (CH, C_7), 121.8 (CH, C_{19}), 115.4 (Quat, C_{16}), 48.7 (CH, C_2), 35.0 (CH_2, C_{10}), 32.3 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3068, 2918, 1734, 1708, 1599, 1576, 1486, 1464, 1434, 1328, 1288, 1247, 1191, 1163, 1120, 1071, 1046, 1001;

HRMS (ESI^+) calculated for $C_{23}H_{18}O_3Na^+$ =365.11482, mass found = 365.11441.

2,2′-Spirobiindane-1,1′-dione, 344



Prepared according to **General Procedure G**.

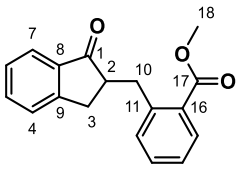
C-Acylation with **360** (20 mg, 0.06 mmol, 1.0 eq), TBAB (2 mg, 0.006 mmol, 0.1 eq), K_2CO_3 (50% aq, 84 µL, 0.60 mmol, 10 eq) for 10 hours. The residue was purified by flash column chromatography, eluting with 1:5 EtOAc/petrol 40-60, to afford **344** as a colourless solid (14 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.76 (d, *J* = 7.7Hz, 1H, H_7), 7.66 (ddd, *J* =7.9, 7.0, 0.8 Hz, 1H, H_5), 7.56 (d, *J* = 7.7 Hz, 1H, H_4), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H, H_6), 3.73 (d, *J* = 17.0 Hz, 1H, H_3), 3.20 (d, *J* = 17.0 Hz, 1H, $H_{3'}$);

LRMS (ESI^+) calculated for $C_{17}H_{13}O_2^+$ = 249, mass found = 249;

The data matched those reported previously.

Methyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 361



To a mixture of **348** (50 mg, 0.19 mmol, 1.0 eq), EDC·HCl (47 mg, 0.24 mmol, 1.3 eq), and DMAP (1 mg, 0.01 mmol, 0.05 eq) in flame dried round-bottom flask was added CH_2Cl_2 (0.5 mL) and the mixture was stirred for 30 minutes. A solution of MeOH (9.9 µL, 0.24 mmol, 1.3 eq) in CH_2Cl_2 (0.5 mL) was added to the solution and stirred for 14 hours. The reaction mixture was concentrated under reduced pressure and then poured onto brine (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **361** as a colourless oil (46 mg, 87%).

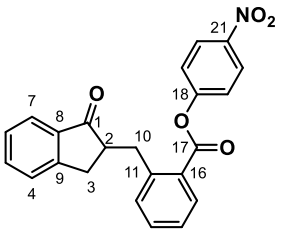
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H, H_{15}), 7.77 (d, *J* = 7.7 Hz, 1H, H_7), 7.56 (td, *J* = 7.4, 0.9 Hz, 1H, H_5), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H, H_{13}), 7.41-7.27 (m, 4H, H_4, H_6, H_{12} & H_{14}), 3.90 (s, 3H, H_{18}), 3.76 (dd, *J* = 13.3, 4.5 Hz, 1H, H_{10}), 3.18-2.97 (m, 4H, H_2, H_3 & $H_{10'}$), 2.97-2.86 (m, 1H, $H_{3''}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.6 (Quat, C_1), 168.0 (Quat, C_{17}), 152.5 (Quat, C_9), 140.5 (Quat, C_{11}), 135.5 (Quat, C_8), 133.7 (CH, C_5), 131.0 (CH, C_{13}), 130.4 (CH, C_{12}), 129.9 (CH, C_{15}), 129.0 (Quat, C_{16}), 126.3 (CH, C_4), 125.5 (CH, C_6/C_{14}), 125.4 (CH, C_6/C_{14}), 122.9 (CH, C_7), 51.1 (CH_3, C_{18}), 47.8 (CH, C_2), 34.0 (CH_2, C_{10}), 31.3 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2951, 2361, 1713, 1607, 1509, 1463, 1434, 1260, 1181, 1151, 1125, 1060, 1036;

HRMS (ESI$^+$) calculated for $C_{18}H_{16}O_3Na^+$ = 303.09917, mass found = 303.09883.

4-Nitrophenyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 362



To a mixture of **348** (100 mg, 0.38 mmol, 1.0 eq), EDC·HCl (108 mg, 0.56 mmol, 1.5 eq), and DMAP (2 mg, 0.01 mmol, 0.05 eq) in flame dried round-bottom flask was added CH_2Cl_2 (0.5 mL) and the

mixture was stirred for 30 minutes. A solution of 2,4,6-Cl_3PhOH (74 mg, 0.38 mmol, 1.3 eq) in CH_2Cl_2 (0.5 mL) was added to the solution and stirred for 14 hours. The reaction mixture was concentrated under reduced pressure and then poured onto brine (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **362** as a colourless oil (117 mg, 70%).

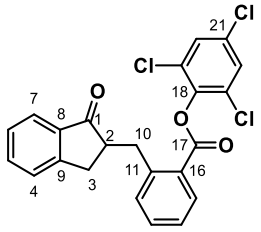
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.33 (d, *J* = 9.0 Hz, 1H, H_{20}), 8.19 (d, *J* = 7.7 Hz, 1H, H_{15}), 7.76 (d, *J* = 7.7 Hz, 1H, H_7), 7.59 (td, *J* = 7.6, 1.0 Hz, 1H, H_{13}), 7.57 (td, *J* = 7.4, 0.7 Hz, 1H, H_5) 7.47-7.39 (m, 5H, H_4, H_{12}, H_{14} & H_{21}), 7.37 (t, *J* = 7.5 Hz, 1H, H_6), 3.82 (dd, *J* = 16.8, 8.8 Hz, 1H, H_{10}), 3.21 (dd, *J* = 16.7, 6.7 Hz, 1H, H_3) 3.18-3.10 (m, 2H, H_2 $H_{10'}$), 2.97-2.86 (dd, *J* = 16.7, 3.1 Hz, 1H, $H_{3'}$)

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.3 (Quat, C_1), 167.8 (Quat, C_{17}), 155.6 (Quat, C_{18}), 153.3 (Quat, C_9), 145.5 (Quat, C_{21}), 143.0 (Quat, C_{11}), 136.5 (Quat, C_8), 134.8 (CH, C_5), 133.4 (CH, C_{13}), 132.1 (CH, C_{15}), 131.7 (CH, C_{12}), 127.9 (Quat, C_{16}), 127.5 (CH, C_{14}), 126.9 (CH, C_4) 126.5 (CH, C_6), 125.3 (CH, C_{20}), 124.0 (CH, C_7), 122.0 (CH, C_{19}), 48.5 (CH, C_2), 23.4 (CH_2, C_{10}), 32.5 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2925, 2362, 2340, 1742, 1708, 1593, 1522, 1489, 1347, 1246, 1204, 1163, 1113, 1033;

HRMS (ESI$^+$) calculated for $C_{23}H_{17}NO_5Na^+$ = 410.0999, mass found = 410.0998.

2,4,6-Trichlorophenyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 363



To a mixture of **348** (100 mg, 0.38 mmol, 1.0 eq), EDC·HCl (108 mg, 0.56 mmol, 1.5 eq), and DMAP (2 mg, 0.01 mmol, 0.05 eq) in flame dried round-bottom flask was added CH_2Cl_2 (0.5 mL) and the mixture was stirred for 30 minutes. A solution of 4-NO_2PhOH (52 mg, 0.38 mmol, 1.3 eq) in CH_2Cl_2 (0.5 mL) was added to the solution and stirred for 14 hours. The reaction mixture was concentrated

under reduced pressure and then poured onto brine (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, to afford **363** as a colourless oil (126 mg, 87%).

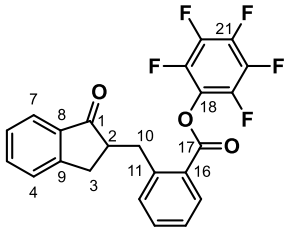
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = δ 8.29 (dd, *J* = 7.9, 1.5 Hz, 1H, H_{15}), 7.76 (dt, *J* = 7.6, 1.0 Hz, 1H, H_7), 7.58 (td, *J* = 7.7, 1.2 Hz, 1H, H_{13}), 7.55 (td, *J* = 7.3, 1.0 Hz, 1H, H_5), 7.46 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{12}), 7.45-7.32 (m, 5H, H_4, H_6, H_{14} & H_{20}), 3.73 (dd, *J* = 13.5, 5.2 Hz, 1H, H_{10}), 3.30-3.06 (m, 3H, H_2, H_3 & $H_{10'}$), 2.93 (dd, *J* = 16.3, 3.5 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.4 (Quat, C_1), 163.4 (Quat, C_{17}), 153.4 (Quat, C_9), 143.4 (Quat, C_{18}), 143.1 (Quat, C_{11}), 136.5, (Quat, C_8) 134.7 (CH, C_5), 133.5 (CH, C_{13}), 132.1 (Quat, C_{21}), 132.0 (CH, C_{12}), 131.8 (CH, C_{15}), 129.8 (Quat, C_{19}), 128.7 (CH, C_{20}), 127.4 (CH, C_6), 127.3 (Quat, C_{16}), 126.8 (CH, C_{14}), 126.5 (CH, C_4), 124.0 (CH, C_7), 48.7 (CH, C_2), 34.6 (CH_2, C_{10}), 32.3 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2924, 2852, 2361, 2341, 1753, 1712, 1602, 1564, 1449, 1387, 1224, 1141, 1114, 1019;

HRMS (ACI$^+$) calculated for $C_{23}H_{16}{}^{35}Cl_3O_3^+$ = 445.0160, mass found = 445.0155.

Pentafluorophenyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 364



To a mixture of **348** (400 mg, 1.50 mmol, 1.0 eq), EDC·HCl (432 mg, 2.25 mmol, 1.5 eq), and DMAP (9 mg, 0.08 mmol, 0.05 eq) in flame dried round-bottom flask was added CH_2Cl_2 (0.5 mL) and the mixture was stirred for 30 minutes. A solution of 2,3,4,5,6-pentafluorophenol (276 mg, 1.50 mmol, 1.0 eq) in CH_2Cl_2 (0.5 mL) was added to the solution and stirred for 14 hours. The reaction mixture was concentrated under reduced pressure and then poured onto brine (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and

concentrated. The residue was purified by flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, to afford **364** as a colourless oil that solidified on standing to give a white solid (554 mg, 73%).

mp = 83-88 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.23 (dd, *J* = 7.9, 1.3 Hz, 1H, H_{15}), 7.76 (d, *J* = 7.7 Hz, 1H, H_7), 7.61 (td, *J* = 7.6, 1.4 Hz, 1H, H_{13}), 7.57 (td, *J* = 7.5, 1.1 Hz, 1H, H_5), 7.46 (dd, *J* = 7.8, 1.2 Hz, 1H, H_{12}), 7.43 (td, *J* = 7.4, 1.0 Hz, 1H, H_{14}), 7.41 (dt, *J* = 7.5, 0.8 Hz, 1H, H_4), 7.36 (ddd, *J* = 7.6, 7.2, 0.6 Hz, 1H, H_6), 3.76 (dd, *J* = 13.2, 5.0 Hz, 1H, H_{10}), 3.23-3.06 (m, 3H, H_2, H_3, $H_{10'}$), 2.89 (dd, *J* = 16.9, 4.1 Hz, 1H, $H_{3'}$);

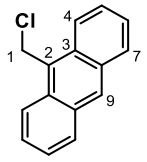
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 206.2 (Quat, C_1), 161.8 (Quat, C_{17}), 152.2 (Quat, C_9), 142.7 (Quat, C_{11}), 140.3 (ddq, *J* = 247.9, 12.1, 3.9 Hz, CF, C_{19}), 138.5 (dtt, *J* = 253.4, 13.5, 3.8 Hz, CF, C_{21}), 136.9 (dtdd, *J* = 251.6, 14.1, 4.3, 3.8 Hz, CF, C_{20}), 135.4 (Quat, C_8), 133.8 (CH, C_5), 133.0 (CH, C_{13}), 131.2 (CH, C_{12}), 131.1 (CH, C_{15}), 126.4 (CH, C_6), 125.9 (CH, C_{14}), 125.5 (CH, C_4), 125.1 (Quat, C_{12}), 124.2 (tt, *J* = 14.3, 2.4 Hz, Quat, C_{18}), 123.0 (CH, C_7), 47.5 (CH, C_2), 34.0 (CH_2, C_{10}), 31.3 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.4 (m, 2F, F_{19}), −157.9 (t, *J* = 43.4, 1F, F_{21}), −162.2 (m, 2F, F_{20});

FTIR (film) ν_{max}/cm^{-1} = 2928, 1759, 1712, 1602, 1519, 1488, 1466, 1320, 1288, 1273, 1227, 1145, 1115, 1030;

HRMS (ESI^+) calculated for $C_{23}H_{13}O_3F_5Na^+$ = 455.06771, mass found = 455.06750.

9-(Chloromethyl)anthracene, 534

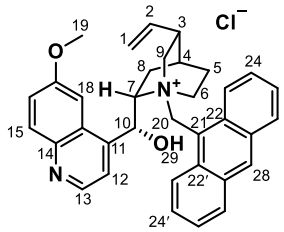


Analogously to a literature procedure,[182] PCl_3 (4.78 mL, 54.8 mmol, 1.17 eq) was added to a stirred suspension of 9-anthracenemethanol (9.76 g, 46.9 mmol, 1.0 eq) in toluene (250 mL) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C and then allowed to warm to room temperature. Saturated aqueous Na_2CO_3 (150 mL) was added and the mixture stirred for 10 minutes at which point the solution had cooled back down to room temperature. The phases were separated and

the organic layer was washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **534** as a yellow solid (10.1 g, 95%) which was used without any further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ_H = 8.51 (s, 1H, H_9), 8.33 (dq, *J* = 8.9, 1.0 Hz, 2H, H_4), 8.05 (ddt, *J* = 8.3, 1.5, 0.7 Hz, 2H, H_7), 7.71-7.43 (m, 4H, H_5 & H_6), 5.64 (s, 2H, H_1)

_N_-(9-Anthracenylmethyl)quininium chloride, Y



According to a literature procedure,[154c] to a suspension of quinine (14.0 g, 43.1 mmol, 1.0 eq) in toluene (280 mL) was added 9-(chloromethyl)anthracene **534** (9.98 g, 44.0 mmol, 1.02 eq), and the mixture heated to reflux for 2 hours. The mixture was cooled to room temperature and then poured onto Et_2O (700 mL) and the suspension filtered. The precipitate was washed with Et_2O (140 mL) and then dried under a vacuum. The yellow residue was collected in CH_2Cl_2 (700 mL) and the resulting suspension heated to reflux. After 2 hours had elapsed the solution was cooled to −15 °C, and Et_2O (140 mL) was added at this temperature. The precipitate was filtered and dried to give a light-yellow solid **Y** (8.17 g, 37%).

$[\alpha]_D^{20}$ = -420.0 ° (c = 0.8, $CHCl_3$)

mp = 148-150 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 9.03 (d, *J* = 9.0 Hz, 1H, H_{23}), 8.58 (d, *J* = 9.0 Hz, 1H, $H_{23'}$), 8.56 (d, *J* = 4.5 Hz, 1H, H_{13}), 8.35 (s, 1H, H_{28}), 8.03 (d, *J* = 6.1 Hz, 1H, H_{29}), 7.98 (d, *J* = 4.5 Hz, 1H, H_{12}), 7.96 (d, *J* = 9.2 Hz, 1H, H_{15}), 7.92 (d, *J* = 8.2 Hz, 1H, $H_{26'}$), 7.82 (d, *J* = 8.3 Hz, 1H, H_{26}), 7.76 (d, *J* = 2.0 Hz, 1H, H_{18}), 7.60 (ddd, *J* = 8.2, 6.7, 1.4 Hz, 1H, H_{24}), 7.51 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H, $H_{24'}$), 7.41 (dd, *J* = 8.2, 6.6 Hz, 1H, $H_{25'}$), 7.37 (dd, *J* = 8.2, 6.6 Hz, 1H, H_{25}), 7.27 (dd, *J* = 9.1, 2.6 Hz, 1H, H_{16}), 7.02 (d, *J* = 6.4 Hz, 1H, H_{10}), 6.89 (d, *J* = 13.9 Hz, 1H, H_{20}), 6.29 (d, *J* = 13.9 Hz, 1H, $H_{20'}$), 5.51 (ddd, *J* = 17.1, 10.5,

6.6 Hz, 1H, H_2), 5.06 (t, *J* = 11.0 Hz, 1H, H_6), 4.98 (dd, *J* = 11.0, 0.9 Hz, 1H, H_1), 4.95 (dd, *J* = 4.2, 0.8 Hz, 1H, $H_{1'}$), 4.43 (t, *J* = 8.7 Hz, 1H, H_7), 3.93 (s, 3H, H_{19}), 3.54 (ddd, *J* = 13.0, 4.7, 1.8 Hz, 1H, H_9), 2.81 (dd, *J* = 11.6, 4.8 Hz, 1H, $H_{4'}$), 2.63 (dd, *J* = 12.9, 10.7 Hz, 1H, $H_{9'}$), 2.23-2.10 (m, 3H, H_3, H_5 & H_8), 1.46-1.35 (m, 2H, $H_{5'}$ & $H_{8'}$);

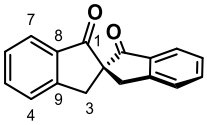
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 158.2 (Quat, C_{17}), 147.7 (CH, C_{13}), 144.4 (Quat, C_{14}), 143.7 (Quat, C_{18}), 136.6 (CH, C_2), 133.4 (Quat, C_{22}), 132.9 (Quat, $C_{22'}$), 132.2 (CH, C_{15}), 132.0 (CH, C_{28}), 131.2 (Quat, C_{27}), 130.9 (Quat, $C_{27'}$), 130.0 (CH, $C_{26'}$), 128.9 (CH, C_{26}), 128.7 (CH, C_{24}), 127.9 (CH, $C_{24'}$), 126.4 (Quat, C_{11}), 125.9 (CH, C_{23}), 125.8 (CH, C_{25}), 125.1 (CH, $C_{25'}$), 123.9 (CH, $C_{23'}$), 121.1 (CH, C_{16}), 121.0 (CH, C_{12}), 118.1 (Quat, C_{21}), 117.7 (CH, C_1), 102.1 (CH, C_{18}), 71.1 (CH, C_7), 65.8 (CH, C_{10}), 61.1 (CH, C_9), 57.2 (CH, C_{20}), 56.4 (CH, C_{19}), 52.7 (CH, C_6), 38.4 (CH, C_3), 25.9 (CH, C_4), 25.4 (CH, C_5), 22.4 (CH, C_8);

FTIR (film) ν_{max}/cm^{-1} = 3088, 2363, 2210, 1751, 1622, 1509, 1473, 1450, 1431, 1363, 1259, 1240, 1227, 1031;

LRMS (ESI^+) calculated for $C_{35}H_{35}N_2O_2^+$ = 515 mass found = 515.

The data matched those of the literature.[154c]

(+)-(2*S*)-2,2'-Spirobiindane-1,1'-dione, (+)-(2*S*)- 344



Asymmetric: Prepared according to **General Procedure G** with **364** (50 mg, 0.12 mmol, 1.0 eq), **Y** (6.4 mg, 12 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (245 µL, 1.15 mmol, 10 eq) in toluene (1.1 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:5 EtOAc/petrol 40-60, afforded the title compound **360** as a white solid (27 mg, 93%, 97:3 *er*).

Asymmetric (gram scale): Prepared according to **General Procedure G** with **364** (1.42 g, 3.28 mmol, 1.0 eq), **Y** (181 mg, 0.328 mmol, 0.1 eq), 50% w/w aqueous potassium phosphate (6.97 mL, 32.8 mmol, 10 eq) in toluene (32.8 mL). Reaction conditions: 48 h. Purification *via* flash column

chromatography, eluting with 1:5 EtOAc/petrol 40-60, afforded the title compound **364** as a white solid (750 mg, 92%, 97:3 *er*).

mp = 170-172 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.76 (d, *J* = 7.7Hz, 1H, H_7), 7.66 (ddd, *J* =7.9, 7.0, 0.8 Hz, 1H, H_5), 7.56 (d, *J* = 7.7 Hz, 1H, H_4), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H, H_6), 3.73 (d, *J* = 17.0 Hz, 1H, H_3), 3.20 (d, *J* = 17.0 Hz, 1H, $H_{3'}$);

LRMS (ESI$^+$) calculated for $C_{17}H_{13}O_2^+$ = 249, mass found = 249;

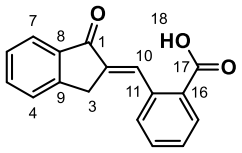
$[\alpha]_D^{25}$ = +123.5 (c = 0.65, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 250 nm)

τ_R (minor) = 9.0 min, τ_R (major) = 15.3 min.

The data matched those reported previously.

(*E*)-2-((1-Oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 369

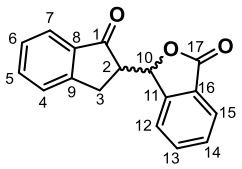


According to a literature procedure,[138] 1-indanone (2.20 g, 16.7 mmol, 1.0 eq) and 2-carboxybenzaldehyde (2.50 g, 16.7 mmol, 1.0 eq) were dissolved in EtOH (40 mL) and to this solution was added aqueous NaOH (1 M, 30 mL, 1.8 eq). The reaction mixture was stirred for 15 minutes, before being quenched with cold water (50 mL). The mixture was extracted with Et_2O (2 × 50 mL) and the organic extracts discarded. The aqueous layer was acidified carefully with 2.5 M H_2SO_4 and filtered. The precipitate **369** was used without any further purification (4.13 g, 94%).

^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ_H = 13.26 (s, 1H, H_{18}), 8.16 (s, 1H, H_{10}), 8.04-7.41 (m, 8H, H_4, H_5, H_6, H_7, H_{12}, H_{13}, H_{14}, H_{15}), 4.04 (d, *J* = 1.2 Hz, 1H, H_3);

LRMS (ESI$^+$) calculated for $C_{17}H_{14}O_3Na^+$ = 287, mass found = 297;

3-(1-Oxo-2,3-dihydro-1*H*-inden-2-yl)isobenzofuran-1(3*H*)-one, 370



1-indanone (3.00 g, 11.3 mmol) and 2-carboxybenzaldehyde (3.42 g, 11.3 mmol, 1.0 eq) were stirred in MeOH (40 mL) and to this solution was added aqueous NaOH (5 M, 5.88 mL, 2.6 eq). The solution was stirred at room temperature for 20 hours and quenched with saturated aqueous NH_4Cl and then buffered to pH 6 with AcOH. The precipitate was filtered and purified by flash column chromatography, eluting with 1:9 MeOH/CH_2Cl_2 to afford **370** as a 1:1 mixture of diastereoisomers (5.65 g, 94%).

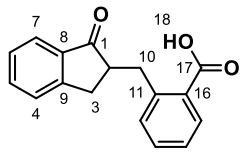
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H, H_{Ar}), 7.90-7.86 (m, 1H, $H_{Ar'}$), 7.83-7.70 (m, 2H, $2H_{Ar}$), 7.62-7.51 (m, 5H, $3H_{Ar}$ & $2H_{Ar'}$), 7.50-7.42 (m, 2H, $2H_{Ar'}$), 7.42-7.28 (m, 4H, $2H_{Ar}$ & $2H_{Ar'}$), 7.12-7.06 (m, 1H, $H_{Ar'}$), 6.20 (d, *J* = 2.7 Hz, 1H, H_{10}), 6.17 (d, *J* = 4.3 Hz, 1H, $H_{10'}$), 3.71 (ddd, *J* = 8.1, 4.3, 4.3 Hz, 1H, $H_{2'}$), 3.30 (ddd, *J* = 8.4, 4.7, 2.7 Hz, 1H, H_2), 3.18 (dd, *J* = 17.5, 8.1 Hz, 1H, $H_{3'}$), 2.87 (dd, *J* = 17.3, 8.3 Hz, 1H, H_3), 2.51 (dd, *J* = 17.3, 4.6 Hz, 1H, H_3), 2.36 (dd, *J* = 17.5, 4.4 Hz, 1H, $H_{3'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 204.2 (Quat, C', C_1), 203.9 (Quat, C_1), 170.4 (Quat, C', C_{17}) 170.4 (Quat, C_{17}), 153.9 (Quat, C', C_9), 153.6 (Quat, C_9), 148.8 (Quat, C_{11}), 146.6 (Quat, C', C_{11}), 137.0 (Quat, C', C_8), 136.4 (Quat, C_8), 135.8 (CH, C', C_{Ar}), 135.7 (CH, C_{Ar}), 134.9 (CH, C_{Ar}), 134.6 (CH, C', C_{Ar}), 129.9 (CH, C_{Ar}) 129.9 (CH, C', C_{Ar}), 128.1 (CH, C', C_{Ar}), 128.1 (CH, C_{Ar}), 127.3 (Quat, C', C_{16}), 127.0 (Quat, C_{16}), 126.9 (CH, C_{Ar}), 126.8 (CH, C', C_{Ar}), 126.3 (CH, C_{Ar}), 126.1 (CH, C', C_{Ar}), 124.6 (CH, C_{Ar}), 124.3 (CH, C', C_{Ar}), 122.7 (CH, C', C_{Ar}), 122.2 (CH, C_{Ar}), 80.9 (CH, C', C_{10}), 79.6 (CH, C_{10}), 50.4 (CH, C_2), 50.4 (CH, C', C_2), 27.6 (CH_2, C', C_3), 26.2 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2920, 1759, 1709, 1607, 1466, 1434, 1351, 1286, 1213, 1153, 1060, 1040, 1003;

HRMS (ESI$^+$) calculated for $C_{17}H_{12}O_3Na^+$ = 287.06787, mass found = 287.06757.

2-(1-Oxoindan-2-ylmethyl)benzoic acid, 348



This compound was prepared according to **General Procedure B**.

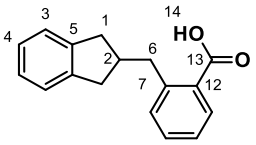
Hydrogenation with unsaturated acid **369** (1.00 g, 3.78 mmol, 1.0 eq), 10% Pd/C (100 mg, 10 wt%) in EtOAc (37.8 mL). The residue was purified by recrystallization (PhH) to afford **348** as a colourless solid (716 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.09 (dd, *J* = 7.8, 1.3 Hz, 1H, H_{15}), 7.78 (d, *J* = 7.6 Hz, 1H, H_7), 7.55 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, H_{13}), 7.50 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H, H_5), 7.43-7.30 (m, 4H, H_4, H_6, H_{12} & H_{14}), 3.87-3.75 (m, 1H, H_{10}), 3.23-3.10 (m, 3H, H_2, H_3, H_{10}), 2.96-2.85 (m, 1H, H_3);

LRMS (ESI$^+$) calculated for $C_{17}H_{14}O_3Na^+$ = 289, mass found = 289.

The data matched thos reported previously.

2-((2,3-Dihydro-1*H*-inden-2-yl)methyl)benzoic acid, 371



A stirred suspension of **369** (500 mg, 1.89 mmol, 1.0 eq) and 10% Pd/C (50 mg, 10 wt%) in EtOH (13 mL) in an autoclave was purged with H_2 by pressurizing to 5 bar of H_2 and releasing the pressure (× 2). The apparatus was then pressurized to 5 bar H_2 and stirred. After 5 hours had elapsed, the atmosphere of H_2 was removed and the reaction mixture filtered through Celite® with CH_2Cl_2. The resulting solution was concentrated and the residue purified by recrystallization (PhH) to afford **371** as a colourless solid (455 mg, 95%).

mp = 140-142 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 11.48 (br s, 1H, H_{14}), 8.10 (dd, *J* = 7.8, 1.5 Hz, 1H, H_{11}), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H, H_9), 7.45-7.28 (m, 2H, H_8 & H_{10}), 7.24-7.03 (m, 4H, H_3 & H_4), 3.27 (d, *J* = 7.1 Hz, 2H,

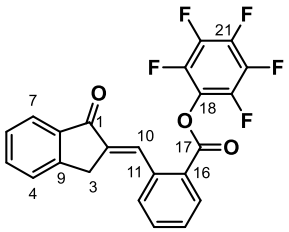
H_6), 2.97 (dd, *J* = 15.3, 7.2 Hz, 2H, H_1), 2.85 (sept, *J* = 7.0 Hz, 1H, H_2), 2.73 (dd, *J* = 15.3, 7.2 Hz, 2H, $H_{1'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.3 (Quat, C_{13}), 144.4 (Quat, C_7), 143.3 (Quat (C_5), 132.8 (CH, C_9), 131.9 (CH, C_{11}), 131.7 (CH, C_{10}), 128.3 (Quat, C_{12}), 126.2 (CH, C_8), 126.1 (CH, C_4), 124.4 (CH, C_3), 41.7 (CH, C_2), 39.7 (CH_2, C_6), 39.0 (CH_2, C_1);

FTIR (film) ν_{max}/cm^{-1} = 2939, 2645, 2360, 1681, 1601, 1575, 1489, 1450, 1407, 1311, 1273, 1139, 1084;

HRMS (ESI^+) calculated for $C_{17}H_{16}O_2Na^+$ = 275.10425, mass found = 275.10425.

Pentafluorophenyl (*E*)-2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 380



$(COCl)_2$ (192 µL, 2.27 mmol, 1.2 eq) was added to a stirred solution of **369** (500 mg, 1.89 mmol, 1.0 eq) in CH_2Cl_2 (5 mL), followed by 1 drop of DMF. After evolution of gas had ceased (30 minutes), the mixture was concentrated. The residue was then redissolved in CH_2Cl_2 (5 mL) and to this solution was added 2,3,4,5,6-pentafluorophenol (345 mg, 1.89 mmol, 1.0 eq) and Et_3N (457 µL, 5.67 mmol, 3.0 eq). The reaction mixture was stirred for 2 hours upon which it was quenched by addition of water (20 mL) and diluted in CH_2Cl_2 (20 mL). The organic layer was washed with water (20 mL), 1 M aqueous HCl (20 mL), and brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **380** as a yellow solid (679 mg, 83%).

mp = 124-126 °C;

^1H NMR (500 MHz, $CDCl_3$) δ_H = 8.28 (dd, *J* = 7.9, 0.9 Hz, 1H, H_{15}), 8.22 (dd, *J* = 2.1, 2.1 Hz, 1H, H_{10}), 7.90 (d, *J* = 7.6 Hz, 1H, H_7), 7.77-7.70 (m, 2H, H_{13} & H_{12}), 7.63-7.54 (m, 2H, H_5 & H_{14}), 7.48 (d, *J* = 7.7 Hz, 1H, H_4), 7.42 (ddd, *J* = 7.6, 7.4, 0.7 Hz, 1H, H_6), 3.89 (d, *J* = 1.6 Hz, 2H, H_3);

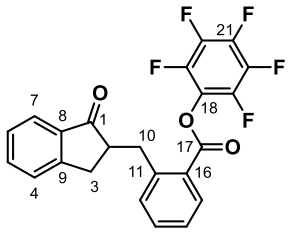
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 193.4 (Quat, C_1), 162.2 (Quat, C_{17}), 149.7 (Quat, C_9), 141.3 (ddq, *J* = 252.2, 11.7, 3.9 Hz, CF, C_{19}), 139.6 (dtt, *J* = 251.8, 13.4, 3.8 Hz, CF, C_{21}), 138.8 (Quat, C_{11}), 138.1 (Quat, C_8), 138.0 (ddddd, *J* = 253.6, 13.5, 13.3, 5.1, 2.6 Hz, CF, C_{20}), 137.4 (Quat, C_2), 134.8 (CH, C_5), 133.9 (CH, C_{13}), 132.3 (CH, C_{10}), 132.1 (CH, C_{15}), 130.1 (CH, C_{12}), 128.9 (CH, C_{14}), 127.7 (CH, C_6), 126.9 (Quat, C_{16}), 126.2 (CH, C_4), 125.2 (tt, *J* = 13.8, 2.8 Hz, C_{18}), 124.7 (CH, C_7), 31.2 (CH, C_{10});

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.1 (m, 2F, F_{19}), −157.7 (t, *J* = 21.6 Hz, 1F, F_{21}), −162.1 (m, 2F, F_{20});

FTIR (film) ν_{max}/cm^{-1} = 3054, 1758, 1701, 1637, 1518, 1468, 1324, 1296, 1265, 1232, 1208, 1184, 1145, 1127, 1089, 1030;

HRMS (ESI^+) calculated for $C_{23}H_{12}O_3F_5^+$ = 431.07011, mass found = 431.06976.

Pentafluorophenyl 2-((1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)benzoate, 364



Prepared according to **General Procedure B**.

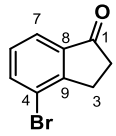
Hydrogenation with unsaturated ester **380** (100 mg, 0.232 mmol), 10% Pd/C (10 mg, 10 wt%) in EtOAc (1.8 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **364** as a colourless oil that solidified on standing (64 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.23 (dd, *J* = 7.9, 1.3 Hz, 1H, H_{15}), 7.76 (d, *J* = 7.7 Hz, 1H, H_7), 7.61 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H, H_{13}), 7.57 (dd, *J* = 7.5, 7.5, 1.1 Hz, 1H, H_5), 7.46 (dd, *J* = 7.8, 1.2 Hz, 1H, H_{14}), 7.43 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H, H_{12}), 7.41 (ddd, *J* = 7.5, 0.8, 0.8 Hz, 1H, H_4), 7.36 (ddd, *J* = 7.6, 7.2, 0.6 Hz, 1H, H_6), 3.77 (dd, *J* = 13.2, 5.0 Hz, 1H, $_{10}$), 3.23-3.0.6 (m, 3H, H_3, H_2, H_{10}), 2.89 (dd, *J* = 16.9, 4.1 Hz, 1H, H_3);

LRMS (ESI^+) calculated for $C_{23}H_{14}O_3F_5^+$ = 433, mass found = 433.

The data matched those obtained previously.

4-Bromo-1-indanone, 387



According to a literature procedure,[183] 3-(2-bromophenyl)propionic acid (2.00 g, 8.72 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (9 mL) at 0 °C. $(COCl)_2$ (638 µL, 13.1 ml, 1.5 eq) was added, followed by 1 drop of DMF and the reaction stirred until evolution of gas stopped. The solution was concentrated, the residue dissolved in CH_2Cl_2 (9 mL) and the solution added to a stirred suspension of $AlCl_3$ (1.28 g, 9.60 mml, 1.1 eq) in CH_2Cl_2 (9 mL). The reaction mixture was stirred for 2 hours upon which it was quenched with water (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, to afford **387** as a white crystalline solid (1.10 g, 60%).

mp = 94-96 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.76 (dd, *J* = 7.8, 1.0 Hz, 1H, H_7), 7.70 (d, *J* = 7.6 Hz, 1H, H_5), 7.27 (ddt, *J* = 7.6, 7.6, 0.8 Hz, 1H, H_6), 3.10-3.04 (m, 2H, H_3), 2.76-2.69 (m, 2H, H_2);

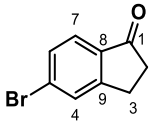
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 206.1 (Quat, C_1), 154.7 (Quat, C_9), 139.1 (Quat, C_8), 137.4 (CH, C_5), 129.1 (CH, C_6), 122.6 (CH, C_7), 122.3 (Quat, C_4), 36.2 (CH_2, C_2), 27.0 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2930, 1710, 1594, 1457, 1445, 1428, 1402, 1323, 1281, 1255, 1193, 1163, 1123, 1034;

HRMS (FI$^+$) calculated for $C_9H_7BrO^+$ = 209.9680, 211.9660, mass found = 209.9687, 211.9669.

