Bifunctional Iminophosphorane Superbase Catalysed Amide Enolisation for Enantioselective Intramolecular Reactions



A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy (DPhil)

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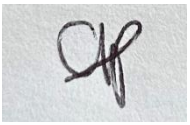
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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from February 2020 until October 2024, under the supervision of Professor Darren J. Dixon. All of this work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

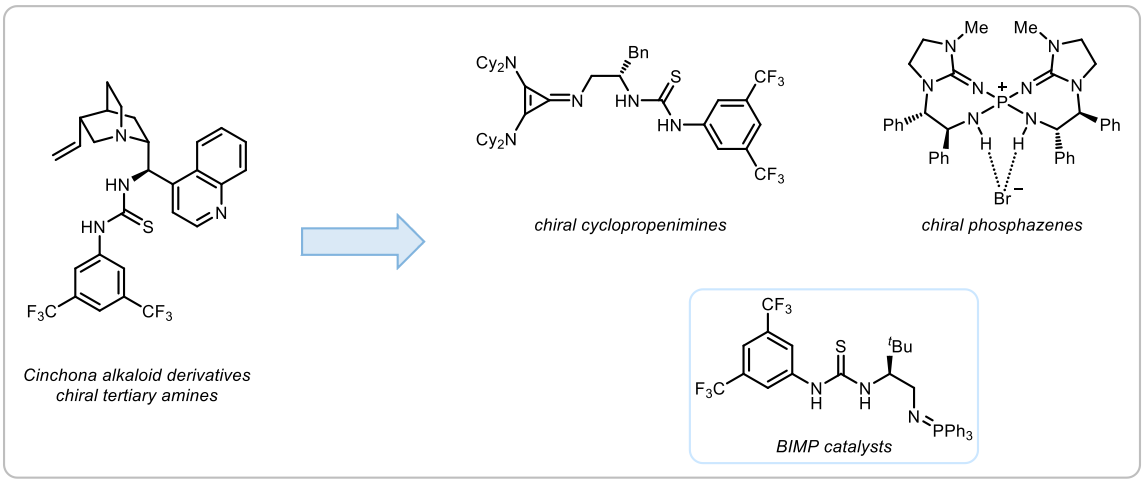


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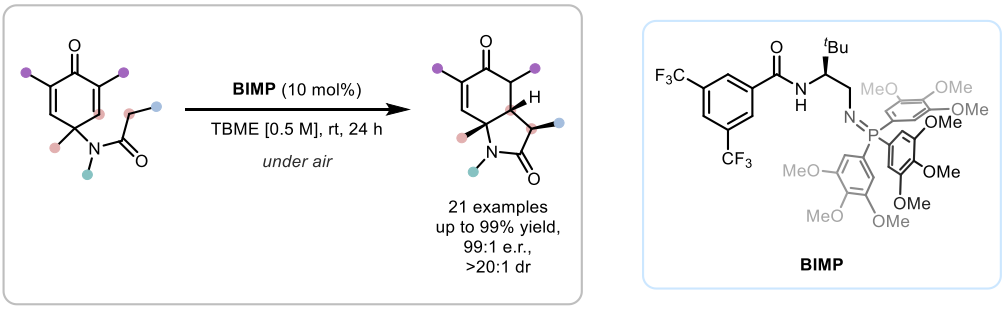
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Abstract

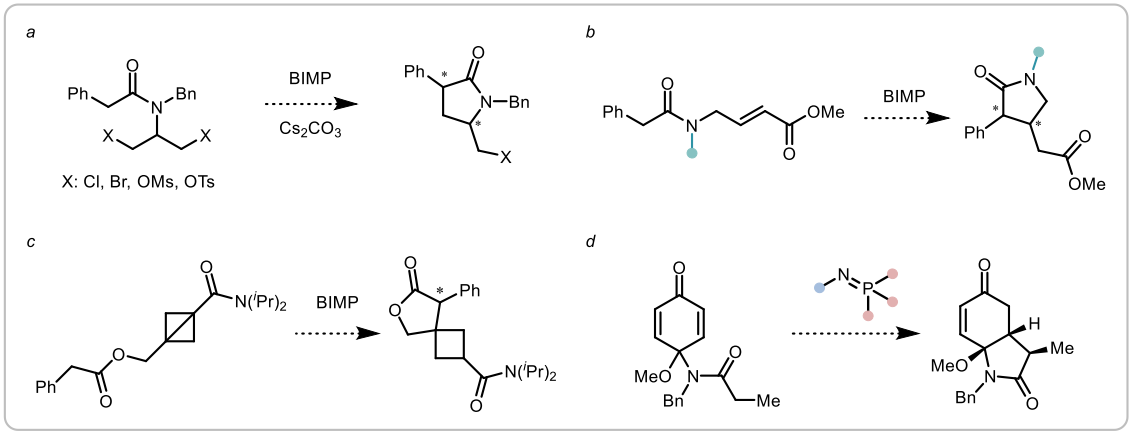
Chapter 1 introduces the preparation of enantioenriched compounds, with increasing focus on enantioselective organocatalysis, Brønsted base/H-bond donor catalysis and enantioselective superbase organocatalysis. The history and development of various organocatalysts will be discussed, culminating in the discovery, development and applications of bifunctional iminophosphorane (BIMP) catalysts.



Chapter 2 describes the development of a BIMP-catalysed enolisation of 2-arylacetyl and α-alkenyl amides for an enantioselective intramolecular Michael addition to tethered 2,5-cyclohexadienones. The substrate scope of this reaction, a preparative scale synthesis and further functionalisation of products formed will be detailed.



Chapter 3 details our efforts in reacting 2-arylacetamide and ester pronucleophiles with various intramolecular sp^2 and sp^3 electrophiles through BIMP catalysis. Efforts to increase the Brønsted basicity of BIMP catalysts with the view towards facilitating reactions involving very high pK_a pronucleophiles such as α-alkyl amides and esters will also be discussed.


a
Ph
O
N
Bn
X
X
X: Cl, Br, OMs, OTs
BIMP
Cs2CO3
Ph
O
N
Bn
X
b
Ph
O
N
OMe
O
BIMP
O
N
Ph
O
OMe
c
O
N(iPr)2
O
Ph
O
BIMP
O
O
Ph
O
N(iPr)2
d
O
MeO
N
O
Bn
Me
N
P
O
H
Me
MeO
N
Bn
O

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Thank you Tim for helping me with the X-ray crystal structure for compound **319**, and for the times spent preparing problem sheets, hanging out with the group at the pub, and talking about music. Thank you Anna, Cailean, Kitty, Nick and Alberto for our many conversations in and around G5, and for being friendly and helpful lab mates. Thank you Szymon for being a good friend, and for the times we've spent talking about life and going to Linacre for lunch. Thank you Rodan for regularly joining me in the walking group whenever we go for group socials when most will cycle, and for the many conversations we've had. Thank you Dong-Hang for your friendliness and approachability, and I am happy to see you join the BIMP team again. Kang, it was great being in the BIMP team together, thank you for all the times we've shared.

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Abbreviations

(+)	Dextrorotatory
(-)	Levorotatory
δ	NMR chemical shift
ν_{max}	Infrared absorption maximum
Ac	Acetyl
aq.	Aqueous
Ar	Aryl
atm	Standard atmosphere
ATR	Attenuated total reflectance
BCB	Bicyclo[1.1.0]butane
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BIMP	Bifunctional iminophosphorane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Box	(Bis)oxazoline
br	Broad
br s	Broad singlet
c	Concentration
C	Celsius
COD	1,5-Cyclooctadiene
Conc.	Concentrated
COSY	Correlation spectroscopy
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
d	Doublet
D-	Dextrorotatory
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene

DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dddd	Doublet of doublet of doublet of doublets
ddt	Doublet of doublet of triplets
de	Diastereomeric excess
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPP	Diphenylphosphinoyl
dq	Doublet of quartets
dqd	Doublet of quartet of doublets
dr	Diastereomeric ratio
dt	Doublet of triplets
dtd	Doublet of triplet of doublets
E	Entgegen (opposite)
EDCI·HCl	1-Ethyl-3-carbodiimide hydrochloride
ee	Enantiomeric excess
eq.	Equivalents
e.r.	Enantiomeric ratio
e.s.	Enantiospecificity
ESI	Electrospray ionisation
Et	Ethyl
FCC	Flash column chromatography

FT	Fourier transform
g	Grams
h	Hour (unit of time) or Hextet (NMR multiplet)
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uronium
Hept	Heptet
HG	Hoveyda-Grubbs
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
^{i}Bu	Isobutyl
^{i}Pr	Isopropyl
IR	Infrared
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
L-	Levorotatory
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m-	Meta
M	Molar (unit of concentration)
Me	Methyl
min	Minutes
mL	Millilitres
mol	Moles

m. p.	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
m/Z	Mass to charge ratio
NaDA	Sodium diisopropylamide
NaHMDS	Sodium bis(trimethylsilyl)amide
*n*Bu	*n*-Butyl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
*n*Pr	*n*-Propyl
Nu	Nucleophile
p	Pentet
p-	Para
Ph	Phenyl
PIDA	Phenyliodine (III) diacetate
piv	Pivaloyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PS	Polystyrene
pt	Pentet of triplets
q	Quartet
qd	Quartet of doublets
qdd	Quartet of doublet of doublets
quant.	Quantitative (100%)
Re	Rectus (right)
R_f	Retention factor

rt	Room temperature
sat.	Saturated aqueous solution
SFC	Supercritical fluid chromatography
Si	Sinister (left)
SM	Starting material
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBD	Triazabicyclodecene
TBME	*tert*-Butyl methyl ether
TBS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
td	Triplet of doublets
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
tol	Tolyl
Ts	*para*-Toluenesulfonyl
tt	Triplet of triplets
ttt	Triplet of triplet of triplets
UPLC	Ultra performance liquid chromatography
UV	Ultraviolet
Z	Zusammen (together)

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Chapter 1: Introduction to BIMP Catalysis

1.1 The Importance of Chirality

Stereochemical configuration, which refers to the spatial arrangement of atoms in a molecule, has played a key role in biochemistry and medicine due to the naturally chiral structures of many biological molecules. Normally, it refers to the configuration of four distinct atoms or groups around a tetrahedral sp^3 hybridised carbon atom in a molecule, as that structure would have a non-superposable mirror image.

Stereocentres are regularly incorporated into drug molecules to improve their interactions with chiral biological molecules in target binding sites. Historically, many chiral drug molecules have been synthesised as racemic mixtures, often with the two stereoisomers having different pharmacological properties due to diastereomeric *in vivo* interactions. Most of these differences are minor and benign, but enantiomers of active pharmaceutical compounds have been responsible for side effects as well as the production of toxic metabolic products.[1] For instance, both isomers of bupivacaine **1** (**Figure 1**) show equal biological activity as a local anaesthetic while the (*R*)-isomer exhibits much more pronounced cardiotoxicity than the (*S*)-isomer, levobupivacaine. Levobupivacaine was thus developed and approved for clinical use in Europe and the US as a single isomer and has shown comparable bioactivity with decreased cardiotoxicity as compared to the previously marketed bupivacaine racemic mixture.[2] There has therefore been an increased awareness of the need for drug molecules to be prepared in enantiopure form in order to better study the activity of all enantiomers individually and prevent undesired side effects caused by overactive or inactive enantiomers.

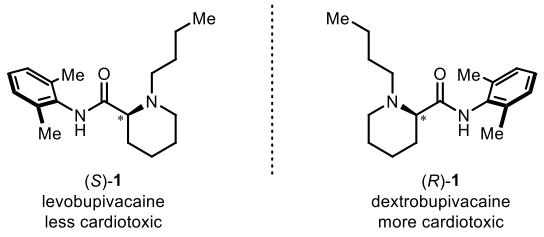


Figure 1. Enantiomeric structures of bupivacaine **1**.

1.2 Preparation of Enantioenriched Compounds

There are a number of approaches to prepare enantioenriched compounds (**Figure 2**). These can be broadly classed into a few categories, namely (1) chiral resolution, (2) synthesis from the chiral pool, (3) diastereoselective synthesis with chiral auxiliaries and (4) enantioselective catalysis.

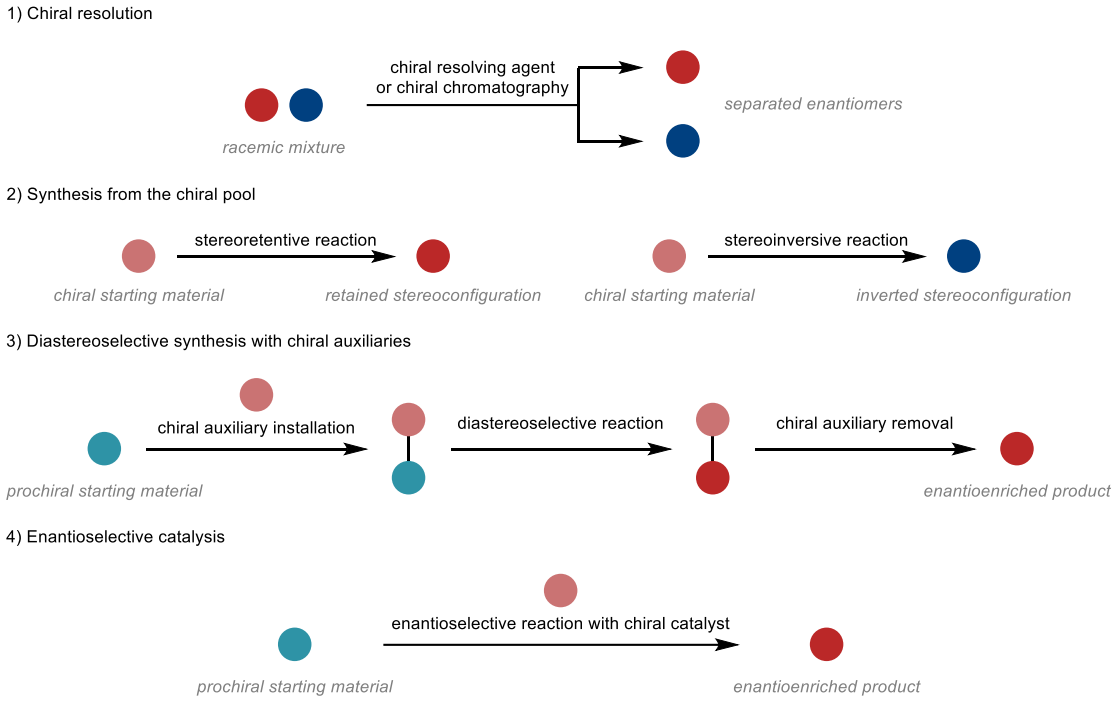


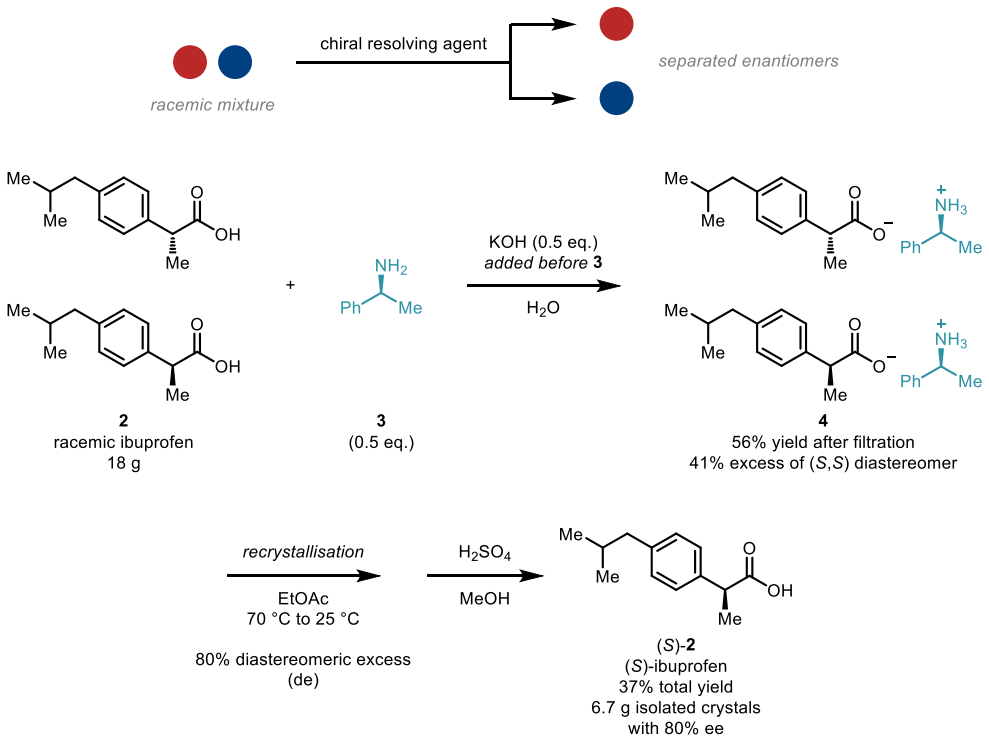
Figure 2. Various strategies for the preparation of enantioenriched compounds.

1.2.1 Chiral Resolution

Chiral resolution has been employed for more than a hundred years to isolate a single enantiomer from a mixture of both enantiomers of a target compound, using a chiral resolving agent to differentially interact with each enantiomer through diastereomeric interactions.[3] Even in recent years, chiral resolution remains among the most common tools used in the pharmaceutical industry to generate enantiopure material.[4, 5]

A common chiral resolution method on an industrial scale involves reacting the target Brønsted basic or acidic compound with an enantiopure organic acid or base respectively to form diastereomeric salts which can be separated by selective crystallisation. A recent discovery in this area involves the isolation of acidic (*S*)-ibuprofen **2** in 80% ee through the use of the readily available enantiopure base (*S*)-(-)-α-methylbenzylamine **3** as a chiral resolving agent (**Scheme 1**).[5] 0.5 eq. of **3** and 0.5 eq. of achiral base

KOH were used in the formation of diastereomeric salts **4** as this combination of equivalent ratios led to the greatest recovery of (*S*, *S*) enriched salt crystals **4** after filtration among all the combinations of equivalent ratios tested. Due to the high solubility of the potassium salt of **2** in aqueous media, the authors postulated that the presence of KOH facilitated the selective crystallisation of (*S*, *S*) salts **4**, with potassium salt formation unlikely to be a competing process. Both diastereomeric salts **4** exhibited different physical properties including their solubilities in common organic solvents such as EtOAc, allowing the isolation of the recrystallised salts **4** and subsequently ibuprofen **2** in a greater 80% de and ee respectively. A key limitation of this method is that only chiral acids and bases can be separated into their constituent enantiomers through diastereomeric salt formation and crystallisation.



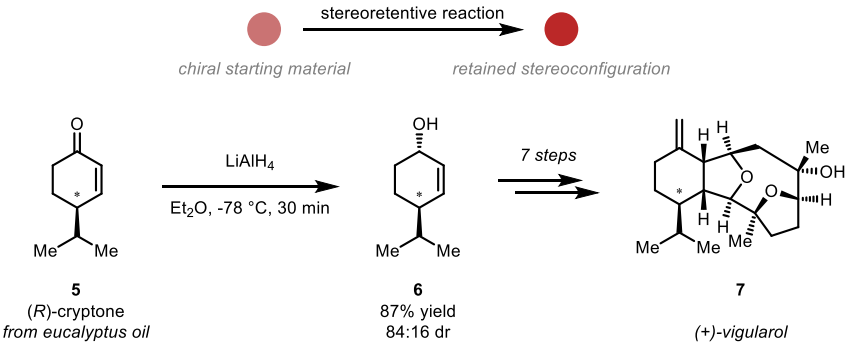
Scheme 1. Isolation of (*S*)-ibuprofen **2** through crystallisation of diastereomeric salts (2023).

Chiral column chromatography, where a chiral stationary phase is used as a chiral resolving agent, is also commonly employed for the resolution of mixtures of enantiomers on a smaller scale. This chiral stationary phase, typically made of polysaccharides and cyclodextrin in chiral HPLC, forms different diastereomeric interactions with the two enantiomers, allowing them to flow through the column at different rates and elute separately. Chiral chromatography effectively isolates both single enantiomers

from a mixture and is an efficient tool when both enantiomers are needed in a pure form, such as when both enantiomers of a drug candidate are to be studied.[5, 6]

The main limitation of chiral resolution occurs when one of the two enantiomers is deemed unnecessary. In this case, nearly all chiral resolution methods suffer from the necessary wastage of all material associated with that enantiomer, which makes up 50% of an initial racemic mixture. The only exception to this is when dynamic kinetic resolution (DKR) is applied, where a mixture of epimerisable substrate enantiomers can be wholly converted to the desired product enantiomer by controlling the relative reaction rates of both substrate enantiomers.[7]

1.2.2 Synthesis from the Chiral Pool

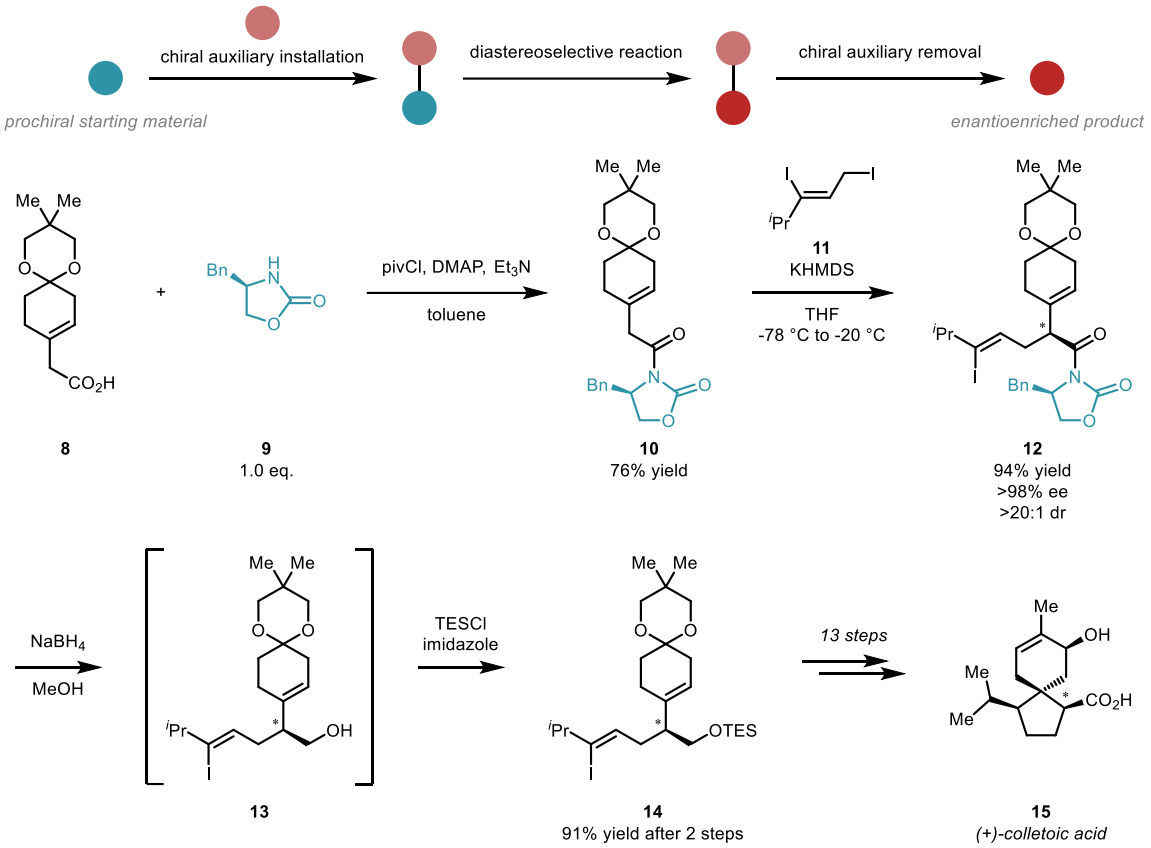


Scheme 2. Hoppe's total synthesis of (+)-vigulariol **7** (2008).

Naturally occurring enantiopure molecules such as amino acids, sugars and terpenes are ultimately necessary to produce enantiopure compounds, either directly or indirectly. These abundant molecules are easily obtainable from various natural sources at a low cost, rendering them preferred starting materials for chirality generation.[8] Most reactions that make use of chiral pool starting materials are stereoretentive, where the stereochemical configuration of the starting material is retained in the product. A few reactions, including S_N2 substitution reactions, are stereoinversive, where the product has an inverted stereochemical configuration as compared to the starting material. An example of a compound that can be prepared from chiral pool starting materials is the bioactive diterpene natural product (+)-vigulariol **7**. **7** was synthesised by Hoppe and coworkers in an eight-step procedure from the readily available terpene (*R*)-cryptone **5** derived from commercial eucalyptus oil, with the configuration at the stereocentre retained through to the natural product **7** (**Scheme 2**).[9] The main

limitation of the use of chiral pool starting materials such as **5** is that only one enantiomer of these compounds can normally be isolated from biological sources, making the synthesis of products derived from the other enantiomer much more challenging.

1.2.3 Diastereoselective Synthesis with Chiral Auxiliaries



Scheme 3. Rivas' synthesis of (+)-colletoic acid **15** with a chiral oxazolidinone (2016).

The use of chiral auxiliaries has risen as an effective solution to the above-mentioned problems. Where the target compound cannot be synthesised easily from the chiral pool, chiral auxiliaries can be attached to prochiral substrates to impart high and predictable diastereocontrol in the subsequent key reaction. The diastereomers formed would have different physical properties and can be separated by conventional methods such as flash column chromatography, allowing the stereoselective isolation of the target compound. These chiral auxiliaries, typically derived from chiral pool starting materials such as amino acids, are designed to be easy to install and cleave from the product without any loss in stereochemical purity. An example of a widely used chiral auxiliary system is Evans' oxazolidinones, which impart stereocontrol in numerous reactions including the aldol reaction and asymmetric α-

alkylations.[10] Chiral oxazolidinone auxiliary **9** was employed by Rivas and coworkers in an asymmetric α-alkylation step in the synthesis of bioactive (+)-colletoic acid **15** (**Scheme 3**).[11] The product of this stereoselective step, **12**, was generated in an excellent 94% yield, >98% ee and >20:1 dr.

Despite their many applications, chiral auxiliaries such as **9** are needed in stoichiometric amounts in the process, which leads to poor atom economy.[12] Their installation and removal also necessarily adds two or more extra steps to the synthetic sequence, which naturally reduces the overall efficiency of the synthetic route. However, the above example is an exception, where the treatment of **12** with $NaBH_4$ in methanol results in both the removal of the chiral oxazolidinone auxiliary **9** as well as the reduction of the carbonyl group to form alcohol **13**, which would otherwise have to be a separate step.

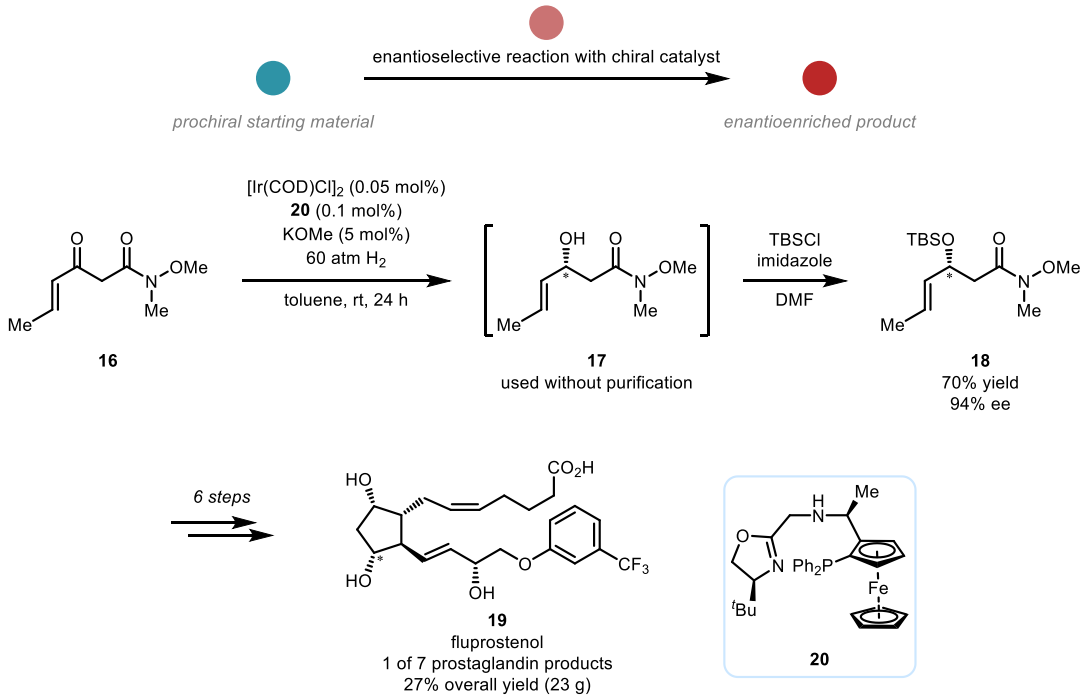
1.2.4 Enantioselective Catalysis

The direct conversion of prochiral starting materials to enantioenriched products in one step would greatly increase the efficiency of synthetic routes towards enantioenriched compounds. To this end, organic chemists have sought to develop methods which would allow the induction of enantioselectivity using only catalytic amounts of chiral compounds, as opposed to stoichiometric amounts of chiral auxiliaries, while utilising similar diastereomeric interactions. These catalysts include transition metal complexes, enzymes and small chiral organic molecules, all of which have significantly impacted the field of chemical synthesis.

Transition metal complexes used in enantioselective reactions typically involve a metal centre bound to chiral organic ligands. The complex would bind to the achiral reactants and facilitate their enantioselective reactivity by energetically favouring one diastereomeric transition state over the other. The impact of the development of transition metal catalysts for enantioselective reactivity has been widely recognised with the 2001 Nobel Prize in Chemistry awarded to Noyori and Knowles, and Sharpless for their work on asymmetric hydrogenation and oxidation reactions respectively.[13]

An example of the use of transition metal complexes in enantioselective synthesis was reported by Zhang and coworkers. A transition metal catalysed asymmetric hydrogenation step was incorporated in their recent total synthesis of prostaglandins, which are a family of essential hormones as well as drug

molecules such as fluprostenol **19** (**Scheme 4**).[14] Iridium complex **20** containing a chiral ferrocene ligand was employed as the catalyst in this reaction, and TBS protection of the resultant crude chiral alcohol **17** produced the TBS-protected alcohol **18** in 70% yield over both steps and 94% ee. This is impressive given the low catalyst loading of 0.05 mol% in the asymmetric hydrogenation step.

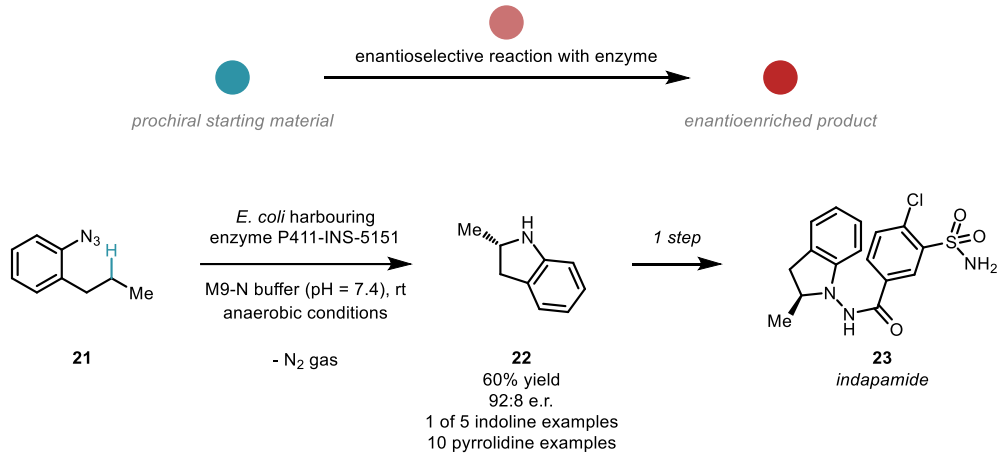


Scheme 4. Zhang's total synthesis of prostaglandins with a Ir-catalysed asymmetric hydrogenation step (2021).

Even though transition metal catalysts have the potential to afford enantiopure compounds with a substrate : catalyst ratio of up to 20 000:1,[15] precious metals typically used to make these catalysts such as Ir, Rh and Pd can be expensive and toxic. There has been much interest in the development of earth-abundant metal catalysts, but there is still some way to go before they are capable of being utilised as competent replacements for precious metal catalysts in promoting key enantioselective reactions.

The use of enzymes for enantioselective organic reactions is a solution to the above-mentioned problems with transition metal catalysts, owing to their abundance in nature and non-toxicity. Composed of many L-α-amino acids joined together by peptide bonds, they are capable of catalysing reactions with high regio-, chemo- and stereoselectivity. Natural enzymes have typically been used as part of whole living organisms such as bacteria and yeast. As co-crystallisation of enzyme-substrate complexes and computational tools have advanced our understanding of enzyme structure and reaction

mechanisms,[16] unnatural enzyme variants have been developed by rational design as well as directed evolution to catalyse new reactions.[17] The significant impact of the development of this enzyme engineering process has become widely recognised with the Nobel Prize in Chemistry awarded to Frances Arnold in 2018 for her work on the directed evolution of enzymes.[18] An example of a reaction catalysed by an evolved enzyme is the enantioselective intramolecular C(sp^3)−H amination with organic azides for the construction of chiral *N*-heterocycles (**Scheme 5**), which was recently reported by Arnold and coworkers.[19] A variant of the natural cytochrome P450 oxidative enzymes, P411-INS-5151, with 30 amino acids changed from wild-type cytochrome $P450_{BM3}$ was discovered to be optimal for the construction of indolines **22** using this method. This enzyme is coordinated to an iron-containing haem group in *E. coli* bacteria, with the reaction performed *in vivo* under anaerobic conditions and nitrogen gas formed as a reaction byproduct. With enzyme P411-INS-5151, the indoline **22** was formed in 60% isolated yield and 92:8 e.r., and is a precursor to the anti-hypertensive drug indapamide **23**.



Scheme 5. Arnold's modified cytochrome P411 catalysed enantioselective C(sp^3)−H amination (2023).

The key limitations of the use of enzymes are that enzyme activity is highly substrate dependent, and tedious optimisation cycles with specialised equipment and processes are required to attain optimal enzyme activity for a target substrate. In the reaction described in **Scheme 5**, different enzyme variants were optimal for the effective synthesis of different *N*-heterocycles such as pyrrolidines and indolines. A wide spectrum of known enzyme variants was initially screened for activity in the optimisation of the reaction to synthesise a pyrrolidine, with the best enzyme from this screen subjected to eight rounds of directed evolution. Out of the enzymes used for this optimisation study, when the intended product

was changed to indoline **22**, the best-performing enzyme variant P411-PYS-5148 yielded the desired indoline product in 46% yield and a poor 48:52 e.r. This enzyme was then subjected to two rounds of directed evolution to improve the yield and enantioselectivity of this reaction. Each round of directed evolution requires the testing of many modified enzymes, typically with variations in amino acids at a specific position in the sequence.

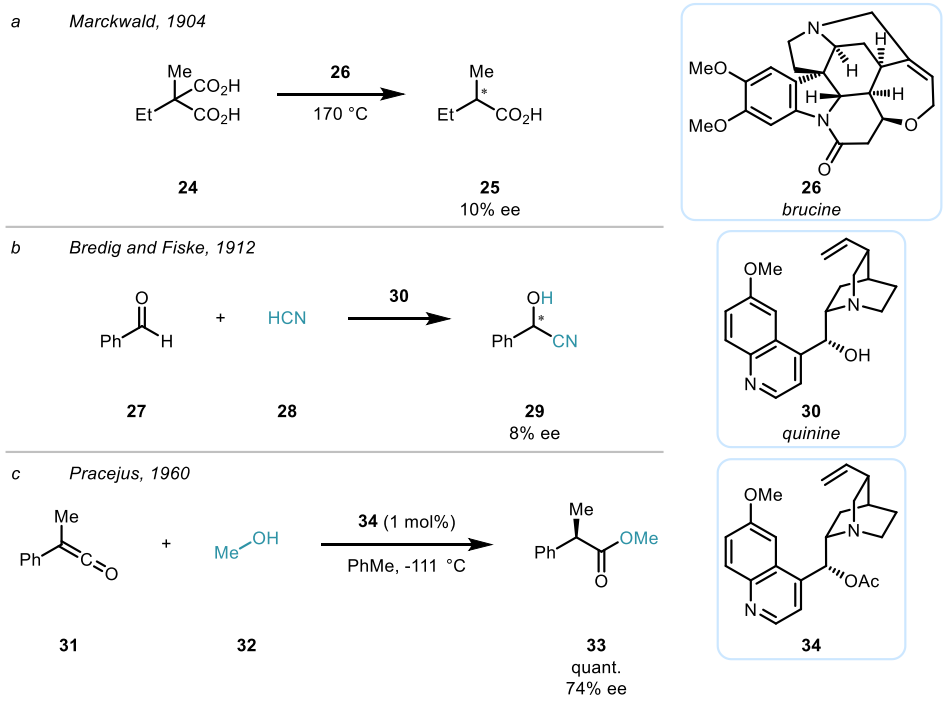
Small chiral organic molecules have also been shown to be capable of being good catalysts for enantioselective reactions by interacting with prochiral substrates through covalent, ionic or H-bonding interactions. Although these catalysts have been used for over a century, organocatalysis as a concept was not formalised until 2000, when the research groups of List[20] and MacMillan[21] published methods involving enamine and iminium catalysis respectively, with these publications being the basis of the award of the Nobel Prize in Chemistry in 2021. Organocatalysts are complementary to enzymes and transition metal catalysts, with a few advantages – they are relatively inexpensive to prepare, non-toxic, stable in air and can be prepared and used in typical synthetic chemistry laboratories.[22] The development of the field of asymmetric organocatalysis will be discussed in greater detail.

1.3 The Emergence of Enantioselective Organocatalysis

The earliest example of enantioselective reactivity catalysed by a small organic molecule was reported by Marckwald in 1904, detailing a decarboxylation of α-methyl-α-ethylmalonic acid **24** catalysed by brucine **26** (**Scheme 6a**).[23] Polarimetric measurements revealed an enantiomeric excess of 10% in the product **25**. However, stoichiometric amounts of **26** were required to form the brucine salts necessary for the induction of enantioselectivity through stereoselective protonation at the α-carbon. The substrate scope was also very limited, with reactions of similar substrates yielding racemic products.[24]

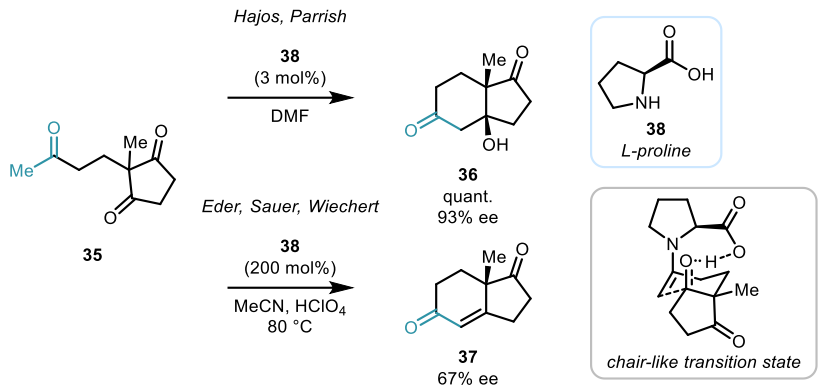
This discovery was followed eight years later by an enantioselective nucleophilic addition of HCN **28** to benzaldehyde **27** by Bredig and Fiske in 1912 (**Scheme 6b**).[25] With the *Cinchona* alkaloids quinine **30** or quinidine as chiral organic catalysts, the mandelonitrile product **29** was obtained in 8% ee. Years later, in 1960, a similar *Cinchona* alkaloid catalyst, **34**, was employed by Pracejus in the enantioselective nucleophilic addition of methanol **32** to phenyl(methyl)ketene **31** (**Scheme 6c**).[26] A much higher

enantioselectivity of 74% ee was observed in this reaction, which proceeded at a low temperature of –111 °C with a low catalyst loading of 1 mol%. It is believed that the basic tertiary amine groups in **30** or **34** would be protonated by the nucleophiles **28** or **32**, with these protonated catalysts facilitating the enantioselective cyanide addition or protonation step to form the enantioenriched products **29** or **33**.

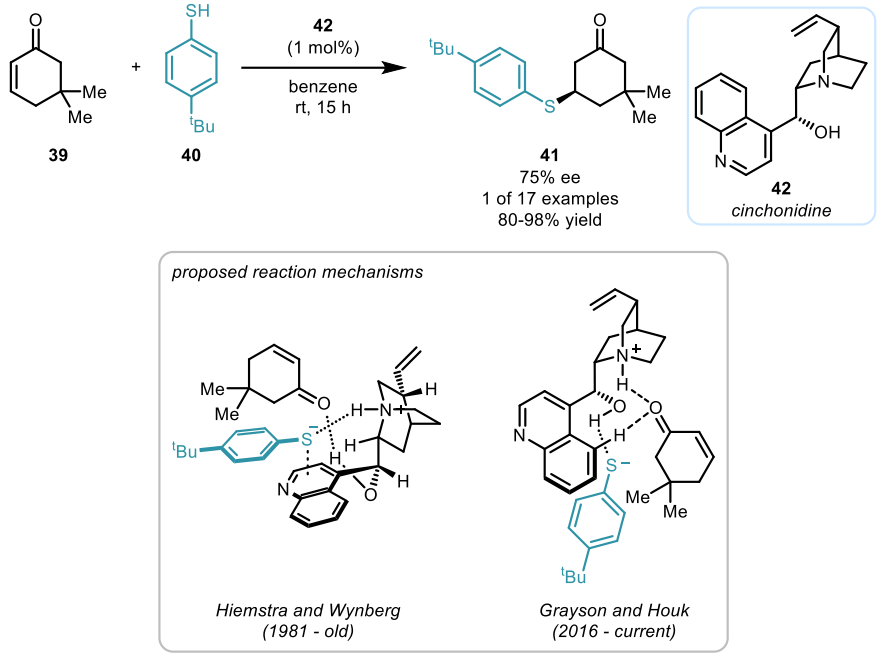


Scheme 6. Early examples of enantioselective reactions catalysed by small organic molecules (1912-1960).

The first highly enantioselective reaction catalysed by a small organic molecule was discovered in the early 1970s, when Hajos and Parrish of Hoffmann-La Roche[27] as well as Eder, Sauer and Wiechert of Schering[28] independently developed an enantioselective intramolecular aldol reaction (**Scheme 7**). This transformation was catalysed by the naturally occurring amino acid proline **38** and yielded the bicyclic aldol product **36** in an impressive 93% ee. The aptly-named Hajos-Parrish-Eder-Sauer-Wiechert reaction is thought to proceed *via* the initial formation of a reactive enamine intermediate, and a chair-like transition structure is created where H-bonding interactions between the carboxylic acid in **38** and the ketone in substrate **35** influence the stereochemical outcome of the C–C bond-forming aldol reaction. Although covalent interactions are formed between **38** and **35**, the catalyst loading can be as low as 3 mol% due to the effective hydrolysis of the iminium ion product formed, regenerating the active catalyst **38** and yielding the ketone product **36**.



Scheme 7. The Hajos-Parrish-Eder-Sauer-Wiechert reaction (1971).

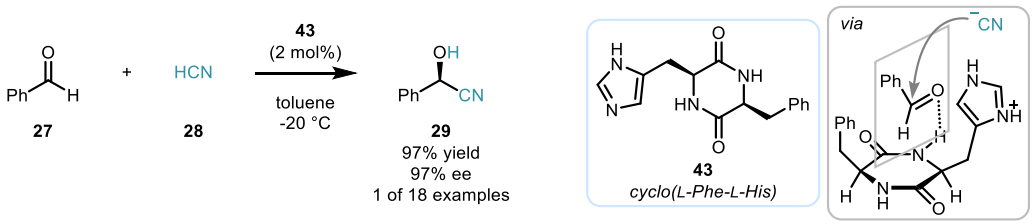


Scheme 8. Wynberg's cinchonidine-catalysed sulfa-Michael addition (1977).

Subsequently, Wynberg and coworkers reported an early example of non-covalent organocatalysis with their enantioselective sulfa-Michael addition of thiophenols **40** to cyclic enones **39** (**Scheme 8**).[29] *Cinchona* alkaloid quinine **30** was used to catalyse this reaction. In a follow-up paper with an expanded substrate scope, it was reported that the use of cinchonidine **42** as a catalyst led to improved enantioselectivity in the reaction and three different types of non-covalent interactions were thought to be involved in facilitating the enantioselectivity of this reaction. These interactions include (1) H-bonding between the free hydroxyl group in **42** and the carbonyl oxygen in **39**, (2) ionic bonding between the thiophenoxide ion formed from deprotonation of **40** and the ammonium salt derived from **42** and (3) dispersion forces between the thiophenoxide ion and the heteroaromatic quinoline group in **42**.[30]

Much later in 2016, Grayson and Houk conducted a detailed computational study on the reaction and argued that the above model was the preferred pre-reaction complex rather than the lowest energy transition structure leading to the experimentally-observed major product. A different transition structure was proposed, which involved a different set of catalyst-substrate interactions, namely (1) H-bonding between the free hydroxyl group in **42** and the thiophenoxide ion derived from **40**, (2) H-bonding between the ammonium salt derived from **42** and the carbonyl oxygen in **39** and (3) dispersion interactions between a C–H of the quinoline ring and the carbonyl oxygen in **39**.[31]

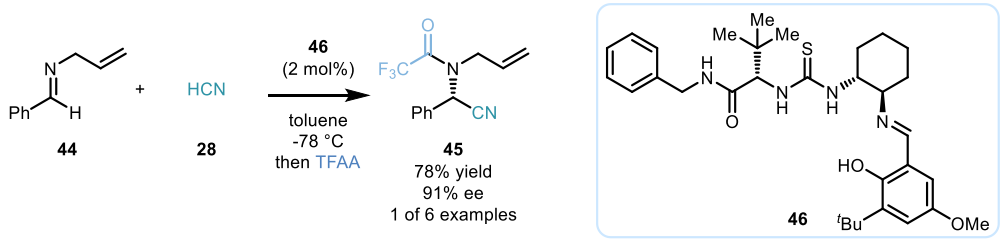
Another early example of non-covalent organocatalysis was revealed in 1981 by Oku and Inoue, who disclosed a novel cyclic dipeptide catalyst, *cyclo*(L-Phe-L-His) **43**, formed from the condensation of two naturally occurring amino acids, L-phenylalanine and L-histidine.[32] Designed to mimic the natural enzyme oxynitrilase, this catalyst efficiently promoted the enantioselective nucleophilic addition of HCN **28** to benzaldehyde **27**, yielding (*R*)-mandelonitrile **29** in 97% yield and 97% ee upon further investigation, along with a broad substrate scope which includes aliphatic aldehydes (**Scheme 9**).[33] These results are superior to those of Bredig and Fiske (**Scheme 6b**). H-bonding is thought to exist between the carbonyl oxygen of **27** and the peptide hydrogen of the histidine residue in **43**. The phenyl group in **27** points away from **43** and the aromatic ring of the phenylalanine residue hinders one face of **27** from nucleophilic attack by the cyanide and facilitates its enantioselective addition to the less hindered face.



Scheme 9. Inoue's nucleophilic addition of HCN **28** to benzaldehyde **27** (1981).

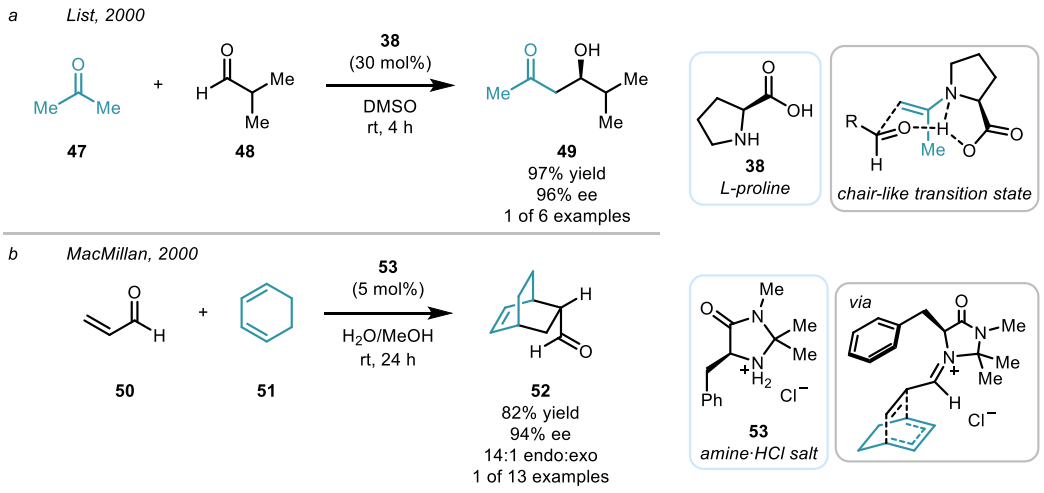
A novel organocatalyst scaffold was introduced by Sigman and Jacobsen in 1998 for an enantioselective Strecker reaction between various aldimines **44** and HCN **28**.[34] Catalyst **46** consists of a Schiff base and a thiourea H-bond donor moiety and was originally designed as a ligand for transition metal catalysis. With catalyst **46**, cyanohydrin **45** was formed in 78% yield and 91% ee (**Scheme 10**), with the initial substrate scope of six examples being expanded a few years later to include ketimines.[35] This general

bifunctional catalyst scaffold later proved to effectively facilitate similar reactions of imines with various nucleophiles including silyl-ketene acetals,[36] phosphites,[37] nitroalkanes,[38] as well as indoles for acyl Pictet–Spengler reactions.[39]



Scheme 10. Jacobsen's enantioselective Strecker reaction (1998).

In 2000, List and coworkers developed an intermolecular proline-catalysed asymmetric aldol reaction between acetone **47** and various non-enolisable aldehydes **48** (**Scheme 11a**).[20] Like the Hajos-Parrish-Eder-Sauer-Wiechert reaction (**Scheme 7**), this reaction is believed to proceed *via* the condensation of proline **38** and **47** and subsequent tautomerisation, forming a more nucleophilic enamine intermediate which undergoes nucleophilic addition to aldehyde **48**. The high enantioselectivity of the product **49** of up to 96% ee can be explained by a Zimmerman-Traxler chair-like transition state, where the bulky substituent in **48** occupies a pseudo-equatorial position. H-bonding interactions between the carbonyl oxygen in **48** and both the enamine and carboxylic acid hydrogens in the enamine create a tricyclic framework which controls the enantiofacial selectivity of the aldol reaction.



Scheme 11. (a) List's proline-catalysed enantioselective aldol reaction (2000). (b) MacMillan's chiral amine-catalysed enantioselective Diels-Alder reaction (2000).

Later that year, MacMillan and coworkers disclosed a chiral amine-catalysed reaction involving α,β-unsaturated aldehydes **50** and various cyclic and acyclic dienes **51** (**Scheme 11b**).[21] The chiral secondary amine·HCl salt catalyst **53** undergoes a condensation reaction with **50** to form an iminium ion, lowering the LUMO energy level and activating the electrophile for cycloaddition with **51**. The bicyclic product **52** was formed enantioselectively in 94% ee, with two proposed reasons for the high enantioselectivity. Firstly, during the condensation reaction, the vinyl group of **50** points away from the *gem*-dimethyl substituent in **53**, avoiding unfavourable allylic 1,3 strain and leading to the stereoselective formation of the (*E*)-iminium isomer. Secondly, the benzyl group in **53** blocks one face of the iminium ion dienophile, leaving the other face exposed for a stereoselective cycloaddition reaction.

As both the above articles celebrated the advantages of the use of small organic molecule catalysts in facilitating enantioselective reactions, the synthetic chemistry community began to take considerable interest in this field of organocatalysis, which began to develop rapidly. Many different types of organocatalysts were developed, including covalent, H-bond donor, nucleophilic, superacid, superbase, chiral phosphoric acids, phase-transfer ammonium salts and many others.[40] Among this new wave of catalysts, Brønsted base/H-bond donor bifunctional organocatalysts will be discussed further.

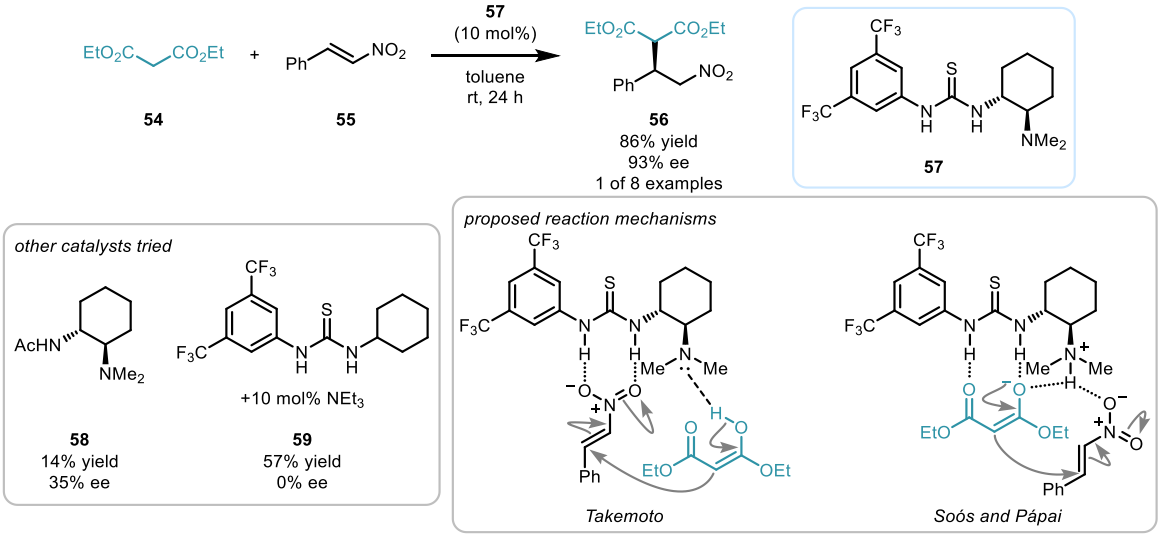
1.4 The Development of Brønsted Base/H-bond Donor Organocatalysis

1.4.1 The Emergence of Brønsted Base/H-bond Donor Organocatalysis

H-bonding between a catalyst and a H-bond acceptor group in one of the reactants such as a carbonyl group has been shown in the above examples to have a significant effect on the reactivity and stereoselectivity of a reaction. This H-bonding is thought to activate the substrate for reaction with a nucleophile through the lowering of its LUMO. At the same time, many of the catalysts used in the above reactions utilise multiple modes of substrate activation, as more activation modes enhance the effectiveness of the catalyst. Bifunctional catalysis, which utilises two distinct modes of substrate activation, allows the synergistic activation of both the nucleophile and the electrophile with just one catalyst scaffold. In Brønsted base/H-bond donor catalysis, the pronucleophile is deprotonated by a Brønsted base such as an amine, activating it for reaction with an electrophile, which is activated by the

H-bond donor group of the same catalyst. This form of catalysis has the potential to facilitate reactions between two relatively unreactive reaction partners, such as a pronucleophile with a high pK_a and a weak electrophile.[41]

Takemoto and coworkers were the first to design a Brønsted base/H-bond donor bifunctional organocatalyst **57** bearing both a tertiary amine and a 3,5-$(CF_3)_2C_6H_3$ thiourea moiety assembled around a chiral *trans*-diamine backbone. They applied this catalyst to a Michael addition of malonates **54** to nitroolefins **55**, which yielded the addition product **56** in an impressive 93% ee (**Scheme 12**).[42] Other catalysts were investigated for this reaction, including **58** which contains the same tertiary amine group but a different H-bond donor group and **59** which contains the thiourea moiety without the chiral tertiary amine. Catalysts **58** and **59** with 10 mol% NEt_3 yielded product **56** in lower yields and enantioselectivities than catalyst **57**, showing that both the thiourea and tertiary amine groups in **57** are required for high reactivity and enantioselectivity and thereby showcasing the power of bifunctional Brønsted base/H-bond donor organocatalysis.

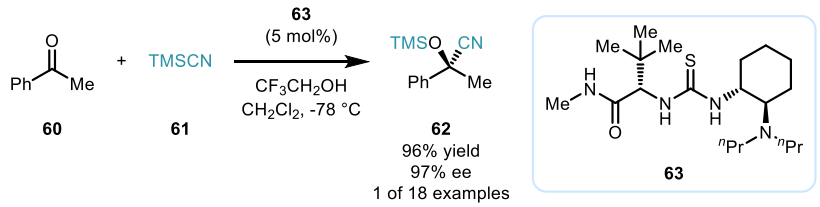


Scheme 12. Takemoto's enantioselective Michael addition of malonates **54** to nitroolefins **55** (2003).

The elucidation of the mechanism of this reaction had not been straightforward. In a follow-up paper, Takemoto proposed that the reaction proceeds through H-bonding between the thiourea moiety in **57** and the nitro group in **55**, deprotonation of **54** by the tertiary amine group in **57** and the deprotonated malonate adding to the less-hindered face of **55**.[43] On the other hand, Soós, Pápai and coworkers performed computational DFT studies on this reaction and thereby proposed an alternative mechanism

involving H-bonding between the thiourea moiety in **57** and the deprotonated malonate derived from **54** as well as interactions between the nitro group in **55** and the protonated tertiary ammonium group in **57**.[44] With a small energy difference between the two mechanisms of 2.7 kcal/mol, and the same enantiomeric outcome predicted in both, it is likely that both mechanisms occur simultaneously and the true mechanism is a hybrid of both proposed mechanisms.

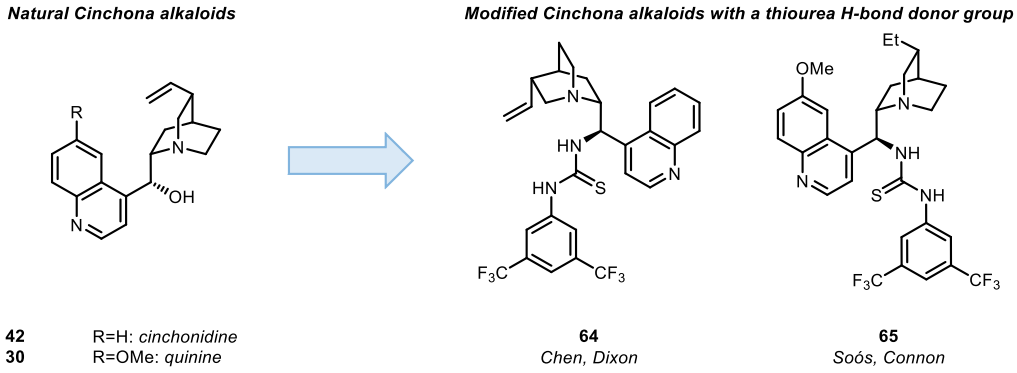
Another Brønsted base/H-bond donor organocatalyst was reported by Fuerst and Jacobsen two years later in 2005. A variant of Jacobsen's previously disclosed Schiff base catalyst **46** (**Scheme 10**), this tertiary amine catalyst **63** was employed in the enantioselective cyanosilylation of carbonyl compounds **60**, where catalyst **46** was insufficient to activate the pronucleophile TMSCN **61**, yielding little product **62**. With catalyst **63**, **62** was obtained from acetophenone **60** and **61** in 96% yield and 97% ee (**Scheme 13**). [45]



Scheme 13. Jacobsen's enantioselective cyanosilylation of carbonyl compounds **60** (2005).