The data matched those of the literature.[139]

5-Bromo-1-indanone, 389



According to a literature procedure,[140] To a round-bottom flask containing 3-(3-bromophenyl)propionic acid (2.00 g, 8.72 mmol, 1.0 eq) at 0 °C was added $ClSO_3H$ (26.1 mL) and the reaction mixture stirred at 0 °C for 3 hours. The reaction mixture was poured slowly onto fast-stirring ice water (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:49 EtOAc/petrol 40-60, to afford **389** as a white crystalline solid (1.22 g, 66%).

mp = 106-108 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.65 (s, 1H, H_4), 7.60 (d, *J* = 7.8 Hz, 1H, H_7), 7.50 (d, *J* = 8.1 Hz, 1H, H_6), 3.17-3.09 (m, 2H, H_3), 2.72-2.64 (m, 2H, H_2);

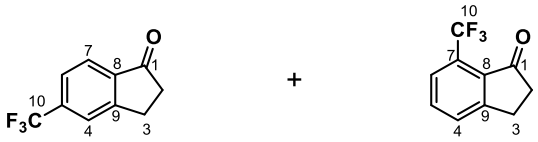
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 205.6 (Quat, C_1), 156.7 (Quat, C_9), 135.9 (Quat, C_8), 131.0 (CH, C_6), 130.0 (CH, C_4), 130.0 (Quat, C_7), 125.0 (CH, C_4), 36.2 (CH_2, C_2), 25.6 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3071, 2923, 1702, 1591, 1570, 1436, 1412, 1318, 1287, 1266, 1196, 1168, 1140, 1119, 1102, 1052, 1032;

LRMS (ESI^+) calculated for $C_9H_7BrONa^+$ = 233, 235, mass found = 233, 235.

The data matched those of the literature.[139]

5-Trifluoromethylindan-1-one, 391, & 7-trifluoromethylindan-1-one, 392



391 **392**

Ice-cooled $ClSO_3H$ (21.8 mL) was added to a 100 mL round-bottom flask containing 3-[3-(trifluoromethyl)phenyl]propionic acid (2.00 g, 0.917 mmol, 1.0 eq) and the mixture stirred for 4 hours at 0 °C. The mixture was then slowly poured onto ice water (250 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified

by flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, to afford **391** (684 mg, 38%) and **392** (100 mg, 6%).

391:

mp = 58-60 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.85 (dt, *J* = 8.0, 0.8 Hz, 1H, H_6), 7.76 (dt, *J* = 1.7, 0.9 Hz, 1H, H_4), 7.62 (ddd, *J* = 8.0, 1.5, 0.8 Hz, 1H, H_7), 3.30-3.17 (m, 2H, H_3), 2.87-2.69 (m, 2H, H_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 205.8 (Quat, C_1), 155.1 (Quat, C_9), 139.7 (Quat, C_8), 135.9 (q, *J* = 32.0 Hz, Quat, C_5), 124.7 (t, *J* = 273.0 Hz, CF_3, C_{10}), 124.5 (q, *J* = 3.7 Hz, CH, C_6), 124.3 (CH, C_7), 124.0 (q, *J* = 3.9 Hz, CH, C_4), 36.4 (CH_2, C_2), 25.8 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −56.2;

FTIR (film) ν_{max}/cm^{-1} = 2937, 1715, 1616, 1596, 1488, 1429, 1403, 1326, 1292, 1277, 1246, 1198, 1163, 1128, 1106, 1058, 1032;

HRMS (EI^+) calculated for $C_{10}H_7F_3O^+$ = 200.0449, mass found = 200.0449.

The data matched those of the literature.[184]

392:

mp = 64-66 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.79-7.51 (m, 3H, H_4, H_5 & H_6), 3.28-3.08 (m, 2H, H_3), 2.82-2.63 (m, 2H, H_2);

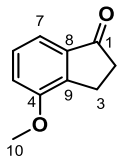
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 202.7 (Quat, C_1), 157.3 (Quat, C_9), 133.9 (CH, C_5), 133.9 (Quat, C_8), 130.7 (CH, C_4), 127.0 (d, *J* = 34.3 Hz, Quat, C_7), 125.1 (q, *J* = 6.0 Hz, H_6), 122.7 (q, *J* = 273.7 Hz, CF_3, C_{10}), 36.6 (CH_2, C_2), 25.8 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −61.5;

FTIR (film) ν_{max}/cm^{-1} = 3100, 2925, 1717, 1599, 1484, 1435, 1411, 1322, 1294, 1251, 1201, 1157, 1129, 1108, 1034;

HRMS (ESI^+) calculated for $C_{10}H_8F_3O^+$ = 201.0522, mass found = 201.0524.

4-Methoxy-1-indanone, 393



According to a literature procedure,[185] to a solution of 4-hydroxy-1-indanone (2.00 g, 13.6 mmol, 1.0 eq) in acetone (60 mL) was added K_2CO_3 (2.24 g, 16.1 mmol, 1.2 eq) and iodomethane (0.98 mL, 16.1 mmol, 1.2 eq). The reaction mixture was stirred at reflux for 9 hours and then cooled to room temperature and concentrated under reduced pressure. Water (50 mL) and CH_2Cl_2 (50 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography, eluting with CH_2Cl_2 to afford **393** as a white crystalline solid (2.07 g, 93%).

mp = 102-104 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.36-7.29 (m, 2H, H_6 & H_7), 7.05-7.00 (m, 1H, H_5), 3.90 (s, 3H, H_{10}), 3.05-3.00 (m, 2H, H_3), 2.69-2.64 (m, 2H, H_2);

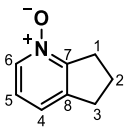
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 208.3 (Quat, C_1), 157.1 (Quat, C_4), 144.1 (Quat, C_9), 138.6 (Quat, C_8), 128.8 (CH, C_6), 115.3 (CH, C_5), 114.7 (CH, C_7), 55.5 (CH_3, C_{10}), 36.2 (CH_2, C_2), 22.5 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3007, 2971, 2929, 2842, 1699, 1602, 1591, 1484, 1462, 1437, 1399, 1293, 1262, 1245, 1191, 1175, 1162, 1078, 1068, 1033;

LRMS (ESI$^+$) calculated for $C_{10}H_{11}O_2^+$ = 163, mass found = 163.

The data matched those of the literature.[185]

6,7-Dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide, 395



According to a literature procedure,[142] *m*-CPBA (70% w/w, 3.57 g, 14.5 mmol, 1.0 eq) was slowly added to a stirred solution of 2,3-cyclopentenopyridine (1.65 g, 13.8 mmol, 1.0 eq) in CH_2Cl_2

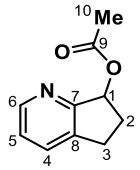
(16 mL). The reaction mixture was stirred for 2 hours and then concentrated under reduced pressure. The crude residue **395** was used without further purification (1.55 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.04 (dd, *J* = 6.2, 1.2 Hz, 1H, H_6), 7.11 (d, *J* = 7.5 Hz, 1H, H_4), 7.09-7.03 (m, 1H, H_5), 3.17 (t, *J* = 7.7 Hz, 2H, H_3), 3.02 (t, *J* = 7.6 Hz, 2H, H_1), 2.18 (p, *J* = 7.7 Hz, 2H, H_2);

LRMS (ESI$^+$) calculated for $C_8H_{10}NO^+$ = 136, mass found = 136.

The data matched those of the literature.[142]

6,7-Dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl acetate, 396



According to a literature procedure,[142] a solution of **395** (1.55 g, 11.5 mmol, 1.0 eq) in acetic anhydride (14 mL) was heated to 100 °C for two hours. The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography, eluting with ethyl acetate, to afford **396** as a brown oil (1.47 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.50 (ddt, *J* = 4.9, 1.7, 0.9 Hz, 1H, H_6), 7.59 (dq, *J* = 7.7, 1.1 Hz, 1H, H_4), 7.19 (dd, *J* = 7.6, 4.8 Hz, 1H, H_5), 6.12 (dd, *J* = 7.5, 5.0 Hz, 1H, H_1), 3.11-2.99 (m, 1H, H_3), 2.94-2.81 (m, 1H, $H_{3'}$), 2.71-2.58 (m, 1H, H_2), 2.11 (s, 3H, H_{10}), 2.10-2.00 (m, 1H, $H_{2'}$);

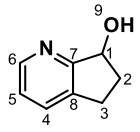
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.9 (Quat, C_9), 160.4 (Quat, C_7), 148.8 (CH, C_6), 137.5 (Quat, C_6), 133.2 (CH, C_4), 123.4 (CH, C_5), 77.2 (CH, C_1), 30.8 (CH_2, C_2), 27.8 (CH_2, C_3), 21.2 (CH_3, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 2941, 1734, 1582, 1495, 1425, 1372, 1237, 1157, 1046;

LRMS (ESI$^+$) calculated for $C_{10}H_{12}NO_2^+$ = 178, mass found = 178.

The data matched those of the literature.[142]

6,7-Dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol, 397



According to a literature procedure,[142] to a solution of potassium hydroxide (439 mg, 7.82 mmol, 1.05 eq) in EtOH (8.0 mL) was added a stirred solution of **396** (1.32 g, 7.45 mmol, 1.0 eq) in EtOH (3.5 mL). The reaction mixture was stirred for 1 hour and then extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate, to afford **397** as a brown solid (764 mg, 65%).

mp = 66-68 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.40 (ddt, *J* = 5.0, 1.7, 0.9 Hz, 1H, H_6), 7.56 (dq, *J* = 7.7, 1.2 Hz, 1H, H_4), 7.13 (dd, *J* = 7.6, 5.0 Hz, 1H, H_5), 6.04 (br s, 1H, H_9), 5.26 (dd, *J* = 7.5, 6.0 Hz, 1H, H_1), 3.05 (dddt, *J* = 16.3, 8.9, 4.3, 1.0 Hz, 1H, H_3), 2.94-2.74 (m, 1H, H_2), 2.54 (dddd, *J* = 13.4, 8.4, 7.4, 4.3 Hz, 1H, $H_{3'}$), 2.07 (dddd, *J* = 13.2, 8.9, 7.1, 6.0 Hz, 1H, $H_{2'}$);

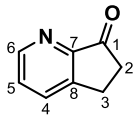
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 165.1 (Quat, C_7), 147.7 (CH, C_6), 136.6 (Quat, C_8), 133.5 (CH, C_4), 122.7 (Quat, C_5), 74.1 (CH, C_1), 32.8 (CH_2, C_2), 27.5 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3218, 2938, 1588, 1440, 1422, 1330, 1240, 1152, 1075, 1021;

LRMS (ESI$^+$) calculated for $C_8H_{10}NO^+$ = 136, mass found = 136.

The data matched those of the literature.[142]

5,6-Dihydro-7*H*-cyclopenta[*b*]pyridin-7-one, 398



According to a literature procedure,[142] A solution of DMSO (788 µL, 11.1 mmol, 2.0 eq) in CH_2Cl_2 (8.0 mL) was added dropwise to a solution of $(COCl)_2$ (479 µL, 5.66 mmol, 1.02 eq) in CH_2Cl_2 (1.0 mL) under an argon atmosphere at −78 °C and the mixture stirred for 15 minutes. To this solution was added a solution of **397** (750 mg, 5.55 mmol, 1.0 eq) in CH_2Cl_2 (3.0 mL) followed by rapid addition of Et_3N (2.42 mL, 22.2 mmol, 4.0 eq) and the reaction mixture stirred for 24 hours. The reaction mixture was quenched with water (40 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers washed with saturated aqueous

$NaHCO_3$ (40 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate, to afford **398** as a green solid (630 mg, 65%).

mp = 100-102 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.72 (ddt, *J* = 4.6, 1.6, 0.8 Hz, 1H, H_6), 7.86 (ddt, *J* = 7.9, 1.7, 0.9 Hz, 1H, H_4), 7.42 (dd, *J* = 7.9, 4.5 Hz, 1H, H_5), 3.19-3.06 (m, 2H, H_2), 2.77-2.61 (m, 2H, H_3);

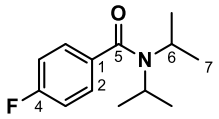
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 205.4 (Quat, C_1), 154.1 (Quat, C_7), 150.7 (CH, C_6), 149.6 (Quat, C_8), 135.4 (CH, C_4), 127.4 (CH, C_5), 34.9 (CH_2, C_2), 23.5 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 3406, 2047, 2930, 1711, 1586, 1466, 1417, 1314, 1298, 1245, 1202, 1152, 1098, 1066;

LRMS (ESI^+) calculated for $C_8H_8NO^+$ = 134, mass found = 134.

The data matched those of the literature.[142]

4-Fluoro-*N*,*N*-diisopropylbenzamide, 535



According to a literature procedure,[186] a stirred solution of 4-fluorobenzoic acid (5.00 g, 35.7 mmol, 1.0 eq) in thionyl chloride (26.0 mL, 357 mmol, 10 eq) was heated to reflux. After two hours had elapsed, the solution was concentrated under reduced pressure and the residual oil azeotroped with toluene (2 × 25 mL). The resulting acid chloride was dissolved in CH_2Cl_2 (15 mL) and stirred. To this solution was slowly added a solution of diisopropylamine (7.50 mL, 101 mmol, 2.5 eq) in CH_2Cl_2 (25 mL). The reaction mixture was stirred for 2 hours upon which it was quenched with water (30 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with 1M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, to afford **535** as a white solid (6.48 g, 81%.).

mp = 93-95 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.30 (ddt, *J* = 8.7, 5.4, 2.6 Hz, 2H, H_2), 7.05 (tt, *J* = 9.0, 2.3 Hz, 2H, H_3), 3.66 (br s, 2H, H_6), 1.33 (br s, 12H, H_7);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −116.2;

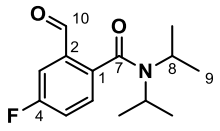
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.1 (Quat, C_5), 162.8 (d, *J* = 248 Hz, Quat, C_4), 135.0 (d, *J* = 3.6 Hz, Quat, C_1), 127.7 (d, *J* = 8.0 Hz, CH, C_2), 115.5 (d, *J* = 21.2 Hz (CH, C_3), 45.6 (br, CH, C_6), 20.7 (CH_3, C_7);

FTIR (film) ν_{max}/cm^{-1} = 2987, 2969, 2931, 2361, 1616, 1602, 1509, 1469, 1446, 1371, 1341, 1299, 1223, 1191, 1154, 1140, 1093, 1038, 1013;

LRMS (ESI^+) calculated for $C_{13}H_{19}FNO^+$ = 224, mass found = 224.

The data matched those of the literature.[186]

4-Fluoro-2-formyl-*N*,*N*-diisopropylbenzamide, 536



According to a literature procedure,[186] **535** (5.00 g, 22.4 mmol, 1.0 eq) was dissolved in THF (40 mL) and cooled to −78 °C. ^{n}BuLi (1.6 M in hexanes, 16.8 mL, 26.9 mmol, 1.2 eq) was added dropwise, upon which the colour of the solution changed from colourless to deep red, and the solution stirred for 2 hours. The solution was allowed to warm to -50 °C and DMF (2.31 mL, 30.0 mL, 1.3 eq) was added dropwise. The cooling bath was removed and the reaction mixture allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) and the mixture extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **536** as a white solid (5.12 g, 91%.).

mp = 100-102 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.10 (d, *J* = 2.4 Hz, 1H, H_{10}) 7.61 (ddd, *J* = 8.6, 2.4, 0.7 Hz, 1H, H_6). 7.34-7.26 (m, 2H, H_3 & H_5), 3.56 (ds, *J* = 17.0, 6.7 Hz, 2H, H_8), 1.58 (d, *J* = 6.8 Hz, 6H, H_9), 1.10 (d, *J* = 6.7 Hz, 6H, $H_{9'}$);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −110.8;

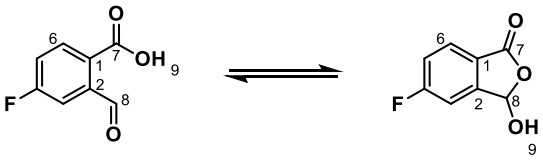
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 189.2 (CH, C_{10}), 167.3 (Quat, C_7), 162.4 (d, *J* = 251 Hz, Quat, C_4), 137.7 (d, *J* = 3.8 Hz, Quat, C_1), 134.4 (d, *J* = 6.0 Hz, Quat, C_2), 128.0 (d, *J* = 7.6 Hz, CH, C_6), 121.4 (d, *J* = 22.3 Hz, CH, C_5), 115.4 (d, *J* = 22.3 Hz, CH, C_3), 51.4 (CH, C_8), 46.3 (CH, $C_{8'}$), 20.6 (CH_3, C_9), 20.4 (CH_3, $C_{9'}$);

FTIR (film) ν_{max}/cm^{-1} = 2972, 1698, 1627, 1442, 1372, 1340, 1296, 1264, 1242, 1147, 1035;

LRMS (ESI^+) calculated for $C_{14}H_{19}FNO_2^+$ = 252, mass found = 252.

The data matched those of the literature.[186]

4-Fluoro-2-formylbenzoic acid, 405

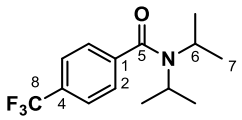


Analogously to a literature procedure,[187] A solution of **536** (3.00 g, 11.9 mmol, 1.0 eq) in AcOH (25 mL) and 3 M aqueous HCl (25 mL) was refluxed for 18 hours. The reaction mixture was concentrated and the crude solid dissolved in saturated $NaHCO_3$ (20 mL). The aqueous layer was washed with EtOAc (2 × 20 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were cooled to 0 °C and then carefully acidified with conc HCl until a precipitate was formed. The crude product **405** was used without any further purification (1.10 g, 55%).

^{1}H NMR (500 MHz, ($CDCl_3$) δ_H = 7.89 (dd, *J* = 8.2, 4.6, 1H, H_2), 7.34-7.27 (m, 2H, H_3 & H_5), 6.60, (s, 1H, H_8), 4.59 (br s, 1H, H_9);

LRMS (ESI^+) calculated for $C_8H_5FO_3Na^+$ = 191, mass found = 191.

4-Trifluoromethyl-*N*,*N*-diisopropylbenzamide, 537



4-Fluorobenzoic acid (10.0 g, 52.6 mmol, 1.0 eq) was suspended in thionyl chloride (38.0 mL, 526 mmol, 10 eq) and then heated to reflux for 2 hours. The solution was then concentrated under reduced pressure and the residual oil azeotroped with toluene (2 × 25 mL). The resulting acid chloride was dissolved in CH_2Cl_2 (105 mL) and stirred. To this solution was slowly added diisopropylamine (8.1 mL, 57.9 mmol, 1.1 eq) and Et_3N (9.22 mL, 65.8 mmol, 1.25 eq). The reaction mixture was stirred for 2 hours upon which it was quenched with water (30 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with 1M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, to afford **537** as a yellow oil (11.4 g, 79%.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.65 (d, *J* = 8.1 Hz, 2H, H_3), 7.41 (d, *J* = 7.9 Hz, 2H, H_4), 3.69 (br s, 1H, H_6), 3.57 (br s, 1H, H_6), 1.70 (br s, 6H, H_7), 1.22 (br s, 6H, H_7);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −62.7;

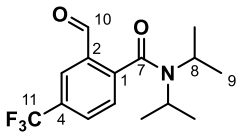
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.5 (Quat, C_5), 142.3 (Quat, C_1), 130.7 (q, *J* = 32.5 Hz, Quat, C_4), 126.0 (CH, C_2), 125.6 (q, *J* = 3.8 Hz, CH, C_3), 123.9 (q, *J* = 272.6 Hz, CF_3, C_{11}), 46.2 (m, CH, C_8), 51.0 (m, CH, C_8), 20.7 (CH_3, C_9);

FTIR (film) ν_{max}/cm^{-1} = 2972, 1631, 1518, 1441, 1372, 1344, 1321, 1213, 1163, 1124, 1108, 1064, 1037, 1017;

LRMS (ESI^+) calculated for $C_{14}H_{19}F_3NO^+$ = 274, mass found = 274.

The data matched those of the literature.[186]

4-Trifluoromethyl-2-formyl-*N*,*N*-diisopropylbenzamide, 538



According to a literature procedure,[186] **537** (5.68 g, 20.8 mmol, 1.0 eq) was dissolved in THF (48 mL) and cooled to −78 °C. ^{n}BuLi (2.5 M in hexanes, 10.0 mL, 25.0 mmol, 1.2 eq) was added dropwise, upon which the colour of the solution changed from colourless to deep red, and the solution stirred for 2 hours. The solution was allowed to warm to -50 °C and DMF (2.15 mL, 31.2 mmol, 1.3 eq) was added dropwise. The cooling bath was removed and the reaction mixture allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) and the mixture extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **538** as a yellow solid (5.14 g, 82%).

mp = 76−78 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.12 (s, 1H, H_{10}), 8.25-8.12 (m, 1H, H_3), 7.86 (dd, *J* = 7.9, 1.9 Hz, 1H, H_5), 7.43 (d, *J* = 7.9 Hz, 1H, H_6), 3.58 (sept, *J* = 6.7 Hz, 2H, H_8), 3.52 (sept, *J* = 6.7 Hz, 2H, H_8) 1.60, (d, *J* = 6.8 Hz, 6H, H_9), 1.12 (d, *J* = 6.7 Hz, 6H, H_9);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −63.0;

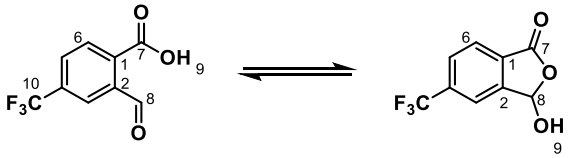
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 189.1 (CH, C_{10}), 166.8 (Quat, C_7), 144.0 (Quat, C_1), 132.7 (Quat, C_2), 131.3 (q, *J* = 33.7 Hz, Quat, C_4), 130.6 (q, *J* = 3.5 Hz, CH, C_5), 126.8 (CH, C_4), 126.6 (q, *J* = 3.8 Hz, CH, C_3), 123.2 (q, *J* = 272.5 Hz, CF_3, C_{11}), 51.4 (CH, C_8), 46.4 (CH, C_8), 20.5 (CH, C_9), 20.3 (CH, C_9);

FTIR (film) ν_{max}/cm^{-1} = 2795, 1704, 1631, 1574, 1502, 1443, 1372, 1327, 1257, 1212, 1168, 1126, 1092, 1066, 1034;

LRMS (ESI^+) calculated for $C_{15}H_{18}F_3NO_2^+$ = 302, mass found = 302.

The data matched those of the literature.[186]

4-Trifluoromethyl-2-formylbenzoic acid, 406



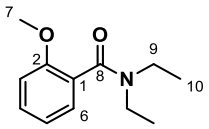
In analogy to a literature procedure,[187] A solution of **538** (4.35 g, 14.4 mmol, 1.0 eq) in AcOH (25 mL) and 3 M aqueous HCl (25 mL) was refluxed for 18 hours. The reaction mixture was concentrated and the crude solid dissolved in saturated $NaHCO_3$ (20 mL). The aqueous layer was washed with EtOAc (2 × 20 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were cooled to 0 °C and then carefully acidified with conc HCl until a precipitate was formed. The precipitate, **406**, was used without any further purification (1.51 g, 48%).

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H = 8.42 (s, 1H, H_8), 8.18-7.86 (m, 3H, H_3, H_5 & H_6), 6.77 (s, 1H, H_9);

^{19}F NMR (471 MHz, $(CD_3)_2SO$) δ_F = −61.2;

LRMS (ESI^-) calculated for $C_9H_5F_3O_3^-$ = 217, mass found = 217.

***N*,*N*-Diethyl-2-methoxybenzamide, 539**



According to a literature procedure,[188] a stirred solution of 2-methoxybenzoic acid (3.00 g, 19.7 mmol, 1.0 eq) in thionyl chloride (6 mL, 82.2 mmol, 4.5 eq) was heated to reflux. After two hours had elapsed, the solution was concentrated under reduced pressure and the residual oil azeotroped with toluene (2 × 5 mL). The resulting acid chloride was dissolved in CH_2Cl_2 (10 mL) and stirred. To this solution was slowly added a solution of diethylamine (5.1 mL, 49.3 mmol, 2.5 eq) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 2 hours upon which it was quenched with water (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with 1 M aqueous HCl (50 mL) and water (50 mL), dried

over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 2:3 EtOAc/petrol 40-60, to afford **539** as a colourless oil (4.10 g, quant).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H, H_4), 7.17 (dd, *J* = 7.5, 1.7 Hz, 1H, H_6), 6.95 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H, H_5), 6.88 (d, *J* = 8.3 Hz, 1H, H_3), 3.80 (s, 3H, H_7), 3.66-3.45 (m, 2H, H_9), 3.12 (q, *J* = 7.1 Hz, 2H, H_9), 1.22 (t, *J* = 7.1 Hz, 3H, H_{10}), 1.01 (t, *J* = 7.1 Hz, 3H, H_{10});

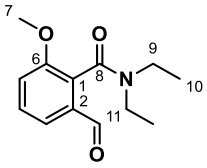
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.8 (Quat, C_8), 155.2 (Quat, C_2), 129.9 (CH, C_4), 127.4 (CH, C_6), 127.0 (Quat, C_1), 120.7 (CH, C_3), 110.9 (CH, C_5), 55.5 (CH_3, C_7), 42.7 (CH_2, C_9), 38.8 (CH_2, $C_{9'}$), 14.0 (CH_3, C_{10}), 12.9 (CH_3, $C_{10'}$);

FTIR (film) ν_{max}/cm^{-1} = 2971, 2935, 1629, 1623, 1600, 1494, 1474, 1460, 1425, 1380, 1363, 1318, 1293, 1274, 1244, 1222, 1180, 1163, 1123, 1087, 1046, 1023;

LRMS (ESI^+) calculated for $C_{12}H_{18}NO_2^+$ = 208, mass found = 208.

The data matched those of the literature.[188]

N,*N*-Diethyl-2-formyl-6-methoxybenzamide, 540



According to a literature procedure,[187] to a solution of TMEDA (1.25 mL, 8.32 mmol, 1.15 eq) in THF (20 mL), cooled to −78 °C, was added ^{s}BuLi (1.3 M in cyclohexane/hexane 92:8, 6.93 mL, 8.32 mmol, 1.15 eq). The solution was stirred for 15 minutes and then a solution of **539** (1.50 g, 7.24 mmol, 1.0 eq) in THF (5 mL) was added dropwise and the mixture stirred at −78 °C. After 2 hours had elapsed, DMF (1.12 mL, 14.5 mmol, 2.0 eq) was added dropwise and the reaction mixture allowed to warm slowly to room temperature by removal of the cooling bath and stirred for half an hour. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and the mixture extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was

purified by flash column chromatography, eluting with 2:1 EtOAc/petrol 40-60, to afford **540** as a colourless oil (1.69 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.97 (d, *J* = 0.5, Hz, 1H, H_{11}), 7.51 (dd, *J* = 7.5, 1.1 Hz, 1H, H_3), 7.44 (ddd, *J* = 8.1, 7.6, 0.5 Hz, 1H, H_4), 7.15 (dd, *J* = 8.1, 1.0 Hz, 1H, H_5), 3.84 (s, 3H, H_7), 3.71 (dq, *J* = 14.3, 6.9 Hz, 1H, H_9), 3.52 (dq, *J* = 14.2, 6.9 Hz, 1H, H_9), 3.09 (q, *J* = 7.2 Hz, 2H, $H_{9'}$), 1.27 (t, *J* = 7.1 Hz, 3H, H_{10}), 0.99 (t, *J* = 7.1 Hz, 3H, $H_{10'}$);

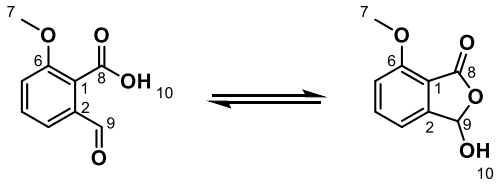
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 190.6 (CH, C_{11}), 165.8 (Quat, C_8), 155.7 (Quat, C_6), 133.6 (Quat, C_2), 129.9 (CH, C_4), 129.1 (Quat, C_1), 121.2 (CH, C_3), 116.5 (CH, C_5), 55.0 (CH_3, C_7), 42.8 (CH_2, C_9), 39.0 (CH_2, $C_{9'}$), 13.7 (CH_3, C_{10}), 12.6 (CH_3, $C_{10'}$);

FTIR (film) ν_{max}/cm^{-1} = 2974, 2936, 1703, 1629, 1622, 1593, 1579, 1485, 1468, 1431, 1380, 1363, 1308, 1284, 1265, 1244, 1220, 1188, 1106, 1065;

LRMS (ESI^+) calculated for $C_{13}H_{18}NO_3^+$ = 236, mass found = 236.

The data matched those of the literature.[187]

2-Formyl-6-methoxybenzoic acid, 407



According to a literature procedure,[187] a solution of **407** (1.08 g, 4.58 mmol, 1.0 eq) in AcOH (10 mL) and 3 M aqueous HCl (10 mL) was heated to reflux for 18 hours. The reaction mixture was concentrated and the crude solid dissolved in saturated $NaHCO_3$ (20 mL). The aqueous layer was washed with EtOAc (2 × 20 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were cooled to 0 °C and then carefully acidified with conc HCl until a precipitate was formed. The precipitate was purified by recrystallization (petrol 60-80/EtOAc) to afford 23 as a colourless crystalline solid (250 mg, 30%).

mp = 138-140 °C;

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H = 8.00 (s, H_{10}), 7.73 (t, *J* = 7.9 Hz, 1H, H_4), 7.20 (d, *J* = 8.3 Hz, 1H, H_3), 7.16 (d, *J* = 7.4 Hz, 1H, H_5), 6.53 (br s, 1H, H_9), 3.91 (s, 3H, H_7);

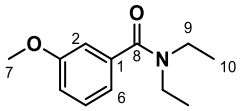
^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C = 167.3 (Quat, C_8), 158.7 (Quat, C_6), 151.3 (Quat, C_2), 138.0 (CH, C_4), 116.4 (CH, C_3), 114.6 (Quat, C_1), 114.0 (CH, C_5), 97.8 (CH, C_9), 57.2 (CH_3, C_7);

FTIR (film) ν_{max}/cm^{-1} = 3399, 2360, 1748, 1610, 1488, 1288, 1206, 1141, 1042;

LRMS (ESI^+) calculated for $C_9H_8O_4Na^+$ = 203, mass found = 203.

The data matched those of the literature.[187]

_N_,_N_-Diethyl-3-methoxybenzamide, 541



According to a literature procedure,[188] a stirred solution of 3-methoxybenzoic acid (5.00 g, 32.9 mmol, 1.0 eq) in thionyl chloride (36.0 mL, 329 mmol, 4.2 eq) was heated to reflux. After two hours had elapsed, the solution was concentrated under reduced pressure and the residual oil azeotroped with toluene (2 × 10 mL). The resulting acid chloride was dissolved in CH_2Cl_2 (15 mL) and stirred. To this solution was slowly added a solution of diethylamine (8.5 mL, 82.2 mmol, 2.5 eq) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 2 hours upon which it was quenched with saturated aqueous NH_4Cl (50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with 1 M aqueous HCl (50 mL) and water (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **541** as an orange oil (6.33 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.28 (ddd, *J* = 8.1, 7.5, 0.6 Hz, 1H, H_3), 6.94-6.88 (m, 3H, H_2, H_4 & H_6), 3.81 (s, 3H, H_7), 3.53 (br s, 2H, H_9), 3.25 (br s, 2H, $H_{9'}$), 1.24 (br s, 3H, H_{10}), 1.09 (br s, 3H, $H_{10'}$);

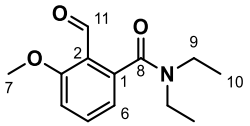
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 171.0 (Quat, C_8), 159.5 (Quat, C_3), 138.6 (Quat, C_1), 129.5 (CH, C_5), 118.4 (CH, C_6), 115.0 (CH, C), 111.7 (CH, C_2), 55.3 (CH_3, C_7), 43.2 (CH_2, C_9), 39.2 (CH_2, $C_{9'}$), 14.3 (CH_3, C_{10}), 12.9 (CH_3, $C_{10'}$);

FTIR (film) ν_{max}/cm^{-1} = 2971, 2936, 1630, 1579, 1473, 1458, 1431, 1381, 1364, 1317, 1290, 1252, 1240, 1219, 1166, 1101, 1045;

LRMS (ESI^+) calculated for $C_{12}H_{18}NO_2^+$ = 208, mass found = 208.

The data matched those of the literature.[188]

_N_,_N_-Diethyl-2-formyl-3-methoxybenzamide, 542



According to a literature procedure,[187] to a solution of TMEDA (3.48 mL, 23.2 mmol, 1.15 eq) in THF (50 mL) at −78 °C, was added ^{s}BuLi (1.3 M in cyclohexane/hexane 92:8, 17.8 mL, 23.2 mmol, 1.15 eq). The solution was stirred for 15 minutes and then **541** (4.18 g, 20.2 mmol, 1.0 eq) was added dropwise over 15 minutes and the mixture stirred at −78 °C. After 2 hours had elapsed, DMF (3.12 mL, 40.3 mmol, 2.0 eq) was added dropwise and the reaction mixture allowed to warm slowly to room temperature by removal of the cooling bath and stirred for half an hour. The reaction mixture was quenched with saturated aqueous NH_4Cl (80 mL) and the mixture extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 3:2 EtOAc/petrol 40-60, to afford **542** as a colourless oil (3.47 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 10.46 (d, *J* = 0.7 Hz, 1H, H_{11}), 7.53 (dd, *J* = 8.5, 7.5 Hz, 1H, H_5), 6.98 (dd, *J* = 8.4, 0.7 Hz, 1H, H_4), 6.82 (dd, *J* = 7.8, 0.8 Hz, 1H H_6), 3.92 (s, 3H, H_7), 3.56 (q, *J* = 7.1 Hz, 2H, H_9), 3.04 (q, *J* = 7.2 Hz, 2H, $H_{9'}$), 1.30 (t, *J* = 7.1 Hz, 3H, H_{10}), 0.99 (t, *J* = 7.1 Hz, 3H, $H_{10'}$);

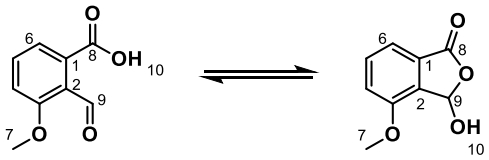
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 189.3 (CH, C_{11}), 169.7 (Quat, C_8), 162.1 (Quat, C_3), 139.4 (Quat, C_1), 135.6 (CH, C_5), 121.2 (Quat, C_2), 119.1 (CH, C_6), 111.8 (CH, C_4), 56.0 (CH_3, C_7), 42.4 (CH_2, C_9), 38.6 (CH_2, C_9), 13.5 (CH_3, C_{10}), 12.1 (CH_3, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 2973, 2936, 2873, 1691, 1578, 1485, 1460, 1432, 1298, 1380, 1363, 1347, 1316, 1290, 1267, 1230, 1184, 1130, 1102, 1080, 1055, 1007;

LRMS (ESI$^+$) calculated for $C_{13}H_{18}NO_3^+$ = 236, mass found = 236.