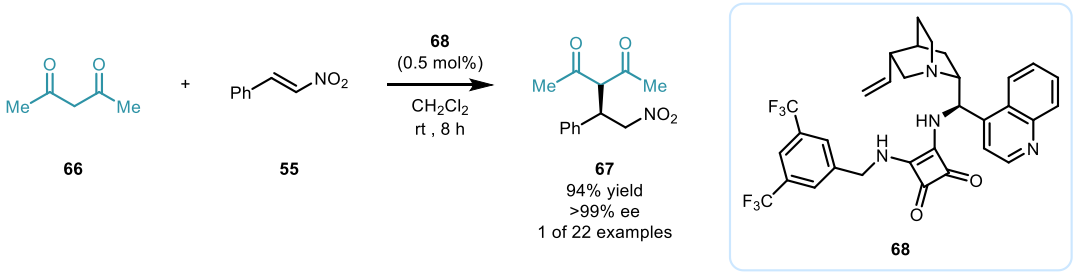
1.4.2 *Cinchona* alkaloid-derived Brønsted Base/H-bond Donor Catalysts

Cinchona alkaloids such as quinine **30** and cinchonidine **42** are naturally occurring chiral tertiary amines with their hydroxyl group providing some H-bonding ability. They have been used for a long time as effective catalysts for stereoselective reactions (**Scheme 6b**, **8**) due to their rigid chiral scaffolds and strong Brønsted basicity. A few research groups, seeking to take advantage of their Brønsted basicity, have sought to modify the *Cinchona* alkaloid scaffold, most commonly at the free hydroxyl group or the quinoline ring, to design effective Brønsted base/H-bond donor catalysts for challenging stereoselective reactions. Taking inspiration from the work of Takemoto (**Scheme 12**) and Jacobsen (**Scheme 10, 13**), in 2005, Chen,[46] Soós,[47] Dixon[48] and Connon[49] independently developed modified *Cinchona* alkaloids **64** and **65** containing thiourea H-bond donor groups (**Scheme 14**). These catalysts were found to be effective in facilitating enantioselective Michael additions of thiophenols, nitroalkanes and malonates to unsaturated imides, enones and nitroolefins.



Scheme 14. Modified *Cinchona* alkaloids **64** and **65** incorporating a thiourea H-bond donor group.

Other H-bond donor groups were soon introduced into the *Cinchona* alkaloid scaffold. In 2008, Rawal and coworkers developed catalyst **68**, which contains a squaramide H-bond donor group and is derived from *epi*-cinchonidine **42**.[50] Catalyst **68** was applied to a Michael addition of 1,3-dicarbonyl compounds **66** to nitrostyrenes **55** (**Scheme 15**), where the reaction proceeded in 94% yield and >99% ee with a catalyst loading of only 0.5 mol%.



Scheme 15. Rawal's enantioselective Michael addition of 1,3-dicarbonyl compounds **66** to nitrostyrenes **55** (2008).

1.5 Enantioselective Superbase Catalysis

Notwithstanding the effectiveness of the chiral tertiary amine/H-bond donor catalysts mentioned above, their effectiveness decreases as the acidity of the pronucleophile decreases. The above examples involve pronucleophiles at the lower end of the pK_a scale, which are more acidic and are deprotonated more easily than those with higher pK_a values (**Figure 3**).[51] These pronucleophiles have pK_a values below 18 in DMSO, as the tertiary amine catalysts used in these reactions have pK_{BH+} values similar to that of triethylamine, which is 18.8 in MeCN.[52] At the higher end of the pK_a scale, tertiary amine catalysts have insufficient basicity to deprotonate the pronucleophile and activate it for reaction with an electrophile.

Fortunately, a few other nitrogen-containing functional groups have been found to be more basic than amines (**Figure 4**).[53, 54] The commonly accepted definition of an organosuperbase is a compound which has comparable or higher basicity as compared to 1,8-bis(dimethylamino)naphthalene, otherwise known as Proton-sponge® (18.6 in MeCN, 7.5 in DMSO).[54] Superbasic organic functional groups include guanidines,[55] cyclopropeneimines[56] and phosphazenes, which contain additional N and P atoms to allow their positively-charged protonated form to be stabilised by resonance. Their incorporation in organocatalysts has the potential to expand the reaction scope of Brønsted base/H-bond donor organocatalysis to include pronucleophiles of higher pK_a values which would be unreactive with tertiary amine catalysts, such as ketones, esters and amides.

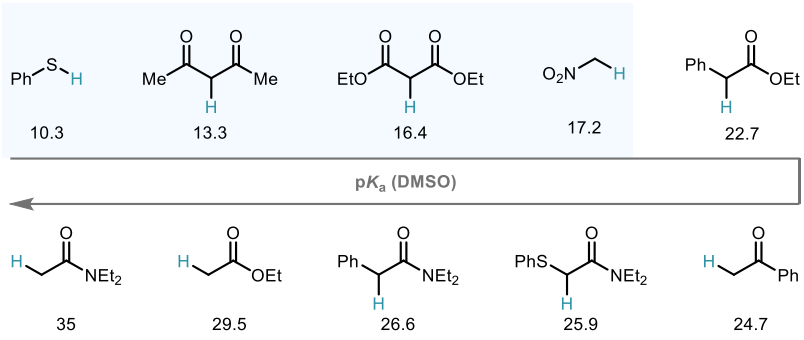


Figure 3. pK_a scale of selected common pronucleophiles in DMSO.

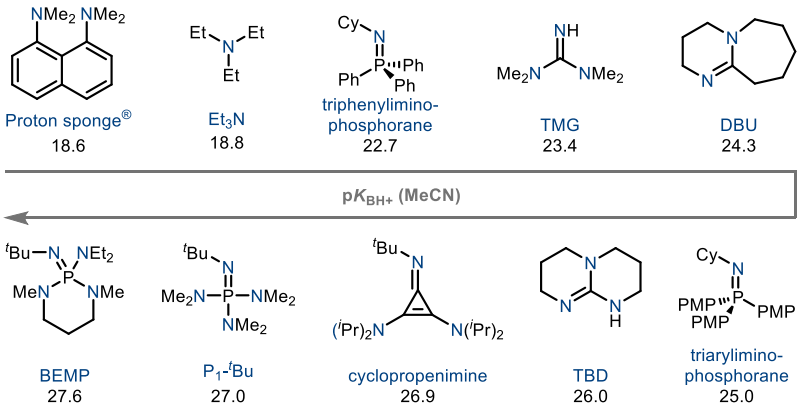
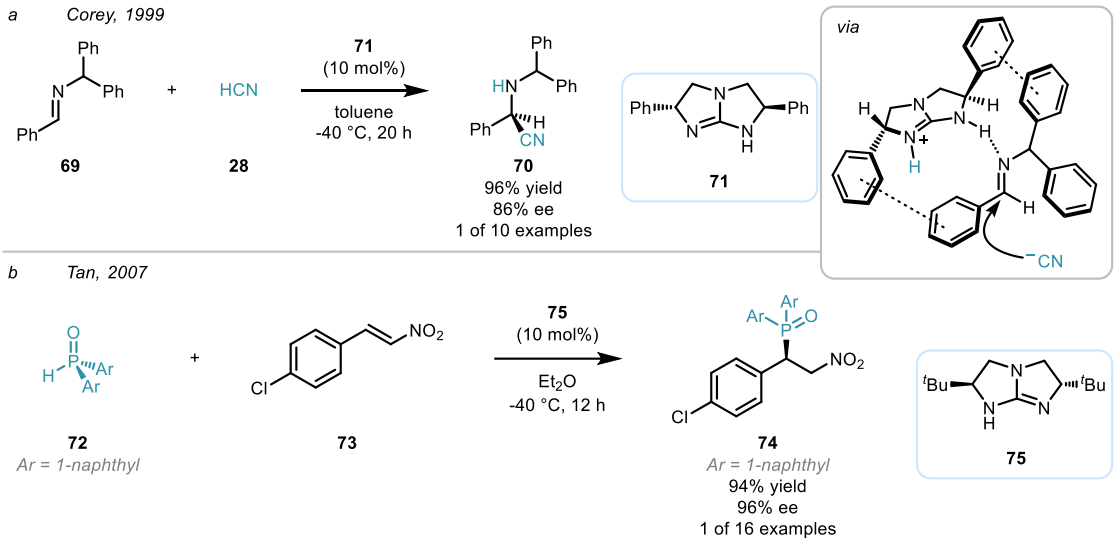


Figure 4. pK_{BH+} scale of selected organosuperbases in MeCN.

1.5.1 Guanidines (pK_{BH+} ~ 23 – 26 in MeCN)

An early example of highly enantioselective superbase organocatalysis was reported by Corey and Grogan in 1999, where the chiral bicyclic guanidine catalyst **71** promoted a Strecker synthesis of chiral α-amino nitriles **70** from *N*-benzhydryl imines **69** (**Scheme 16a**).[57] The (*R*)-isomer of **70** was isolated

cleanly in 96% yield and 86% ee. The authors postulated that four types of interactions were involved in directing the enantioselectivity of this reaction, namely (1) H-bonding between the guanidine H atom in **71** and the imine N atom in **69**, (2) π-stacking between one of the benzhydryl phenyl groups in **69** and one of the phenyl groups in **71**, (3) van der Waals attractions between the phenyl group conjugated to the imine of **69** and the guanidine core and distal phenyl edge of **71**, and (4) ionic bonding between the cyanide ion formed from deprotonation of **5** and the guanidinium ion formed from protonation of **71**. Catalyst **71** was shown to be recoverable in 80-90% yield from the crude reaction mixture by extraction with oxalic acid and basification of the oxalic acid wash with 1 M NaOH.

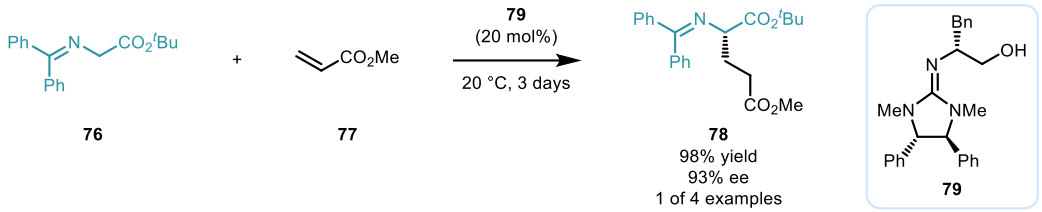


Scheme 16. (a) Corey's chiral bicyclic guanidine-catalysed enantioselective Strecker reaction (1999). (b) Tan's chiral bicyclic guanidine-catalysed phospha-Michael addition (2007).

A few years later in 2007, Tan and coworkers disclosed a phospha-Michael addition of secondary phosphine oxides **72** to nitrostyrenes **73** catalysed by a similar catalyst **75** (**Scheme 16b**).[58] This work was produced following their investigations into the synthesis and catalytic ability of differently-substituted bicyclic guanidines, where they observed that the bulkier *tert*-butyl substituents in **75** would lead to increased reaction enantioselectivity as compared to phenyl substituents in **71**.[59] With catalyst **75**, **74** was isolated in 94% yield and 96% ee.

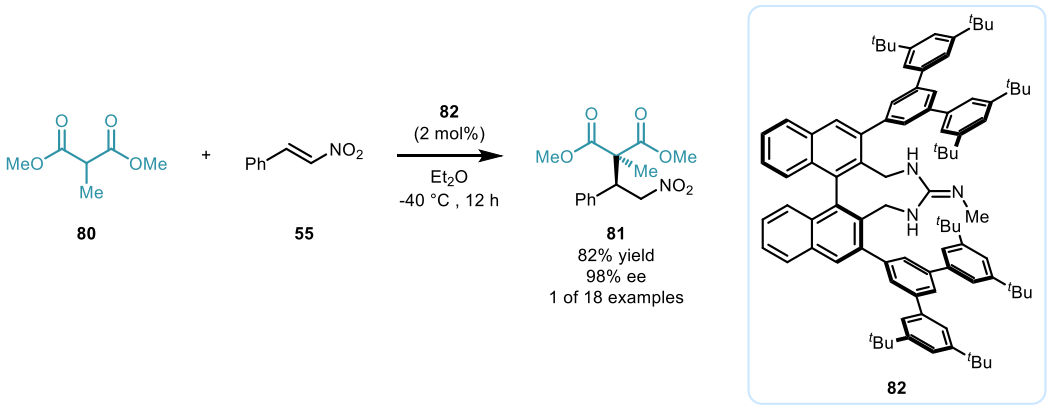
In 2001, Ishikawa and coworkers reported a Michael addition of glycine imines **76** to acrylates **77** and other unsaturated electrophiles using the chiral cyclic guanidine catalyst **79** containing a primary alcohol

H-bond donor group (**Scheme 17**).[60] This reaction was conducted neat with 3.6 eq. of **77** and over a long reaction time of 3 days and furnished the product **78** in 98% yield and 93% ee. Replacing catalyst **79** with *Cinchona* alkaloid quinine **30** gave no reaction, showing that the high Brønsted basicity of catalyst **79** was sufficient to deprotonate and activate the nucleophile **76** unlike the weaker tertiary amine in **30**. Effective H-bonding between catalyst **79** and the ester group in **76** was also shown to be essential for reactivity, as the use of a related catalyst without a H-bond donor group resulted in no reaction.



Scheme 17. Ishikawa's guanidine-catalysed Michael addition of glycine imines **76** to acrylates **77** (2001).

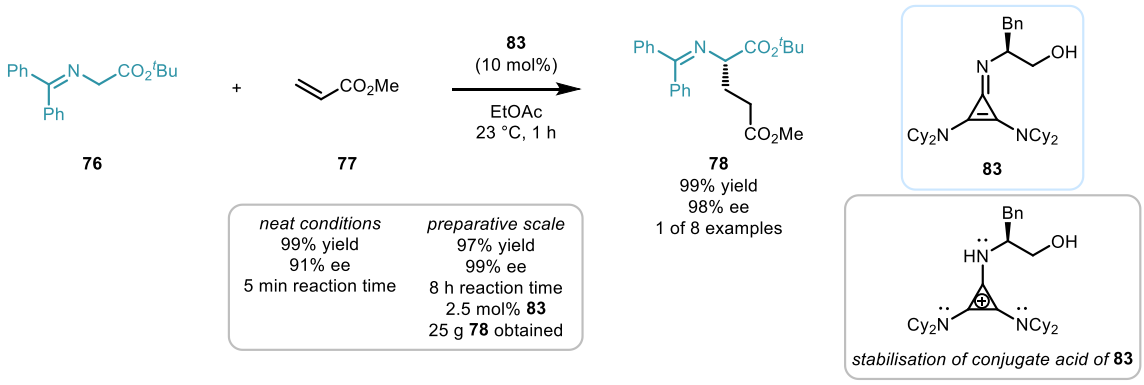
In 2006, Terada and coworkers disclosed an axially chiral guanidine catalyst **82** applied to a Michael addition of 1,3-dicarbonyl compounds and malonates **80** to nitroalkenes **55** (**Scheme 18**).[61] The bulky substituent 3,5-bis(3,5-di-*tert*-butylphenyl)-phenyl on the binaphthyl backbone of **82** was crucial for the induction of enantioselectivity in this reaction, with the nitroalkane product **81** obtained in 82% yield and an impressive 98% ee. **82** was able to be recovered almost quantitatively (96%) from a 10 mmol scaled-up reaction mixture as a HCl salt after column purification and an acidic workup. This salt could then be neutralised by a basic resin to the active form of the catalyst and reused in subsequent reactions.



Scheme 18. Terada's guanidine-catalysed Michael addition of malonates **80** to nitroalkenes **55** (2006).

1.5.2 Cyclopropenimines (pK_{BH+} ~ 26.9 in MeCN)

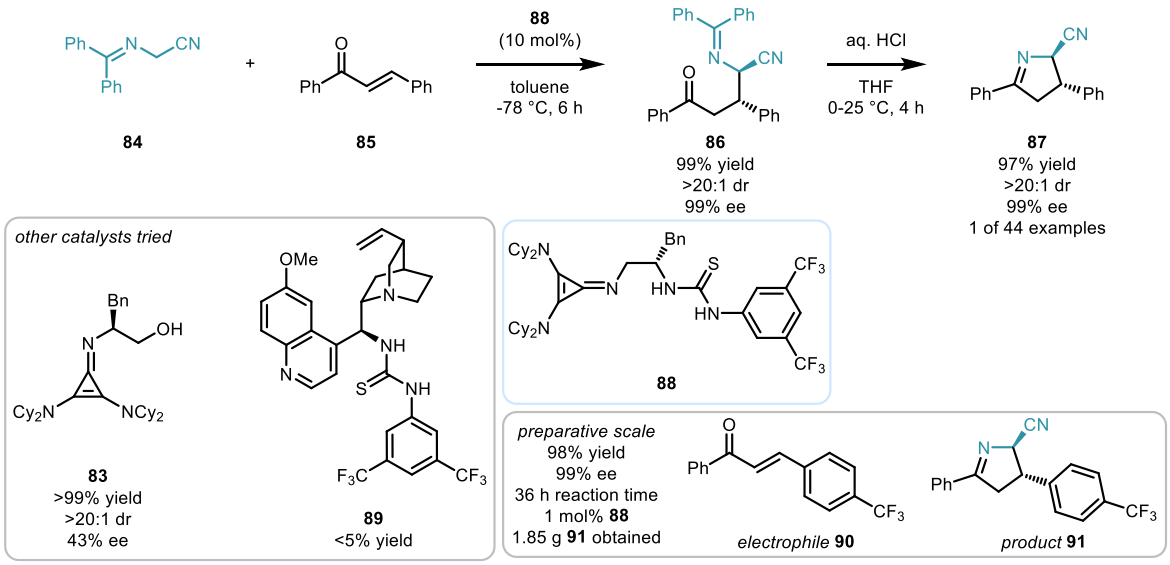
Chiral cyclopropenimines were first developed and reported by Bandar and Lambert in 2012.[56a] Upon protonation of a cyclopropenimine at the imine N atom, a 2π-electron cyclopropenium ion is formed, which is the smallest ring system that satisfies Hückel's aromaticity rules. This aromatic resonance, along with the lone pairs of electrons on all three N atoms, stabilises the positive charge, rendering cyclopropenimines more basic than guanidines (**Figure 4**). To showcase the superiority of chiral cyclopropenimines to guanidines, the authors employed cyclopropenimine catalyst **83** in an established guanidine-catalysed Michael addition of glycine imines **76** to acrylates **77** (**Scheme 17**). Catalyst **83** yielded the product **78** in 99% yield and 98% ee after only one hour (**Scheme 19**), as compared to the much longer reaction time of three days with guanidine catalyst **79** under neat conditions. The reaction with catalyst **83** under neat conditions was completed in 5 min with 99% yield and 91% ee. It was found that the hydroxyl group was essential for both the reactivity and enantioselectivity of this reaction, and it is likely to act as a H-bond donor. This reaction was successfully scaled-up to preparative scale with 25 g of **78** isolated in 97% yield and 99% ee with a lowered catalyst loading of 2.5 mol% of **83**.



Scheme 19. Lambert's cyclopropenimine-catalysed Michael addition of glycine imines **76** to acrylates **77** (2012).

A recent application of chiral cyclopropenimines was disclosed by Lee and coworkers, who developed thiourea-bearing cyclopropenimine catalyst **88** for an enantioselective Michael addition of α-iminonitriles **84** to enones **85** (**Scheme 20**).[62] The products **86** were then converted to useful α-chiral nitrile-containing 1-pyrroline derivatives **87** by cyclocondensation with aq. HCl. Catalyst **88** gave rise to enhanced H-bonding ability with two H-bond donors in the thiourea moiety as compared to Lambert's **83**, with initial addition product **86** formed in 99% yield, >20:1 dr and 99% ee using catalyst **88** but only

43% ee after 12 hours using catalyst **83**. *Cinchona* alkaloid-based catalyst **89** gave <5% yield after 7 days at 25 °C. As α-iminonitriles have a high pK_a of 17.8 in DMSO,[63] cyclopropenimines (pK_{BH+} ~ 26.9 in MeCN, **Figure 4**) are sufficiently Brønsted basic to deprotonate and activate them at the α-position for reaction with electrophiles such as **85**, unlike tertiary amine-bearing catalysts such as **89**. This reaction sequence employing a different electrophile **90** was successfully scaled-up to gram scale, yielding product **91** in 98% yield and 99% ee with a lowered catalyst loading of 1 mol% of **88**.



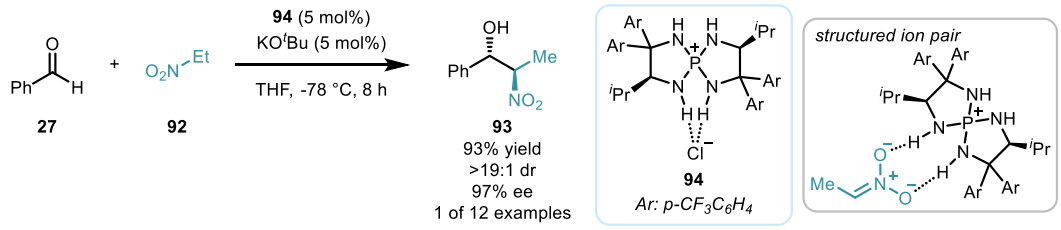
Scheme 20. Lee's cyclopropenimine-catalysed Michael addition of α-iminonitriles **84** to enones **85** (2024).

A key limitation of the use of cyclopropenimine catalysts such as **83** and **88** is their quick decomposition and thus the need for them to be stored carefully. Catalyst **83** was observed to have a half-life of only around 12 days at room temperature, with the decomposition pathway postulated to be an internal deprotonation of the hydroxyl group, oxazolidine formation and subsequent opening of the strained cyclopropene ring. However, a sample of **88** stored at -20 °C remained 94% intact after 30 days and the HCl salt of **83** was found to be indefinitely stable at room temperature, with similar observations made for catalyst **88**. As these catalysts are stored as their HCl salts, these salts would have to be converted into the active freebase catalysts before use, typically through a tedious base wash procedure.

1.5.3 Phosphazenes (pK_{BH+} ~ 26+ in MeCN)

Achiral phosphazenes were reported as early as the 1980s by Schwesinger and coworkers, who argued that phosphazenes, which are phosphorus-centred compounds with each P(V) centre forming three P–

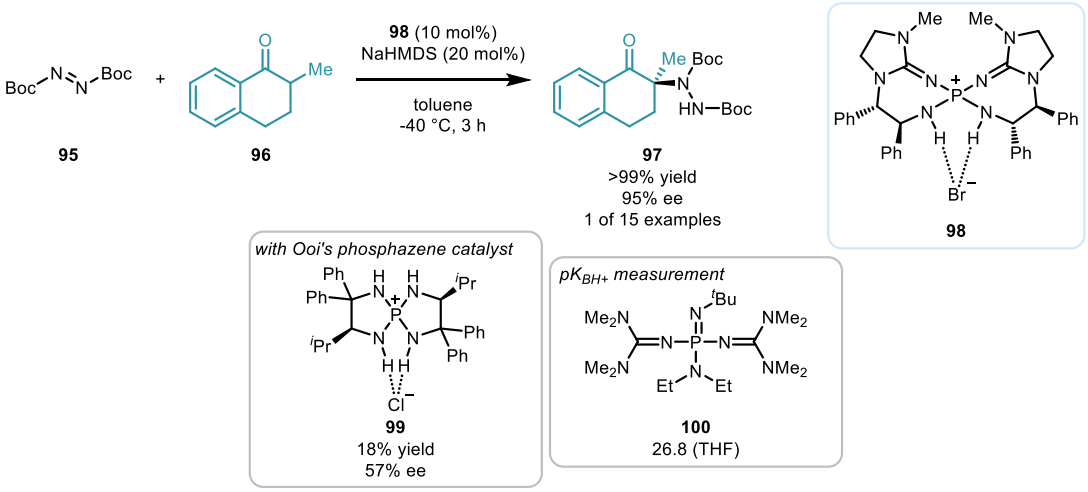
N single bonds and a P=N double bond, were among the most Brønsted basic nitrogen-containing non-ionic bases.[64] Their Brønsted basicity was also found to increase significantly as the number of P(V) centres increases due to an increased stabilisation of the positive charge upon protonation. However, it was not until 2007 that Ooi and coworkers disclosed the first chiral phosphazene organocatalyst **94** applied to a Henry reaction of nitroalkanes **92** to aldehydes **27** (**Scheme 21**).[65] The P_1 spirocyclic **94** effectively catalysed and induced stereoselectivity in this reaction, yielding the product **93** in 93% yield, >19:1 dr and 97% ee. Like the cyclopropenimines **83** and **88** above, catalyst **94** was stored as the HCl salt to prevent decomposition and freebased *in situ* with an equivalent of KO*t*Bu to form the active catalyst. Upon deprotonation of **92**, a structured ion pair was thought to be formed between catalyst **94**, which has multiple H-bond donors, and the resultant nitronate anion, which functions as a bidentate H-bond acceptor. This structured ion pair was thought to facilitate the stereoselective addition of the nitronate ion to aldehyde **27**, giving rise to the high stereoselectivity of the reaction.



Scheme 21. Ooi's phosphazene-catalysed enantioselective Henry reaction (2007).

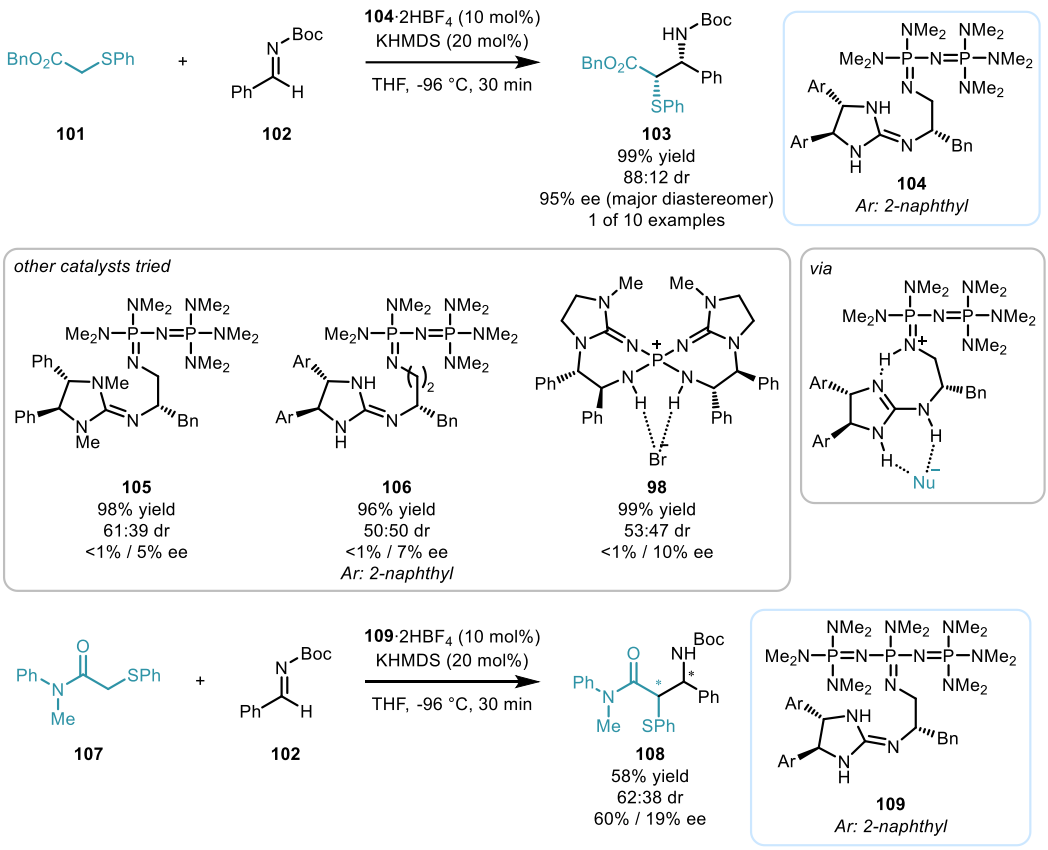
In 2013, Takeda and Terada disclosed the chiral bis(guanidino)iminophosphorane catalyst **98** applied to the addition of 2-alkyltetralones **96** to di-*tert*-butyl-azodicarboxylate **95** (**Scheme 22**).[66] With two guanidine subunits attached to two of the N atoms in the phosphazene, the authors postulated that the extended resonance stabilisation of the positive charge upon protonation would enhance the basicity of the novel phosphazene. The pK_{BH+} of achiral bis(guanidino)iminophosphorane **100** was measured as 26.8 in THF, highlighting the strong Brønsted basicity of these compounds. 2-Alkyltetralones **96** were selected as the pronucleophiles to be tested due to their low acidity and steric congestion around the α-position. Like catalyst **94**, catalyst **98** was stored as the HBr salt and freebased *in situ* with two equivalents of NaHMDS to form the active catalyst. The product **97** containing a quaternary chiral centre was obtained in an excellent >99% yield and 95% ee but in only 18% yield and 57% ee using catalyst **99**

bearing Ooi's P_1-phosphazene scaffold, showing the superiority of bis(guanidino)iminophosphorane catalysts.



Scheme 22. Terada's phosphazene-catalysed enantioselective addition of 2-alkyltetralones **96** to azodicarboxylates **95** (2013).

The first effective higher-order chiral phosphazene catalyst **104**, a chiral P_2-phosphazene connected to a guanidine scaffold by a chiral two-carbon linker, was disclosed by Terada and coworkers in 2020.[67] This bifunctional catalyst was employed in an enantioselective Mannich-type addition of an α-phenylthioacetate **101** to an *N*-Boc imine **102** (**Scheme 23**). The Mannich adduct **103** was obtained in 99% yield, 88:12 dr and 95% ee of the major diastereomer while strong achiral bases TBD and P_1-*t*Bu (pK_{BH+} = 26.0 and 27.0 respectively in MeCN, **Figure 4**) gave no reaction. The authors postulated that the phosphazene subunit acts as an organosuperbase while the guanidine subunit functions as a substrate recognition site with H-bond donating ability, and that a seven-membered cyclic structure with an intramolecular H-bond forms upon protonation of **104**. Other catalysts including **98**, as well as **105** and **106**, which are minor modifications of catalyst **104**, were tested in this reaction, giving rise to low stereoselectivities. This highlights the importance of H-bond donation in substrate recognition and optimal cooperation between the guanidine and phosphazene subunits. Although an α-phenylthioacetamide substrate **107** was unreactive in the reaction with catalyst **104**, the use of P_3-phosphazene catalyst **109** was found to improve reactivity, giving the desired product **108** in 58% yield, 62:38 dr and 60% and 19% ee of the major and minor diastereomer respectively. Catalysts **104** and **109** were stored as HBF_4 complexes and freebased with KHMDS *in situ* prior to use.



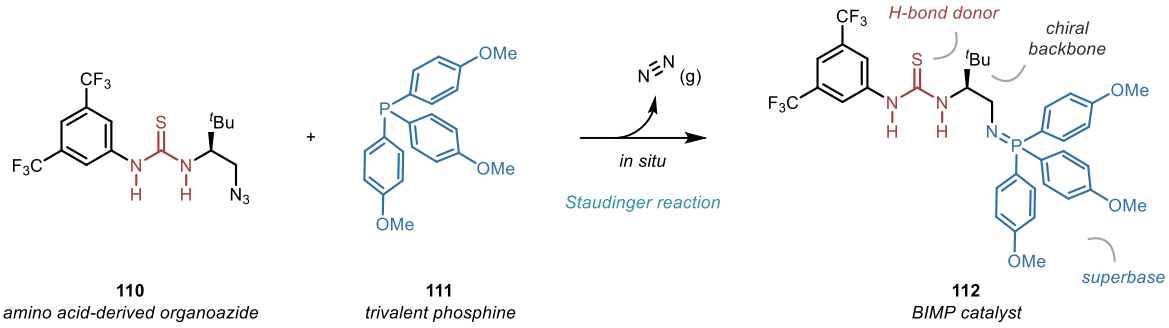
Scheme 23. Terada's P_2- and P_3-phosphazene-catalysed enantioselective Mannich-type reactions (2020).

1.6 Bifunctional Iminophosphorane (BIMP) Catalysis

1.6.1 Introduction to BIMP Catalysis

Desiring to develop a modular strong Brønsted base/H-bond donor bifunctional organocatalyst system, Dixon and coworkers disclosed novel bifunctional iminophosphorane (BIMP) catalysts **112** in 2013.[53a, 68] BIMP catalysts contain a strongly Brønsted basic iminophosphorane (pK_{BH+} ~ 22.7 – 25.0 in MeCN, **Figure 4**), which is formed *in situ* by reacting a chiral organoazide **110** with a trivalent phosphine **111** in a Staudinger reaction with nitrogen gas as the only byproduct. This obviates the need for the careful storage and handling typical of strong Brønsted bases. The amino acid-derived organoazide **110** contains at least one H-bond donor group such as a thiourea, urea, amide or squaramide for substrate activation, as well as one or more chiral centres (**Scheme 24**). The use of commercially available triphenylphosphine would give rise to an iminophosphorane pK_{BH+} of approximately 22.7 in MeCN while employing the electron-donating tris(4-methoxyphenyl)phosphane ($P(PMP)_3$) **111** would lead to a higher iminophosphorane pK_{BH+} of approximately 25.0 in MeCN (**Figure 4**). Thus, the formation of

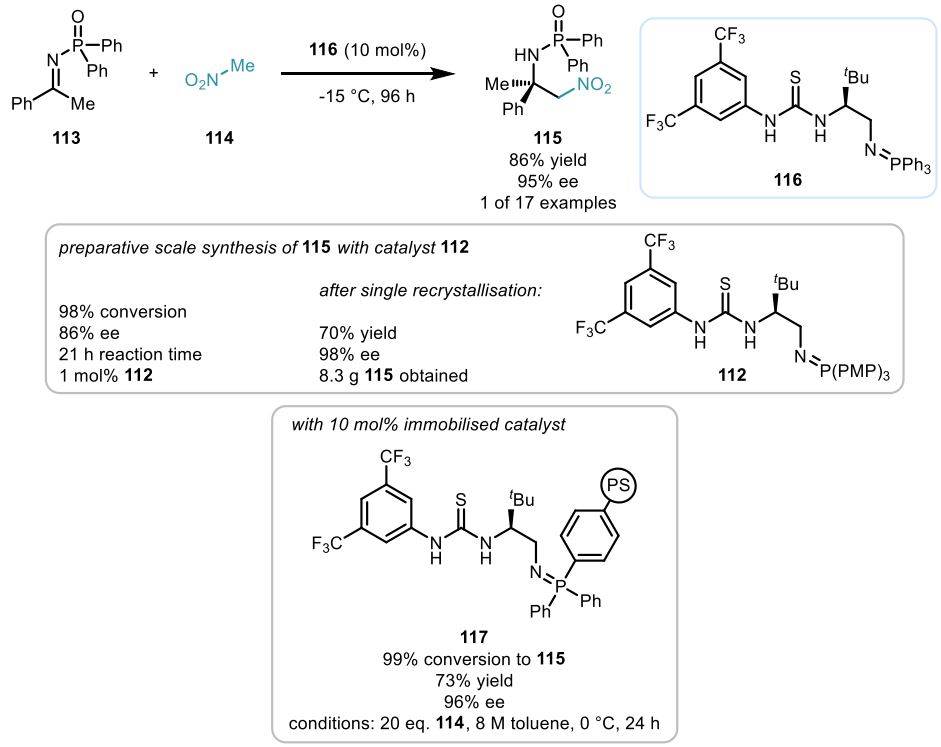
BIMP catalysts *in situ* allows for late stage tuning of the basicity and electronic properties of the iminophosphorane. BIMP catalysts have been found to be stable to both air and moisture and could be stored for over two years at -20 °C without any meaningful loss in activity.[69]



Scheme 24. Design and synthesis of BIMP catalysts.

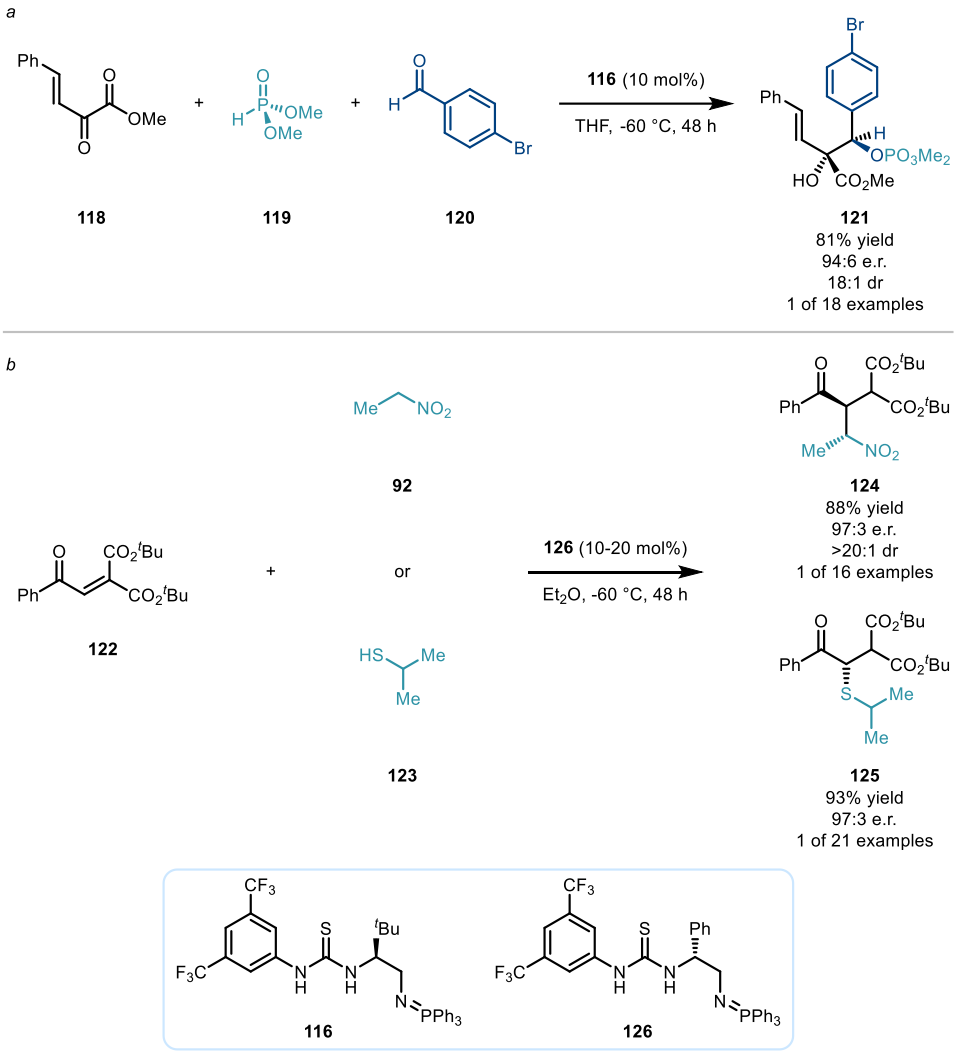
1.6.2 Reactivity of 1st Generation BIMP Catalysts

BIMP catalysts were initially applied to a nitro-Mannich reaction of nitromethane **114** to ketone-derived *N*-diphenylphosphinoyl (DPP) imines **113** conducted in neat nitromethane **114** (**Scheme 25**).[53a] With catalyst **116** bearing a thiourea H-bond donor group, a single chiral centre and phenyl substituents at the P atom of the iminophosphorane, the addition product **115** was formed in 86% yield and 95% ee. *Cinchona* alkaloid-derived catalyst **64** (**Scheme 14**) yielded no product after 32 hours at room temperature, showing the superior Brønsted basicity of the iminophosphorane in **116** as compared to the tertiary amine in **64**. Being bench-stable and not requiring specialised procedures for their handling, a slightly modified BIMP catalyst was readily applied to a preparative scale synthesis, yielding 8.3 g or 70% yield of **115** in 98% ee after a single recrystallisation with only 1 mol% of more reactive catalyst **112**. This product was further recrystallised to obtain enantiopure **115** and then derivatised to a 1,2-diamine as well as a quaternary α-amino acid without any loss of enantioselectivity. A few years later, catalyst **112** was employed in a phospha-Mannich reaction involving *N*-DPP-protected ketimines **113** and diethyl phosphite,[70] while catalyst **117**, which is an immobilised version of catalyst **116** on a polystyrene-based solid support, yielded nitro-Mannich product **115** in comparable yields and enantioselectivities to the reaction with homogeneous BIMP catalyst **116**.[71]



Scheme 25. Dixon's BIMP-catalysed ketimine nitro-Mannich reaction (2013).

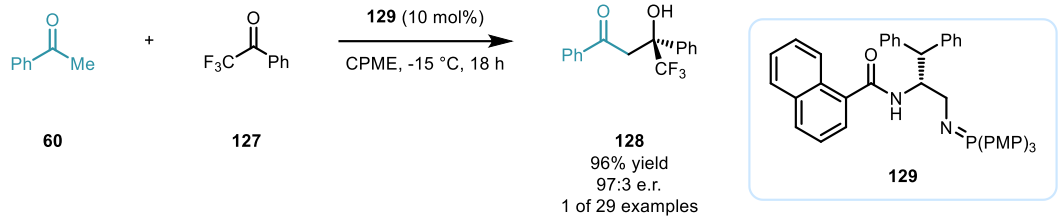
Catalyst **116** was employed by Johnson and coworkers in an enantioselective three-component Pudovik addition-phospha-Brook rearrangement cascade (**Scheme 26a**).[72] BIMP catalysts were found sufficiently Brønsted basic to deprotonate the dimethyl phosphite nucleophile **119** for the initial Pudovik 1,2-addition to benzylidene pyruvates **118** at cryogenic temperatures to minimise undesired side reactions, unlike *Cinchona* alkaloid-derived catalysts. A subsequent phospha-Brook rearrangement results in the formation of an enolate which is trapped by aromatic aldehyde **120**, yielding the product **121** in 81% yield, 18:1 dr and 94:6 e.r. Johnson and coworkers continued their investigations into BIMP-catalysed reactivity, utilising phenyl-substituted catalyst **126** in Michael additions of nitroalkanes **92**[73] and alkyl thiols **123**[74] to enone diesters **122** (**Scheme 26b**). These reactions were successfully scaled-up to gram scale and the addition products **124** and **125** were derivatised to five-membered lactams and lactones respectively.



Scheme 26. Johnson's BIMP-catalysed 1,2- and 1,4-additions (2016-2018).

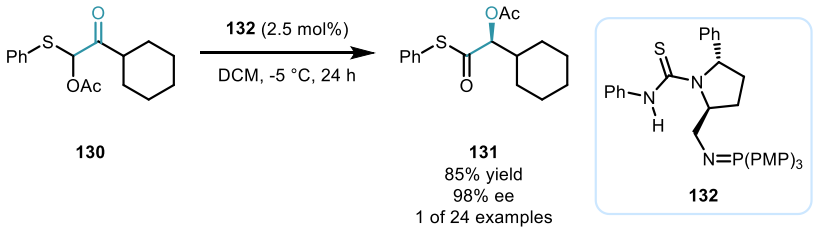
A BIMP-catalysed enantioselective aldol addition of unreactive aryl ketones **60** to α-fluorinated ketones **127** was developed (**Scheme 27**).[75] Aliphatic ketones have been used extensively in proline-catalysed aldol reactions (**Schemes 7** and **11a**) due to the ease of formation of a reactive chiral enamine intermediate. However, aryl ketones are much less reactive in enamine catalysis and are also challenging to activate directly by deprotonation at their α-position due to their low acidity, with a high pK_a of approximately 24.7 in DMSO (**Figure 3**). Prior to this work, Takemoto's tertiary amine catalyst **57** (**Scheme 12**) was utilised in similar aldol reactions involving aryl ketones. However, long reaction times of up to 144 hours were necessary to achieve sufficient conversion to product.[76] With BIMP catalyst **129** possessing an amide H-bond donor group and a benzhydryl substituent, the addition product **128** was obtained in 96% yield and 97:3 e.r. after only 18 hours at -15 °C. The pK_{BH+} of catalyst **129** was

measured as 25.5 in MeCN, which suggests that the strong Brønsted basicity of **129** accounts for the >1400-fold rate enhancement of the BIMP-catalysed reaction as compared to the reaction catalysed by tertiary amine catalyst **57**. As no reaction was observed when catalyst **129** was *N*-methylated, both the amide H-bond donor and the iminophosphorane in **129** are likely involved in substrate activation. Catalyst **129** was recovered in 96% yield after a successful gram-scale reaction simply by precipitation upon addition of water to the crude reaction mixture, and the recovered catalyst **129** was utilised in further reactions with no erosion in yield or enantioselectivity.



Scheme 27. Dixon's BIMP-catalysed aldol addition of aryl ketones **60** to α-fluorinated ketones **127** (2020).

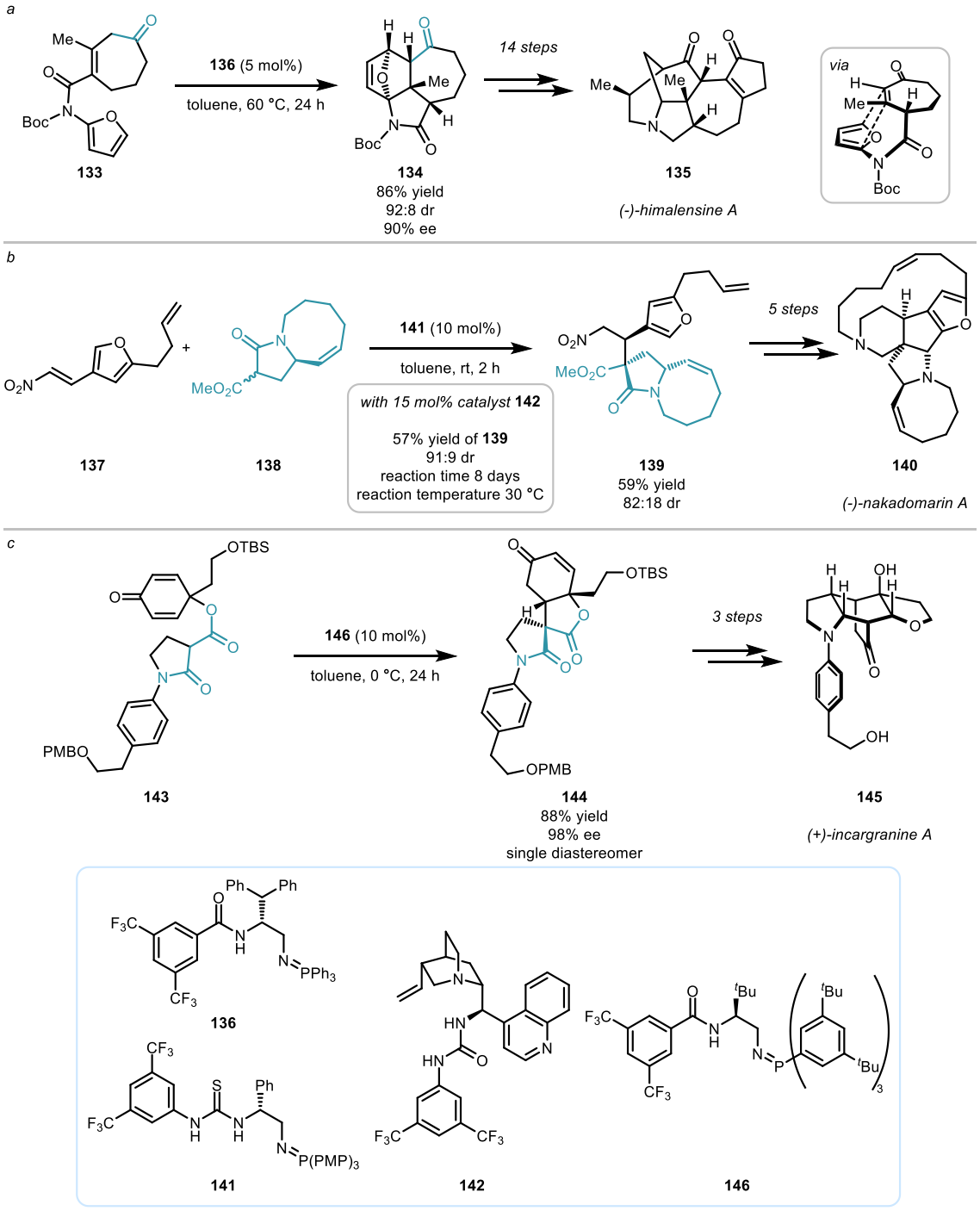
An L-proline-derived cyclic BIMP catalyst **132** was developed recently by Kobayashi, Vo-Thanh and coworkers for an enantioselective acyl-transfer/protonation of α-acyloxy-β-ketosulfides **130** (**Scheme 28**).[77] This intramolecular reaction yielded the acylated product **131** in 85% yield and 98% ee with a catalyst loading of 2.5 mol%. The compact cyclic catalyst structure is thought to increase asymmetric induction by bringing the nucleophilic and electrophilic components close to the chiral centre.



Scheme 28. Kobayashi and Vo-Thanh's BIMP-catalysed acyl-transfer/protonation of α-acyloxy-β-ketosulfides **130** (2024).

BIMP catalysts **136**, **141**, **146** have also been employed in key steps in the total syntheses of (-)-himalensine A **135**,[78] (-)-nakadomarin A **140**[79] and (+)-incargranine A **145** (**Scheme 29**).[80] In the synthesis of **135**, *Cinchona* alkaloid-derived catalysts were initially tried in the key enantio- and diastereoselective prototropic shift/intramolecular amidofuran Diels–Alder (IMDAF) cascade.

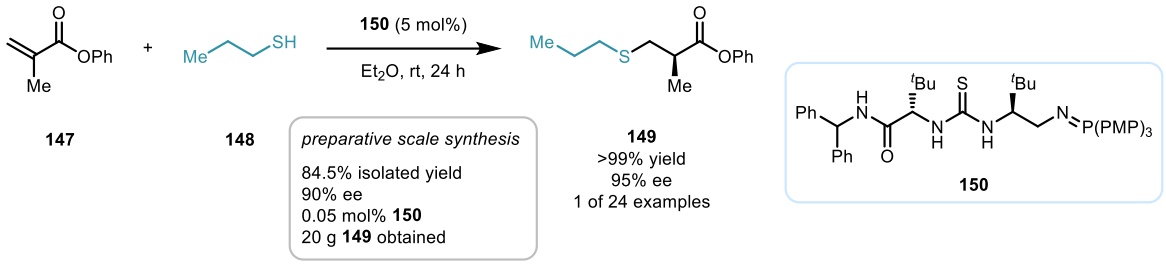
However, long reaction times of 7 to 11 days were required at 20 mol% catalyst loading. With only 5 mol% of BIMP catalyst **136**, the cyclised product **134** was formed in 86% yield, 92:8 dr and 90% ee on a multigram scale after 24 hours (**Scheme 29a**). Catalyst **136** contains an amide H-bond donor group and was formed from its azide and phosphine components in the reaction mixture containing substrate **133** instead of in a separate preformation step.[78]



Scheme 29. BIMP-catalysed key steps in various total syntheses (2017-2024).

BIMP catalyst **141** also proved superior to *Cinchona* alkaloid-derived catalyst **142** in a diastereoselective Michael addition of bicyclic malonamate ester **138** to furan nitroolefin **137**, which is the key step in the synthesis of (-)-nakadomarin A **140**. The reaction time was significantly reduced from eight days to two hours (**Scheme 29b**).[79] As for the synthesis of (+)-incargranine A **145**, another BIMP catalyst **146** containing an amide H-bond donor group was employed in a key step involving an intramolecular Michael addition of a tethered malonamate ester pronucleophile to a 2,5-cyclohexadienone **143**. The tricyclic product **144** was obtained in 88% yield and 98% ee as a single diastereomer (**Scheme 29c**).[80]

1.6.3 Reactivity of 2nd Generation BIMP Catalysts

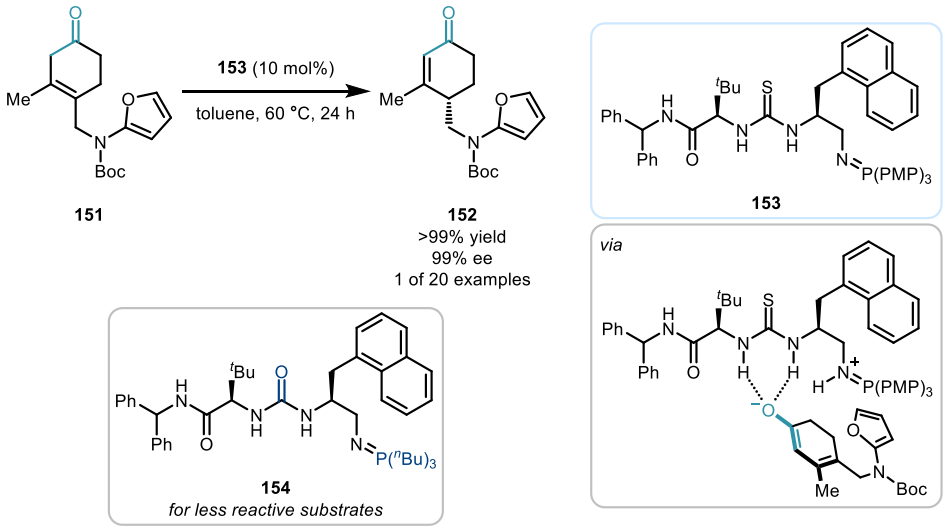


Scheme 30. Dixon's BIMP-catalysed sulfa-Michael addition to α-substituted acrylate esters **147** (2015).

The above 1st generation BIMP catalysts were tried in a sulfa-Michael addition of alkyl thiols **148** to unactivated α-substituted acrylate esters **147**.[81] However, after attempting the reaction with BIMP catalysts encompassing many combinations of H-bond donor groups and substituents at the P atom of the iminophosphorane as well as at the distal end of the catalyst, only moderate enantioselectivities of up to 72% ee were obtained. Taking inspiration from Jacobsen's catalyst design (**Scheme 10, 13**), an additional stereogenic centre and an amide H-bond donor group were incorporated into the BIMP catalyst structure. After a few iterations, 2nd generation BIMP catalyst **150** successfully promoted the challenging reaction between **147** and **148** to form the product **149** in an impressive >99% yield and 95% ee (**Scheme 30**). The authors postulated that the additional stereocentre facilitated the induction of enantioselectivity in the protonation of the transient enolate intermediate upon formation of the C–S bond. This reaction was scaled-up to a 100 mmol scale with the catalyst loading reduced to only 0.05 mol% or ~40 mg, with almost full conversion to **149** and 90% ee achieved in 24 hours. The scope of the sulfa-Michael addition was later expanded to β-substituted acrylate esters[82] and alkenyl benzimidazoles[83] using similar 2nd generation BIMP catalysts, while a 1st generation BIMP catalyst

promoted a Michael addition of nitroalkanes to β-substituted acrylate esters.[84] Catalyst **150** also enabled an intramolecular oxa-Michael reaction to β-substituted acrylate esters and acrylamides, yielding medicinally-relevant tetrahydrofurans and tetrahydropyrans.[85]

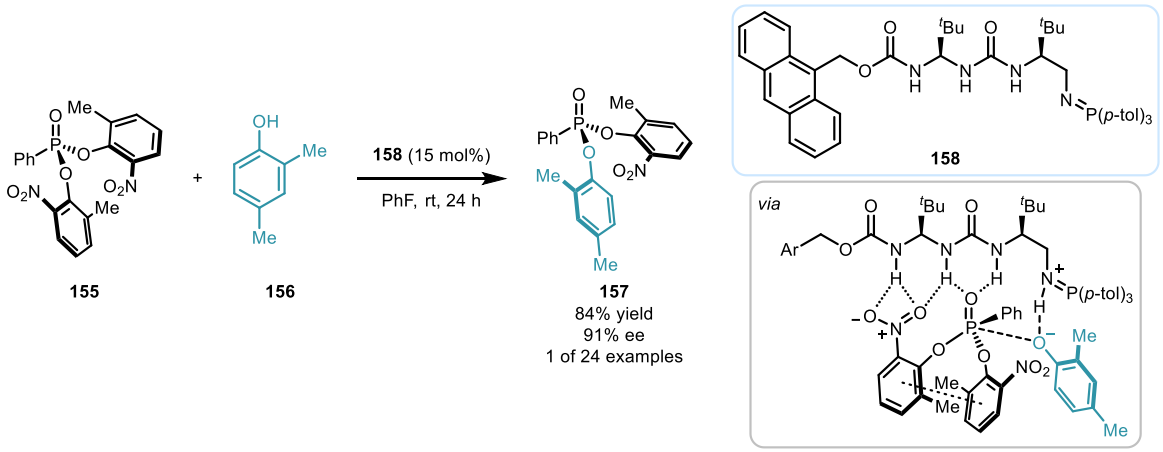
A similar 2nd generation BIMP catalyst **153** was employed in an enantioselective 1,3-prototropic shift in substituted β,γ-unsaturated cyclohexenones **151** (**Scheme 31**).[86] BIMP catalysts are thought to be sufficiently Brønsted basic to deprotonate the weakly acidic ketone α-proton, resulting in the formation of an extended enolate. Enantioselective reprotonation at the substituted γ-position would then lead to the formation of enantioenriched conjugated cyclohexenones **152**. With catalyst **153**, product **152** was formed in an impressive >99% yield and 99% ee, which was a significant improvement on the results attained using 1st generation BIMP catalysts. Replacing the substituents on the P atom of the iminophosphorane with *n*-butyl groups, and the thiourea H-bond donor group with a urea in catalyst **154** improved reactivity in less reactive substrates, showcasing the late-stage tunability of BIMP catalysts. Computational analysis revealed that both the H atoms in the thiourea H-bond donor group in **153** were involved in H-bonding to the carbonyl oxygen, activating the substrate for α-proton abstraction and controlling the enantiofacial selectivity in the γ-protonation step.



Scheme 31. Dixon's BIMP-catalysed prototropic shift (2020).

2nd generation BIMP catalyst **158** containing a ureidopeptide skeleton was utilised in an enantioselective desymmetrisation of prochiral phosphonate esters **155** (**Scheme 32**) with *ortho*-substituted phenol nucleophiles **156**.[87] This reaction involves an enantioselective nucleophilic substitution at a P(V) centre,

with the choice of leaving group having a significant influence on the reactivity and stereoselectivity of the reaction. 2-Methyl-6-nitrophenol was found to be a suitable leaving group, permitting catalyst turnover while cooperating with catalyst **158** to induce high levels of enantioselectivity in the enantioenriched P(V) products **157**. The use of the ureidopeptide H-bond motif in catalyst **158** was inspired by the tertiary amine catalyst design of Palomo and coworkers,[88] and the basicity of **158** was improved with the incorporation of *p*-tolyl substituents on the P atom of the iminophosphorane instead of phenyl substituents. These products can undergo a subsequent enantiospecific nucleophilic substitution with *O*-, *N*- and *S*-based nucleophiles to displace the remaining leaving group, leading to the formation of biologically relevant P(V) compounds. Computational studies suggest that several non-covalent interactions including H-bonds, π-stacking between the nitrophenol leaving groups and CH–π interactions were instrumental in stabilising the transition state leading to the formation of the preferred enantiomer of **157**. This desymmetrisation reaction was later improved with the use of thiazolidinone leaving groups to accommodate wider ranges of phenol nucleophiles **156**, substituents on the P(V) electrophile **155** and nucleophiles in the subsequent enantiospecific substitution step.[89]

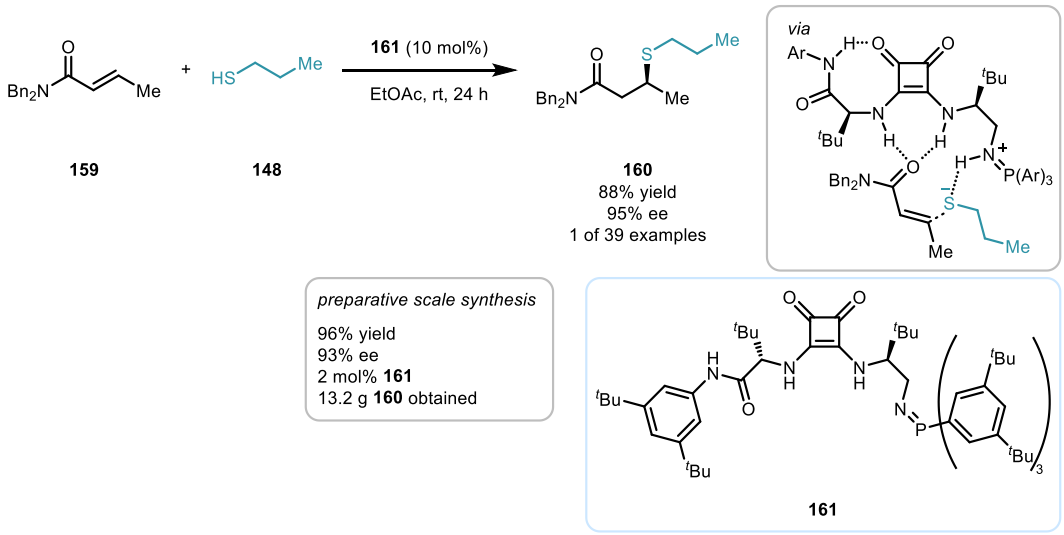


Scheme 32. Dixon's BIMP-catalysed desymmetrisation of phosphonate esters **155** (2023).

1.6.4 Reactivity of 3rd Generation BIMP Catalysts

The above 1st and 2nd generation BIMP catalysts were tried in a sulfa-Michael addition of alkyl thiols **148** to very weakly electrophilic unactivated α,β-unsaturated amides **159** (**Scheme 33**). Good yields of β-thioamide product **160** were attained, but with enantioselectivities of up to 55% with BIMP catalysts containing *p*-methoxyphenyl substituents on the P atom of the iminophosphorane. Inspired by the work

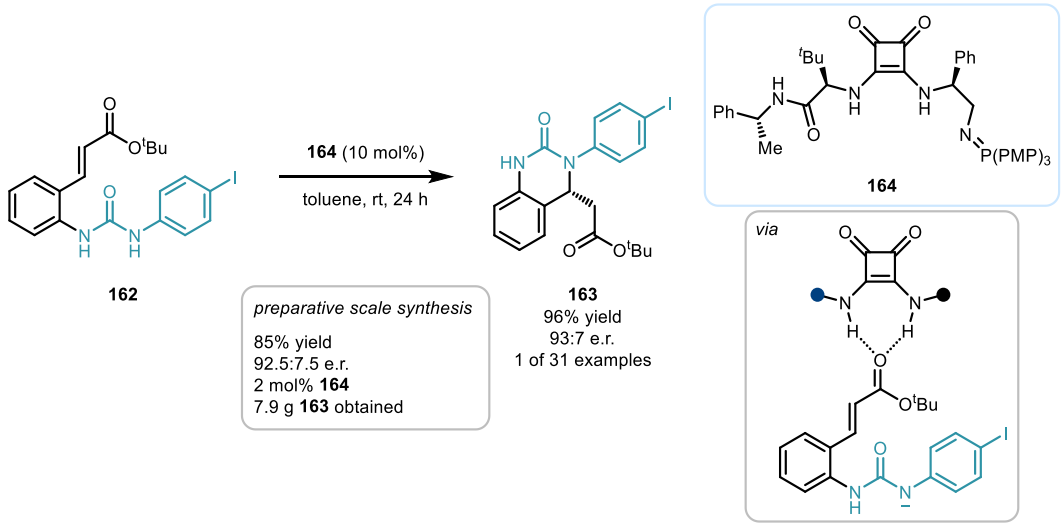
of Rawal and coworkers (**Scheme 15**), a squaramide H-bond donor group was incorporated into the BIMP catalyst scaffold, giving a boost in enantioselectivity. The authors postulated that the high Brønsted acidity of the squaramide moiety would enhance H-bonding between the catalyst and substrates, leading to better stabilisation of the transition state. The enantioselectivity was further enhanced by adding an additional stereocentre onto the distal side of the squaramide moiety and incorporating sterically bulky 3,5-di-*tert*-butylphenyl substituents on the P atom of the iminophosphorane. Product **160** was obtained in 88% yield and 95% ee with the optimal catalyst **161**. Computational calculations revealed that intramolecular H-bonding between one of the squaramide O atoms and the amide H atom in catalyst **161** fixes the conformational freedom in the catalyst. This creates a three-dimensional pocket for substrates **159** and **148** to form multiple H-bonding, CH−π and π−π stabilising interactions with catalyst **161** in the favoured transition state structure. This reaction was successfully scaled up to a 40 mmol scale with a reduced catalyst loading of 2 mol%, yielding 13.2 g and 96% yield of product **160** in 93% ee.[90]



Scheme 33. Dixon's BIMP-catalysed sulfa-Michael addition to α,β-unsaturated amides **159** (2022).

A similar BIMP catalyst **164** containing three stereogenic centres was employed in a challenging intramolecular aza-Michael addition of a high pK_a urea to a weakly electrophilic tethered β-substituted acrylate ester **162** (**Scheme 34**).[91] 1st and 2nd generation BIMP catalysts were tried in this reaction, where the hydroquinazoline product **163** was obtained in good yields, albeit with low to moderate enantioselectivities. The introduction of a squaramide H-bond donor group and additional stereocentres

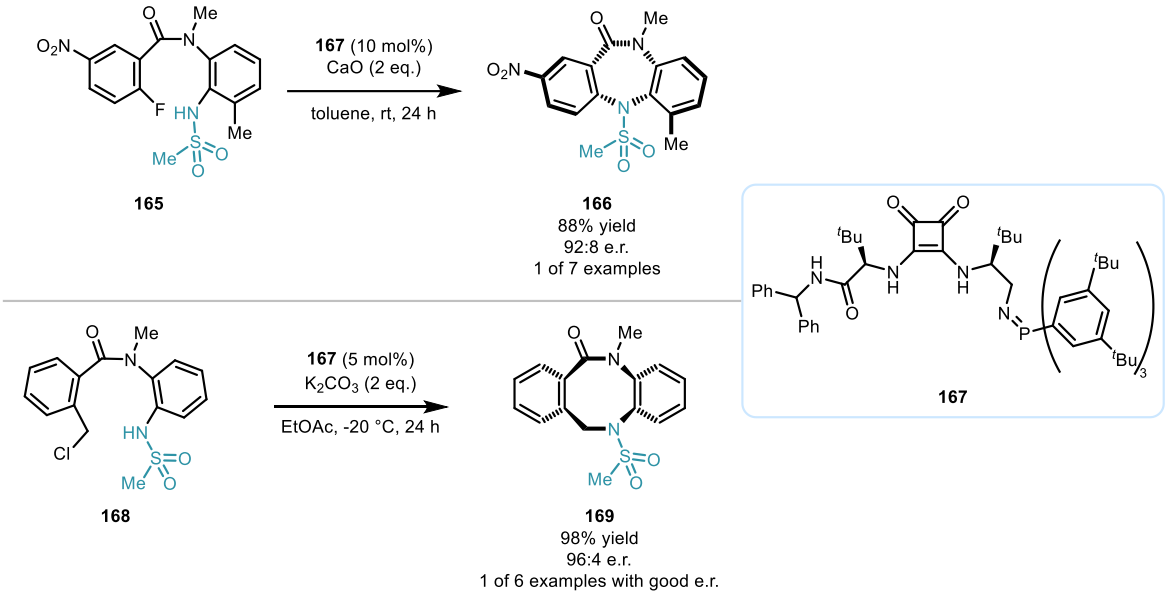
into the BIMP catalyst boosted the enantioselectivity of this reaction, giving rise to the formation of **163** in 96% yield and 93:7 e.r. with catalyst **164**. The authors postulated that the improved stereoselectivity could be attributed to the increased Brønsted acidity of the squaramide moiety enhancing H-bonding between catalyst **164** and the ester carbonyl oxygen in **162** in a way similar to the above reaction (**Scheme 33**), or to the different bond angles created at the squaramide. This was substantiated by computational studies, which revealed that the conformation of the squaramide in catalyst **164** creates a pocket-like binding site which facilitates multiple stabilising CH–π, CO–π and H-bonding interactions between substrate **162** and catalyst **164** with minimal steric repulsion in the favoured transition state structure. This reaction was successfully scaled up to a 20 mmol scale with a reduced catalyst loading of 2 mol%, yielding 7.9 g and 85% yield of product **163** in 92.5:7.5 e.r.



Scheme 34. Dixon's BIMP-catalysed intramolecular aza-Michael addition to α,β-unsaturated esters **162** (2021).

Very recently, Miller and coworkers reported 3rd generation BIMP-catalysed enantioselective intramolecular S_NAr and S_N2 reactions to construct inherently chiral seven- and eight-membered rings **166** and **169** respectively (**Scheme 35**).[92] For the formation of seven-membered ring **166** *via* a S_NAr reaction, catalyst **167** containing both an amide and a squaramide H-bond donor was employed, along with calcium oxide, which functions as a weak achiral stoichiometric base to facilitate catalyst turnover. Product **166** was obtained in 88% yield and 92:8 e.r. after 24 hours at room temperature. As for the formation of 8-membered ring **169** through a S_N2 reaction, 5 mol% of catalyst **167** and 2 eq. of weak achiral base K_2CO_3 were employed, yielding **169** in 98% yield and 96:4 e.r. after 24 hours at -20 °C. In

both reactions, computational studies revealed H-bonding interactions between the squaramide H-bond donor group of catalyst **167** and the sulfonamide in achiral substrates **165** and **168** in the transition structure. The presence of intramolecular H-bonding between the amide and squaramide in catalyst **167** in a similar way to catalyst **161** (see **Scheme 33**) was also revealed. However, van der Waals dispersion interactions were shown to contribute more significantly to the induction of enantioselectivity in both reactions, explaining the high enantioselectivities observed with bulky 3,5-di-*tert*-butylphenyl substituents on the P atom of the iminophosphorane in **167**.



Scheme 35. Miller's BIMP-catalysed intramolecular cyclisation to form chiral seven- and eight-membered rings **166** and **169** (2024).

1.7 Thesis Aims

There remains much untapped potential in the utility of BIMP catalysts for reactions employing unreactive pronucleophiles with very high pK_a. Noting that the maximum pK_{BH+} value of BIMP catalysts has been reported to be around 25.0 in MeCN,[53a, 75] the aim of this thesis was to explore their potential with pronucleophiles with a typical pK_a value above this value, with substrate and catalyst modifications where necessary.

We began our exploration with amide pronucleophiles, where deprotonation results in the active enolate nucleophiles. Their pK_a values range from around 26.6 to 35 in DMSO (**Figure 3**). There had not been

any previous reports of a completely metal-free enantioselective amide enolisation and subsequent reaction in the literature, although previous investigations in the Dixon group had shown that the BIMP catalyst system might allow such reactivity. 2,5-Cyclohexadienones were chosen as a suitably reactive intramolecular electrophile for this proposed reaction. The findings are presented in **Chapter 2**.

We recognised the limitations of the above reaction and thus sought to explore the potential of BIMP catalysts with amide pronucleophiles with different electrophiles, as well as with a much more unreactive α-alkyl amide. The findings are presented in **Chapter 3.**

Chapter 4 will report detailed experimental procedures for all work carried out in the above projects and spectroscopic data for all synthesised compounds.

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Chapter 2: Enantioselective Desymmetrisation of Amide-Tethered Cyclohexadienones

2.1 Chapter Overview

This chapter describes the development of a BIMP-catalysed enolisation of 2-arylacetyl and α-alkenyl amides for an enantioselective and diastereoselective intramolecular desymmetrisation/Michael addition to tethered 2,5-cyclohexadienones. This transformation represents the first reported metal-free stereoselective reaction involving the enolisation of unactivated amide pronucleophiles by α-C–H deprotonation, with previous methods requiring transition metals, alkali metal superbases and/or activating groups. The method discussed in this chapter employs a 1st generation BIMP organosuperbase catalyst and generates the enantioenriched 3D-fused oxindole derivative products in up to 99% yield, up to >20:1 dr and up to 99:1 e.r. using a simple and robust protocol.

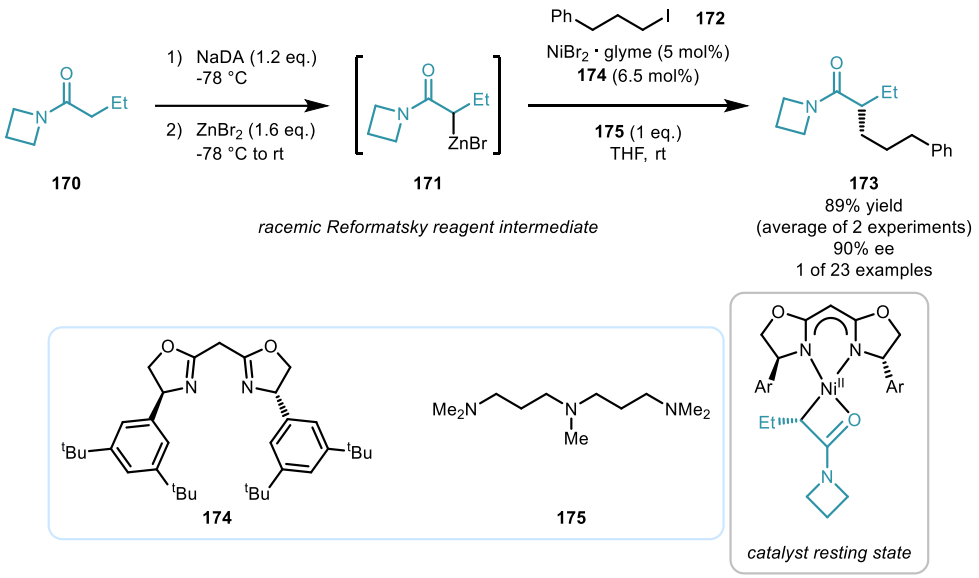
2.2 Introduction

2.2.1 Amide Enolisation for Enantioselective Reactivity

Carboxamides are ubiquitous motifs in naturally occurring biological molecules and synthesised drug molecules. Within the amide functional group, the carbonyl group is conjugated to the lone pair of electrons on the nitrogen atom. Thus, the carbonyl group is less electron-withdrawing as compared to aldehyde or ketone carbonyl groups, providing less resonance stabilisation in the enolate formed *via* α-C–H deprotonation. The α-protons of amides (pK_a in DMSO ≈ 26.6 for *N*,*N*-dimethyl-2-phenylacetamide, **Figure 3**)[1] have been shown experimentally to be significantly less acidic than those of their corresponding aldehydes or ketones (pK_a in DMSO ≈ 19.8 for 2-phenylacetone),[2] highlighting the challenging nature of amide enolisation. Accordingly, deprotonation of amides at the α-position for downstream reactivity with electrophiles would typically involve the use of stoichiometric amounts of strong metal-containing non-nucleophilic bases such as lithium diisopropylamide (LDA) or potassium bis(trimethylsilyl)amide (KHMDS).[3] A catalytic enolisation strategy for the enantioselective installation

of an electrophile at the α-position of an amide would be a valuable atom-economical tool in the synthesis of many chiral compounds.

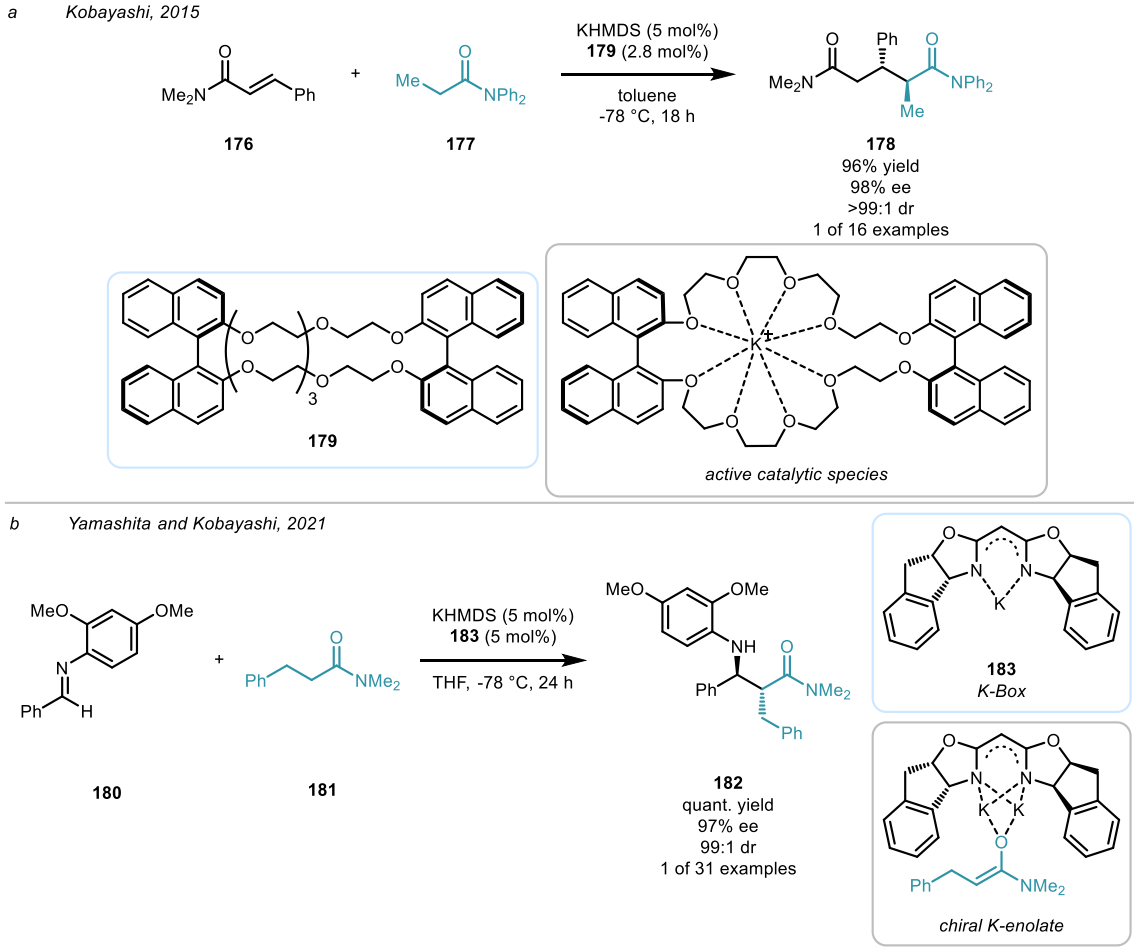
To this end, a few transition metal catalysed methods have been developed using both activated and unactivated "simple" carboxamide substrates.[4-6] Among these methods is a recent study by Fu and coworkers, where a chiral nickel catalyst made by reacting $NiBr_2$·glyme and chiral bisoxazoline ligand **174** is employed in an enantioselective α-alkylation of simple amides **170** with alkyl iodide electrophiles **172** (**Scheme 36**).[7] This reaction involves a two-step procedure in which a racemic Reformatsky reagent intermediate **171** is pre-formed using stoichiometric quantities of sodium diisopropylamide (NaDA) and zinc bromide. The α-alkylated products **173** were obtained in excellent enantioselectivities of mostly 90% ee or above. The catalyst resting state was characterised by X-ray crystallography and shows the central Ni atom bound to both the carbonyl oxygen and the α-carbon, with efficient stereochemical induction by the bulky aromatic groups on ligand **174**.



Scheme 36. Fu's nickel-catalysed α-alkylation of amides **170** (2022).

A small number of reported amide enolisation reactions require the simultaneous use of an inorganic base and a chiral organocatalyst or ligand. In 2015, Kobayashi and coworkers disclosed the first catalytic enantioselective Michael addition of unactivated amides **177** to α,β-unsaturated amides **176**, utilising a catalyst system composed of KHMDS and macrocyclic chiral crown ether ligand **179** (**Scheme 37a**).[8] Even though this is a challenging reaction involving a weakly acidic pronucleophile (pK_a ~ 35 in

DMSO)[1] and a very unreactive electrophile, the addition products **178** were obtained in very high yields of at least 89% and excellent stereoselectivities of >99:1 dr and 93-98% ee for all recorded examples. The structure of the catalytically active 1:1 potassium–**179** complex, deduced by X-ray crystallography, consists of ligand **179** enclosing a central potassium cation, forming the active chiral cationic catalyst. This reaction was later performed successfully using a solid superbase K/γ-Al_2O_3 in place of KHMDS, which has potential applications in continuous flow chemistry,[9] while an achiral crown ether 18-crown-6 was employed in an addition reaction of amide **177** to alkene electrophiles.[10]



Scheme 37. (a) Kobayashi's enantioselective Michael addition of amides **177** to α,β-unsaturated amides **176** (2015). (b) Yamashita and Kobayashi's enantioselective Mannich reaction of imines **180** with amides **181** (2021).

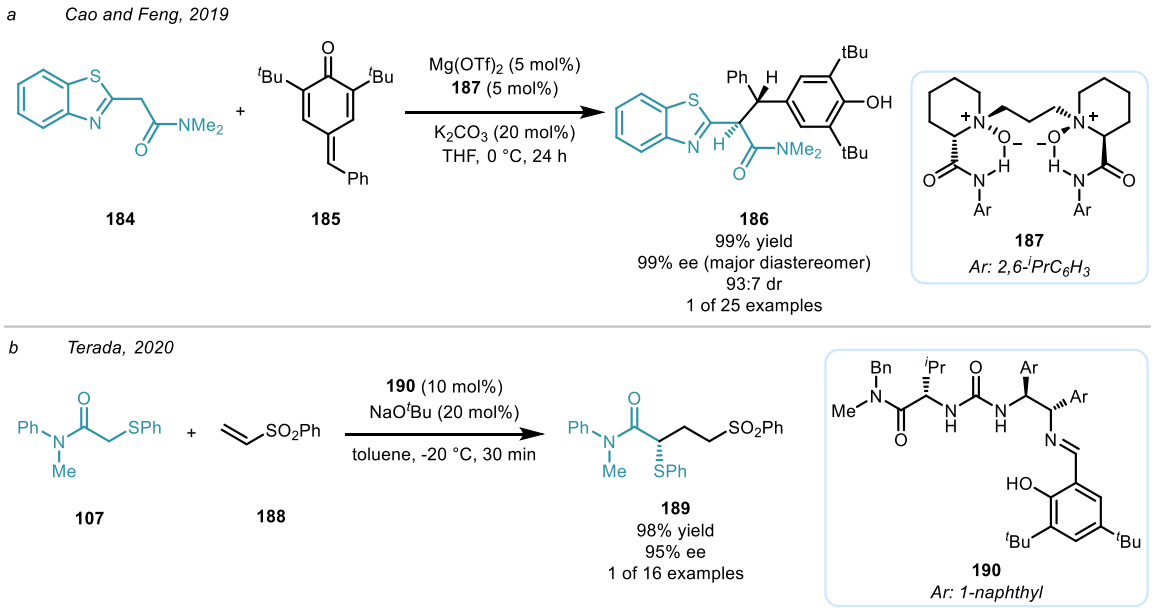
A few years later, Yamashita and Kobayashi revealed a stereoselective Mannich reaction between aldimines **180** and similar simple amides **181** using a catalyst system comprising KHMDS and chiral bis(oxazoline) potassium (K-Box) salt **183** (**Scheme 37b**).[11] Attempting this reaction with chiral crown ether ligands such as **179** gave the addition product **182** in low stereoselectivity, while typical chiral

bis(oxazoline) (Box) ligands gave no reaction. It was found that KHMDS reacted with a Box ligand to give K-Box salt **183**, which was discovered to be a surprisingly effective ligand for the chiral modification of strongly Brønsted basic KHMDS. With the optimised catalyst system, product **182** was obtained in quantitative yield, 97% ee and 99:1 dr. Computational studies revealed that the two K^+ ions were both involved in binding to the O atom of the amide enolate, forming a chiral *K*-enolate.

Other research groups have focused their efforts on the enantioselective α-functionalisation of activated amide substrates. In 2019, Cao and Feng disclosed a stereoselective 1,6-conjugate addition of 2-azaarylacetamide pronucleophiles **184** to *p*-quinone methides **185** (**Scheme 38a**).[12] This reaction is catalysed by a chiral Mg(II)/*N,N*′-dioxide complex created *in situ* from a 1:1 ratio of $Mg(OTf)_2$ and *N,N*′-dioxide ligand **187**, and K_2CO_3 acts as a base to generate the active enolate pronucleophile. Prior to this report, transition metal catalysts were employed in enantioselective Michael additions of pronucleophiles **184** to nitroalkenes[4b] and allylic carbonates.[4c] The authors postulated that both the N atom in the heterocycle and the O atom in the amide enolate coordinate to the Mg(II) centre of the active catalyst, creating a transition state structure where the *Si*-face of the amide enolate selectively reacts with the *Si*-face of the electrophile **185**. The phenol-containing product **186** which contains a *gem*(1,1)-diaryl skeleton and two new contiguous stereocentres was formed in 99% yield, 93:7 dr and 99% ee of the major diastereomer.

Soon afterwards, Terada and coworkers reported an enantioselective Michael addition of weakly activated α-thioacetamides **107** (pK_a ~ 25.9 in DMSO, **Figure 3**) to various unsaturated electrophiles **188** including sulfones, esters, enones as well as *N*-Boc imines (**Scheme 38b**).[13] The catalyst system employed in this reaction consists of sodium *tert*-butoxide (NaO^{t}Bu) and chiral urea **190**, which is deprotonated by the strongly Brønsted basic NaO^{t}Bu at one of the N atoms to form a ureate, which functions as the active anionic Brønsted base catalyst. The authors postulated that the ureate could be a potent chiral superbase catalyst, due to the high estimated pK_a value of a *N*,*N*'-dialkyl urea of about 25 in DMSO[14] as well as its ability to also function as a substrate recognition site. In addition to the urea moiety, catalyst **190** contains a chiral amide moiety, a Schiff base and a phenoxide which function as additional sites for substrate-catalyst interactions to improve stereochemical induction. With catalyst

190, the product **189** was obtained in 98% yield and 95% ee after a reaction time of only 30 minutes. The reaction scope was later expanded to include α-substituted vinyl sulfone and acrylate ester electrophiles,[15] while a similar chiral ureate catalyst was utilised in an enantioselective hydrophosphinylation of 1-alkenylphosphine oxides.[16] Terada and coworkers also disclosed a separate reaction involving the Mannich-type addition of α-thioacetamide **107** to an *N*-Boc imine using a P_3-phosphazene catalyst (**Scheme 23**).[17]



Scheme 38. (a) Cao and Feng's enantioselective 1,6-conjugate addition with 2-azaarylacetamide pronucleophiles **184** (2019). (b) Terada's enantioselective Michael addition with α-thioacetamide pronucleophiles **107** (2020).

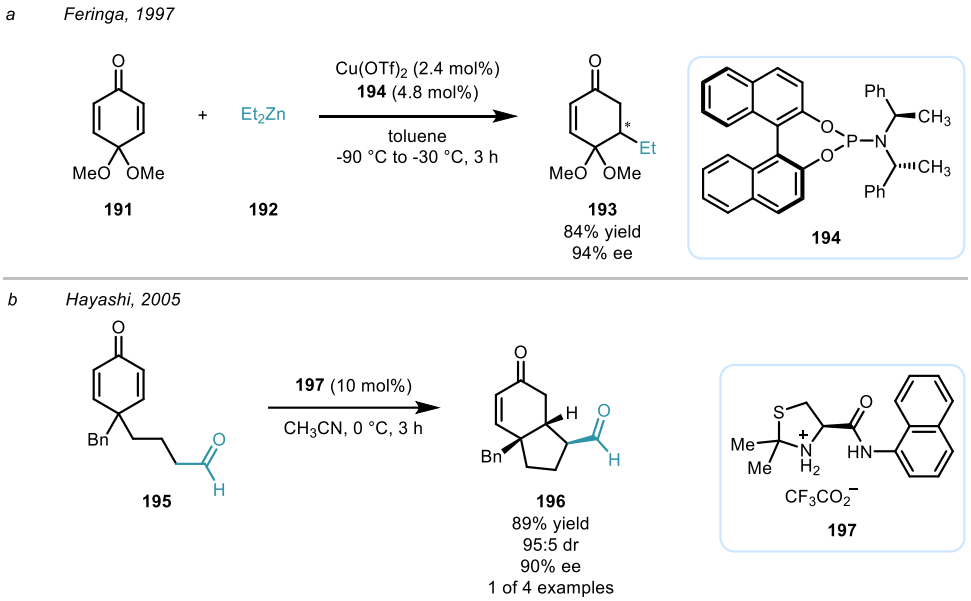
All of the above methods would necessarily involve the formation of a metallic amide enolate as the key nucleophilic species, with no known previous reports involving non-metal bases.

2.2.2 Enantioselective Michael Additions for Cyclohexadienone Desymmetrisations

Phenol-derived 2,5-cyclohexadienones are versatile compounds which can act as capable Michael acceptors, in addition to being employed in enantioselective Heck[18], enyne cyclisation[19] and Diels-Alder[20] reactions. Several methods have been reported for their stereoselective desymmetrisation, where reaction occurs selectively on one face of the cyclohexadienone with one of the two enones. These methods generate privileged scaffolds containing multiple stereocentres that are used as key

intermediates in the synthesis of many natural products. The products of such desymmetrisation reactions also retain an enone, which is useful for further functionalisation.[21]

The first example of an enantioselective Michael addition involving symmetrical 2,5-cyclohexadienone electrophiles was reported in 1997 by Feringa and coworkers. In this report, a catalyst consisting of a Cu centre with chiral binaphthol-derived phosphoramidite ligands **194** promoted the Michael addition of diethylzinc **192** to 4,4-dimethoxycyclohexa-2,5-dien-1-one **191** (**Scheme 39a**).[22] For this single example, the alkylated product **193** was formed in 84% yield and 94% ee after three hours at cryogenic temperatures to prevent aromatisation. Soon afterwards, the scope of this reaction was expanded to 10 examples which include non-identical substituents at the 4-position, as well as the use of different dialkylzinc reagents.[23] A Rh catalyst, [RhCl((*R*)-BINAP)]$_2$, was subsequently employed in a similar transformation using an arylzinc reagent as the nucleophilic species.[24]

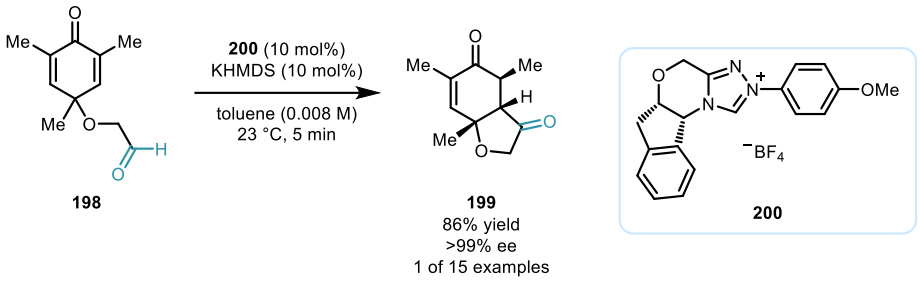


Scheme 39. (a) Feringa's Cu-catalysed Michael addition of diethylzinc **192** to cyclohexadienone **191** (1997). (b) Hayashi's intramolecular desymmetrisation of aldehyde-tethered cyclohexadienones **195** (2005).

The first intramolecular organocatalytic enantioselective desymmetrisation of 2,5-cyclohexadienones was disclosed in 2005 by Hayashi and coworkers (**Scheme 39b**).[25] This report describes a Michael addition of aldehydes to tethered cyclohexadienones **195** catalysed by cysteine derivative **197**. With catalyst **197** facilitating the formation of a chiral enamine from aldehyde **195**, the addition product **196**

containing three new contiguous stereocentres was obtained in 89% yield, 95:5 dr and 90% ee and only with a *cis*-fused configuration in the bicyclic system. Proline-derived catalysts were subsequently used in the enamine-catalysed desymmetrisation of aldehyde-tethered cyclohexadienones.[26]

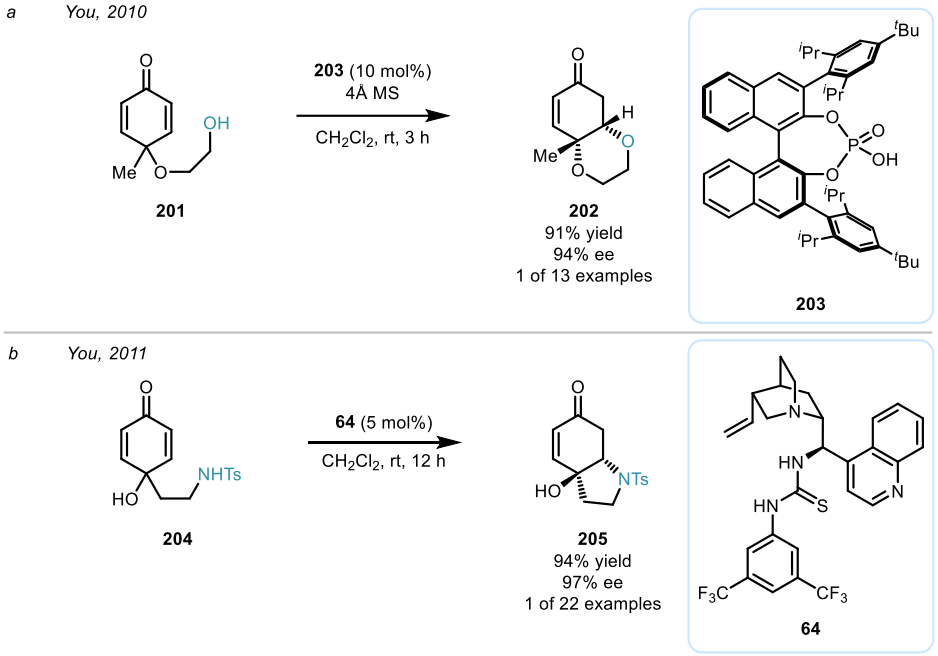
Shortly afterwards, Rovis disclosed an intramolecular Stetter reaction leading to the desymmetrisation of aldehyde-tethered cyclohexadienones **198** catalysed by aminoindanol-derived triazolium salt **200** (**Scheme 40**).[27] The hydrobenzofuranone product **199** with three contiguous stereocentres was obtained in 86% yield as a single enantiomer and diastereomer after only five minutes, with a broad substrate scope including cyclohexadienones substituted in their 2- and 6-positions, as well as their 3- and 5-positions. Dilute conditions were optimal for this reaction, which was conducted in 0.008 M of toluene. The scope of this reaction was later expanded to bicyclic and spirocyclic substrates, leading to tricyclic products.[28]



Scheme 40. Rovis' enantioselective Stetter reaction to tethered cyclohexadienones **198** (2006).

In 2010, You and coworkers reported a desymmetrisation of alcohol-tethered cyclohexadienones **201** using chiral phosphoric acid catalyst **203** (**Scheme 41a**).[29] This intramolecular oxa-Michael addition yielded the *cis*-fused 1,4-dioxane derivative **202** in 91% yield and 94% ee, and this method was applied to the total synthesis of the natural products cleroindicin C, D and F. It is believed that catalyst **203** functions not only as a Brønsted acid but also as a H-bond donor to the carbonyl group in **201** and a H-bond acceptor to the hydroxyl group in **201**, with these H-bonds enabling both reactivity and the induction of enantioselectivity in product **202**. The desymmetrisation of cyclohexadienone **201** by iminium catalysis was later reported, employing a chiral primary amine salt.[30] Another moderately enantioselective intramolecular oxa-Michael addition to a tethered cyclohexadienone, catalysed by *Cinchona* alkaloid derivative **89**, was reported as a key step in a formal synthesis of (±)-morphine.[31]

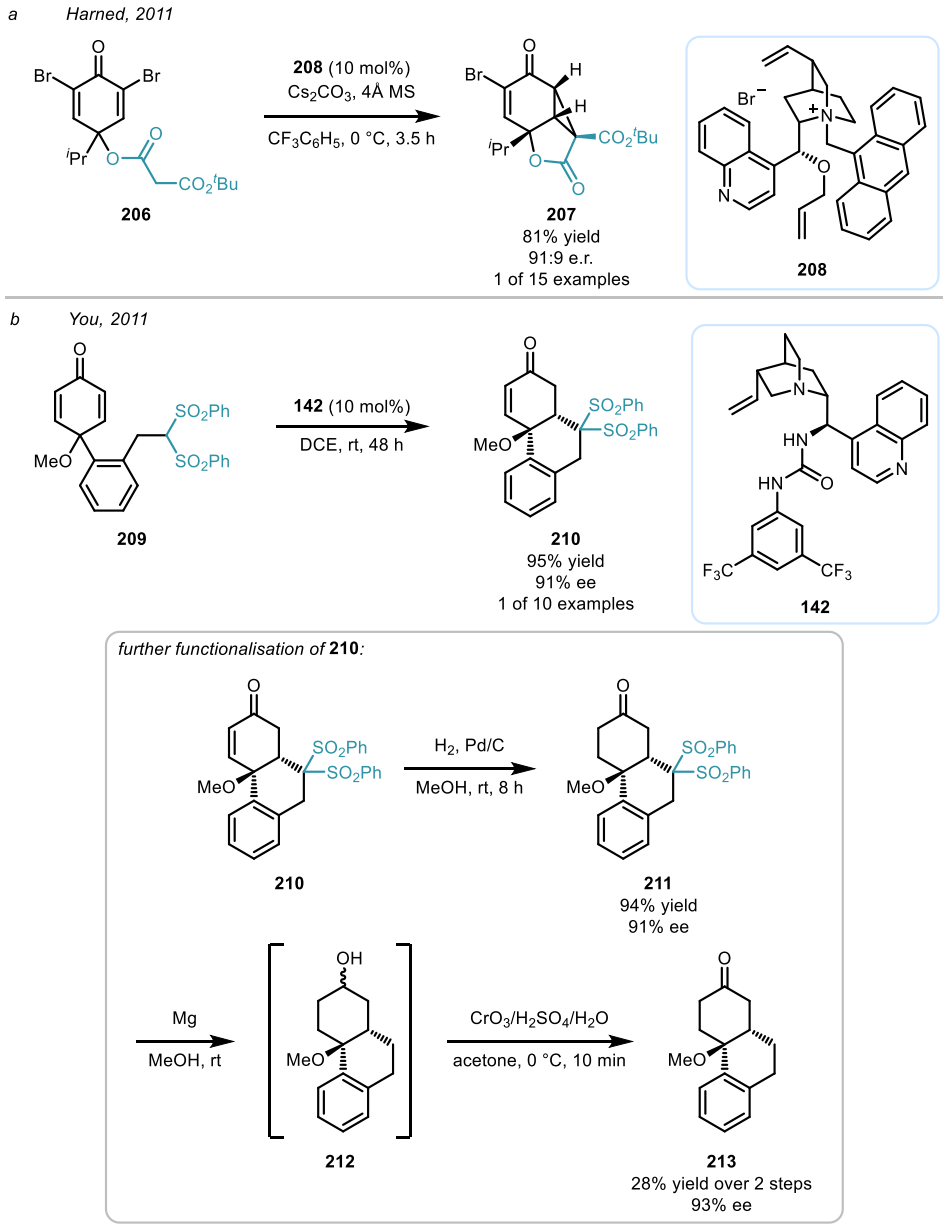
In a subsequent report by You and coworkers, *Cinchona* alkaloid derivative **64** (discussed in detail in **1.4.2**) was employed in a Brønsted base/H-bond donor catalysed desymmetrisation of tosylamide-tethered cyclohexadienones **204** (**Scheme 41b**).[32] This intramolecular aza-Michael addition yielded the *cis*-fused pyrrolidine product **205** in 94% yield and 97% ee, and this methodology was applied to the total synthesis of the natural product (-)-Mesembrine. The thiourea H-bond donor was found to be essential for both reactivity and enantioselectivity, and a sufficiently acidic N-H was required in substrate **204** for deprotonation by tertiary amine catalyst **64**.



Scheme 41. (a) You's chiral phosphoric acid catalysed oxa-Michael addition (2010). (b) You's *Cinchona* alkaloid derivative catalysed aza-Michael addition (2011).

Apart from the heteroatom-centred pronucleophiles discussed above, carbon-centred pronucleophiles were also employed in intramolecular enantioselective cyclohexadienone desymmetrisation/Michael addition reactions. Harned and coworkers reported a Michael addition of activated malonate pronucleophiles to tethered cyclohexadienones **206** using a *Cinchona* alkaloid-derived phase-transfer catalyst **208** (**Scheme 42a**).[33] With Cs_2CO_3 used as a base to deprotonate the malonate pronucleophile, an enolate can form on the carbonyl oxygen of either one of the two ester groups present in **206**. Ionic interactions can form rapidly between this enolate and the quaternary ammonium salt in **208**, allowing the induction of stereoselectivity in the subsequent Michael addition step. This reaction yielded the *cis*-

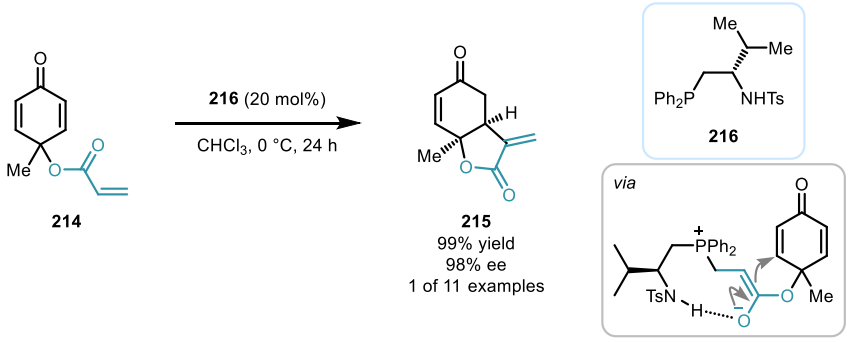
fused tricyclic lactone **207** in 81% yield and 91:9 e.r. as a single diastereomer, and the use of a 2,6-dibromocyclohexadienone in **206** resulted in cyclopropane formation in **207**, along with the desired Michael addition. The isopropyl group at the 4-position of the cyclohexadienone in **206** provided some steric bulk which helped to uplift the enantioselectivity of product **207** formed.



Scheme 42. (a) Harned's Michael addition catalysed by a *Cinchona* alkaloid-derived phase-transfer catalyst (2011). (b) You's *Cinchona* alkaloid derivative catalysed Michael addition (2011).

Shortly afterwards, You and coworkers disclosed a complementary Michael addition of activated bisphenylsulfonyl methylene pronucleophiles to tethered cyclohexadienones **209** catalysed by *Cinchona*

alkaloid-derived urea **142** (**Scheme 42b**).[34] The product **210** was formed in 95% yield and 91% ee, and the double H-bond donation from the urea in catalyst **142** was shown to be essential in the induction of stereoselectivity in product **210**. **210** was further functionalised, initially through a hydrogenation of the remaining C=C double bond. The phenylsulfonyl activating groups were then removed from the hydrogenated product **211** by reducing it with activated Mg in methanol, followed by Jones oxidation to alcohol **212** to form the ketone product **213**. No loss in enantioselectivity was observed throughout this sequence of reactions.

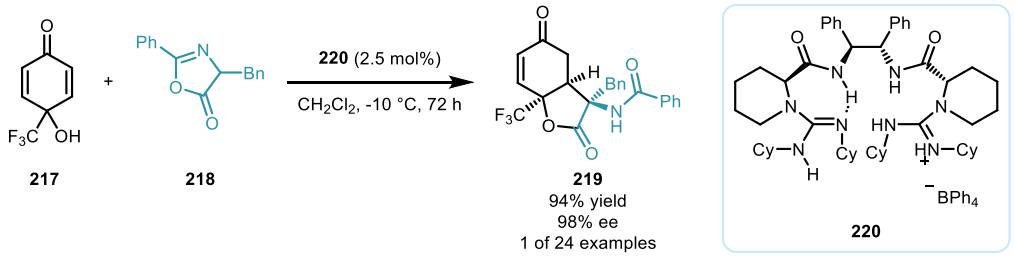


Scheme 43. Sasai's enantioselective intramolecular Rauhut-Currier reaction (2012).

Sasai and coworkers disclosed an enantioselective intramolecular Rauhut-Currier reaction of cyclohexadienones **214** tethered to acrylate esters (**Scheme 43**).[35] This reaction was catalysed by acid-base organocatalyst **216** containing a Brønsted acidic tosylamide group and a Lewis basic diphenylphosphine group. With catalyst **216,** the *cis*-fused α-alkylidene-γ-butyrolactone product **215** was obtained in an impressive 99% yield and 98% ee at a low reaction temperature of 0 °C. The authors postulated that the mechanism of this reaction involves two Michael addition steps. An initial Michael addition of the phosphine to the acrylate ester generates a phosphonium enolate, which is stabilised by H-bond donation from the tosylamide N-H. A subsequent enantioselective Michael addition of this phosphonium enolate to the cyclohexadienone followed by a retro-Michael reaction results in the formation of enantioenriched product **215** and the regeneration of catalyst **216**. The (*S*,*S*)-configuration is favoured in the final Michael addition to avoid steric interactions between the isopropyl group of catalyst **216** and the methyl substituent at the 4-position of the cyclohexadienone. Chiral sulfinamide phosphine catalysts were also shown to be successful in this reaction.[36] Sasai and coworkers subsequently reported domino reactions of allenic[37] and alkynyl[38] esters with alcohol- and sulfonamide-

tethered cyclohexadienones involving a Rauhut-Currier step, and the reaction scope was later expanded to include cyclohexadienones with tethered allenoates,[39] acrylamides,[40] enones[41] and enals.[42]

Liu and coworkers disclosed an intermolecular Michael addition/ lactonisation cascade involving alcohol-tethered cyclohexadienones **217** and azlactones **218** catalysed by chiral bisguanidinium hemisalt **220** (**Scheme 44**).[43] Catalyst **220** functions as a bifunctional Brønsted base/H-bond donor catalyst, where the freebase guanidine subunit deprotonates the azlactone at the α-position of the carbonyl group to form an active enolate nucleophile. Double H-bond donation from the guanidinium salt and neighbouring amide in catalyst **220** to the carbonyl oxygen atom in cyclohexadienone **217** activates the cyclohexadienone electrophile for a Michael addition with the enolate, which occurs enantioselectively *via* a *Re*–*Re* face contact due to steric hindrance from the phenyl and cyclohexyl groups in catalyst **220**. The nucleophilic hydroxyl group in **217** then undergoes a transesterification with the ester carbonyl group in azlactone **218**, forming the *cis*-fused lactone product **219** in 94% yield and 98% ee as a single diastereomer, with 93% to 99% ee for all substrates tested.



Scheme 44. Liu's bisguanidinium hemisalt catalysed Michael addition/ lactonisation cascade (2019).

The pronucleophiles in the above examples are mostly restricted to organometallic compounds, aldehydes, heteroatom-centred pronucleophiles, unsaturated carbonyl compounds for Rauhut-Currier reactions as well as methylene groups adjacent to multiple electron-withdrawing groups to stabilise the negative charge formed by deprotonation. Where Brønsted base organocatalysts were employed, they have been restricted to tertiary amine catalysts, with only one example utilising a more Brønsted basic guanidine. The use of a more Brønsted basic chiral organocatalyst has the potential to expand the scope of metal-free enantioselective cyclohexadienone desymmetrisations involving a Michael addition step to include less acidic, more inert pronucleophiles, and is the focus of this thesis work.

2.2.3 Aim of This Project

We aimed to develop the first entirely metal-free amide enolisation for an enantioselective Michael addition to tethered 2,5-cyclohexadienones, which were identified as potentially suitable intramolecular electrophiles. As amides are weakly acidic and exhibit very high pK_a values in DMSO (**Figure 3**), a competent catalyst for this reaction would have to be sufficiently Brønsted basic to deprotonate the amide at the α-position to form the reactive amide enolate. As the pK_{BH+} of BIMP catalysts has been measured to be approximately 25.0 in MeCN (**Section 1.7**), they have the potential to be effective catalysts for this reaction.

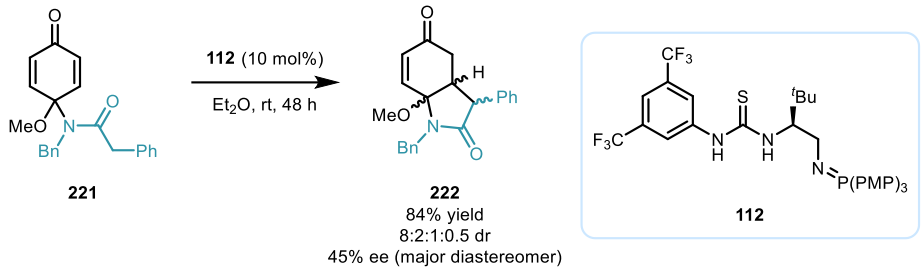
Even so, the deprotonation of the amide by the BIMP catalyst would likely be the rate limiting step in this reaction. As the 5-exo-trig intramolecular Michael addition of the amide enolate to the cyclohexadienone would likely be relatively fast, the cyclohexadienone would effectively function as an intramolecular "trap" for the amide enolate, thereby facilitating the formation of the desired products by exploiting a high local anion concentration.

The bicyclic products of this reaction would contain three contiguous stereogenic centres, like many of the products in **2.2.2**. Furthermore, they would contain a sp^3-rich, structurally defined lactam, which renders them dearomatised enantioenriched oxindoles. As there are numerous occurrences of oxindoles in bioactive natural products, the products of this reaction could be applicable in drug discovery.[44]

2.3 Reaction Discovery and Optimisation

2.3.1 Proof of Concept

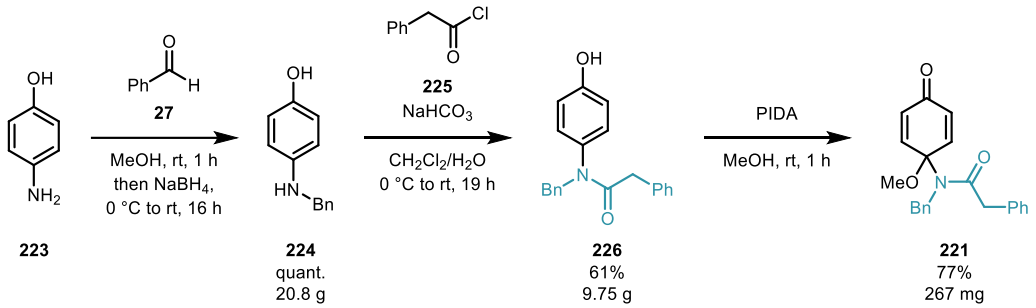
Previous investigations into the reactivity of BIMP catalysts on cyclohexadienones tethered to various carbon-centred pronucleophiles had revealed that they are potentially competent catalysts for the enantioselective desymmetrisation of malonamate- and amide-tethered cyclohexadienones. Only one experiment involving amide-tethered cyclohexadienone **221** was carried out with BIMP catalyst **112**, which yielded the oxindole derivative **222** in 84% yield, 8:2:1:0.5 dr and 45% ee of the major diastereomer after a reaction time of 48 hours (**Scheme 45**). This experiment was performed by Jinchao Yang, a former student in the Dixon group. [45]



Scheme 45. BIMP-catalysed desymmetrisation of amide-tethered cyclohexadienone **221** (2016).

2.3.2 Initial Catalyst Screen

Based on the result obtained in **Scheme 45**, **221** was chosen as the model substrate for our optimisation studies for the above reaction. **221** Was prepared from readily available 4-aminophenol **223** in three steps (**Scheme 46**) – (1) reductive amination with benzaldehyde **27**, (2) Schotten-Baumann amide formation with 2-phenylacetyl chloride **225** and (3) phenol oxidation with phenyliodine (III) diacetate (PIDA). The first two steps proceeded smoothly on a multigram scale while the last step was performed on a smaller scale to achieve full conversion to product **221** in optimal yield. On a larger scale, various issues were experienced including incomplete conversion to product **221** and tedious purification, which reduced the isolated yield of **221**.



Scheme 46. Synthesis of substrate **221**.

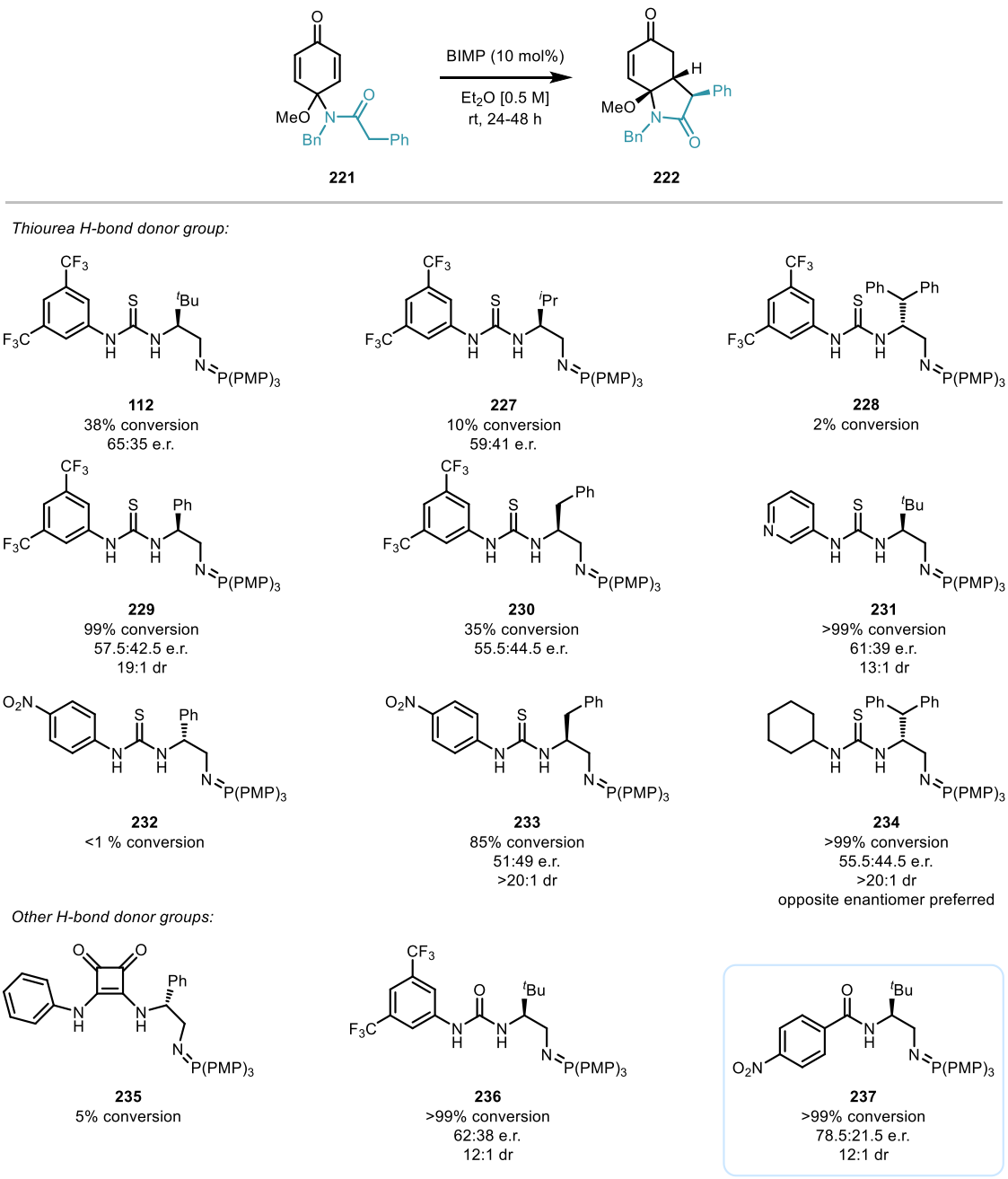
We began our optimisation studies with 1st generation BIMP catalysts bearing various combinations of substitution patterns and H-bond donors and derived from commercially available $P(PMP)_3$ and chiral azides previously synthesised in the Dixon group (**Scheme 47**). All reactions were carried out on a 0.1 mmol scale with 10 mol% of BIMP catalyst in 0.5 M of Et_2O at room temperature for 24 or 48 hours, and the BIMP catalyst was removed from the crude reaction mixture by passing it through a silica plug eluting with 1:1 pentane: EtOAc. As substrate **221** and product **222** coelute in a pentane/EtOAc solvent

system, with only a small difference in R_f values in other solvent systems tested, reaction efficiency was measured by ^{1}H NMR analysis of this filtered mixture. The integrals of the starting material and product peaks, particularly those attributed to the H atoms attached to the enone C atoms or the H atoms in the methoxy group, were used to calculate the approximate percentage conversion of **221** to **222**, as no obvious side products were observed on NMR. Unlike the result in **Scheme 45**, only two diastereomers were observed, typically with a much higher dr. As for the reaction with catalyst **112**, **222** was obtained in 38% conversion and 65:35 e.r.

A few BIMP catalysts bearing a thiourea H-bond donor group and a 3,5-trifluoromethylphenyl substituent at the distal end of the catalyst were tried, as these catalysts are most similar in structure to **112**. Changing the *tert*-butyl group at the chiral centre in catalyst **112** to isopropyl, benzhydryl, phenyl and benzyl groups in catalysts **227**, **228**, **229** and **230** resulted in a lowered e.r. in all instances. However, a high 99% conversion to **222** was achieved with catalyst **229** bearing a phenyl group at the chiral centre.

BIMP catalysts bearing different substituents at the distal end of the catalyst were also tested. The use of 3-pyridyl-substituted catalyst **231** led to the formation of **222** in >99% conversion, 61:39 e.r. and 13:1 dr. 4-NO_2-substituted catalysts **232** and **233** bearing a phenyl and a benzyl group at their respective chiral centres were tried, with **222** obtained in <1% conversion and 85% conversion, 51:49 e.r. and >20:1 dr respectively. With cyclohexyl-substituted catalyst **234**, **222** was obtained in >99% conversion, 55.5:44.5 e.r. and >20:1 dr.

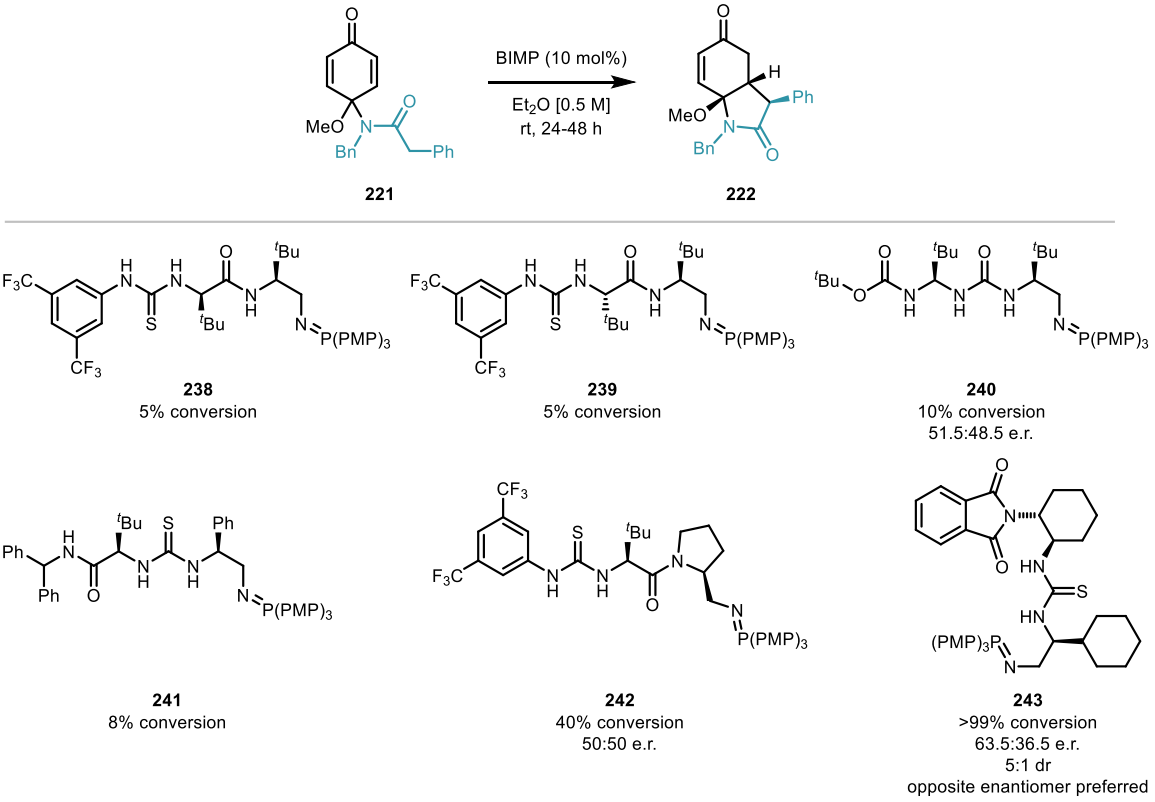
A possible reason for the disparity in conversions to **222** observed is that the chiral azides used in BIMP catalyst formation may not have been of good quality, as the azides were typically stored at room temperature over months or years, and their quality was not analysed prior to reaction. Furthermore, BIMP catalysts are sensitive to very small amounts of acidic contaminants present in the reaction vessel, which means that the efficacy of the reaction is affected by the quality of the starting material **221** used. As the stereoselectivity of the reaction is unlikely to be greatly affected by the conversion to product **222** due to amide enolisation being the rate-determining step, reactions leading to poor conversions were not repeated at this stage.



Scheme 47. Initial screening of 1st generation BIMP catalysts. PMP: *para*-methoxyphenyl. Conversion and dr (recorded only for conversions above 60%) were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase. Racemic product **222** was formed with achiral phosphazene BEMP for screening of chiral HPLC columns. Absolute stereochemical configuration of **222** was determined as (3*S*,3a*R*,7a*S*) by X-ray crystallography.