The data matched those of the literature.[187]

2-Formyl-3-methoxybenzoic acid, 408



According to a literature procedure,[187] a solution of **542** (3.00 g, 12.8 mmol, 1.0 eq) in AcOH (60 mL) and 3 M aqueous HCl (60 mL) was refluxed for 18 hours. The reaction mixture was concentrated and the crude solid dissolved in saturated $NaHCO_3$ (60 mL). The aqueous layer was washed with EtOAc (2 × 50 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were cooled to 0 °C and then carefully acidified with conc HCl until a precipitate was formed. The precipitate was purified by recrystallization (petrol 60-80/EtOAc) to afford **408** as a colourless crystalline solid (1.17 g, 51%).

mp = 154-156 °C;

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H = 8.02 (d, *J* = 8.4 Hz, 1H, H_{10}), 7.62 (t, *J* = 7.9 Hz, 1H, H_3), 7.38 (d, *J* = 8.1 Hz, 1H, $H_{2/4}$), 7.37 (d, *J* = 7.5 Hz, 1H, $H_{2/4}$), 6.66 (d, J= 8.2 Hz, 1H, H_9), 3.90 (s, 3H, H_7);

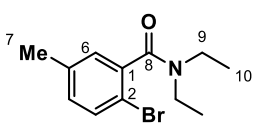
^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C = 168.9 (Quat, C_8), 155.6 (Quat, C_3), 134.7 (Quat, C_2), 133.1 (CH, C_5), 128.8 (Quat, C_1), 117.4 (CH, C_6), 116.4 (CH, C_4), 97.6 (CH, C_9), 56.3 (CH_3, C_7);

FTIR (film) ν_{max}/cm^{-1} = 3365, 1723, 1615, 1491, 1467, 1442, 1359, 1319, 1282, 1263, 1209, 1172, 1117, 1099, 1046;

LRMS (ESI$^+$) calculated for $C_9H_8O_4Na^+$ = 203, mass found = 203.

The data matched those of the literature.[189]

2-Bromo-*N*,*N*-diethyl-5-methylbenzamide, 410



A stirred solution of 2-bromo-5-methylbenzoic acid (3.00 g, 14.0 mmol, 1.0 eq) in thionyl chloride (10.0 mL, 139.5 mmol, 10 eq) was heated to reflux. After two hours had elapsed, the solution was concentrated under reduced pressure and the residual oil azeotroped with toluene (2 × 10 mL). The resulting acid chloride was dissolved in CH_2Cl_2 (10 mL) and stirred. To this solution was slowly added a solution of diethylamine (3.6 mL, 34.8 mmol, 2.5 eq) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 2 hours upon which it was quenched with water (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:3 EtOAc/petrol 40-60, to afford **410** as a colourless oil (3.26 g, 86%).

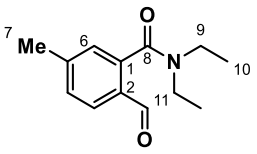
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 (d, *J* = 8.1 Hz, 1H, H_4), 7.07-6.99 (m, 2H, H_6 & H_3), 3.80 (dq, *J* = 14.1, 6.9 Hz, 1H, $H_{9'}$), 3.32 (dq, *J* = 14.1, 6.9 Hz, 1H, $H_{9'}$), 3.14 (dq, *J* = 4.7, 7.1 Hz, 2H, H_9), 2.30 (s, 3H, H_7), 1.26 (t, *J* = 7.2 Hz, 3H, $H_{10'}$), 1.05 (t, *J* = 7.1 Hz, 3H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.6 (Quat, C_8), 138.6 (Quat, C_1), 137.6 (Quat, C_5), 132.4 (CH, C_4), 130.8 (CH, C_3), 128.1 (CH, C_6), 115.8 (Quat, C_2), 42.7 (CH_2, C_9), 38.8 (CH_2, $C_{9'}$), 20.9 (CH_3, C_7), 13.9 (CH_3, C_{10}), 12.6 (CH_3, $C_{10'}$);

FTIR (film) ν_{max}/cm^{-1} = 2974, 2933, 1633, 1458, 1433, 1361, 1314, 1296, 1261, 1219, 1171, 1106, 1030;

HRMS (ESI^+) calculated for $C_{12}H_{17}{}^{79}BrNO_3{}^+$ = 270.0488, mass found = 270.0488.

N,*N*-Diethyl-2-formyl-5-methylbenzamide, 411



According to a literature procedure,[190] to a solution of ^{i}PrMgCl (2.0 M in THF, 6.0 mL, 12.0 mmol, 1.2 eq) in THF (16 mL) at 0 °C, was added ^{n}BuLi (2.5 M in hexane, 9.60 mL, 24.0 mmol, 2.4 eq). The solution was then cooled to −78 °C and a solution of **410** (2.70 g, 10.0 mmol, 1.0 eq) in THF (12 mL)

was added dropwise. The solution was stirred for 2 hours before DMF (3.1 mL, 40.0 mmol, 4.0 eq) was added. The reaction mixture was stirred for 4 hours at −78 °C before being quenched with saturated aqueous NH_4Cl (50 mL) at that temperature. The quenched reaction mixture was allowed to warm to room temperature by removal of the cooling bath. The mixture was extracted with EtOAc (3 × 50 mL) and the organic phase were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography, eluting with 1:1 EtOAc/petrol 40-60, to afford **411** as a colourless oil (1.68 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.98 (s, 1H, H_{11}), 7.81 (d, *J* = 7.9 Hz, 1H, H_5), 7.32 (d, *J* = 7.9 Hz, 1H, H_4), 7.14 (s, 1H, H_2), 3.60, (q, *J* = 6.9 Hz, 2H, $H_{9'}$), 3.10 (q, *J* = 7.1 Hz, 2H, H_9), 2.43 (s, 3H, H_7), 1.29 (t, *J* = 7.1 Hz, 3H, $H_{10'}$), 1.02 (t, *J* = 7.1 Hz, 3H, H_{10});

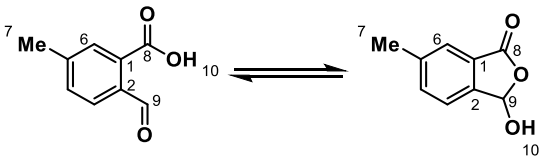
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 190.2 (CH, C_{11}), 168.9 (Quat, C_8), 145.5 (Quat, C_5), 139.7 (Quat, C_1), 130.2 (Quat, C_2), 130.1 (CH, C_4), 129.9 (CH, C_6), 127.4 (CH, C_3), 42.9 (CH_2, C_9), 39.0 (CH_2, $C_{9'}$), 21.8 (CH_3, C_7), 13.9 (CH_3, C_{10}), 12.6 (CH_3, $C_{10'}$);

FTIR (film) ν_{max}/cm^{-1} = 2987, 2967, 2931, 2361, 1616, 1602, 1509, 1469, 1446, 1437, 1371, 1342, 1299, 1223, 1191, 1154, 1140, 1093, 1038, 1013;

LRMS (ESI^+) calculated for $C_{13}H_{18}O_2^+$ = 220, mass found = 220.

The data matched those of the literature.[190]

2-Formyl-5-methylbenzoic acid, 412



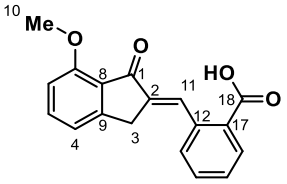
Analogously to a literature procedure,[187] a solution of **411** (1.60, g, 7.30 mmol, 1.0 eq) in AcOH (15 mL) and 3 M aqueous HCl (15 mL) was refluxed for 18 hours. The reaction mixture was concentrated and the crude solid dissolved in saturated $NaHCO_3$ (20 mL). The aqueous layer was washed with EtOAc (2 × 20 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were cooled to 0 °C and then carefully acidified

with conc HCl until a precipitate was formed. The crude product **412** was used without any further purification (600 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.97 (s, 1H, H_6), 7.50 (d, *J* = 8.2 Hz, 1H, H_4), 7.20 (d, *J* = 7.8 Hz, 1H, H_5), 6.33 (s, 1H, H_9), 2.47 (s, 3H, H_7);

LRMS (ESI^+) calculated for $C_9H_8O_3Na^+$ = 187, mass found = 187.

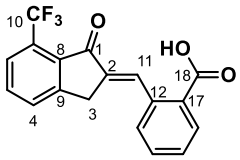
2-((7-Methoxy-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 415



Prepared according to **General Procedure E.**

Aldol condensation with 7-methoxy-1-indanone **286** (75 mg, 0.46 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (69 mg, 0.46 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 0.83 mL, 0.83 mmol, 1.8 eq) in EtOH (1.1 mL). Crude unsaturated acid **415** was obtained as a white solid (85 mg, 62%).

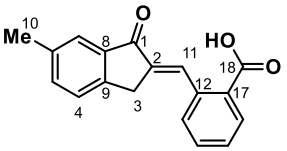
2-((1-Oxo-7-(trifluoromethyl)-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 416



Prepared according to **General Procedure E.**

Aldol condensation with 7-(trifluoromethyl)-1-indanone **392** (100 mg, 0.500 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (75 mg, 0.50 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 0.90 mL, 0.90 mmol, 1.8 eq) in ethanol (1.20 mL). Crude unsaturated acid **416** was obtained as a white solid (155 mg, 93%).

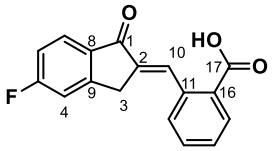
2-((6-Methyl-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 417



Prepared according to **General Procedure E.**

Aldol condensation with 6-methyl-1-indanone **383** (100 mg, 0.684 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (103 mg, 0.684 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.23 mL, 1.23 mmol, 1.8 eq) in ethanol (1.6 mL). Crude unsaturated acid **417** was obtained as a white solid (146 mg, 77%).

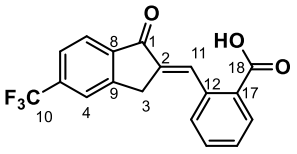
2-((5-Fluoro-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 418



Prepared according to **General Procedure E.**

Aldol condensation with 5-fluoro-1-indanone **384** (100 mg, 0.666 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (100 mg, 0.666 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.20 mL, 1.20 mmol, 1.8 eq) in EtOH (1.6 mL). Crude unsaturated acid **418** was obtained as a pink solid (132 mg, 70%).

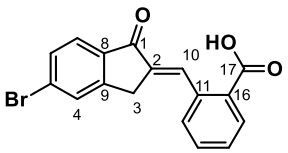
2-((1-Oxo-5-(trifluoromethyl)-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 419



Prepared according to **General Procedure E.**

Aldol condensation with 5-(trifluoromethyl)-1-indanone **391** (70 mg, 0.35 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (53 mg, 0.35 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 0.63 mL, 0.63 mmol, 1.8 eq) in ethanol (0.84 mL). Crude unsaturated acid **419** was obtained as a yellow powder (121 mg, 73%).

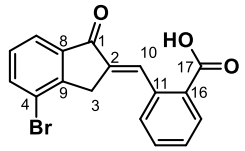
2-((5-Bromo-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 420



Prepared according to **General Procedure E.**

Aldol condensation with 5-bromo-1-indanone **389** (445 mg, 2.11 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (318 mg, 2.11 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 3.81 mL, 3.81 mmol, 1.8 eq) in EtOH (5.09 mL). Crude unsaturated acid **420** was obtained as a pale yellow solid (504 mg, 68%).

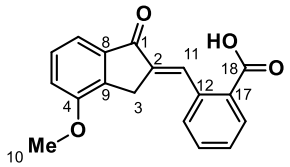
2-((4-Bromo-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 421



Prepared according to **General Procedure E.**

Aldol condensation with 4-bromo-1-indanone **387** (100 mg, 0.473 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (71 mg, 0.47 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 0.85 mL, 0.85 mmol, 1.8 eq) in EtOH (1.15 mL). Crude unsaturated acid **421** was obtained as a white solid (154 mg, 66%).

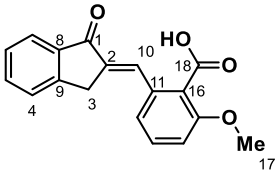
2-((4-Methoxy-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 422



Prepared according to **General Procedure E.**

Aldol condensation with 4-methoxy-1-indanone **393** (150 mg, 0.925 mmol, 1.0 eq), *o*-carboxybenzaldehyde **368** (139 mg, 0.925 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.67 mL, 1.67 mmol, 1.8 eq) in EtOH (2.2 mL). Crude unsaturated acid **422** was obtained as a white solid (226 mg, 83%).

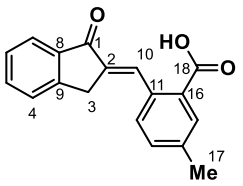
2-Methoxy-6-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 424



Prepared according to **General Procedure E.**

Aldol condensation with 1-indanone **353** (80 mg, 0.61 mmol, 1.0 eq), 2-formyl-6-methoxybenzoic acid **407** (110 mg, 0.61 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.09 mL, 1.09 mmol, 1.8 eq) in ethanol (1.5 mL). Crude unsaturated acid **424** was obtained as a white solid (154 mg, 86%).

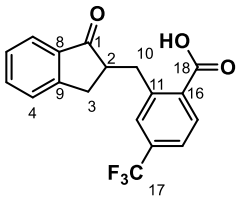
5-Methyl-2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 425



Prepared according to **General Procedure E.**

Aldol condensation with 1-indanone **353** (100 mg, 0.757 mmol, 1.0 eq), 2-formyl-5-methylbenzoic acid **412** (124 mg, 0.757 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.36 mL, 1.36 mmol, 1.8 eq) in ethanol (1.8 mL). Crude unsaturated acid **425** was obtained as a white solid (140 mg, 66%).

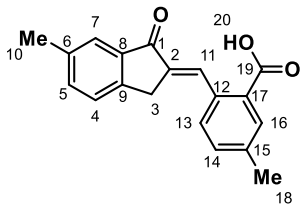
2-((1-Oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)-4-(trifluoromethyl)benzoic acid, 426



Prepared according to **General Procedure E.**

Aldol condensation with 1-indanone **353** (85 mg, 0.64 mmol, 1.0 eq), 2-formyl-4-(trifluoromethyl)benzoic acid **406** (140 mg, 0.643 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.16 mL, 1.16 mmol, 1.8 eq) in ethanol (1.55 mL). Crude unsaturated acid **426** was obtained as a yellow powder (120 mg, 85%).

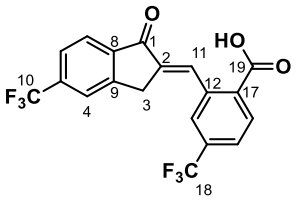
5-Methyl-2-((6-methyl-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 427



Prepared according to **General Procedure E.**

Aldol condensation with 6-methyl-1-indanone **383** (89 mg, 0.61 mmol, 1.0 eq), 2-formyl-5-methylbenzoic acid **412** (100 mg, 0.609 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.10 mL, 1.10 mmol, 1.8 eq) in ethanol (1.46 mL). Crude unsaturated acid **427** was obtained as a pale yellow solid (95 mg, 51%).

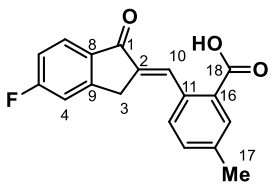
2-((1-Oxo-5-(trifluoromethyl)-1,3-dihydro-2*H*-inden-2-ylidene)methyl)-4-(trifluoromethyl)benzoic acid, 428



Prepared according to **General Procedure E.**

Aldol condensation with 6-(trifluoromethyl)-1-indanone **391** (144 mg, 0.719 mmol, 1.0 eq), 2-formyl-5-(trifluoromethyl)benzoic acid **406** (157 mg, 0.719 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.29 mL, 1.29 mmol, 1.8 eq) in ethanol (1.7 mL). Crude unsaturated acid **428** was obtained as a pale yellow solid (271 mg, 95%).

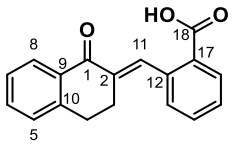
2-((5-Fluoro-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)-5-methylbenzoic acid, 429



Prepared according to **General Procedure E.**

Aldol condensation with 5-fluoro-1-indanone **384** (100 mg, 0.666 mmol, 1.0 eq), 2-formyl-5-methylbenzoic acid **412** (110 mg, 0.666 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 1.20 mL, 1.20 mmol, 1.8 eq) in EtOH (1.60 mL). Crude unsaturated acid **429** was obtained as a white solid (120 mg, 61%).

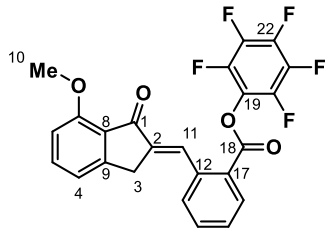
2-((1-Oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl)benzoic acid, 432



Prepared according to **General Procedure E**.

Aldol condensation with 1-tetralone **385** (1.00 g, 6.83 mmol, 1.0 eq), 2-carboxybenzoic acid **368** (1.03 g, 6.83 mmol, 1.0 eq), aqueous sodium hydroxide (1 M, 12.3 mL, 12.3 mmol, 1.8 eq) in ethanol (16.4 mL). Crude unsaturated acid **432** was obtained as a white solid (1.22 g, 64%).

Pentafluorophenyl 2-((7-methoxy-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 433



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **415** (85 mg, 0.29 mmol, 1.0 eq), oxalyl chloride (37 µL, 0.43 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.0 mL) then pentafluorophenol (53 mg, 0.29 mmol, 1.0 eq), Et_3N (95 µL, 0.87 mmol, 3.0 eq) in CH_2Cl_2 (1.0 mL). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded title compound **433** as a white solid (82 mg, 62%).

mp = 164-166 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.24 (dd, *J* = 7.8, 1.4 Hz, 1H, H_{16}), 8.14 (t, *J* = 2.3 Hz, 1H, H_{11}), 7.75-7.66 (m, 2H, H_{14} & H_{16}), 7.56-7.50 (m, 2H, H_5 & H_{15}), 7.02 (dt, *J* = 7.6, 0.8 Hz, 1H, H_4), 6.86-6.82 (m, 1H, H_6), 3.98 (s, 3H, H_{10});

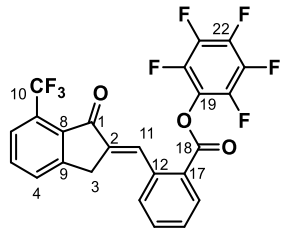
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 191.3 (Quat, C_1), 162.4 (Quat, C_{18}), 159.0 (Quat, C_7), 152.1 (Quat, C_9), 138.8 (Quat, C_2), 137.7 (Quat, C_{12}), 136.5 (CH, C_{11}), 133.8 (CH, C_{14}), 132.1 (CH, C_5), 131.2 (CH, C_{16}), 130.1 (CH, C_{13}), 128.7 (CH, C_{15}), 127.0 (Quat, C_8), 126.4 (Quat, C_{17}), 117.9 (CH, C_4), 109.4 (CH, C_6), 55.9 (CH_2, C_{10}), 31.1 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.0, −157.8, −162.2;

FTIR (neat) ν/cm^{-1} = 2841, 1759, 1699, 1637, 1596, 1520, 1482, 1266, 1235, 1199, 1144, 105, 1065, 1032;

HRMS (ESI^+) calculated for $C_{24}H_{14}O_4F_5^+$ = 461.0807, mass found = 461.0801.

Pentafluorophenyl 2-((1-oxo-7-(trifluoromethyl)-1,3-dihydro-2*H*-inden-2-ylidene)methyl) benzoate, 434



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **416** (155 mg, 0.466 mmol, 1.0 eq), oxalyl chloride (60 µL, 0.70 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.1 mL) then pentafluorophenol (86 mg, 0.47 mmol, 1.0 eq), Et_3N (194 µL, 1.40 mmol, 3.0 eq) in CH_2Cl_2 (1.1 mL). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded title compound **434** as a yellow solid (131 mg, 57%).

mp = 154-156 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.30 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{16}), 8.24 (t, *J* = 2.4 Hz, 1H, H_{11}), 7.75 (td, *J* = 7.7, 1.4 Hz, 1H, H_{14}), 7.73-7.67 (m, 4H, H_4, H_5, H_6, H_{13}), 7.59 (td, *J* = 7.7, 1.4 Hz, 1H, H_{15}), 3.93 (d, *J* = 2.3 Hz, 2H, H_3);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 189.6 (Quat, C_1), 162.1 (Quat, C_{18}), 151.8 (Quat, C_9), 138.6 (Quat, C_{12}), 136.1 (CH, C_{11}), 134.9 (Quat, C_2), 134.0 (q, *J* = 1.5 Hz, CH, C_5), 133.8 (q, *J* = 6.1 Hz, Quat, C_8),

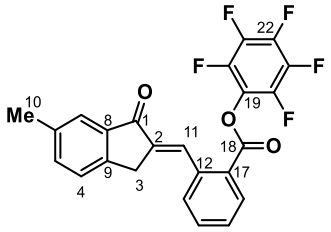
133.7 (CH, C_{14}), 132.1 (CH, C_{15}), 130.1 (CH, C_{12}), 130.0 (CH, C_4), 129.1 (CH, C_{14}), 127.8 (q, *J* = 34.7 Hz, Quat, C_7), 126.9 (Quat, C_{17}), 125.5 (q, *J* = 6.0 Hz, CH, C_6), 122.7 (q, *J* = 273.8 Hz, CF_3, C_{10}), 31.1 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −61.5, −152.3, −157.5, −162.1;

FTIR (neat) ν/cm^{-1} = 2360, 1758, 1708, 1636, 1599, 1521, 1484, 1414, 1322, 1251, 1234, 1203, 1160, 1142, 1101, 1034;

HRMS (ESI$^+$) calculated for $C_{24}H_{11}O_3F_8^+$ = 499.0575, mass found = 499.0576.

Pentafluorophenyl 2-((6-methyl-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 435



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **417** (146 mg, 0.525 mmol, 1.0 eq), oxalyl chloride (66.6 µL, 0.787 mmol, 1.0 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.5 mL) then pentafluorophenol (96 mg, 0.53 mmol, 1.0 eq), Et_3N (218 µL, 1.56 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **435** as a white solid (88 mg, 38%).

mp = 152-154 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.28 (dd, *J* = 8.0, 1.4 Hz, 1H, H_{16}), 8.20 (t, *J* = 2.3 Hz, 1H, H_{11}), 7.76-7.69 (m, 3H, H_7, H_{14}, H_{13}), 7.56 (td, *J* = 7.9, 6.9, 1.7 Hz, 1H, H_{15}), 7.42 (dd, *J* = 7.7, 1.7 Hz, 1H, H_5), 7.37 (dd, *J* = 7.8, 0.9 Hz, 1H, H_4), 3.84 (d, *J* = 1.6 Hz, 2H, H_3), 2.43 (s, 3H, H_{10});

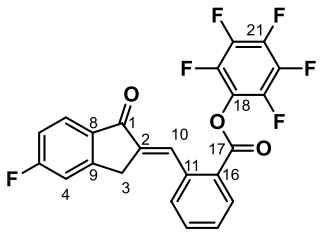
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 193.5 (Quat, C_1), 162.2 (Quat, C_{18}), 147.1 (Quat, C_9), 138.9 (Quat, C_2), 138.2 (Quat, C_{12}), 138.0 (Quat, C_6), 137.7 (Quat, C_8), 136.0 (CH, C_{11}), 133.8 (CH, C_{14}), 132.0 (CH, C_5), 132.0 (CH, C_{16}), 130.1 (CH, C_{13}), 128.8 (CH, C_{15}), 126.9 (Quat, C_{17}), 125.8 (CH, C_4), 124.6 (CH, C_7), 30.8 (CH_2, C_3), 21.2 (CH_3, C_{10});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.1, −157.7, −162.2;

FTIR (neat) ν/cm^{-1} = 2926, 2361, 1760, 1701, 1637, 1520, 1284, 1234, 1160, 1116, 1093, 1031;

HRMS (ESI$^+$) calculated for $C_{24}H_{14}O_3F_5^+$ = 445.0858, mass found = 445.0859.

Pentafluorophenyl 2-((5-fluoro-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 436



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **418** (132 mg, 0.468 mmol, 1.0 eq), oxalyl chloride (59.4 µL, 0.702 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.5 mL) then pentafluorophenol (86 mg, 0.47 mmol, 1.0 eq), Et_3N (192 µL, 1.41 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **436** as a white solid (157 mg, 75%).

mp = 148-150 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.29 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{15}), 8.20 (t, *J* = 2.3 Hz, 1H, H_{10}), 7.91 (dd, *J* = 8.4, 5.3 Hz, 1H, H_7), 7.75 (td, *J* = 7.6, 1.4 Hz, 1H, H_{13}), 7.69 (dd, *J* = 7.8, 1.4 Hz, 1H, H_{12}), 7.58 (td, *J* = 7.6, 1.5 Hz, 1H, H_{14}), 7.20-7.06 (m, 2H, H_4, H_6), 3.87 (d, *J* = 2.2 Hz, 2H, H_3);

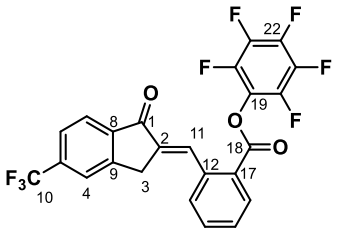
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 191.6 (Quat, C_1), 167.0 (d, *J* = 255.6 Hz, CF, C_5), 162.2 (Quat, C_{17}), 152.5 (d, *J* = 10.3 Hz, Quat, C_9), 138.6 (Quat, C_{11}), 137.0 (Quat, C_8), 134.5 (Quat, C_2), 133.9 (CH, C_{13}), 132.5 (CH, C_{10}), 132.1 (CH, C_{15}), 130.0 (CH, C_{12}), 129.0 (CH, C_{14}), 127.0 (d, *J* = 10.4 Hz, CH, C_7), 126.8 (Quat, C_{16}), 116.0 (d, *J* = 23.8 Hz, CH, C_6), 112.9 (d, *J* = 22.6 Hz, CH, C_4), 31.1 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −102.1, −152.2, −157.6, −162.1;

FTIR (neat) ν/cm^{-1} = 1758, 1702, 1618, 1593, 1518, 1481, 1332, 1264, 1233, 1145, 1127, 1086, 1030;

HRMS (ESI$^+$) calculated for $C_{23}H_{11}O_3F_6^+$ = 449.0607, mass found = 449.0608.

Pentafluorophenyl 2-((1-oxo-5-(trifluoromethyl)-1,3-dihydro-2*H*-inden-2-ylidene)methyl) benzoate, 437



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **419** (120 mg, 0.361 mmol, 1.0 eq), oxalyl chloride (45.8 µL, 0.542 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop)in CH_2Cl_2 (1.5 mL) then pentafluorophenol (66 mg, 0.36 mmol, 1.0 eq), Et_3N (151 µL, 1.08 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:20 EtOAc/petrol 40-60, afforded title compound **437** as a yellow solid (88 mg, 42%).

mp = 108-110 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.25 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{16}), 8.22 (t, *J* = 2.3 Hz, 1H, H_{11}), 7.95 (d, *J* = 8.2 Hz, 1H, H_7), 7.74-7.60 (m, 4H, H_4, H_6, H_{13}, H_{14}), 7.54 (td, *J* = 7.6, 1.3 Hz, 1H, H_{15}), 3.88 (d, *J* = 1.4 Hz, 2H, H_3);

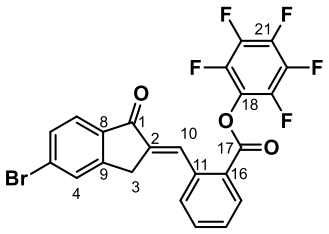
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 192.3 (Quat, C_1), 162.1 (Quat, C_{18}), 149.7 (Quat, C_9), 140.7 (Quat, C_2), 138.4 (Quat, C_{12}), 136.5 (CH, C_{11}), 135.9 (q, *J* = 32.3 Hz, Quat, C_5), 134.0 (CH, C_{14}), 133.9 (Quat, C_8), 132.2 (CH, C_{16}), 130.0 (CH, C_{13}), 129.3 (CH, C_7), 126.9 (Quat, C_{17}), 125.2 (CH, C_{15}), 124.9 (q, *J* = 3.6 Hz, CH, C_6), 123.6 (q, *J* = 273.1 Hz, CF_3, C_{10}), 123.4 (q, *J* = 3.9 Hz, CH, C_4), 31.2 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −62.8, −152.2, −157.4, −162.0;

FTIR (neat) v/cm^{-1} = 2981, 1761, 1707, 1638, 1521, 1483, 1434, 1382, 1327, 1264, 1236, 1206, 1169, 1131, 1060, 1033;

HRMS (ESI$^+$) calculated for $C_{24}H_{10}O_3F_8Na^+$ = 521.0394, mass found = 521.0393.

Pentafluorophenyl 2-((5-bromo-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 438



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid 4**20** (504 mg, 1.46 mmol, 1.0 eq), oxalyl chloride (187 µL, 2.21 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (6 mL) then pentafluorophenol (271 mg, 1.46 mmol, 1.0 eq), Et_3N (620 µL, 4.40 mmol, 3.0 eq) in CH_2Cl_2 (6 mL). Purification *via* flash column chromatography, eluting with 1:9 to 1:3 EtOAc/petrol 40-60, afforded title compound **438** as a brown solid (717 mg, 96%).

mp = 188-190 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.30 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{15}), 8.24 (t, *J* = 2.2 Hz, 1H, H_{10}), 7.80-7.72 (m, 2H, H_7, H_{13}), 7.68 (d, *J* = 7.6 Hz, 1H, H_{12}), 7.65 (d, *J* = 1.0 Hz, 1H, H_4), 7.60-7.54 (m, 2H, H_6, H_{14}), 3.87 (d, *J* = 2.3 Hz, 2H, H_3);

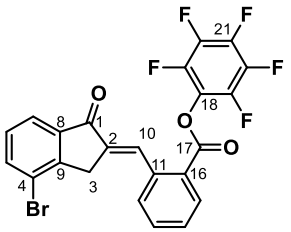
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 192.2 (Quat, C_1), 162.1 (Quat, C_{17}), 151.2 (Quat, C_9), 138.5 (Quat, C_{11}), 137.0 (Quat, C_8), 136.7 (Quat, C_2), 134.0 (CH, C_{13}), 133.1 (CH, C_{10}), 132.2 (CH, C_{15}), 131.4 (CH, C_{12}), 130.0 (CH, C_{14}), 129.9 (Quat, C_{16}), 129.5 (CH, C_6), 129.1 (CH, C_4), 126.8 (Quat, C_5), 125.9 (CH, C_7), 30.9 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.2, −157.5, −162.1;

FTIR (neat) ν/cm^{-1} = 2362, 1756, 1697, 1619, 1598, 1575, 1518, 1417, 1319, 1263, 1234, 1298, 1093, 1034;

HRMS (ESI$^+$) calculated for $C_{23}H_{11}O_3{}^{79}BrF_5{}^+$ = 508.9806, mass found = 508.9808.

Pentafluorophenyl 2-((4-bromo-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 439



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **421** (154 mg, 0.449 mmol, 1.0 eq), oxalyl chloride (56.9 µL, 0.673 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.3 mL) then pentafluorophenol (83 mg, 0.45 mmol, 1.0 eq), Et_3N (188 µL, 1.35 mmol, 3.0 eq) in CH_2Cl_2 (1.3 mL). Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, followed by recrystallization with EtOAc/petrol 60-80 afforded title compound **439** as a yellow solid (132 mg, 62%).

mp = 108-110 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.31 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{15}), 8.27 (t, *J* = 2.2 Hz, 1H, H_{10}), 7.86 (dd, *J* = 7.6, 0.9 Hz, 1H, H_7), 7.83-7.71 (m, 3H, H_5, H_{12}, H_{13}), 7.60 (td, *J* = 7.7, 1.3 Hz, 1H, H_{14}), 7.34 (tt, *J* = 7.6, 0.8 Hz, 1H, H_6), 3.81 (d, *J* = 2.1 Hz, 2H, H_3);

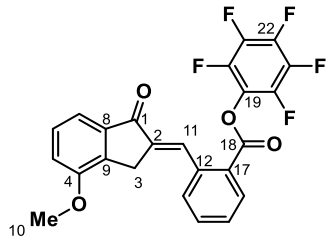
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 191.6 (Quat, C_1), 161.1 (Quat, C_{17}), 148.6 (Quat, C_9), 139.1 (Quat, C_{11}), 137.4 (Quat, C_8), 136.4 (CH, C_5), 135.3 (Quat, C_2), 133.1 (CH, C_{13}), 132.6 (CH, C_{10}), 131.1 (CH, C_{15}), 129.0 (CH, C_{12}), 128.5 (CH, C_6), 128.2 (CH, C_{14}), 125.8 (Quat, C_{16}), 122.4 (CH, C_7), 120.7 (Quat, C_4), 31.3 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.2, −157.6, −162.1;

FTIR (neat) ν/cm^{-1} = 1759, 1707, 1639, 1598, 1520, 1459, 1325, 1266, 1235, 1124, 1098, 1032;

HRMS (ACI$^+$) calculated for $C_{23}H_{10}O_3{}^{79}BrF_5{}^+$ = 508.9806, mass found = 508.9807.

Pentafluorophenyl 2-((4-methoxy-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 440



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **422** (226 mg, 0.768 mmol, 1.0 eq), oxalyl chloride (98.0 µL, 1.15 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (2.5 mL) then pentafluorophenol (142 mg, 0.768 mmol, 1.0 eq), Et_3N (321 µL, 2.30 mmol, 3.0 eq) in CH_2Cl_2 (2.5 mL). Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded title compound **440** as a white solid (300 mg, 84%).

mp = 110-112 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.28 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{16}), 8.23 (t, *J* = 2.1 Hz, 1H, H_{11}), 7.93-7.70 (m, 2H, H_{13}, H_{14}), 7.68-7.53 (m, 1H, H_{15}), 7.50 (dd, *J* = 7.6, 0.8 Hz, 1H, H_7), 7.39 (t, *J* = 7.8 Hz, 1H, H_6), 7.07 (dd, *J* = 8.0, 0.8 Hz, 1H, H_5), 3.91 (s, 3H, H_{10}), 3.78 (d, *J* = 2.1 Hz, 2H, H_{11});

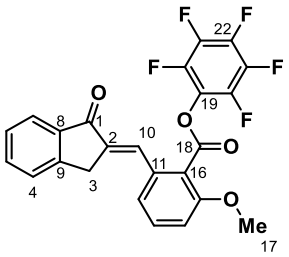
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 193.8 (Quat, C_1), 162.2 (Quat, C_{18}), 156.6 (Quat, C_4), 139.4 (Quat, C_2), 138.7 (Quat, C_8), 138.6 (Quat, C_9), 137.3 (Quat, C_{12}), 134.0 (CH, C_{14}), 132.6 (CH, C_{11}), 132.0 (CH, C_{16}), 130.2 (CH, C_{13}), 129.2 (CH, C_6), 128.9 (CH, C_{15}), 126.8 (Quat, C_{16}), 116.3 (CH, C_7), 115.2 (CH, C_5), 55.5 (CH_3, C_{10}), 28.1 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.2, −157.7, −162.2;

FTIR (neat) ν/cm^{-1} = 2981, 2359, 1760, 1704, 1635, 1604, 1520, 1489, 1279, 1234, 1146, 1077, 1032;

HRMS (ESI$^+$) calculated for $C_{24}H_{13}O_4F_5Na^+$ = 483.0626, mass found = 483.0625.

Pentafluorophenyl 2-methoxy-6-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 441



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **424** (154 mg, 0.523 mmol, 1.0 eq), oxalyl chloride (66.0 µL, 0.785 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.5 mL) then pentafluorophenol (99 mg, 0.52 mmol, 1.0 eq), Et_3N (217 µL, 1.57 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Purification *via* flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, afforded title compound **441** as a white solid (63 mg, 25%).

mp = 196-198 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.92 (dt, *J* = 7.6, 1.0 Hz, 1H, H_7), 7.79 (t, *J* = 2.2 Hz, 1H, H_{10}), 7.62 (td, *J* = 7.4, 1.2 Hz, 1H, H_5), 7.57 (t, *J* = 8.1 Hz, 1H, H_{13}), 7.52 (dp, *J* = 7.6, 1.0 Hz, 1H, H_4), 7.43 (td, *J* = 7.3, 0.9 Hz, 1H, H_6), 7.37 (d, *J* = 7.8 Hz, 1H, H_{12}), 7.06 (dd, *J* = 8.5, 0.8 Hz, 1H, H_{14}), 3.99 (d, *J* = 2.2 Hz, 2H, H_3), 3.95 (s, 3H, H_{17});

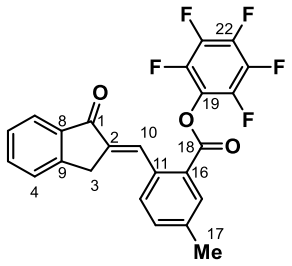
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 193.2 (Quat, C_1), 163.0 (Quat, C_{18}), 157.6 (Quat, C_{15}), 149.6 (Quat, C_9), 138.5 (Quat, C_2), 137.9 (Quat, C_{11}), 135.2 (Quat, C_8), 134.9 (CH, C_5), 132.1 (CH, C_{10}), 129.2 (CH, C_{13}), 127.8 (CH, C_6), 126.2 (CH, C_4), 124.7 (CH, C_7), 121.9 (Quat, C_{16}), 120.9 (CH, C_{13}), 111.9 (CH, C_{15}), 56.3 (CH_3, C_{17}), 32.0 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −151.0, −157.7, −162.0;

FTIR (neat) ν/cm^{-1} = 2923, 2847, 2360, 2120, 1771, 1701, 1632, 1611, 1575, 1519, 1471, 1455, 1282, 1263, 1228, 1138, 1094, 1073, 1026;

HRMS (ESI$^+$) calculated for $C_{24}H_{13}O_3F_5Na^+$ = 483.0626, mass found = 483.0624.

Pentafluorophenyl 5-methyl-2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 442



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **425** (140 mg, 0.500 mmol, 1.0 eq), oxalyl chloride (63.5 µL, 0.750 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.5 mL) then pentafluorophenol (93 mg, 0.50 mmol, 1.0 eq), Et_3N (211 µL, 1.50 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **442** as a white solid (170 mg, 76%).

mp = 110-112 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.21 (t, *J* = 1.9 Hz, 1H, H_{10}), 8.08 (d, *J* = 1.8 Hz, 1H, H_{15}), 7.90 (dt, *J* = 7.7, 0.9 Hz, 1H, H_7), 7.63 (d, *J* = 8.0 Hz, 1H, H_{12}), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H, H_5), 7.54 (dd, *J* = 7.9, 1.9 Hz, 1H, H_{13}), 7.49 (dt, *J* = 7.7, 1.0 Hz, 1H, H_4), 7.42 (td, *J* = 7.4, 1.0 Hz, 1H, H_6), 3.89 (d, *J* = 2.2 Hz, 2H, H_3), 2.51 (s, 3H, H_{17});

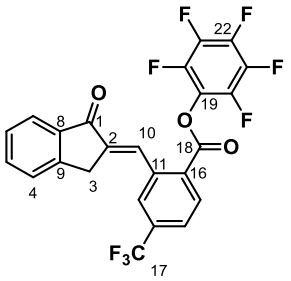
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 193.5 (Quat, C_1), 162.4 (Quat, C_{18}), 149.7 (Quat, C_9), 139.4 (Quat, C_2), 138.2 (Quat, C_{11}), 136.9 (Quat, C_{14}), 135.7 (Quat, C_8), 134.7 (CH, C_5), 134.6 (CH, C_{13}), 132.6 (CH, C_{15}), 132.2 (CH, C_{10}), 130.1 (CH, C_{12}), 127.7 (CH, C_6), 126.9 (Quat, C_{17}), 126.1 (CH, C_4), 124.6 (CH, C_7), 31.3 (CH_2, C_3), 21.2 (CH_3, C_{17});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.1, −157.7, −162.2;

FTIR (neat) ν/cm^{-1} = 1758, 1701, 1634, 1609, 1519, 1494, 1468, 1325, 1296, 1253, 1176, 1142, 1092, 1033;

HRMS (ESI$^+$) calculated for $C_{24}H_{14}O_3F_5^+$ = 445.0858, mass found = 445.0857.

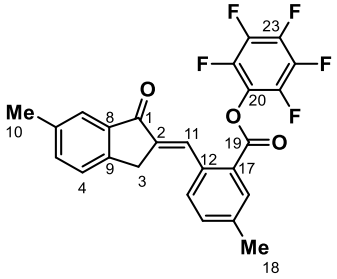
Pentafluorophenyl 2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)-4-(trifluoromethyl) benzoate, 443



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **425** (120 mg, 0.361 mmol, 1.0 eq), oxalyl chloride (45.8 µL, 0.542 mmol, 1.0 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.5 mL) then pentafluorophenol (67 mg, 0.36 mmol, 1.0 eq), Et_3N (151 µL, 1.08 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Crude unsaturated ester **443** was obtained as a yellow solid (126 mg, 70%).

Pentafluorophenyl 5-methyl-2-((6-methyl-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl) benzoate, 444



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **427** (88 mg, 0.32 mmol, 1.0 eq), oxalyl chloride (41 µL, 0.48 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1 mL) then pentafluorophenol (55 mg, 0.32 mmol, 1.0 eq), Et_3N (78 µL, 0.96 mmol, 3.0 eq) in CH_2Cl_2 (1 mL). Purification *via* flash column chromatography, eluting with 1:9 to 3:7 EtOAc/petrol 40-60, afforded title compound **444** as a yellow solid (113 mg, 83%).

mp = 168-170 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.11 (t, *J* = 2.2 Hz, 1H, H_{11}), 8.00 (d, *J* = 1.8 Hz, 1H, H_{16}), 7.63 (dt, *J* = 1.6, 0.8 Hz, 1H, H_7), 7.55 (d, *J* = 8.0 Hz, 1H, H_{14}), 7.46 (dd, *J* = 8.0, 1.8 Hz, 1H, H_{13}), 7.34 (dd, *J* = 7.9, 1.7 Hz, 1H, H_5), 7.30 (dd, *J* = 7.8, 0.9 Hz, 1H, H_4), 3.77 (d, *J* = 1.4 Hz, 2H, H_3), 2.43 (s, 3H. H_{18}), 2.35 (s, 3H, H_{10});

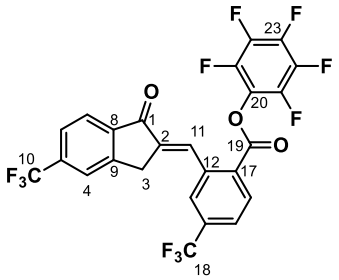
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 193.6 (Quat, C_1), 162.4 (Quat, C_{19}), 147.1 (Quat, C_9), 139.3 (Quat, C_2), 138.3 (Quat, C_{12}), 137.7 (Quat, C_{15}), 137.4 (Quat, C_6), 135.9 (CH, C_5), 135.8 (Quat, C_8), 134.5 (CH, C_{13}), 132.5 (CH, C_{16}), 131.9 (CH, C_{11}), 130.1 (CH, C_{14}), 126.9 (Quat, C_{17}), 125.8 (CH, C_4), 124.6 (CH, C_7), 31.0 (CH_2, C_3), 21.2 (CH_3, C_{18}), 21.2 (CH_3, C_{10});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.1, −157.8, −162.3;

FTIR (neat) ν/cm^{-1} = 2925, 2361, 1756, 1699, 1629, 1520, 1493, 1428, 1319, 1284, 1251, 1178, 1138, 1118, 1138, 1096, 1032;

HRMS (ESI$^+$) calculated for $C_{25}H_{16}O_3F_5^+$ = 459.1014, mass found = 459.1013.

Pentafluorophenyl 2-((1-oxo-5-(trifluoromethyl)-1,3-dihydro-2*H*-inden-2-ylidene)methyl)-4-(trifluoromethyl)benzoate, 445



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **428** (271 mg, 0.677 mmol, 1.0 eq), oxalyl chloride (86.3 µL, 1.02 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (2.0 mL) then pentafluorophenol (125 mg, 0.677 mmol), Et_3N (283 µL, 2.03 mmol, 3.0 eq) in CH_2Cl_2 (2.0 mL). Purification *via* flash column chromatography, eluting with 3:97 to 5:95 EtOAc/petrol 40-60, afforded title compound **445** as a yellow solid (160 mg, 42%).

mp = 115-117 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.42 (d, *J* = 8.2 Hz, 1H, H_{16}), 8.24 (t, *J* = 2.2 Hz, 1H, H_{11}), 8.00 (d, *J* = 8.0 Hz, 1H, H_7), 7.96 (d, *J* = 1.7 Hz, 1H, H_{13}), 7.85 (dd, *J* = 8.3, 1.7 Hz, 1H, H_{15}), 7.81 (s, 1H, H_4), 7.70 (d, *J* = 8.2 Hz, 1H, H_6), 3.97 (d, *J* = 2.2 Hz, 2H, H_3);

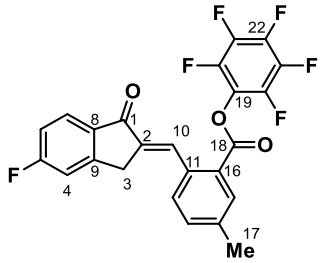
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 191.9 (Quat, C_1), 161.3 (Quat, C_{19}), 149.5 (Quat, C_9), 140.4 (Quat, C_2), 139.1 (Quat, C_{12}), 137.8 (Quat, C_8), 136.2 (q, *J* = 32.4 Hz, Quat, C_{14}), 135.6 (q, *J* = 33.3 Hz, Quat, C_5), 132.7 (CH, C_{15}), 131.9 (CH, C_{11}), 130.1 (Quat, C_{17}), 126.7 (q, *J* = 4.0 Hz, CH, C_{13}), 125.9 (q, *J* = 3.4 Hz, CH, C_{16}), 125.2 (CH, C_7), 125.0 (q, *J* = 3.8 Hz, CH, C_6), 123.6 (q, *J* = 4.0 Hz, CH, C_4), 123.5 (q, *J* = 272.8 Hz, CF_3, C_{18}), 123.0 (d, *J* = 273.4 Hz, CF_3 ,C_{10}), 30.9 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −63.0, −63.4, −152.2, −156.8, −161.6;

FTIR (neat) ν/cm^{-1} = 2361, 2341, 1767, 1713, 1522, 1434, 1329, 1238, 1174, 1134, 1082, 1059, 1038;

HRMS (ESI$^+$) calculated for $C_{25}H_9O_3F_{11}Na^+$ = 589.0268, mass found = 589.0264.

Pentafluorophenyl 2-((5-fluoro-1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)-5-methyl benzoate, 446



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **429** (120 mg, 0.405 mmol, 1.0 eq), oxalyl chloride (51.5 µL, 0.608 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (1.5 mL) then pentafluorophenol (75 mg, 0.40 mmol, 1.0 eq), Et_3N (170 µL, 1.22 mmol, 3.0 eq) in CH_2Cl_2 (1.5 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **446** as a yellow solid (130 mg, 69%).

mp = 136-138 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.19 (d, *J* = 2.2 Hz, 1H, H_{10}), 8.08 (d, *J* = 1.7 Hz, 1H, H_{15}), 7.90 (dd, *J* = 8.4, 5.3 Hz, 1H, H_7), 7.60 (d, *J* = 7.9 Hz, 1H, H_{12}), 7.54 (dd, *J* = 8.0, 1.8 Hz, 1H, H_{13}), 7.14 (dd, *J* = 8.4, 2.1 Hz, 1H, H_4), 7.11 (td, *J* = 8.7, 2.3 Hz, 1H, H_6), 3.88 (br s, 2H, H_3), 2.50 (s, 3H, H_{17});

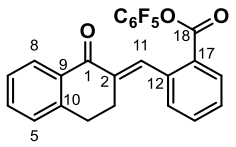
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 191.7 (Quat, C_1), 167.0 (d, *J* = 256.1 Hz, CF, C_5), 162.3 (Quat, C_{18}), 152.5 (d, *J* = 10.1 Hz, Quat, C_9), 139.5 (Quat, C_2), 136.5 (Quat, C_{11}), 135.5 (Quat, C_{14}), 134.6 (CH, C_{13}), 134.6 (d, *J* = 1.9 Hz, Quat, C_8), 132.6 (CH, C_{15}), 132.4 (CH, C_{10}), 130.0 (CH, C_{12}), 126.9 (d, *J* = 10.2 Hz, CH, C_7), 126.9 (Quat, C_{16}), 116.0 (d, *J* = 23.6 Hz, CH, C_6), 112.9 (d, *J* = 22.6 Hz, CH, C_4), 31.3 (d, *J* = 2.2 Hz, CH_2, C_3), 21.2 (CH_3, C_{17});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −102.3, −152.2, −157.7, −162.2.;

FTIR (neat) ν/cm^{-1} = 3658, 2981, 2924, 2358, 1759, 1699, 1618, 1520, 1462, 1382, 1251, 1150, 1085, 1034;

HRMS (ESI$^+$) calculated for $C_{24}H_{13}O_3F_6^+$ = 463.0763, mass found = 463.0761.

Pentafluorophenyl 2-((1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl)benzoate, 447



Prepared according to **General Procedure F**.

Esterification with crude unsaturated acid **432** (1.22 g, 4.38 mmol, 1.0 eq), oxalyl chloride (557 µL, 6.57 mmol, 1.5 eq), *N*,*N*-dimethylformamide (1 drop) in CH_2Cl_2 (13 mL) then pentafluorophenol (806 mg, 4.38 mmol, 1.0 eq), Et_3N (1.84 mL, 13.1 mmol, 3.0 eq) in CH_2Cl_2 (13 mL). Purification *via* flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, afforded title compound **447** as a white solid (0.830 g, 43%).

mp = 58-60 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.30 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{16}), 8.16 (d, *J* = 1.6 Hz, 1H, H_{11}), 8.13 (d, *J* = 8.0, 1.2 Hz, 1H, H_4), 7.74-7.68 (m, 1H, H_{14}) 7.55 (td, *J* = 7.7, 1.3 Hz, 1H, H_{15}), 7.48 (td, *J* = 7.4,

1.5 Hz, 1H, H_6), 7.41 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{13}), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H, H_5), 7.24 (dd, *J* = 7.6, 1.2 Hz, 1H, H_7), 3.00-2.77 (m, 4H, H_3 & H_4);

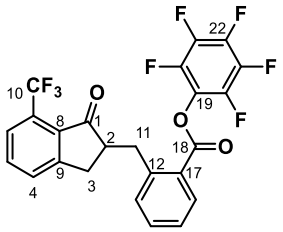
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 187.5 (Quat, C_1), 167.2 (Quat, C_{18}), 143.5 (Quat, C_2), 143.1 (Quat, C_{10}), 139.5 (Quat, C_5), 135.5 (CH, C_{11}), 133.8 (CH, H_{14}), 133.4 (CH, C_6), 133.3 (Quat, C_{13}), 132.0 (CH, C_{16}), 130.7 (CH, C_{13}), 128.5 (CH, C_7), 128.3 (CH, C_{15}), 128.3 (CH, C_4), 127.1 (CH, C_5), 126.4 (Quat, C_{18}), 29.1 (CH_2, C_4), 27.2 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −153.8, −158.8, −161.7;

FTIR (neat) ν/cm^{-1} = 2927, 1782, 1738, 1671, 1597, 1468, 1360, 1314, 1285, 1243, 1217, 1123, 1052, 1012;

HRMS (ESI$^+$) calculated for $C_{24}H_{14}O_3F_5^+$ = 445.0858, mass found = 445.0858.

Pentafluorophenyl 2-((1-oxo-7-(trifluoromethyl)-2,3-dihydro-1*H*-inden-2-yl)methyl) benzoate, 448



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **434** (100 mg, 0.201 mmol, 1.0 eq), 10% Pd/C (10 mg, 10 wt%) in EtOAc (2.0 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **448** as a colourless oil (56 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.24 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{16}), 7.81-7.57 (m, 4H, H_5, H_6, H_{13}, H_{14}), 7.48 (dd, *J* = 7.7, 1.3 Hz, 1H, H_4), 7.43 (td, *J* = 7.7, 1.3 Hz, 1H, H_{15}), 3.73 (dd, *J* = 13.4, 5.5 Hz, 1H, H_{11}), 3.25 (dd, *J* = 17.0, 7.9 Hz, 1H, H_3), 3.23 (dd, *J* = 13.6, 8.7 Hz, 1H, $H_{11'}$), 3.19-3.11 (m, 1H, H_2), 2.94 (dd, *J* = 17.0, 4.7 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 203.1 (Quat, C_1), 162.9 (Quat, C_{18}), 155.2 (Quat, C_9), 143.5 (Quat, C_{12}), 134.1 (CH, C_{14}), 134.0 (CH, C_5), 133.2 (Quat, C_8), 132.4 (CH, C_4), 132.1 (CH, C_{16}), 130.4 (CH, C_{13}),

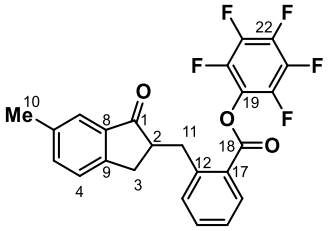
127.1 (q, *J* = 34.5 Hz, Quat, C_7), 127.1 (CH, C_{15}), 126.1 (Quat, C_{17}), 125.2 (q, *J* = 6.0 Hz, CH, C_6), 122.7 (d, *J* = 273.7 Hz, CF_3, C_{10}), 49.1 (CH, C_2), 34.8 (CH_2, C_{11}), 32.4 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −61.6, −152.5, −157.8, −162.2;

FTIR (neat) ν/cm^{-1} = 2928, 2360, 2121, 1759, 1724, 1601, 1521, 1487, 1454, 1433, 1325, 1229. 1144, 1112, 1031;

HRMS (ESI$^+$) calculated for $C_{24}H_{12}O_3F_8Na^+$ = 523.0551, mass found = 523.0552.

Pentafluorophenyl 2-((6-methyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 449



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **435** (85 mg, 0.19 mmol, 1.0 eq), 10% Pd/C (8 mg, 10 wt%) in EtOAc (1.9 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **449** as a colourless oil (78 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.22 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{16}), 7.60 (td, *J* = 7.6, 1.4 Hz, 1H, H_{14}), 7.56 (d, *J* = 1.6 Hz, 1H, H_7), 7.42 (m, 3H, H_5, H_{13}, H_{15}), 7.29 (d, *J* = 7.8 Hz, 1H, H_4), 3.75 (dd, *J* = 13.1, 4.9 Hz, 1H, H_{11}), 3.22-3.04 (m, 3H, H_2, H_3, $H_{11'}$), 2.83 (dd, *J* = 16.6, 3.6 Hz, 1H, $H_{3'}$), 2.39 (s, 3H, H_{10});

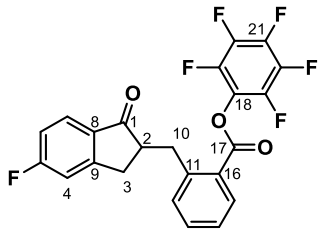
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.3 (Quat, C_1), 162.9 (Quat, C_{18}), 150.6 (Quat, C_9), 143.9 (Quat, C_{12}), 137.4 (Quat, C_6), 136.6 (Quat, C_8), 136.0 (CH, C_5), 134.0 (CH, C_{14}), 132.2 (CH, C_{16}), 132.0 (CH, C_{13}), 126.9 (CH, C_{15}), 126.2 (CH, C_4), 126.2 (Quat, C_{17}), 124.0 (CH, C_7), 48.8 (CH, C_2), 35.1 (CH_2, C_{10}), 32.0 (CH_2, C_3), 21.1 (CH_3, C_{10});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.5, −158.0, −162.3;

FTIR (neat) ν/cm^{-1} = 2927, 1760, 1711, 1618, 1520, 1492, 1282, 1228, 1146, 1113, 1030;

HRMS (ESI$^+$) calculated for $C_{24}H_{16}O_3F_5^+$ = 447.1014, mass found = 447.1014.

Pentafluorophenyl 2-((5-fluoro-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 450



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **436** (100 mg, 0.223 mmol, 1.0 eq), 10% Pd/C (10 mg, 10 wt%) in EtOAc (2.2 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **450** as a white solid (86 mg, 86%).

mp = 74-76 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.24 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{15}), 7.76 (dd, *J* = 9.1, 5.3 Hz, 1H, H_7), 7.61 (td, *J* = 7.6, 1.4 Hz, 1H, H_{13}), 7.52-7.38 (m, 2H, H_{12}, H_{14}), 7.15-6.95 (m, 2H, H_4, H_6), 3.74 (dd, *J* = 12.7, 4.3 Hz, 1H, H_{10}), 3.54-3.02 (m, 3H, H_2, H_3, $H_{10'}$), 2.88 (dd, *J* = 17.2, 3.5 Hz, 1H, $H_{3'}$);

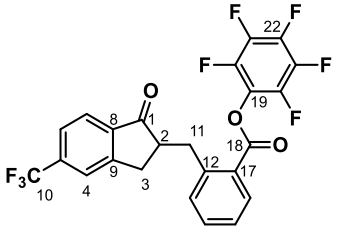
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 205.2 (Quat, C_1), 167.3 (d, *J* = 256.1 Hz, CF, C_5), 162.8 (Quat, C_{17}), 156.1 (d, *J* = 10.0 Hz, Quat, C_9), 143.5 (Quat, C_{11}), 134.1 (CH, C_{13}), 132.8 (d, *J* = 1.8 Hz, Quat, C_8), 132.2 (CH, C_{12}), 132.1 (CH, C_{15}), 127.1 (CH, C_{14}), 126.3 (d, *J* = 10.6 Hz, CH, C_7), 126.1 (Quat, C_{16}), 115.8 (d, *J* = 23.8 Hz, CH, C_6), 113.1 (d, *J* = 22.2 Hz, CH, C_4), 48.7 (CH, C_2), 35.0 (CH_2, C_{10}), 32.2 (d, *J* = 2.1 Hz, CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −102.8, −152.5, −157.8, −162.2;

FTIR (neat) ν/cm^{-1} = 3066, 1760, 1714, 1617, 1594, 1520, 1483, 1248, 1229, 1144, 1085, 1031;

HRMS (ESI$^+$) calculated for $C_{23}H_{13}O_3F_6^+$ = 451.0763, mass found = 451.0762.

Pentafluorophenyl 2-((1-oxo-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-2-yl)methyl) benzoate, 451



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **437** (88 mg, 0.18 mmol, 1.0 eq), 10% Pd/C (9 mg, 10 wt%) in EtOAc (1.8 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **451** as a colourless oil (80 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.18 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{16}), 7.78 (d, *J* = 8.0 Hz, 1H, H_7), 7.61 (s, 1H, H_4), 7.59-7.52 (m, 2H, H_6, H_{14}), 7.42-7.31 (m, 2H, H_{13}, H_{15}), 3.76-3.61 (m, 1H, H_{11}), 3.19 (dd, *J* = 17.0, 6.9 Hz, 1H, H_3), 3.14-3.03 (m, 2H, H_2, $H_{11'}$), 2.89 (dd, *J* = 17.0, 3.4 Hz, 1H, $H_{3'}$);

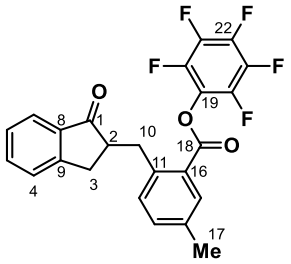
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 206.1 (Quat, C_1), 162.8 (Quat, C_{18}), 153.3 (Quat, C_9), 143.3 (Quat, C_{12}), 139.1 (Quat, C_8), 136.1 (q, *J* = 32.1 Hz, Quat, C_5), 134.2 (CH, C_{14}), 132.2 (CH, C_{13}), 132.2 (CH, C_{16}), 127.2 (CH, C_{15}), 126.1 (Quat, C_{17}), 124.6 (q, *J* = 3.6 Hz, CH, C_6), 124.6 (CH, C_7), 123.7 (q, *J* = 3.9 Hz, CH, C_4), 123.6 (q, *J* = 273.3 Hz, CF_3, C_{10}), 48.8 (CH, C_2), 35.0 (CH_2, C_{11}), 32.3 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −62.9, −152.5, −157.7, −162.1;

FTIR (neat) ν/cm^{-1} = 2920, 1760, 1721, 1600, 1520, 1490, 1432, 1326, 1228, 1169, 1131, 1059, 1031;

HRMS (ESI$^+$) calculated for $C_{24}H_{12}O_3F_8Na^+$ = 523.0551, mass found = 523.0550.

Pentafluorophenyl 5-methyl-2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 452



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **442** (140 mg, 0.315 mmol, 1.0 eq), 10% Pd/C (14 mg, 10 wt%) in EtOAc (3.2 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **452** as a colourless oil (64 mg, 46%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.03 (dd, *J* = 1.8, 0.8 Hz, 1H, H_{15}), 7.76 (dt, *J* = 7.7, 1.0 Hz, 1H, H_7), 7.56 (td, *J* = 7.5, 1.2 Hz, 1H, H_5), 7.43-7.38 (m, 2H, H_4, H_{13}), 7.38-7.32 (m, 2H, H_6, H_{12}), 3.70 (dd, *J* =

12.7, 4.5 Hz, 1H, H_{10}), 3.19 (dd, *J* = 17.0, 7.3 Hz, 1H, H_3), 3.15-3.02 (m, 2H, H_2, $H_{10'}$), 2.87 (dd, *J* = 17.0, 3.9 Hz, 1H, $H_{3'}$), 2.43 (s, 3H, H_{17});

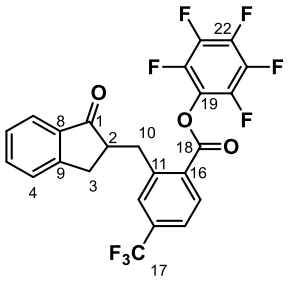
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.3 (Quat, C_1), 163.0 (Quat, C_{18}), 153.3 (Quat, C_9), 140.7 (Quat, C_{11}), 136.8 (Quat, C_{14}), 136.5 (Quat, C_8), 134.8 (CH, C_{13}), 134.7 (CH, C_5), 132.4 (CH, C_{15}), 132.1 (CH, C_{12}), 127.4 (CH, C_6), 126.5 (CH, C_4), 125.9 (Quat, C_{16}), 124.0 (CH, C_7), 48.5 (CH, C_2), 34.7 (CH_2, C_{10}), 32.3 (CH_2, C_3), 20.9 (CH_3, C_{17});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.5, −158.0, −162.3;

FTIR (neat) ν/cm^{-1} = 2980, 1759, 1714, 1610, 1520, 1465, 1254, 1208, 1176, 1145, 1031;

HRMS (ESI$^+$) calculated for $C_{24}H_{16}O_3F_5^+$ = 447.1014, mass found = 447.1015.

Pentafluorophenyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)-4-(trifluoromethyl) benzoate, 453



Prepared according to **General Procedure B**.

Hydrogenation with crude unsaturated ester **443** (89 mg, 0.18 mmol, 1.0 eq), 10% Pd/C (9 mg, 10 wt%) in EtOAc (1.8 mL). Purification *via* flash column chromatography, eluting with 1:19 to 1:9 EtOAc/petrol 40-60, afforded title compound **453** as a colourless oil (36 mg, 35%) and recovered starting material **443** (31 mg, 33%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.32 (d, *J* = 8.2 Hz, 1H, H_{15}), 7.77 (d, *J* = 7.7 Hz, 1H, H_7), 7.75 (d, *J* = 1.7 Hz, 1H, H_{12}), 7.69 (dd, *J* = 8.2, 1.8 Hz, 1H, H_{14}), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H, H_5), 7.43 (d, *J* = 7.7 Hz, 1H, H_4), 7.38 (t, *J* = 7.4 Hz, 1H, H_6), 3.80 (dd, *J* = 13.8, 5.6 Hz, 1H, H_{10}), 3.25 (dd, *J* = 17.2, 8.1 Hz, 1H, H_3), 3.20 (dd, *J* = 13.6, 9.2 Hz, 1H, $H_{10'}$), 3.13-3.02 (m, 1H, H_2), 2.89 (dd, *J* = 17.0, 4.4 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 206.5 (Quat, C_1), 162.1 (Quat, C_{18}), 152.9 (Quat, C_9), 144.6 (Quat, C_{11}), 136.2 (Quat, C_8), 135.2 (q, *J* = 33.0 Hz, Quat, C_{13}), 135.0 (CH, C_5), 132.4 (CH, C_{15}), 129.6 (Quat,

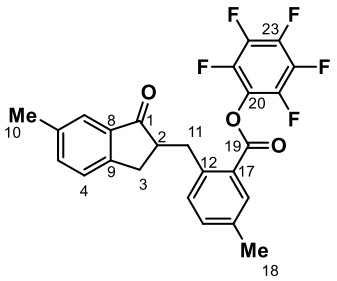
C_{16}), 128.8 (q, *J* = 3.7 Hz, CH, C_{12}), 127.6 (CH, C_6), 126.5 (CH, C_4), 124.1 (CH, C_7), 123.8 (q, *J* = 3.7 Hz, CH, C_{14}), 123.2 (d, *J* = 273.1 Hz, CF_3, C_{17}), 48.2 (CH, C_2), 35.1 (CH_2, C_{10}), 32.5 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −63.4, −152.3, −157.2, −161.8;

FTIR (neat) ν/cm^{-1} = 3563, 2981, 2925, 2358, 1767 1716, 1521, 1463, 1382, 1332, 1237, 1138, 1084, 1035;

HRMS (ESI$^+$) calculated for $C_{24}H_{13}O_3F_8^+$ = 501.0732, mass found = 501.0731.

Pentafluorophenyl 5-methyl-2-((6-methyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 454



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **444** (56 mg, 0.11 mmol, 1.0 eq), 10% Pd/C (6 mg, 10 wt%) in EtOAc (1.2 mL). Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, afforded title compound **454** as a colourless oil (45 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.02 (d, *J* = 1.9 Hz, 1H, H_{16}), 7.55 (d, *J* = 1.5 Hz, 1H, H_7), 7.41 (dd, *J* = 8.4, 1.9 Hz, 1H, H_{14}), 7.38 (dd, *J* = 8.2, 1.6 Hz, 1H, H_4), 7.33 (d, *J* = 7.9 Hz, 1H, H_{13}), 7.28 (d, *J* = 7.8 Hz, 1H, H_5), 4.14-3.37 (m, 1H, H_{11}), 3.30-2.99 (m, 3H, H_2, H_3, $H_{11'}$), 2.88-2.69 (m, 1H, $H_{3'}$), 2.43 (s, 3H, H_{18}), 2.39 (s, 3H, H_{10});

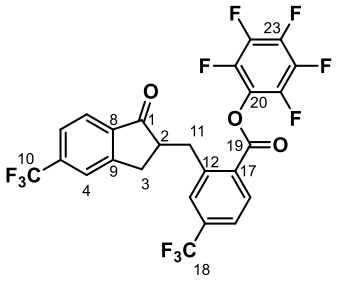
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 207.4 (Quat, C_1), 163.0 (Quat, C_{19}), 150.7 (Quat, C_9), 140.7 (Quat, C_{11}), 137.4 (Quat, C_{15}), 136.7 (Quat, C_6), 136.6 (Quat, C_8), 136.0 (CH, C_5), 134.8 (CH, C_{14}), 132.4 (CH, C_{13}), 132.1 (CH, C_{16}), 126.2 (CH, C_4), 125.9 (Quat, C_{17}), 123.9 (CH, C_7), 48.9 (CH, C_2), 34.8 (CH_2, C_{11}), 32.0 (CH_2, C_3), 21.1 (CH_3, C_{10}), 20.9 (CH_3, C_{18});

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.4, −158.1, −162.2;

FTIR (neat) ν/cm^{-1} = 3020, 2925, 2358, 1759, 1711, 1520, 1282, 1255, 1215, 1176, 1032;

HRMS (ESI$^+$) calculated for $C_{25}H_{18}O_3F_5^+$ = 461.1171, mass found = 461.1170.