With dismal results obtained from the screening of 1st generation BIMP catalysts bearing a thiourea H-bond donor group, other H-bond donor groups were tested. Catalysts **235** and **236** containing double H-bond donating groups (squaramide and urea respectively) led to the formation of **222** in 5%

conversion and >99% conversion, 62:38 e.r. and 12:1 dr respectively. The highest enantioselectivity of **222** in this set of results was attained with catalyst **237**, which contains an amide H-bond donor group, a distal 4-nitrophenyl group and a *tert*-butyl group at the chiral centre. With **237**, **222** was obtained in >99% conversion, 12:1 dr and 78.5:21.5 e.r. of the major diastereomer. This suggests that a single H-bond donor in the BIMP catalyst provides more effective H-bonding to substrate **221** than double H-bond donors, creating a transition state structure that allows a greater induction of enantioselectivity in this intramolecular reaction.

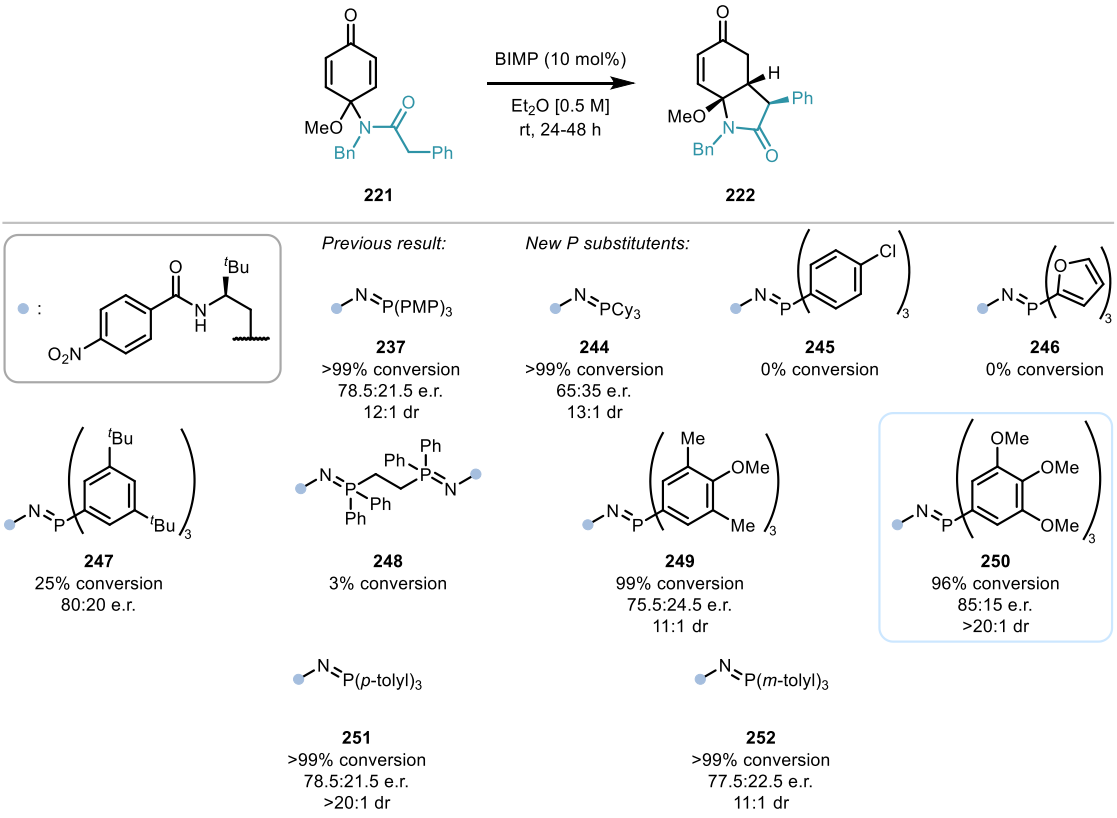


Scheme 48. Screening of 2nd generation BIMP catalysts. PMP: *para*-methoxyphenyl. Conversion and dr (recorded only for conversions above 60%) were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase.

2nd Generation BIMP catalysts were also tried in this reaction (**Scheme 48**). Enantiomeric catalysts **238** and **239** containing both amide and thiourea H-bond donor groups both led to the formation of **222** in a low 5% conversion. Catalyst **240** bears the same ureidopeptide skeleton as catalyst **158** employed in a highly enantioselective desymmetrisation of phosphonate esters (**Scheme 32**). However, its use in this cyclohexadienone desymmetrisation reaction led to the formation of **222** in a dismal 10% conversion

and 51.5:48.5 e.r. Catalyst **241** bears the same general scaffold as the first disclosed 2nd generation BIMP catalyst **150** used in an enantioselective sulfa-Michael addition (**Scheme 30**) and catalyst **153** employed in an enantioselective 1,3-prototropic shift (**Scheme 31**). However, its use in this reaction led to the formation of **222** in only 8% conversion. With proline-derived **242**, **222** was formed in 40% conversion and 50:50 e.r. Catalyst **243** containing a phthalimide and a thiourea assembled around a chiral *trans*-diamine backbone induced a preference for the opposite enantiomer of **222** to most of the other catalysts tested, with **222** obtained in >99% conversion, 63.5: 36.5 e.r. and 5:1 dr. With no improvement in enantioselectivity observed in this set of results, 1st generation catalyst **237** was selected as a starting point for further catalyst optimisation.

2.3.3 Phosphine Screen



Scheme 49. Phosphine screen. Conversion and dr (recorded only for conversions above 60%) were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase.

Next, the azide precursor to catalyst **237** was used in combination with various trivalent phosphine precursors in the Staudinger reaction to create catalysts with different electronic and steric properties in

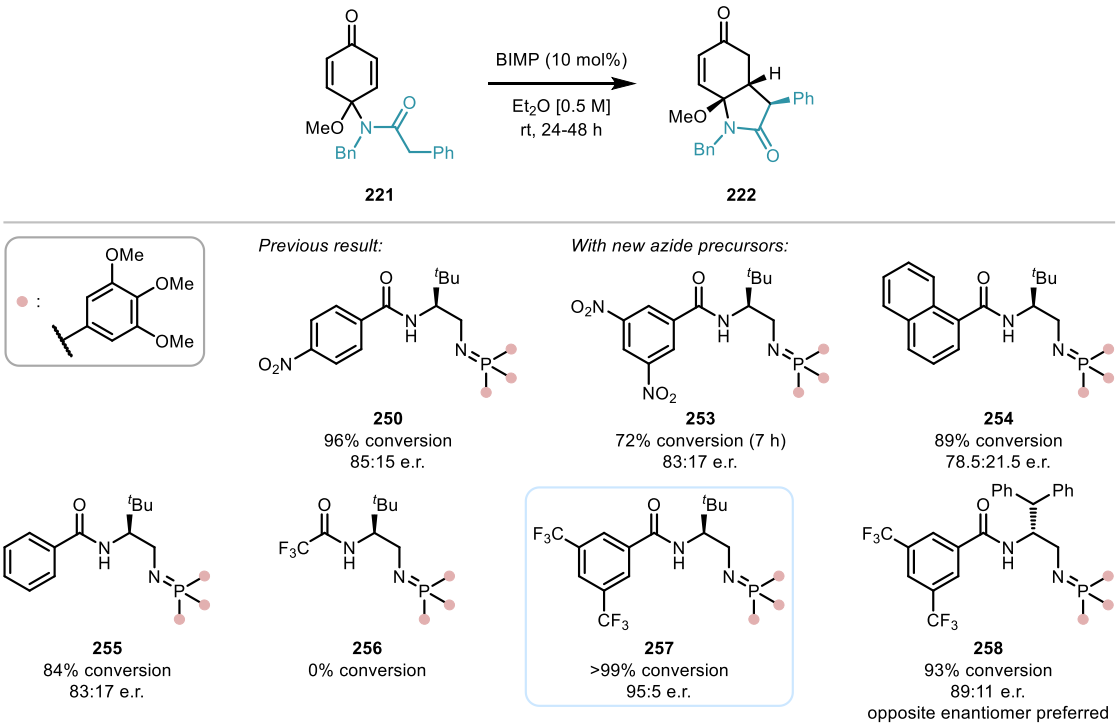
the vicinity of the iminophosphorane superbase to those formed using $P(PMP)_3$. These BIMP catalysts were tested in the reaction, and it was found that the nature of the substituents attached to the P atom of the iminophosphorane can have a significant impact on reactivity and stereoselectivity (**Scheme 49**). No conversion to product **222** was observed with electron-withdrawing 4-chlorophenyl substituents in catalyst **245** and 2-furyl substituents in catalyst **246**. Catalyst **248** containing two iminophosphoranes and two amide H-bond donor groups led to only 3% conversion to **222**, while sterically bulky 3,5-*tert*-butylphenyl substituents in catalyst **247** gave rise to 25% conversion to **222** in 80:20 e.r. Excellent conversions were achieved with cyclohexyl, 3,5-methyl-4-methoxyphenyl, *p*-tolyl and *m*-tolyl substituents in catalysts **244**, **249**, **251** and **252** but with **222** obtained in enantioselectivities similar to or slightly lower than that obtained with catalyst **237**. The greatest induction of stereoselectivity was observed with the use of catalyst **250** with electron-donating 3,4,5-trimethoxyphenyl substituents attached to the P atom, with **222** obtained in 96% conversion, 85:15 e.r. and >20:1 dr.

2.3.4 Amide H-bond Donor Catalyst Screen

As only one 1st generation BIMP precursor azide containing an amide H-bond donor had been tested at this point, a few chiral azides containing amide H-bond donor groups were synthesised and tested in this reaction (**Scheme 50**). The use of catalyst **256** with an electron-withdrawing trifluoromethyl group attached to the carbonyl carbon of the amide led to no conversion to product **222**. This is explained by the relative acidities of amides containing different substituents at the carbonyl carbon. The primary amide form of **256**, 2,2,2-trifluoroacetamide, has a pK_a of 17.15 in DMSO whereas the primary amide form of **255**, benzamide, has a much higher pK_a of 23.35 in DMSO.[46] Thus, the trifluoroacetamide H-bond donor group in **256** is highly acidic and self-deprotonation of **256** by the iminophosphorane at the N atom of the amide can occur easily. This forms a zwitterion, which reduces the basicity of **256** and its ability to deprotonate the amide pronucleophile in substrate **221**.

Catalysts **250**, **253**, **257** and **258** all contain electron-withdrawing nitro and trifluoromethyl groups on the aromatic ring attached to the carbonyl carbon of the amide, which increase the partial positive charge on the H atom of the amide to form stronger H-bonds to substrate **221**. Catalyst **254** contains a 1-naphthyl group attached to the carbonyl carbon, which exhibits greater resonance but otherwise similar

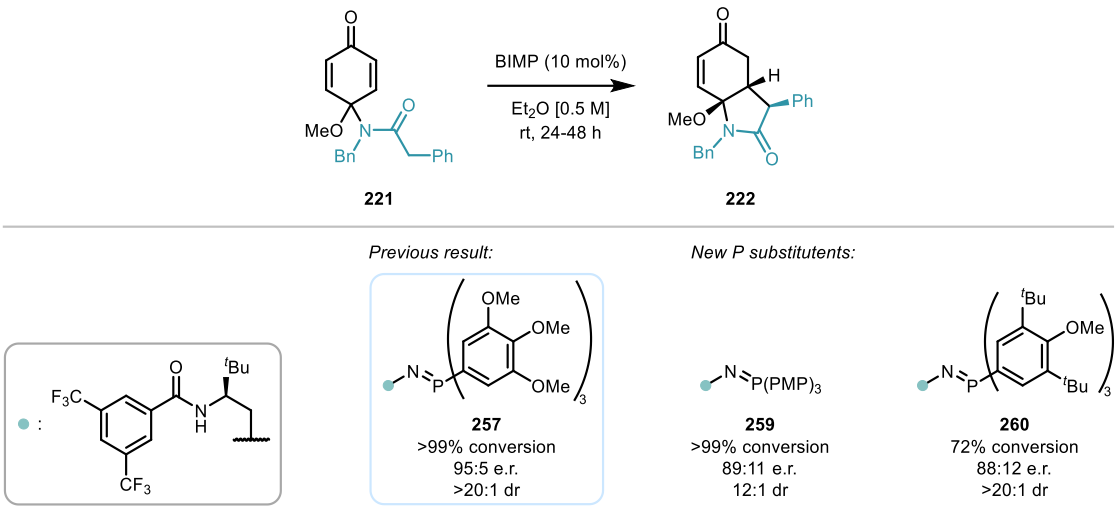
electronic properties to the phenyl group in **255**. A slight drop in both conversion and e.r. was recorded with catalysts **253**, **254** and **255** as compared to catalyst **250**. However, a surprisingly significant uplift in e.r. was observed with catalyst **257** bearing a 3,5-trifluoromethylphenyl substituent at the carbonyl carbon, with product **222** obtained in >99% conversion, 95:5 e.r. and >20:1 dr. Replacing the *tert*-butyl chiral backbone in **257** with a benzhydryl group in **258** gave a slightly reduced conversion and e.r. of 93% and 89:11 respectively, confirming the effectiveness of chiral induction from the *tert*-butyl group.



Scheme 50. Screening of amide H-bond donor catalysts. Conversion and dr (all catalysts **253** to **258** gave >20:1 dr) were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase.

A further small phosphine screen was performed with the azide precursor to catalyst **257** (**Scheme 51**). The use of commercially available P(PMP)$_3$ as the phosphine precursor to catalyst **259** yielded **222** in >99% conversion, 89:11 e.r. and 12:1 dr, which is incidentally the same dr obtained with catalyst **237** (**Scheme 47**). With sterically bulky 3,5-*tert*-butyl-4-methoxyphenyl substituents attached to the P atom in catalyst **260**, a lowered conversion to **222** of 72% was observed, with the stereoselectivity remaining relatively high at 88:12 e.r. and >20:1 dr. These results confirmed that 3,4,5-trimethoxyphenyl

substituents attached to the P atom of the iminophosphorane in **257** resulted in the most effective stereochemical induction in product **222**.

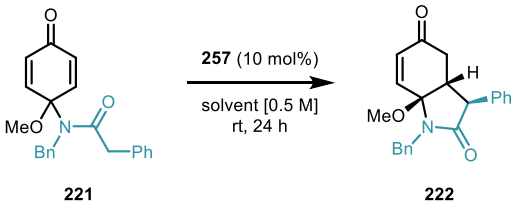


Scheme 51. Final phosphine screen. Conversions and dr were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase.

2.3.5 Solvent and Conditions Screen

Having found catalyst **257** to be optimal for promoting the enantioselective desymmetrisation of **221**, we proceeded to find out the optimal solvent and conditions for this reaction. Various common organic solvents were tried, and the results showed that there were significant solvent effects on the reaction (**Table 1**). The use of chlorinated solvent CH_2Cl_2 led to a low 15% conversion to **222** (entry 2), likely due to the presence of small amounts of acidic HCl in the reaction mixture deactivating catalyst **257**. Thus, 1.0 eq. of inorganic base K_2CO_3 was added to the reaction mixture with CH_2Cl_2 to neutralise any HCl formed, which increased the conversion to 57% (entry 3). However, a lowered e.r. of 90:10 as compared to the reaction with Et_2O (entry 1) was obtained for the product **222**. The use of polar solvents EtOAc and THF both led to 94% conversion to **222** and 91.5:8.5 and 92.5:7.5 e.r. respectively (entries 4-5), while the use of DME, a slightly less polar ether containing two O atoms, led to the formation of **222** in a slightly higher 95% conversion and 93.5:6.5 e.r. (entry 6). These results can be explained by the critical role of H-bonding from the BIMP catalyst **257** in promoting the forward reaction and inducing stereoselectivity in product **222**. The above-mentioned polar aprotic solvents contain O atoms that can function as H-bond acceptors which can interact with the amide H-bond

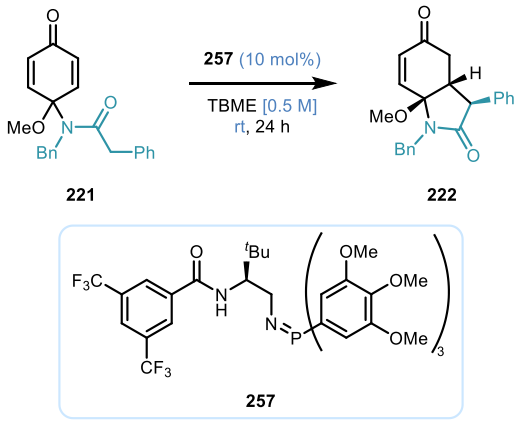
donor group in **257**, disrupting H-bonding interactions between **257** and substrate **221** in the transition state. Relatively non-polar TBME, CPME and toluene gave the highest enantioselectivities of **222** of 96:4 e.r. and above due to their inability to form strong H-bonds with **257** (entries 7-9). TBME, which led to the formation of **222** in >99% conversion, 96.5:3.5 e.r. and >20:1 dr, was chosen as the optimal solvent for this reaction.



entry	solvent	conversion (%)	e.r.
1	Et_2O	>99	95:5
2	CH_2Cl_2	15	not determined
3	CH_2Cl_2 + 1.0 eq. K_2CO_3	57	90:10
4	EtOAc	94	91.5:8.5
5	THF	94	92.5:7.5
6	DME	95	93.5:6.5
7	CPME	>99	96:4
8	toluene	>99	96:4
9	TBME	>99	96.5:3.5

Table 1. Solvent screen. Conversions and dr (>20:1 dr for all entries except entry 2 where dr was not determined) were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase.

Other reaction conditions including concentration, temperature and catalyst loading were also investigated in this reaction, with the results shown below (**Table 2**). The original conditions of 0.5 M TBME at room temperature with 10 mol% **257** (entry 1) proved effective in this reaction and no changes were made. Although no significant changes in conversion and stereoselectivity were observed with changes in the reaction concentration (entries 2 and 3), the activity of catalyst **257** decreased greatly when the temperature was lowered to 0 °C and -22 °C (entries 4 and 5). Nonetheless, the reaction at 0 °C resulted in an increased e.r. of **222** of 97.5:2.5. Lowered catalyst loadings of 5 mol% and 1 mol% also greatly reduced the reaction rate, with **222** obtained in only 46% and 0% conversion respectively (entries 6 and 7). This is due to smaller amounts of catalyst **257** available to deprotonate the amide pronucleophile in **221**, leading to a reduced rate of amide enolate formation and thus an insufficient anion concentration to promote the intramolecular Michael addition.



entry	changes in conditions	conversion (%)	e.r.
1	-	>99	96.5:3.5
2	0.2 M	>99	96:4
3	1.0 M	99	96:4
4	0 °C	64	97.5:2.5
5	-22 °C	5	not determined
6	5 mol% **257**	46	not determined
7	1 mol% **257**	0	not determined

Table 2. Conditions screen. Conversions and dr (>20:1 dr for all entries except 5-7 where dr was not determined) were determined by comparing characteristic peaks on ^{1}H NMR. e.r. of the major diastereomer was determined by HPLC analysis on a chiral stationary phase.

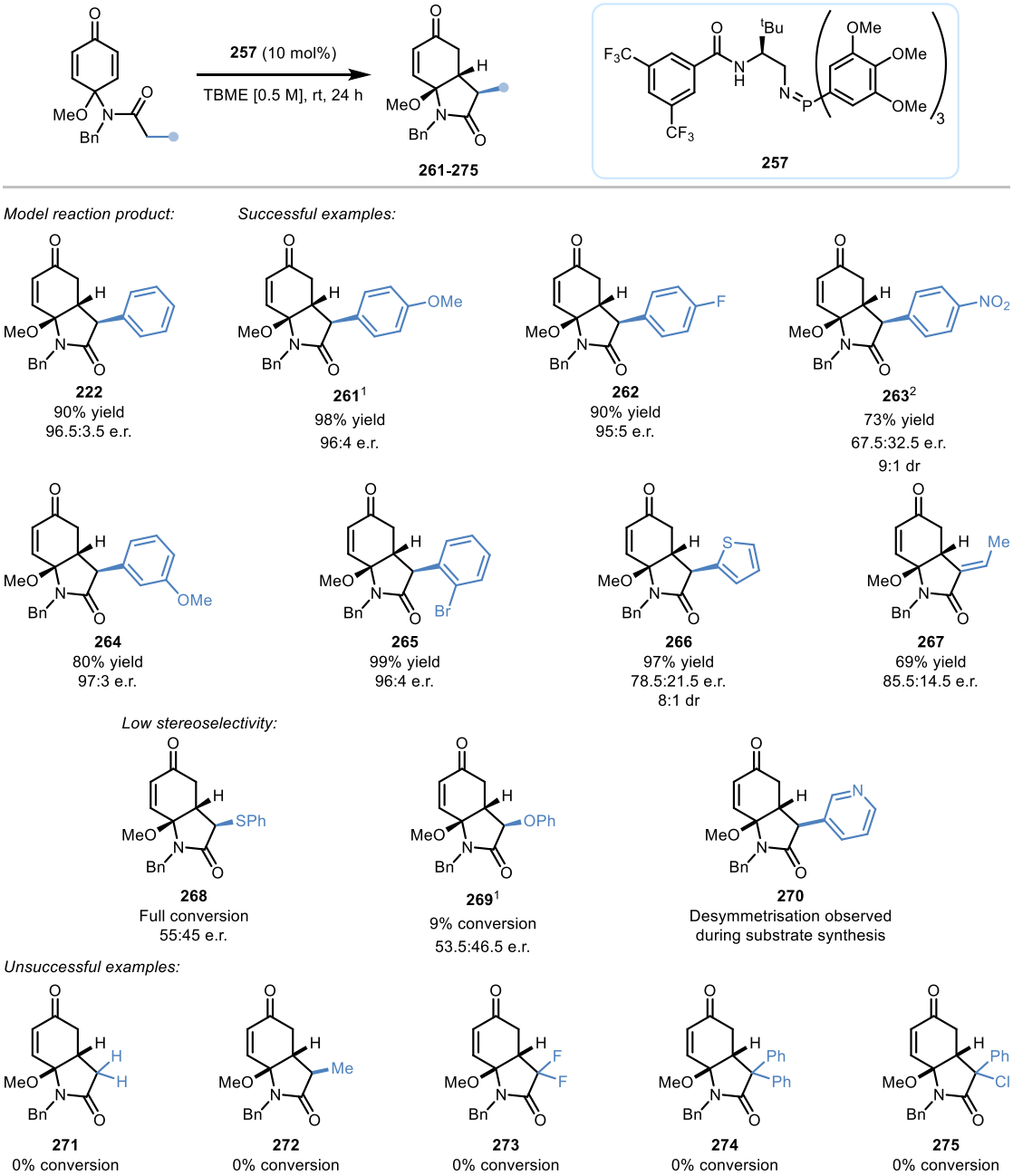
2.4 Substrate Scope

2.4.1 Substitutions at the α-Carbon

After establishing the optimal conditions for the model reaction, the substrate scope was explored. A range of substrates was prepared using the same general route used for the preparation of **221** (**Scheme 46**) with **225** replaced with differently-substituted acyl chlorides or carboxylic acids (see **4.2.3** for full experimental details). The BIMP-catalysed reactions were performed on a 0.1 mmol scale, and a wide range of aromatic substituents at the α-carbon of the amide, as well as a 2-thiophenyl substituent (**266**), were tolerated in this reaction (**Scheme 52**). Both electron-donating (**261**) and electron-withdrawing phenyl substituents (**262**-**265**) were tolerated. However, these substitution patterns greatly influence the acidity of the amide pronucleophile. The electron-donating 4-methoxyphenyl substituent in the precursor to **261** would destabilise the developing negative charge during deprotonation at the α-position, leading to greater difficulty in the formation of an amide enolate. The reaction proved to be sluggish at room temperature, with heating to 50 °C required to achieve full conversion and 98% yield of **261**. **261** was obtained in high stereoselectivity at 96:4 e.r. and >20:1 dr, which was an impressive result given the increased reaction temperature.

Mildly electron-withdrawing aromatic substituents 4-fluoro- (**262**), 3-methoxy- (**264**) and even bulky 2-bromophenyl (**265**) were well tolerated, with the products obtained in excellent yields and

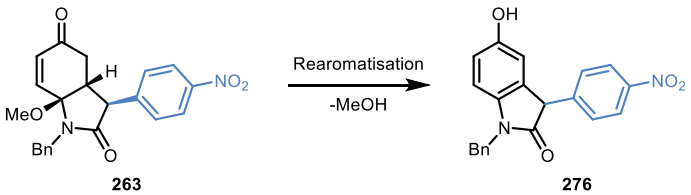
stereoselectivities under the standard reaction conditions. Electron-withdrawing substituents at the α-carbon would stabilise the developing negative charge during deprotonation at the α-position, facilitating the formation of the active enolate nucleophile and increasing reaction efficiency.



Scheme 52. Substrate scope of α-carbon substituents. Isolated yields for successful examples. >20:1 dr where dr is not mentioned. e.r. determined by HPLC on a chiral stationary phase. [1]Reaction carried out at 50 °C. [2]Reaction quenched after 5 min.

However, with increasing electron-withdrawing ability and/or the presence of heteroatoms at certain positions on the substrate, the ability of catalyst **257** to induce stereochemistry in the products decreased drastically. 2-Thiophenyl-substituted **266** was formed in 97% yield but in a reduced stereoselectivity of 78.5:21.5 e.r. and 8:1 dr, while 4-nitrophenyl-substituted **263** was obtained in 73% yield, 67.5:32.5 e.r. and 9:1 dr. Both reactions were complete in under one hour, and the stereoselectivity remained low when the reaction temperature was reduced to 0 °C. Time-resolved NMR experiments revealed no change in the dr of both **266** and **263** over time, implying an irreversible Michael addition step. Upon isolation of a pure sample of the major diastereomer of **263**, it was resubjected to the reaction conditions, where it rapidly equilibrated to a 9:1 mixture of diastereomers. This suggests rapid and reversible proton exchange between **263** and catalyst **257**, and therefore that the observed diastereoselectivity is under thermodynamic control. This particular experiment was performed by Daniel Rozsar and is included for completeness.

A separate problem was encountered with highly electron-withdrawing substituents - their rapid rearomatisation and elimination of methanol when treated with chlorinated solvents such as $CDCl_3$ (**Scheme 53**). This was observed to occur with 4-nitrophenyl-substituted **263**, and the rearomatised product **276** was obtained as a racemic mixture with a complete loss of enantioselectivity (see **4.2.5** for characterisation). Small amounts of acidic HCl are typically present in chlorinated solvents, which facilitates protonation at the methoxy group in **263**, giving rise to the formation of a stable tertiary conjugated carbocation upon elimination of methanol. Electron-withdrawing substituents at the α-carbon would favour amide enolisation, increasing the degree of conjugation, the stability of the carbocation and thus favouring the elimination of methanol and rearomatisation. Fortunately, most reaction products have been resistant to this process, and sensitive products could be handled carefully with the avoidance of chlorinated solvents, therefore this has not been further investigated in the project.



Scheme 53. Rearomatisation of **263**.

The precursor to **267** contains a terminal alkene at the α-position. After the desired Michael addition/desymmetrisation reaction, a subsequent stereoselective 1,3-prototropic shift led to the formation of internal alkene **267** in 69% yield and 85.5:14.5 e.r. as only the *E*-isomer.

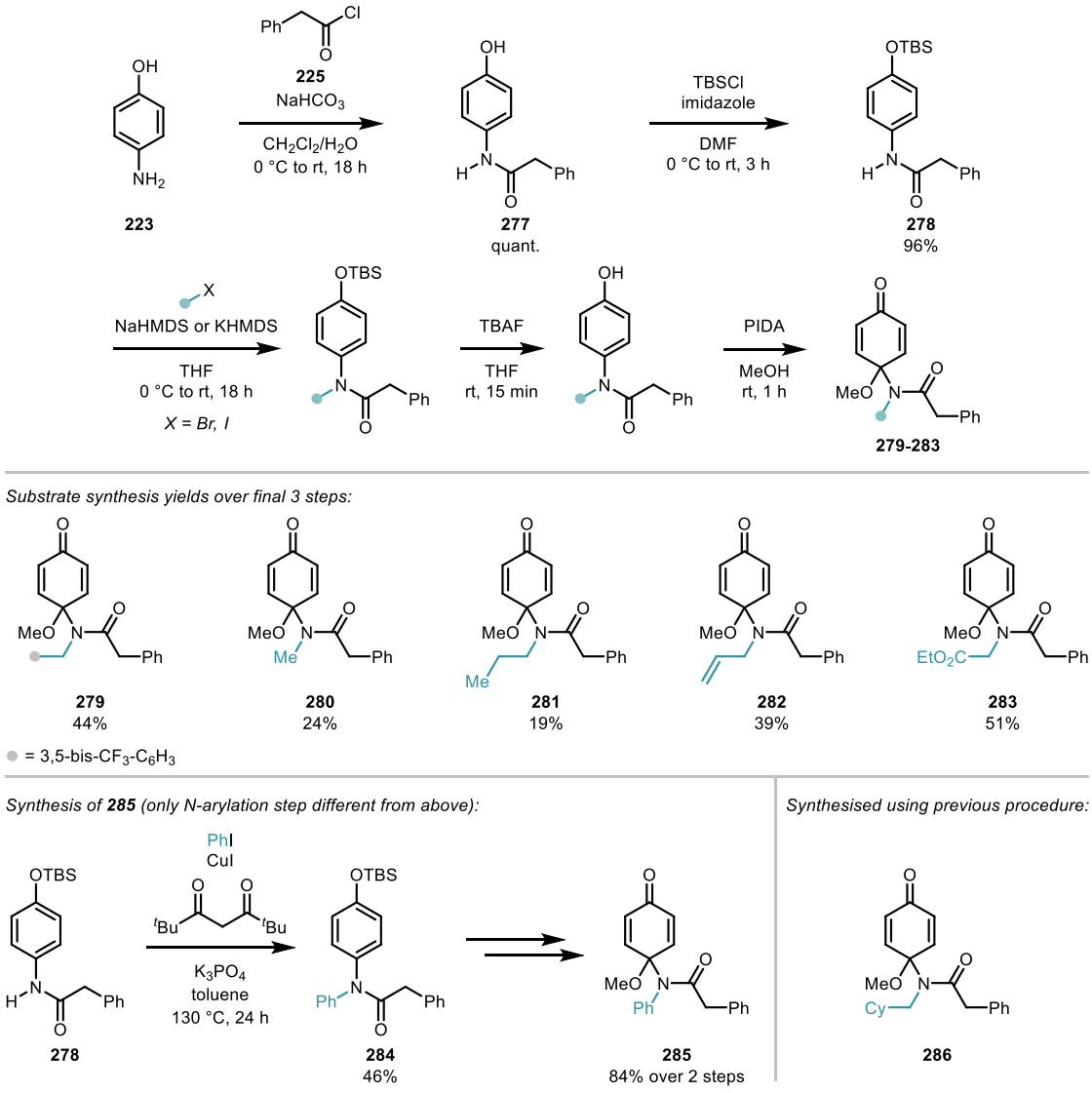
With a phenyl sulfide (**268**) and a phenol ether (**269**) at the α-position, the enantioselectivity drops to 55:45 e.r. and 53.5:46.5 e.r. respectively. This suggests that either the presence of the heteroatoms at the α-position or the broadly different structures of these substrates as compared to the model substrate is likely to prevent optimal stereochemical induction by catalyst **257**. 3-Pyridyl-substituted **270** was observed on NMR while attempting to synthesise its precursor substrate. The 3-pyridyl substituent was likely to be so highly electron-withdrawing and amide-activating that only a weak base such as sodium bicarbonate used in the workup procedure was required to form the amide enolate and promote the desired reaction. BIMP catalysts would likely provide poor stereochemical control in this instance.

Unfortunately, several substrates were not tolerated. Under the optimised reaction conditions, only starting material was obtained when the reaction was tried with substrates bearing only H atoms (**271**), a methyl group (**272**) or two substituents at the α-carbon (**273**-**275**). The amides in the precursors to **271**-**273** are much less acidic as compared to 2-arylacteamides (pK_a ~ 35 instead of 26.6 in DMSO)[1] and are more difficult to deprotonate with catalyst **257**. This is due to the resonance stabilisation of the developing negative charge by the phenyl group during deprotonation at the α-carbon to form the enolate, which is absent when there are only alkyl substituents at the α-position. As for α-disubstituted **273**-**275**, steric hindrance and the availability of only one α-proton rather than two for deprotonation prevent the desired reaction from occurring.

2.4.2 Substitutions at the N atom

Next, substrates with different substituents attached to the N atom of the amide were explored. To streamline their synthesis, a different synthetic route was mostly used (**Scheme 54**). In this route, the different *N*-substituents were installed in an amide *N*-alkylation step with TBS-protected phenol intermediate **278**. When free phenol **277** was employed in this *N*-alkylation step, *O*-alkylation was observed. Thus, the installation of a protecting group at the phenolic OH and subsequent deprotection were two necessary steps added to this sequence to prevent *O*-alkylation. TBS was found to be a suitable

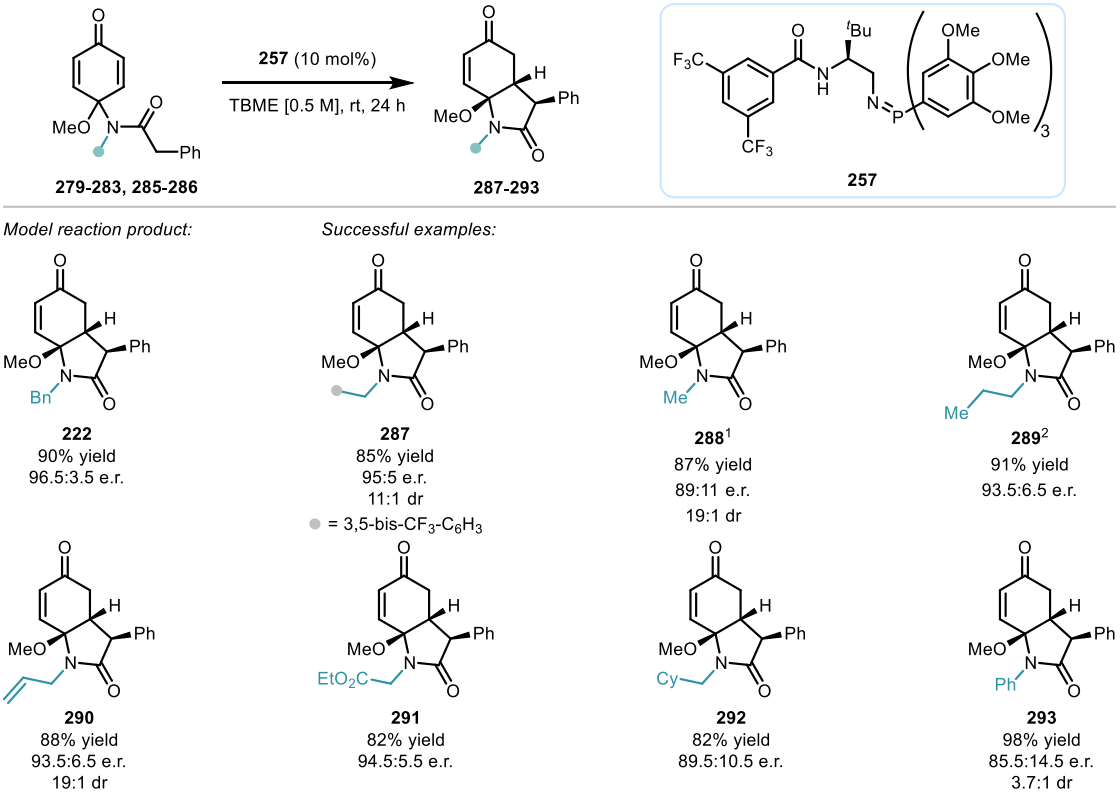
protecting group, as it was stable through the amide *N*-alkylation step and yet it was easily cleaved in 15 min with TBAF afterwards. This route was most amenable to primary alkyl substituents, with substrates **279** to **283** synthesised in moderate overall yields. In the synthesis of *N*-phenyl substrate **285**, the *N*-alkylation step was replaced with a Cu-catalysed *N*-arylation step. A sluggish *N*-alkylation step with (bromomethyl)cyclohexane meant that *N*-methyl cyclohexyl substrate **286** was prepared using the previously established procedure (**Scheme 46**), while no *N*-alkylation was observed with a secondary alkyl bromide, bromocyclohexane.



Scheme 54. Synthesis of *N*-substituted substrates **279**-**286**.

Substrates **279**-**283** and **285**-**286** were subjected to the optimised reaction conditions (**Scheme 55**), where products **287**-**293** were obtained in excellent yields and mostly good stereoselectivities. The

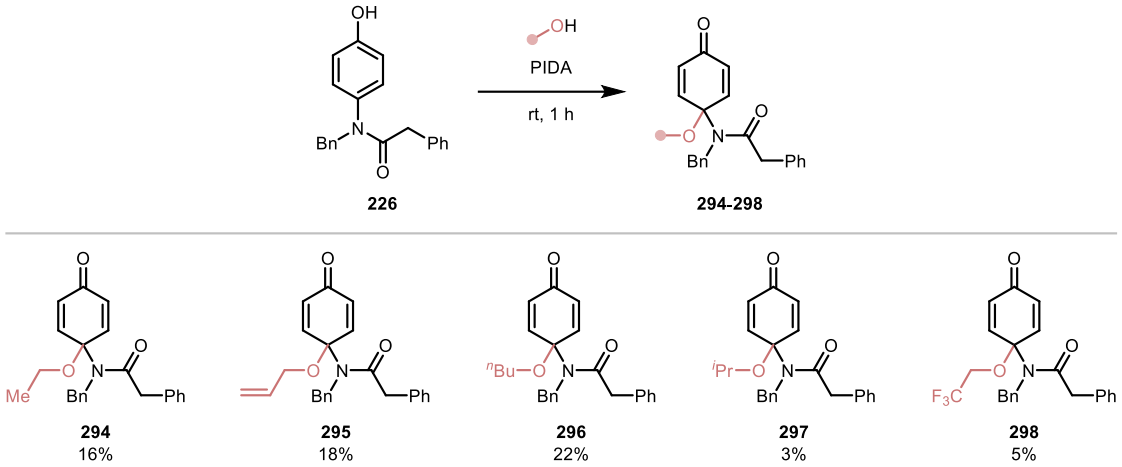
decreased stereoselectivities observed in comparison to **222** can be attributed to structural differences around the N atom, leading to suboptimal binding to catalyst **257**. *N*-Phenyl-substituted **293** was formed in 98% yield but in a reduced stereoselectivity of 85.5:14.5 e.r. and 3.7:1 dr, and this is likely attributed to the increased steric bulk around the N atom with the phenyl group, which prevents effective stereochemical induction from catalyst **257**.



Scheme 55. Substrate scope of *N*-substituents. Isolated yields. >20:1 dr where dr is not mentioned. e.r. determined by HPLC on a chiral stationary phase. [1]Reaction carried out at 50 °C. [2]15 mol% catalyst loading.

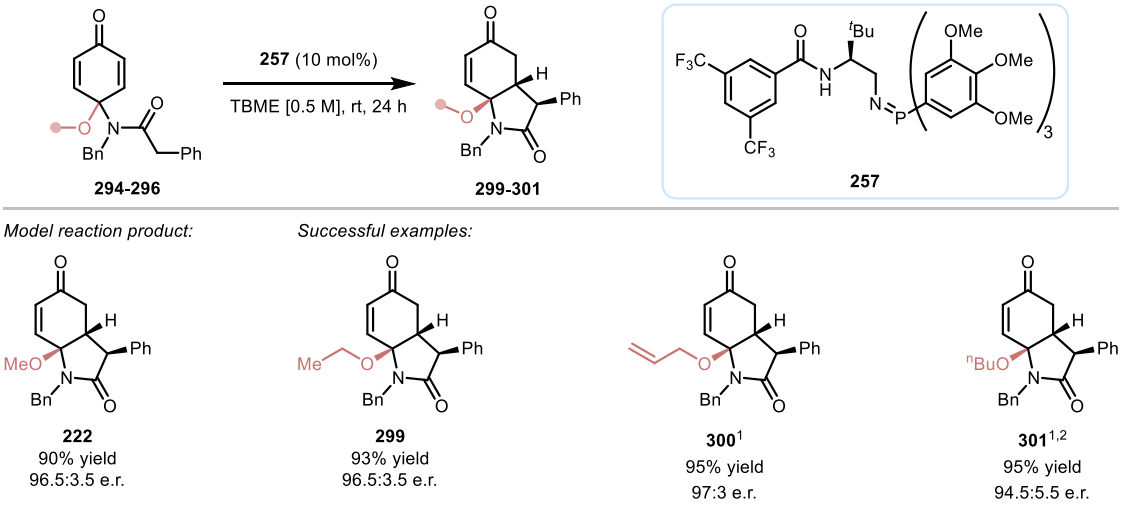
2.4.3 Substitutions at the 4-position of the Cyclohexadienone

Substrates with different substituents at the 4-position of the cyclohexadienone were then investigated. Substrates **294**-**298** were prepared in just one oxidation step from amide **226** with the hypervalent iodine reagent PIDA and the corresponding alcohols (**Scheme 56**). These substrates were obtained in lower yields in this reaction as compared to model substrate **221**, and this is likely due to the greater size of the alcohols as compared to methanol, and greater difficulty in forming a quaternary sp^3 centre at the 4-position with a larger substituent.



Scheme 56. Synthesis of substrates bearing different substituents at the 4-position of the cyclohexadienone.

Substrates **294**-**296** which were obtained in useful yields were then tested in the reaction. Under the optimised reaction conditions, products **299**-**301** were formed in high stereoselectivities at similar levels to **222** (**Scheme 57**). Reactivity, however, decreased with increasing bulk at the 4-position, and full conversion to *n*-butoxy-substituted product **301** was only achieved with a reaction temperature of 50 °C and an increased catalyst loading of 15 mol% of **257**. Similarly, 15 mol% of **257** was required to achieve full conversion to allyloxy-substituted **300**.

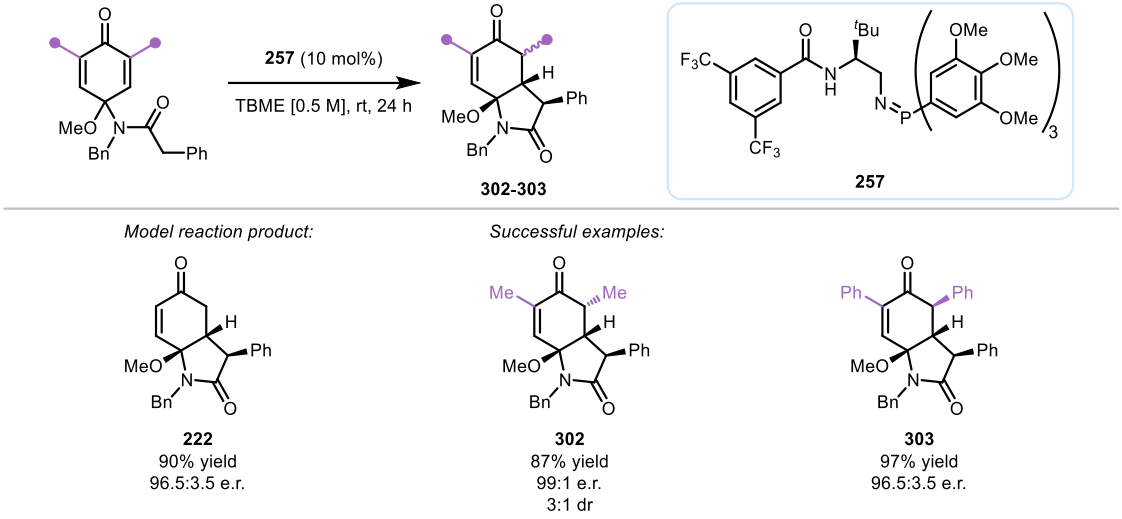


Scheme 57. Scope of substrates bearing different substituents at the 4-position of the cyclohexadienone.

Isolated yields. >20:1 dr for all examples. [1]15 mol% catalyst loading. [2]Reaction carried out at 50 °C.

2.4.4 Reactions of 2,6-Disubstituted Cyclohexadienones

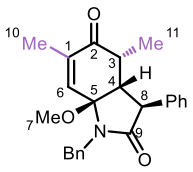
Substrates containing substituents on the enone carbon atoms on the cyclohexadienone were also explored in this reaction. As we desired this reaction to be a desymmetrisation, the substituents on both sides of the cyclohexadienone were kept identical. Employing 2,6-disubstituted 4-nitro or 4-aminophenols as the starting materials, the corresponding cyclohexadienone substrates were synthesised by transfer hydrogenation of the nitro group to an aniline if required and then using the general procedure described in **Scheme 46**. The 2,6-disubstituted cyclohexadienone products **302-303** were obtained in excellent yields and stereoselectivities of up to 99:1 e.r. and >20:1 dr under the optimal conditions (**Scheme 58**).



Scheme 58. Scope of 2,6-disubstituted cyclohexadienone substrates. Isolated yields. >20:1 dr where dr is not mentioned.

The relative stereochemical configurations of **302** and **303** were then determined, and numbers are assigned to their carbon atoms to facilitate discussion (**Figures 5** and **6**). The absolute stereochemical configurations at C4, C5 and C8 in **302** and **303** are likely to be the same as in **222,** which was determined by X-ray crystallography (see **Section 2.5**), due to the use of the same catalyst **257** in the formation of all three products. The $[\alpha]_D^{25}$ values measured for **222**, **302** and **303** all have the same negative sign, which supports this similarity in stereochemical configuration. The relative stereochemical configurations at C3 were determined by ^{1}H two-dimensional NOESY NMR experiments, which show peaks correlating atoms that are near to each other in space. For instance, if the H atom at C3 is pointing

into the concave face of the bicyclic system, it would be near to the H atom at C8 in space and a peak correlating both H atoms would show up in the NOESY spectrum.



302

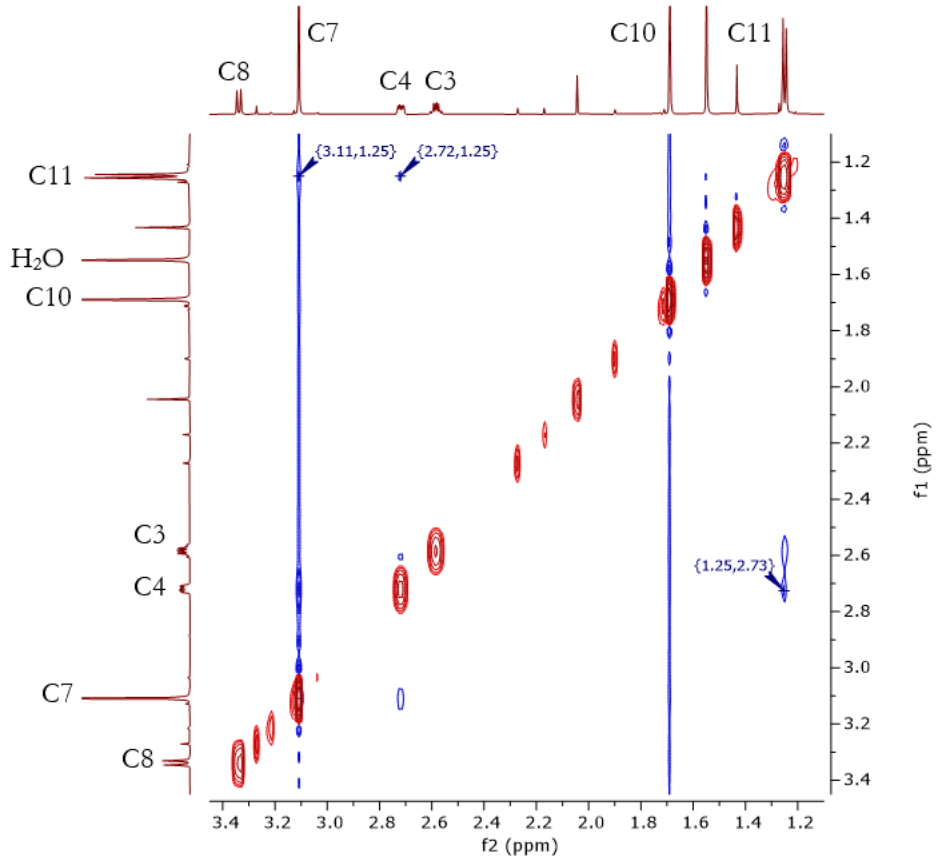


Figure 5. Numbering of carbon atoms and NOESY spectrum of the minor diastereomer of **302**.

In the ^{1}H NMR spectrum of the major diastereomer of **302**, the peaks attributed to the H atoms at C4 and C8 have overlapping chemical shifts, making it difficult to determine the relative stereochemical configuration at C3 through peaks in the NOESY spectrum in that region. These peaks attributed to the H atoms at C4 and C8 have different chemical shifts in the minor diastereomer of **302**, which is likely to have the opposite stereochemical configuration at C3. In the NOESY spectrum of the minor diastereomer, the signals attributed to the H atom at C3 are relatively weak, thus the peaks attributed to the three H atoms at C11 were used instead to determine the position of the methyl group in space

relative to the other H atoms in the molecule. Peaks correlating the H atoms at C11 with the H atom at C4 were observed, meaning that the methyl group likely points in the same direction as the H atom at C4 (**Figure 5**). This is also confirmed by the absence of peaks correlating the H atoms at C11 with the H atom at C8 which points in the opposite direction, as well as the presence of a peak correlating the H atoms at C11 with the three H atoms at C7. Therefore, in the major diastereomer, it is likely that the methyl group points in the opposite direction to the H atom at C4 and the phenyl group at C8.

In the NOESY spectrum of the major diastereomer of **303**, peaks correlating the H atom at C3 with the H atom at C8 were observed, meaning that these two H atoms likely face each other. The phenyl group at C3 likely points in the same direction as the phenyl group at C8, the H atom at C4 and the methoxy group at C5 (**Figure 6**). A possible reason for the different relative stereochemical configurations of the major diastereomers of **302** and **303** is the greater size and steric bulk of the phenyl group in **303** as compared to the methyl group in **302**, which makes it more likely for the phenyl group to point away from the concave face of the bicyclic system to minimise steric repulsion. This also explains the much greater diastereomeric ratio observed for **303**.

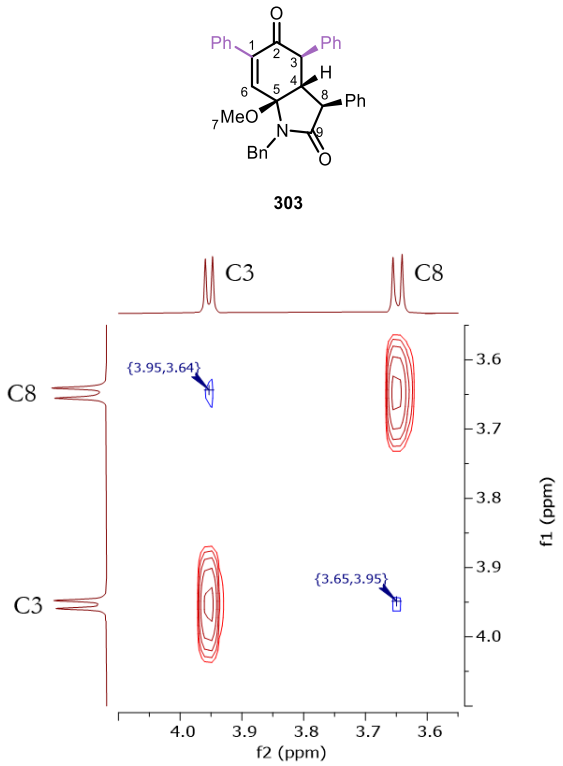
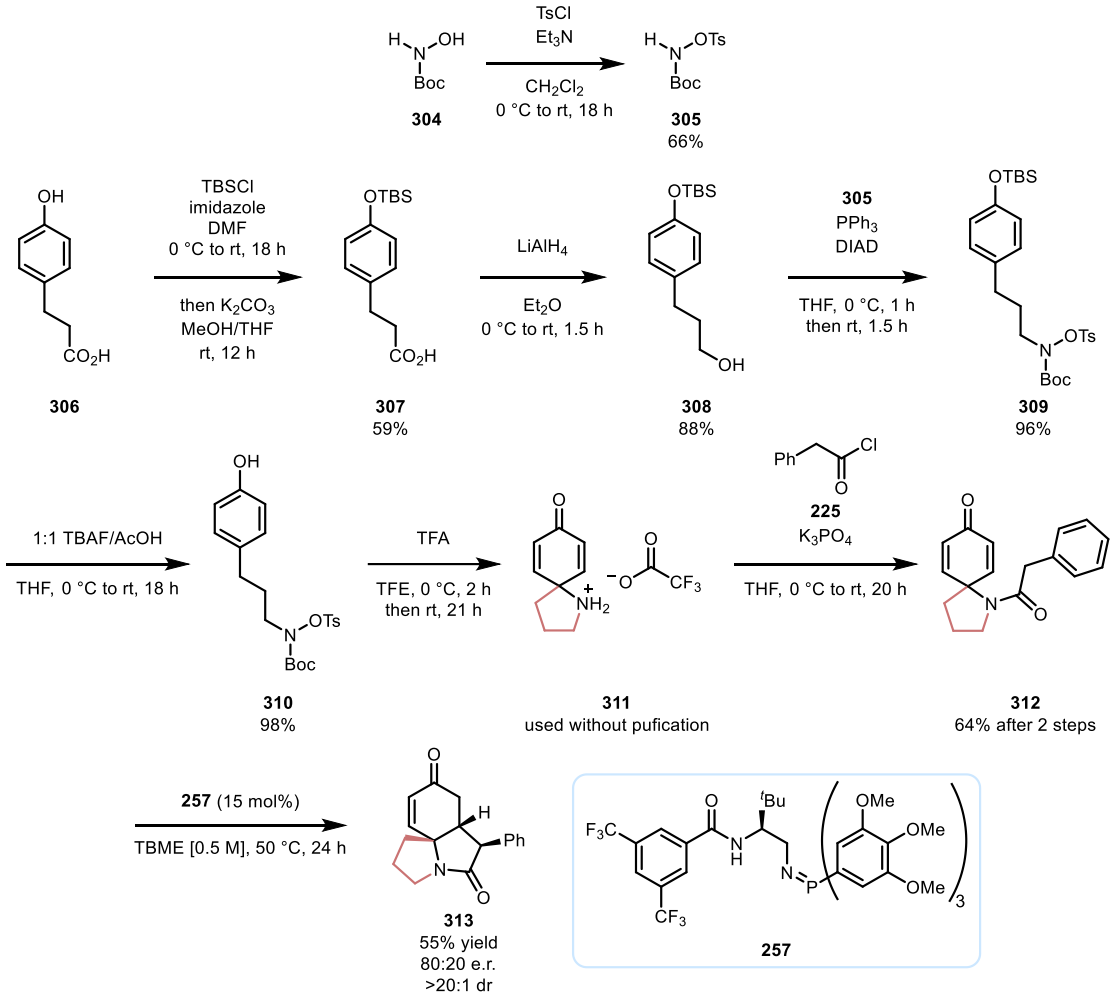


Figure 6. Numbering of carbon atoms and NOESY spectrum of the major diastereomer of **303**.

2.4.5 Reactions Involving Other Substrates

Spirocyclic substrate **312** was synthesised according to a literature procedure reported by Bower and coworkers using commercially available *tert*-butyl hydroxycarbamate **304** and phenol **306** (**Scheme 59**).[47] The key dearomatisation step to form cyclohexadienone **311** involves *N*-(tosyloxy)carbamate **310** tethered to the 4-position of a phenol through a three-carbon alkyl chain as the starting material. Trifluoroacetic acid and 2,2,2-trifluoroethanol were used as the dearomatising reagent and solvent, as opposed to PIDA in methanol for all the other substrates. **310** Was generated by deprotection of the TBS protecting group in **309**, which was prepared in a Mitsunobu reaction between alcohol **308** and *tert*-butyl (tosyloxy)carbamate **305**. The spirocyclic ammonium trifluoroacetate salt **311** was reacted with 2-phenylacetyl chloride **225** to form amide substrate **312**.

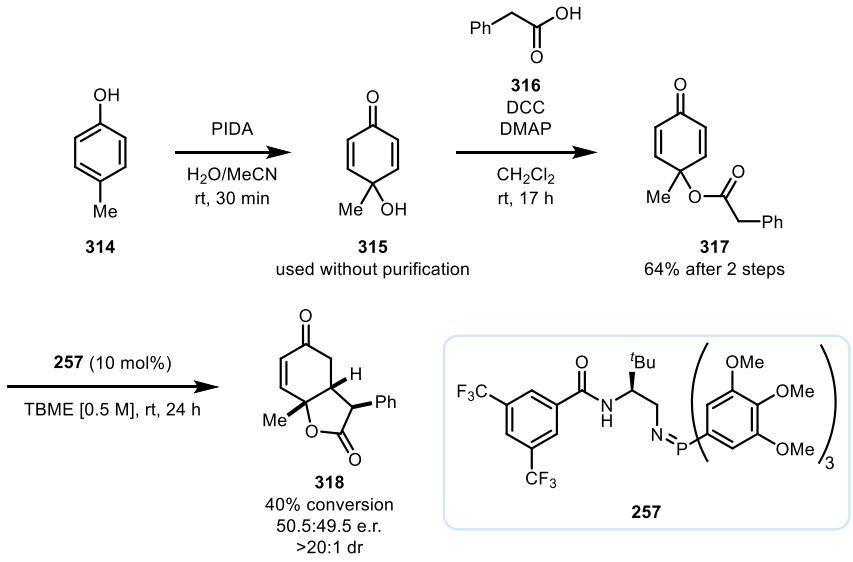


Scheme 59. Synthesis of spirocyclic substrate **312** and desymmetrisation. Isolated yields.

For the cyclohexadienone desymmetrisation reaction, substrate **312** was unreactive under the optimal conditions, possibly due to the additional ring strain. The reaction at 50 °C with 15 mol% **257** yielded the tricyclic product **313** in 55% yield, 80:20 e.r. and >20:1 dr.

An ester substrate **317** was synthesised in a two-step procedure,[45, 48] and tested in the key reaction (**Scheme 60**). Unlike most of the amide substrates, **317** contains a methyl group at the 4-position of the cyclohexadienone, which is created in the initial step by oxidation of *p*-cresol **314** with PIDA in H_2O/MeCN. The product **315** formed contains an alcohol at the 4-position of the cyclohexadienone, which is coupled with 2-phenylacetic acid **316** using DCC and DMAP in CH_2Cl_2 to form ester **317**.

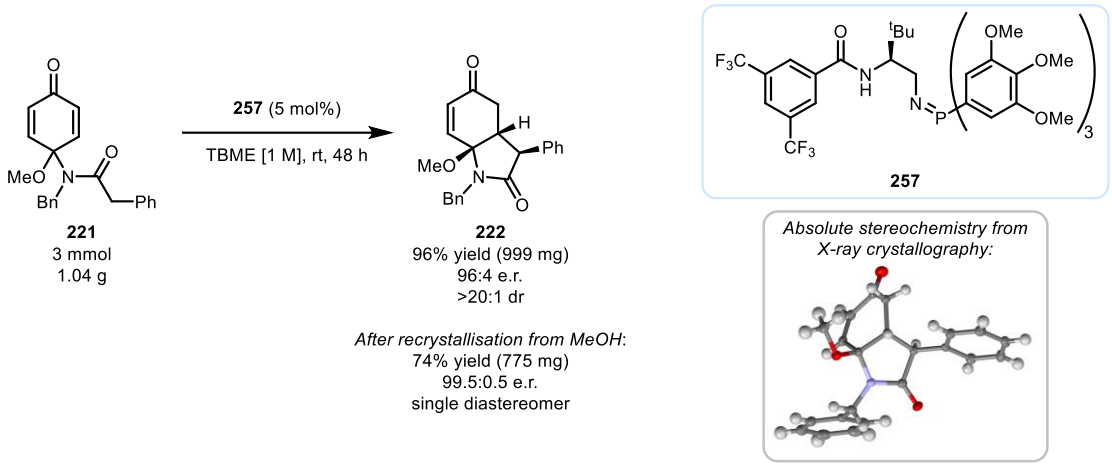
As esters are more reactive pronucleophiles as compared to amides based on their pK_a values in DMSO,[1] this reaction was expected to proceed smoothly. However, only 40% conversion to the lactone product **318** was observed, and its e.r. was determined to be 50.5:49.5, which is very close to the 50:50 ratio in a racemic mixture. This suggests poor stereochemical induction by the BIMP catalyst **257**, and that the replacement of the N atom in amide substrates with an O atom in **317** results in very different electronic and steric properties around the α-carbon. The greater electronegativity of the O atom as compared to the N atom also potentially results in a lowered electron density on the π-conjugated carbonyl O atom, leading to weaker H-bonding to catalyst **257**.