Pentafluorophenyl 2-((1-oxo-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-2-yl)methyl)-4-(trifluoromethyl)benzoate, 455



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **445** (160 mg, 0.11 mmol, 1.0 eq), 10% Pd/C (16 mg, 10 wt%) in EtOAc (2.9 mL). Purification *via* recrystallization from EtOAc/petrol 60-80 afforded title compound **455** as a yellow crystalline solid (123 mg, 77%).

mp = 98-100 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.35 (d, *J* = 8.1 Hz, 1H, H_{16}), 7.87 (d, *J* = 7.9 Hz, 1H, H_7), 7.73 (s, 1H, H_{13}), 7.72 (d, *J* = 7.7 Hz, 1H, H_{15}), 7.71 (s, 1H, H_4), 7.64 (d, *J* = 7.9 Hz, 1H, H_6) 3.78 (dd, *J* = 13.6, 5.7 Hz, 1H, H_{11}), 3.32 (dd, *J* = 17.2, 7.9 Hz, 1H, H_3), 3.23 (dd, *J* = 13.6, 9.0 Hz, 1H, $H_{11'}$), 3.16 (dddd, *J* = 9.0, 8.0, 5.7, 4.5 Hz, 1H, H_2), 2.96 (dd, *J* = 17.2, 4.5 Hz, 1H, $H_{3'}$);

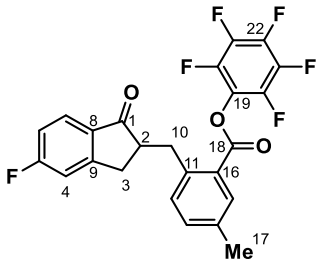
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 205.5 (Quat, C_1), 162.0 (Quat, C_{19}), 152.9 (Quat, C_9), 144.1 (Quat, C_{12}), 138.9 (Quat, C_8), 136.3 (q, *J* = 32.1 Hz, Quat, C_5), 135.4 (q, *J* = 33.0 Hz, Quat, C_{14}), 132.5 (CH, C_{16}), 129.5 (Quat, C_{17}), 128.9 (q, *J* = 3.7 Hz, CH, C_{13}), 124.8 (q, *J* = 3.8 Hz, CH, C_6), 124.7 (CH, C_7), 124.1 (q, *J* = 3.9 Hz, CH, C_{15}), 123.8 (q, *J* = 3.9 Hz, CH, C_4), 123.6 (q, *J* = 273.3 Hz, CF_3, C_5), 123.2 (q, *J* = 272.6 Hz, CF_3, C_{18}), 48.6 (CH, C_2), 35.0 (CH_2, C_{11}), 32.4 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −62.9, −63.4, −152.4, −156.9, −161.7;

FTIR (neat) ν/cm^{-1} = 2981, 1766, 1722, 1521, 1433, 1328, 1231, 1171, 1133, 1084, 1059, 1035;

HRMS (ACI$^+$) calculated for $C_{25}H_{12}O_3F_{11}^+$ = 569.0605, mass found = 569.0607.

Pentafluorophenyl 2-((5-fluoro-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)-5-methyl benzoate, 456



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **446** (120 mg, 0.260 mmol, 1.0 eq), 10% Pd/C (12 mg, 10 wt%) in EtOAc (2.6 mL). Purification *via* flash column chromatography, eluting with 3:37 EtOAc/petrol 40-60, afforded title compound **456** as a white solid (112 mg, 93%).

mp = 62-66 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.03 (d, *J* = 1.3 Hz, 1H, H_{15}), 7.75 (dd, *J* = 9.2, 5.3 Hz, 1H, H_7), 7.41 (dd, *J* = 7.8, 1.9 Hz, 1H, H_{13}), 7.32 (d, *J* = 7.9 Hz, 1H, H_{12}), 7.13-6.99 (m, 2H, H_4, H_6), 3.95-3.59 (m, 1H, H_{10}), 3.21-3.06 (m, 3H, H_2, H_3, $H_{10'}$), 2.86 (dd, *J* = 17.1, 3.1 Hz, 1H, $H_{3'}$), 2.43 (s, 3H, H_{17});

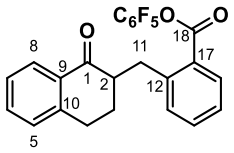
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 205.4 (Quat, C_1), 167.2 (d, *J* = 256.1 Hz, CF, C_5), 163.0 (Quat, C_{18}), 156.2 (d, *J* = 10.0 Hz, Quat, C_9), 140.4 (Quat, C_{11}), 136.9 (Quat, C_{14}), 134.9 (CH, C_{13}), 132.8 (d, *J* = 1.8 Hz, Quat, C_8), 132.5 (CH, C_{15}), 132.1 (CH, C_{12}), 126.3 (d, *J* = 10.5 Hz, CH, C_7), 125.9 (Quat, C_{16}), 115.8 (d, *J* = 23.8 Hz, CH, $C_{4/6}$), 113.1 (d, *J* = 22.0 Hz, CH, $C_{4/6}$), 48.8 (CH, C_2), 34.6 (CH_2, C_{10}), 32.2 (d, *J* = 2.2 Hz, CH_2, C_3), 20.9 (CH_3, C_{17});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −102.9, −152.5, −157.9, −162.2;

FTIR (neat) ν/cm^{-1} = 2930, 1759, 1715, 1617, 1594, 1520, 1482, 1434, 1333, 1248, 1208, 1176, 1144, 1084, 1032;

HRMS (ESI$^+$) calculated for $C_{24}H_{14}O_3F_6Na^+$ = 487.0739, mass found = 487.0740.

Pentafluoro-6λ^8-hexa-1,3,5-triyn-1-yl 2-((1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)benzoate, 457



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **447** (826 mg, 1.85 mmol, 1.0 eq), 10% Pd/C (83 mg, 10 wt%) in EtOAc (18.8 mL). Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, afforded title compound **457** as a white solid (290 mg, 35%).

mp = 78-80 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.23 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{16}), 8.04 (dd, *J* = 7.9, 1.4 Hz, 1H, H_8), 7.61 (td, *J* = 7.6, 1.5 Hz, 1H, H_{14}), 7.53-7.37 (m, 3H, H_6, H_{13} & H_{15}), 7.29 (t, *J* = 7.6 Hz, 1H, H_7), 7.21 (d, *J* = 7.6 Hz, 1H, H_5), 3.93 (dd, *J* = 13.5, 5.3 Hz, 1H, H_{11}), 3.04 (dd, *J* = 13.5, 8.2 Hz, 1H, $H_{11'}$), 3.00-2.92 (m, 2H, H_4), 2.86 (ddt, *J* = 12.8, 8.2, 4.9 Hz, 1H, H_2), 2.13 (dq, *J* = 13.0, 4.3 Hz, 1H, H_3), 1.91 (tdd, *J* = 12.9, 9.4, 6.6 Hz, 1H, $H_{3'}$);

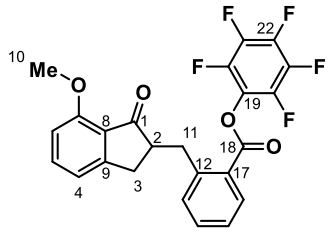
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 199.1 (Quat, C_1), 162.8 (Quat, C_{18}), 144.5 (Quat, C_{12}), 143.9 (Quat, C_{10}), 133.8 (CH, H_{14}), 133.2 (CH, C_{13}), 133.0 (CH, C_6), 132.5 (CH_2, C_9), 132.0 (CH, C_{16}), 128.7 (CH, C_5), 127.5 (CH, C_8), 126.8 (CH, C_{15}), 126.6 (CH, C_7), 126.2 (Quat, C_{17}), 49.3 (CH, C_2), 34.4 (CH_2, C_{11}), 29.0 (CH_2, C_4), 28.6 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.5, −158.1, −162.3;

FTIR (neat) ν/cm^{-1} = 2981, 1761, 1684, 1520, 1234, 1146, 1030;

HRMS (ESI$^+$) calculated for $C_{24}H_{16}O_3F_5^+$ = 447.1014, mass found = 447.1016.

Pentafluorophenyl 2-((7-methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 458



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **433** (78 mg, 0.17 mmol, 1.0 eq), platinum(IV) oxide (7 mg, 10 wt%) in EtOAc (1.7 mL). Purification *via* flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, afforded title compound **458** as a white solid (50 mg, 64%).

mp = 70-72 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.20 (dd, *J* = 7.9, 1.4 Hz, 1H, C_{16}), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H, C_{14}), 7.53-7.44 (m, 2H, C_5 & C_{13}), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H, C_{15}), 6.93 (dt, *J* = 7.6, 0.8 Hz, 1H, H_4), 6.77 (d, *J* = 8.2 Hz, 1H, H_6), 3.94 (s, 3H, H_{10}), 3.72 (dd, *J* = 13.7, 5.4 Hz, 1H, H_{11}), 3.24-3.11 (m, 2H, H_3 & H_{11}), 3.05 (dddd, *J* = 8.8, 7.9, 5.3, 4.3 Hz, 1H, H_2), 2.86-2.74 (m, 1H, $H_{3'}$);

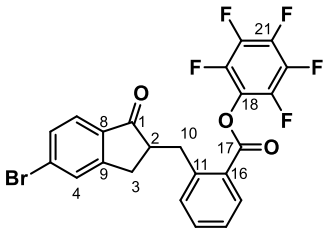
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 204.9 (Quat, C_1), 163.0 (Quat, C_{18}), 158.2 (Quat, C_8), 155.9 (Quat, C_7), 143.8 (Quat, C_{12}), 136.5 (CH, C_5), 134.0 (CH, C_{14}), 132.3 (CH, C_{13}), 132.0 (CH, C_{16}), 126.8 (CH, C_{15}), 126.3 (Quat, C_8), 124.5 (Quat, C_{17}), 118.3 (CH, C_4), 109.0 (CH, C_6), 55.8 (CH_3, C_{10}), 48.9 (CH, C_2), 34.9 (CH_2, C_{11}), 32.0 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.4, −158.0, −162.3;

FTIR (neat) ν/cm^{-1} = 3073, 2925, 2363, 1760, 1709, 1597, 1520, 1481, 1451, 1275, 1228, 1200, 1144, 1114, 1066, 1030;

HRMS (ESI$^+$) calculated for $C_{24}H_{16}O_4F_5^+$ = 463.0963, mass found = 463.0961.

Pentafluorophenyl 2-((5-bromo-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 459



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **438** (717 mg, 1.41 mmol, 1.0 eq), platinum(IV) oxide (72 mg, 10 wt%) in EtOAc (14.3 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **459** as a white solid (491 mg, 68%).

mp = 88-90 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.24 (dd, *J* = 8.2, 1.5 Hz, 1H, H_{15}), 7.70-7.59 (m, 2H, H_7, H_{13}), 7.59-7.55 (m, 1H, H_4), 7.50 (ddt, *J* = 8.0, 1.5, 0.7 Hz, 1H, H_6), 7.47-7.40 (m, 2H, H_{12}, H_{14}), 3.74 (dd, *J* = 13.2, 5.0 Hz, 1H, H_{10}), 3.57-3.04 (m, 3H, H_2, H_3, $H_{10'}$), 2.88 (dd, *J* = 17.1, 4.0 Hz, 1H, $H_{3'}$);

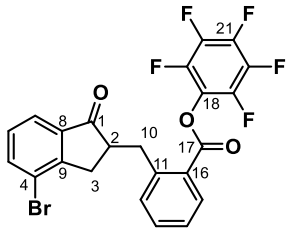
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 205.9 (Quat, C_1), 162.8 (Quat, C_{17}), 154.9 (Quat, C_9), 143.4 (Quat, C_{11}), 135.2 (Quat, C_8), 134.1 (CH, C_{13}), 132.2 (CH, C_{12}), 132.1 (CH, C_{15}), 131.1 (CH, C_6), 130.2 (Quat, C_{16}), 129.8 (CH, C_4), 127.1 (CH, C_{14}), 126.1 (Quat, C_5), 125.3 (CH, C_7), 48.5 (CH, C_2), 35.0 (CH_2, C_{10}), 32.0 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.5, −157.8, −162.2;

FTIR (neat) v/cm^{-1} = 2980, 1760, 1715, 1597, 1520, 1228, 1031;

HRMS (ESI$^+$) calculated for $C_{23}H_{13}O_3{}^{79}BrF_5{}^+$ = 532.9782, mass found = 532.9783.

Pentafluorophenyl 2-((4-bromo-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 460



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **439** (124 mg, 0.244 mmol, 1.0 eq), platinum(IV) oxide (12 mg, 10 wt%) in EtOAc (2.4 mL). Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, afforded title compound **460** as a colourless oil (79 mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.27 (dd, *J* = 7.9, 1.4 Hz, 1H, H_{15}), 7.75 (dd, *J* = 7.7, 1.0 Hz, 1H, H_7), 7.71 (dd, *J* = 7.6, 0.9 Hz, 1H, H_5), 7.64 (td, *J* = 7.6, 1.5 Hz, 1H, H_{13}), 7.49-7.43 (m, 2H, H_{12}, H_{14}), 7.28 (t, *J* = 7.6 Hz, 1H, H_6), 3.91-3.71 (m, 1H, H_{10}), 3.30-3.07 (m, 3H, H_2, H_3, $H_{10'}$), 2.91-2.76 (m, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 206.3 (Quat, C_1), 162.8 (Quat, C_{17}), 152.9 (Quat, C_9), 143.4 (Quat, C_{11}), 138.4 (Quat, C_8), 137.6 (CH, C_7), 134.2 (CH, C_{13}), 132.3 (CH, C_{15}), 132.2 (CH, C_{12}), 129.3 (CH, C_6),

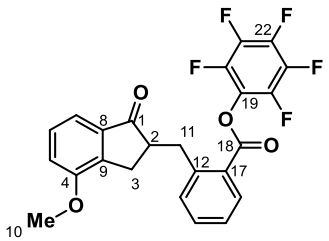
127.2 (CH, C_{14}), 126.0 (Quat, C_{16}), 122.9 (CH, C_5), 122.2 (Quat, C_4), 48.4 (CH, C_2), 35.2 (CH_2, C_{10}), 33.5 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.4, −157.9, −162.2;

FTIR (neat) ν/cm^{-1} = 2981, 1759, 1719, 1599, 1520, 1457, 1326, 121, 1229, 1145, 1120, 1030;

HRMS (ACI$^+$) calculated for $C_{23}H_{12}O_3{}^{79}BrF_5{}^+$ = 510.9963, mass found = 510.9967.

Pentafluorophenyl 2-((4-methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 461



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **440** (284 mg, 0.617 mmol, 1.0 eq), platinum(IV) oxide (28 mg, 10 wt%) in EtOAc (6.2 mL). Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded title compound **461** as a colourless oil (73 mg, 26%) and recovered starting material **440** (163 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.23 (dd, *J* = 7.9, 1.5 Hz, 1H, H_{16}), 7.61 (td, *J* = 7.6, 1.5 Hz, 1H, H_{14}), 7.46 (dd, *J* = 7.7, 1.3 Hz, 1H, H_{13}), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H, H_{15}), 7.39-7.31 (m, 2H, H_6, H_7), 7.02 (dd, *J* = 7.1, 1.9 Hz, 1H, H_5), 3.87 (s, 3H, H_{10}), 3.80-3.56 (m, 1H, H_{11}), 3.53-2.95 (m, 3H, H_2, H_3, $H_{11'}$), 2.88-2.53 (m, 1H, $H_{3'}$);

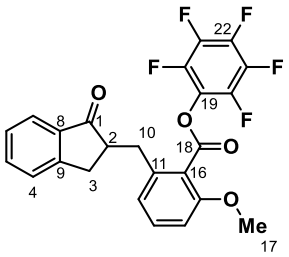
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.3 (Quat, C_1), 162.8 (Quat, C_{18}), 156.9 (Quat, C_4), 143.8 (Quat, C_{12}), 142.1 (Quat, C_9), 137.9 (Quat, C_8), 134.0 (CH, C_{14}), 132.1 (CH, C_{13}), 132.1 (CH, C_{16}), 129.0 (CH, C_6), 126.9 (CH, C_{15}), 126.1 (Quat, C_{17}), 115.6 (CH, C_7), 114.9 (CH, C_5), 55.4 (CH_3, C_{10}), 48.2 (CH, C_2), 35.3 (CH_2, C_{11}), 29.0 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.4, −158.1, −162.4;

FTIR (neat) ν/cm^{-1} = 3659, 2981, 1759, 1715, 1601, 1520, 1488, 1382, 1264, 1232, 1146, 1071, 1030;

HRMS (ESI$^+$) calculated for $C_{24}H_{16}O_4F_5{}^+$ = 463.0963, mass found = 463.0962.

Pentafluorophenyl 2-methoxy-6-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 462



Prepared according to **General Procedure B**.

Hydrogenation with unsaturated ester **441** (62 mg, 0.14 mmol, 1.0 eq), platinum(IV) oxide (6 mg, 10 wt%) in EtOAc (1.4 mL). Purification *via* flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, afforded title compound **462** as a white solid (34 mg, 55%).

mp = 102-104 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.78 (dt, *J* = 7.7, 1.0 Hz, 1H, H_7), 7.56 (td, *J* = 7.5, 1.2 Hz, 1H, H_5), 7.45-7.32 (m, 3H H_4, H_6 & H_{13}), 6.99 (dd, *J* = 7.9, 0.8 Hz, 1H, H_{12}), 6.89 (dd, *J* = 8.4, 0.8 Hz, 1H, H_{14}), 3.91 (s, 3H, H_{17}), 3.47 (dd, *J* = 14.4, 4.9 Hz, 1H, H_{10}), 3.19 (dd, *J* = 17.1, 7.9 Hz, 1H, H_3), 3.08 (ddt, *J* = 9.5, 7.9, 4.6 Hz, 1H, CH, C_2), 2.91 (dd, *J* = 17.1, 4.4 Hz, 1H, $H_{3'}$), 2.82 (dd, *J* = 14.4, 9.8 Hz, 1H, $H_{10'}$);

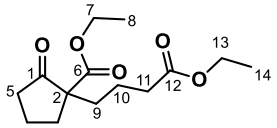
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 207.0 (Quat, C_1), 164.1 (Quat, C_{18}), 157.3 (Quat, C_{15}), 153.4 (Quat, C_9), 139.5 (Quat, C_{11}), 136.3 (Quat, C_8), 134.9 (CH, C_5), 132.1 (CH, C_{13}), 127.5 (CH, C_6), 126.6 (CH, C_4), 124.1 (CH, C_7), 121.9 (CH, C_6), 121.0 (Quat, C_{16}), 109.3 (CH, C_{14}), 56.1 (CH_3, C_{17}), 48.5 (CH, C_2), 33.7 (CH_2, C_{10}), 32.0 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −151.3, −157.8, −162.2;

FTIR (neat) ν/cm^{-1} = 2942, 1774, 1713, 1586, 1520, 1473, 1438, 1274, 1221, 1087, 1031;

HRMS (ESI$^+$) calculated for $C_{24}H_{16}O_3F_5^+$ = 485.0783, mass found = 485.0781.

Ethyl 1-(4-ethoxy-4-oxobutyl)-2-oxocyclopentane-1-carboxylate, 465



Analogously to a literature procedure,[191] ethyl 2-oxocyclopentanecarboxylate (1.00 g, 6.40 mmol, 1.0 eq) in DMF (4 mL) was added to a suspension of sodium hydride (260 mg, 10.8 mmol, 1.7 eq)

in DMF (4 mL). The mixture was cooled to 0 °C, and once the evolution of H_2 had ceased, ethyl 4-bromobutyrate (1.01 mL, 7.04 mmol, 1.1 eq) was added and the resulting mixture heated to reflux for 14 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water (100 mL) was added and the black suspension extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and the residue purified by distillation to afford **465** as a colourless liquid (284 mg, 16%). bp = 126 °C (0.6 mbar);

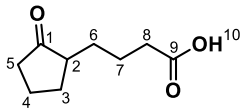
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.18 (q, *J* = 7.3 Hz, 2H, H_7), 4.12 (q, *J* = 7.0 Hz, 2H, H_8), 2.39-2.08 (m, 5H, H_3, H_5 & H_{11}), 1.93-1.63 (m, 3H, $H_{3'}$, H_9), 1.54-1.42 (m, 2H, H_4), 1.42-1.18 (m, 8H, H_8 H_{10} & H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 212.8 (Quat C_1), 173.3 (Quat, C_6), 169.5 (Quat, C_6), 61.4 (CH_2, C_7), 60.4 (CH_2, C_{13}), 60.3 (Quat, C_2), 38.1 (CH_2, C_5), 34.2 (CH_2, C11), 33.4 (CH_2, C3), 32.1 (CH_2, C_9), 20.7 (CH_2, C_4), 19.4 (CH_2, C_{10}), 14.2 (CH_3, C_8 *or* C_{14}), 14.2 (CH_3, C_8 *or* C_{14});

FTIR (neat) ν/cm^{-1} = 2924, 2854, 1754, 1727, 1648, 1465, 1447, 1370, 1338, 1300, 1251, 1179, 1157, 1028;

LRMS (ESI$^+$) calculated for $C_{14}H_{22}O_5Na^+$ = 293, mass found = 293.

3-(2-Oxocyclopentyl)butanoic acid, 466

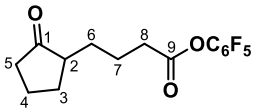


Aqueous HCl (3.5 M, 8.0 mL, 28 eq) was added to a round-bottom flask containing **465** (270 mg, 1.00 mmol, 1.0 eq) and the solution heated to reflux for 12 hours. The solution was then extracted with Et_2O (3 × 20 mL) and the combined organic extracts were then extracted with saturated aqueous $NaHCO_3$ (2 × 20 mL). The basic aqueous extracts were then acidified to pH 2 with 3 M HCl and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue used without any further purification to afford **466** as a yellow oil (150 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 2.45-2.34 (m, 2H, H_8), 2.34-2.20 (m, 2H, H_2 & H_5), 2.20-1.94 (m, 3H, $H_{5'}$, H_6 & H_7), 1.89-1.62 (m, 4H, H_3, $H_{6'}$ & $H_{7'}$), 1.53 (dtd, *J* = 12.4, 10.8, 6.5 Hz, 1H, H_4), 1.40-1.27 (m, 1H, H_4);

LRMS (ESI$^+$) calculated for $C_8H_{12}O_3^+$ = 193, mass found = 193.

Pentafluorophenyl 3-(2-Oxocyclopentyl)butanoate, 473



Prepared according to **General Procedure A**.

Esterification with crude acid **466** (150 mg, 0.882 mmol, 1.0 eq), EDC·HCl (203 mg, 1.06 mmol, 1.5 eq), DMAP (6 mg, 0.04 mmol, 0.05 eq), and pentafluorophenol (157 mg, 0.821 mmol, 0.93 eq) in CH_2Cl_2 (2.5 mL). Purification *via* flash column chromatography, eluting with 1:19 EtOAc/heptane afforded title compound **473** as a colourless oil that solidified on standing to a white solid (136 mg, 48%).

mp = 44-46 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 2.76-2.60, (m, 2H, H_8), 2.38-2.29 (m, 1H, H_5), 2.26 (ddq, *J* = 12.5, 6.5, 2.1 Hz, 1H, H_3), 2.18-1.98 (m, 3H, H_2, H_4 & $H_{5'}$), 1.91-1.72 (m, 4H, $H_{4'}$, H_6 & H_7), 1.62-1.49 (m, 1H, $H_{3'}$), 1.45-1.35 (m, 1H, $H_{6'}$);

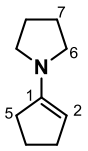
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 220.6 (Quat, C_1), 169.2 (Quat, C_9), 48.8 (CH, C_2), 38.0 (CH_2, C_5), 33.3 (CH_2, C_8), 29.6 (CH_2, C_3), 28.9 (CH_2, C_6), 22.8 (CH_2, C_7), 20.7 (CH_2, C_4);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.8, −158.1, −162.4;

FTIR (neat) ν/cm^{-1} = 2965, 2878, 1791, 1739, 1655, 1520, 1470, 1456, 1409, 1358, 1273, 1156, 1134, 1091, 1045, 1026, 1004;

HRMS (ESI$^+$) calculated for $C_{15}H_{13}F_5O_3Na^+$ = 359.0677, mass found = 359.0677.

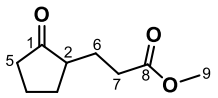
1-(Cyclopent-1-en-1-yl)pyrrolidine, 469



According to a literature procedure,[192] cyclopentane (2.10 mL, 23.8 mmol, 1.0 eq) and pyrrolidine (3.37 mL, 40.3 mmol, 1.7 eq) were heated to reflux in toluene (4 mL) with a Dean-Stark apparatus. The mixture was concentrated under reduced pressure and the residue purified by Kugelröhr distillation to afford **469** as a colourless oil (2.43 g, 74%). **469** was extremely unstable at room temperature, and required redistillation before use after storage at −78 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.05 (s, 1H, H_2), 3.31-2.76 (m, 4H, H_6), 2.66-2.08 (m, 4H, H_3 & H_5), 2.08-1.48 (m, 6H, H_4 & H_7)

Ethyl 3-(2-oxocyclopentyl)propanoate, 471



According to a literature procedure,[193] enamine **469** (2.0 mL, 13.7 mmol, 1.0 eq) and methyl acrylate (2.34 mL, 26.0 mL, 1.9 eq) were dissolved in dry 1,4-dioxane (5.7 mL) and the solution heated to reflux for 3.5 hours. Water (2.2 mL) was then added and the solution heated to reflux for a further 30 minutes. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was dissolved in EtOAc (25 mL) and washed with 1 M aqueous HCl (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by distillation to afford **471** (644 mg, 28%).

bp = 135 °C (20 mbar);

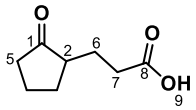
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 3.66 (s, 3H, H_9), 2.46-2.39 (m, 2H, H_8), 2.30 (dddt, *J* = 18.6, 8.6, 3.0, 1.5 Hz, 1H, H_5), 2.22 (ddddd, *J* = 14.0, 12.1, 10.1, 6.3, 4.5 Hz, 1H, H_3), 2.17-1.96 (m, 3H, $H_{3'}$, $H_{5'}$, H_6), 1.77 (dtdd, *J* = 12.8, 10.6, 8.4, 6.4 Hz, 1H, H_4), 1.68-1.56 (m, 1H, $H_{6'}$), 1.50 (dtd, *J* = 12.5, 10.7, 6.6 Hz, 1H, $H_{4'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 220.4 (Quat, C_1), 173.7 (Quat, C_8), 51.6 (CH_3, C_9), 48.3 (CH, C_2), 38.0 (CH_2, C_5), 31.9 (CH_2, C_7), 29.5 (CH_2, C_3), 24.9 (CH_2, C_6), 20.6 (CH_2, C_4);

FTIR (neat) v/cm^{-1} = 2955, 2876, 2255, 1733, 1638, 1437, 1407, 1370, 1312, 1255, 1199, 1156, 1120, 1005;

LRMS (ESI$^+$) calculated for $C_9H_{14}O_3Na^+$ = 193, mass found = 193.

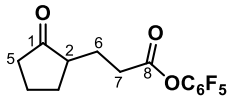
Ethyl 3-(2-oxocyclopentyl)propanoate, 472



Lithium hydroxide monohydrate (212 mg, 5.28 mmol, 1.5 eq) was added to a solution of **471** (600 mg, 3.52 mmol, 1.0 eq) in THF (23 mL) and water (10 mL). The reaction mixture was stirred vigorously for 20 hours and then concentrated under reduced pressure. The residue was dissolved in water (30 mL), acidified to pH 2 with 1 M aqueous HCl, and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude product **472** (386 mg, 70%) was used without any further purification

LRMS (ESI$^+$) calculated for $C_8H_{12}O_3Na^+$ = 179, mass found = 179.

Pentafluorophenyl 3-(2-oxocyclopentyl)propanoate, 474



Prepared according to **General Procedure A**.

Esterification with crude acid **472** (350 mg, 2.24 mmol, 1.0 eq), EDC·HCl (559 mg, 2.91 mmol, 1.3 eq), DMAP (14 mg, 0.11 mmol, 0.05 eq), and pentafluorophenol (413 mg, 2.24 mmol, 1.0 eq) in CH_2Cl_2 (7.5 mL). Purification *via* flash column chromatography, eluting with 1:19 EtOAc/heptane afforded title compound **474** as a colourless oil (455 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 2.92-2.71 (m, 2H, H_7), 2.41-2.32 (m, 1H, H_5), 2.29 (dddt, *J* = 12.1, 8.2, 6.4, 2.1 Hz, 1H, H_3), 2.22-2.12 (m, 3H, H_2, $H_{5'}$ & H_7), 2.06 (dddt, *J* = 13.7, 9.0, 6.6, 2.5 Hz, 1H, H_4), 1.90-1.72 (m, 2H, $H_{4'}$ & $H_{6'}$), 1.57 (dtd, *J* = 12.3, 10.8, 6.6 Hz, 1H, $H_{3'}$);

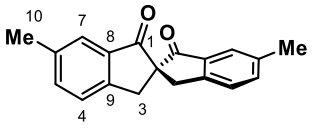
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 220.2 (Quat, C_1), 169.2 (Quat, C_8), 47.9 (CH, C_2), 38.0 (CH_2, C_5), 31.2 (CH_2, C_7), 29.6 (CH_2, C_3), 24.6 (CH_2, C_6), 20.6 (CH_2, C_4);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −152.8, −158.0, −162.4;

FTIR (neat) ν/cm^{-1} = 2968, 2879, 1788, 1738, 1655, 1518, 1471, 1455, 1408, 1380, 1300, 1275, 1255, 1221, 1202, 1158, 1133, 1087, 1044, 1003;

HRMS (ESI$^+$) calculated for $C_{14}H_{11}F_5O_3Na^+$ = 345.0521, mass found = 345.0522.

(*S*)-6,6′-Dimethyl-2,2′-spirobiindane-1,1′-dione, 475



Asymmetric: Prepared according to **General Procedure G** with **444** (45 mg, 0.098 mmol, 1.0 eq), **Y** (5.4 mg, 9.8 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (208 µL, 0.977 mmol, 1.0 eq) in toluene (0.98 mL). Reaction conditions: 120 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **574** as a white solid (23 mg, 84%, 92:8 *er*).

Racemic: Prepared according to **General Procedure G** with **444** (4 mg, 9 µmol, 1.0 eq), TBAB (0.3 mg, 1 µmol, 0.1 eq), potassium hydroxide (1.0 mg, 18 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**475** was prepared by small-scale preparative TLC (1:9 EtOAc/petrol 40-60).

mp = 186-188 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.55 (d, *J* = 1.7 Hz, 2H, H_7), 7.47 (dd, *J* = 7.9, 1.7 Hz, 2H, H_5), 7.44 (dd, *J* = 7.8, 0.9 Hz, 2H, H_4), 3.66 (d, *J* = 16.7 Hz, 2H, H_3), 3.13 (d, *J* = 16.8 Hz, 2H, $H_{3'}$), 2.41 (s, 6H, H_{10});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 202.9 (Quat, C_1), 151.3 (Quat, C_9), 137.8 (Quat, C_6), 136.5 (CH, C_5), 135.7 (Quat, C_8), 126.0 (CH, C_4), 124.8 (CH, C_7), 66.1 (Quat, C_2), 37.8 (CH_2, C_3), 21.1 (CH_3, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 2923, 1709, 1689, 1613, 1581, 1494, 1420, 1279, 1220, 1157, 1034;

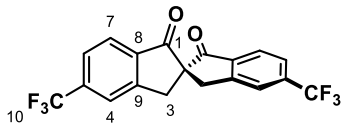
HRMS (ESI$^+$) calculated for $C_{19}H_{16}O_2Na^+$ = 299.1043, mass found = 299.1043;

$[\alpha]_D^{25}$ = +104.7 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 299 nm)

τ_R (minor) = 7.7 min, τ_R (major) = 24.8 min.

(*S*)-6,6′-Bis(trifluoromethyl)-2,2′-spirobiindane-1,1′-dione, 476



Asymmetric: Prepared according to **General Procedure G** with **455** (50 mg, 0.088 mmol, 1.0 eq), **Y** (4.9 mg, 8.8 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (187 µL, 0.880 mmol, 10 eq) in toluene (0.88 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **476** as a white solid (32 mg, 95%, 95:5 *er*).

Racemic: Prepared according to **General Procedure G** with **455** (5 mg, 9 µmol, 1.0 eq), TBAB (0.3 mg, 0.9 µmol, 0.1 eq), potassium hydroxide (1.0 mg, 18 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**476** was prepared by small-scale preparative TLC (1:9 EtOAc/petrol 40-60).

mp = 174-176 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.81 (d, *J* = 7.8 Hz, 2H, H_7), 7.80 (s, 2H, H_4), 7.63 (dd, *J* = 7.8, 1.3 Hz, 2H, H_6), 3.74 (d, *J* = 17.3 Hz, 2H, H_3), 3.23 (d, *J* = 17.5 Hz, 2H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 200.9 (Quat, C_1), 153.8 (Quat, C_9), 137.8 (Quat, C_8), 136.9 (q, *J* = 32.4 Hz, Quat, C_5), 125.8 (CH, H_7), 125.3 (q, *J* = 3.7 Hz, CH, H_6), 123.8 (q, *J* = 3.9 Hz, CH, H_4), 123.6 (q, *J* = 273.3 Hz, CF_3, C_{10}), 66.2 (Quat, C_2), 37.7 (CH_2, C_3);

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −63.0;

FTIR (film) ν_{max}/cm^{-1} = 3650, 2981, 2361, 1733, 1699, 1433, 1382, 1336, 1299, 1269, 1205, 1169, 1135, 1109, 1057, 1027;

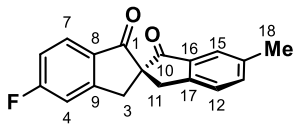
HRMS (EI^+) calculated for $C_{19}H_{10}F_6O_2^+$ = 384.0585, mass found = 384.0587;

$[\alpha]_D^{25}$ = +79.4 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 2% isopropanol, 98% hexane, 1.0 mL/min, λ = 250 nm)

τ_R (minor) = 20.7 min, τ_R (major) = 23.0 min.

(*S*)-5-Fluoro-6'-methyl-2,2'-spirobiindane-1,1'-dione, 477



Asymmetric: Prepared according to **General Procedure G** with **456** (50 mg, 0.11 mmol, 1.0 eq), **Y** (5.9 mg, 11 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (229 µL, 1.08 mmol, 10 eq) in toluene (1.1 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, afforded the title compound **477** as a white solid (30 mg, 99%, 95:5 *er*).