Scheme 60. Synthesis of ester substrate **317** and desymmetrisation.

2.5 Preparative Scale Synthesis and Derivatisation

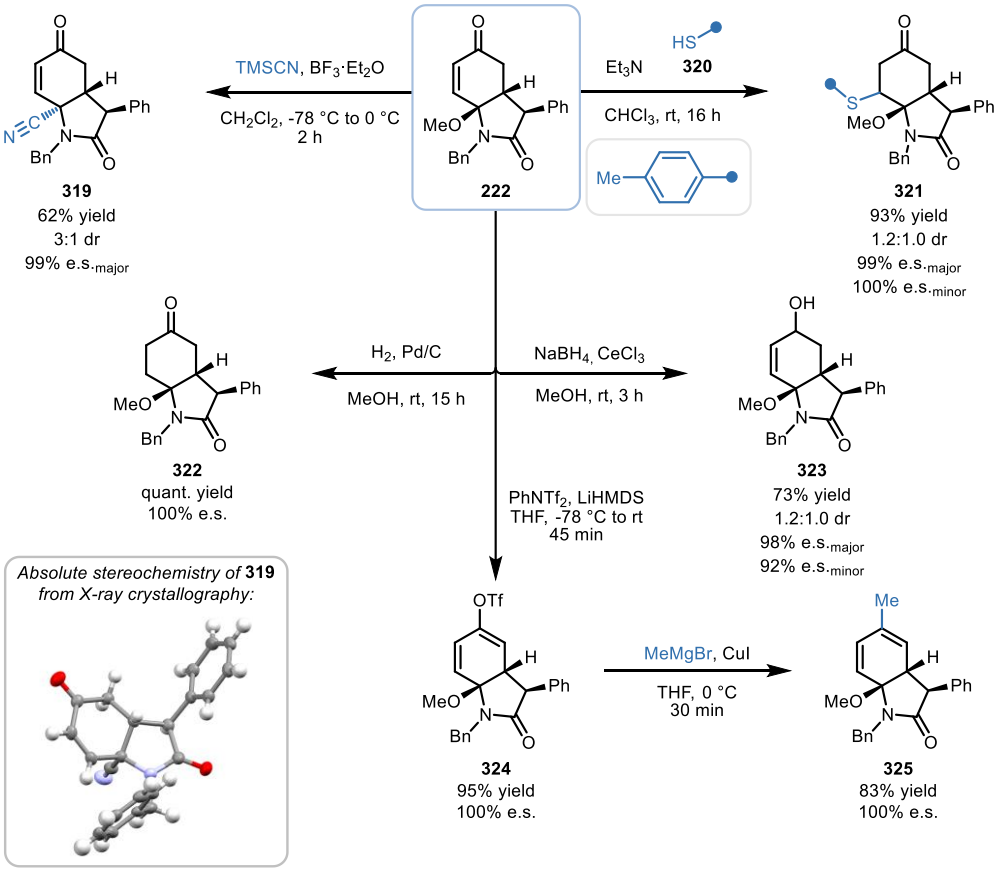
After establishing the scope and limitations of this reaction, a gram-scale reaction was explored. The model reaction was scaled up to a 3 mmol (one gram) scale, with the catalyst loading reduced to 5 mol% from 10 mol% previously (**Scheme 61**). After a reaction time of 48 hours, **222** was obtained in full conversion and 96% isolated yield, 96:4 e.r. and >20:1 dr, and recrystallisation from methanol allowed the isolation of crystals of 99.5:0.5 e.r. in 74% yield as a single diastereomer. The absolute stereochemical configuration of **222** of (3*S*,3a*R*,7a*S*) was confirmed by single crystal X-ray diffraction analysis.[49]



Scheme 61. Gram-scale reaction with model substrate **221**.

The various functional groups in product **222** were then exploited in several derivatisations, using the highly enantioenriched **222** as the starting material (**Scheme 62**). Firstly, the methoxy group at the 4-position of the cyclohexenone in **222** underwent a Lewis acid-catalysed nucleophilic substitution with TMSCN to form nitrile product **319**. **319** Contains an all-carbon quaternary stereogenic centre and was obtained in 62% yield and 3:1 dr but with no erosion in e.r. The stereochemical configuration of the major diastereomer of **319** was confirmed by single crystal X-ray diffraction analysis,[49] which suggests that the stereoinversive S_N2 mechanism is dominant under the reaction conditions. The remaining enone functionality in **222** was then exploited in a non-stereoselective sulfa-Michael addition with 4-methylthiophenol **320** in the presence of triethylamine, forming the adduct **321** in 93% yield, 1.2:1.0 dr and 99% and 100% e.s. for both diastereomers. Hydrogenation of the C=C bond in **222** with Pd/C yielded cyclohexanone **322** in quantitative yield and 100% e.s., while chemoselective reduction of the

carbonyl group with $NaBH_4$ and $CeCl_3$ yielded secondary allylic alcohol **323** in 73% yield, 1.2:1.0 dr and 98% e.s. (major diastereoisomer). Like the sulfa-Michael addition, this reaction is not stereoselective, with the addition of hydrogen to both faces of the cyclohexenone with almost equal preference. Finally, the enolisable ketone was functionalised to obtain dienyl triflate **324** under standard conditions in 95% yield and with no loss in enantiopurity. **324** Was further functionalised in a rapid CuI-catalysed Kumada-type coupling reaction with MeMgBr, forming methylated 1,3-cyclohexadiene **325** in 83% yield and 100% e.s.



Scheme 62. Various functionalisations of **222**.

2.6 pK_{BH+} Determination of Catalyst 257

The Brønsted basicity of BIMP catalyst **257** was then explored. The pK_{BH+} values of previously disclosed BIMP catalysts were determined experimentally by the following method,[50] which was used for the determination of the pK_{BH+} value of **257** to provide a meaningful comparison.

NMR spectroscopy was used as the analytical tool due to the ease of performing NMR experiments in a typical synthetic chemistry laboratory environment, as well as the ease of obtaining numerical data in the form of chemical shift values from NMR spectra.[51] This method requires a base with a known pK_{BH+} value so that through comparison of the chemical shift values of NMR samples containing **257** with or without the known base, the pK_{BH+} value of **257** could be estimated. *N*, *N'*, *N'* tetramethylguanidine (TMG) was selected as the known base due to its availability and a pK_{BH+} of 23.3 in MeCN,[52] which is close to the expected pK_{BH+} values of BIMP catalysts such as **257**. With "A" representing catalyst **257** and "B" representing TMG, we can make use of the following chemical considerations:

$$AH^+ + B \underset{}{\overset{K_1}{\rightleftharpoons}} A + BH^+$$

$$K_1 = \frac{[A][BH^+]}{[AH^+][B]} = \frac{[A][H^+]}{[AH^+]} \div \frac{[B][H^+]}{[BH^+]} = \frac{K_{AH+}}{K_{BH+}}$$

$$\log K_1 = \log K_{AH+} - \log K_{BH+}$$

As $pK_{AH+} = -\log K_{AH+}$ and $pK_{BH+} = -\log K_{BH+}$,

$$pK_{AH+} = pK_{BH+} - \log K_1 \quad \textbf{[1]}$$

As proton exchange occurs quickly on an NMR timescale, the observed chemical shift (δ_{obs}) of a peak of a salt of **257** is the weighted average of the chemical shifts of its protonated (δ_{AH+}) and freebase (δ_A) forms, as illustrated by the following equation:

$$\delta_{obs} = x_{AH+}\delta_{AH+} + x_A\delta_A$$

As x_{AH+} and x_A are the mole fractions of the protonated and freebase forms respectively, we can say that:

$$x_{AH+} + x_A = 1 \text{ and so } \delta_{obs} = x_{AH+}\delta_{AH+} + (1 - x_{AH+})\delta_A$$

$$= \delta_A + x_{AH+}(\delta_{AH+} - \delta_A)$$

$$x_{AH+} = \frac{(\delta_{obs} - \delta_A)}{(\delta_{AH+} - \delta_A)} \quad \textbf{[2]}$$

In an equimolar mixture of AH^+ and B, K_1 can be represented in terms of x_{AH+} as:

$$[A] = [BH^+] \text{ and } [AH^+] = [B] \text{ so}$$

$$K_1 = \frac{[A][BH^+]}{[AH^+][B]} = \frac{[A]^2}{[AH^+]^2} = \frac{{x_A}^2}{{x_{AH+}}^2} = \frac{(1-x_{AH+})^2}{{x_{AH+}}^2} \quad \textbf{[3]}$$

Equations **[1]**, **[2]** and **[3]** above are used in the calculations of the estimated pK_{BH+} of catalyst **257** in CD_3CN from the chemical shifts of specific peaks in ^{13}C and ^{31}P NMR of the freebase and protonated forms of **257**, and in an equimolar mixture of **257** and TMG. The chemical shifts of CH_2-N=**P**R_3 and **C**H_2-N=PR_3 of all three forms were obtained and used to calculate the estimated pK_{BH+} of catalyst **257** in CD_3CN (see **4.2.9** for full experimental details, chemical shift values and calculations). The pK_{BH+} value of catalyst **257** was estimated to be 25.6 in CD_3CN, which is comparable to pK_{BH+} values of previously disclosed BIMP catalysts.[50]

2.7 Conclusion

In summary, this chapter describes the first metal-free amide enolisation for a stereoselective intramolecular Michael addition to tethered 2,5-cyclohexadienones. This powerful BIMP catalysed methodology tolerates a wide range of substituents at four different positions on the substrate, yielding the dearomatised oxindole products in high yields, enantioselectivities and diastereoselectivities. A gram-scale reaction with the model substrate **221** has been successfully carried out with a reduced catalyst loading of 5 mol%, yielding product **222** in 99.5:0.5 e.r. after a single recrystallisation. This dearomatised oxindole product contains multiple functional groups for further functionalisation, allowing the rapid synthesis of enantioenriched bicyclic lactams which have potential medicinal applications.

A key limitation of this reaction is that the substrate scope is limited by the pK_{BH+} of BIMP catalysts of approximately 25.0 in MeCN. This effectively excludes alkyl substituents at the α-position of the amide. The development of more basic BIMP catalysts will help to address this limitation, and this will be discussed in detail in the next chapter.

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Chapter 3: Amide Enolisation for Other Enantioselective Reactions

3.1 Chapter Overview

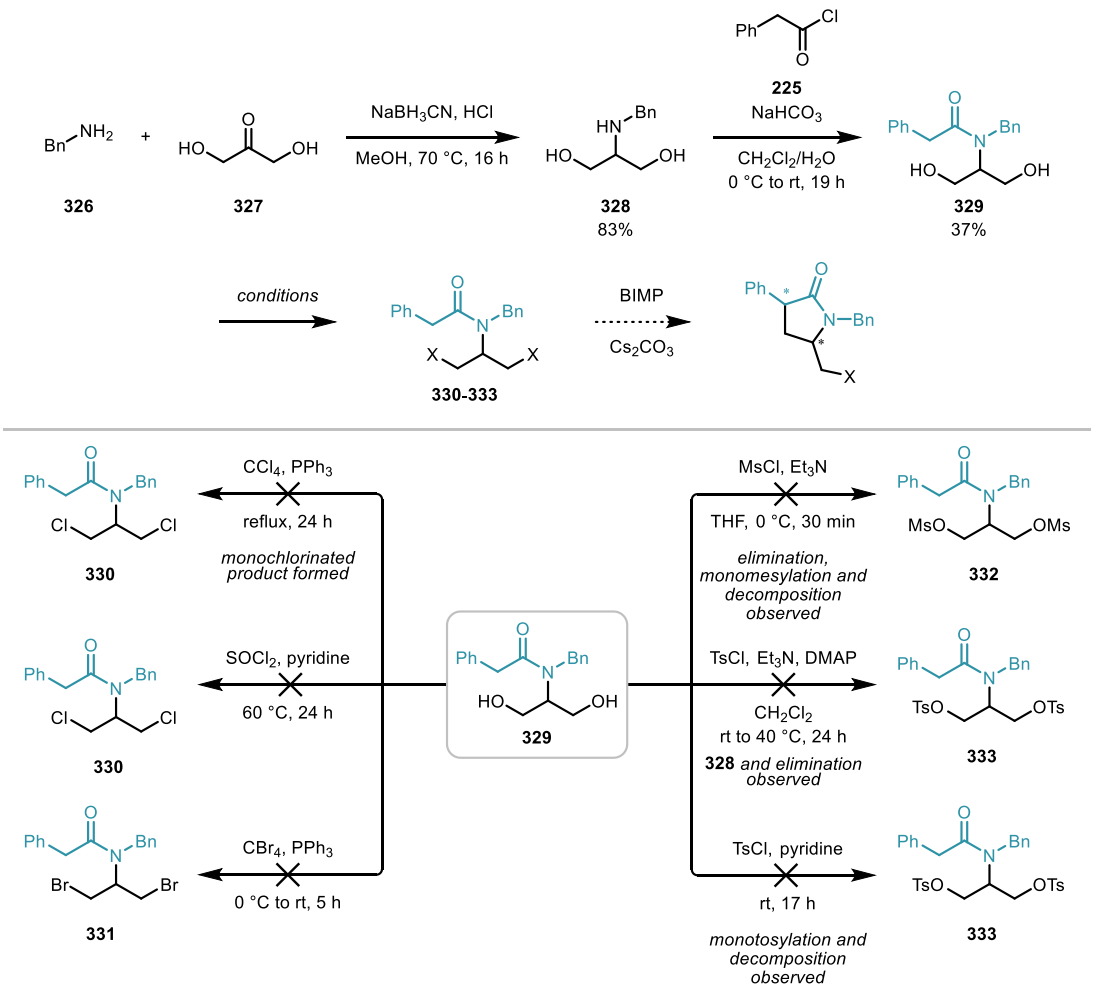
This chapter is a continuation of the work described in **Chapter 2** on a novel BIMP-catalysed desymmetrisation of amide-tethered 2,5-cyclohexadienones. With the successful development of this transformation, other electrophiles tethered to amide pronucleophiles were explored for BIMP-catalysed desymmetrisation reactions. Additionally, efforts were made towards the development of more Brønsted basic BIMP catalysts with the aim of facilitating reactions involving very inert α-alkyl amide pronucleophiles.

3.2 Desymmetrisation Triggered by Stereoselective S_N2 Reactions

Initially, we desired to explore the potential of BIMP catalysis for intramolecular reactions between amide pronucleophiles and electrophiles for S_N2 reactions such as alkyl halides and sulfonates. A three-step route similar to that shown in **Scheme 46** was proposed for the synthesis of possible substrates **330**-**333** for such reactions (**Scheme 63**). The steps involve (1) a reductive amination of commercially available 1,3-dihydroxyacetone **327** with benzylamine **326**, (2) Schotten-Baumann amide formation with 2-phenylacetyl chloride **225** and (3) replacement of the hydroxyl groups with suitable leaving groups. It was hoped that these substrates would undergo an intramolecular stereoselective S_N2 reaction in the presence of a highly Brønsted basic BIMP catalyst to form the active amide enolate nucleophile and stoichiometric Cs_2CO_3 to neutralise any HCl, HBr, MsOH or TsOH formed in the reaction. The proposed BIMP-catalysed reactions would be desymmetrisation reactions similar to that described in **Chapter 2** and the products formed would contain a five-membered lactam with two stereocentres.

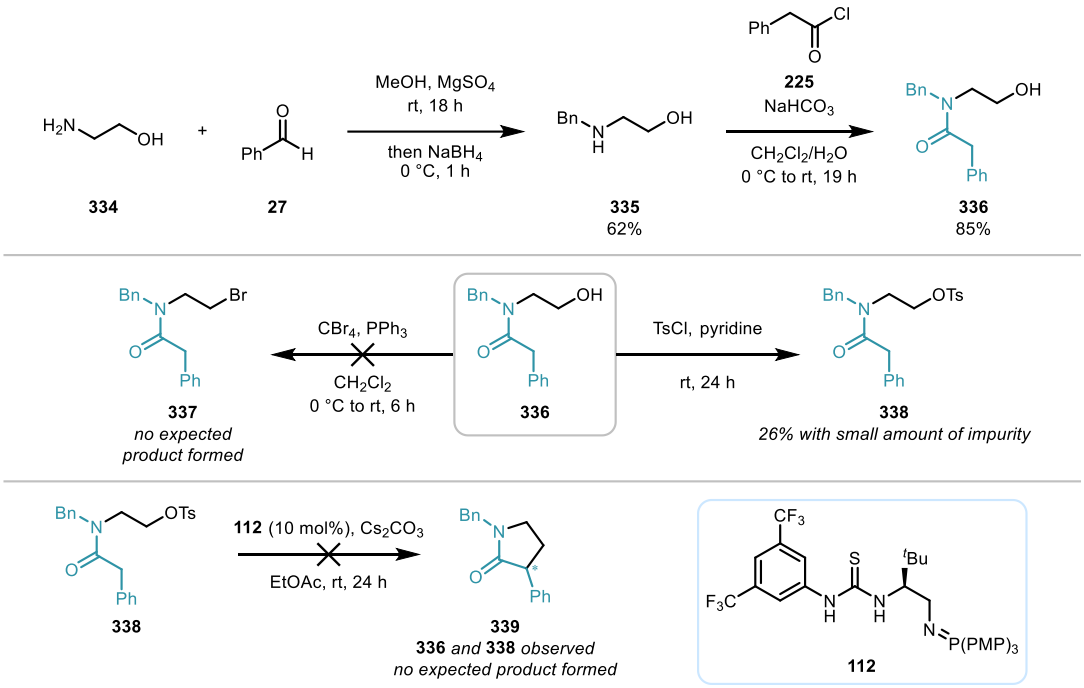
The first two steps were successfully carried out after a few attempts, yielding novel amide diol **329** in moderate yield. However, various attempts to replace the hydroxyl groups with leaving groups such as chlorides (**330**), bromides (**331**) mesylates (**332**) and tosylates (**333**) were unsuccessful. An Appel reaction

with triphenylphosphine in neat carbon tetrachloride led to the formation of a monochlorinated product rather than dichlorinated product **330**. Attempts to form **330** with thionyl chloride and pyridine were unsuccessful, while attempts to employ Appel conditions with carbon tetrabromide to form dibrominated product **331** were also unsuccessful. Reacting **329** with mesyl chloride led to the formation of many side products rather than the desired dimesylated product **332**, while reacting **329** with tosyl chloride in the presence of bases such as triethylamine, DMAP and pyridine resulted in no formation of the desired ditosylated product **333**. A few examples of such transformations involving similar amide diols were found in the literature, where the reaction substrates do not bear any aromatic or sterically bulky groups, and the hydroxyl groups are either further apart from each other or constrained substituents in a pyrrolidine ring.[1]



Scheme 63. Proposed synthesis of substrates for intramolecular S_N2 reactions involving amide pronucleophiles.

As any desired reaction would occur on only one instead of both hydroxyl groups, the use of simpler substrates **337**-**338** with only one S_N2 leaving group was considered. The synthetic route to brominated **337** and tosylated **338**, both novel compounds, involves the same general steps as the previously proposed substrates (**Scheme 64**). **338** Was successfully obtained, but no desired S_N2 reaction occurred in the presence of a BIMP catalyst, **112**.

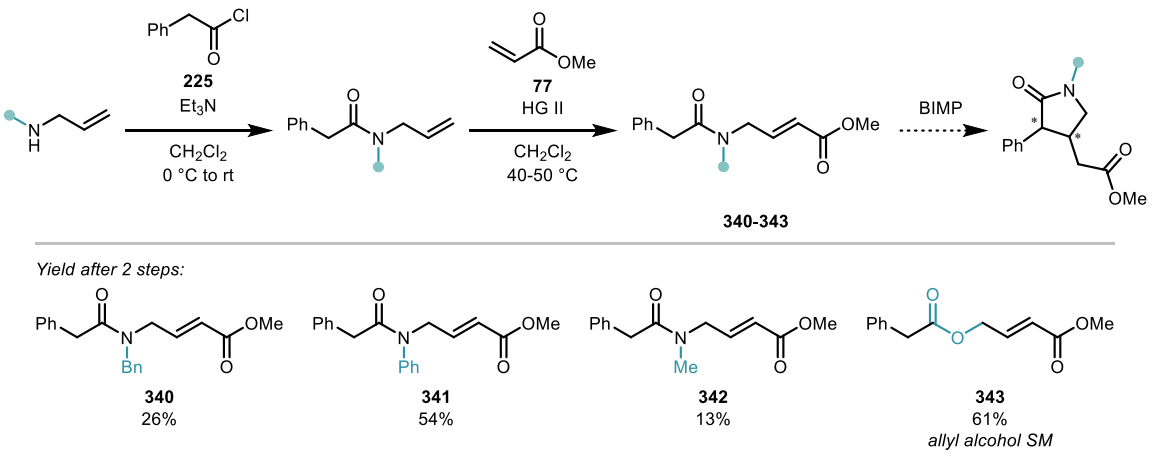


Scheme 64. Synthesis of substrates for BIMP-catalysed intramolecular S_N2 reaction.

Due to the difficulty in the synthesis, isolation and reaction of substrates **337**-**338**, we decided to shift our efforts towards other similar reactions in the hope of successfully expanding the scope of BIMP-catalysed reactions involving amide pronucleophiles.

3.3 Reactions Involving Unsaturated Electrophiles

The use of unsaturated electrophiles besides cyclohexadienones for enantioselective intramolecular Michael additions was then considered. It was hoped that the H-bond donating ability of BIMP catalysts would facilitate reactions between amide and ester pronucleophiles and comparatively less electrophilic functional groups such as acrylate esters.[2] The synthesis of these substrates involves a two-step route comprising (1) amide or ester formation with 2-phenylacetyl chloride **225** and (2) alkene metathesis with Hoveyda-Grubbs II catalyst (**Scheme 65**).

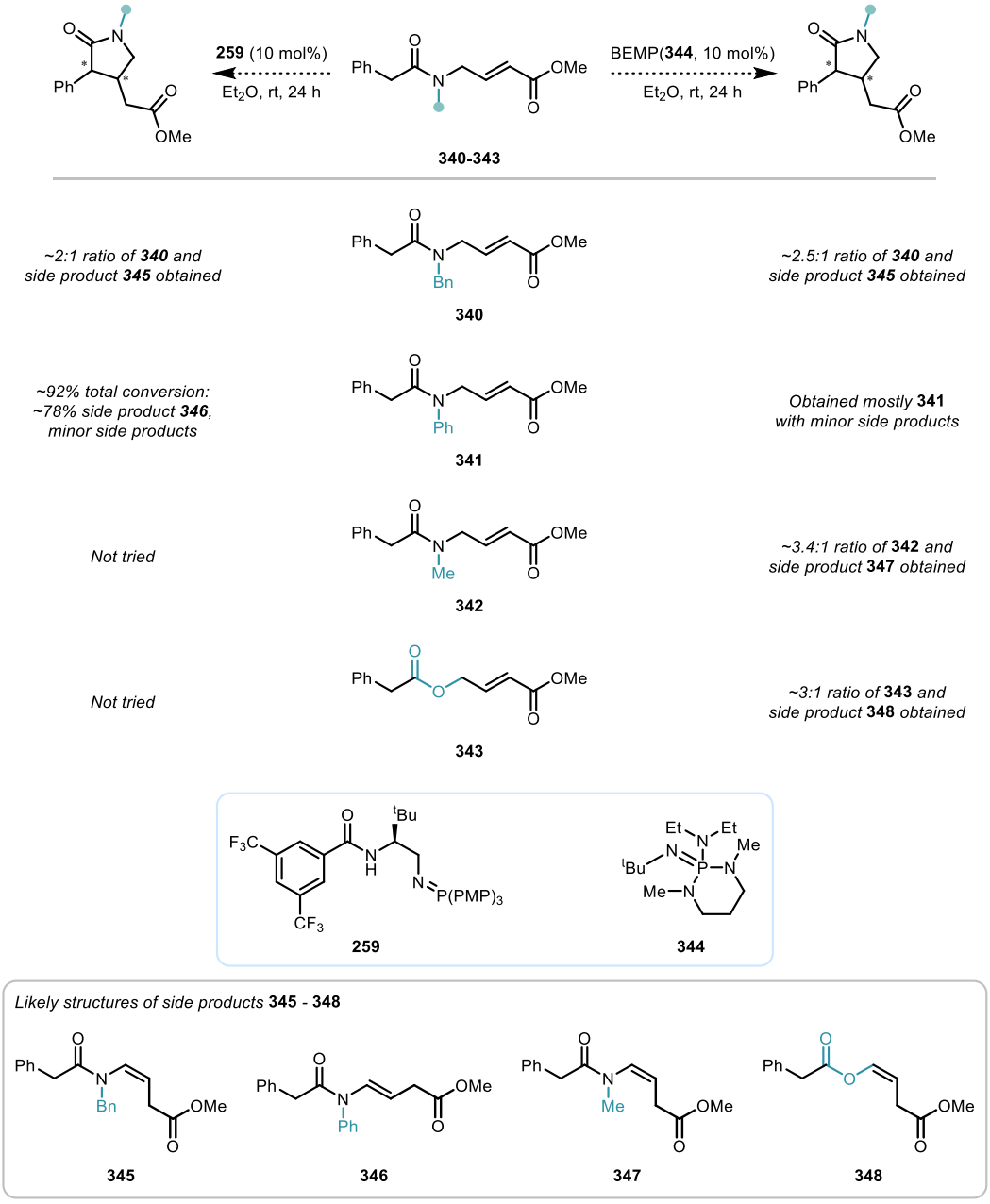


Scheme 65. Synthesis of substrates for BIMP-catalysed intramolecular Michael addition.

The amide substrates **340**-**342** and the ester substrate **343** were obtained and reacted with 10 mol% of BIMP catalyst **259** as well as achiral superbase BEMP **344** (**Scheme 66**). With substrate **340**, no expected lactam product was obtained according to the crude ^{1}H NMR spectra of the reactions with both bases **259** and **344**. Instead, substrate **340** and a few side products were observed, with a major side product **345** and a few minor side products. **345** was isolated and its ^{1}H NMR spectrum was used to determine its likely structure (see **4.3.4** for characterisation). The relatively small coupling constant of the alkene protons of 7.8 Hz suggests that the alkene in **345** is likely to have a *cis* configuration. This alkene is also likely to be located adjacent to the N atom of the amide rather than in conjugation with the ester carbonyl group, as the peak corresponding to the alkene proton at the distal end away from the methylene group has a high chemical shift of 6.12 ppm. This suggests that **345** is likely to be a product of a 1,3-prototropic shift reaction. A 2:1 and 2.5:1 ratio of **340** to **345** was observed with BIMP **259** and BEMP **344** respectively.

With substrate **341**, the reaction with BIMP catalyst **259** similarly yielded no expected lactam product but approximately 78% conversion to a major side product **346** with other minor side products. The ^{1}H and ^{13}C NMR spectra of **346** were used to determine its likely structure (see **4.3.4** for characterisation). Unlike side product **345** derived from substrate **340**, **346** likely contains a *trans* alkene due to the larger coupling constant of the alkene protons of 14.4 – 14.5 Hz. The peak corresponding to the alkene proton at the distal end away from the methylene group has a high chemical shift of 7.58 ppm, which means that an *N*-alkenyl amide is likely to be formed. Hence, like **345**, **346** is likely to be a product of a 1,3-

prototropic shift. The ^{13}C NMR spectrum of **346** shows that the molecule contains the same number of carbon atoms as **341** with the presence of both an amide and an ester, supporting the above deductions. The reaction of **341** with BEMP **344** resulted in the isolation of mainly substrate **341** with no **346** and only very minor side products even after heating the reaction vessel to 50 °C.



Scheme 66. Attempted intramolecular Michael additions catalysed by BEMP **344** or BIMP catalyst **259**.

With substrates **342** and **343**, only the reactions with achiral BEMP **344** were tried. The reaction with substrate **342** yielded a mixture with a 3.4:1 ratio of **342** and a side product **347**, similarly without any expected lactam product obtained. The ^{1}H NMR spectrum of this mixture was used to determine the

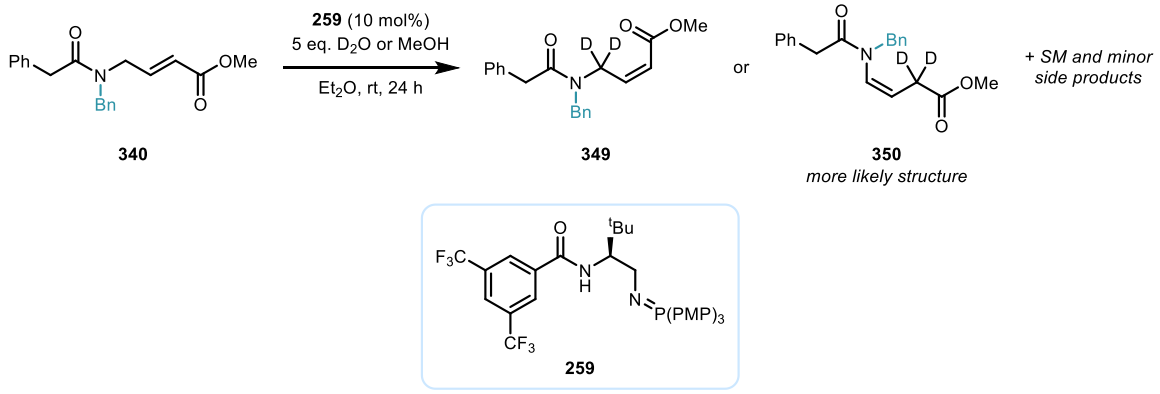
likely structure of **347** (see **4.3.4** for characterisation). Like side product **345**, the relatively small coupling constant of the alkene protons of 7.9 Hz suggests that the alkene in **347** is likely to have a *cis* configuration. This alkene is also likely to be located adjacent to the N atom of the amide, as the peak corresponding to the alkene proton at the distal end away from the methylene group has a high chemical shift of 6.34 ppm. This suggests that **347**, like **345** and **346**, is likely to be a product of a 1,3-prototropic shift reaction.

A similar result was obtained with ester substrate **343** and BEMP **344**, with a 3:1 ratio of **343** and a major side product **348** with minor side products and no expected lactam product. The ^{1}H NMR spectrum of this mixture was used to determine the likely structure of **348**, which is similar to that of **345** and **347**. (see **4.3.4** for characterisation). The small coupling constant of the alkene protons of 6.4 Hz suggests that the alkene in **348** is likely to have a *cis* configuration. The peak corresponding to the alkene proton at the distal end away from the methylene group has a high chemical shift of 7.18 ppm, which means that an *O*-alkenyl ester is likely to be formed. This suggests that **348**, like **345**, **346** and **347**, is likely to be a product of a 1,3-prototropic shift reaction.

It became apparent that deprotonation at the γ-position of the acrylate ester, which is the position adjacent to the N or O atom of the amide or ester pronucleophile, was a competing process, due to the ease of formation of *N*- and *O*-alkenyl amide and ester side products from substrates **340**-**343**. Thus, deuterium incorporation experiments were performed to compare the relative ease of deprotonation at two positions on the substrate: the α-carbon of the amide or ester pronucleophile and the γ-position of the intended acrylate ester electrophile (**Scheme 67**). *N*-Benzyl amide substrate **340** was reacted with BIMP catalyst **259** under the above conditions (**Scheme 66**) in the presence of 5 eq. deuterium electrophiles D_2O or MeOD.

Both reactions led to very similar outcomes and products formed, with only a slightly higher level of conversion to a main deuterium-incorporated product in the reaction with D_2O. This product was isolated and its ^{1}H NMR spectrum shows two simple 1H doublets in the region associated with alkene protons, at 6.12 ppm and 5.69 ppm. These two alkene protons represented are coupled to each other with a coupling constant of 7.8 Hz, which is a relatively small value, suggesting that this product likely

contains a *cis* alkene. Due to the absence of multiplets showing coupling with allylic protons, unlike in substrate **340** or side product **345** derived from **340**, this product likely contains two deuterium atoms incorporated at the allylic position, substituting both the H atoms. As a 2H singlet at 3.65 ppm corresponds to the protons attached to the α-carbon of the amide, there is likely no deuterium incorporation at that position. Thus, the proposed structure of this product could be either **349** or **350** which have the same molecular mass, with **350** being a product of a 1,3-prototropic shift. However, as the chemical shifts of the alkene protons in this product are more similar to **345** (6.12, 5.71 ppm) than to **340** (6.82, 6.75, 5.88, 5.77 ppm, two rotamers), **350** is the more likely structure (see **4.3.4** for characterisation). No further attempts were made to determine the exact structure of the product. This suggests that the γ-position of the acrylate ester is deprotonated much more easily as compared to the α-carbon of the amide or ester pronucleophile, meaning that our proposed reaction was not viable, and our work had to be directed elsewhere.

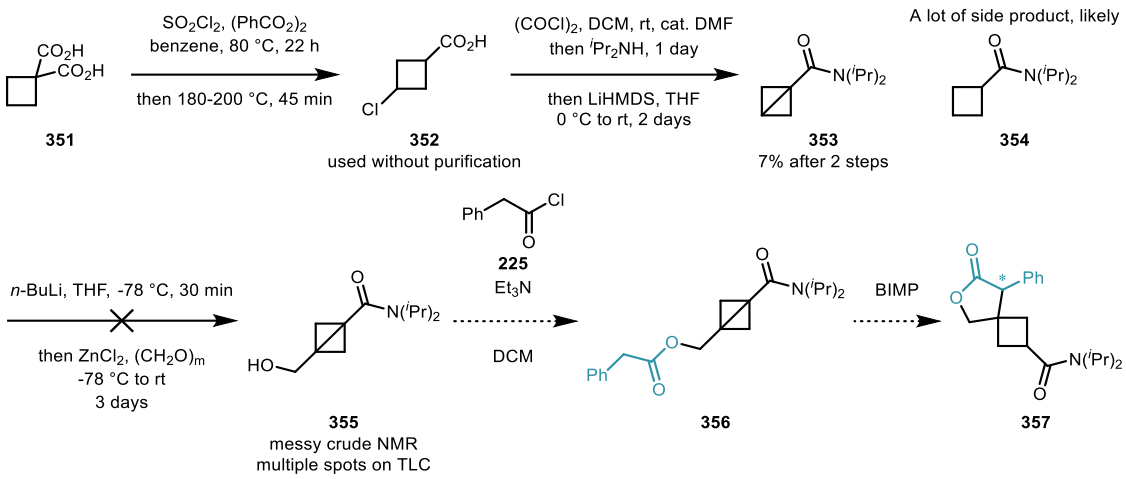


Scheme 67. Deuterium incorporation experiments with substrate **340**.

3.4 Reactions with Bicyclo[1.1.0]butane Electrophiles

The use of intramolecular bicyclo[1.1.0]butane (BCB) electrophiles was then explored. Upon formation of the active amide or ester enolate nucleophile, a nucleophilic addition onto the other side of the BCB bridge could occur, which would relieve the ring strain and lead to the formation of spirocyclic product **357** containing a cyclobutane ring. Attempts were made to synthesise the intended bridge-substituted substrate **356** containing an ester pronucleophile according to a literature procedure with some modifications to the route (**Scheme 68**).[3]

Due to the smaller scale used in our reactions as opposed to the literature procedure, impure crude **352** produced from the chlorination and decarboxylation steps was used in the subsequent amide and BCB formation step without purification by distillation to minimise product loss. BCB amide **353** was formed in a low 7% yield after 2 steps, due to the formation of a major side product, which was deduced to likely be cyclobutane amide **354**. A key primary alcohol intermediate **355** could not be cleanly isolated after the next step and this work was discontinued due to difficulties in substrate synthesis.



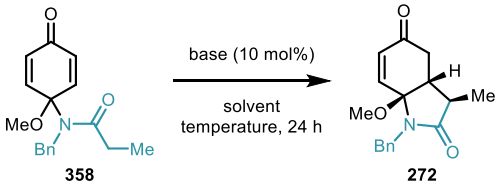
Scheme 68. Synthesis of ester-tethered BCB substrate **356**.

3.5 Development of More Basic BIMP Catalysts

3.5.1 Reactions of α-alkyl Amide and Ester Substrates with Known Bases

We turned our attention towards developing catalysts for reactions involving inert α-alkyl amide pronucleophiles, which were unsuccessful substrates in our cyclohexadienone desymmetrisation reaction (**Scheme 52**). The model substrate for this investigation, α-methyl amide **358**, was first reacted with various achiral superbases as well as chiral BIMP catalyst **362** to determine its reactivity in terms of conversion to **272** (**Table 3**). Catalyst **362** was derived from the same azide component as catalyst **257**, the optimal catalyst in the previously developed cyclohexadienone desymmetrisation reaction (see **Chapter 2**). The phosphine used in the synthesis of BIMP catalysts **361** and **362**, 4,4',4"-phosphanetriyltris(*N*,*N*-dimethylaniline), was synthesised by Daniel Rozsar and cyclohexyl azide-derived base **361** was found to have an experimentally determined pK_{BH+} of 26.90 to 28.07 in MeCN.[4] It was hoped that this higher pK_{BH+} value as compared to other BIMP catalysts derived from PPh_3,

P(PMP)$_3$ and tris-(3,4,5-trimethoxyphenyl)phosphine would translate to greater reactivity in the proposed cyclohexadienone desymmetrisation reaction with **358**.[5]



entry	base	solvent	temperature	conversion (%)
1	**344**	TBME	rt	0
2	**359**	Et_2O	50 °C	3
3	**360**	Et_2O	50 °C	trace (impure)
4	**361**	MeCN	50 °C	0
5	**362**	TBME	rt	3
6	NaHMDS	THF	-78 °C	83 (1.5 h)

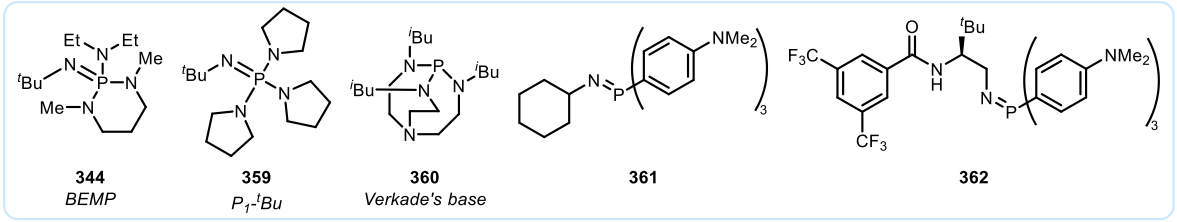
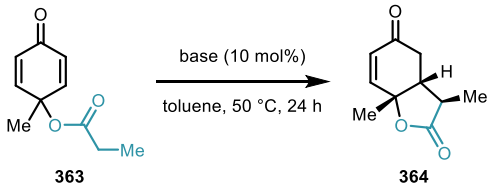


Table 3. Reaction of α-methyl amide-tethered cyclohexadienones with various bases.

Most of the bases tested were insufficiently Brønsted basic to deprotonate the amide in **358** at the α-position, resulting in little or no conversion to **272** (entries 1 to 5). Only the inorganic base NaHMDS was sufficiently Brønsted basic, yielding product **272** in a substantial 83% conversion after a reaction time of only 1.5 hours (entry 6). The corresponding ester substrate **363**, which has a lower pK_a and is likely to be more reactive,[6] was synthesised according to the procedure described in **Scheme 60** and tested with a similar set of organic bases (**Table 4**). Although the three bases tried gave slightly different conversions, all of them gave mostly starting material **363** and no product **364** could be isolated.



entry	base	conversion (%)
1	**344**	<1
2	**359**	2
3	**360**	3

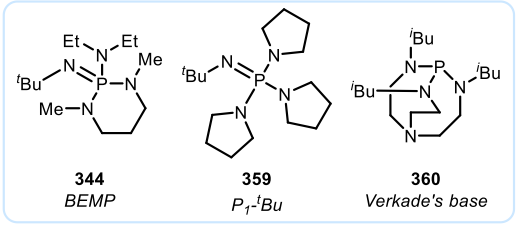
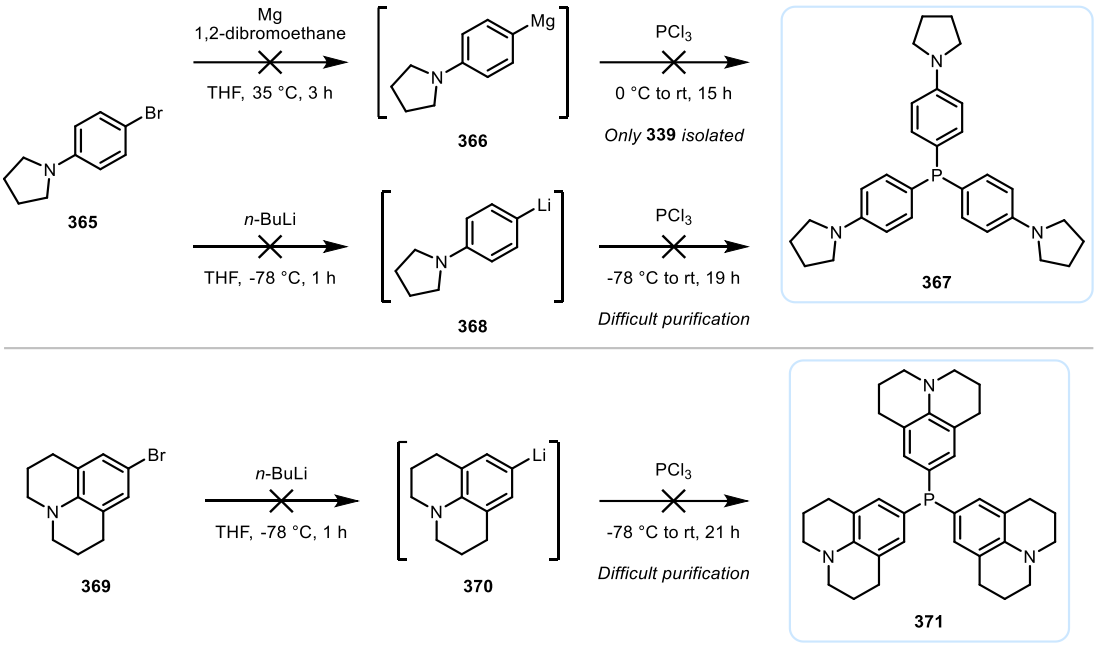


Table 4. Reaction of α-methyl ester-tethered cyclohexadienones with various bases.

3.5.2 Phosphine Synthesis

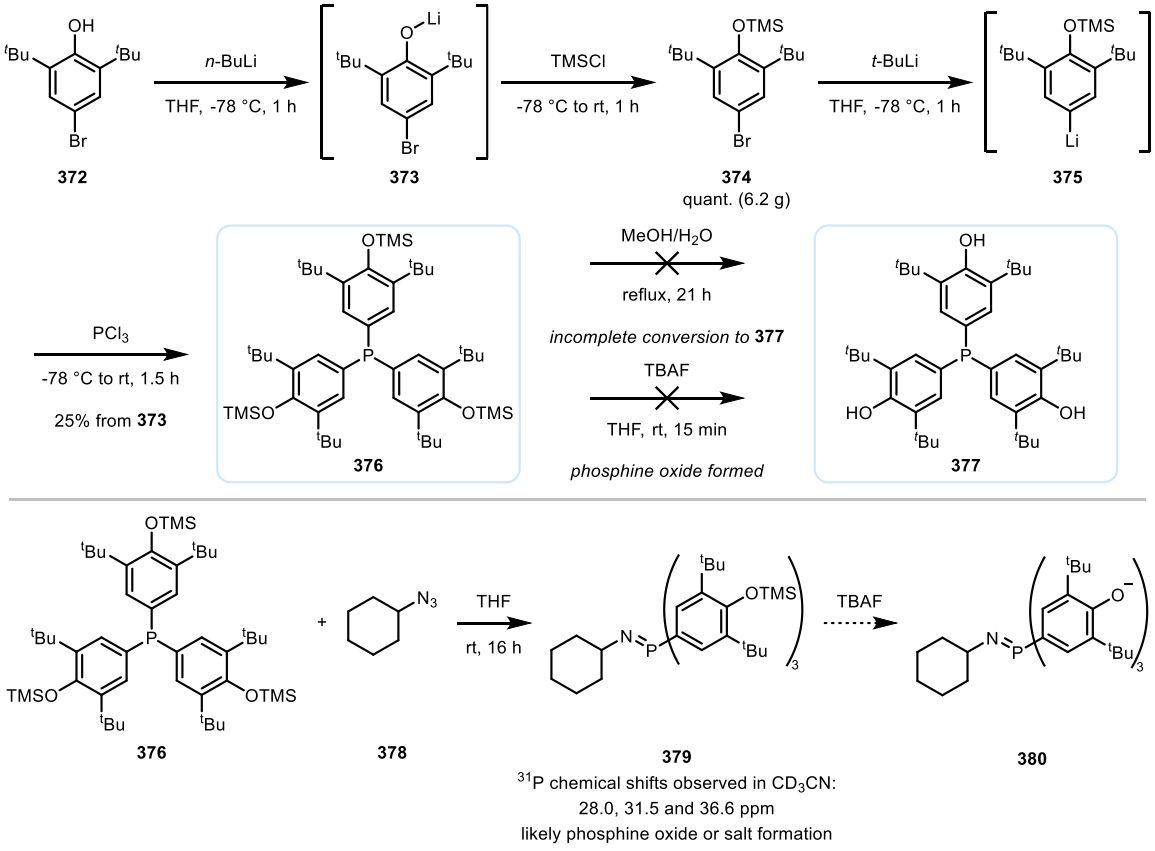


Scheme 69. Attempted synthesis of nitrogen-containing phosphines.

Following the high experimentally-determined pK_{BH+} of an iminophosphorane **361** derived from nitrogen-containing phosphine 4,4',4"-phosphanetriyltris(*N*,*N*-dimethylaniline) and cyclohexyl azide,[4] we looked into the synthesis of a library of similar nitrogen-containing phosphines (**Scheme 69**). The typical route for the preparation of trivalent aryl phosphines involves the generation of an organometallic species from an aryl bromide for nucleophilic substitution with PCl_3. Pyrrolidine- and julolidine-containing phosphines **367** and **371** are similar in structure to 4,4',4"-phosphanetriyltris(*N*,*N*-dimethylaniline), with greater conformational rigidity due to the pyrrolidine rings and the rigid julolidine structure. The synthesis of phosphine **367** was attempted using a literature procedure for the synthesis of 4,4',4"-phosphanetriyltris(*N*,*N*-dimethylaniline),[4,7] which led to the isolation of only starting material bromide **365**. A similar procedure involving the generation of organolithium **368** instead of organomagnesium species **366** from the aryl bromide precursor **365** led to difficulties in the purification and isolation of **367**. **367** is likely air-sensitive and oxidises easily. In the crude ^{31}P NMR spectrum of the reaction mixture, a peak likely attributed to the phosphine oxide shows at 30.7 ppm in $CDCl_3$ alongside a peak at -10.6 ppm which corresponds to the main product, as well as a few unidentified peaks. Various purification strategies including trituration, recrystallisation and flash column

chromatography did not lead to the isolation of any pure product. This procedure was used in the synthesis of phosphine **371** from aryl bromide **369** where similar difficulties in purification and isolation were experienced.

We turned our attention to the synthesis of phenol-containing phosphines (**Scheme 70**). It was believed that the generation of a BIMP catalyst with such a phosphine would result in a highly electron-rich iminophosphorane upon deprotonation of the phenol groups by an external base. Using a literature procedure,[8] TMS-protected bromide **374** was synthesised in quantitative yield and was reacted with *t*-BuLi and PCl_3 to form phosphine **376** in 25% yield after multiple rounds of purification.[9] Attempts to deprotect the TMS groups on phosphine **376** with MeOH in H_2O and TBAF in THF led to sluggish formation of phosphine **377** and phosphine oxide formation respectively. The two main phosphorus-containing products in the reaction with TBAF showed relatively high chemical shifts of 32.8 and 32.1 ppm on ^{31}P NMR in $CDCl_3$, which likely correspond to oxidised phosphine **376**.



Scheme 70. Synthesis and activity of phenol- and TMS protected phenol-containing phosphines.

Phosphine **376** was then used in a Staudinger reaction with cyclohexyl azide **378** in an attempt to form iminophosphorane **379**. We reasoned that the TMS protecting groups in **379** could be deprotected with TBAF to form anionic **380** in one pot immediately after the formation of **379**, which was hoped to eliminate any issues with phosphine oxide formation. However, when a ^{31}P NMR spectrum of the crude reaction mixture was taken after 16 hours in CD_3CN, three main peaks with relatively high chemical shifts of 28.0, 31.5 and 36.6 ppm were observed. This is much higher than the 10.2 ppm obtained for BIMP catalyst **257** and suggests that **380** was unlikely to be formed, or it was present in only the protonated form without the presence of an acid in the reaction mixture. **376** was likely to be air-sensitive, resulting in phosphine oxide formation either while in storage or in the Staudinger reaction mixture.

3.6 Conclusion and Future Work

In conclusion, various attempts to increase the scope of BIMP-catalysed reactions involving amide or ester pronucleophiles with various intramolecular sp^2 and sp^3 electrophiles have not been successful. Issues with substrate synthesis, competing or sluggish reactivity led us to explore different ways to improve the Brønsted basicity of BIMP catalysts to allow new reactivity with unreactive substrates in our previously disclosed reaction (**Chapter 2**, **Scheme 52**).

α-Methyl amide- and ester-tethered cyclohexadienones **358** and **363** were shown to be unreactive with different bases tried. This investigation also revealed that the Brønsted basicity of any developed catalyst would need to be at least comparable to NaHMDS for the intended desymmetrisation reaction involving these unreactive substrates to proceed.

Attempts were made to synthesise various heteroatom-containing phosphines for use as iminophosphorane precursors to tune the basicity of the iminophosphorane. However, the intended phosphines were shown to be air-sensitive and easily oxidised.

Nevertheless, all of the progress made in the Dixon group so far to improve the Brønsted basicity and efficiency of BIMP catalysts highlights their tunability and shows that the iminophosphorane in BIMP catalysts is not confined to a narrow set of pK_{BH+} values. Efforts remain ongoing to develop more

effective BIMP catalysts for reactions between inert pronucleophiles and electrophiles through modifications at all components of the BIMP catalyst, from the substituents at the P atom to the type of H-bond donor used.

3.7 References for Chapter 3

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Chapter 4: Experimental Details

4.1 General Experimental Details

All **solvents** were obtained from commercial suppliers or dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. All water used was purified via a Merck Millipore reverse osmosis purification system prior to use. All **reagents** were obtained from commercial suppliers and used directly as supplied unless otherwise stated. Solutions were evaporated under reduced pressure using a Büchi rotary evaporator.

Manual **flash column chromatography** (FCC) was carried out using Merck Silica gel 60, particle size 40-63 μm or basic alumina. Eluent systems are provided as solvent ratios or in v/v% with respect to the more polar component. All reactions were followed by **thin layer chromatography** (TLC) when practical, using Merck aluminium-backed Silicagel 60 F254 fluorescent treated silica which was visualised under UV light (λ_{max} = 254 or 365 nm) or by staining with aqueous basic $KMnO_4$.

Enantiomeric ratios (e.r.) were determined by chiral high-performance liquid chromatography (HPLC). Chiral HPLC analysis was performed on an Agilent 1200 series instrument using an appropriate chiral stationary phase column, specified in the individual experiment, and by comparing the samples with the appropriate racemic mixtures. In one instance, chiral supercritical fluid chromatography (SFC) analysis was performed on a Waters Acquity UPC2 instrument.

^{1}H, ^{13}C, ^{19}F and ^{31}P **NMR spectra** were recorded using Bruker AVIIIHD 400 Nanobay, Bruker AVIII 600 and Bruker NEO 600 spectrometers using $CDCl_3$, DMSO-*d*$_6$, CD_3OD, C_6D_6, toluene-*d*$_8$ and CD_3CN. Chemical shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane (δ_{TMS} 0.00 ppm) and referenced to the solvent residual peak (^{1}H: δ_{CDCl3} 7.26 ppm, $\delta_{DMSO\text{-}d6}$ 2.50 ppm, δ_{CD3OD} 3.31 ppm, δ_{C6D6} 7.16 ppm, $\delta_{toluene\text{-}d8}$ 7.00 ppm, δ_{CD3CN} 1.94 ppm; ^{13}C: δ_{CDCl3} 77.2 ppm, $\delta_{DMSO\text{-}d6}$ 39.5 ppm, δ_{CD3OD} 49.0 ppm, δ_{C6D6} 128.1 ppm, $\delta_{toluene\text{-}d8}$ 20.4 ppm, δ_{CD3CN} 1.3 ppm). Coupling constants (*J*) are quoted in Hertz (Hz), rounded to the nearest 0.1 Hz. The ^{1}H, ^{13}C and ^{19}F NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of atoms if greater than 1, assignment) with singlet multiplicities not reported for ^{13}C, ^{19}F and ^{31}P NMR spectra and assignments made only for novel

compounds. Two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy was utilised to assist the assignment of ^{1}H and ^{13}C signals. Spectra were analyzed using Mestrelab MestReNova 15.0.1 software.

The NMR spectra and e.r. of the reaction products are normally recorded only for the major diastereomer.

Low resolution mass spectra (LRMS) were recorded on a Waters LCT Premier mass spectrometer operating in positive and negative ionisation modes. **High resolution mass spectra** (HRMS) were recorded on a Bruker μTOF mass spectrometer or on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe. **IR spectra** were recorded on a Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Only selected absorption maxima are reported.

Melting points were recorded in degrees Celsius (°C), using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected.

Specific rotations ($[\alpha]_D^{25}$) are reported in 10^{-1} deg·cm^2 g^{-1}; D refers to the D-line of sodium (589 nm). Measurements are recorded at 25 °C. Specific rotations were calculated from optical rotations measured using a Perkin Elmer Model 341 polarimeter with a sodium lamp and a cell length of 1 dm, concentrations (*c*) are reported in g/100 mL.

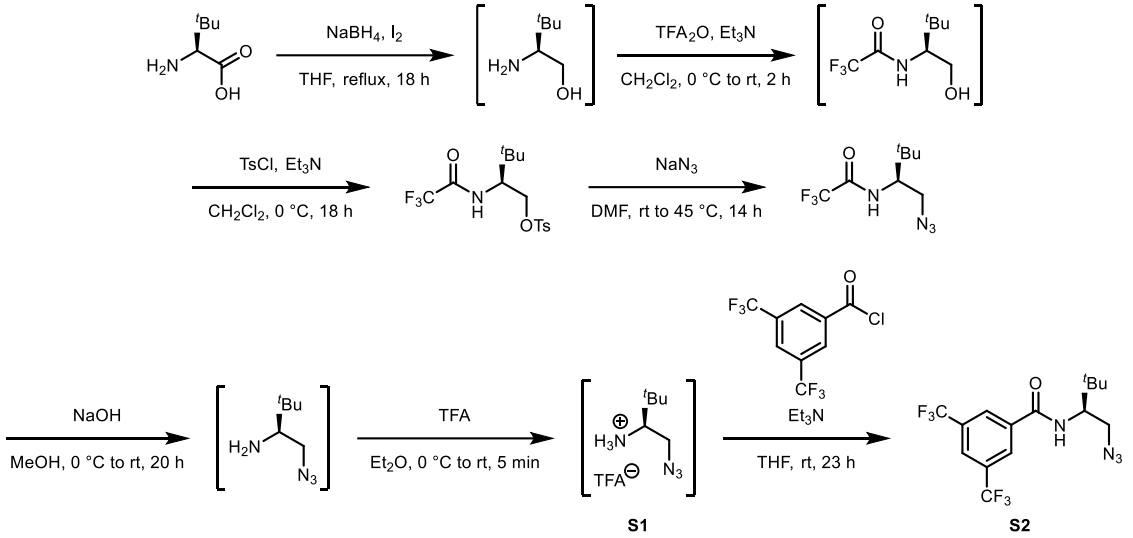
Compound names were generated using PerkinElmer ChemDraw 23.1.1.

4.2 Experimental Details for Chapter 2

4.2.1 Synthesis of Precursors of BIMP Catalyst 257

Synthesis of Azide Precursor

The ammonium azide **S1** was synthesised following a procedure previously reported by our group,[1] which was then reacted with the corresponding acyl chloride to form amide-bearing **S2**, the azide precursor to catalyst **257** (**Scheme 71**).

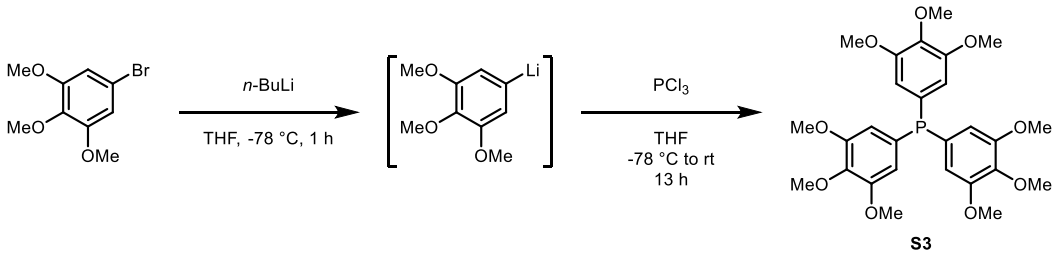


Scheme 71. Synthesis of BIMP catalyst azide precursor **S2**.

***N*-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-3,5-bis(trifluoromethyl)benzamideazide** (**S2**) was prepared according to a modified literature procedure.[2] **S1** was dissolved in anhydrous THF (16 mL) under a nitrogen atmosphere, and 3,5-bis(trifluoromethyl)benzoyl chloride (0.9 mL, 4.8 mmol, 1.2 eq.) and triethylamine (1.5 mL, 10.8 mmol, 2.7 eq.) were added. The resulting suspension was stirred at room temperature for 23 hours before quenching with water (20 mL). The reaction mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 9:1) and trituration with pentane yielded **S2** as a colourless solid (815 mg, 2.13 mmol, 53%). Analytical data is consistent with the published literature.[3]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 2H), 8.03 (s, 1H), 6.09 (d, J = 9.9 Hz, 1H), 4.26 (ddd, J = 9.9, 7.5, 4.0 Hz, 1H), 3.70 (dd, J = 12.8, 4.0 Hz, 1H), 3.47 (dd, J = 12.8, 7.5 Hz, 1H), 1.05 (s, 9H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 165.0, 136.9, 132.5 (q, J^2_F = 34.0 Hz, 2C), 127.5 – 127.3 (m, 2C), 125.3 (hept, J^3_F = 3.6 Hz) 123.0 (q, J^1_F = 273.0 Hz, $\underline{C}F_3$, 2C), 57.2, 51.8, 34.6, 27.0 (3C); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -62.9.

Synthesis of Phosphine Precursor



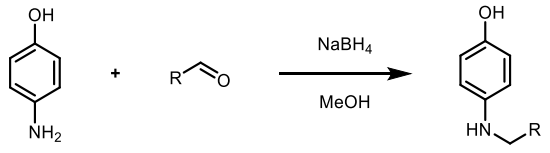
S3

Tris(3,4,5-trimethoxyphenyl)phosphane (S3) was prepared according to a modified literature procedure.[4] 5-bromo-1,2,3-trimethoxybenzene (2.47 g, 10.0 mmol, 5.0 eq.) was dissolved in degassed THF (13 mL, 0.77 M) under a nitrogen atmosphere. The solution was then cooled to -78 °C and *n*-BuLi (2.5 M in hexanes, 4.0 mL, 10.0 mmol, 5.0 eq.) was added dropwise over 10 min. The mixture was stirred for one hour at -78 °C, after which PCl_3 (0.17 mL, 2.0 mmol, 1.0 eq.) was added to the solution dropwise. The reaction mixture was stirred at -78 °C for one hour, then slowly warmed up to room temperature and stirred for an additional 12 hours. Water (5 mL) was added to the mixture, which was then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine (10 mL of each), then dried over anhydrous $MgSO_4$. Volatiles were removed *in vacuo*. The residue was recrystallised in refluxing EtOH (7.5 mL), then cooled and kept at -20 °C overnight. The product was filtered and washed with cold ethanol. Phosphine **S3** was obtained as a colourless crystalline solid (690 mg, 1.30 mmol, 65%). Analytical data is consistent with the published literature.[5]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.57 (d, *J* = 7.9 Hz, 6H), 3.86 (s, 9H), 3.75 (s, 18H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 153.4 (d, *J* = 9.5 Hz, 6C), 138.9 (3C), 132.2 (d, *J* = 10.9 Hz, 3C), 110.6 (d, *J* = 22.0 Hz, 6C), 61.0 (3C), 56.3 (6C); **^{31}P NMR** ($CDCl_3$, 162 MHz) δ 2.29.