Racemic: Prepared according to **General Procedure G** with **456** (5 mg, 10 µmol, 1.0 eq), TBAB (0.4 mg, 1 µmol, 0.1 eq), potassium hydroxide (1.2 mg, 21 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**477** was prepared by small-scale preparative TLC (3:17 EtOAc/petrol 40-60).

mp = 170-180 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.75 (dd, *J* = 8.5, 5.3 Hz, 1H, H_7), 7.55 (s, 1H, H_{15}), 7.48 (dd, *J* = 7.9, 1.6 Hz, 1H, H_{13}), 7.44 (d, *J* = 7.9 Hz, 1H, H_{12}), 7.22 (dd, *J* = 8.4, 2.1 Hz, 1H, H_4), 7.11 (td, *J* = 8.6, 2.3 Hz, 1H, H_6), 3.69 (d, *J* = 17.2 Hz, 1H, H_3), 3.66 (d, *J* = 16.8 Hz, 1H, H_{11}), 3.16 (d, *J* = 17.2 Hz, 1H, $H_{3'}$), 3.13 (d, *J* = 16.8 Hz, 1H, $H_{11'}$), 2.41 (s, 3H, H_{18});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 202.4 (Quat, C_{10}), 200.8 (Quat, C_1), 167.5 (d, *J* = 257.4 Hz, CF, C_5), 156.7 (d, *J* = 10.3 Hz, Quat, C_9), 151.1 (Quat, C_{17}), 137.9 (Quat, C_{14}), 136.7 (CH, C_{13}), 135.4 (Quat, C_{16}), 131.8 (Quat, C_8), 127.1 (d, *J* = 11.0 Hz, CH, C_7), 126.0 (CH, C_{12}), 124.9 (CH, C_{15}), 116.2 (d, *J* = 23.9 Hz, CH, C_6), 113.1 (d, *J* = 22.9 Hz, CH, C_4), 65.9 (Quat, C_2), 37.7 (d, *J* = 2.3 Hz, CH_2, C_3), 37.6 (CH_2, C_{11}), 21.1 (CH_3, C_{18});

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −101.8;

FTIR (film) ν_{max}/cm^{-1} = 2923, 2852, 1718, 1692, 113, 1592, 1493, 1483, 1427, 1336, 1297, 1281, 1254, 1225, 1156, 1131, 1086, 1032;

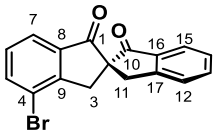
HRMS (ESI$^+$) calculated for $C_{18}H_{14}O_2F^+$ = 281.0972, mass found = 281.0972;

$[\alpha]_D^{25}$ = +116.6 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 299 nm)

τ_R (minor) = 9.8 min, τ_R (major) = 15.6 min.

(*S*)-4-Bromo-2,2'-spirobiindane-1,1'-dione, 478



Asymmetric: Prepared according to **General Procedure G** with **460** (50 mg, 0.098 mmol, 1.0 eq), **Y** (5.4 mg, 9.8 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (208 µL, 0.978 mmol, 10 eq) in toluene (0.98 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **478** as a white solid (32 mg, 99%, 93:7 *er*).

Racemic: Prepared according to **General Procedure G** with **460** (2 mg, 4 µmol, 1.0 eq), TBAB (0.1 mg, 0.4 µmol, 0.1 eq), potassium hydroxide (0.4 mg, 8 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**478** was prepared by small-scale preparative TLC (1:9 EtOAc/petrol 40-60).

mp = 250-252 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.83 (dd, *J* = 7.8, 1.0 Hz, 1H, H_7), 7.77 (d, *J* = 7.5 Hz, 1H, H_{15}), 7.72 (dd, *J* = 7.6, 0.9 Hz, 1H, H_5), 7.67 (td, *J* = 7.5, 1.2 Hz, 1H, H_{13}), 7.57 (dt, *J* = 7.8, 1.0 Hz, 1H, H_{12}), 7.43 (td, *J* = 7.5, 0.7 Hz, 1H, H_{14}), 7.33 (tt, *J* = 7.7, 0.9 Hz, 1H, H_6), 3.73 (d, *J* = 17.0 Hz, 1H, H_{11}), 3.68 (d, *J* = 17.6 Hz, 1H, H_3), 3.24 (d, *J* = 17.0 Hz, 1H, $H_{11'}$), 3.12 (d, *J* = 17.6 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 202.1 (Quat, C_{10}), 202.1 (Quat, C_1), 153.7 (Quat, C_{17}), 153.5 (Quat, C_9), 138.0 (CH, C_7), 137.4 (Quat, C_8), 135.5 (Quat, C_{16}), 135.2 (CH, C_{13}), 129.6 (CH, C_6), 128.0 (CH, C_{14}), 126.4 (CH, C_{12}), 125.1 (CH, C_{15}), 123.7 (CH, C_5), 121.8 (Quat, C_4), 65.2 (Quat, C2), 39.1 (CH_2, C_3), 38.1 (CH_2, C_{11});

FTIR (film) ν_{max}/cm^{-1} = 3655, 2981, 1718, 1692, 1597, 1462, 1382, 1257, 1151, 1073;

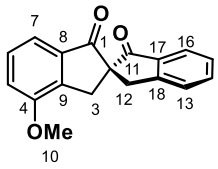
HRMS (ESI$^+$) calculated for $C_{17}H_{11}O_2{}^{79}BrNa^+$ = 348.9835, mass found = 348.9836;

$[\alpha]_D{}^{25}$ = +112.9 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 2% isopropanol, 98% hexane, 1.0 mL/min, λ = 254 nm)

τ_R (minor) = 10.1 min, τ_R (major) = 14.4 min.

(*S*)-4-Methoxy-2,2'-spirobiindane-1,1'-dione, 479



Asymmetric: Prepared according to **General Procedure G** with **461** (50 mg, 0.11 mmol, 1.0 eq), **Y** (6.0 mg, 11 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (230 µL, 1.08 mmol, 10 eq) in toluene (1.1 mL). Reaction conditions: 120 h. Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded the title compound **479** as a white solid (30 mg, 99%, 94:6 *er*).

Racemic: Prepared according to **General Procedure G** with **461** (5.0 mg, 11 µmol, 1.0 eq), TBAB (0.4 mg, 1 µmol, 0.1 eq), potassium hydroxide (1.2 mg, 22 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**479** was prepared by small-scale preparative TLC (1:4 EtOAc/petrol 40-60).

mp = 188-190 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.76 (d, *J* = 7.6 Hz, 1H, H_{16}), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H, H_{14}), 7.56 (dd, *J* = 7.7, 1.5 Hz, 1H, H_{13}), 7.41 (t, *J* = 7.5 Hz, 1H, H_{15}), 7.39 (d, *J* = 6.8 Hz, 1H, H_7), 7.35 (dd, *J* = 7.8, 6.7 Hz, 1H, H_6), 7.09 (dd, *J* = 7.6, 1.1 Hz, 1H, H_5), 3.93 (s, 3H, H_{10}), 3.71 (d, *J* = 17.0 Hz, 1H, H_{12}), 3.66 (d, *J* = 17.4 Hz, 1H, H_3), 3.20 (d, *J* = 16.9 Hz, 1H, $H_{12'}$), 3.06 (d, *J* = 17.4 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 203.0 (Quat, C_1), 202.8 (Quat, C_{11}), 156.9 (Quat, C_4), 154.0 (Quat, C_{18}), 142.9 (Quat, C_9), 137.0 (Quat, C_8), 135.6 (Quat, C_{17}), 135.4 (CH, C_{14}), 129.5 (CH, C_6), 127.9 (CH, C_{15}), 126.5 (CH, C_{13}), 125.0 (CH, C_{16}), 116.5 (CH, C_7), 115.6 (CH, C_5), 65.3 (Quat, C_2), 55.7 (CH_3, C_{10}), 38.3 (CH_2, C_{12}), 35.1 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2922, 2852, 1687, 1603, 1488, 1463, 1441, 1422, 1286, 1263, 1212, 1152, 1130, 1080, 1031;

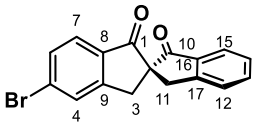
HRMS (ESI^+) calculated for $C_{18}H_{15}O_3^+$ = 279.1016, mass found = 279.1017;

$[\alpha]_D^{25}$ = +87.8 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 250 nm).

τ_R (minor) = 11.6 min, τ_R (major) = 16.6 min.

(*S*)-5-Bromo-2,2′-spirobiindane-1,1′-dione, 480



Asymmetric: Prepared according to **General Procedure G** with **459** (46 mg, 0.090 mmol, 1.0 eq), **Y** (5.0 mg, 9.0 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (191 µL, 0.900 mmol, 10 eq) in toluene (0.90 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **480** as a white solid (27 mg, 91%, 96:4 *er*).

Asymmetric (2): Prepared according to **General Procedure G** with **459** (260 mg, 0.509 mmol, 1.0 eq), **Y** (28 mg, 51 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (1.08 mL, 5.09 mmol, 10 eq) in toluene (5.1 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **480** as a white solid (151 mg, 91%, 95:5 *er*). The spectral data for **480** matched those obtained previously.

Racemic: Prepared according to **General Procedure C** with **459** (2.0 mg, 3.9 µmol, 1.0 eq), TBAB (0.1 mg, 0.4 µmol, 0.1 eq), potassium hydroxide (0.4 mg, 8 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**480** was prepared by small-scale preparative TLC (1:9 EtOAc/petrol 40-60).

mp = 52-54 °C;

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.75 (d, *J* = 7.6 Hz, 1H, H_{15}), 7.74 (s, 1H, H_4), 7.66 (td, *J* = 7.4, 1.2 Hz, 1H, H_{13}), 7.60 (d, *J* = 8.2 Hz, 1H, H_7), 7.58-7.52 (m, 2H, H_6 & H_{12}), 7.41 (td, *J* = 8.4, 7.2, 0.8 Hz, 1H,

H_{14}), 3.72 (d, *J* = 12.6 Hz, 1H, H_{11}), 3.68 (d, *J* = 12.7 Hz, 1H, H_3), 3.20 (d, *J* = 6.7 Hz, 1H, $H_{11'}$), 3.16 (d, *J* = 7.0 Hz, 1H, $H_{3'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 202.1 (Quat, C_{10}), 201.4 (Quat, C_1), 155.3 (Quat, C_{17}), 153.7 (Quat, C_9), 135.5 (CH, C_{13}), 135.2 (Quat, C_{16}), 134.3 (Quat, C_8), 131.5 (CH, C_6), 130.9 (Quat, C_5), 129.7 (CH, C_4), 127.9 (CH, C_{14}), 126.4 (CH, C_{12}), 126.0 (CH, C_7), 125.0 (CH, C_{15}), 65.4 (Quat, C_2), 37.8 (CH_2, C_{11}), 37.6 (CH_2, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2197, 1722, 1694, 1595, 1463, 1421, 1315, 1290, 1264, 1207, 1135, 1058, 1027;

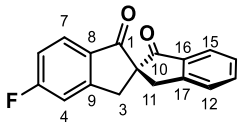
HRMS (ESI^+) calculated for $C_{17}H_{11}O_2{}^{79}BrNa^+$= 348.9835, mass found = 384.9837;

$[\alpha]_D{}^{25}$ = +163.0 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 250 nm)

τ_R (minor) = 10.7 min, τ_R (major) = 13.0 min.

(*S*)-5-Fluoro-2,2'-spirobiindane-1,1'-dione, 481



Asymmetric: Prepared according to **General Procedure G** with **450** (45 mg, 0.11 mmol, 1.0 eq), **Y** (5.5 mg, 10 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (212 µL, 1.00 mmol, 10 eq) in toluene (1.0 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 3:17 EtOAc/petrol 40-60, afforded the title compound **481** as a white solid (26 mg, 98%, 96:4 *er*).

Racemic: Prepared according to **General Procedure G** with **450** (5.0 mg, 11 µmol, 1.0 eq), TBAB (0.3 mg, 1 µmol, 0.1 eq), potassium hydroxide (1.2 mg, 22 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**481** was prepared by small-scale preparative TLC (3:17 EtOAc/petrol 40-60).

mp = 180-182 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.75 (dd, *J* = 8.6, 5.3 Hz, 1H, H_7), 7.75 (d, *J* = 7.8 Hz, 1H, H_{15}), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H, H_{13}), 7.56 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{12}), 7.41 (td, *J* = 7.7, 7.1, 0.6 Hz, 1H, H_{14}), 7.22 (dt, *J* = 8.4, 1.9, 1.1 Hz, 1H, H_4), 7.11 (td, *J* = 8.7, 2.3 Hz, 1H, H_6), 3.72 (d, *J* = 16.9 Hz, 1H, H_{11}), 3.67 (d, *J* = 17.2 Hz, 1H, H_3), 3.19 (d, *J* = 17.0 Hz, 1H, $H_{11'}$), 3.16 (d, *J* = 17.1 Hz, 1H, $H_{3'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 202.4 (Quat, C_{10}), 200.7 (Quat C_1), 167.5 (d, *J* = 257.5 Hz, CF, C_5), 156.7 (d, *J* = 10.4 Hz, Quat, C_9), 153.7 (Quat, C_{17}), 135.4 (CH, C_{13}), 135.2 (Quat, C_{16}), 131.8 (d, *J* = 1.5 Hz, Quat, C_8), 127.9 (CH, C_{14}), 127.2 (d, *J* = 10.5 Hz, CH, C_7), 126.4 (CH, C_{12}), 125.0 (CH, C_{15}), 116.2 (d, *J* = 23.9 Hz, CH, C_6), 113.1 (d, *J* = 22.9 Hz, CH, C_4), 65.6 (Quat, C_2), 37.9 (CH_2, C_{11}), 37.8 (d, *J* = 2.9 Hz, CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −101.7;

FTIR (film) ν_{max}/cm^{-1} = 2923, 1713, 1688, 1605, 1590, 1475, 1464, 1427, 1328, 1295, 1275, 1252, 1211, 1187, 1132, 1088, 1039;

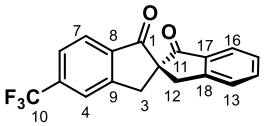
HRMS (ESI^+) calculated for $C_{17}H_{12}O_2F^+$ = 267.0816, mass found = 267.0817;

$[\alpha]_D^{25}$ = +134.6 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 210 nm)

τ_R (minor) = 10.4 min, τ_R (major) = 14.7 min.

(*S*)-5-(Trifluoromethyl)-2,2'-spirobiindane-1,1'-dione, 482



Asymmetric (1): Prepared according to **General Procedure G** with **451** (20 mg, 40 µmol, 1.0 eq), **Y** (2.2 mg, 4.0 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (85 µL, 0.40 mmol, 10 eq) in toluene (0.46 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:19 EtOAc/petrol 40-60, afforded the title compound **482** as a white solid (11 mg, 94%, 95:5 *er*).

Asymmetric (2): Prepared according to **General Procedure G** with **453** (32 mg, 64 µmol, 1.0 eq), **Y** (3.5 mg, 6.4 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (136 µL, 0.64 mmol, 10 eq)

in toluene (0.64 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **482-2** as a white solid (20 mg, 96%, 93:7 *er*).

Racemic: Prepared according to **General Procedure G** with **451** (2 mg, 4 µmol, 1.0 eq), TBAB (0.1 mg, 0.4 µmol, 0.1 eq), potassium hydroxide (0.4 mg, 8 µmol, 2.0 eq) in toluene (0.05 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**482** was prepared by small-scale preparative TLC (1:9 EtOAc/petrol 40-60).

mp = 135-137 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.87 (d, *J* = 8.0 Hz, 1H, H_7), 7.85 (d, *J* = 1.5 Hz, 1H, H_4), 7.77 (d, *J* = 7.7 Hz, 1H, H_{16}), 7.70-7.66 (m, 2H, H_{14}, H_6), 7.58 (dt, *J* = 7.7, 0.9 Hz, 1H, H_{13}), 7.44 (td, *J* = 7.4, 0.6 Hz, 1H, H_{15}), 3.78 (d, *J* = 17.1 Hz, 1H, H_3), 3.75 (d, *J* = 17.0 Hz, 1H, H_{12}), 3.26 (d, *J* = 17.2 Hz, 1H, $H_{3'}$), 3.23 (d, *J* = 16.9 Hz, 1H, $H_{12'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 201.8 (Quat, C_1), 201.7 (Quat C_{11}), 153.9 (Quat, C_{18}), 153.6 (Quat, C_9), 138.1 (Quat, C_8), 136.5 (q, *J* = 32.3 Hz, Quat, C_5), 135.6 (CH, C_{14}), 135.0 (Quat, C_{17}), 128.0 (CH, C_{15}), 126.4 (CH, C_{13}), 125.4 (CH, C_7), 125.1 (CH, C_{16}), 125.0 (q, *J* = 3.6 Hz, CH, C_6), 123.6 (q, *J* = 3.9 Hz, CH, C_4), 123.6 (q, *J* = 273.3 Hz, CF_3, C_{10}), 65.7, 37.9 (CH_2, C_3), 37.8 (CH_2, C_{12});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −62.9;

FTIR (film) ν_{max}/cm^{-1} = 2981, 1730, 1700, 1607, 1432, 1383, 1328, 1293, 1271, 1209, 1169, 1130, 1059;

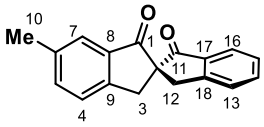
HRMS (ESI^+) calculated for $C_{18}H_{11}O_2F_3Na^+$ = 339.0603, mass found = 339.0606;

$[\alpha]_D^{25}$ = +90.8 (95:5 *er*, c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak IA, 2% isopropanol, 98% hexane, 1.0 mL/min, λ = 250 nm)

τ_R (minor) = 23.9 min, τ_R (major) = 26.8 min.

(*S*)-6-Methyl-2,2'-spirobiindane-1,1'-dione, 483



Asymmetric (1): Prepared according to **General Procedure G** with **449** (50 mg, 0.11 mmol, 1.0 eq), **Y** (6.2 mg, 11 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (238 µL, 1.12 mmol, 10 eq) in toluene (1.1 mL). Reaction conditions: 120 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **483** as a white solid (21 mg, 71%, 99:1 *er*).

Asymmetric (2): Prepared according to **General Procedure G** with **452** (48 mg, 0.11 mmol, 1.0 eq), **Y** (5.9 mg, 11 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (230 µL, 1.08 mmol, 10 eq) in toluene (1.1 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, afforded the title compound **483-2** as a white solid (28 mg, 99%, 96:4 *er*).

Racemic: Prepared according to **General Procedure G** with **449** (4 mg, 9 µmol, 1.0 eq), TBAB (0.3 mg, 0.9 µmol, 0.1 eq), potassium hydroxide (1.0 mg, 18 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**483** was prepared by small-scale preparative TLC (1:9 EtOAc/petrol 40-60).

mp = 176-178 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.76 (dt, *J* = 7.7, 0.9 Hz, 1H, H_{16}), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H, H_{14}), 7.57-7.54 (m, 2H, H_{13}, H_7), 7.48 (dd, *J* = 7.9, 1.6 Hz, 1H, H_5), 7.44 (dd, *J* = 7.9, 0.9 Hz, 1H, H_4), 7.41 (dq, *J* = 7.6, 0.8 Hz, 1H, H_{15}), 3.72 (d, *J* = 16.9 Hz, 1H, H_{12}), 3.67 (d, *J* = 16.7 Hz, 1H, H_3), 3.19 (d, *J* = 17.0 Hz, 1H, $H_{12'}$), 3.14 (d, *J* = 16.8 Hz, 1H, $H_{3'}$), 2.42 (s, 3H, H_{10});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 202.8 (Quat, C_1), 202.7 (Quat, C_{11}), 153.9 (Quat, C_{18}), 151.2 (Quat, C_9), 137.8 (Quat, C_6), 136.6 (CH, C_5), 135.6 (Quat, C_8), 135.5 (Quat, C_{17}), 135.2 (CH, C_{14}), 127.8 (CH, C_{15}), 126.4 (CH, C_{13}), 126.0 (CH, C_4), 124.9 (CH, C_{16}), 124.8 (CH, C_7), 65.7 (Quat, C_2), 38.1 (CH_2, C_{12}), 37.8 (CH_2, C_3), 21.1 (CH_3, C_{10});

FTIR (film) ν_{max}/cm^{-1} = 2924, 2359, 1711, 1691, 1606, 1585, 1494, 1462, 1420, 1323, 1276, 1208, 1189, 1156, 1030;

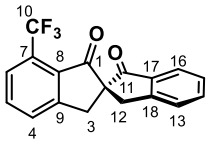
HRMS (ESI^+) calculated for $C_{18}H_{15}O_2^+$ = 263.1067, mass found = 263.1069;

$[\alpha]_D^{25}$ = +133.3 (99:1 *er*, c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 299 nm)

τ_R (minor) = 8.5 min, τ_R (major) = 18.6 min.

(*S*)-7-(Trifluoromethyl)-2,2'-spirobiindane-1,1'-dione, 484



Asymmetric: Prepared according to **General Procedure G** with **448** (50 mg, 0.10 mmol, 1.0 eq), **Y** (5.5 mg, 10 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (212 µL, 1.00 mmol, 10 eq) in toluene (1.0 mL). Reaction conditions: 48 h. Purification *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, afforded the title compound **484** as a white solid (28 mg, 88%, 95:5 *er*).

Racemic: Prepared according to **General Procedure G** with **448** (5 mg, 10 µmol, 1.0 eq), TBAB (0.3 mg, 1 µmol, 0.1 eq), potassium hydroxide (1.2 mg, 20 µmol, 2.0 eq) in toluene (0.1 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**484** was prepared by small-scale preparative TLC (1:4 EtOAc/petrol 40-60).

mp = 168-170 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.78-7.69 (m, 4H, H_4, H_5, H_6, H_{16}), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H, H_{14}), 7.56 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{13}), 7.41 (td, *J* = 7.4, 1.0 Hz, 1H, H_{15}), 3.76 (d, *J* = 16.9 Hz, 1H, H_{12}), 3.74 (d, *J* = 17.1 Hz, 1H, H_{3A}), 3.24 (d, *J* = 17.1 Hz, 1H, H_3), 3.20 (d, *J* = 16.8 Hz, 1H, $H_{12'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 201.5 (CH, C_{11}), 198.6 (CH, C_1), 155.9 (Quat, C_9), 153.7 (Quat, C_{18}), 135.5 (CH, C_{14}), 134.9 (Quat, C_{17}), 134.5 (CH, C_4/C_5), 132.0 (Quat, C_8), 130.2 (CH, C_4/C_5), 127.9 (CH, C_{15}), 127.8 (q, *J* = 33.2 Hz, Quat, C_7), 126.3 (CH, C_{13}), 125.6 (q, *J* = 5.8 Hz, CH, C_6), 125.1 (CH, C_{16}), 122.5 (q, *J* = 273.5 Hz, CF_3, C_{10}), 65.8 (Quat, C_2), 37.7 (CH_2, C_{12}), 37.4 (CH_2, C_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −61.7;

FTIR (film) ν_{max}/cm^{-1} = 2926, 1730, 1699, 1602, 1509, 1465, 1424, 1324, 1294, 1275, 1250, 1206, 1138, 1113, 1028;

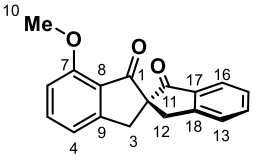
HRMS (ESI^+) calculated for $C_{18}H_{12}O_2F_3^+$ = 317.0784, mass found = 317.0787;

$[\alpha]_D^{25}$ = +114.2 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 10% isopropanol, 90% hexane, 1.0 mL/min, λ = 250 nm)

τ_R (minor) = 10.7 min, τ_R (major) = 26.0 min.

(*S*)-7-Methoxy-2,2'-spirobiindane-1,1'-dione, 485



Asymmetric (1): Prepared according to **General Procedure G** with **458** (42 mg, 91 µmol, 1.0 eq), **Y** (4.0 mg, 9.1 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (145 µL, 0.908 mmol, 10 eq) in toluene (0.91 mL). Reaction conditions: 120 h. Purification *via* flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, afforded the title compound **485** as a white solid (8 mg, 37%, 83:7 *er*) and recovered starting material **458** (23 mg, 55%).

Asymmetric (2): Prepared according to **General Procedure G** with **462** (30 mg, 69 µmol, 1.0 eq), **Y** (4.0 mg, 6.9 µmol, 0.1 eq), 50% w/w aqueous potassium phosphate (145 µL, 0.693 mmol, 10 eq) in toluene (0.69 mL). Reaction conditions: 24 h. Purification *via* flash column chromatography, eluting with 3:7 EtOAc/petrol 40-60, afforded the title compound **485-2** as a white solid (15 mg, 94%, 83:7 *er*).

Racemic: Prepared according to **General Procedure G** with **458** (2.5 mg, 5.4 µmol, 1.0 eq), TBAB (0.2 mg, 0.5 µmol, 0.1 eq), potassium hydroxide (0.6 mg, 11 µmol, 2.0 eq) in toluene (0.05 mL). Reaction conditions: 24 h. An analytical HPLC sample of (*rac*)-**485** was prepared by small-scale preparative TLC (3:7 EtOAc/petrol 40-60).

mp = 148-150 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.74 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{16}), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H, H_{14}), 7.58 (dd, *J* = 8.3, 7.6 Hz, 1H, H_5), 7.55 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{13}), 7.39 (td, *J* = 7.4, 0.5 Hz, 1H, H_{15}), 7.09 (dd, *J* = 7.5, 0.9 Hz, 1H, H_4), 6.82 (d, *J* = 8.2 Hz, 1H, H_6), 3.92 (s, 3H, H_{10}), 3.73 (d, *J* = 17.0 Hz, 1H, H_{12}), 3.64 (d, *J* = 17.0 Hz, 1H, H_3), 3.14 (d, *J* = 17.0 Hz, 1H, $H_{12'}$), 3.13 (d, *J* = 17.0 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 202.8 (Quat, C_{11}), 199.9 (Quat, C_1), 158.8 (Quat, C_7), 156.1 (Quat, C_{18}), 154.0 (Quat, C_9), 137.0 (CH, C_5), 135.5 (Quat, C_{17}), 135.2 (CH, C_{14}), 127.7 (CH, C_{15}), 126.3 (CH, C_{13}), 124.8 (CH, C_{16}), 123.7 (Quat, C_8), 118.1 (CH, C_4), 109.3 (CH, C_6), 65.6 (Quat, C_2), 55.8 (Quat, C_{10}), 38.1 (Quat, C_{12}), 37.7 (Quat, C_3);

FTIR (film) ν_{max}/cm^{-1} = 2981, 1717, 1692, 1545, 1481, 1295, 1275, 1239, 1202, 1088, 1024;

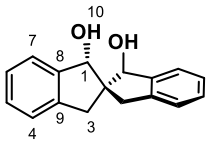
HRMS (ESI^+) calculated for $C_{18}H_{14}O_3Na^+$ = 301.0835, mass found = 301.0836;

$[\alpha]_D^{25}$ = +60.1 (78:22 *er*, c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 254 nm)

τ_R (minor) = 11.3 min, τ_R (major) = 19.5 min.

(*S*)-*cis*,*cis*-2,2'-Spirobiindane-1,1'-diol, 349



Asymmetric: Prepared according to a modified literature procedure.[130]

tert-Butyllithium (1.7 M in pentane, 376 µL, 0.604 mmol, 3.0 eq) was slowly added to a solution of DIBAL-H (1.0 M in THF, 604 µL, 0.604 mmol, 3.0 eq) at −78 °C. The yellow solution was stirred for 5 minutes, warmed to room temperature, at which point the solution turned colourless, and then cooled to −78 °C. To this solution, a suspension of **344** (50 mg, 0.20 mmol, 1.0 eq) in THF (1.5 mL) was added dropwise over 10 minutes (0.3 mL additional THF was used to rinse in the remaining suspension from the syringe) and the reaction mixture was stirred for 10 hours at −78 °C. Saturated aqueous NH_4Cl at −78 °C was added and the mixture allowed to warm to room temperature, after which time the mixture was poured into a beaker containing chloroform (10 mL) and saturated

aqueous NH_4Cl (5 mL) and stirred for 30 minutes. The precipitated aluminium salts were removed *via* filtration through Celite® and the biphasic mixture extracted with chloroform (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid (45 mg, 91%, >20:1:1 *dr*). The residue was purified *via* flash column chromatography, eluting with 1:49 ethanol/chloroform, to afford **349** as a white solid (45 mg, 91%, 97:3 *er*, >20:1:1 *dr*). The spectral data for **349** matched those reported in the literature.[130]

Asymmetric (2): *tert*-Butyllithium (1.7 M in pentane, 376 µL, 0.604 mmol, 3.0 eq) was slowly added to a solution of DIBAL-H (1.0 M in hexane, 665 µL, 0.665 mmol, 3.3 eq) at −78 °C. The colourless solution was stirred for 5 minutes, warmed to room temperature, and then cooled to −78 °C. To this solution, a suspension of **344** (50 mg, 0.20 mmol, 1.0 eq) in THF (1.5 mL) was added dropwise over 10 minutes (0.3 mL additional THF was used to rinse in the remaining suspension from the syringe) and the reaction mixture was stirred for 10 hours at −78 °C. Saturated aqueous NH_4Cl was added at −78 °C and the mixture allowed to warm to room temperature, after which time the mixture was poured into a beaker containing chloroform (10 mL) and saturated aqueous NH_4Cl (5 mL) and stirred for 30 minutes. The precipitated aluminium salts were removed *via* filtration through Celite® and the biphasic mixture extracted with chloroform (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid (48 mg, 95% 7:1:0 *dr*). The residue was purified *via* flash column chromatography, eluting with 1:99 ethanol/chloroform, to afford **349** as a white solid (39 mg, 78%, 99:1 *er*, >20:1:1 *dr*). The spectral data for **344** matched those obtained previously.

Racemic: Prepared according to a literature procedure.[130]

tert-Butyllithium (1.7 M in pentane, 376 µL, 0.604 mmol, 3.0 eq) was slowly added to a solution of DIBAL-H (1.0 M in THF, 604 µL, 0.604 mmol, 3.0 eq) at −78 °C. The yellow solution was stirred for 5 minutes, warmed to room temperature, at which point the solution turned colourless, and then cooled to −78 °C. To this solution, a suspension of (*rac*)-**344** (50 mg, 0.20 mmol, 1.0 eq) in THF

(1.5 mL) was added (0.3 mL additional THF was used to rinse in the remaining suspension from the syringe) and the stirred reaction mixture was allowed to warm to room temperature overnight. Saturated aqueous NH_4Cl was added and the mixture was poured into a beaker containing chloroform (10 mL) and saturated aqueous NH_4Cl (5 mL) and stirred for 30 minutes. The precipitated aluminium salts were removed *via* filtration through Celite® and the biphasic mixture extracted with chloroform (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford a white solid (48 mg, 96%, >20:1:1 *dr*). The residue was purified *via* flash column chromatography, eluting with 1:49 ethanol/chloroform, to afford (*rac*)-**349** as a white solid (48 mg, 96%, >20:1:1 *dr*). The spectral data for (*rac*)-**349** matched those obtained previously.

mp = 196-198 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.48 (dd, *J* = 6.0, 2.4 Hz, 2H, H_4), 7.34-7.27 (m, 4H, H_5, H_6), 7.23 (dd, *J* = 6.0, 2.4 Hz, 2H, H_7), 5.19 (d, *J* = 3.2 Hz, 2H, H_1), 3.17 (d, *J* = 15.6 Hz, 2H, H_3), 2.95 (d, *J* = 3.5 Hz, 2H, H_{10}), 2.55 (d, *J* = 15.5 Hz, 2H, $H_{3'}$);

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ_H = 7.39 (dd, *J* = 7.5, 1.9 Hz, 2H, H_4), 7.26-7.19 (m, 6H, H_5, H_6, H_7), 5.41 (d, *J* = 2.9 Hz, 2H, H_{10}), 4.97 (d, *J* = 3.0 Hz, 2H, H_1), 3.02 (d, *J* = 15.3 Hz, 2H, H_3), 2.39 (d, *J* = 15.3 Hz, 2H, $H_{3'}$);

^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C = 145.2 (Quat, C_8), 143.2 (Quat C_9), 128.5 (CH, C_5), 126.9 (CH, C_6), 125.5 (CH, C_4 & C_7), 80.4 (CH, C_1), 58.8 (Quat, C_2), 42.2 (CH_2, C_3);

N.B. only 8 carbon peaks in the ^{13}C spectrum due to two coincidental peaks at 125.5 ppm.

FTIR (film) ν_{max}/cm^{-1} = 3365, 3362, 2981, 2892, 1708, 1475, 1462, 1383, 1250, 1152, 1072, 1028;

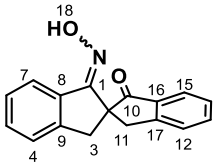
LRMS (ESI^+) calculated for $C_{17}H_{16}O_2Na^+$ = 275, mass found = 275;

$[\alpha]_D^{25}$ = +38.0 (97:3 *er*, c = 0.10, acetone);

Chiral HPLC: (Chiralpak AS, 15% isopropanol, 85% hexane, 0.5 mL/min, λ = 273 nm)

τ_R (minor) = 15.0 min, τ_R (major) = 19.2 min.

1′-(Hydroxyimino)-1′,3′-dihydro-2,2′-spirobi[inden]-1(3*H*)-one, 501



Analogously to a literature procedure,[194] spirobiindanone **344** (50 mg, 0.201 mmol, 1.0 eq), hydroxylamine hydrochloride (113 mg, 1.61 mmol, 8.0 eq) and NaOAc (135 mg, 1.61 mmol, 8.0 eq) were dissolved in ethanol and potassium hydroxide was added (7.5 M, 108 µL, 0.804 mmol, 4.0 eq). The reaction mixture was heated to reflux for 4 hours and then diluted in water (20 mL). The subsequent suspension was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:9 to 3:7 EtOAc/petrol 40-60, to afford **501** as a yellow solid (26 mg, 49%).

mp = >200 °C;

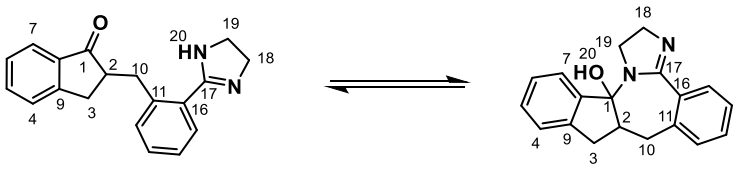
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.87 (d, *J* = 7.7 Hz, 1H, H_{15}), 7.71 (br s, 1H, H_{18}), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H, H_{13}), 7.61 (d, *J* = 7.7 Hz, 1H, H_7), 7.49 (dt, *J* = 7.7, 1.0 Hz, 1H, H_{12}), 7.48-7.42 (m, 1H, H_{14}), 7.39 (td, *J* = 7.4, 1.2 Hz, 1H, H_5), 7.34-7.24 (m, 2H, H_4 & H_6), 3.92 (d, *J* = 17.0 Hz, 1H, H_{11}), 3.56 (d, *J* = 16.7 Hz, 1H, H_3), 3.20 (d, *J* = 17.0 Hz, 1H, $H_{11'}$), 3.03 (d, *J* = 16.8 Hz, 1H, $H_{3'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 204.4 (Quat, C_{10}), 162.9 (Quat, C_1), 151.0 (Quat, C_{17}), 145.0 (Quat, C_9), 135.1 (Quat, C_{16}), 134.1 (Quat, C_8), 133.9 (CH, C_{13}), 129.9 (CH, C_5), 126.6 (CH, C_6), 126.5 (CH, C_{14}), 125.3 (CH, C_{12}), 124.2 (CH, C_4), 123.5 (CH, C_{15}), 121.0 (CH, C_7), 56.9 (Quat, C_2), 43.9 (CH_2, C_3), 40.5 (CH_2, C_{11});

FTIR (film) ν_{max}/cm^{-1} = 3180, 3073, 2918, 2851, 1713, 1646, 1604, 1455, 1426, 1327, 1291, 1218, 1098, 1003;

HRMS (ESI$^+$) calculated for $C_{17}H_{14}O_2N^+$ = 264.1019, mass found = 264.1019;

2-(2-(4,5-dihydro-1*H*-imidazol-2-yl)benzyl)-2,3-dihydro-1*H*-inden-1-one, 505



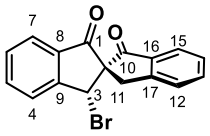
Ethylenediamine (5.4 µL, 0.081 mmol, 1.0 eq) was added to a solution of **344** (20 mg, 0.081 mmol, 1.0 eq) and acetic acid (0.23 µL, 0.05 eq) in ethanol (2 mL). The mixture was heated to reflux for 24 hours, cooled to room temperature and concentrated. The residue was purified by flash column chromatography, eluting with 2:8:1 EtOAc/petrol 40-60/Et_3N to afford **505** as a yellow oil (20 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.30 (dd, *J* = 7.5, 1.2 Hz, 1H, H_{15}), 7.00 (td, *J* = 7.4, 1.5 Hz, 1H, H_{13}), 6.95-6.86 (m, 4H, H_{Ar}), 6.86-6.78 (m, 2H, H_{Ar}), 4.14 (ddd, *J* = 11.2, 6.3, 1.7 Hz, 1H, H_{19}), 3.89 (td, *J* = 10.8, 6.5 Hz, 1H, $H_{19'}$), 3.45-3.30 (m, 2H, H_3 & H_{18}), 3.30-3.11 (m, 2H, H_{10} & $H_{18'}$), 3.08 (dddd, *J* = 8.0, 5.4, 2.6, 1.0 Hz, 1H, H_2), 2.75 (d, *J* = 16.4 Hz, 1H, $H_{3'}$), 2.53 (dd, *J* = 13.4, 2.6 Hz, 1H, $H_{10'}$), 2.19 (br s, 1H, H_{20});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 168.1 (Quat, C_{17}), 143.7 (Quat, C_8), 142.4 (Quat, C_9), 135.9 (Quat, C_{11}), 135.5 (Quat, C_{16}), 130.0 (CH, C_{13}), 128.8 (CH, C_{Ar}), 128.5 (CH, C_{Ar}), 128.5 (CH, C_{15}), 126.9 (CH, C_{Ar}), 126.7 (CH, C_{Ar}), 124.4 (CH, C_{Ar}), 121.4 (CH, C_{Ar}), 90.1 (Quat, C_1), 52.7 (CH, C_2), 49.4 (CH_2, C_{19}), 43.9 (CH_2, C_{18}), 38.6 (CH_2, C_{10}), 35.6 (CH_2, C_3);

HRMS (ESI$^+$) calculated for $C_{19}H_{19}N_2O^+$ = 291.1492, mass found = 291.1493;

(*S*)-3-Bromo-2,2'-spirobiindane-1,1'-dione, 506



Asymmetric: In a 10 mL screw-topped vial, **344** (50 mg, 0.20 mmol, 1.0 eq), *N*-bromosuccinimide (37 mg, 0.21 mmol, 1.02 eq) and AIBN (1.7 mg, 10 µmol, 0.05 eq) were dissolved in carbon tetrachloride (3.6 mL). The reaction mixture was heated at reflux for 16 hours, after which it was allowed to cool to room temperature. The mixture was then filtered through a sintered funnel and

the residue washed with carbon tetrachloride (15 mL). The filtrate was concentrated under reduced pressure to yield a white solid (65 mg, >20:1 *dr*) which was purified *via* flash column chromatography, eluting with toluene, to afford **506** as a white solid (59 mg, 88%, 97:3 *er*, >20:1 *dr*).

Racemic: In a 7 mL screw-topped vial, (*rac*)-**344** (20 mg, 81 µmol, 1.0 eq), *N*-bromosuccinimide (14 mg, 81 µmol, 1.0 eq), and AIBN (0.5 mg, 4 µmol, 0.05 eq) were dissolved in carbon tetrachloride (1.4 mL). The reaction mixture was heated at reflux for 16 hours, after which it was allowed to cool to room temperature. The mixture was then filtered through a sintered funnel and the residue washed with carbon tetrachloride (10 mL). The filtrate was concentrated under reduced pressure and purified *via* preparatory TLC, eluting with toluene, to afford (*rac*)-**506** as a white solid (24 mg, 90%, >20:1 *dr*).

mp = 80-82 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.85-7.73 (m, 3H, H_4, H_7, H_{15}), 7.71-7.66 (m, 2H, H_5, H_{13}), 7.62 (dd, *J* = 7.9, 0.8 Hz, 1H, H_{12}), 7.52 (td, *J* = 7.3, 1.4 Hz, 1H, H_6), 7.42 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, H_8), 5.91 (s, 1H, H_3), 3.76 (d, *J* = 17.4 Hz, 1H, H_{11}), 3.72 (d, *J* = 17.4 Hz, 1H, $H_{11'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 199.2 (Quat, C_1), 197.9 (Quat, C_{10}), 154.5 (Quat, C_{17}), 153.8 (Quat, C_9), 136.0 (CH, C_4), 135.9 (CH, C_{13}), 134.3 (Quat, C_8), 133.8 (Quat, C_{16}), 130.1 (CH, C_6), 128.0 (CH, C_8), 127.1 (CH, C_7), 126.3 (CH, C_{12}), 125.1 (CH, C_5), 124.9 (CH, C_{15}), 71.4 (Quat, C_2), 50.7 (CH, C_3), 37.8 (CH_2, C_{11});

FTIR (film) ν_{max}/cm^{-1} = 2919, 2850, 2362, 1728, 1703, 1603, 1465, 1423, 1329, 1271, 1211, 1190, 1153;

Compound **506** was not detected by ACI, EI or ESI mass spectrometry;

$[\alpha]_D^{25}$ = +173.0 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak AD-H, 20% isopropanol, 980% hexane, 1.0 mL/min, λ = 250 nm)

τ_R (minor) = 8.0 min, τ_R (major) = 12.8 min.

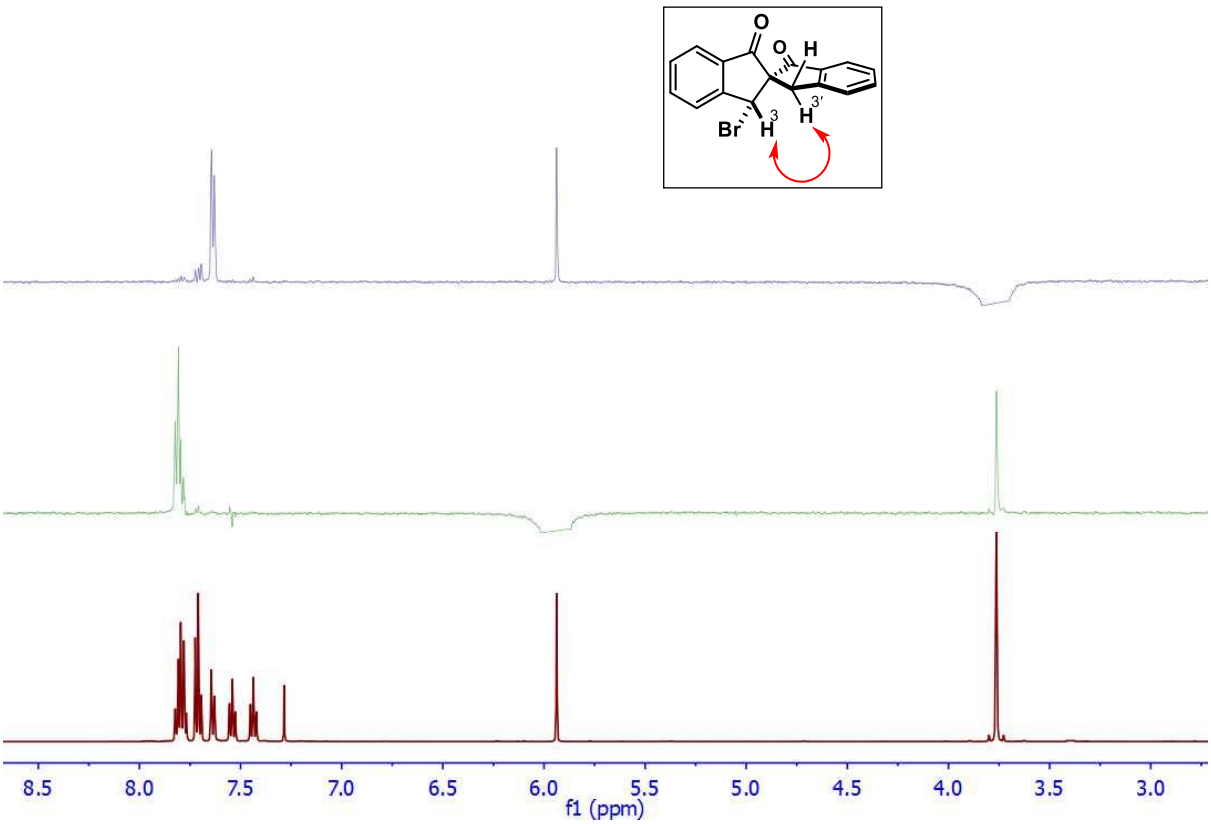
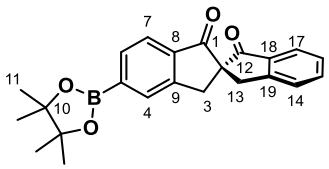


Figure 31 1D nOe data for compound **506** in $CDCl_3$ (mixing time = 0.8 s)

(*S*)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2'-spirobiindane-1,1'-dione, 507



This compound was prepared in analogy to a literature procedure.[190]

A 3.5 mL screw-topped vial was charged with **480** (95:5 *er*, 30 mg, 0.092 mmol, 1.0 eq), bis(pinacolato)diboron (28 mg, 0.11 mmol, 1.2 eq), potassium acetate (27 mg, 0.27 mmol, 3.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (3.4 mg, 4.6 µmol, 0.05 eq) under an atmosphere of argon. To this was added 1,4-dioxane (0.5 mL) and the mixture heated at reflux for 24 hours. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL) and water (5 mL), and filtered through Celite®. The layers were separated and the aqueous layer extracted with EtOAc (5 mL × 2). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified

via flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **507** as a white solid (24 mg, 70%).

mp = 194-196 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.02 (d, *J* = 1.9 Hz, 1H, H_4), 7.84 (dd, *J* = 7.7, 1.0 Hz, 1H, H_7), 7.75 (dt, *J* = 7.4, 0.6 Hz, 1H, H_{17}), 7.74 (dd, *J* = 7.4, 0.5 Hz, 1H, H_6), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H, H_{15}), 7.56 (dt, *J* = 7.7, 0.9 Hz, 1H, H_{14}), 7.41 (td, *J* = 7.4, 1.0 Hz, 1H, H_{16}), 3.73 (d, *J* = 17.0 Hz, 1H, H_{13}), 3.72 (d, *J* = 16.9 Hz, 1H, H_3), 3.19 (d, *J* = 17.1 Hz, 1H, $H_{13'}$), 3.18 (d, *J* = 16.9 Hz, 1H, $H_{3'}$), 1.38 (s, 12H, H_{11});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 203.0 (Quat, C_1), 202.5 (Quat, C_{12}), 153.8 (Quat, C_{19}), 152.8 (Quat, C_9), 137.4 (Quat, C_8), 135.4 (Quat, C_{18}), 135.3 (CH, C_{15}), 133.8 (CH, C_7), 132.7 (CH, C_4), 127.8 (CH, C_{16}), 126.4 (CH, C_{14}), 124.9 (CH, C_{17}), 123.9 (CH, C_6), 84.4 (Quat, C_{10}), 65.6 (Quat, C_2), 38.1 (CH_2, C_3/C_{13}), 38.0 (CH_2, C_3/C_{13}), 24.9 (CH_3, C_{11});

N.B. C_5 not observed in ^{13}C NMR spectrum.

FTIR (film) ν_{max}/cm^{-1} = 2977, 2921, 1725, 1698, 1607, 1487, 1412, 1360, 1337, 1266, 1208, 1142, 1073, 1027;

HRMS (ACI$^+$) calculated for $C_{23}H_{23}{}^{79}BrO_4{}^+$ = 375.1775, mass found = 375.1762;

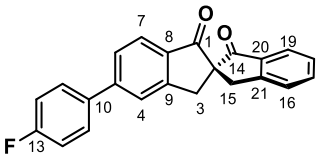
$[\alpha]_D{}^{25}$ = +86.3 (c = 1.0, $CHCl_3$).

To calculate the *er* of **507**, it was converted to **508** in analogy to a literature procedure, assuming no degradation in enantioenrichment in this process.[195]

To a solution of **507** (20 mg, 0.05 mmol, 1.0 eq) in degassed toluene (2.9 mL) and water (0.57 mL) were added 1-fluoro-4-iodobenzene (61 µL, 0.53 mmol, 10.0 eq), tetrakis(triphenylphosphine)palladium(0) (6 mg, 5 µmol, 0.10 eq), and cesium carbonate (52 mg, 0.16 mmol, 3.0 eq) at room temperature. The mixture was heated at 100 °C for 12 hours and then cooled to room temperature. The mixture was diluted with water (2 mL) and extracted with EtOAc (5 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography,

eluting with 1:4 EtOAc/petrol 40-60, to afford **508** as a white solid (12 mg, 66%, 95:5 *er*). The data matched those obtained previously.

(*S*)-5-(4-Fluorophenyl)-2,2'-spirobiindane-1,1'-dione, 508



This compound was prepared in analogy to a literature procedure.[196]

Asymmetric: 480 (95:5 *er*, 30 mg, 0.092 mmol, 1.0 eq) and 4-fluorophenylboronic acid (19 mg, 0.14 mmol, 1.5 eq) were dissolved in toluene (0.64 mL) and aqueous Na_2CO_3 (2 M, 0.28 mL, 0.55 mmol, 6.0 eq). The mixture was degassed by freeze-pump-thawing[2] (× 3) and flushed with nitrogen. Under a stream of nitrogen, tetrakis(triphenylphosphine)palladium(0) (5.3 mg, 4.6 µmol, 0.05 eq) was added and the mixture heated at reflux for 7 hours. After cooling to room temperature, the phases were separated and the aqueous layer washed with EtOAc (5 mL × 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography, eluting with 1:4 EtOAc/petrol 40-60, to afford **508** as a white solid (86%, 27 mg, 95:5 *er*).

Racemic: (*rac*)-**480** (10 mg, 31 µmol, 1.0 eq) and 4-fluorophenylboronic acid (6.4 mg, 45 µmol, 1.5 eq) were dissolved in toluene (0.21 mL) and aqueous Na_2CO_3 (2 M, 90 µL, 0.18 mmol, 6.0 eq). The mixture was degassed by freeze-pump-thawing[2] (× 3) and flushed with nitrogen. Under a stream of nitrogen, tetrakis(triphenylphosphine)palladium(0) (2 mg, 0.002 mmol, 0.05 eq) was added and the mixture heated at reflux for 7 hours. After cooling to room temperature, the phases were separated and the aqueous layer washed with EtOAc (2 × 2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified *via* preparatory TLC, eluting with 1:4 EtOAc/petrol 40-60, to afford (*rac*)-**508** as a white solid (4 mg, 38%).

mp = 186-188 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.82 (d, *J* = 8.0 Hz, 1H, H_7), 7.78 (d, *J* = 7.7 Hz, 1H, H_{19}), 7.71 (dd, *J* = 1.6, 0.8 Hz, 1H, H_4), 7.67 (td, *J* = 7.5, 1.2 Hz, 1H, H_{17}), 7.63 (ddt, *J* = 8.8, 5.2, 3.0 Hz, 2H, H_{11}), 7.59 (dd, *J* = 7.3, 1.4 Hz, 1H, H_6), 7.58 (dt, *J* = 7.5, 0.8 Hz, 1H, H_{16}), 7.43 (td, *J* = 7.4, 0.6 Hz, 1H, H_{18}), 7.18 (tt, *J* = 8.5, 2.0 Hz, 2H, H_{12}), 3.77 (d, *J* = 16.9 Hz, 1H, H_3), 3.76 (d, *J* = 16.9 Hz, 1H, H_{15}), 3.24 (d, *J* = 17.0 Hz, 1H, $H_{3'}$), 3.22 (d, *J* = 16.9 Hz, 1H, $H_{15'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 201.7 (Quat, C_1), 201.0 (Quat, C_{14}), 162.1 (d, *J* = 248.5 Hz, CF, C_{13}), 153.5 (Quat, C_9), 152.8 (Quat, C_{21}), 146.3 (Quat, C_5), 135.2 (d, *J* = 3.3 Hz, Quat, C_{10}), 134.4 (Quat, C_{20}), 134.3 (CH, C_{17}), 133.3 (Quat, C_8), 128.2 (d, *J* = 8.4 Hz, CH, C_{11}), 126.8 (CH, C_{12}), 126.1 (CH, C_{16}), 125.3 (CH, C_{18}), 124.3 (CH, C_7), 123.9 (CH, C_{19}), 123.7 (CH, C_4), 115.0 (d, *J* = 21.7 Hz, CH, C_{12}), 64.6 (Quat, C_2), 37.0 (CH, C_3 & C_{15});

N.B. only 20 carbon peaks in the ^{13}C spectrum due to two coincidental peaks at 37.0 ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = −113.6;

FTIR (film) ν_{max}/cm^{-1} = 2919, 2850, 1720, 1694, 1605, 1517, 1463, 1425, 1275, 1236, 1161, 1025;

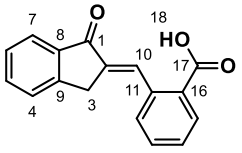
HRMS (EI^+) calculated for $C_{23}H_{15}O_2F^+$ = 342.1056, mass found = 342.1054;

$[\alpha]_D^{25}$ = +29.2 (c = 0.5, $CHCl_3$);

Chiral HPLC: (Chiralpak IA, 20% isopropanol, 80% hexane, 1.0 mL/min, λ = 299 nm)

τ_R (minor) = 15.5 min, τ_R (major) = 26.7 min.

2-((1-Oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoic acid, 369



According to a literature procedure,[138] 1-indanone (15.0 g, 114 mmo, 1.0 eql) and 2-carboxybenzaldehyde (17.0 g, 114 mmol, 1.0 eq) were dissolved in EtOH (272 mL) and to this solution was added aqueous NaOH (1 M, 204 mL, 1.8 eq). The reaction mixture was stirred for 15 minutes, before being diluted with cold water (75 mL). The mixture was extracted with TBME (150 mL) and the organic extracts discarded. The aqueous layer was acidified carefully with

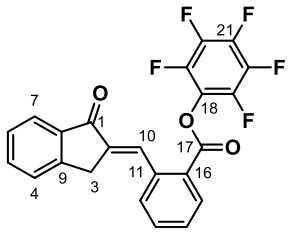
10 M H_2SO_4, filtered and the filter cake washed with 100 mL water. The precipitate **369** was dried in a vacuum oven at 40 °C overnight (10 mbar) and used without any further purification (26.0 g, 87%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H = 13.18 (s, 1H, H_{18}), 8.14 (d, *J* = 2.3 Hz, 1H, H_{10}), 7.94 (dd, *J* = 7.8, 1.4 Hz, 1H, H_{15}), 7.88 (d, *J* = 7.8 Hz, 1H, H_7), 7.81 (d, *J* = 7.6 Hz, 1H, H_4), 7.76-7.60 (m, 3H, H_5, H_{13} & H_{14}), 7.57-7.43 (m, 2H, H_6 & H_{12}), 4.02 (d, *J* = 2.2 Hz, 2H, H_3);

LRMS (ESI^+) calculated for $C_{17}H_{14}O_3Na^+$ = 287, mass found = 297;

The data matched those obtained previously.

Pentafluorophenyl 2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate, 380



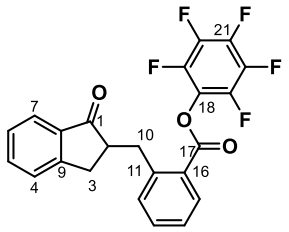
$(COCl)_2$ (20.4 mL, 238 mmol, 1.5 eq) was added dropwise to a stirred solution of **369** (42.0 g, 159 mmol, 1.0 eq) in CH_2Cl_2 (420 mL) and DMF (1.0 mL). After evolution of gas had ceased (30 minutes), 2,3,4,5,6-pentafluorophenol (32.2 g, 175 mmol, 1.1 eq) was added, followed by Et_3N (48.7 mL, 350 mmol, 2.2 eq). The reaction mixture was stirred for 2 hours upon which it was quenched by addition of water (320 mL) and CH_2Cl_2 (175 mL). The layers were separated and he organic layer was washed with 6 M HCl (225 mL) and brine (320 mL) and the solvent evaporated at atmospheric pressure. The residue was purified by crystallization from ^{i}PrOAc (300 mL, 60 °C → rt at −0.1 °C/minute, then stirred at 25 °C for 6 hours) to afford **380** as a tan solid (34.0 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.28 (d, *J* = 7.9 Hz, 1H, H_{15}), 8.22 (d, *J* = 2.3 Hz, 1H, H_{10}), 7.91 (d, *J* = 7.7 Hz, 1H, H_7), 7.81-7.67 (m, 2H, H_{13} & H_{12}), 7.67-7.55 (m, 2H, H_5 & H_{14}), 7.55-7.48 (m, 1H, H_4), 7.48-7.39 (m, 1H, H_6), 3.89 (d, *J* = 2.3 Hz, 2H, H_3);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = −152.1 (m, 2F, F_{19}), −157.7 (t, *J* = 21.6 Hz, 1F, F_{21}), −162.1 (m, 2F, F_{20});

The data matched those obtained previously.

Pentafluorophenyl 2-((1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzoate, 364



5 g scale: A stirred suspension of JM1R163 (1% Pt/C, 2.5 g, 50 wt%) and **380** (5.0 g, 12 mmol, 1.0 eq) in EtOAc (150 mL) in a miniclave was pressurised to 3 bar with nitrogen and the pressure vented 3 times. The vessel was then pressurised to 3 bar with hydrogen and vented twice. Finally, the vessel was pressurised to 3 bar and the reaction mixture stirred for 2.5 hours. The reaction was sampled by venting the hydrogen atmosphere and taking an aliquot with a needle through a sidearm to find that the starting material had all been consumed (by reverse HPLC analysis). The suspension was filtered through Celite® and the solvent was evaporated under reduced pressure to afford crude **364** (5.0 g, 99%). The residue was combined with the residue from the 20 g reaction for purification.

20 g scale: A stirred suspension of JM1R163 (1% Pt/C, 10 g, 50 wt%) and **380** (20.0 g, 48 mmol, 1.0 eq) in EtOAc (600 mL) in an autoclave was pressurised to 4 bar with nitrogen and the pressure vented 4 times. The vessel was then pressurised to 4 bar with hydrogen and vented twice. Finally, the vessel was pressurised to 4 bar and the reaction mixture stirred for 4 hours. The reaction was sampled by venting the hydrogen atmosphere and taking an aliquot with a needle through a sidearm to find that the starting material had all been consumed (by reverse HPLC analysis). The suspension was filtered through Celite® and the solvent was evaporated under reduced pressure to yield crude **364** (20.4 g, quant).

The combined crude reaction mixtures were purified first by flash column chromatography, eluting with 1:9 EtOAc/petrol 40-60, and then purified by recrystallization from ^{i}PrOH (200 mL, 65 °C → rt) to afford **364** as clear crystals (18.0 g, 71% overall).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.28 (d, *J* = 7.9 Hz, 1H, H_{15}), 8.22 (d, *J* = 2.3 Hz, 1H, H_{10}), 7.91 (d, *J* = 7.7 Hz, 1H, H_7), 7.81-7.67 (m, 2H, H_{13} & H_{12}), 7.67-7.55 (m, 2H, H_5 & H_{14}), 7.55-7.48 (m, 1H, H_4), 7.48-7.39 (m, 1H, H_6), 3.89 (d, *J* = 2.3 Hz, 2H, H_3);

The data matched those obtained previously.

7.4 Kinetic Analysis of *C*-Acylation Reaction

All data used for the following experiments is included in the supplementary electronic information.

Construction of Standard Curves for HPLC Calibration

Standard curves for all 4 analytes, both enantiomers of both **364** and **344**, were constructed using the range of concentrations that would be observed in the reaction mixture, using 9-methylanthracene as the internal standard.

9-Methylanthracene **520** (3.8 µL of a 2.584 mM stock solution: 248.4 mg **520**; 1.292 mmol; diluted in ^{i}PrOH to 500 mL) and toluene (3 µL) were added to HPLC vials that were then made up to 1.603 mL with hexane (800 µL) and various amounts of stock solutions of **364** and **344**. The remaining volume was made up with ^{i}PrOH.

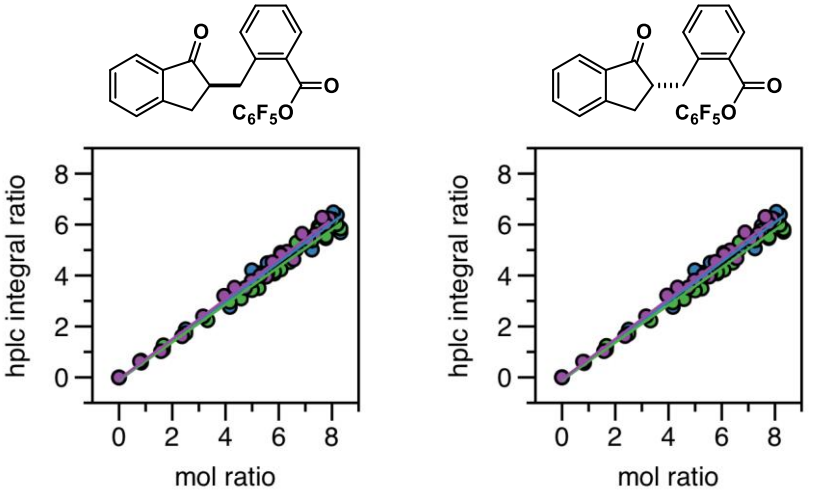
Standard Curve 1: A stock solution of **364** (15.2 mg, 35.2 mmol) was made up to 100 mL with ^{i}PrOH to give a concentration of 352 mM; samples in the range 0-465 µL were used. A stock solution of **344** (19.1 mg, 76.9 mmol) was made up to 100 mL with ^{i}PrOH to give a concentration of 769 mM; samples in the range 0-213 µL were used.

Standard Curve 2: A stock solution of **364** (12.9 mg, 29.8 mmol) was made up to 100 mL with ^{i}PrOH to give a concentration of 298 mM; samples in the range 0-465 µL were used. A stock solution of **344** (19.3 mg, 77.7 mmol) was made up to 100 mL with ^{i}PrOH to give a concentration of 777 mM; samples in the range 0-213 µL were used.

Standard Curve 3: A stock solution of **364** (13.6 mg, 31.5 mmol) was made up to 100 mL with ^{i}PrOH to give a concentration of 315 mM; samples in the range 0-465 µL were used. A stock solution of **344** (18.2 mg, 73.3 mmol) was made up to 100 mL with ^{i}PrOH to give a concentration of 733 mM; samples in the range 0-213 µL were used.

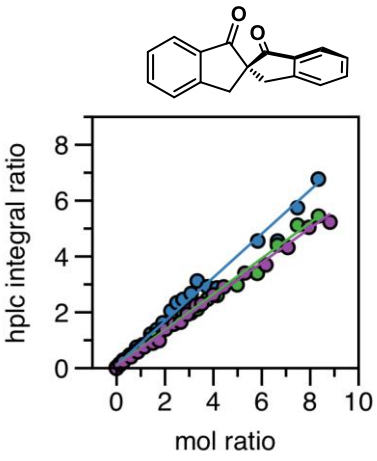
The following plots were produced by plotting the mole ratio of analyte **364** *or* **344** to standard **520** against the ratio of HPLC signal integrations of analyte **364** *or* **344** against standard **520**. Points

outside 1.5 σ were removed and linear regression analyses were carried out. The mean slopes were calculated to give the conversion factor for assaying each analyte.

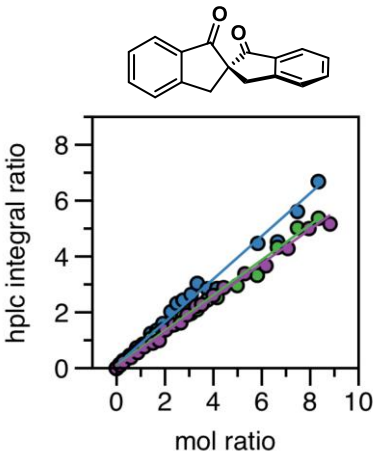


ISC1 slope = 0.77358
R^2 = 0.9824
ISC2 slope = 0.73828
R^2 = 0.9911
ISC3 slope = 0.78535
R^2 = 0.9965
mean slope = 0.7657 ± 0.0068

ISC1 slope = 0.77707
R^2 = 0.9824
ISC2 slope = 0.73664
R^2 = 0.9911
ISC3 slope = 0.78882
R^2 = 0.9965
mean slope = 0.7675 ± 0.0075



ISC1 slope = 0.77358
R^2 = 0.9824
ISC2 slope = 0.73828
R^2 = 0.9911
ISC3 slope = 0.78535
R^2 = 0.9965
mean slope = 0.7657 ± 0.0068



ISC1 slope = 0.77707
R^2 = 0.9824
ISC2 slope = 0.73664
R^2 = 0.9911
ISC3 slope = 0.78882
R^2 = 0.9965
mean slope = 0.7675 ± 0.0075

Standard Curve Verification

The reaction was carried in triplicate out according to **General Procedure H** with substrate **364** (50 mg), catalyst **Y** (6.7 mg), and potassium phosphate (242 µL) in toluene (1.46 mL). The reaction

was halted after 24 hours at which point an aliquot was taken and analysed by HPLC, and the reaction mixture immediately quenched by addition of saturated aqueous NH_4Cl. After workup, the residue was purified by flash column chromatography, eluting with 1:19 to 1:4 EtOAc/petrol 40-60, to afford the recovered starting material **364** (29.6 mg) and product **344** (9.2 mg). The HPLC analysis predicted we would recover 27.5mg of **364** and 8.5 mg of **344**.

48 Hour Reaction Profile

The reaction was carried out, in triplicate, according to **General Procedure H** with **Y** (8.4 mg), substrate **364** (63.0 mg) and potassium phosphate (305 µL). Aliquots were taken every hour for 48 hours.

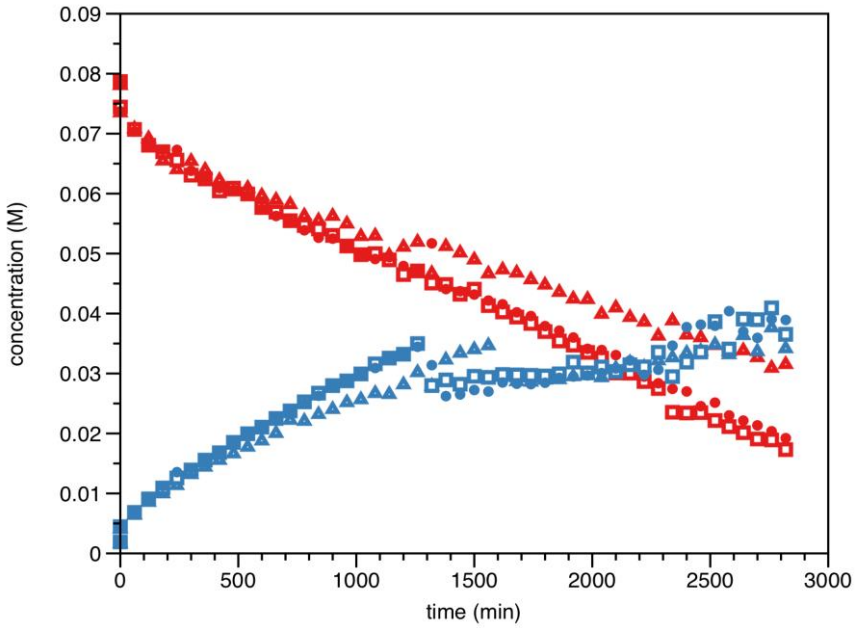


Figure 17: Reaction Profile over 48 Hours

Catalyst Order

The reaction was carried out, in triplicate, according to **General Procedure H** with **Y** (1.68-25.2 mg), substrate **364** (63 mg) and potassium phosphate (305 μL).

[**Y**] /M	ln[**Y**]	Run 1		Run 2		Run 3		Average	
		v_0 /Mmin^{-1}	lnv_0	v_0 /Mmin^{-1}	lnv_0	v_0 /Mmin^{-1}	lnv_0	lnv_0	st dev
0.002	–6.35	1.81E-05	–10.9	1.92E-05	–10.9	1.80E-05	–10.9	–10.90	0.03
0.005	–5.49	2.49E-05	–10.6	2.86E-05	–10.5	2.74E-05	–10.5	–10.52	0.06
0.010	–4.75	5.22E-05	–9.86	5.33E-05	–9.84	5.33E-05	–9.84	–9.847	0.009
0.010	–4.75	6.39E-05	–9.66	6.34E-05	–9.66	6.46E-05	–9.65	–9.657	0.007
0.015	–4.39	1.13E-04	–9.09	1.13E-04	–9.08	1.03E-04	–9.18	–9.119	0.05
0.020	–4.07	9.37E-05	–9.28	8.66E-05	–9.35			–9.315	0.04
0.030	–3.66	1.68E-04	–8.69	1.68E-04	–8.72			–8.707	0.02

Substrate Order

The reaction was carried out, in triplicate, according to **General Procedure H** with **Y** (8.4 mg), substrate **364** (31.5-79 mg) and potassium phosphate (305 μL).