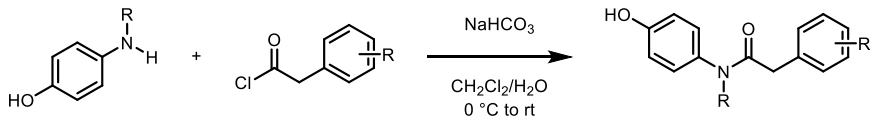
4.2.2 Synthesis of Starting Materials – General Procedures

Procedure 1 – reductive amination



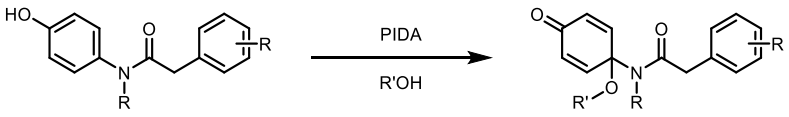
The aldehyde (1.4 eq.) was added to a solution of 4-aminophenol (1.0 eq.) in methanol (0.5 M). The reaction mixture was stirred for one hour at room temperature before adding $NaBH_4$ (1.6 eq.) at 0 °C slowly over a period of 40 min. The mixture was stirred overnight and then quenched with water (0.3 mL / 1 mmol SM). After the removal of methanol *in vacuo*, water (1 - 2 mL / 1 mmol SM) was added to dissolve the mixture, which was extracted with EtOAc (3 x 3 mL / 1 mmol SM). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated, and triturated with pentane (0.5 mL / 1 mmol SM) to yield the product.

Procedure 2 – Schotten-Baumann amide formation



The amine (1.0 eq.) was dissolved in a biphasic mixture containing CH_2Cl_2 (0.36 M) and water (1.14 M). After cooling to 0 °C, $NaHCO_3$ (2.0 eq.) and the acyl chloride (1.05 eq.) were added to the reaction mixture. The mixture was warmed to room temperature and stirred until consumption of the amine as indicated by TLC (2 - 20 hours). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL / 1 mmol SM). The organic layer was dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

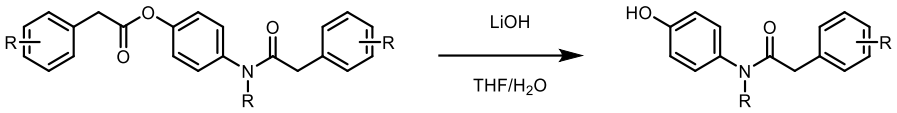
Procedure 3 – phenol oxidation



According to a modified literature procedure,[6] the amide (1.0 eq.) was dissolved in the alcohol (0.05 - 0.1 M). Phenyliodine (III) diacetate (PIDA, 1.2 eq.) was added to the reaction mixture, which was then stirred for one hour or until all the starting material was consumed, as indicated by TLC. The reaction was quenched with sat. $NaHCO_3$ (20 mL/1 mmol SM) and extracted with Et_2O (3 x 20 mL/1 mmol

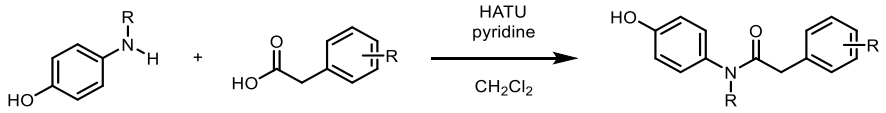
SM). The organic layer was dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

Procedure 4 – ester hydrolysis



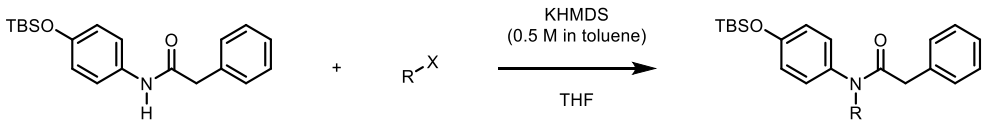
According to a modified literature procedure,[7] the ester (1.0 eq.) was dissolved in THF (0.5 M) and water (1.2 M) and LiOH (5.0 eq.) was added. The mixture was stirred for 3 hours or until consumption of the ester as indicated by TLC. The reaction mixture was then washed with 1 M HCl (10 mL / 1 mmol SM). The aqueous layer was extracted with EtOAc (10 mL / 1 mmol SM). The organic layers were washed with brine (10 mL / 1 mmol SM), dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

Procedure 5 – amide coupling



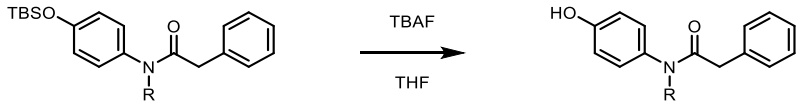
According to a modified literature procedure,[8] the carboxylic acid (1.0 eq.), amine (1.1 eq.) and HATU (1.1 eq.) were dissolved in CH_2Cl_2 (0.5 M). The mixture was allowed to stir at room temperature for 3 min before pyridine (2.0 eq.) was added dropwise. The reaction mixture was then left to stir until consumption of the limiting reagent as indicated by TLC (2 - 24 hours). The reaction mixture was washed with sat. $NaHCO_3$ (10 mL / 1 mmol SM) and extracted with CH_2Cl_2 (4 x 10 mL / 1 mmol SM). The combined organic layers were dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

Procedure 6 – amide *N*-alkylation



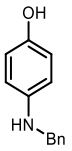
The amide (1.0 eq.) was dissolved in anhydrous THF (0.15 M) under a nitrogen atmosphere. The solution was cooled to 0 °C and KHMDS (0.5 M in toluene, 1.1 eq.) was added. The reaction mixture was stirred at 0 °C for 15 min and the alkyl halide (2.0 eq.) was then added dropwise. The mixture was warmed to room temperature and stirred until consumption of the limiting reagent as indicated by TLC. The reaction mixture was quenched with water (10 mL / 1 mmol SM) and the aqueous layer was extracted with EtOAc (3 x 10 mL / 1 mmol SM). The combined organic layers were washed with brine (10 mL / 1 mmol SM), dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

Procedure 7 – deprotection of TBS-protected phenol



The silyl ether (1.0 eq.) was dissolved in anhydrous THF (0.1 M). 1 M tetrabutylammonium fluoride (TBAF) in THF solution (2.7 eq.) was added to the reaction mixture, which was then stirred for 15 min or until consumption of the silyl ether as indicated by TLC. The reaction was quenched with water (10 mL / 1 mmol SM) and extracted with EtOAc (5 mL / 1 mmol SM) and the organic layer was washed with water and brine (10 mL each / 1 mmol SM). The organic layer was then dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

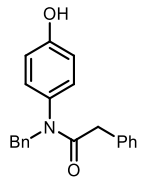
4.2.3 Synthesis of Starting Materials – Specific Procedures and Analytical Data



4-Benzylaminophenol (224) was prepared according to **Procedure 1** and was obtained as a brown solid after trituration with pentane (20.8 g, 104 mmol, quant.). Analytical data is consistent with the published literature.[9]

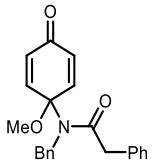
^{1}H NMR (CDCl3, 400 MHz) δ 7.41 – 7.27 (m, 5H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 4.28 (s, 2H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 148.0, 142.5, 139.8, 128.7 (2C), 127.7 (2C), 127.3, 116.4 (2C), 114.5 (2C), 49.5.

Synthesis of **222** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-phenylacetamide (226)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 2:1 – 1:1) yielded **226** as a colourless solid (9.75 g, 30.7 mmol, 61%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 – 7.15 (m, 8H, ArH), 7.08 – 7.05 (m, 2H, ArH), 6.72 (s, 4H, ArH), 5.59 (br s, 1H, OH), 4.84 (s, 2H, NCH_2), 3.47 (s, 2H, $CH_2C{=}O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.0 (C=O), 156.2 (ArC), 137.4 (ArC), 135.4 (ArC), 134.3 (ArC), 129.8 (ArC, 2C), 129.2 (ArC, 2C), 129.1 (ArC, 2C), 128.5 (ArC, 4C, 2 peaks), 127.5 (ArC), 126.8 (ArC), 116.3 (ArC, 2C), 53.6 (NCH_2), 41.3 ($CH_2C{=}O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{20}NO_2^+$ $[M+H]^+$: 318.1489, found 318.1492; **m. p.**: 142 – 144 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3270, 3030, 1625, 1513, 1272, 726, 699.

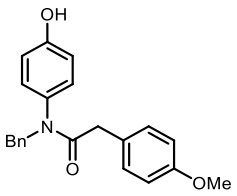


***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (221)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 3:1) yielded **221** as a brown solid (267 mg, 0.769 mmol, 77%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.37 (m, 2H, ArH), 7.34 – 7.21 (m, 6H, ArH), 7.13 – 7.11 (m, 2H, ArH), 6.64 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.34 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 4.76 (s, 2H, NCH_2), 3.63 (s, 2H, $CH_2C{=}O$), 3.17 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone C=O), 172.1 (amide C=O), 144.3 (CHC(N)CH, 2C), 138.6 (ArC), 134.4 (ArC), 129.9 (ArC, 2C), 129.0

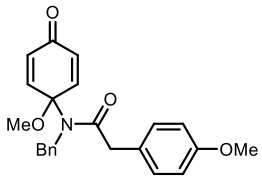
(CHC(O)CH, 2C), 129.0 (ArC, 2C), 128.9 (ArC, 2C), 127.5 (ArC), 127.2 (ArC), 126.5 (ArC, 2C), 83.6 ($COCH_3$), 51.0 ($COCH_3$), 47.1 (NCH_2), 42.6 ($CH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{22}NO_3^+$ $[M+H]^+$: 348.1594, found 348.1594; **m. p.**: 87 – 89 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3030, 1664, 1075, 701.

Synthesis of **261** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(4-methoxyphenyl)acetamide (S4)** was prepared according to **Procedure 2** and was obtained as a yellow solid after trituration in CH_2Cl_2 (600 mg, 1.73 mmol, 86%).

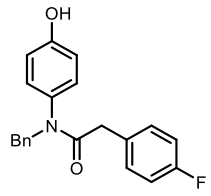
^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.64 (s, 1H, OH), 7.30 – 7.19 (m, 3H, ArH), 7.17 – 7.12 (m, 2H, ArH), 6.96 (d, J = 8.7 Hz, 2H, ArH), 6.87 (d, J = 8.7 Hz, 2H, ArH), 6.81 (d, J = 8.6 Hz, 2H, ArH), 6.71 (d, J = 8.8 Hz, 2H, ArH), 4.78 (s, 2H, NCH_2), 3.71 (s, 3H, $ArOCH_3$), 3.34 (s, 2H, $CH_2C=O$); **^{13}C NMR** (DMSO-d_6, 101 MHz) δ 170.7 (C=O), 157.8 (ArC), 156.7 (ArC), 137.8 (ArC), 133.3 (ArC), 130.1 (ArC, 2C), 129.4 (ArC, 2C), 128.2 (ArC, 2C), 128.0 (ArC, 2C), 127.8 (ArC), 127.0 (ArC), 115.8 (ArC, 2C), 113.5 (ArC, 2C), 55.0 ($ArOCH_3$), 52.3 (NCH_2), 39.1 ($CH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{22}NO_3^+$ $[M+H]^+$: 348.1594, found 348.1594; **m. p.**: 170 – 174 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3249, 2948, 1619, 1509, 1250, 1159, 1028, 839, 740, 609.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(4-methoxyphenyl)acetamide (S5)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 1:1) yielded **S5** as an off-white solid (362 mg, 0.959 mmol, 51%).

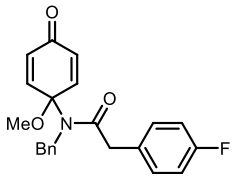
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.37 (m, 2H, ArH) 7.34 – 7.29 (m, 3H, ArH), 7.03 (d, *J* = 8.6 Hz, 2H, ArH), 6.83 (d, *J* = 8.6 Hz, 2H, ArH), 6.63 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.33 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 4.76 (s, 2H, NCH_2), 3.78 (s, 3H, $ArOCH_3$), 3.56 (s, 2H, $CH_2C{=}O$), 3.17 (s, 3H, $NCOCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone C=O), 172.5 (amide C=O), 158.8 (ArC), 144.3 (CHC(N)CH, 2C), 138.7 (ArC), 130.0 (ArC, 2C), 129.9 (CHC(O)CH, 2C), 129.0 (ArC, 2C), 127.5 (ArC), 126.4 (ArC, 2C), 126.3 (ArC), 114.3 (ArC, 2C), 83.6 ($COCH_3$), 55.4 ($ArOCH_3$), 51.0($NCOCH_3$), 47.0 (NCH_2), 41.7 ($CH_2C{=}O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_4^+$ $[M+H]^+$: 378.1700, found 378.1695; **m. p.**: 116 – 118 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2938, 1662, 1512, 1248, 1076.

Synthesis of **262** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(4-fluorophenyl)acetamide (S6)** was prepared according to **Procedures 2** and **4**. FCC (pentane : EtOAc = 3:1) yielded **S6** as a colourless solid (94.0 mg, 0.280 mmol, 28% and 205 mg, 0.611 mmol, 76%).

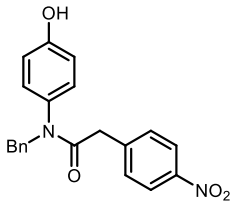
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 – 7.22 (m, 3H, ArH), 7.18 – 7.13 (m, 2H, ArH), 7.04 – 6.99 (m, 2H, ArH), 6.90 (t, *J* = 8.7 Hz, 2H, ArH), 6.75 – 6.67 (m, 4H, ArH), 4.84 (s, 2H, NCH_2), 3.45 (s, 2H, $CH_2C{=}O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.1 (C=O), 161.9 (d, J^1_F = 245.7 Hz, ArC), 156.5 (ArC), 137.2 (ArC), 134.0 (ArC), 131.0 (d, J^4_F = 3.2 Hz, ArC), 130.8 (d, J^3_F = 8.0 Hz, ArC, 2C), 129.7 (ArC, 2C), 129.0 (ArC, 2C), 128.5 (ArC, 2C), 127.6 (ArC), 116.4 (ArC, 2C), 115.3 (d, J^2_F = 21.5 Hz, ArC, 2C), 53.7 (NCH_2), 40.4 ($CH_2C{=}O$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -116.4 (tt, *J* = 8.6, 5.5 Hz); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{19}FNO_2^+$ $[M+H]^+$: 336.1394, found 336.1392; **m. p.**: 142 – 144 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3255, 1623, 1440, 1270, 1221, 1158, 840, 730, 700.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(4-fluorophenyl)acetamide (S7)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 3:1) yielded **S7** as a yellow solid (144 mg, 0.394 mmol, 65%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.37 (m, 2H, ArH), 7.35 – 7.28 (m, 3H, ArH), 7.08 – 7.03 (m, 2H, ArH), 6.96 (t, *J* = 8.7 Hz, 2H, ArH), 6.63 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.34 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 4.78 (s, 2H, NCH_2), 3.59 (s, 2H, CH_2C=O), 3.18 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.2 (ketone C=O), 172.0 (amide C=O), 162.1 (d, J^1_F = 246.5 Hz, ArC), 144.2 (CHC(N)CH, 2C), 138.5 (ArC), 130.7 (d, J^3_F = 8.0 Hz, ArC, 2C), 130.1 (overlapping d, ArC), 130.0 (CHC(O)CH, 2C), 129.1 (ArC, 2C), 127.6 (ArC), 126.4 (ArC, 2C), 115.6 (d, J^2_F = 21.3 Hz, ArC, 2C), 83.6 ($COCH_3$), 51.0 ($COCH_3$), 47.1 (NCH_2), 41.6 (CH_2C=O); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -115.8 (tt, *J* = 8.8, 5.3 Hz); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{21}FNO_3^+$ $[M+H]^+$: 366.1500, found 366.1502; **m. p.**: 96 – 98 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1661, 1605, 1509, 1390, 1221, 1158, 1076, 820, 705.

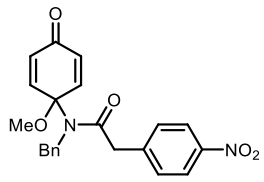
Synthesis of **263** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(4-nitrophenyl)acetamide (S8)** was prepared according to **Procedure 5**. FCC (pentane : EtOAc = 2:1) yielded **S8** as a colourless solid (1.40 g, 3.86 mmol, 97%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.67 (br s, 1H, OH), 8.13 (d, *J* = 8.7 Hz, 2H, ArH), 7.37 (d, *J* = 8.8 Hz, 2H, ArH), 7.30 – 7.19 (m, 3H, ArH), 7.19 – 7.14 (m, 2H, ArH), 6.93 (d, *J* = 8.7 Hz, 2H, ArH), 6.72 (d, *J* = 8.8 Hz, 2H, ArH), 4.80 (s, 2H, NCH_2), 3.60 (s, 2H, CH_2C=O); **^{13}C NMR** (DMSO-d_6, 101 MHz)

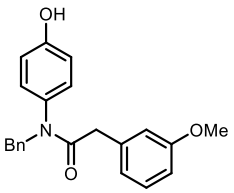
δ 169.4 (C=O), 156.9 (ArC), 146.2 (ArC), 144.2 (ArC), 137.5 (ArC), 132.9 (ArC), 130.7 (ArC, 2C), 129.4 (ArC, 2C), 128.2 (ArC, 2C), 128.1 (ArC, 2C), 127.1 (ArC), 123.1 (ArC, 2C), 115.9 (ArC, 2C), 52.4 (NCH_2), 40.0 (CH_2C=O); **HRMS** (ESI-, m/Z): exact mass calculated for $C_{21}H_{17}N_2O_4^-$ $[M-H]^-$: 361.1194, found 361.1190; **m. p.**: 149 – 151 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3154, 1619, 1510, 1345, 1196, 847, 731, 702.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(4-nitrophenyl)acetamide (S9)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **S9** as a yellow solid (201 mg, 0.512 mmol, 79%).

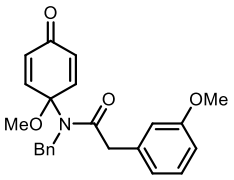
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, *J* = 8.7 Hz, 2H, ArH), 7.44 – 7.38 (m, 2H, ArH), 7.36 – 7.30 (m, 3H, ArH), 7.23 (d, *J* = 8.7 Hz, 2H, ArH), 6.64 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.36 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 4.82 (s, 2H, NCH_2), 3.73 (s, 2H, CH_2C=O), 3.20 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.0 (ketone C=O), 170.7 (amide C=O), 147.2 (ArC), 143.9 (CHC(N)CH, 2C), 141.9 (ArC), 138.2 (ArC), 130.4 (ArC, 2C), 130.3 (CHC(O)CH, 2C), 129.2 (ArC, 2C), 127.8 (ArC), 126.4 (ArC, 2C), 123.8 (ArC, 2C), 83.8 ($COCH_3$), 51.1 ($COCH_3$), 47.3 (NCH_2), 42.0 (CH_2C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{21}N_2O_5^+$ $[M+H]^+$: 393.1445, found 393.1445; **m. p.**: 120 – 122 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1662, 1518, 1345, 1075, 705.

Synthesis of **264** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(3-methoxyphenyl)acetamide (S10)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 1:1) yielded **S10** as a colourless solid (449 mg, 1.29 mmol, 65 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.21 (m, 3H, ArH), 7.19 – 7.15 (m, 2H, ArH), 7.14 – 7.10 (m, 1H, ArH), 6.74 – 6.68 (m, 5H, ArH), 6.64 – 6.61 (m, 2H, ArH), 4.84 (s, 2H, NCH_2), 3.72 (s, 3H, $ArOCH_3$), 3.46 (s, 2H, $CH_2C{=}O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.7 (C=O), 159.7 (ArC), 155.9 (ArC), 137.4 (ArC), 136.9 (ArC), 134.6 (ArC), 129.9 (ArC, 2C), 129.4 (ArC), 129.1 (ArC, 2C), 128.5 (ArC, 2C), 127.5 (ArC), 121.6 (ArC), 116.3 (ArC, 2C), 114.5 (ArC), 112.7 (ArC), 55.3 ($ArOCH_3$), 53.6 (NCH_2), 41.3 ($CH_2C{=}O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{22}NO_3^+$ $[M+H]^+$: 348.1594, found 348.1597; **m. p.**: 116 – 118 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3254, 3031, 1624, 1595, 1513, 1271, 770, 700.

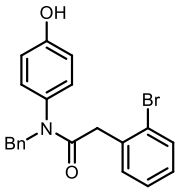


***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(3-methoxyphenyl)acetamide (S11)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 3:1) yielded **S11** as a yellow solid (379 mg, 1.00 mmol, 80 %).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.37 (m, 2H, ArH), 7.34 – 7.29 (m, 3H, ArH), 7.21 (t, J = 7.9 Hz, 1H, ArH), 6.78 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H, ArH), 6.71 (ddd, J = 7.5, 1.7, 0.9 Hz, 1H, ArH), 6.67 (t, J = 2.1 Hz, 1H, ArH), 6.64 (d, J = 10.2 Hz, 2H, CHC(N)CH), 6.34 (d, J = 10.2 Hz, 2H, CHC(O)CH), 4.75 (s, 2H, NCH_2), 3.76 (s, 3H, $ArOCH_3$), 3.59 (s, 2H, $CH_2C{=}O$), 3.17 (s, 3H, $NCOCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone C=O), 172.0 (amide C=O), 160.0 (ArC), 144.3 (CHC(N)CH, 2C), 138.6 (ArC), 135.8 (ArC), 129.9 (CHC(O)CH, 2C), 129.8 (ArC, 2C), 129.0 (ArC, 2C), 127.5 (ArC), 126.4 (ArC, 2C), 121.3 (ArC), 114.6 (ArC), 112.7 (ArC), 83.6 ($COCH_3$), 55.3 ($ArOCH_3$), 51.0 ($NCOCH_3$), 47.1 (NCH_2), 42.7 ($CH_2C{=}O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_4^+$ $[M+H]^+$:

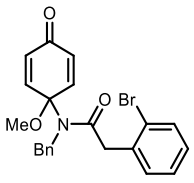
378.1700, found 378.1702; **m. p.**: 89 – 91 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3031, 2939, 2835, 1662, 1600, 1492, 1261, 1077, 1065, 1050.

Synthesis of **265** precursor:



***N*-Benzyl-2-(2-bromophenyl)-*N*-(4-hydroxyphenyl)acetamide (S12)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 1:1) yielded **S12** as a colourless solid (620 mg, 1.56 mmol, 78%).

^{1}H NMR (CD_3OD, 400 MHz) δ 7.51 (dt, *J* = 8.0, 0.9 Hz, 1H, ArH), 7.29 – 7.19 (m, 7H, ArH), 7.13 (ddd, *J* = 8.0, 5.5, 3.6 Hz, 1H, ArH), 6.90 (d, *J* = 8.8 Hz, 2H, ArH), 6.73 (d, *J* = 8.8 Hz, 2H, ArH), 4.86 (s, 2H, NCH_2), 3.57 (s, 2H, CH_2C=O); **^{13}C NMR** (CD_3OD, 101 MHz) δ 172.6 (C=O), 158.8 (ArC), 138.7 (ArC), 137.3 (ArC), 134.5 (ArC), 133.5 (ArC), 133.0 (ArC), 130.5 (ArC, 2C), 129.9 (ArC, 2C), 129.7 (ArC), 129.4 (ArC, 2C), 128.5 (ArC), 128.5 (ArC), 125.9 (ArC), 117.1 (ArC, 2C), 54.3 (NCH_2), 43.0 (CH_2C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{19}BrNO_2^+$ $[M+H]^+$: 396.0594, found 396.0590; **m. p.**: 169 – 171 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3403, 2505, 1633, 1513, 1440, 1269, 1028, 842, 746, 731, 702.

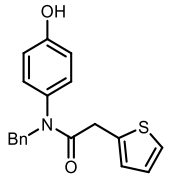


***N*-Benzyl-2-(2-bromophenyl)-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)acetamide (S13)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 1:1) yielded **S13** as a yellow solid (551 mg, 1.29 mmol, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (dd, *J* = 8.0, 1.3 Hz, 1H, ArH), 7.42 – 7.36 (m, 4H, ArH), 7.35 – 7.28 (m, 1H, ArH), 7.23 (td, *J* = 7.5, 1.3 Hz, 1H, ArH), 7.16 (dd, *J* = 7.7, 1.8 Hz, 1H, ArH), 7.10 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H, ArH), 6.69 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.34 (d, *J* = 10.2 Hz, 2H,

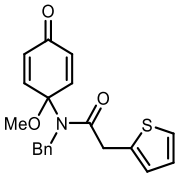
C<u>H</u>C(O)C<u>H</u>), 4.88 (s, 2H, NC<u>H</u>$_2$), 3.73 (s, 2H, C<u>H</u>$_2$C=O), 3.21 (s, 3H, COC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone <u>C</u>=O), 171.1 (amide <u>C</u>=O), 144.2 (<u>C</u>HC(N)<u>C</u>H, 2C), 138.4 (Ar<u>C</u>), 134.9 (Ar<u>C</u>), 132.8 (Ar<u>C</u>), 131.7 (Ar<u>C</u>), 130.0 (<u>C</u>HC(O)<u>C</u>H, 2C), 128.9 (Ar<u>C</u>, 2C), 127.7 (Ar<u>C</u>), 127.6 (Ar<u>C</u>), 126.7 (Ar<u>C</u>), 125.0 (Ar<u>C</u>), 83.7 (<u>C</u>OCH$_3$), 51.0 (CO<u>C</u>H$_3$), 47.4 (N<u>C</u>H$_2$), 43.1 (<u>C</u>H$_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{21}BrNO_3^+$ $[M+H]^+$: 426.0699, found 426.0694; **m. p.**: 120 – 122 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1666, 1396, 1077, 1029, 954, 731.

Synthesis of **266** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(thiophen-2-yl)acetamide (S14)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 2:1) yielded **S14** as a yellow solid (774 mg, 2.39 mmol, 60%).

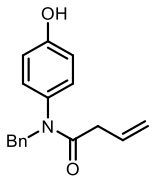
^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.71 (s, 1H, O<u>H</u>), 7.33 (dd, J = 5.1, 1.3 Hz, 1H, Ar<u>H</u>), 7.30 – 7.15 (m, 5H, Ar<u>H</u>), 6.94 – 6.88 (m, 3H, Ar<u>H</u>), 6.78 – 6.70 (m, 3H, Ar<u>H</u>), 4.82 (s, 2H, NC<u>H</u>$_2$), 3.66 (s, 2H, C<u>H</u>$_2$C=O); **^{13}C NMR** (DMSO-d_6, 101 MHz) δ 169.3 (<u>C</u>=O), 156.8 (Ar<u>C</u>), 137.5 (Ar<u>C</u>), 137.1 (Ar<u>C</u>), 132.9 (Ar<u>C</u>), 129.2 (Ar<u>C</u>, 2C), 128.2 (Ar<u>C</u>, 2C), 128.0 (Ar<u>C</u>, 2C), 127.0 (Ar<u>C</u>), 126.3 (Ar<u>C</u>), 126.1 (Ar<u>C</u>), 125.0 (Ar<u>C</u>), 115.8 (Ar<u>C</u>, 2C), 52.4 (N<u>C</u>H$_2$), 34.5 (<u>C</u>H$_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{19}H_{18}NO_2S^+$ $[M+H]^+$: 324.1053, found 324.1053; **m. p.**: 164 – 166 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3258, 1623, 1511, 1273, 1225, 838, 701.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(thiophen-2-yl)acetamide (S15)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 4:1 – 1:1) yielded **S15** as a brown solid (177 mg, 0.501 mmol, 54%).

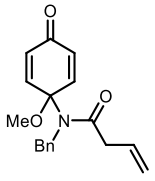
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.36 (m, 2H, ArH), 7.34 – 7.28 (m, 3H, ArH), 7.19 (dd, *J* = 5.2, 1.2 Hz, 1H, ArH), 6.93 (dd, *J* = 5.2, 3.5 Hz, 1H, ArH), 6.78 (dd, *J* = 3.5, 1.1 Hz, 1H, ArH), 6.64 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.35 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 4.80 (s, 2H, NCH_2), 3.83 (s, 2H, CH_2C=O), 3.19 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.2 (ketone C=O), 171.1 (amide C=O), 144.1 (CHC(N)CH, 2C), 138.4 (ArC), 135.8 (ArC), 130.1 (CHC(O)CH, 2C), 129.1 (ArC, 2C), 127.6 (ArC), 126.9 (ArC), 126.5 (ArC, 2C), 126.5 (ArC), 125.2 (ArC), 83.7 ($COCH_3$), 51.1 ($COCH_3$), 47.2 (NCH_2), 37.1 (CH_2C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{20}H_{20}NO_3S^+$ $[M+H]^+$: 354.1158, found 354.1155; **m. p.**: 78 – 80 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2937, 1665, 1455, 1392, 1075, 702.

Synthesis of **267** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)but-3-enamide (S16)** was prepared according to **Procedure 5**. FCC (pentane : EtOAc = 3:1) yielded **S16** as a colourless solid (900 mg, 3.37 mmol, 84%).

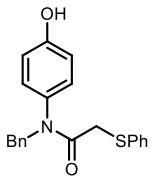
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (br s, 1H, OH), 7.28 – 7.22 (m, 3H, ArH), 7.22 – 7.14 (m, 2H, ArH), 6.86 – 6.76 (m, 4H, ArH), 5.89 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H, H_2C=CHCH_2), 5.07 (dq, *J* = 10.1, 1.4 Hz, 1H, H_AH_BC=$CHCH_2$), 4.95 (dq, *J* = 17.1, 1.6 Hz, 1H, H_AH_BC=$CHCH_2$), 4.84 (s, 2H, NCH_2), 2.91 (dt, *J* = 6.8, 1.5 Hz, 2H, H_2C=$CHCH_2C$=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.2 (C=O), 156.5 (ArC), 137.3 (ArC), 134.0 (ArC), 131.7 (H_2C=$CHCH_2$), 129.5 (ArC, 2C), 129.1 (ArC, 2C), 128.5 (ArC, 2C), 127.6 (ArC), 118.3 (H_2C=$CHCH_2$), 116.5 (ArC, 2C), 53.5 (NCH_2), 39.5 (H_2C=$CHCH_2C$=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{17}H_{18}NO_2^+$ $[M+H]^+$: 268.1332, found 268.1329; **m. p.**: 140 – 142 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3256, 1625, 1514, 1444, 1273, 919, 842, 731, 701.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)but-3-enamide (S17)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 1:1) yielded **S17** as a yellow oil (606 mg, 2.04 mmol, 68%).

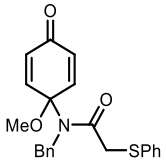
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 – 7.34 (m, 2H, ArH), 7.32 – 7.26 (m, 3H, ArH), 6.63 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.34 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 5.89 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, H_2C=CHCH$_2$), 5.13 (dq, *J* = 10.2, 1.4 Hz, 1H, H_AH_BC=CHCH$_2$), 5.01 (dq, *J* = 17.1, 1.5 Hz, 1H, H_AH_BC=CHCH$_2$), 4.77 (s, 2H, NCH$_2$), 3.18 (s, 3H, COCH$_3$), 3.10 (dt, *J* = 6.6, 1.5 Hz, 2H, H_2C=CHCH$_2$C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone C=O), 172.2 (amide C=O), 144.4 (CHC(N)CH, 2C), 138.5 (ArC), 131.1 (H_2C=CHCH$_2$), 130.0 (CHC(O)CH, 2C), 128.9 (ArC, 2C), 127.5 (ArC), 126.5 (ArC, 2C), 118.5 (H_2C=CHCH$_2$), 83.5 (COCH$_3$), 51.0 (COCH$_3$), 47.0 (NCH$_2$), 40.5 (H_2C=CHCH$_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{18}H_{20}NO_3^+$ [M+H]$^+$: 298.1438, found 298.1434; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3080, 2916, 2850, 1667, 1634, 1401, 1077, 955, 921, 739, 706.

Synthesis of **268** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(phenylthio)acetamide (S18)** was prepared according to **Procedure 5**. FCC (pentane : EtOAc = 3:1 – 1:1) yielded **S18** as a colourless solid (197 mg, 0.565 mmol, 56%).

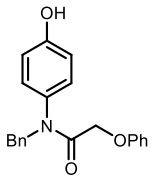
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 – 7.31 (m, 2H, ArH), 7.27 – 7.12 (m, 8H, ArH), 6.78 – 6.71 (m, 4H, ArH), 6.59 (br s, 1H, OH), 4.83 (s, 2H, NCH$_2$), 3.52 (s, 2H, SCH$_2$C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.5 (C=O), 156.4 (ArC), 137.1 (ArC), 135.6 (ArC), 134.0 (ArC), 130.7 (ArC, 2C), 129.7 (ArC, 2C), 129.1 (ArC, 2C), 129.1 (ArC, 2C), 128.5 (ArC, 2C), 127.6 (ArC), 127.0 (ArC), 116.6 (ArC, 2C), 53.9 (NCH$_2$), 37.7 (SCH$_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{20}NO_2S^+$ [M+H]$^+$: 350.1209, found 350.1203; **m. p.**: 128 – 130 °C.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(phenylthio)acetamide (S19)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 3:1) yielded **S19** as a yellow oil (78.0 mg, 0.206 mmol, 41%).

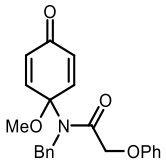
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.20 (m, 10H, ArH), 6.56 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.31 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 4.82 (s, 2H, NCH_2), 3.68 (s, 2H, $SCH_2C{=}O$), 3.19 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.1 (ketone C=O), 169.5 (amide C=O), 144.0 (CHC(N)CH), 138.1 (ArC), 133.2 (ArC), 130.8 (ArC, 2C), 130.1 (CHC(O)CH), 129.0 (ArC, 2C), 127.6 (ArC), 127.3 (ArC), 126.5 (ArC, 2C), 83.7 ($COCH_3$), 51.1 ($COCH_3$), 47.2 (NCH_2), 39.3 ($SCH_2C{=}O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{22}NO_3S^+$ $[M+H]^+$: 380.1315, found 380.1305.

Synthesis of **269** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-phenoxyacetamide (S20)** was prepared according to **Procedure 5**. FCC (pentane : EtOAc = 3:1 – 2:1) yielded **S20** as a colourless solid (291 mg, 0.873 mol, 87%).

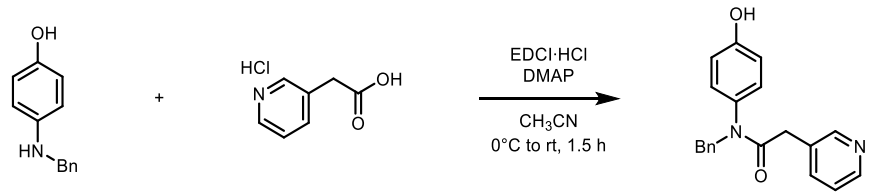
^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.70 (br s, 1H, OH), 7.32 – 7.15 (m, 7H, ArH), 7.05 (d, *J* = 8.8 Hz, 2H), 6.92 (tt, *J* = 7.3, 1.0 Hz, 1H, ArH), 6.77 (d, *J* = 7.7 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.79 (s, 2H, NCH_2), 4.44 (s, 2H, $OCH_2C{=}O$).



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenoxyacetamide (S21)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **S21** as an off-white solid (146 mg, 0.402 mol, 52%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.33 (m, 2H, ArH), 7.32 – 7.20 (m, 5H, ArH), 6.95 (tt, *J* = 7.2, 1.1 Hz, 1H, ArH), 6.84 – 6.79 (m, 2H, ArH), 6.61 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.33 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 4.81 (s, 2H, NCH_2), 4.65 (s, 2H, $OCH_2C{=}O$), 3.20 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 184.8 (ketone C=O), 169.1 (amide C=O), 158.1 (ArC), 143.8 (CHC(N)CH), 138.1 (ArC), 130.5 (CHC(O)CH), 129.7 (ArC, 2C), 129.0 (ArC, 2C), 127.7 (ArC), 126.8 (ArC, 2C), 121.8 (ArC), 114.9 (ArC, 2C), 84.0 ($COCH_3$), 68.4 ($OCH_2C{=}O$), 51.1 ($COCH_3$), 46.6 (NCH_2); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{22}NO_4^+$ $[M+H]^+$: 364.1543, found 364.1536; **m. p.**: 116 – 118 °C.

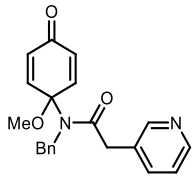
Synthesis of **270** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2-(pyridin-3-yl)acetamide (S22)** was prepared according to a modified literature procedure.[10] 2-pyridine-3-ylacetic acid (382 mg, 2.2 mmol, 1.1 eq.) and aniline **224** (399 mg, 2.0 mmol, 1.0 eq.) were dissolved in acetonitrile (20 mL, 0.1 M) and cooled to 0 °C. 1-ethyl-3-carbodiimide hydrochloride (422 mg, 2.2 mmol, 1.1 eq.) and 4-dimethylaminopyridine (24 mg, 0.2 mmol, 10 mol%) were added to the reaction mixture. The mixture was warmed to room temperature and stirred for 1.5 hours until consumption of the aniline as indicated by TLC. The reaction mixture was washed with 2 M HCl, water and brine (10 mL each time). The organic layer was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (4% MeOH in CH_2Cl_2) yielded **S22** as a red-brown solid (148 mg, 0.465 mol, 23%).

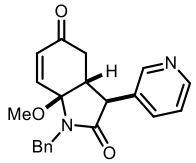
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (dd, *J* = 4.9, 1.6 Hz, 1H, ArH), 7.96 – 7.93 (m, 1H, ArH), 7.90 (dt, *J* = 7.9, 2.0 Hz, 1H, ArH), 7.32 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H, ArH), 7.25 – 7.21 (m, 3H, ArH), 7.18 –

7.12 (m, 2H, ArH), 6.75 (d, *J* = 8.9 Hz, 2H, ArH), 6.66 (d, *J* = 8.8 Hz, 2H, ArH), 4.81 (s, 2H, NCH$_2$), 3.50 (s, 2H, CH$_2$C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.5 (C=O), 157.8 (ArC), 148.9 (ArC), 146.9 (ArC), 138.2 (ArC), 137.1 (ArC), 133.1 (ArC), 132.2 (ArC), 129.6 (ArC, 2C), 129.0 (ArC, 2C), 128.5 (ArC, 2C), 127.6 (ArC), 124.1 (ArC), 116.6 (ArC, 2C), 53.6 (NCH$_2$), 38.4 (CH$_2$C=O); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{20}H_{19}N_2O_2^+$ [M+H]$^+$: 319.1, found 319.0; **m. p.**: 140 – 142 °C.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-(pyridin-3-yl)acetamide (S23)** was prepared according to **Procedure 3**. FCC (2% MeOH in CH_2Cl_2) yielded a mixture of **S23** and **270** as a brown oil (180 mg altogether, 0.517 mmol, quant.).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 – 8.46 (m, 1H, ArH), 8.27 (s, 1H, ArH), 7.54 – 7.48 (m, 1H, ArH), 7.44 – 7.38 (m, 2H, ArH), 7.38 – 7.30 (m, 3H, ArH), 7.25 – 7.20 (m, 1H, ArH), 6.65 (d, *J* = 10.3 Hz, 2H, 2H, CHC(N)CH), 6.36 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 4.82 (s, 2H, NCH$_2$), 3.63 (s, 2H, CH$_2$C=O), 3.20 (s, 3H, COCH$_3$); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{21}N_2O_3^+$ [M+H]$^+$: 349.2, found 349.2.

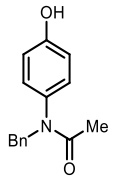


1-Benzyl-7a-methoxy-3-(pyridin-3-yl)-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (270) was formed together with **S23**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H, ArH), 8.50 (d, *J* = 1.8 Hz, 1H, ArH), 7.56 (dt, *J* = 7.9, 2.0 Hz, 1H, ArH), 7.40 – 7.27 (m, 6H, ArH), 6.41 (dd, *J* = 10.5, 2.0 Hz, 1H, CH=CHC=O), 6.04 (dd, *J* = 10.4, 1.0 Hz, 1H, CH=CHC=O), 4.82 (d, *J* = 15.0 Hz, 1H, NCH$_A$H$_B$), 4.52 4.42 (d, *J* = 15.0 Hz, 1H, NCH$_A$H$_B$), 3.34 (d, *J* = 10.9 Hz, 1H, ArCHC=O), 3.26 (s, 3H, COCH$_3$), 2.97 (ddt, *J* =

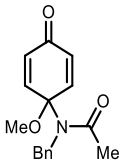
10.8, 6.0, 2.9 Hz, 1H, C<u>H</u>CH$_2$C=O), 2.73 (dd, *J* = 17.0, 6.0 Hz, 1H, CHC<u>H$_A$</u>H$_B$C=O), 2.49 (ddd, *J* = 17.0, 2.8, 1.0 Hz, 1H, CHCH$_A$<u>H$_B$</u>C=O).

Synthesis of **271** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)acetamide (S24)** was prepared according to **Procedure 2**. FCC (EtOAc) yielded **S24** as an off-white solid (460 mg, 1.91 mol, 64%).

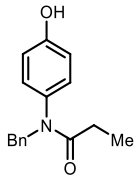
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 – 7.16 (m, 5H, Ar<u>H</u>), 6.82 (d, *J* = 9.0 Hz, 2H, Ar<u>H</u>), 6.76 (d, *J* = 8.9 Hz, 2H, Ar<u>H</u>), 4.84 (s, 2H, NC<u>H$_2$</u>), 1.88 (s, 3H, C<u>H$_3$</u>C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.5 (<u>C</u>=O), 156.2 (Ar<u>C</u>), 137.5 (Ar<u>C</u>), 135.1 (Ar<u>C</u>), 129.4 (Ar<u>C</u>, 2C), 129.0 (Ar<u>C</u>, 2C), 128.5 (Ar<u>C</u>, 2C), 127.5 (Ar<u>C</u>), 116.4 (Ar<u>C</u>, 2C), 53.2 (N<u>C</u>H$_2$), 22.7 (<u>C</u>H$_3$C=O); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{15}H_{16}NO_2^+$ $[M+H]^+$: 242.1, found 242.0.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)acetamide (S25)** was prepared according to **Procedure 3**. FCC (2% MeOH in CH_2Cl_2) yielded **S25** as a brown oil (77.0 mg, 0.284 mol, 26%).

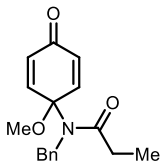
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.33 (m, 2H, Ar<u>H</u>), 7.31 – 7.25 (m, 3H, Ar<u>H</u>), 6.63 (d, *J* = 10.3 Hz, 2H, C<u>H</u>C(N)C<u>H</u>), 6.33 (d, *J* = 10.3 Hz, 2H, C<u>H</u>C(O)C<u>H</u>), 4.74 (s, 2H, NC<u>H$_2$</u>), 3.18 (s, 3H, COC<u>H$_3$</u>), 2.10 (s, 3H, C<u>H$_3$</u>C=O); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{16}H_{17}NNaO_3^+$ $[M+Na]^+$: 294.1, found 294.0.

Synthesis of **272** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)propionamide (S26)** was prepared according to **Procedure 5**. FCC (pentane : EtOAc = 4:1 – 2:1) yielded **S26** as a colourless solid (180 mg, 0.707 mmol, 71%).

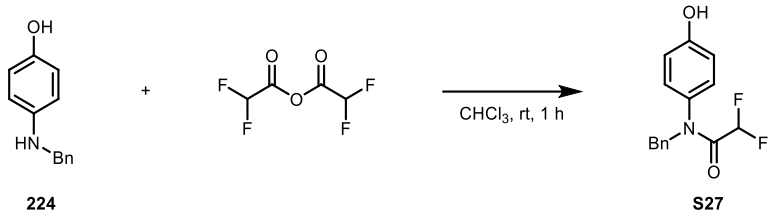
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 – 7.15 (m, 5H, ArH), 6.83 – 6.75 (m, 4H, ArH), 5.66 (br s, 1H, OH), 4.84 (s, 2H, NCH_2), 2.09 (q, *J* = 7.5 Hz, 2H, $CH_3CH_2C{=}O$), 1.07 (t, *J* = 7.5 Hz, 3H, $CH_3CH_2C{=}O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 175.3 (C=O), 156.5 (ArC), 137.5 (ArC), 134.3 (ArC), 129.4 (ArC, 2C), 129.0 (ArC, 2C), 128.5 (ArC, 2C), 127.5 (ArC), 116.5 (ArC, 2C), 53.5 (NCH_2), 27.9 ($CH_3CH_2C{=}O$), 10.0 ($CH_3CH_2C{=}O$); **m. p.**: 130 – 132 °C; **LRMS** (ESI+, m/Z): exact mass calculated for $C_{16}H_{18}NO_2^+$ $[M+H]^+$: 256.1332, found 256.1330.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)propionamide (358)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 1:1) yielded **358** as a brown oil (151 mg, 0.527 mmol, 87%).

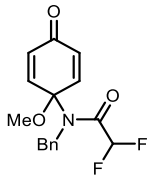
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.34 (m, 2H, ArH), 7.32 – 7.23 (m, 3H, ArH), 6.64 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.35 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 4.76 (s, 2H, NCH_2), 3.18 (s, 3H, $COCH_3$), 2.32 (q, *J* = 7.3 Hz, 2H, $CH_3CH_2C{=}O$), 1.04 (t, *J* = 7.3 Hz, 3H, $CH_3CH_2C{=}O$) **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.2 (ketone C=O), 175.0 (amide C=O), 144.6 (CHC(N)CH), 138.8 (ArC), 129.8 (CHC(O)CH), 128.9 (ArC, 2C), 127.4 (ArC), 126.5 (ArC, 2C), 83.6 ($COCH_3$), 50.9 ($COCH_3$), 47.1 (NCH_2), 28.7 ($CH_3CH_2C{=}O$), 9.1 ($CH_3CH_2C{=}O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{17}H_{20}NO_3^+$ $[M+H]^+$: 286.1438, found 286.1433.

Synthesis of **273** precursor:



***N*-Benzyl-2,2-difluoro-*N*-(4-hydroxyphenyl)acetamide (S27)** was prepared according to a modified literature procedure.[11] Aniline **224** (598 mg, 3 mmol, 1.0 eq.) was suspended in $CHCl_3$ (6 mL, 0.5 M) under a nitrogen atmosphere, and 2,2-difluoroacetic anhydride (0.82 mL, 6.6 mmol, 2.2 eq.) was added dropwise. The reaction mixture was stirred for one hour at room temperature until consumption of the aniline as indicated by TLC. The reaction mixture was quenched with 3 mL water and the layers were separated. The organic layer was washed with water (6 mL), dried over anhydrous $MgSO_4$, concentrated and triturated with pentane (10 mL) to yield **S27** as a colourless solid (820 mg, 2.96 mmol, 99%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 – 7.22 (m, 3H, ArH), 7.19 – 7.12 (m, 2H, ArH), 7.07 (br s, 1H, OH), 6.86 (d, J = 8.9 Hz, 2H, ArH), 6.78 (d, J = 8.9 Hz, 2H, ArH), 5.77 (t, J = 53.6 Hz, 1H, CHF_2C=O), 4.85 (s, 2H, NCH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 162.6 (t, J^2_F = 26.6 Hz, C=O), 157.2 (ArC), 135.6 (ArC), 130.4 (ArC), 129.8 (ArC, 2C), 129.3 (ArC, 2C), 128.7 (ArC, 2C), 128.2 (ArC), 116.7 (ArC, 2C), 105.8 (t, J^1_F = 245.2 Hz, CHF_2C=O), 54.3 (NCH_2); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -123.3 (d, J = 53.7 Hz); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{15}H_{13}F_2NNaO_2^+$ $[M+Na]^+$: 300.1, found 300.0.

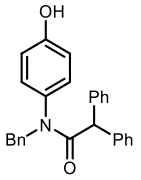


***N*-Benzyl-2,2-difluoro-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)acetamide (S28)** was prepared according to **Procedure 3**. FCC (2% MeOH in CH_2Cl_2) yielded **S28** as a yellow oil (200 mg, 0.651 mmol, 22%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.26 (m, 3H, ArH), 7.25 – 7.20 (m, 2H, ArH), 6.53 (d, J = 10.3 Hz, 2H, CHC(N)CH), 6.35 (d, J = 10.3 Hz, 2H, CHC(O)CH), 6.24 (t, J = 53.6 Hz, 1H, CHF_2C=O), 4.77 (s, 2H, NCH_2), 3.23 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 184.3 (ketone C=O), amide

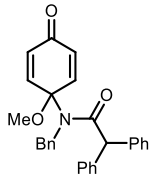
C=O not observed, 143.4 (CHC(N)CH, 2C), 137.2 (ArC), 131.5 (CHC(O)CH, 2C), 129.0 (ArC, 2C), 127.9 (ArC), 127.2 (ArC, 2C), 108.5 (t, J'_F = 248.8 Hz, CHF_2C=O), 84.8 ($COCH_3$), 51.5 ($COCH_3$), 47.1 (NCH_2); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -122.0 (d, *J* = 53.7 Hz); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{16}H_{16}F_2NO_3^+$ $[M+H]^+$: 308.1093, found 308.1089.

Synthesis of **274** precursor:



***N*-Benzyl-*N*-(4-hydroxyphenyl)-2,2-diphenylacetamide (S29)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 3:1) yielded **S29** as a colourless solid (600 mg 1.52 mmol, 51%).

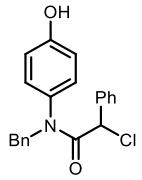
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 – 7.14 (m, 15H, ArH), 6.70 – 6.61 (m, 4H, ArH), 4.91 (s, 1H, Ph_2CHC=O), 4.87 (s, 2H, NCH_2); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{27}H_{23}NNaO_2^+$ $[M+Na]^+$: 416.2, found 416.2.



***N*-Benzyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2,2-diphenylacetamide (S30)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **S30** as a light yellow solid (548 mg 1.29 mmol, 85%).

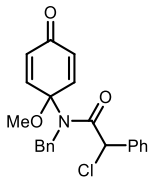
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 – 7.42 (m, 2H, ArH), 7.41 – 7.34 (m, 3H, ArH), 7.31 – 7.19 (m, 6H, ArH), 7.08 – 7.00 (m, 4H, ArH), 6.66 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.36 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 5.01 (s, 1H, Ph_2CHC=O), 4.67 (s, 2H, NCH_2), 3.16 (s, 3H, $COCH_3$); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{28}H_{26}NO_3^+$ $[M+H]^+$: 424.2, found 424.2.

Synthesis of **275** precursor:



***N*-Benzyl-2-chloro-*N*-(4-hydroxyphenyl)-2-phenylacetamide (S31)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 4:1) yielded **S31** as a colourless oil (225 mg, 0.639 mmol, 32%).

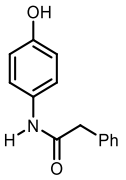
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 – 6.17 (m, 14H, ArH), 5.36 (s, 1H, CHClC=O), 4.90 (d, *J* = 14.2 Hz, 1H, NCH_AH_B), 4.76 (d, *J* = 14.1 Hz, 1H, NCH_AH_B); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 168.6 (C=O), 156.9 (ArC), 136.5 (ArC), 136.4 (ArC), 132.7 (ArC), 129.7 (ArC, 2C), 129.1 (ArC), 129.0 (ArC, 2C), 128.8 (ArC, 2C), 128.6 (ArC, 2C), 128.3 (ArC, 2C), 127.8 (ArC), 116.6 (ArC, 2C), 57.5 (CHClC=O), 54.4 (NCH_2); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{19}ClNO_2^+$ $[M+H]^+$: 352.1099, found 352.1090.



***N*-Benzyl-2-chloro-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (S32)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 4:1) yielded **S32** as a yellow oil (167 mg, 0.438 mmol, 80%).

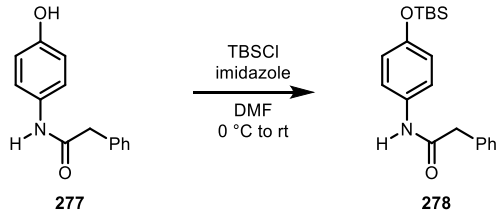
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 – 7.22 (m, 10H, ArH), 6.72 (dd, *J* = 10.3, 3.2 Hz, 1H, $CH_AC(N)CH_B$), 6.52 (dd, *J* = 10.3, 3.2 Hz, 1H, $CH_AC(N)CH_B$), 6.41 (dd, *J* = 10.3, 2.1 Hz, 1H, $CH_AC(O)CH_B$), 6.35 (dd, *J* = 10.2, 2.0 Hz, 1H, $CH_AC(O)CH_B$), 5.48 (s, 1H, CHClC=O), 4.86 (d, *J* = 17.8 Hz, 1H, NCH_AH_B), 4.77 (d, *J* = 17.7 Hz, 1H, NCH_AH_B), 3.20 (s, 3H, $COCH_3$); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{21}ClNNaO_3^+$ $[M+H]^+$: 404.1, found 404.0.

Synthesis of **279**-**285**:



***N*-(4-Hydroxyphenyl)-2-phenylacetamide (277)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 1:1) yielded **277** as a colourless solid (5.90 g, 26.0 mmol, 99%). Analytical data is consistent with the published literature.[12]

^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H, OH), 9.15 (s, 1H, NH), 7.36 (d, J = 8.9 Hz, 2H, ArH), 7.33 – 7.28 (m, 4H, ArH), 7.26 – 7.20 (m, 1H, ArH), 6.67 (d, J = 8.9 Hz, 2H, ArH), 3.57 (s, 2H, CH_2C=O); **^{13}C NMR** (CD_3OD, 101 MHz) δ 172.1 (C=O), 155.5 (ArC), 137.0 (ArC), 131.6 (ArC), 130.1 (ArC, 2C), 129.6 (ArC, 2C), 127.9 (ArC), 123.5 (ArC, 2C), 116.2 (ArC, 2C), 44.5 (CH_2C=O); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{14}H_{14}NO_2^+$ $[M+H]^+$: 228.1, found 228.0.

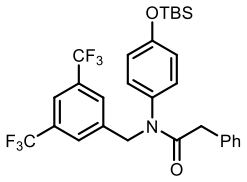


***N*-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-phenylacetamide (278)** was prepared in a procedure for the TBS protection of **277**. Alcohol **277** (3.6 g, 16.0 mmol, 1.0 eq.) and imidazole (4.4 g, 64.0 mmol, 4.0 eq.) were dissolved in anhydrous *N*,*N*-dimethylformamide (DMF, 80 mL, 0.2 M) under a nitrogen atmosphere. After cooling to 0 °C, *tert*-butyldimethylsilyl chloride (TBSCl, 4.8 g, 32.0 mmol, 2.0 eq.) was added to the reaction mixture. The mixture was warmed to room temperature and stirred for 3 hours until consumption of **277** as indicated by TLC. The reaction mixture was quenched with 100 mL water and the aqueous phase was extracted with Et_2O (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 4:1 – 3:1) yielded **278** as an off-white solid (5.20 g, 15.2 mmol, 96%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.37 (m, 2H, ArH), 7.36 – 7.30 (m, 3H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 6.97 (s, 1H, NH) 6.75 (d, J = 8.9 Hz, 2H, ArH), 3.72 (s, 2H, CH_2C=O), 0.96 (s, 9H,

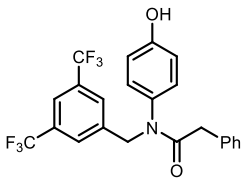
SiC($C\underline{H}_3$)$_3$), 0.15 (s, 6H, Si($C\underline{H}_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.1 ($\underline{C}$=O), 152.6 (Ar$\underline{C}$), 134.8 (Ar$\underline{C}$), 131.5 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$, 2C), 129.3 (Ar$\underline{C}$, 2C), 127.7 (Ar$\underline{C}$), 121.7 (Ar$\underline{C}$, 2C), 120.4 (Ar$\underline{C}$, 2C), 44.8 ($\underline{C}H_2$C=O), 25.8 (SiC($\underline{C}H_3$)$_3$, 3C), 18.3 (Si$\underline{C}$(CH_3)$_3$), -4.4 (Si($\underline{C}H_3$)$_2$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{20}H_{28}NO_2Si^+$ $[M+H]^+$: 342.1884, found 342.1884; **m. p.**: 99 – 101 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3288, 2930, 2858, 1655, 1509, 1253, 914, 839, 698.

Synthesis of **279**:



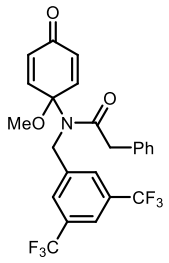
***N*-(3,5-Bis(trifluoromethyl)benzyl)-*N*-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-phenylacetamide (S33)** was prepared according to **Procedure 6**. FCC (pentane : EtOAc = 9:1) yielded **S33** as a yellow oil (758 mg, 1.34 mmol, 67%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (s, 1H, Ar$\underline{H}$), 7.63 (s, 2H, Ar$\underline{H}$), 7.26 – 7.17 (m, 3H, Ar$\underline{H}$), 7.04 – 7.00 (m, 2H, Ar$\underline{H}$), 6.76 (d, J = 8.8 Hz, 2H, Ar$\underline{H}$), 6.67 (d, J = 8.7 Hz, 2H, Ar$\underline{H}$), 4.94 (s, 2H, NC$\underline{H}_2$), 3.51 (s, 2H, C$\underline{H}_2$C=O), 0.99 (s, 9H, SiC($C\underline{H}_3$)$_3$), 0.21 (s, 6H, Si($C\underline{H}_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.8 (C=O), 156.0 (Ar$\underline{C}$), 140.3 (Ar$\underline{C}$), 135.1 (Ar$\underline{C}$), 135.0 (Ar$\underline{C}$), 131.8 (q, J^2_F = 33.4 Hz, Ar$\underline{C}$, 2C), 129.6 (Ar$\underline{C}$, 2C), 129.0 (Ar$\underline{C}$, 4C), 128.6 (Ar$\underline{C}$, 2C), 126.9 (Ar$\underline{C}$), 123.3 (q, J^1_F = 273.6 Hz, $\underline{C}F_3$, 2C), 121.5 (hept, J^3_F = 3.9 Hz, Ar$\underline{C}$), 121.3 (Ar$\underline{C}$, 2C), 52.7 (N$\underline{C}H_2$), 41.4 ($\underline{C}H_2$C=O), 25.7 (SiC($\underline{C}H_3$)$_3$, 3C), 18.4 (Si$\underline{C}$(CH_3)$_3$), -4.4 (Si($\underline{C}H_3$)$_2$, 2C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm): -62.9; **HRMS** (ESI+, m/Z): exact mass calculated for $C_{29}H_{32}F_6NO_2Si^+$ $[M+H]^+$: 568.2101, found 568.2096; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2933, 1657, 1506, 1276, 1171, 1131, 900, 840, 782, 732, 707, 682.



***N*-(3,5-Bis(trifluoromethyl)benzyl)-*N*-(4-hydroxyphenyl)-2-phenylacetamide (S34)** was prepared according to **Procedure 7**. FCC (pentane: EtOAc = 3:1) yielded **S34** as a colourless solid (521 mg, 1.15 mmol, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (s, 1H, ArH), 7.65 (s, 2H, ArH), 7.24 – 7.15 (m, 3H, ArH), 7.06 – 7.01 (m, 2H, ArH), 6.88 (br s, 1H, OH), 6.75 (d, J = 8.9 Hz, 2H, ArH), 6.68 (d, J = 8.9 Hz, 2H, ArH), 4.94 (s, 2H, NCH_2), 3.53 (s, 2H, CH_2C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 173.0 (C=O), 156.9 (ArC), 139.9 (ArC), 134.8 (ArC), 133.6 (ArC), 131.9 (q, J^2_F = 33.5 Hz, ArC, 2C), 129.4 (ArC, 2C), 129.0 (ArC, 2C), 128.9 (m, ArC, 2C), 128.6 (ArC, 2C), 127.0 (ArC), 123.3 (q, J^1_F = 273.9 Hz, CF_3, 2C), 121.6 (hept, J^3_F = 4.0 Hz, ArC), 116.7 (ArC, 2C), 53.1 (NCH_2), 41.2 (CH_2C=O); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm): -62.9; **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{18}F_6NO_2^+$ $[M+H]^+$: 454.1236, found 454.1231; **m. p.**: 120 – 122 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1628, 1514, 1278, 1172, 1132, 682.