[**364**] /M	ln[**364**]	Run 1		Run 2		Run 3		Average	
		v_0 /Mmin^{-1}	lnv_0	v_0 /Mmin^{-1}	lnv_0	v_0 /Mmin^{-1}	lnv_0	lnv_0	st dev
0.05	–3.19	5.20E-05	–9.86	5.50E-05	–9.81	5.34E-05	–9.84	–9.847	0.02
0.79	–2.78	4.59E-05	–9.99	4.65E-05	–9.97	4.72E-05	–19.96	–9.976	0.06
0.10	–2.49	5.22E-05	–9.86	5.33E-05	–9.84	5.33E-05	–9.84	–9.847	0.009
0.10	–2.49	6.39E-05	–9.66	6.34E-05	–9.66	6.46E-05	–9.65	–9.657	0.007
0.125	–2.27	4.45E-05	–10.00	4.23E-05	–10.1			–10.05	0.03

Base Order from Base Equivalents

The reaction was carried out, in triplicate, according to **General Procedure H** with **Y** (8.4 mg), substrate **364** (63 mg) and 4.77 M (saturated) potassium phosphate (31.5-610 µL).

$[K_3PO_4]$ /eq	$\ln[K_3PO_4]$	Run 1		Run 2		Run 3		Average	
		ν_0 /Mmin^{-1}	$\ln\nu_0$	ν_0 /Mmin^{-1}	$\ln\nu_0$	ν_0 /Mmin^{-1}	$\ln\nu_0$	$\ln\nu_0$	st dev
1	–1.93	9.29E-05	–9.28	9.22E-05	–9.29	9.36E-05	–9.28	–9.284	0.006
5	–0.780	5.71E-05	–9.77	5.83E-05	–9.75	5.97E-05	–9.72	–9.749	0.018
10	–0.190	5.22E-05	–9.86	5.33E-05	–9.84	5.33E-05	–9.84	–9.847	0.009
10	–0.190	6.39E-05	–9.66	6.34E-05	–9.66	6.46E-05	–9.65	–9.657	0.007
20	0.343	5.61E-05	–9.79	5.67E-05	–9.78	5.45E-05	–9.82	–9.795	0.017

Base Order from Base Concentration

The reaction was carried out, in triplicate, according to **General Procedure H** with **Y** (8.4 mg), substrate **364** (63 mg) and (1.22-4.77 M) potassium phosphate (305 µL).

$[K_3PO_4]$ /M	Run 1		Run 2		Run 3		Average	
	ν_0 /Mmin^{-1}	$\ln\nu_0$	ν_0 /Mmin^{-1}	$\ln\nu_0$	ν_0 /Mmin^{-1}	$\ln\nu_0$	$\ln\nu_0$	st dev
1.23	6.87E-05	–9.28					–9.585	
2.39	6.98E-05	–9.77					–9.569	
3.54	6.47E-05	–9.86					–9.645	
4.77	5.22E-05	–9.86	5.33E-05	–9.84	5.33E-05	–9.84	–9.847	0.009
4.77	6.39E-05	–9.66	6.34E-05	–9.66	6.46E-05	–9.65	–9.657	0.007

Kinetic Dependence on Stirring Speed

The reaction was carried out, in triplicate, according to **General Procedure H** with **Y** (8.4 mg), substrate **364** (63 mg) and potassium phosphate (305 µL). Stirring speeds were between 500 and 1400 rpm.

Stirring Speed /rpm	Run 1		Run 2		Run 3		Average	
	v_0 /Mmin^{-1}	lnv_0	v_0 /Mmin^{-1}	lnv_0	v_0 /Mmin^{-1}	lnv_0	lnv_0	st dev
500	4.04E-05	–10.1					–10.12	
750	5.85E-05	–9.75					–9.747	
1000	5.22E-05	–9.86	5.33E-05	–9.84	5.33E-05	–9.84	–9.847	0.009
1000	6.39E-05	–9.66	6.34E-05	–9.66	6.46E-05	–9.65	–9.657	0.007
1400	6.84E-05	–9.59					–9.590	

Kinetic Resolution

The reaction was carried out, according to **General Procedure H** with **Y** (19.1 mg), 9-methylanthracene **520** (2.2 mg) substrates (+)-**364** *or* (−)-**364** *or* (±)-**364** (50 mg) and potassium phosphate (242 µL).

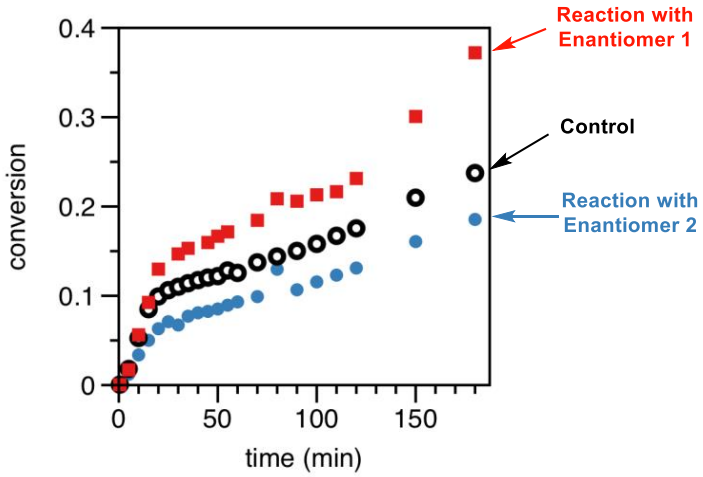
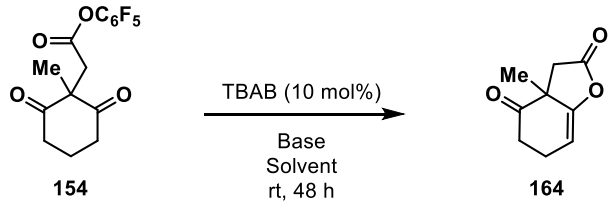


Figure 27: Reaction Profile with Different Enantiomers of Starting Material

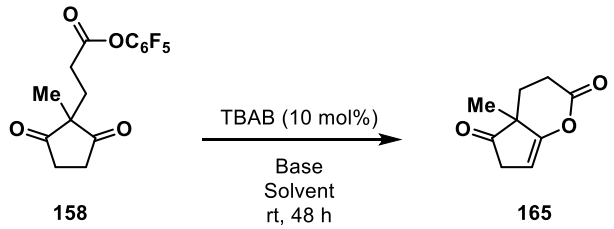
8. Appendices

Appendix A – Full Optimization Tables for Cyclization of Diketoesters 154, 158 & 162



Entry	**Solvent**	**Base**	**164**:**154**:hydrolysis[a]
1	Toluene	KF (2 eq)	31:68:1
2	Toluene	KF (50% aq, 5 eq)	33:67:0
3	Toluene	KOH (2 eq)	22:78:0
4	Toluene	KO^{t}Bu (2 eq)	6:94:0
5	Toluene	K_2CO_3 (2 eq)	32:68:0
6	Toluene	K_2CO_3 (50% aq, 5 eq)	24:76:0
7	Toluene	K_3PO_4 (2 eq)	50:50:0
8	Toluene	K_3PO_4 (2 eq)	20:80:0[b]
9	Toluene	K_3PO_4 (50% aq, 5 eq)	21:79:0
10	CH_2Cl_2	KF (2 eq)	15:85:0
11	CH_2Cl_2	KF (50% aq, 5 eq)	14:86:0
12	CH_2Cl_2	KOH (2 eq)	7:93:0
13	CH_2Cl_2	KO^{t}Bu (2 eq)	6:94:0
14	CH_2Cl_2	K_2CO_3 (2 eq)	17:83:0
15	CH_2Cl_2	K_2CO_3 (50% aq, 5 eq)	21:79:0
16	CH_2Cl_2	K_3PO_4 (2 eq)	70:30:0
17	CH_2Cl_2	K_3PO_4 (2 eq)	32:68:0[b]
18	CH_2Cl_2	K_3PO_4 (50% aq, 5 eq)	28:72:0
19	TBME	K_3PO_4 (2 eq)	0:100:0[b]
20	Heptane	K_3PO_4 (2 eq)	26:72:2[b]

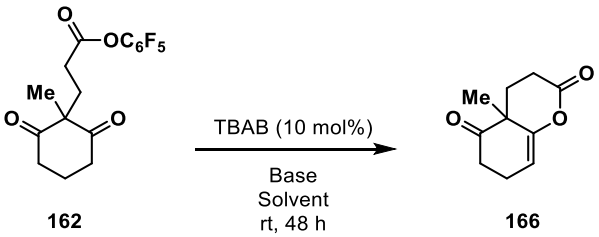
[a] Determined by uncalibrated reverse-phase HPLC
[b] Determined by ^{1}H NMR Spectroscopy



Entry	**Solvent**	**Base**	**165**:**158**:hydrolysis[a]
1	Toluene	KF (2 eq)	20:80:0
2	Toluene	KF (50% aq, 5 eq)	14:86:0
3	Toluene	KOH (2 eq)	20:80:0
4	Toluene	KO^{t}Bu (2 eq)	14:86:0
5	Toluene	K_2CO_3 (2 eq)	40:60:0
6	Toluene	K_2CO_3 (50% aq, 5 eq)	-
7	Toluene	K_3PO_4 (2 eq)	45:55:0

8	Toluene	K_3PO_4 (2 eq)	24:73:3[b]
9	Toluene	K_3PO_4 (50% aq, 5 eq)	-
10	CH_2Cl_2	KF (2 eq)	12:88:0
11	CH_2Cl_2	KF (50% aq, 5 eq)	13:87:0
12	CH_2Cl_2	KOH (2 eq)	22:78:0
13	CH_2Cl_2	KO^{t}Bu (2 eq)	18:82:0
14	CH_2Cl_2	K_2CO_3 (2 eq)	30:55:15
15	CH_2Cl_2	K_2CO_3 (50% aq, 5 eq)	-
16	CH_2Cl_2	K_3PO_4 (2 eq)	58:42:0
17	CH_2Cl_2	K_3PO_4 (2 eq)	32:68:0[b]
18	CH_2Cl_2	K_3PO_4 (50% aq, 5 eq)	-

[a] Determined by uncalibrated reverse-phase HPLC
[b] Determined by ^{1}H NMR Spectroscopy

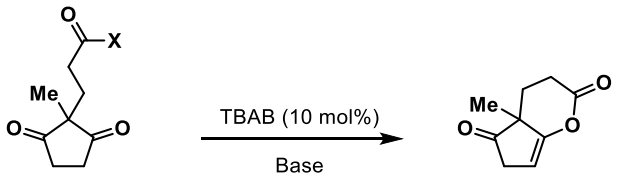


162 **166**

Entry	**Solvent**	**Base**	**162**:**166**:hydrolysis[a]
1	Toluene	KF (2 eq)	24:72:1
2	Toluene	KF (50% aq, 5 eq)	17:79:1
3	Toluene	KOH (2 eq)	9:78:13
4	Toluene	KO^{t}Bu (2 eq)	17:77:6
5	Toluene	K_2CO_3 (2 eq)	38:62:0
6	Toluene	K_2CO_3 (50% aq, 5 eq)	31:56:13
7	Toluene	K_3PO_4 (2 eq)	41:59:0
8	Toluene	K_3PO_4 (2 eq)	29:71:0[b]
9	Toluene	K_3PO_4 (50% aq, 5 eq)	-
10	CH_2Cl_2	KF (2 eq)	13:86:1
11	CH_2Cl_2	KF (50% aq, 5 eq)	9:55:44
12	CH_2Cl_2	KOH (2 eq)	14:86:0
13	CH_2Cl_2	KO^{t}Bu (2 eq)	0:82:18
14	CH_2Cl_2	K_2CO_3 (2 eq)	38:55:7
15	CH_2Cl_2	K_2CO_3 (50% aq, 5 eq)	33:67:0
16	CH_2Cl_2	K_3PO_4 (2 eq)	50:45:5
17	CH_2Cl_2	K_3PO_4 (2 eq)	40:60:0[b]
18	CH_2Cl_2	K_3PO_4 (50% aq, 5 eq)	33:67:0

[a] Determined by uncalibrated reverse-phase HPLC
[b] Determined by ^{1}H NMR Spectroscopy

Appendix B – Full Optimization Tables for Cyclization of Diketones 168–171



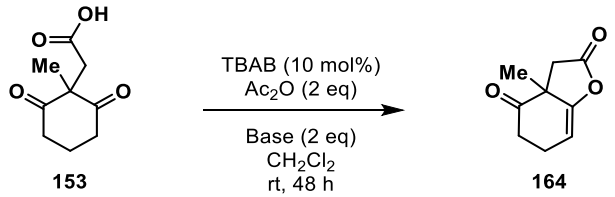
168 X = OPh
169 X = NHS
170 X = Cl
171 X = Im

165

Entry	**X**	**Base**	**165**:starting material :hydrolysis[a]
1	OPh	KF	0:100:0
2	OPh	KOH	0:82:18
3	OPh	K_2CO_3	0:0:100
4	OPh	K_3PO_4	0:63:37
5	OPh	KOAc	0:100:0
6	NHS	KF	32:68:0
7	NHS	KOH	31:64:5
8	NHS	K_2CO_3	29:22:49
9	NHS	K_2CO_3	19:10:71[b]
10	NHS	K_3PO_4	21:18:61
11	NHS	K_3PO_4	13:10:77[b]
12	NHS	KOAc	27:73:0
13	Cl	KF	23:12:65
14	Cl	KOH	0:0:0
15	Cl	K_2CO_3	9:5:86
16	Cl	K_3PO_4	18:8:74
17	Cl	KOAc	15:11:74
18	Im	KF	0:0:100
19	Im	KOH	0:0:0
20	Im	K_2CO_3	0:10:30
21	Im	K_3PO_4	0:0:0
22	Im	KOAc	0:60:40

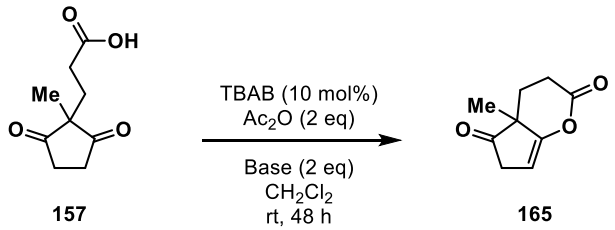
[a] Determined by uncalibrated reverse-phase HPLC;
the remaining material was converted to an unknown by-product
[b] Determined by ^{1}H NMR Spectroscopy

Appendix C – Full Optimization Tables for Cyclization of Diketoacids 153, 157 & 161



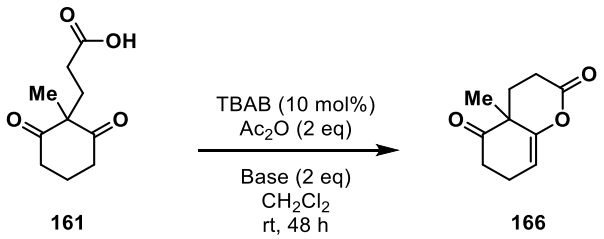
Entry	**Base**	**164:153**[a]
1	KF	40:60
2	$KHCO_3$	38:62
3	KOAc	50:50
4	KOAc	15:85[b]
5	K_2CO_3	45:55
6	K_3PO_4	46:54
7	KOH	34:66

[a] Determined by uncalibrated reverse-phase HPLC
[b] Determined by ^{1}H NMR Spectroscopy



Entry	**Base**	**165:157**[a]
1	KF	33:67
2	$KHCO_3$	45:55
3	KOAc	52:48
4	KOAc	27:73[b]
5	K_2CO_3	53:47
6	K_3PO_4	42:58
7	KOH	65:35

[a] Determined by uncalibrated reverse-phase HPLC
[b] Determined by ^{1}H NMR Spectroscopy



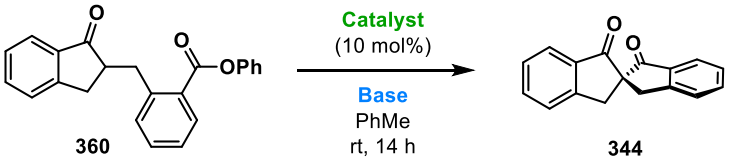
161 166

Entry	**Base**	**166:161**[a]
1	KF	39:61
2	$KHCO_3$	55:45
3	KOAc	65:35
4	KOAc	48:52[b]
5	K_2CO_3	54:46
6	K_3PO_4	50:50
7	KOH	58:42

[a] Determined by uncalibrated reverse-phase HPLC

[b] Determined by ^1H NMR Spectroscopy

Appendix D – Full Optimization Table for Cyclization of Phenyl Ester 360



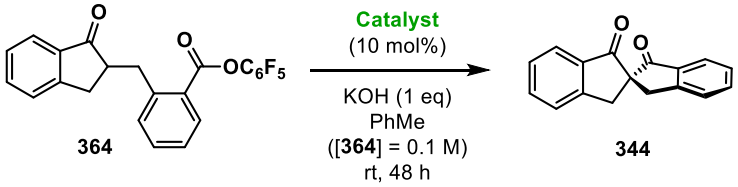
Entry	Catalyst	Base	*er*[a]
1	B	KOH (50% aq, 10 eq)	hydrolysis
2	B	KOH (1.0 eq)	59:41
3	B	K_2CO_3 (50% aq, 10 eq)	50:50
4	B	K_2CO_3 (1.0 eq)	56:44
5	B	NaOH (1.0 eq)	52:48
6	B	$CsOH·H_2O$ (1.0 eq)	54:46
7	B	$RbOH·H_2O$ (1.0 eq)	54:46
8	K	KOH (1.0 eq)	65:35
9	S	KOH (1.0 eq)	57:43
10	F	KOH (1.0 eq)	58:42
11	H	KOH (1.0 eq)	50:50
12	J	KOH (1.0 eq)	60:40
13	Z	KOH (1.0 eq)	56:44
14	I	KOH (1.0 eq)	50:50
15	AA	KOH (1.0 eq)	58:42
16	AB	KOH (1.0 eq)	56:44
17	AC	KOH (1.0 eq)	53:47
18	D	KOH (1.0 eq)	54:46
19	AD	KOH (1.0 eq)	54:46
20	G	KOH (1.0 eq)	55:45
21	AE	KOH (1.0 eq)	52:48
22	W	KOH (1.0 eq)	55:45
23	T	KOH (1.0 eq)	61:39
24	U	KOH (1.0 eq)	62:38
25	AF	KOH (1.0 eq)	53:47
26	AG	KOH (1.0 eq)	53:47
27	AH	KOH (1.0 eq)	60:40
28	AI	KOH (1.0 eq)	60:40
29	V	KOH (1.0 eq)	58:42
30	L	KOH (1.0 eq)	58:42
31	A	KOH (1.0 eq)	48:52
32	AJ	KOH (1.0 eq)	49:51
33	AK	KOH (1.0 eq)	44:56
34	AL	KOH (1.0 eq)	49:51
35	AM	KOH (1.0 eq)	48:52
36	M	KOH (1.0 eq)	38:62
37	AN	KOH (1.0 eq)	40:60
38	AO	KOH (1.0 eq)	45:55
39	AP	KOH (1.0 eq)	47:53
40	E	KOH (1.0 eq)	43:57
41	Q	KOH (1.0 eq)	69:31
42	R	KOH (1.0 eq)	67:33
43	N	KOH (1.0 eq)	51:49

44	O	KOH (1.0 eq)	49:51
45	P	KOH (1.0 eq)	37:63
46	AX	KOH (1.0 eq)	62:38
47	Q	KOH (0.1 eq)	63:37
48	Q	$NaOPH{\cdot}H_2O$ (0.1 eq)	62:38
49	Q	$NaOPH{\cdot}H_2O$ (1.0 eq)	51:49
50	-	$NaOPH{\cdot}H_2O$ (1.0 eq)	50:50

Reactions carried our according to **General Procedure C**

[a] Determined by HPLC using a chiral stationary phase

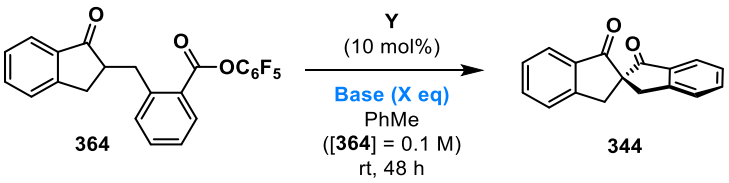
Appendix E – Full Optimization Tables for Cyclization of Pentafluorophenyl Ester 364



Entry	**Catalyst**	*er*[a]
1	Q	42:58
2	A	23:77
3	B	75:25
4	D	79:21
5	E	25:75
6	K	85:15
7	S	no reaction
8	J	79:21
9	AQ	decomposition
10	AL	46:54
11	M	23:77
12	AP	25:75
13	AR	36:62
14	AS	29:71
15	AT	17:83
16	AD	77:23
17	G	76:22
18	AE	61:39
19	W	75:25
20	T	decomposition
21	U	75:25
22	AF	79:21
23	X	80:20
24	AU	74:26
25	AH	72:28
26	AI	decomposition
27	V	80:20
28	AV	decomposition
29	L	87:13
30	Y	88:12
31	N	decomposition
32	Y (-20 °C)	no reaction
33	Y (0 °C)	80:20

Reactions carried our according to **General Procedure D**

[a] Determined by HPLC using a chiral stationary phase

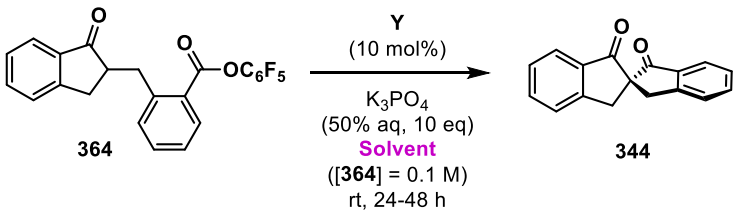


Entry	**Base (eq)**	*er*[a]	Conversion[b]
1	KOH (1)	89:11	62 %
2	KOH (5)	hydrolysis	0 %
3	KOH (10)	hydrolysis	0 %
4	NaOH (2)	75:25	63 %
5	$CsOH.H_2O$ (2)	hydrolysis	0 %
6	$RbOH.H_2O$ (2)	88:12	82 %
7	Li_2CO_3 (5)	no reaction	0 %
8	Na_2CO_3 (5)	96:4	30 %
9	K_2CO_3 (1)	96:4	56 %
10	K_2CO_3 (5)	95:5	50 %
11	K_2CO_3 (50% aq, 10)	96:4	>95 %
12	K_2CO_3 (50% aq, 5)	95:5	88 %
13	K_2CO_3 (33% aq. 10)	96:4	80 %
14	Cs_2CO_3 (5)	91:9	100 %
15	Cs_2CO_3 (1)	90:10	100 %
16	Cs_2CO_3 (50% aq, 10)	93:7	70 %
17	K_3PO_4 (2)	89:11	47 %
18	K_3PO_4 (50% aq, 10)	97:3	100 %
19	K_3PO_4 (sat aq, 10)	96:4	100 %

Reactions carried our according to **General Procedure D**

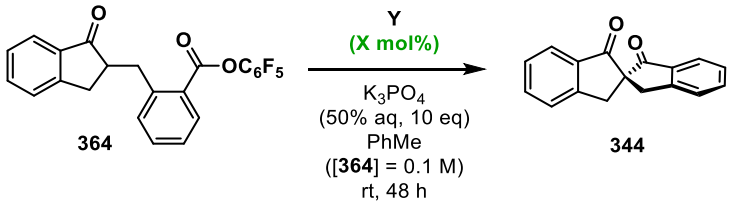
[a] Determined by HPLC using a chiral stationary phase

[b] Determined by ^1H NMR analysis of crude reaction mixture



Entry	Solvent	*er*[a]	time (h)
1	PhMe	97:3	48
2	PhH	95:5	48
3	CCl_4	96:4	48
4	$CHCl_3$	92:8	48
5	CH_2Cl_2	89:11	30
6	Et_2O	78:22	24
7	^{t}BuOMe	80:20	24
8	$^{i}Pr_2O$	81:19	>>48
9	m-xylene	90:10	48
10	p-xylene	94:6	48
11	1,4-dioxane	73:23	48
12	$(CHCl_2)_2$	50:50	24
13	$(CH_2Cl)_2$	87:13	48
14	1:9 $CHCl_3$/PhMe (0.1 M)	96:4	24
15	PhMe (1 M)	89:11	48

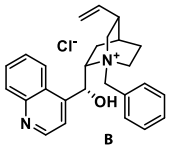
Reactions carried our according to **General Procedure D**
[a] Determined by HPLC using a chiral stationary phase



Entry	Catalyst loading (mol%)	*er*[a]	Conversion[b]
1	10	97:3	100 %
2	5	86:14	70
3	2	83:17	50

Reactions carried our according to **General Procedure D**
[a] Determined by HPLC using a chiral stationary phase
[b] Determined by ^{1}H NMR analysis of crude reaction mixture

Appendix F – Index of Phase-transfer Catalysts Used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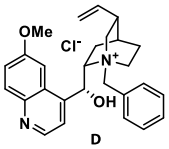
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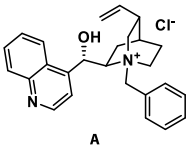
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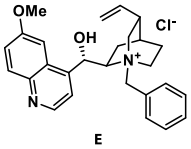
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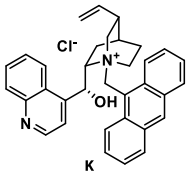
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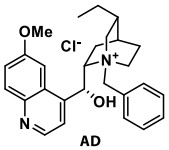
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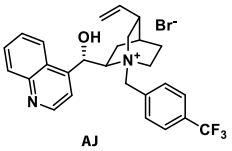
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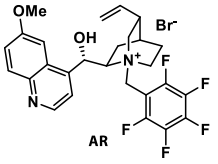
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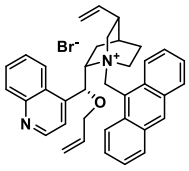
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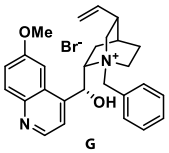
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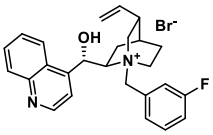
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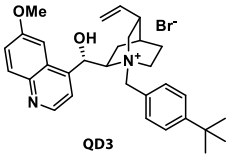
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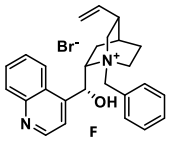
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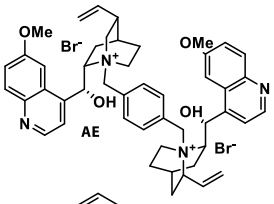
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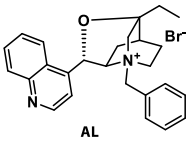
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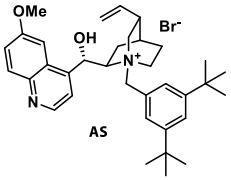
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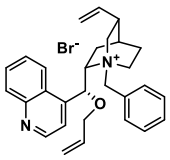
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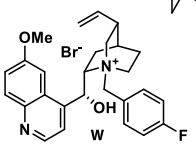
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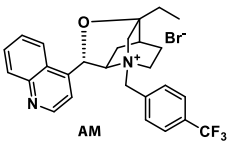
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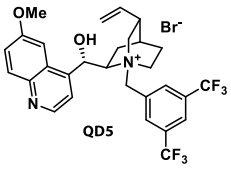
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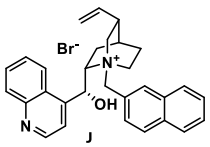
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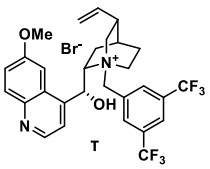
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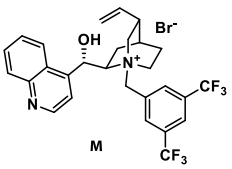
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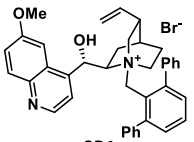
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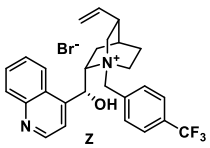
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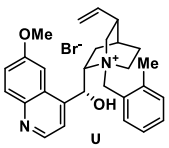
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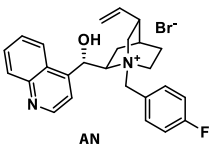
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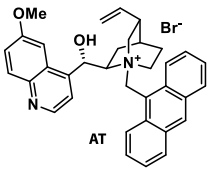
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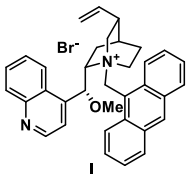
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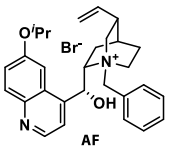
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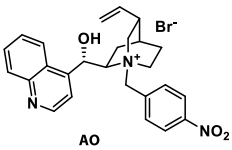
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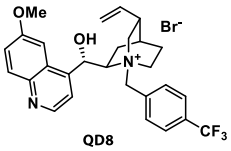
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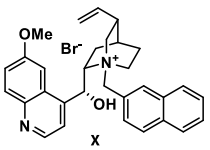
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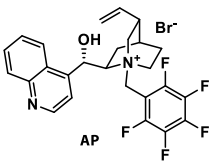
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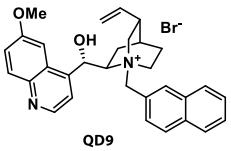
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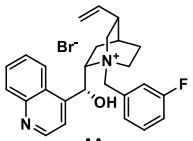
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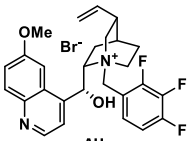
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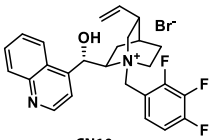
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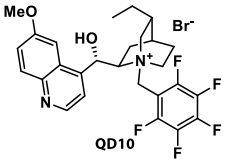
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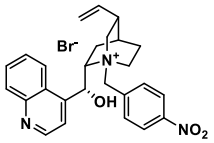
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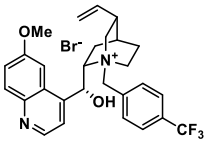
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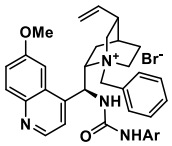
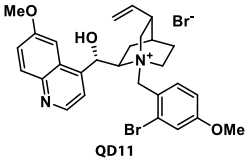
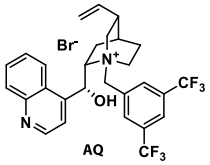

Q Ar = $(4\text{-}NO_2)C_6H_4$
R Ar = $(3,5\text{-}CF_3)C_6H_3$


QD11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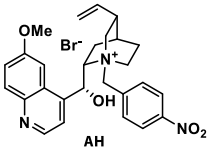
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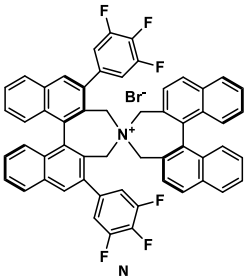
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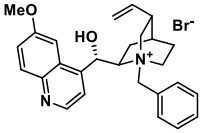
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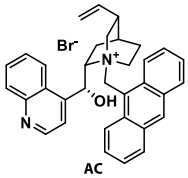
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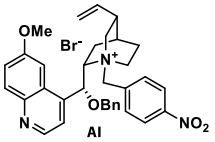
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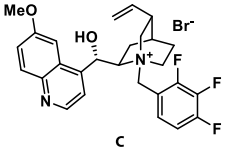
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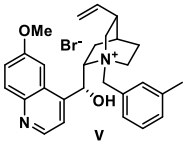
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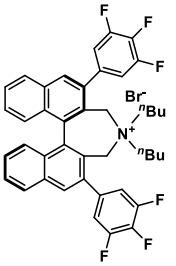
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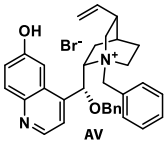
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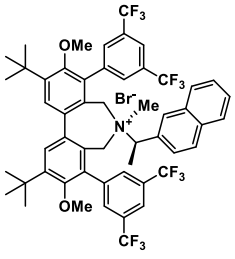
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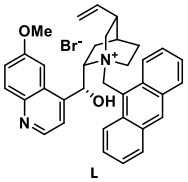
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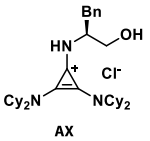
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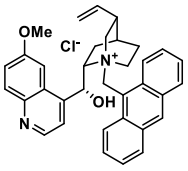
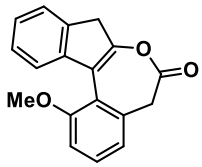
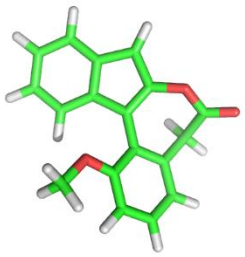

Y

Appendix G – X-ray Crystallographic Data

X-ray crystallographic data for compound **305**, 048JDJ17 BFR537

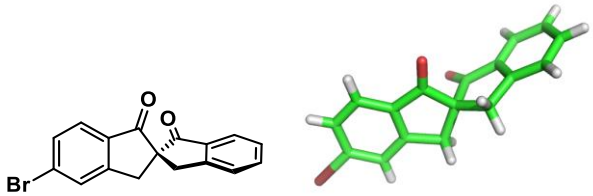


305



Identification code	048JDJ17	
Empirical formula	$C_{18}H_{14}O_3$	
Formula weight	278.31	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P $2_1/n$	
Unit cell dimensions	a = 9.3418 Å	α = 90°
	b = 14.9198Å	β = 112.804°
	c = 10.2120 Å	γ = 90°
Volume	1312.07 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.409 Mg m^{-3}	
Absorption coefficient	0.774 mm^{-1}	
F(000)	584.0	
Crystal size	0.10 x 0.32 x 0.47 mm^3	
Theta range for data collection	5.455° to 75.964°	
Reflections collected	8366	
Independent reflections	2703	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.999	
Final R indices [I>2σ(I)]	R^1 = 0.0369, wR^2 = 0.0983	
R indices (all data)	R^1 = 0.0390, wR^2 = 0.1003	

X-ray crystallographic data for compound **480**, 038JDJ16



480

Identification code	038JDJ16	
Empirical formula	$C_{17}H_{11}BrO_2$	
Formula weight	327.18	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 8.0948 Å	α = 90°
	b = 5.7321 Å	β = 103.5383°
	c = 15.2864 Å	γ = 90 °
Volume	689.584 $Å^3$	
Z,Z'	Z: 2 Z': 0	
Density (calculated)	1.576 Mg m^{-3}	
Absorption coefficient	2.342 mm^{-1}	
F(000)	328.0	
Crystal size	0.03 x 0.13x 0.17 mm^3	
Theta range for data collection	2.973° to 76.140°	
Reflections collected	16778	
Independent reflections	2849	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.997	
Final R indices [I>2σ(I)]	R^1 = 0.0169, wR^2 = 0.0421	
R indices (all data)	R^1 = 0.0170, wR^2 = 0.0422	

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