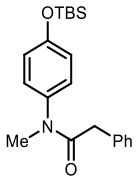


***N*-(3,5-Bis(trifluoromethyl)benzyl)-N-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (279)** was prepared according to **Procedure 3** FCC (pentane : EtOAc = 3:1 – 2:1) yielded **279** as a yellow solid (343 mg, 0.710 mmol, 71%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H, ArH), 7.70 (s, 2H, ArH), 7.32 – 7.22 (m, 3H, ArH), 7.13 – 7.08 (m, 2H, ArH), 6.55 (d, J = 10.2 Hz, 2H, CHC(N)CH), 6.41 (d, J = 10.2 Hz, 2H, CHC(O)CH), 4.83 (s, 2H, NCH_2), 3.65 (s, 2H, CH_2C=O), 3.15 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 184.8 (ketone C=O), 171.7 (amide C=O), 143.6 (CHC(N)CH, 2C), 141.8 (ArC), 133.7 (ArC), 132.2 (q, J^2_F = 33.6 Hz, ArC, 2C), 130.9 (CHC(O)CH, 2C), 129.1 (ArC, 2C), 128.7 (ArC, 2C), 127.5 (ArC), 126.7 (m, ArC, 2C), 123.3 (q, J^1_F = 273.9 Hz, CF_3, 2C), 121.5 (hept, J^3_F = 4.0 Hz, ArC), 83.9 ($COCH_3$), 51.0 ($COCH_3$), 46.8 (NCH_2), 42.9 (CH_2C=O); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm): -62.9; **HRMS** (ESI+,

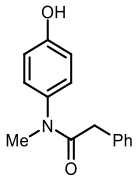
m/Z): exact mass calculated for $C_{24}H_{20}F_6NO_3^+$ [M+H]$^+$: 484.1342, found 484.1338; **m. p.:** 80 – 82 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2981, 1667, 1379, 1278, 1170, 1130.

Synthesis of **280**:



***N*-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-*N*-methyl-2-phenylacetamide (S35)** was prepared according to **Procedure 6**. FCC (pentane: EtOAc = 9:1) yielded **S35** as a yellow oil (164 mg, 0.461 mmol, 46%).

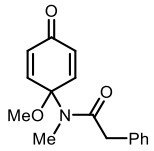
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.15 (m, 3H, Ar<u>H</u>), 7.06 – 7.03 (m, 2H, Ar<u>H</u>), 6.94 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 6.82 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 3.45 (s, 2H, C<u>H</u>$_2$C=O), 3.23 (s, 3H, NC<u>H</u>$_3$), 1.00 (s, 9H, SiC(C<u>H</u>$_3$)$_3$), 0.23 (s, 6H, Si(C<u>H</u>$_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.4 (<u>C</u>=O), 155.4 (Ar<u>C</u>), 137.5 (Ar<u>C</u>), 135.7 (Ar<u>C</u>), 129.2 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.4 (Ar<u>C</u>, 2C), 126.6 (Ar<u>C</u>), 121.1 (Ar<u>C</u>, 2C), 41.1 (<u>C</u>H$_2$C=O), 37.8 (N<u>C</u>H$_3$), 25.8 (SiC(<u>C</u>H$_3$)$_3$, 3C), 18.4 (Si<u>C</u>(CH$_3$)$_3$), -4.3 (Si(<u>C</u>H$_3$)$_2$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{30}NO_2Si^+$ [M+H]$^+$: 356.2040, found 356.2043; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2930, 2858, 1658, 1509, 1256, 913, 839, 782.



***N*-(4-Hydroxyphenyl)-*N*-methyl-2-phenylacetamide (S36)** was prepared according to **Procedure 7**. FCC (pentane: EtOAc = 1:1) yielded **S36** as a colourless solid (113 mg, 0.468 mmol, 99%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.71 (br s, 1H, O<u>H</u>), 7.26 – 7.13 (m, 3H, Ar<u>H</u>), 7.07 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 7.03 (d, *J* = 7.1 Hz, 2H, Ar<u>H</u>), 6.82 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 3.36 (s, 2H, C<u>H</u>$_2$C=O), 3.11 (s, 3H, NC<u>H</u>$_3$); **^{13}C NMR** (DMSO-d_6, 101 MHz) δ 170.2 (<u>C</u>=O), 156.8 (Ar<u>C</u>), 136.1 (Ar<u>C</u>), 135.2 (Ar<u>C</u>), 129.2 (Ar<u>C</u>, 2C), 128.7 (Ar<u>C</u>, 2C), 128.1 (Ar<u>C</u>, 2C), 126.3 (Ar<u>C</u>), 116.1 (Ar<u>C</u>, 2C), 39.9 (<u>C</u>H$_2$C=O), 37.2

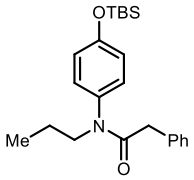
(N<u>C</u>H$_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{15}H_{16}NO_2^+$ [M+H]$^+$: 242.1176, found 242.1176; **m. p.**: 150 – 153 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2920, 2851, 1621, 1593, 1515, 1456, 1267, 1228, 840, 720. 685.



***N*-(1-Methoxy-4-oxocyclohexa-2,5-dien-1-yl)-*N*-methyl-2-phenylacetamide (280)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1 – 1:1) yielded **280** as a brown oil (51.1 mg, 0.19 mmol, 52%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 – 7.29 (m, 2H, Ar<u>H</u>), 7.28 – 7.24 (m, 1H, Ar<u>H</u>), 7.24 – 7.18 (m, 2H, Ar<u>H</u>), 6.67 (d, *J* = 10.2 Hz, 2H, C<u>H</u>C(N)C<u>H</u>), 6.31 (d, *J* = 10.2 Hz, 2H, C<u>H</u>C(O)C<u>H</u>), 3.72 (s, 2H, C<u>H$_2$</u>C=O), 3.21 (s, 3H, COC<u>H$_3$</u>), 3.07 (s, 3H, NC<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.4 (ketone <u>C</u>=O), 171.7 (amide <u>C</u>=O), 143.6 (<u>C</u>HC(N)<u>C</u>H, 2C), 134.2 (Ar<u>C</u>), 129.1 (<u>C</u>HC(O)<u>C</u>H, 2C), 129.0 (Ar<u>C</u>, 2C), 128.9 (Ar<u>C</u>, 2C), 127.2 (Ar<u>C</u>), 82.8 (<u>C</u>OCH$_3$), 51.0 (CO<u>C</u>H$_3$), 43.1 (<u>C</u>H$_2$C=O), 30.5 (N<u>C</u>H$_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{16}H_{18}NO_3^+$ [M+H]$^+$: 272.1281, found 272.1280; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3030, 2937, 1667, 1455, 1375, 1067, 712.

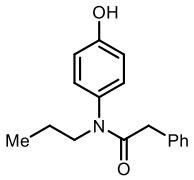
Synthesis of **281**:



***N*-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-phenyl-*N*-propylacetamide (S37)** was prepared according to **Procedure 6**. FCC (pentane : EtOAc = 9:1) yielded **S37** as a yellow oil (590 mg, 1.54 mmol, 82%).

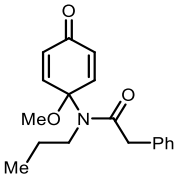
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.14 (m, 3H, Ar<u>H</u>), 7.06 – 7.00 (m, 2H, Ar<u>H</u>), 6.89 (d, *J* = 8.8 Hz, 2H, Ar<u>H</u>), 6.81 (d, *J* = 8.9 Hz, 2H, Ar<u>H</u>), 3.65 – 3.57 (m, 2H, NC<u>H$_2$</u>CH$_2$CH$_3$), 3.41 (s, 2H,

C$\underline{H}_2$C=O), 1.51 (h, *J* = 7.4 Hz, 2H, NCH$_2$C$\underline{H}_2$CH$_3$), 1.00 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.87 (t, *J* = 7.4 Hz, 3H, NCH$_2$CH$_2$C$\underline{H}_3$), 0.23 (s, 6H, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.1 (C=O), 155.4 (ArC), 135.9 (ArC), 135.9 (ArC), 129.8 (ArC, 2C), 129.1 (ArC, 2C), 128.3 (ArC, 2C), 126.5 (ArC), 120.9 (ArC, 2C), 51.1 (NCH$_2$CH$_2$CH$_3$), 41.5 (CH$_2$C=O), 25.8 (SiC(CH$_3$)$_3$, ,3C), 21.0 (NCH$_2$CH$_2$CH$_3$), 18.4 (SiC(CH$_3$)$_3$), 11.4 (NCH$_2$CH$_2$CH$_3$), -4.3 (Si(CH$_3$)$_2$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{34}NO_2Si^+$ $[M+H]^+$: 384.2353, found 384.2342; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2959, 2932, 1657, 1507, 1261, 912, 841, 782.



***N*-(4-Hydroxyphenyl)-2-phenyl-*N*-propylacetamide (S38)** was prepared according to **Procedure 7** FCC (pentane: EtOAc = 2:1) yielded **S38** as a colourless solid (369 mg, 1.37 mmol, 93%).

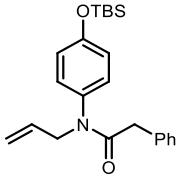
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.14 (m, 3H, ArH), 7.08 – 7.03 (m, 2H, ArH), 6.88 (d, *J* = 8.9 Hz, 2H, ArH), 6.83 (d, *J* = 8.9 Hz, 2H, ArH), 3.64 (t, *J* = 7.6 Hz, 2H, NC$\underline{H}_2$CH$_2$CH$_3$), 3.46 (s, 2H, C$\underline{H}_2$C=O), 1.54 (h, *J* = 7.5 Hz, 2H, NCH$_2$C$\underline{H}_2$CH$_3$), 0.88 (t, *J* = 7.4 Hz, 3H, NCH$_2$CH$_2$C$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.2 (C=O), 156.7 (ArC), 135.5 (ArC), 134.1 (ArC), 129.5 (ArC, 2C), 129.2 (ArC, 2C), 128.5 (ArC, 2C), 126.7 (ArC), 116.5 (ArC, 2C), 51.6 (NCH$_2$CH$_2$CH$_3$), 41.4 (CH$_2$C=O), 20.9 (NCH$_2$CH$_2$CH$_3$), 11.3 (NCH$_2$CH$_2$CH$_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{17}H_{20}NO_2^+$ $[M+H]^+$: 270.1489, found 270.1482; **m. p.**: 78 – 80 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3247, 1625, 1514, 1454, 1419, 1273, 1230, 1137, 842, 724, 696.



***N*-(1-Methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenyl-*N*-propylacetamide (281)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **281** as a brown oil (182 mg, 0.608 mmol, 25%).

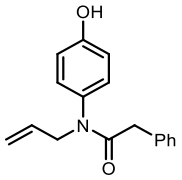
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 – 7.18 (m, 5H, ArH), 6.53 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.34 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 3.72 (s, 2H, CH_2C=O), 3.44 – 3.37 (m, 2H, $NCH_2CH_2CH_3$), 3.19 (s, 3H, $COCH_3$), 1.66 (h, *J* = 7.7 Hz, 2H, $NCH_2CH_2CH_3$), 0.92 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.4 (ketone C=O), 171.2 (amide C=O), 144.8 (CHC(N)CH, 2C), 134.7 (ArC), 130.1 (CHC(O)CH, 2C), 129.0 (ArC, 2C), 128.9 (ArC, 2C), 127.1 (ArC), 83.3 ($COCH_3$), 50.8 ($COCH_3$), 45.9 ($NCH_2CH_2CH_3$), 42.5 (CH_2C=O), 25.2 ($NCH_2CH_2CH_3$), 11.6 ($NCH_2CH_2CH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{18}H_{22}NO_3^+$ $[M+H]^+$: 300.1594, found 300.1590; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2964, 1670, 1634, 1075, 723, 698.

Synthesis of **282**:



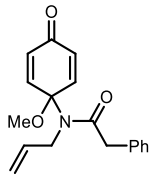
***N*-Allyl-*N*-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-phenylacetamide (S39)** was prepared according to **Procedure 6** . FCC (pentane : EtOAc = 9:1) yielded **S39** as a yellow oil (446 mg, 1.17 mmol, 58%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.15 (m, 3H, ArH), 7.07 – 7.01 (m, 2H, ArH), 6.90 (d, *J* = 8.8 Hz, 2H, ArH), 6.80 (d, *J* = 8.7Hz, 2H, ArH), 5.84 (ddt, *J* = 17.0, 10.2, 6.3 Hz, 1H, $HC=CH_2$), 5.08 (dq, *J* = 10.2, 1.3 Hz, 1H, $HC=CH_AH_B$), 5.03 (dq, *J* = 17.1, 1.5 Hz, 1H, $HC=CH_AH_B$), 4.25 (dt, *J* = 6.4, 1.3 Hz, 2H, NCH_2), 3.45 (s, 2H, CH_2C=O), 1.00 (s, 9H, $SiC(CH_3)_3$), 0.23 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.0 (C=O), 155.5 (ArC), 135.8 (ArC), 135.7 (ArC), 133.3 ($HC=CH_2$), 129.8 (ArC, 2C), 129.2 (ArC, 2C), 128.4 (ArC, 2C), 126.6 (ArC), 120.9 (ArC, 2C), 118.0 ($HC=CH_2$), 52.6 (NCH_2), 41.4 (CH_2C=O), 25.8 ($SiC(CH_3)_3$, 3C), 18.4 ($SiC(CH_3)_3$), -4.3 ($Si(CH_3)_2$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{32}NO_2Si^+$ $[M+H]^+$: 382.2197, found 382.2197; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2930, 2858, 1656, 1506, 1255, 910, 838, 781, 696.



***N*-Allyl-*N*-(4-hydroxyphenyl)-2-phenylacetamide (S40)** was prepared according to **Procedure 7**. FCC (pentane: EtOAc = 3:1 – 1:1) yielded **S40** as a colourless solid (253 mg, 0.663 mmol, 84%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.15 (m, 3H, ArH), 7.08 – 7.04 (m, 2H, ArH), 6.89 (d, *J* = 8.8 Hz, 2H, ArH), 6.81 (d, *J* = 8.8 Hz, 2H, ArH), 5.85 (ddt, *J* = 17.0, 10.3, 6.4 Hz, 1H, HC=CH_2), 5.11 (dq, *J* = 10.1, 1.3 Hz, 1H, HC=CH_AH_B), 5.06 (dq, *J* = 17.1, 1.5 Hz, 1H, HC=CH_AH_B), 4.26 (dt, *J* = 6.4, 1.3 Hz, 2H, NCH_2), 3.48 (s, 2H, CH_2C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.9 (C=O), 156.4 (ArC), 135.4 (ArC), 134.4 (ArC), 132.9 (HC=CH_2), 129.7 (ArC, 2C), 129.2 (ArC, 2C), 128.5 (ArC, 2C), 126.8 (ArC), 118.3 (HC=CH_2), 116.4 (ArC, 2C), 52.9 (NCH_2), 41.3 (CH_2C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{17}H_{18}NO_2^+$ $[M+H]^+$: 268.1332, found 268.1337; **m. p.**: 116 – 118 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3249, 1623, 1513, 1440, 1407, 1272, 1224, 725, 697.

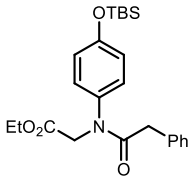


***N*-Allyl-*N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (282)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 3:1 – 2:1) yielded **282** as a brown oil (215 mg, 0.723 mmol, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 – 7.17 (m, 5H, ArH), 6.63 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.33 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 5.91 (ddt, *J* = 17.4, 10.2, 5.0 Hz, 1H, HC=CH_2), 5.31 – 5.25 (m, 2H, HC=CH_2), 4.15 (dt, *J* = 5.0, 1.8 Hz, 2H, NCH_2), 3.72 (s, 2H, CH_2C=O), 3.20 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone C=O), 171.8 (amide C=O), 144.3 (CHC(N)CH, 2C), 135.5 (HC=CH_2), 134.6 (ArC), 129.7 (CHC(O)CH, 2C), 129.1 (ArC, 2C), 128.9 (ArC, 2C), 127.2 (ArC), 117.0 (HC=CH_2), 83.4 ($COCH_3$), 51.0 ($COCH_3$), 45.9 (NCH_2), 42.4 (CH_2C=O); **HRMS** (ESI+, m/Z): exact

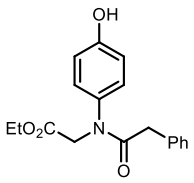
mass calculated for $C_{18}H_{20}NO_3^+$ [M+H]$^+$: 298.1438, found 298.1438; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3029, 2939, 2833, 1659, 1607, 1390, 1076, 1065.

Synthesis of **283**:



Ethyl *N*-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*-(2-phenylacetyl)glycinate (S41) was prepared according to **Procedure 6** with NaHMDS (1 M in THF). FCC (pentane : EtOAc = 9:1) yielded **S41** as a yellow oil (830 mg, 1.94 mmol, 97%).

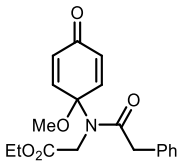
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.25 – 7.20 (m, 2H, ArH), 7.20 – 7.16 (m, 1H, ArH), 7.10 (d, *J* = 8.6 Hz, 2H, ArH), 7.08 – 7.04 (m, 2H, ArH), 6.80 (d, *J* = 8.6 Hz, 2H, ArH), 4.32 (s, 2H, NCH_2), 4.18 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.51 (s, 2H, $CH_2C{=}O$), 1.25 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.00 (s, 9H, $SiC(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 171.8 (amide C=O), 169.3 (ester C=O), 155.8 (ArC), 136.2 (ArC), 135.3 (ArC), 129.6 (ArC, 2C), 129.2 (ArC, 2C), 128.4 (ArC, 2C), 126.7 (ArC), 121.0 (ArC, 2C), 61.3 ($CO_2CH_2CH_3$), 51.8 (NCH_2), 40.8 ($CH_2C{=}O$), 25.8 ($SiC(CH_3)_3$, 3C), 18.4 ($SiC(CH_3)_3$), 14.3 ($CO_2CH_2CH_3$), -4.3 ($Si(CH_3)_2$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{34}NO_4Si^+$ [M+H]$^+$: 428.2252, found 428.2246; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2956, 2931, 2858, 1749, 1664, 1507, 1257, 1195, 911, 840, 782.



Ethyl *N*-(4-hydroxyphenyl)-*N*-(2-phenylacetyl)glycinate (S42) was prepared according to **Procedure 7**. FCC (pentane: EtOAc = 2:1) yielded **S42** as a colourless solid (376 mg, 1.20 mmol, 63%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.24 – 7.20 (m, 2H, ArH), 7.19 – 7.15 (m, 1H, ArH), 7.10 – 7.06 (m, 4H, ArH), 6.78 (d, *J* = 8.7 Hz, 2H, ArH), 4.34 (s, 2H, NCH_2), 4.18 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$),

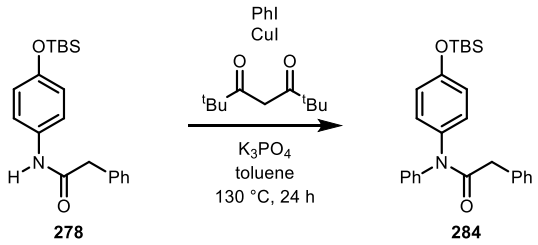
3.54 (s, 2H, C$\underline{H}_2$C=O), 1.24 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 172.8 (amide $\underline{C}$=O), 169.3 (ester C=O), 156.8 (Ar$\underline{C}$), 135.0 (Ar$\underline{C}$), 134.8 (Ar$\underline{C}$), 129.4 (Ar$\underline{C}$, 2C), 129.2 (Ar$\underline{C}$, 2C), 128.5 (Ar$\underline{C}$, 2C), 126.8 (Ar$\underline{C}$), 116.5 (Ar$\underline{C}$, 2C), 61.5 ($CO_2\underline{C}H_2CH_3$), 52.1 (N$\underline{C}H_2$), 40.7 ($\underline{C}H_2$C=O), 14.2 ($CO_2CH_2\underline{C}H_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{18}H_{20}NO_4^+$ $[M+H]^+$: 314.1387, found 314.1387; **m. p.**: 100 – 102 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3296, 3031, 2983, 1746, 1630, 1513, 1272, 1198, 1166, 844, 726, 696.



Ethyl *N*-(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)-*N*-(2-phenylacetyl)glycinate (283) was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **283** as a brown solid (320 mg, 0.932 mmol, 84%).

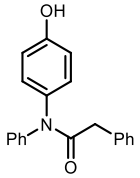
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.33 – 7.29 (m, 2H, Ar$\underline{H}$), 7.27 – 7.23 (m, 1H, Ar$\underline{H}$), 7.19 – 7.17 (m, 2H, Ar$\underline{H}$), 6.61 (d, *J* = 9.8 Hz, 2H, C$\underline{H}$C(N)C$\underline{H}$), 6.37 (d, *J* = 10.1 Hz, 2H, C$\underline{H}$C(O)C$\underline{H}$), 4.29 (s, 2H, NC$\underline{H}_2$), 4.21 (q, *J* = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.65 (br s, 2H, C$\underline{H}_2$C=O), 3.18 (s, 3H, COC$\underline{H}_3$), 1.30 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 185.2 (ketone $\underline{C}$=O), 171.0 (amide $\underline{C}$=O), 170.2 (ester C=O), 144.5 ($\underline{C}$HC(N)$\underline{C}$H, 2C), 133.9 (Ar$\underline{C}$), 130.8 ($\underline{C}$HC(O)$\underline{C}$H, 2C), 129.1 (Ar$\underline{C}$, 2C), 128.9 (Ar$\underline{C}$, 2C), 127.3 (Ar$\underline{C}$), 82.8 ($\underline{C}OCH_3$), 61.7 ($CO_2\underline{C}H_2CH_3$), 51.1 ($CO\underline{C}H_3$), 45.1 (N$\underline{C}H_2$), 42.6 ($\underline{C}H_2$C=O), 14.3 ($CO_2CH_2\underline{C}H_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{19}H_{22}NO_5^+$ $[M+H]^+$: 344.1492, found 344.1493; **m. p.:** 80 – 82 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2982, 1743, 1666, 1632, 1389, 1375, 1201, 1079, 1028, 708.

Synthesis of **285**:



***N*-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-*N*,2-diphenylacetamide (284)** was prepared according to a modified literature procedure.[13] **278** (820 mg, 2.4 mmol, 1.2 eq.), CuI (19 mg, 0.1 mmol, 0.05 eq.), K_3PO_4 (849 mg, 4.0 mmol, 2.0 eq.), PhI (0.22 mL, 2.0 mmol, 1.0 eq.) and 2,2,6,6-tetramethylheptane-3,5-dione (42 µL, 0.2 mmol, 10 mol%) were dissolved in anhydrous degassed toluene (2 mL, 1 M) under a nitrogen atmosphere. The reaction mixture was heated to reflux and stirred for 24 hours at reflux. The mixture was then cooled down and quenched with CH_2Cl_2 (10 mL). The mixture was washed with water (2 x 10 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (10 mL). The combined organic layers were then dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 9:1) yielded **284** as a yellow oil (382 mg, 0.915 mmol, 46%).

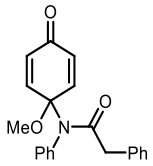
^{1}H NMR (C_6D_6, 50 °C, 600 MHz) δ 7.20 – 7.10 (m, 6H, ArH), 7.06 (t, *J* = 7.3 Hz, 1H, ArH), 7.02 (t, *J* = 7.8 Hz, 2H, ArH), 6.91 (td, *J* = 7.5, 1.1 Hz, 2H, ArH and app. br s, 1H, ArH), 6.67 (d, *J* = 8.6 Hz, 2H, ArH), 3.57 (s, 2H, CH_2C=O), 0.96 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** (C_6D_6, 50 °C, 151 MHz) δ 170.1 (C=O), 154.8 (ArC), 144.2 (ArC), 137.3 (ArC), 136.3 (ArC), 129.5 (ArC, 2C to 4C), 129.1 (ArC, 2C), 128.6 (ArC, 2C), 126.9 (ArC), 126.3 (ArC, 1C or 2C), 120.7 (ArC, 2C), 42.8 (CH_2C=O), 25.8 (SiC(CH_3)$_3$, 3C), 18.4 (SiC(CH_3)$_3$), -4.4 (Si(CH_3)$_2$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{26}H_{32}NO_2Si^+$ $[M+H]^+$: 418.2197, found 418.2189; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1672, 1506, 1256, 914, 841, 782, 695.



***N*-(4-Hydroxyphenyl)-*N*,2-diphenylacetamide (S43)** was prepared according to **Procedure 7**. FCC (pentane: EtOAc = 2:1) yielded **S43** as a colourless solid (242 mg, 0.798 mmol, 88%).

^{1}H NMR (DMSO-d_6, 50 °C, 600 MHz) δ 7.35 (t, *J* = 7.8 Hz, 2H, ArH), 7.31 – 7.18 (m, 6H, ArH), 7.15 – 7.09 (m, 4H, ArH), 6.78 (d, *J* = 8.7 Hz, 2H, ArH), 3.56 (s, 2H, CH_2C=O); **^{13}C NMR** (DMSO-d_6, 50 °C, 151 MHz) δ 170.0 (C=O), 156.4 (ArC), 143.2 (ArC, 1C or 2C), 135.5 (ArC, 1C or 2C), 135.4 (ArC), 133.9 (ArC, 1C or 2C), 129.0 (ArC, 1C or 2C), 128.8 (ArC, 2C), 128.7 (ArC, 1C or 2C), 127.8 (ArC, 2C),

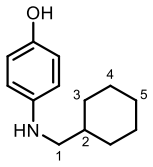
126.8 (ArC, 1C or 2C), 126.0 (ArC), 115.7 (ArC, 2C), 40.8 ($\underline{C}H_2C$=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{20}H_{18}NO_2^+$ $[M+H]^+$: 304.1332, found 304.1328; **m. p.**: 157 – 159 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3328, 1641, 1593, 1511, 1494, 1453, 1382, 1266, 1232, 1032, 724, 695.



***N*-(1-Methoxy-4-oxocyclohexa-2,5-dien-1-yl)-*N*,2-diphenylacetamide** (**285**) was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **285** as a yellow oil (231 mg, 0.693 mmol, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 – 7.35 (m, 3H, ArH), 7.25 – 7.16 (m, 3H, ArH), 7.15 – 7.10 (m, 2H, ArH), 7.00 – 6.96 (m, 2H, ArH), 6.94 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.23 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 3.31 (s, 2H, CH_2C=O), 3.21 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.2 (ketone C=O), 171.8 (amide C=O), 144.6 (CHC(N)CH, 2C), 139.0 (ArC), 134.6 (ArC), 131.0 (ArC, 2C), 129.6 (CHC(O)CH or ArC, 2C), 129.5 (CHC(O)CH or ArC, 2C), 129.3 (ArC, 2C), 129.2 (ArC), 128.5 (ArC, 2C), 126.9 (ArC), 84.3 ($COCH_3$), 51.5 ($CO\underline{C}H_3$), 43.5 ($\underline{C}H_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{20}NO_3^+$ $[M+H]^+$: 334.1438, found 334.1433; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1670, 1496, 1075, 714, 699.

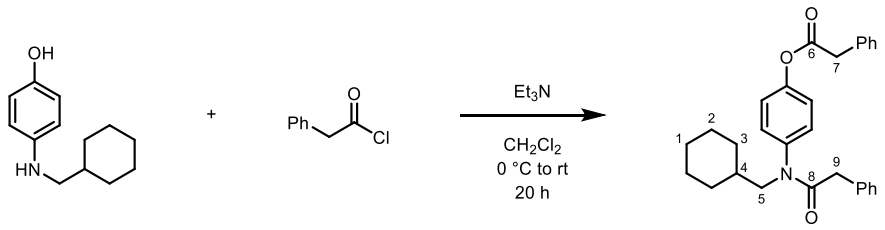
Synthesis of **286**:



4-((Cyclohexylmethyl)amino)phenol (S44) was prepared according to **Procedure 1.** FCC (pentane : EtOAc = 3:1) yielded **S44** as a brown solid (263 mg, 1.28 mmol, 64%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.69 (d, *J* = 8.2 Hz, 1H, ArH), 6.52 (d, *J* = 8.3 Hz, 1H, ArH), 4.03 (br s, 2H, OH and NH), 2.90 (d, *J* = 6.6 Hz, 2H, *C1*), 1.85 – 1.63 (m, 5H, *C3 – C5*), 1.56 (ttt, *J* = 10.2, 6.6,

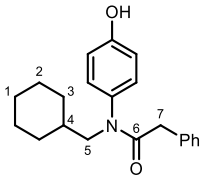
3.4 Hz, 1H, *C2*) 1.34 – 1.09 (m, 3H, *C3* – *C5*), 1.05 – 0.81 (m, 2H, *C3* – *C5*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 147.6 (Ar<u>C</u>), 143.0 (Ar<u>C</u>), 116.3 (Ar<u>C</u>, 2C), 114.4 (Ar<u>C</u>, 2C), 51.9 (*C1*), 37.7 (*C2*), 31.5 (*C3* or *C4*, 2C), 26.7 (*C5*), 26.1 (*C3* or *C4*, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{13}H_{20}NO^+$ $[M+H]^+$: 206.1539, found 206.1536; **m. p.:** 102 – 104 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3317, 2924, 2852, 1515, 1238, 821, 735.



S44 **225** **S45**

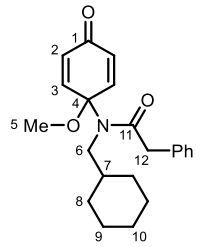
4-(*N*-(Cyclohexylmethyl)-2-phenylacetamido)phenyl 2-phenylacetate (S45) was prepared according to a procedure for amide and ester formation from aminophenol **S44**. **S44** (263 mg, 1.28 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (5 mL, 0.25 M) and triethylamine (0.3 mL, 1.92 mmol, 1.5 eq.) was added. The solution was cooled to 0 °C and 2-phenylacetyl chloride **225** (0.5 mL, 3.84 mmol, 3.0 eq.) was added dropwise. The reaction was slowly warmed to room temperature and stirred for 20 hours. The mixture was then extracted with sat. $NaHCO_3$ (2 x 5 mL), 1 M HCl (2 x 5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 5:1) yielded **S45** as a yellow oil (566 mg, 1.28 mmol, 99%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 – 7.27 (m, 5H, Ar<u>H</u>), 7.25 – 7.14 (m, 3H, Ar<u>H</u>), 7.11 – 6.98 (m, 6H, Ar<u>H</u>), 3.89 (s, 1H, *C7*), 3.55 (d, *J* = 7.5 Hz, 1H, *C5*), 3.42 (s, 1H, *C9*), 1.75 – 1.54 (m, 5H, *C1* –*C3*), 1.52 – 1.39 (m, 1H, *C4*), 1.21 – 1.05 (m, 3H, *C1* –*C3*), 1.05 – 0.91 (m, 2H, *C1* –*C3*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.2 (*C8*), 169.9 (*C6*), 150.1 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 133.3 (Ar<u>C</u>), 129.6 (Ar<u>C</u>, 2C), 129.4 (Ar<u>C</u>, 2C), 129.1 (Ar<u>C</u>, 2C), 128.9 (Ar<u>C</u>, 2C), 128.4 (Ar<u>C</u>, 2C), 127.6 (Ar<u>C</u>), 126.6 (Ar<u>C</u>), 122.7 (Ar<u>C</u>, 2C), 55.6 (*C5*), 41.7 (*C9*), 41.5 (*C7*), 36.1 (*C4*), 30.8 (*C2* or *C3*), 26.5 (*C1*), 25.9 (*C2* or *C3*); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{29}H_{32}NO_3^+$ $[M+H]^+$: 442.2377, found 442.2366; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2925, 2852, 1758, 1655, 1505, 1198, 1120, 728, 697.



***N*-(Cyclohexylmethyl)-*N*-(4-hydroxyphenyl)-2-phenylacetamide (S46)** was prepared according to **Procedure 4**. FCC (pentane : EtOAc = 4:1) yielded **S46** as a yellow oil (196 mg, 0.606 mmol, 47%).

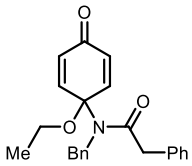
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 – 7.14 (m, 3H, ArH), 7.07 – 7.02 (m, 2H, ArH), 6.90 (d, *J* = 8.9 Hz, 1H, ArH), 6.82 (d, *J* = 8.8 Hz, 2H, ArH), 3.54 (d, *J* = 7.3 Hz, 2H, *C5*), 3.45 (s, 2H, *C7*), 1.75 – 1.55 (m, 5H, *C1 – C3*), 1.47 (dqd, *J* = 10.4, 7.3, 3.7 Hz, 1H, *C4*), 1.21 – 1.06 (m, 3H, *C1 – C3*), 1.06 – 0.91 (m, 2H, *C1 – C3*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.4 (*C6*), 156.4 (ArC), 135.6 (ArC), 134.7 (ArC), 129.5 (ArC, 2C), 129.2 (ArC, 2C), 128.4 (ArC, 2C), 126.7 (ArC), 116.5 (ArC, 2C), 55.8 (*C5*), 41.5 (*C7*), 36.1 (*C4*), 30.9 (*C2* or *C3*), 26.6 (*C1*), 26.0 (*C2* or *C3*); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{26}NO_2^+$ $[M+H]^+$: 324.1958, found 324.1951; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3254, 2925, 2852, 1627, 1513, 1449, 1273, 1143, 910, 840, 725, 696.



***N*-(Cyclohexylmethyl)-*N*-(1-methoxy 4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (286)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 4:1) yielded **286** as a brown solid (67.0 mg, 0.190 mmol, 32%).

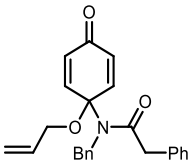
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 – 7.27 (m, 2H, ArH), 7.26 – 7.21 (m, 1H, ArH), 7.21 – 7.16 (m, 2H, ArH), 6.50 (d, *J* = 10.2 Hz, 2H, *C3*), 6.35 (d, *J* = 10.2 Hz, 2H, *C2*), 3.74 (s, 2H, *C12*), 3.35 (d, 2H, *C6*), 3.19 (s, 3H, *C5*), 1.84 – 1.74 (m, 4H, *C8 – C10*), 1.74 – 1.60 (m, 2H, *C7 – C10*), 1.31 – 1.10 (m, 3H, *C8 – C10*), 1.03 – 0.90 (m, 2H, *C8 – C10*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.4 (*C1*), 171.7 (*C11*), 145.1 (*C3*), 134.8 (ArC), 130.4 (*C2*), 129.0 (ArC, 2C), 128.8 (ArC, 2C), 127.0 (ArC), 83.3 (*C4*), 50.7 (*C5*),

50.0 (*C6*), 42.6 (*C12*), 39.6 (*C7*), 31.4 (*C8* or *C9*), 26.5 (*C10*), 26.3 (*C8* or *C9*); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{28}NO_3^+$ $[M+H]^+$: 354.2064, found 354.2055; **m. p.:** 64 – 66 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2928, 2851, 1670, 1654, 1073, 743, 723.



***N*-Benzyl-*N*-(1-ethoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (294)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 3:1) yielded **294** as a yellow oil (41.5 mg, 0.115 mmol, 16%).

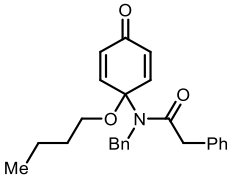
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.36 (m, 6H, ArH), 7.35 – 7.21 (m, 6H, ArH), 7.15 – 7.10 (m, 2H, ArH), 6.64 (d, *J* = 10.2 Hz, 2H, CHC(N)CH), 6.30 (d, *J* = 10.2 Hz, 2H, CHC(O)CH), 4.77 (s, 2H, NCH_2), 3.65 (s, 2H, $CH_2C{=}O$), 3.36 (q, *J* = 7.0 Hz, 2H, $COCH_2CH_3$) 1.08 (t, *J* = 7.0 Hz, $COCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.5 (ketone C=O), 172.0 (amide C=O), 144.9 (CHC(N)CH, 2C), 138.7 (ArC), 134.4 (ArC), 129.4 (CHC(O)CH, 2C), 129.0 (ArC, 2C), 128.9 (ArC, 2C), 128.8 (ArC, 2C), 127.5 (ArC), 127.1 (ArC), 126.6 (ArC, 2C), 83.0 ($COCH_2CH_3$), 59.1 ($COCH_2CH_3$), 47.0 (NCH_2), 42.7 ($CH_2C{=}O$), 15.3 ($COCH_2CH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_3^+$ $[M+H]^+$: 362.1751, found 362.1747; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2925, 1665, 1632, 1390, 1064, 976, 703.



***N*-(1-(Allyloxy)-4-oxocyclohexa-2,5-dien-1-yl)-*N*-benzyl-2-phenylacetamide (295)** was prepared according to **Procedure 3** with 2.0 eq. PIDA. FCC (pentane : EtOAc = 2:1) yielded **295** as a yellow solid (84.7 mg, 0.227 mmol, 18%).

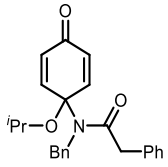
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.36 (m, 2H, ArH), 7.35 – 7.21 (m, 6H, ArH), 7.15 – 7.10 (m, 2H, ArH), 6.67 (d, *J* = 10.1 Hz, 2H, CHC(N)CH), 6.33 (d, *J* = 10.1 Hz, 2H, CHC(O)CH), 5.72 (ddt, *J* = 17.6, 10.3, 5.1 Hz, 1H, $COCH_2CH{=}CH_2$), 5.10 – 5.01 (m, 2H, $COCH_2CH{=}CH_AH_B$ and

$COCH_2CH=CH_AH_B$), 4.80 (s, 2H, NCH_2), 3.85 (dt, *J* = 5.2, 1.6 Hz, 2H, $COCH_2CH=CH_2$), 3.65 (s, 2H, $CH_2C=O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3 (ketone C=O), 172.1 (amide C=O), 144.5 (CHC(N)CH, 2C), 138.5 (ArC), 134.3 (ArC), 133.4 ($COCH_2CH=CH_2$), 129.6 (CHC(O)CH, 2C), 129.0 (ArC, 2C), 129.0 (ArC, 2C), 128.9 (ArC, 2C), 127.6 (ArC), 127.2 (ArC), 126.5 (ArC, 2C), 117.0 ($COCH_2CH=CH_2$), 83.3 ($COCH_3$), 64.3 ($COCH_2CH=CH_2$), 47.1 (NCH_2), 42.6 ($CH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{24}NO_3^+$ $[M+H]^+$: 374.1751, found 374.1743; **m. p.:** 86 – 88 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1665, 1391, 1061, 924, 738, 702.



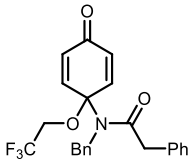
***N*-Benzyl-*N*-(1-butoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (296)** was prepared according to **Procedure 3** with 2.0 eq. PIDA. FCC (pentane : EtOAc = 4:1) yielded **296** as a brown oil (103 mg, 0.264 mmol, 22%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.36 (m, 2H, ArH), 7.34 – 7.21 (m, 6H, ArH), 7.14 – 7.10 (m, 2H, ArH), 6.63 (d, *J* = 10.1 Hz, 2H, CHC(N)CH), 6.32 (d, *J* = 10.1 Hz, 2H, CHC(O)CH), 4.7 (s, 2H, NCH_2), 3.64 (s, 2H, $CH_2C=O$), 3.28 (t, *J* = 6.4 Hz, 2H, $COCH_2CH_2CH_2CH_3$), 1.45 – 1.35 (m, 2H, $COCH_2CH_2CH_2CH_3$), 1.23 – 1.12 (m, 2H, $COCH_2CH_2CH_2CH_3$), 0.79 (t, *J* = 7.4 Hz, 3H, $COCH_2CH_2CH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.5 (ketone C=O), 171.9 (amide C=O), 144.9 (CHC(N)CH, 2C), 138.8 (ArC), 134.4 (ArC), 129.6 (CHC(O)CH, 2C), 129.0 (ArC, 2C), 128.9 (ArC, 2C), 128.9 (ArC, 2C), 127.5 (ArC), 127.2 (ArC), 126.5 (ArC, 2C), 83.0 ($COCH_2CH_2CH_2CH_3$), 63.0 ($COCH_2CH_2CH_2CH_3$), 47.0 (NCH_2), 42.6 ($CH_2C=O$), 31.7 ($COCH_2CH_2CH_2CH_3$), 19.2 ($COCH_2CH_2CH_2CH_3$), 13.8 ($COCH_2CH_2CH_2CH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{25}H_{28}NO_3^+$ $[M+H]^+$: 390.2064, found 390.2056; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2928, 1666, 1496, 1455, 1390, 1358, 1074, 737, 702.



***N*-Benzyl-*N*-(1-isopropoxy-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (297)** was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 2:1) yielded **297** as a brown oil. (25 mg, 0.0667 mmol, 3%).

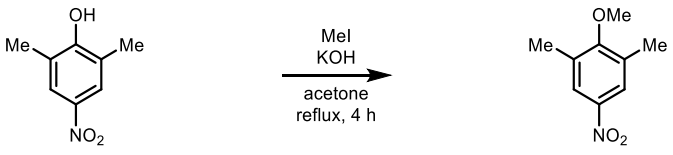
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.20 (m, 8H, ArH), 7.14 – 7.08 (m, 2H, ArH), 6.68 (d, *J* = 10.3 Hz, 2H, CHC(N)CH), 6.29 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 4.75 (s, 2H, NCH_2), 3.69 (hept, *J* = 6.2 Hz, 1H, $(CH_3)_2CH$), 1.03 (d, *J* = 6.2 Hz, 6H, $(CH_3)_2CH$); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{26}NO_3^+$ $[M+H]^+$: 376.2, found 376.2.



***N*-Benzyl-*N*-(4-oxo-1-(2,2,2-trifluoroethoxy)cyclohexa-2,5-dien-1-yl)-2-phenylacetamide (298)** was prepared according to **Procedure 3** with 2.0 eq. PIDA. FCC (pentane : EtOAc = 9:1 – 4:1) yielded **298** as a brown oil. (28 mg, 0.0674 mmol, 5%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.37 (m, 2H, ArH), 7.36 – 7.20 (m, 6H, ArH), 7.15 – 7.10 (m, 2H, ArH), 6.66 (d, *J* = 10.1 Hz, 2H, CHC(N)CH), 6.37 (d, *J* = 10.3 Hz, 2H, CHC(O)CH), 4.78 (s, 2H, NCH_2), 3.67 (q, *J* = 8.2 Hz, 2H, $COCH_2CF_3$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -74.0 (t, *J* = 8.3 Hz); **LRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{21}F_3NO_3^+$ $[M+H]^+$: 416.1, found 416.2.

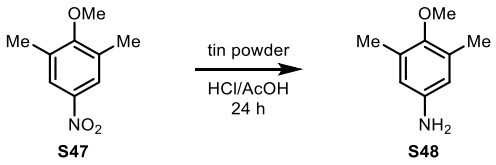
Synthesis of **302** precursor:



S47

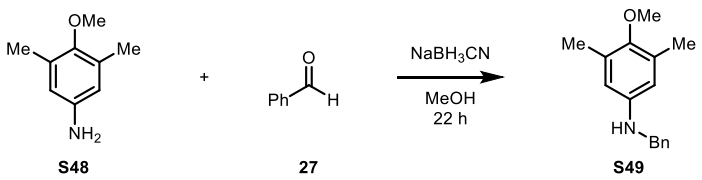
2-Methoxy-1,3-dimethyl-5-nitrobenzene (S47) was prepared according to a literature procedure.[14] 2,6-dimethyl-4-nitrophenol (1.67 g, 10 mmol, 1.0 eq.), iodomethane (2 mL, 30 mmol, 3.0 eq.), and potassium hydroxide (1.40 g, 25 mmol, 2.5 eq.) were dissolved and suspended in acetone (10 mL, 1 M). The mixture was heated to reflux at 80 °C with stirring for 4 hours until consumption of the phenol as indicated by TLC. The reaction mixture was quenched with 10 mL water and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the volatiles were removed *in vacuo* to yield crude **S47** as a pale yellow solid (1.84 g, 10.2 mmol, quant.). Analytical data is consistent with the published literature.[15]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (s, 2H), 3.78 (s, 3H), 2.35 (s, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 162.6, 143.7, 132.5 (2C), 124.4 (2C), 60.0, 16.5 (2C).



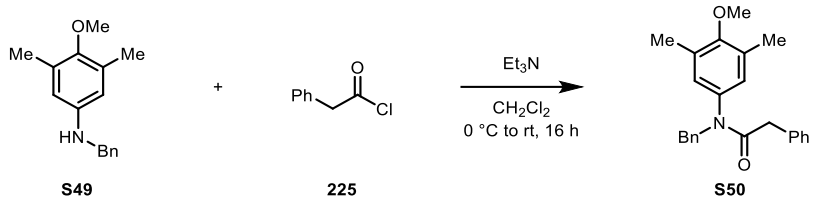
4-Methoxy-3,5-dimethylaniline (S48) was prepared according to a literature procedure.[15] Crude 2,6-dimethyl-4-nitroanisole **S47** (1.84 g, 10.2 mmol, 1.0 eq.) and tin powder (3.86 g, 32.5 mmol, 3.25 eq.) were stirred in a solution of HCl (2 mL) in AcOH (20 mL). After 24 hours, the reaction was diluted with water (150 mL), neutralised carefully with solid $NaHCO_3$, and extracted into EtOAc (150 mL). The organic layer was washed with water (2x40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated to afford **S48** as an orange solid (1.30 g, 8.63 mmol, 86%). Analytical data is consistent with the published literature.[15]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.37 – 6.34 (m, 2H), 3.66 (s, 3H), 3.42 (br s, 2H), 2.22 – 2.20 (m, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 149.8, 142.2, 131.6 (2C), 115.4 (2C), 60.1, 16.2 (2C).



***N*-Benzyl-4-methoxy-3,5-dimethylaniline (S49)** was prepared according to a literature procedure.[15] Sodium cyanoborohydride (1.2 g, 19.0 mmol, 2.2 eq.) was added to a stirring mixture of 3,5-dimethyl-4-methoxyaniline **S48** (1.30 g, 8.63 mmol, 1.0 eq.) and benzaldehyde **27** (1.1 mL, 10.4 mmol, 1.2 eq.) in methanol (40 mL, 0.2 M) for 22 hours. The reaction mixture was concentrated with silica and FCC (pentane : EtOAc = 9:1) yielded **S49** as a pale yellow solid (1.29 g, 5.34 mmol, 62%). Analytical data is consistent with the published literature.[15]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 6.32 (s, 2H), 4.26 (s, 2H), 3.74 (br s, 1H), 3.66 (s, 3H), 2.22 (s, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 149.1, 144.4, 139.8, 131.5 (2C), 128.7 (2C), 127.7 (2C), 127.3, 113.0 (2C), 60.1, 49.0, 16.4 (2C).

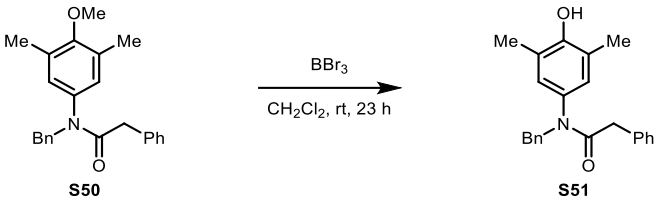


S49 **225** **S50**

***N*-Benzyl-*N*-(4-methoxy-3,5-dimethylphenyl)-2-phenylacetamide (S50)** was prepared by reacting amine **S49** and acyl chloride **225**. **S49** (1.29 g, 5.35 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (20 mL, 0.3 M) and triethylamine (1.1 mL,8.02 mmol, 1.5 eq.) was added. The reaction mixture was cooled to 0 °C and 2-phenylacetyl chloride **225** (0.85 mL, 6.42 mmol, 1.2 eq.) was added dropwise. The reaction was slowly warmed to room temperature and stirred for 16 hours. The mixture was then extracted with sat. $NaHCO_3$ (2 x 20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 9:1 – 4:1) yielded **S50** as a yellow oil (1.85 g, 5.15 mmol, 96%).

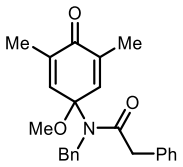
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 – 7.16 (m, 8H, Ar$\underline{H}$), 7.09 – 7.03 (m, 2H, Ar$\underline{H}$), 6.50 (s, 2H, Ar$\underline{H}$), 4.82 (s, 2H, NC$\underline{H}_2$), 3.72 (s, 3H, ArOC$\underline{H}_3$), 3.46 (s, 2H, C$\underline{H}_2$C=O), 2.17 (s, 6H, ArC$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.1 ($\underline{C}$=O), 156.6 (Ar$\underline{C}$), 137.7 (Ar$\underline{C}$), 137.7 (Ar$\underline{C}$), 135.8 (Ar$\underline{C}$), 132.0 (Ar$\underline{C}$, 2C), 129.2 (Ar$\underline{C}$, 2C), 128.8 (Ar$\underline{C}$, 4C), 128.3 (Ar$\underline{C}$, 2C), 128.3 (Ar$\underline{C}$, 2C), 127.3 (Ar$\underline{C}$), 126.6 (Ar$\underline{C}$), 59.9 (ArO$\underline{C}H_3$), 53.3 (N$\underline{C}H_2$), 41.5 ($\underline{C}H_2$C=O), 16.1 (Ar$\underline{C}H_3$, 2C). **HRMS** (ESI+, m/Z): exact mass

calculated for $C_{24}H_{26}NO_2^+$ [M+H]$^+$: 360.1958, found 360.1953; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3407, 1613, 1493, 1201, 700.



***N*-Benzyl-*N*-(4-hydroxy-3,5-dimethylphenyl)-2-phenylacetamide (S51)** was prepared according to a modified literature procedure.[15] Boron tribromide (25 mL of 1 M BBr_3 in CH_2Cl_2, 25 mmol, 5.0 eq.) was added to a stirring mixture of **S50** (1.80 g, 5 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (17 mL, 0.3 M) and the reaction was stirred at room temperature under a nitrogen atmosphere for 23 hours. The reaction was then quenched with methanol (16 mL), extracted into EtOAc (160 mL), and washed with sat. $NaHCO_3$ (2 x 80 mL) and brine (80 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. FCC (pentane : EtOAc = 4:1) yielded **S51** as a colourless solid (1.12 g, 3.23 mmol, 65%). **S51** is unstable in air and was isolated with a small amount of impurity.

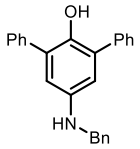
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 – 7.15 (m, 8H, ArH), 7.09 – 7.05 (m, 2H, ArH), 6.46 (s, 2H, ArH), 5.57 (br s, 1H, OH), 4.82 (s, 2H, NCH_2), 3.47 (s, 2H, $PhCH_2C$=O), 2.13 (s, 6H, $ArCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.7 (C=O), 152.2 (ArC), 137.7 (ArC, 2C), 135.8 (ArC), 134.1 (ArC), 129.3 (ArC, 2C), 128.9 (ArC, 2C), 128.5 (ArC, 2C), 128.3 (ArC, 2C), 128.3 (ArC, 2C), 127.3 (ArC), 126.6 (ArC), 124.4 (ArC), 53.5 (NCH_2), 41.3 (CH_2C=O), 16.1 ($ArCH_3$, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_2^+$ [M+H]$^+$: 346.1802, found 346.1799; **m. p.**: 126 – 128 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3372, 1631, 1488, 1201, 736, 700.



***N*-Benzyl-*N*-(1-methoxy-3,5-dimethyl-4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide (S52**) was prepared according to **Procedure 3**. FCC (pentane : EtOAc = 9:1 – 4:1) yielded **S52** as a yellow oil (485 mg, 1.29 mmol, 43%).

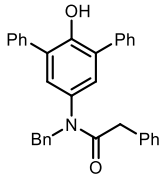
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.21 (m, 8H, ArH), 7.17 – 7.13 (m, 2H, ArH), 6.46 (s, 2H, CH=C(CH_3)C=O), 4.71 (s, 2H, NCH_2), 3.67 (s, 2H, CH_2C=O), 3.13 (s, 3H, COCH_3), 1.90 (s, 6H, CH=C(CH_3)C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 186.6 (ketone C=O), 172.2 (amide C=O), 139.7 (CH=C(CH_3)C=O, 2C), 139.0 (ArC), 136.6 (CH=C(CH_3)C=O, 2C), 134.9 (ArC), 129.0 (ArC, 2C), 128.9 (ArC, 2C), 128.8 (ArC, 2C), 127.3 (ArC), 127.0 (ArC), 126.5 (ArC, 2C), 84.4 (COCH_3), 50.7 (COCH_3), 47.5 (NCH_2), 42.9 (CH_2C=O), 15.9 (CH=C(CH_3)C=O, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{26}NO_3^+$ $[M+H]^+$: 376.1907, found 376.1905; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3030, 1645, 1496, 1454, 1073, 733, 699.

Synthesis of **303** precursor:



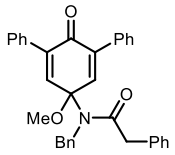
5'-(Benzylamino)-[1,1':3',1''-terphenyl]-2'-ol (S53) was prepared according to **Procedure 1**. FCC (pentane : Et_2O = 9:1) yielded **S53** as a yellow oil (427 mg, 1.21 mmol, 87%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 – 7.51 (m, 4H, ArH), 7.49 – 7.24 (m, 11H, ArH), 6.63 (s, 2H, ArH), 4.89 (br s, 1H, NH or OH), 4.33 (s, 2H, NCH_2), 3.82 (br s, 1H, NH or OH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 142.1 (ArC, 2C), 141.8 (ArC), 139.6 (ArC), 138.2 (ArC, 2C), 129.6 (ArC), 129.4 (ArC, 4C), 128.8 (ArC, 4C), 128.8 (ArC, 2C), 127.8 (ArC, 2C), 127.6 (ArC, 2C), 127.4 (ArC), 114.9 (ArC, 2C), 49.4 (NCH_2); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{25}H_{22}NO^+$ $[M+H]^+$: 352.1696, found 352.1688; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3547, 3414, 3060, 1609, 1468, 1430, 1221, 765, 736, 700.



***N*-Benzyl-*N*-(2'-hydroxy-[1,1':3',1''-terphenyl]-5'-yl)-2-phenylacetamide (S54)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 4:1 – 100% EtOAc) yielded **S54** as a colourless solid (350 mg, 0.745 mmol, 68%).

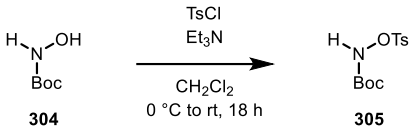
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 – 7.35 (m, 10H, ArH), 7.33 – 7.16 (m, 8H, ArH), 7.15 – 7.08 (m, 2H, ArH), 6.77 (s, 2H, ArH), 5.57 (br s, 1H, OH), 4.92 (s, 2H, NCH_2), 3.62 (s, 2H, CH_2C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.2 (C=O), 149.0 (ArC), 137.6 (ArC), 136.5 (ArC, 2C), 135.6 (ArC), 134.8 (ArC), 130.0 (ArC, 2C), 129.6 (ArC, 2C), 129.2 (ArC, 6C), 129.1 (ArC, 2C), 129.0 (ArC, 4C), 128.5 (ArC, 2C), 128.5 (ArC, 2C), 128.2 (ArC, 2C), 127.5 (ArC), 126.7 (ArC), 53.4 (NCH_2), 41.7 (CH_2C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{33}H_{28}NO_2^+$ $[M+H]^+$: 470.2115, found 470.2106; **m. p.**: 166 – 170 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3318, 3062, 1643, 1629, 1431, 1215, 1113, 910, 730, 699.



***N*-Benzyl-*N*-(5'-methoxy-2'-oxo-2',5'-dihydro-[1,1':3',1''-terphenyl]-5'-yl)-2-phenylacetamide (S55)** was prepared according to **Procedure 3**. FCC (pentane : Et_2O = 4:1 – 2:1) yielded **S55** as a yellow solid (106 mg, 0.212 mmol, 30%).

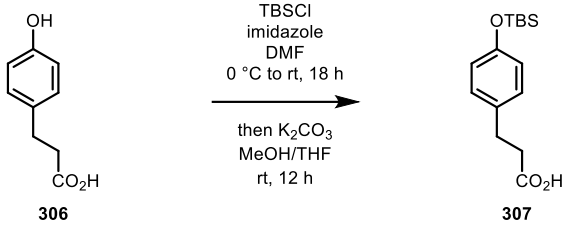
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 – 7.16 (m, 20H, ArH), 6.84 (s, 2H, CHC(N)CH), 4.81 (s, 2H, NCH_2), 3.69 (s, 2H, CH_2C=O), 3.31 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 183.5 (ketone C=O), 172.2 (amide C=O), 140.7 (CHC(N)CH, 2C), 139.8 (ArC or PhCC(O)CPh, 2C), 138.6 (ArC), 135.2 (ArC or PhCC(O)CPh, 2C) 134.5 (ArC), 129.2 (ArC, 4C), 129.0 (ArC, 2C), 128.8 (ArC, 2C), 128.8 (ArC, 2C), 128.4 (ArC, 2C), 128.1 (ArC, 4C), 127.4 (ArC), 127.1 (ArC), 126.4 (ArC, 2C), 84.1 ($COCH_3$), 51.0 ($COCH_3$), 47.3 (NCH_2), 42.9 (CH_2C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{34}H_{30}NO_3^+$ $[M+H]^+$: 500.2220, found 500.2209; **m. p.**: 46 – 48 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1661, 1495, 1121, 1073, 739, 699.

Synthesis of **312**:



***tert*-Butyl (tosyloxy)carbamate (305)** was prepared according to a literature procedure.[16] *tert*-Butyl *N*-hydroxycarbamate **304** (1.33 g, 10.0 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (20 mL, 0.5 M). The solution was cooled to 0 °C and *p*-toluenesulfonyl chloride (2.1 g, 11.0 mmol, 1.1 eq.) and triethylamine (1.5 mL, 11.0 mmol, 1.1 eq.) were added. The mixture was warmed to room temperature and stirred for 18 hours. The reaction was then quenched with water (20 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 4:1) yielded **305** as a colourless solid (1.90 g, 6.62 mmol, 66%). Analytical data is consistent with the published literature.[17]

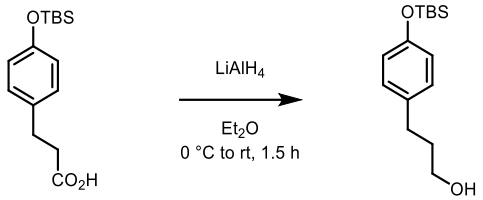
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 2.46 (s, 3H), 1.30 (s, 9H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 154.2, 146.0, 130.8, 129.8 (2C), 129.8 (2C), 84.0, 27.9 (3C), 21.9.



3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)propanoic acid (307) was prepared according to a modified literature procedure.[18] 3-(4-Hydroxyphenyl)propanoic acid **306** (1.66 g, 10.0 mmol, 1.0 eq.) was dissolved in anhydrous DMF (20 mL, 0.5 M) under a nitrogen atmosphere. The solution was cooled to 0 °C and TBSCl (3.32 g, 22.0 mmol, 2.2 eq.) and imidazole (2.25 g, 33.0 mmol, 3.3 eq.) were added. The reaction was warmed to room temperature and stirred for 18 hours. The reaction was quenched with water (50 mL) and the mixture was extracted with pentane (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. MeOH (10 mL), THF (10 mL) and sat. K_2CO_3 (2.5 mL, 20.0 mmol, 2.0 eq.) were added to the crude mixture. The reaction was stirred for 12

hours and then quenched with 1 M HCl at 0 °C until pH ~ 3. The mixture was extracted with Et_2O (3 × 10 mL), dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 9:1) yielded **307** as a colourless solid (1.64 g, 5.85 mmol, 59%). Analytical data is consistent with the published literature.[18]

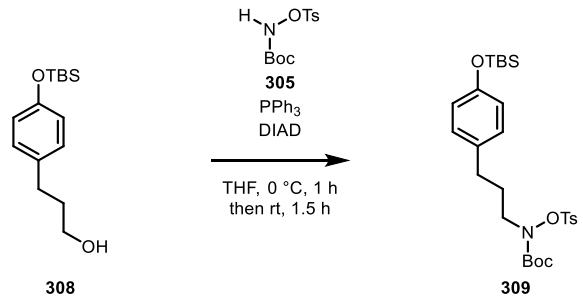
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 0.98 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 178.0, 154.3, 133.0, 129.3 (2C), 120.2 (2C), 35.8, 30.0, 25.8 (3H), 18.3, -4.3 (2H).



307 **308**

3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)propan-1-ol (308) was prepared according to a literature procedure.[18] **307** (1.63 g, 5.8 mmol, 1.0 eq.) was dissolved in anhydrous Et_2O (29 mL, 0.2 M) under a nitrogen atmosphere. The solution was cooled to 0 °C and $LiAlH_4$ (1 M in THF, 11.6 mL, 11.6 mmol, 2.0 eq.) was added dropwise. The reaction was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was then cooled to 0 °C before the addition of water (0.5 mL), 15% aq. NaOH (0.5 mL) and a final portion of water (1.5 mL). The mixture was filtered through Celite®, washed with CH_2Cl_2, dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo* to yield **308** as a colourless oil (1.35 g, 5.07 mmol, 88%). Analytical data is consistent with the published literature.[18]

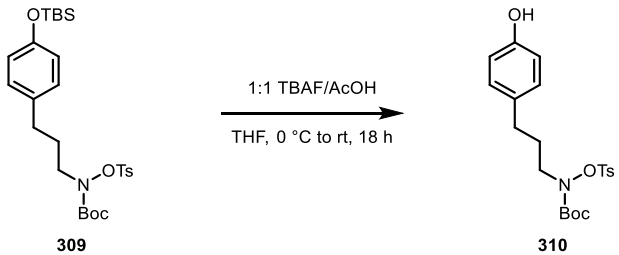
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 3.66 (td, *J* = 6.4, 4.4, Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 1.86 (ddt, *J* = 9.0, 7.6, 6.5 Hz, 2H), 1.28 – 1.22 (m, 1H), 0.98 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 153.9, 134.5, 129.4 (2H), 120.1 (2H), 62.5, 34.5, 31.4, 25.8 (3H), 18.3, -4.3 (2H).



308 309

***tert*-Butyl (3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)propyl)(tosyloxy)carbamate (309)** was prepared according to a literature procedure.[18] Triphenylphosphine (1.56 g, 5.94 mmol, 1.2 eq.) was dissolved in anhydrous THF (10 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C and diisopropyl azodicarboxylate (1.17 mL, 5.94 mmol, 1.2 eq.) was added. The solution was stirred at 0 °C for 30 min and a solution of **308** (1.32 g, 4.95 mmol, 1.0 eq.) and **305** (1.71 g, 5.94 mmol, 1.2 eq.) in anhydrous THF (10 mL, 0.25 M overall) was added. The reaction was stirred at 0 °C for one hour, warmed to room temperature and stirred for a further 1.5 hours. The volatiles were removed *in vacuo* and FCC (pentane : Et_2O = 9:1) yielded **309** as a colourless oil (2.54 g, 4.75 mmol, 96%). Analytical data is consistent with the published literature.[18]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 3.60 (app. br s, 2H), 2.51 (t, *J* = 7.8 Hz, 1H), 1.98 – 1.83 (m, 2H), 1.22 (s, 9H), 0.98 (s, 9H), 0.18 (s, 6H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 155.6, 153.9, 145.8, 133.8, 131.4, 129.8 (2C), 129.6 (2C), 129.2 (2C), 120.0 (2C), 83.3, 52.8, 32.1, 27.7 (3C), 27.7, 25.8 (3C), 21.8, 18.3, -4.3 (2C).

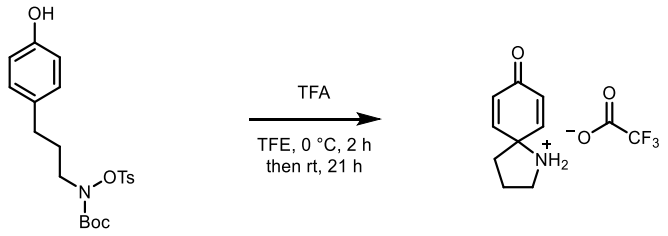


309 310

***tert*-Butyl (3-(4-hydroxyphenyl)propyl)(tosyloxy)carbamate (310)** was prepared according to a modified version of **Procedure 7**. A solution of TBAF (1 M in THF, 4.7 mL, 4.7 mmol, 1.0 eq.) and AcOH (0.27 mL, 4.7 mmol, 1.0 eq.) dissolved in THF (42 mL) was added to silyl ether **309** (2.54 g, 4.7 mmol, 1.0 eq.) dissolved in THF (94 mL, 0.0333 M overall) at 0 °C. FCC (pentane : EtOAc = 4:1)

yielded **310** as a pale yellow oil (1.95 g, 4.63 mmol, 98%). Analytical data is consistent with the published literature.[18]

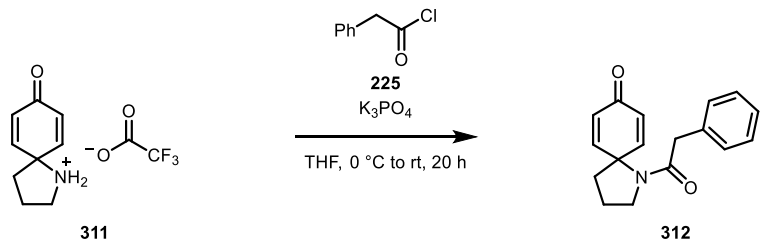
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.61 (app. br s, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.44 (s, 3H), 1.99 – 1.82 (m, 2H), 1.22 (s, 9H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 155.7, 154.1, 145.8, 133.3, 131.4, 129.8 (2C), 129.7 (2C), 129.5 (2C), 115.4 (2C), 83.4, 52.7, 32.0, 27.8 (3C), 21.8.



310 **311**

8-Oxo-1-azaspiro[4.5]deca-6,9-dien-1-ium 2,2,2-trifluoroacetate (311) was prepared according to a modified literature procedure.[18] **310** (422 mg, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous 2,2,2-trifluoroethanol (10 mL, 0.1 M). The solution was cooled to 0 °C and trifluoroacetic acid (0.16 mL, 2.0 mmol, 2.0 eq.) was added. The reaction was stirred for 2 hours at 0 °C, warmed to room temperature and stirred for a further 21 hours. The volatiles were removed *in vacuo* and the crude amine salt **311** was used in the next step without purification. Analytical data is consistent with the published literature.[18]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (d, *J* = 10.2 Hz, 2H), 6.43 (d, *J* = 10.2 Hz, 2H), 3.61 (t, *J* = 7.4 Hz, 2H), 2.41 – 2.31 (m, 2H), 2.29 – 2.23 (m, 2H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.3, 144.6 (2C), 131.6 (2C), 64.4, 46.5, 37.8, 24.7.



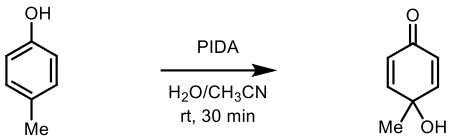
311 **312**

1-(2-Phenylacetyl)-1-azaspiro[4.5]deca-6,9-dien-8-one (312) was prepared according to a literature procedure.[18] The amine salt **311** (263 mg, 1.0 mmol, 1.0 eq.) was dissolved in anhydrous THF (5 mL,

0.2 M) under a nitrogen atmosphere. The solution was cooled to 0 °C and 2-phenylacetyl chloride **225** (0.3 mL, 2.0 mmol, 2.0 eq.) and K_3PO_4 (849 mg, 4.0 mmol, 4.0 eq.) were added. The reaction was warmed to room temperature and stirred overnight. The reaction was then quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. FCC (EtOAc) yielded **312** as a yellow oil and a 3:1 mixture of rotamers *A*:*B* (171 mg, 0.640 mmol, 64% after 2 steps). Analytical data is consistent with the published literature.[18]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 – 7.10 (m, 5H, *A* + *B*), 6.95 (d, *J* = 10.1 Hz, 2H, *B*), 6.76 (d, *J* = 10.1 Hz, 2H, *A*), 6.32 (d, *J* = 10.0 Hz, 2H, *B*), 6.25 (d, *J* = 10.1 Hz, 2H, *A*), 3.86 (t, *J* = 6.9 Hz, 2H, *B*), 3.71 (t, *J* = 6.6 Hz, 2H, *A*), 3.65 (s, 2H, *A*), 3.43 (s, 2H, *B*), 2.25 (t, *J* = 6.9 Hz, 2H, *B*), 2.13 – 1.98 (m, 4H, *A* and 2H, *B*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.4 (*A*), 184.4 (*B*), 170.6 (*B*), 169.5 (*A*), 151.3 (2C, *B*), 150.7 (2C, *A*), 134.8 (*B*), 134.2 (*A*), 129.4 (2C, *B*), 129.0 (2C, *A*), 128.9 (2C, *A*), 128.7 (2C, *B*), 128.5 (2C, *B*), 128.2 (2C, *A*), 127.1 (*A*), 126.8 (*B*), 62.6 (*A*), 62.0 (*B*), 48.9 (*B*), 48.5 (*A*), 42.8 (*A*), 42.0 (*B*), 39.9 (*B*), 38.8 (*A*), 24.5 (*A*), 22.5 (*B*).

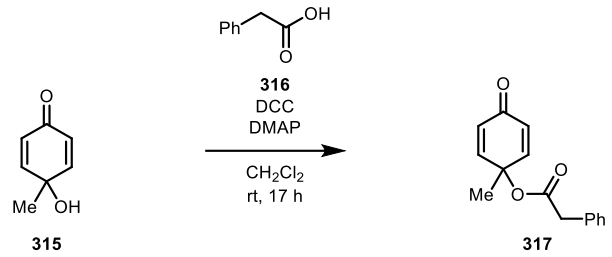
Synthesis of **317**:



314 **315**

4-Hydroxy-4-methylcyclohexa-2,5-dien-1-one (315) was prepared according to a modified literature procedure.[19] Phenyliodine (III) diacetate (PIDA, 354 mg, 1.1 mmol, 1.1 eq.) was added to a solution of *p*-cresol **314** (0.1 mL, 1 mmol, 1.0 eq.) in acetonitrile (7.5 mL) and water (2.5 mL, 0.1 M altogether). The reaction mixture was stirred for 30 min until consumption of **314** as indicated by TLC, diluted with CH_2Cl_2 (15 mL), washed with sat. $NaHCO_3$ and brine (15 mL each), dried over Na_2SO_4 and filtered. Volatiles were removed *in vacuo* yielding crude cyclohexadienone **315** as a red oil which was used in the next step without purification. Analytical data is consistent with the published literature.[20]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (d, *J* = 10.1 Hz, 2H), 6.14 (d, *J* = 10.1 Hz, 2H), 5.10 (br s, 1H), 1.49 (s, 3H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.6, 152.2 (2C), 127.3 (2C), 67.4, 26.8.

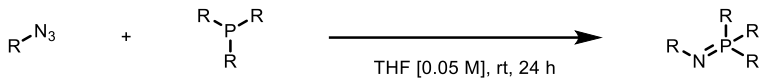


1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-phenylacetate (317) was prepared according to a modified literature procedure.[19] *N*,*N*'-Dicyclohexylcarbodiimide (619 mg, 3 mmol, 3.0 eq.) was added to a solution of **315** (124 mg, 1 mmol, 1.0 eq.), 2-phenylacetic acid **316** (408 mg, 3 mmol, 3.0 eq.), and 4-dimethylaminopyridine (12 mg, 0.1 mmol, 10 mol%) in CH_2Cl_2 (2.5 mL, 0.4 M). The mixture was stirred for 17 hours until consumption of **315** as indicated by TLC, then filtered and concentrated. FCC (pentane : EtOAc = 4:1) yielded **317** as a yellow oil (155 mg, 0.639 mmol, 64% after 2 steps).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.22 (m, 5H, Ar<u>H</u>), 6.84 (d, *J* = 10.2 Hz, 2H, C<u>H</u>C(CH_3)C<u>H</u>), 6.21 (d, *J* = 10.2 Hz, 2H, C<u>H</u>C(O)C<u>H</u>), 3.61 (s, 2H, C<u>H</u>$_2$C=O), 1.55 (s, 3H, CC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.0 (ketone <u>C</u>=O), 170.3 (amide <u>C</u>=O), 148.9 (<u>C</u>HC(CH_3)<u>C</u>H), 133.5 (Ar<u>C</u>), 129.3 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.4 (<u>C</u>HC(O)<u>C</u>H), 127.4 (Ar<u>C</u>), 74.7 (<u>C</u>CH_3), 41.6 (<u>C</u>H_2C=O), 26.4 (C<u>C</u>H_3); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{15}H_{15}O_3^+$ [M+H]$^+$: 243.1016, found 243.1012.

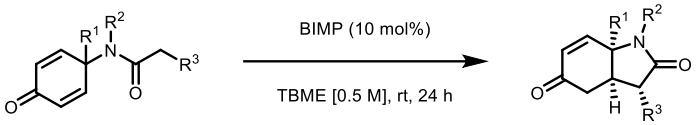
4.2.4 Desymmetrisation Product Synthesis – General Procedures

Procedure 8 – *in situ* generation of BIMP catalysts



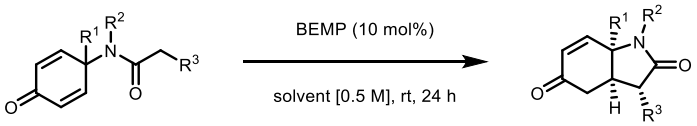
According to a literature procedure,[21] the organoazide (0.01 mmol, 1.0 eq.) and trivalent phosphine (0.01 mmol, 1.0 eq.) were dissolved in anhydrous THF (0.2 mL, 0.05 M) and the reaction mixture was stirred at room temperature for 12 to 24 hours. Volatiles were removed under a stream of nitrogen yielding the crude BIMP catalyst which was used without purification.

Procedure 9 – synthesis of enantiomerically enriched dearomatised oxindole products



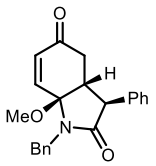
The amide (0.1 mmol, 1.0 eq.) was added to the BIMP catalyst (0.01 mmol, 10 mol%), which were both dissolved in the intended reaction solvent (TBME for all substrate scope examples, 0.2 mL, 0.5 M). After 24 hours of vigorous stirring, crude products were purified by silica gel chromatography as specified in the individual experiment to afford enantioenriched dearomatised oxindole products. The two enantiomers were separated by analytical chiral HPLC using conditions specified in the individual experiment.

Procedure 10 – synthesis of racemic dearomatised oxindole products



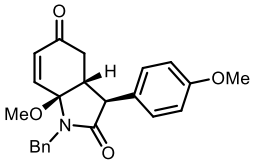
The amide (0.1 mmol, 1.0 eq.) was dissolved in a solvent (THF, Et_2O or TBME, 0.2 mL, 0.5 M). BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) achiral superbase (3 μL, 0.01 mmol, 10 mol%) was added to this solution. After 24 hours of vigorous stirring, crude products were isolated by passing the reaction mixture through a short silica plug eluting with 1:1 pentane : EtOAc to afford racemic dearomatised oxindole products. The two enantiomers were separated by analytical chiral HPLC using conditions specified in the individual experiment.

4.2.5 Desymmetrisation Product Synthesis – Analytical Data



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (222) was prepared according to **Procedure 9.** FCC (hexane : EtOAc = 1:1) yielded **222** as a yellow oil (31.4 mg, 0.0904 mmol, 90%, 96.5:3.5 e.r., >20:1 dr).

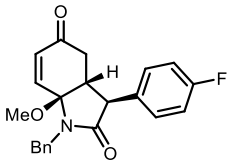
^{1}H NMR (CD_3OD, 400 MHz) δ 7.45 – 7.22 (m, 10H, ArH), 6.60 (dd, *J* = 10.4, 2.0 Hz, 1H, CH=CHC=O), 6.06 (dd, *J* = 10.4, 1.0 Hz, 1H, CH=CHC=O), 4.76 (d, *J* = 15.3 Hz, 1H, NCH_AH_B), 4.52 (d, *J* = 15.4 Hz, 1H, NCH_AH_B), 3.43 (d, *J* = 10.8 Hz, 1H, PhCHC=O), 3.27 (s, 3H, $COCH_3$), 3.08 (ddt, *J* = 10.7, 6.1, 2.4 Hz, 1H, $CHCH_2C=O$), 2.78 (dd, *J* = 17.0, 6.1 Hz, 1H, $CHCH_AH_BC=O$), 2.38 (ddd, *J* = 17.0, 2.6, 1.0 Hz, 1H, $CHCH_AH_BC=O$); **^{13}C NMR** (CD_3OD, 101 MHz) δ 197.9 (ketone C=O), 175.3 (amide C=O), 142.8 (CH=CHC=O), 139.4 (ArC), 137.8 (ArC), 130.6 (CH=CHC=O), 130.1 (ArC, 2C), 130.0 (ArC, 2C), 129.7 (ArC, 2C), 129.2 (ArC, 2C), 128.9 (ArC), 128.6 (ArC), 90.3 ($COCH_3$), 54.7 (PhCHC=O), 51.2 ($COCH_3$), 44.4 ($CHCH_2C=O$), 44.0 (NCH_2), 37.0 ($CHCH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{22}NO_3^+$ $[M+H]^+$: 348.1594, found 348.1595; **m. p.**: 134 – 136 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3031, 2937, 1692, 1395, 1077, 701; **$[\alpha]_D^{25}$ =** -279.9 (*c* = 2.62, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 19.4 min, $t_{(minor)}$ = 33.8 min.



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-(4-methoxyphenyl)-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (261) was prepared according to **Procedure 9** with a reaction temperature of 50 °C. FCC (hexane : EtOAc = 1:1) yielded **261** as a yellow oil (36.9 mg, 0.0978 mmol, 98%, 96:4 e.r., >20:1 dr).

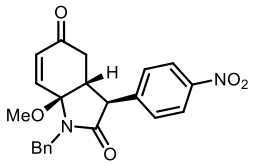
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.25 (m, 5H, ArH), 7.12 (d, *J* = 8.7 Hz, 2H, ArH), 6.91 (d, *J* = 8.7 Hz, 2H, ArH), 6.39 (dd, *J* = 10.4, 2.1 Hz, 1H, CH=CHC=O), 6.01 (dd, *J* = 10.4, 1.0 Hz, 1H, CH=CHC=O), 4.80 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 4.41 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 3.80 (s, 3H, $ArOCH_3$), 3.25 (overlapping d, 1H, ArCHC=O), 3.24 (s, 3H, $NCOCH_3$), 2.91 (ddt, *J* = 11.1, 5.8, 2.3 Hz, 1H, $CHCH_2C=O$), 2.67 (dd, *J* = 17.0, 5.9 Hz, 1H, $CHCH_AH_BC=O$), 2.51 (ddd, *J* = 17.0, 2.5, 1.1 Hz, 1H, $CHCH_AH_BC=O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.1 (ketone C=O), 173.0 (amide C=O), 159.4 (ArC), 141.5 (CH=CHC=O), 138.1 (ArC), 129.9 (ArC, 2C), 129.5 (CH=CHC=O), 128.9 (ArC, 2C), 128.5 (ArC, 2C), 128.1 (ArC), 127.8 (ArC), 114.7 (ArC, 2C), 88.7 ($NCOCH_3$), 55.5 ($ArOCH_3$), 52.7

(CHC=O), 50.5 ($NCOCH_3$), 43.1 (NCH_2 or $CHCH_2C=O$), 43.0 (NCH_2 or $CHCH_2C=O$), 36.2 ($CHCH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_4^+$ $[M+H]^+$: 378.1700, found 378.1703; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3007, 2935, 2837, 1690, 1514, 1394, 1249; **$[\alpha]_D^{25}$ =** -207.0 (c = 3.00, $CHCl_3$); **Chiral HPLC**: CHIRALPAK OD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 24.6 min, $t_{(minor)}$ = 20.2 min.



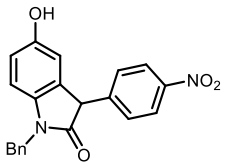
(3*S*,3a*R*,7a*S*)-1-Benzyl-3-(4-fluorophenyl)-7a-methoxy-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (262) was prepared according to **Procedure 9**. FCC (5% EtOAc in CH_2Cl_2) yielded **262** as a colourless solid (32.7 mg, 0.0895 mmol, 90%, 95:5 e.r., >20:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ): 7.40 – 7.25 (m, 5H, ArH), 7.21 – 7.15 (m, 2H, ArH), 7.11 – 7.04 (m, 2H, ArH), 6.39 (dd, J = 10.5, 2.1 Hz, 1H, CH=CHC=O), 6.02 (dd, J = 10.4, 1.0 Hz, 1H, CH=CHC=O), 4.81 (d, J = 14.9 Hz, 1H, NCH_AH_B), 4.41 (d, J = 15.0 Hz, 1H, NCH_AH_B), 3.29 (d, J = 11.0 Hz, 1H, ArCHC=O), 3.25 (s, 3H, $COCH_3$), 2.91 (ddt, J = 10.8, 5.9, 2.3 Hz, 1H, $CHCH_2C=O$), 2.69 (dd, J = 16.9, 5.9 Hz, 1H, $CHCH_AH_BC=O$), 2.48 (ddd, J = 17.0, 2.6, 1.1 Hz, 1H, $CHCH_AH_BC=O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 195.9 (ketone C=O), 172.5 (amide C=O), 162.5 (d, J^1_F = 247.2 Hz, ArC), 141.4 (CH=CHC=O), 137.9 (ArC), 131.8 (d, J^4_F = 3.6 Hz, ArC), 130.5 (d, J^3_F = 8.3 Hz, ArC, 2C), 129.5 (CH=CHC=O), 128.9 (ArC, 2C), 128.4 (ArC, 2C), 127.9 (ArC), 116.2 (d, J^2_F = 21.9 Hz, ArC, 2C), 88.7 ($COCH_3$), 52.7 (CHC=O), 50.6 ($COCH_3$), 43.1 (NCH_2 or $CHCH_2C=O$), 43.0 (NCH_2 or $CHCH_2C=O$), 36.3 ($CHCH_2C=O$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -114.3 (tt, J = 8.0, 5.3 Hz); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{21}FNO_3^+$ $[M+H]^+$: 366.1500, found 366.1492; **m. p.**: 122 – 124 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1695, 1512, 1398, 1226, 1076, 835, 761, 702; **$[\alpha]_D^{25}$ =** -211.4 (c = 3.27, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 230 nm, $t_{(major)}$ = 23.9 min, $t_{(minor)}$ = 27.1 min.



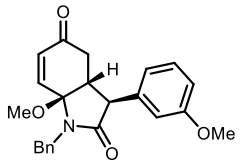
(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-(4-nitrophenyl)-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (263) was prepared according to **Procedure 9** after a reaction time of 5 min. FCC (pentane : EtOAc = 9:1 to 1:1, separable diastereoisomers) afforded **263** as a yellow solid (28.5 mg, 0.0726 mmol, 73%, 67.5:32.5 e.r., 9:1 dr). Performing the reaction at 0 °C or at increased reaction times had no effect on the outcome.

^{1}H NMR (toluene-d_8, 400 MHz) δ 7.77 – 7.68 (m, 2H, ArH), 7.31 – 7.25 (m, 2H, ArH), 7.16 – 7.10 (m, 2H, ArH), 7.08 – 7.03 (m, 1H, ArH), 6.75 – 6.69 (m, 2H, ArH), 5.90 (dd, J = 10.4, 1.9 Hz, 1H, CH=CHC=O), 5.61 (dd, J = 10.4, 0.8 Hz, 1H, 1H, CH=CHC=O), 4.48 (d, J = 14.9 Hz, 1H, NCH_AH_B), 4.14 (d, J = 14.9 Hz, 1H, NCH_AH_B), 2.88 (d, J = 10.5 Hz, 1H, ArCHC=O), 2.65 (s, 3H, $COCH_3$), 2.35 – 2.28 (m, 1H, $CHCH_2C$=O), 2.04 (d, J = 5.6 Hz, 1H, $CHCH_AH_BC$=O), 2.02 – 1.99 (m, 1H, $CHCH_AH_BC$=O); **^{13}C NMR** (toluene-d_8, 101 MHz) δ 193.8 (ketone C=O), 170.7 (amide C=O), 147.7 (ArC), 143.5 (ArC), 140.5 (CH=CHC=O), 138.6 (ArC), 129.7 (CH=CHC=O), 129.6 (ArC, 2C), 128.9 (ArC, 2C), 128.7 (ArC, 2C), 123.9 (ArC, 2C), 88.6 ($COCH_3$), 52.8 (PhCHC=O), 50.0 ($COCH_3$), 43.1 (NCH_2), 43.0 ($CHCH_2C$=O), 36.3 ($CHCH_2C$=O) [one ArC overlaps with toluene-d_8]; **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{20}N_2O_5$ $[M+H]^+$: 393.1445, found 393.1433; **m. p.:** 159 – 161 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1692, 1521, 1398, 1349, 1077, 856, 758, 703; **$[\alpha]_D^{25}$ =** -64.7 (c = 3.80, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 28.2 min, $t_{(major)}$ = 54.7 min.



1-Benzyl-5-hydroxy-3-(4-nitrophenyl)indolin-2-one (276) was formed upon rearomatisation of **263** sometime after treatment with $CDCl_3$**.** FCC (pentane : EtOAc = 1:1) yielded **276** as a yellow solid (50:50 e.r.).

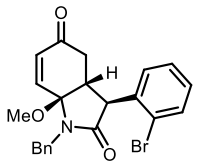
^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ (ppm): 9.17 (s, 1H, OH), 8.25 (d, *J* = 8.8 Hz, 2H, ArH), 7.46 (d, *J* = 8.8 Hz, 2H, ArH), 7.37 – 7.24 (m, 5H, ArH), 6.81 (d, *J* = 8.4 Hz, 1H, ArH), 6.66 (ddd, *J* = 8.4, 2.5, 0.8 Hz, 1H, ArH), 6.57 (dd, *J* = 2.4, 1.2 Hz, 1H, ArH), 5.19 (s, 1H, CHC=O), 4.89 (s, 2H, NCH_2); **^{13}C NMR** (DMSO-*d*$_6$, 101 MHz) δ (ppm): 174.1 (C=O), 153.5 (ArC), 146.8 (ArC), 145.2 (ArC), 136.5 (ArC), 135.0 (ArC), 129.7 (ArC, 2C), 129.1 (ArC), 128.7 (ArC, 2C), 127.4 (ArC), 127.2 (ArC, 2C), 123.9 (ArC, 2C), 114.4 (ArC), 112.6 (ArC), 110.1 (ArC), 51.3 (CHC=O), 43.0 (NCH_2); **HRMS** (ESI-, m/Z): exact mass calculated for $C_{21}H_{15}N_2O_4^-$ [M-H]$^-$: 359.1037, found 359.1037; **m. p.**: >230 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3236, 2922, 2852, 1674, 1510, 1462, 1340, 1197, 818, 742, 728, 695; **Chiral SFC**: Chiralpak® IF, 1500 psi, 30 °C; flow: 1.5 mL/min; 1% to 30% MeOH over 5 min, then from 30% to 50% MeOH in 0.5 min, then hold 50% MeOH for 1.5 min (tR = 5.89 min, 6.34 min).



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-(3-methoxyphenyl)-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (264) was prepared according to **Procedure 9**. FCC (hexane : EtOAc = 1:1) and trituration with pentane yielded **264** as a yellow oil (30.0 mg, 0.0795 mmol, 80%, 97:3 e.r., >20:1 dr).

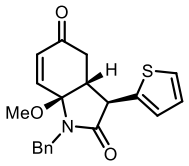
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.25 (m, 6H, ArH), 6.86 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H, ArH), 6.79 (dt, *J* = 7.6, 1.4 Hz, 1H, ArH), 6.75 (t, *J* = 2.1 Hz, 1H, ArH), 6.40 (dd, *J* = 10.4, 2.0 Hz, 1H, CH=CHC=O), 6.01 (dd, *J* = 10.5, 0.9 Hz, 1H, CH=CHC=O), 4.79 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 4.42 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 3.80 (s, 3H, $ArOCH_3$), 3.27 (d, *J* = 10.9 Hz, 1H, ArCHC=O), 3.24 (s, 3H, $NCOCH_3$), 2.98 (ddt, *J* = 10.9, 5.9, 2.4 Hz, 1H, $CHCH_2C$=O), 2.68 (dd, *J* = 17.0, 5.9 Hz, 1H, $CHCH_AH_BC$=O), 2.52 (ddd, *J* = 17.0, 2.6, 1.0 Hz, 1H, $CHCH_AH_BC$=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.0 (ketone C=O), 172.6 (amide C=O), 160.2 (ArC), 141.5 (CH=CHC=O), 138. 1 (ArC), 137.6

(Ar<u>C</u>), 130.2 (Ar<u>C</u>), 129.5 (CH=<u>C</u>HC=O), 128.9 (Ar<u>C</u>, 2C), 128.5 (Ar<u>C</u>, 2C), 127.9 (Ar<u>C</u>), 121.1 (Ar<u>C</u>), 114.9 (Ar<u>C</u>), 113.3 (Ar<u>C</u>), 88.8 (N<u>C</u>OCH$_3$), 55.4 (ArO<u>C</u>H$_3$), 53.5 (<u>C</u>HC=O), 50.6 (NCO<u>C</u>H$_3$), 43.1 (N<u>C</u>H$_2$), 42.8 (<u>C</u>HCH$_2$C=O), 36.4 (CH<u>C</u>H$_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_4^+$ $[M+H]^+$: 378.1700, found 378.1697; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3031, 2927, 2836, 1691, 1395, 702; **$[\alpha]_D^{25}$ =** -208.8 (*c* = 2.73, $CHCl_3$); **Chiral HPLC**: CHIRALPAK IB, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 34.1 min, $t_{(major)}$ = 37.8 min.



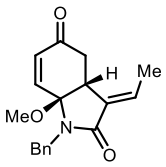
(3*S*,3a*R*,7a*S*)-1-Benzyl-3-(2-bromophenyl)-7a-methoxy-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (265) was prepared according to **Procedure 9**. FCC (pentane : EtOAc = 1:1, silica plug) yielded **265** as a yellow viscous oil (43.0 mg, 0.101 mmol, 99%, 96:4 e.r., >20:1 dr).

^{1}H NMR (C_6D_6, 50 °C, 600 MHz) δ 7.38 (d, *J* = 7.4 Hz, 1H, Ar<u>H</u>), 7.33 (dd, *J* = 8.1, 1.4 Hz, 1H, Ar<u>H</u>), 7.13 (t, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.09 – 7.01 (m, 2H, Ar<u>H</u>), 6.91 (td, *J* = 7.5, 1.4 Hz, 1H, Ar<u>H</u>), 6.70 (td, *J* = 7.6, 1.7 Hz, 1H, Ar<u>H</u>), 6.01 (dd, *J* = 10.4, 1.8 Hz, 1H, C<u>H</u>=CHC=O), 5.73 (d, *J* = 10.4 Hz, 1H, CH=C<u>H</u>C=O), 4.57 (d, *J* = 15.0 Hz, 1H, NC<u>H$_A$</u>H$_B$), 4.32 (d, *J* = 15.0 Hz, 1H, NCH$_A$<u>H$_B$</u>), 3.80 (d, *J* = 10.1 Hz, 1H, PhC<u>H</u>C=O), 2.82 – 2.75 (m, 1H, C<u>H</u>CH$_2$C=O), 2.70 (s, 3H, COC<u>H</u>$_3$), 2.26 (d, *J* = 5.0 Hz, 2H, CHC<u>H</u>$_2$C=O); **^{13}C NMR** (C_6D_6, 50 °C, 151 MHz) δ 194.3 (ketone <u>C</u>=O), 171.6 (amide <u>C</u>=O), 140.8 (<u>C</u>H=CHC=O), 138.9 (Ar<u>C</u>), 137.2 (Ar<u>C</u>), 133.6 (Ar<u>C</u>), 131.6 (Ar<u>C</u>), 130.1 (CH=<u>C</u>HC=O), 129.3 (Ar<u>C</u>), 128.9 (Ar<u>C</u>, 2C), 128.9 (Ar<u>C</u>, 2C), 128.0 (Ar<u>C</u>), 127.8 (Ar<u>C</u>), 125.3 (Ar<u>C</u>), 89.2 (<u>C</u>OCH$_3$), 54.0 (Ph<u>C</u>HC=O), 50.4 (CO<u>C</u>H$_3$), 43.4 (N<u>C</u>H$_2$), 42.9 (<u>C</u>HCH$_2$C=O), 36.9 (CH<u>C</u>H$_2$C=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{21}BrNO_3^+$ $[M+H]^+$: 426.0699, found 426.0690; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2931, 1696, 1397, 1077, 757, 703; **$[\alpha]_D^{25}$** = -268.0 (*c* = 4.26, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 15.9 min, $t_{(minor)}$ = 54.5 min.



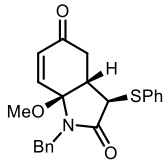
(3*R*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-(thiophen-2-yl)-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (266) was prepared according to **Procedure 9**. FCC (pentane : EtOAc = 1:1, silica plug) yielded **266** as a yellow oil (34.1 mg, 0.0965 mmol, 97%, 78.5:21.5 e.r., 8:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.25 (m, 8H, ArH), 7.03 – 6.99 (m, 2H, ArH), 6.39 (dd, *J* = 10.4, 2.0 Hz, 1H, CH=CHC=O), 6.00 (d, *J* = 10.4 Hz, 1H, CH=CHC=O), 4.81 (d, *J* = 15.1 Hz, 1H, NCH_AH_B), 4.37 (d, *J* = 15.1 Hz, 1H, NCH_AH_B), 3.63 (d, *J* = 10.7 Hz, 1H, ArCHC=O), 3.25 (s, 3H, $COCH_3$), 3.07 (ddt, *J* = 10.8, 5.4, 2.5 Hz, 1H, $CHCH_2C=O$), 2.77 (dd, *J* = 17.1, 5.9 Hz, 1H, $CHCH_AH_BC=O$), 2.65 (dd, *J* = 17.1, 2.9 Hz, 1H, $CHCH_AH_BC=O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 195.6 (ketone C=O), 171.5 (amide C=O), 141.5 (CH=CHC=O), 137.8 (ArC, 2C, 2 peaks), 129.6 (CH=CHC=O), 128.9 (ArC, 2C), 128.4 (ArC, 2C), 127.9 (ArC), 127.3 (ArC), 127.0 (ArC), 125.6 (ArC), 88.7 ($COCH_3$), 50.7 ($COCH_3$), 48.4 (CHC=O), 43.2 (NCH_2), 42.8 ($CHCH_2C=O$), 36.7 ($CHCH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{20}H_{20}NO_3S^+$ $[M+H]^+$: 354.1158, found 354.1158; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3032, 2936, 1688, 1395, 1357, 1280, 1078, 1064, 960, 758, 700; **$[\alpha]_D^{25}$** = -113.2 (*c* = 1.91, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 25.6 min, $t_{(minor)}$ = 29.6 min.



(3a*R*,7a*S*,*E*)-1-Benzyl-3-ethylidene-7a-methoxy-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (267) was prepared according to **Procedure 9**. FCC (CH_2Cl_2 – 5% EtOAc in CH_2Cl_2) yielded **267** as a brown oil (20.8 mg, 0.0700 mmol, 69%, 85.5:14.5 e.r., >20:1 dr). The configuration of the single diastereomer obtained was determined by NOE NMR experiments.

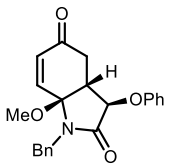
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 – 7.20 (m, 5H, ArH), 6.73 (qd, *J* = 7.2, 1.7 Hz, 1H, CH_3CH=CC=O), 6.55 (d, *J* = 10.5 Hz, 1H, CH=CHC=O), 5.92 (dd, *J* = 10.5, 1.2 Hz, 1H, CH=CHC=O), 5.01 (d, *J* = 15.6 Hz, 1H, NCH_AH_B), 4.21 (d, *J* = 15.6 Hz, 1H, NCH_AH_B), 3.48 (dd, *J* = 12.2, 6.3 Hz, 1H, $CHCH_2C$=O), 3.06 (s, 3H, $COCH_3$), 2.76 (ddd, *J* = 16.1, 6.3, 1.2 Hz, 1H, $CHCH_AH_BC$=O), 2.25 (dd, *J* = 16.1, 12.3 Hz, 1H, $CHCH_AH_BC$=O), 1.90 (d, *J* = 7.2 Hz, 3H, CH_3CH=CC=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.3 (ketone C=O), 168.3 (amide C=O), 143.3 (CH=CHC=O), 137.7 (ArC), 134.0 (ArC), 130.7 (CH_3CH=CC=O), 130.1 (CH=CHC=O), 128.7 (ArC, 2C), 127.6 (CH_3CH=CC=O), 127.5 (ArC, 2C), 87.8 ($COCH_3$), 49.9 ($COCH_3$), 42.6 (NCH_2), 41.0 ($CHCH_2C$=O), 38.7 ($CHCH_2C$=O), 14.5 (CH_3CH=CC=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{18}H_{20}NO_3^+$ $[M+H]^+$: 298.1438, found 298.1435; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1691, 1388, 1055, 917, 744, 703; **$[\alpha]_D^{25}$** = -26.3 (*c* = 2.08, $CHCl_3$); **Chiral HPLC**: CHIRALPAK IB, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 11.4 min, $t_{(minor)}$ = 14.7 min.



(3*R*,3a*S*,7a*S*)-1-Benzyl-7a-methoxy-3-(phenylthio)-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (268) was prepared according to **Procedure 9.** FCC (hexane : EtOAc = 1:1) yielded **268** as a brown oil (0.1 mmol scale, full conversion, difficult to purify, 55:45 e.r.).

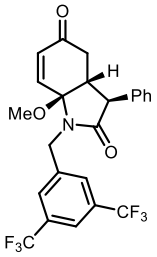
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 – 7.57 (m, 2H, ArH), 7.42 – 7.22 (m, 8H, ArH), 6.37 (dd, *J* = 10.4, 1.8 Hz, 1H, CH=CHC=O), 5.94 (dd, *J* = 10.5, 0.9 Hz, 1H, CH=CHC=O), 4.58 (d, *J* = 14.9 Hz, 1H, NCH_AH_B), 4.39 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 3.30 (d, *J* = 10.0 Hz, 1H, PhCHC=O), 2.82 (s, 3H, $COCH_3$), 2.83 – 2.72 (overlapping m, 2H, $CHCH_2C$=O and $CHCH_AH_BC$=O), 2.66 (dd, *J* = 16.4, 5.8 Hz, 1H, $CHCH_AH_BC$=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 195.4 (ketone C=O), 170.7 (amide C=O), 141.5 (CH=CHC=O), 137.4 (ArC), 134.8 (ArC, 2C), 131.5 (ArC), 129.4 (CH=CHC=O), 129.3 (ArC, 2C), 129.0 (ArC), 128.8 (ArC, 2C), 128.4 (ArC, 2C), 127.9 (ArC), 88.6 ($COCH_3$), 53.2 (PhCHC=O), 50.3 ($COCH_3$), 43.4 (NCH_2), 38.7 ($CHCH_2C$=O), 35.9 ($CHCH_2C$=O); **HRMS** (ESI+, m/Z): exact mass

calculated for $C_{22}H_{22}NO_3S^+$ [M+H]$^+$: 380.1315, found 380.1309; **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 20.5 min, $t_{(minor)}$ = 18.1 min.



(3*R*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-phenoxy-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (269) was prepared according to **Procedure 9.** FCC (pentane : EtOAc = 4:1 – 3:1) yielded **269** as a brown solid (0.1 mmol scale, 9% conversion, 53.5:46.5 e.r.).

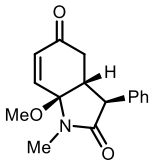
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.22 (m, 5H, ArH), 7.20 – 7.08 (m, 4H, ArH), 7.04 (tt, *J* = 7.5, 1.1 Hz, 1H, ArH), 6.41 (dd, *J* = 10.5, 2.0 Hz, 1H, CH=CHC=O), 5.96 (dd, *J* = 10.4, 0.9 Hz, 1H, CH=CHC=O), 4.79 (d, *J* = 14.9 Hz, 1H, NCH_AH_B), 4.51 (d, *J* = 9.3 Hz, 1H, PhCHC=O), 4.36 (d, *J* = 14.9 Hz, 1H, NCH_AH_B), 3.23 (s, 3H, $COCH_3$), 3.18 (dddd, *J* = 9.2, 5.5, 3.3, 2.0 Hz, 1H, $CHCH_2C$=O), 2.79 (dd, *J* = 17.2, 5.6 Hz, 1H, $CHCH_AH_BC$=O), 2.72 (ddd, *J* = 17.2, 3.2, 0.9 Hz, 1H, $CHCH_AH_BC$=O); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 16.2 min, $t_{(minor)}$ = 14.2 min.



(3*S*,3a*R*,7a*S*)-1-(3,5-Bis(trifluoromethyl)benzyl)-7a-methoxy-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (287) was prepared according to **Procedure 9**. FCC (hexane : EtOAc = 2:1) yielded **287** as a yellow oil (41.0 mg, 0.0848 mmol, 85%, 95:5 e.r., 11:1 dr).

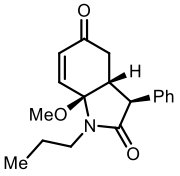
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 2H, ArH), 7.83 (s, 1H, ArH), 7.42 – 7.29 (m, 3H, ArH), 7.20 – 7.15 (m, 2H, ArH), 6.50 (dd, *J* = 10.4, 2.1 Hz, 1H, CH=CHC=O), 6.20 (dd, *J* = 10.4, 0.9 Hz, 1H, CH=CHC=O), 4.72 (d, *J* = 15.3 Hz, 1H, NCH_AH_B), 4.65 (d, *J* = 15.3 Hz, 1H, NCH_AH_B), 3.31 (d, *J* =

10.8 Hz, 1H, ArC<u>H</u>C=O), 3.27 (s, 3H, COC<u>H</u>$_3$), 2.98 (ddt, J = 10.7, 6.0, 2.4 Hz, 1H, C<u>H</u>CH$_2$), 2.72 (dd, J = 17.1, 6.0 Hz, 1H, CH<u>CH$_A$</u>H$_B$), 2.57 (ddd, J = 17.2, 2.6, 1.0 Hz, 1H, CHCH$_A$<u>H$_B$</u>); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 195.4 (ketone <u>C</u>=O), 172.9 (amide <u>C</u>=O), 140.5 (Ar<u>C</u> or <u>C</u>H=CHC=O), 140.4 (Ar<u>C</u> or <u>C</u>H=CHC=O), 135.8 (Ar<u>C</u>), 132.2 (q, J^2_F = 33.6 Hz, Ar<u>C</u>, 2C), 130.9 (CH=<u>C</u>HC=O), 129.3 (Ar<u>C</u>, 2C), 128.7 (Ar<u>C</u>, 4C, 2 peaks), 128.2 (Ar<u>C</u>), 123.3 (q, J^1_F = 273.6 Hz, <u>C</u>F$_3$, 2C), 121.8 (hept, J^3_F = 3.9 Hz, Ar<u>C</u>) 88.5 (<u>C</u>OCH$_3$), 53.6 (<u>C</u>HC=O), 51.1 (CO<u>C</u>H$_3$), 44.0 (<u>C</u>HCH$_2$), 42.6 (N<u>C</u>H$_2$), 36.7 (CH<u>C</u>H$_2$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm): -62.9; **HRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{20}F_6NO_3^+$ $[M+H]^+$: 484.1342, found 484.1340; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2940, 1696, 1381, 1352, 1279, 1172, 1130, 902, 702, 682; **$[\alpha]_D^{25}$** = -121.8 (c = 3.56, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 11.7 min, $t_{(major)}$ = 24.1 min.



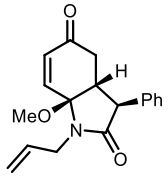
(3*S*,3a*R*,7a*S*)-7a-Methoxy-1-methyl-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (288) was prepared according to **Procedure 9** with a reaction temperature of 50 °C. FCC (hexane : EtOAc = 1:2) yielded **288** as a brown oil (23.4 mg, 0.0862 mmol, 87%, 89:11 e.r., 19:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.28 (m, 3H, Ar<u>H</u>), 7.21 – 7.15 (m, 2H, Ar<u>H</u>), 6.68 (dd, J = 10.4, 2.1 Hz, 1H, C<u>H</u>=CHC=O), 6.20 (dd, J = 10.4, 1.0 Hz, 1H, CH=C<u>H</u>C=O), 3.37 (s, 3H, COC<u>H</u>$_3$), 3.19 (d, J = 11.0 Hz, 1H, PhC<u>H</u>C=O), 2.94 (s, 3H, NC<u>H</u>$_3$), 2.96 – 2.89 (m, 1H, C<u>H</u>CH$_2$C=O), 2.71 (dd, J = 17.0, 6.0 Hz, 1H, CHC<u>H$_A$</u>H$_B$C=O), 2.52 (ddd, J = 17.0, 2.3, 1.1 Hz, 1H, CHCH$_A$<u>H$_B$</u>C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.1 (ketone <u>C</u>=O), 172.6 (amide <u>C</u>=O), 140.2 (<u>C</u>H=CHC=O), 136.3 (Ar<u>C</u>), 130.1 (CH=<u>C</u>HC=O), 129.2 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.0 (Ar<u>C</u>), 87.9 (<u>C</u>OCH$_3$), 53.5 (Ph<u>C</u>HC=O), 49.9 (CO<u>C</u>H$_3$), 42.3 (<u>C</u>HCH$_2$C=O), 35.9 (CH<u>C</u>H$_2$C=O), 25.0 (N<u>C</u>H$_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{16}H_{18}NO_3^+$ $[M+H]^+$: 272.1281, found 272.1282; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1694, 1393, 1077, 984, 795, 760, 701; **$[\alpha]_D^{25}$** = -131.1 (c = 2.11, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 10.0 min, $t_{(major)}$ = 15.7 min.



(3*S*,3a*R*,7a*S*)-7a-Methoxy-3-phenyl-1-propyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (289) was prepared according to **Procedure 9** with a catalyst loading of 15 mol%. FCC (5% EtOAc in CH_2Cl_2) yielded **289** as a yellow oil (27.2 mg, 0.0909 mmol, 91%, 93.5:6.5 e.r., >20:1 dr).

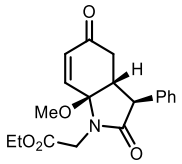
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.33 (m, 2H, ArH), 7.32 – 7.27 (m, 1H, ArH), 7.20 – 7.14 (m, 2H, ArH), 6.67 (dd, *J* = 10.4, 2.0 Hz, 1H, CH=CHC=O), 6.19 (dd, *J* = 10.4, 1.1 Hz, 1H, CH=CHC=O), 3.36 (s, 3H, $COCH_3$), 3.35 – 3.18 (m, 2H, $NCH_2CH_2CH_3$), 3.18 (d, *J* = 10.9 Hz, 1H, PhCHC=O), 2.91 (ddt, *J* = 10.8, 6.0, 2.4 Hz, 1H, $CHCH_2C$=O), 2.69 (dd, *J* = 17.0, 6.0 Hz, 1H, $CHCH_AH_BC$=O), 2.51 (ddd, *J* = 17.0, 2.6, 1.1 Hz, 1H, $CHCH_AH_BC$=O), 1.90 – 1.60 (m, 2H, $NCH_2CH_2CH_3$), 0.97 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.2 (ketone C=O), 172.7 (amide C=O), 141.4 (CH=CHC=O), 136.4 (ArC), 129.9 (CH=CHC=O), 129.1 (ArC, 2C), 128.8 (ArC, 2C), 127.9 (ArC), 88.5 ($COCH_3$), 53.5 (PhCHC=O), 50.3 ($COCH_3$), 42.9 ($CHCH_2C$=O), 41.8 ($NCH_2CH_2CH_3$), 36.5 ($CHCH_2C$=O), 22.6 ($NCH_2CH_2CH_3$), 11.9 ($NCH_2CH_2CH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{18}H_{22}NO_3^+$ $[M+H]^+$: 300.1594, found 300.1588; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2967, 1691, 1399, 1078, 761, 700; **$[\alpha]_D^{25}$** = -188.9 (*c* = 2.68, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 19.9 min, $t_{(major)}$ = 27.0 min.



(3*S*,3a*R*,7a*S*)-1-Allyl-7a-methoxy-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (290) was prepared according to **Procedure 9**. FCC (hexane : EtOAc = 2:1) yielded **290** as a brown oil (26.0 mg, 0.0874 mmol, 88%, 93.5:6.5 e.r., 19:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.34 (m, 2H, ArH), 7.33 – 7.28 (m, 1H, ArH), 7.21 – 7.15 (m, 2H, ArH), 6.71 (dd, *J* = 10.4, 2.1 Hz, 1H, CH=CHC=O), 6.16 (dd, *J* = 10.4, 1.0 Hz, 1H, CH=CHC=O),

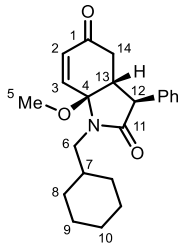
5.96 (dddd, *J* = 17.1, 10.2, 6.9, 5.3 Hz, 1H, C<u>H</u>=CH$_2$), 5.27 (dq, *J* = 17.2, 1.5 Hz, 1H, CH=C<u>H$_A$</u>H$_B$), 5.22 (dq, *J* = 10.1, 1.2 Hz, 1H, CH=CH$_A$<u>H$_B$</u>), 4.17 (ddt, *J* = 15.5, 5.3, 1.7 Hz, 1H, NC<u>H$_A$</u>H$_B$), 3.85 (ddt, *J* = 15.4, 6.8, 1.3 Hz, 1H, NCH$_A$<u>H$_B$</u>), 3.36 (s, 3H, COC<u>H$_3$</u>), 3.23 (d, *J* = 11.0 Hz, 1H, ArC<u>H</u>C=O), 2.94 (ddt, *J* = 10.8, 6.0, 2.3 Hz, 1H, C<u>H</u>CH$_2$), 2.70 (dd, *J* = 17.0, 6.0 Hz, 1H, CH<u>CH$_A$</u>H$_B$), 2.52 (ddd, *J* = 17.0, 2.5, 1.1 Hz, 1H, CHCH$_A$<u>H$_B$</u>); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.1 (ketone <u>C</u>=O), 172.3 (amide <u>C</u>=O), 141.6 (<u>C</u>H=CHC=O), 136.2 (Ar<u>C</u>), 133.6 (H<u>C</u>=CH$_2$), 129.6 (CH=<u>C</u>HC=O), 129.2 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.0 (Ar<u>C</u>), 118.1 (HC=<u>C</u>H$_2$), 88.5 (<u>C</u>OCH$_3$), 53.4 (<u>C</u>HC=O), 50.3 (CO<u>C</u>H$_3$), 42.7 (<u>C</u>HCH$_2$), 42.2 (N<u>C</u>H$_2$), 36.2 (CH<u>C</u>H$_2$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{18}H_{20}NO_3^+$ $[M+H]^+$: 298.1438, found 298.1436; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3030, 2942, 1695, 1392, 1076, 701; **$[\alpha]_D^{25}$** = -260.9 (*c* = 2.18, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 13.1 min, $t_{(major)}$ = 16.0 min.



Ethyl 2-((3*S*,3a*R*,7a*S*)-7a-methoxy-2,5-dioxo-3-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indol-1-yl)acetate (291) was prepared according to **Procedure 9**. FCC (hexane : EtOAc = 1:1) yielded **291** as a pale-yellow oil (28.0 mg, 0.0815 mmol, 82%, 94.5:5.5 e.r., >20:1 dr).

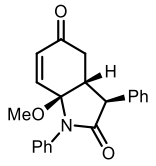
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.28 (m, 3H, Ar<u>H</u>), 7.23 – 7.18 (m, 2H, Ar<u>H</u>), 6.56 (dd, *J* = 10.3, 2.1 Hz, 1H, C<u>H</u>=CHC=O), 6.20 (dd, *J* = 10.3, 1.0 Hz, 1H, CH=C<u>H</u>C=O), 4.23 (qd, *J* = 7.1, 5.0 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.16 (d, *J* = 17.3 Hz, 1H, NC<u>H$_A$</u>H$_B$), 3.98 (d, *J* = 17.3 Hz, 1H, NCH$_A$<u>H$_B$</u>), 3.39 (s, 3H, COC<u>H$_3$</u>), 3.30 (d, *J* = 11.0 Hz, 1H, ArC<u>H</u>C=O), 3.01 (ddt, *J* = 11.0, 5.9, 2.3 Hz, 1H, C<u>H</u>CH$_2$), 2.70 (dd, *J* = 17.1, 5.9 Hz, 1H, CH<u>CH$_A$</u>H$_B$), 2.55 (ddd, *J* = 17.1, 2.3, 1.1 Hz, 1H, CHCH$_A$<u>H$_B$</u>), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 195.9 (ketone <u>C</u>=O), 172.6 (amide <u>C</u>=O), 168.3 (ester <u>C</u>=O), 141.1 (<u>C</u>H=CHC=O), 135.9 (Ar<u>C</u>), 129.7 (CH=<u>C</u>HC=O), 129.2 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.0 (Ar<u>C</u>), 87.8 (<u>C</u>OCH$_3$), 61.8 ($CO_2\underline{C}H_2CH_3$), 53.2 (<u>C</u>HC=O), 50.4 (CO<u>C</u>H$_3$), 43.2 (<u>C</u>HCH$_2$), 40.7 (N<u>C</u>H$_2$), 36.0 (CH<u>C</u>H$_2$), 14.2 ($CO_2CH_2\underline{C}H_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{19}H_{21}NO_5Na^+$ $[M+Na]^+$: 366.1312, found 366.1307; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2986, 2940, 1748,

1709, 1687, 1415, 1395, 1203, 1082, 969, 701; **[α]$_D^{25}$** = -204.3 (*c* = 2.55, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 14.6 min, $t_{(major)}$ = 27.0 min.



(3*S*,3a*R*,7a*S*)-1-(Cyclohexylmethyl)-7a-methoxy-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (292) was prepared according to **Procedure 9**. FCC (hexane : EtOAc = 1:1) yielded **292** as a yellow oil (29.0 mg, 0.0820 mmol, 82%, 89.5:10.5 e.r., >20:1 dr).

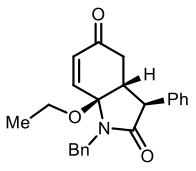
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.33 (m, 2H, ArH), 7.32 – 7.27 (m, 1H, ArH), 7.21 – 7.15 (m, 2H, ArH), 6.69 (dd, *J* = 10.4, 2.0 Hz, 1H, *C3*), 6.21 (dd, *J* = 10.4, 0.9 Hz, 1H, *C2*), 3.36 (s, 3H, *C5*), 3.26 – 3.14 (overlapping m, 3H, *C6* and *C12*), 2.91 (dddd, *J* = 10.7, 6.0, 2.9, 2.0 Hz, 1H, *C13*), 2.70 (dd, *J* = 17.0, 6.0 Hz, 1H, *C14*), 2.52 (ddd, *J* = 16.9, 3.0, 1.0 Hz, 1H, *C14*), 1.90 – 1.63 (m, 6H, *C7 – C10*), 1.33 – 1.10 (m, 3H, *C8 – C10*), 1.07 – 0.93 (m, 2H, *C8 – C10*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.2 (*C1*), 173.0 (*C11*), 141.5 (*C3*), 136.5 (ArC), 130.2 *(C2*), 129.1 (ArC, 2C), 128.8 (ArC, 2C), 127.8 (ArC), 88.6 (*C4*), 53.6 (*C12*), 50.8 (*C5*), 46.2 (*C6*), 43.3 (*C13*), 37.4 (*C7*), 36.9 (*C14*), 31.5 (*C8 – C10*), 31.2 (*C8 – C10*), 26.5 (*C8 – C10*), 26.0 (*C8 – C10*, 2C); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{28}NO_3^+$ $[M+H]^+$: 354.2064, found 354.2057: **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2926, 2852, 1692, 1397, 1077, 757, 700; **[α]$_D^{25}$** = -118.3 (*c* = 3.04, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 15.6 min, $t_{(major)}$ = 20.0 min.



(3*S*,3a*R*,7a*S*)-7a-Methoxy-1,3-diphenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (293) was prepared according to **Procedure 9** FCC (pentane : EtOAc = 4:1) yielded **293** as a yellow solid (34.8

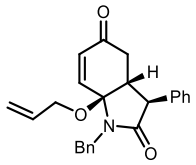
mg, 0.104 mmol, 98%, 85.5:14.5 e.r., 3.7:1 dr). For NMR assignments, the major and minor diastereomers are referred to as *A* and *B* respectively.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 – 7.26 (m, 10H, ArH), 6.59 (dd, *J* = 10.4, 1.7 Hz, 1H, CH=CHC=O, *A*), 6.53 (d, *J* = 10.4 Hz, 1H, CH=CHC=O, *B*), 6.24 (dd, *J* = 10.4, 0.6 Hz, 1H, CH=CHC=O, *A*), 6.17 (dd, *J* = 10.4, 1.2 Hz, 1H, CH=CHC=O, *B*), 4.54 (d, *J* = 7.2 Hz, 1H, PhCHC=O, *B*), 3.42 (d, *J* = 9.8 Hz, 1H, PhCHC=O, *A*), 3.40 (s, 3H, $COCH_3$, *A* + *B*), 3.35 (ddd, *J* = 12.7, 7.1, 5.5 Hz, 1H, $CHCH_2C$=O, *B*), 3.13 (dddd, *J* = 9.8, 5.8, 3.9, 1.7 Hz, 1H, $CHCH_2C$=O, *A*), 2.81 (dd, *J* = 16.9, 5.9 Hz, 1H, $CHCH_AH_BC$=O, *A*), 2.61 (ddd, *J* = 16.9, 3.9, 0.6 Hz, 1H, $CHCH_AH_BC$=O, *A*), 2.24 (dd, *J* = 16.1, 12.7 Hz, 1H, $CHCH_AH_BC$=O, *B*), 2.00 (ddd, *J* = 16.1, 5.5, 1.2 Hz, 1H, $CHCH_AH_BC$=O, *B*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 197.2 (ketone C=O, *B*), 196.1 (ketone C=O, *A*), 173.4 (amide C=O, *B*), 172.8 (amide C=O, *A*), 143.7 (CH=CHC=O, *B*), 141.5 (CH=CHC=O, *A*), 136.3 (ArC, *A*), 135.4 (ArC, *B*), 135.0 (ArC, *A*), 133.5 (ArC, *B*), 133.2 (CH=CHC=O, *B*), 130.7 (CH=CHC=O, *A*), 129.6 (ArC, 2C, *B*), 129.4 (ArC, 2C, *A*), 129.4 (ArC, 2C, *B*), 129.1 (ArC, 2C, *A*), 128.8 (ArC, 2C, *A* and ArC, 2C, *B*), 128.5 (ArC, 2C, *A*), 128.4 (ArC, *A*), 128.3 (ArC, *B*), 127.9 (ArC, *A*), 127.8 (ArC, *B*), 90.6 ($COCH_3$, *B*), 89.8 ($COCH_3$, *A*), 54.0 (PhCHC=O, *A*), 51.9 ($COCH_3$, *B*), 51.4 ($COCH_3$, *A*), 49.6 (PhCHC=O, *B*), 43.9 ($CHCH_2C$=O, *A*), 40.5 ($CHCH_2C$=O, *B*), 39.0 ($CHCH_2C$=O, *B*), 37.5 ($CHCH_2C$=O, *A*); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{21}H_{20}NO_3^+$ $[M+H]^+$: 334.1438, found 334.1432; **m. p.:** 158 – 160 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1713, 1689, 1496, 1368, 1059, 757, 698; **$[\alpha]_D^{25}$** = -90.7 (*c* = 3.20, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 21.1 min, $t_{(minor)}$ = 64.0 min.



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-ethoxy-3-phenyl-1,3a,4,7a-tetrahydro-2H-indole-2,5(3*H*)-dione (299) was prepared according to **Procedure 9**. FCC (hexane : EtOAc = 1:1) yielded **299** as a yellow oil (33.5 mg, 0.0927 mmol, 93%, 96.5:3.5 e.r., >20:1 dr).

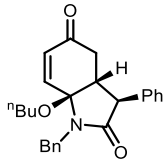
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.26 (m, 3H, ArH), 7.24 – 7.18 (m, 2H, ArH), 6.39 (dd, *J* = 10.4, 2.0 Hz, 1H, CH=CHC=O), 6.01 (dd, *J* = 10.4, 1.0 Hz, 1H, CH=CHC=O), 4.82 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 4.43 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 3.55 (dq, *J* = 8.7, 6.9 Hz, 1H, $COCH_AH_BCH_3$), 3.42 (dq, *J* = 8.7, 7.0 Hz, 1H, $COCH_AH_BCH_3$), 3.30 (d, *J* = 11.0 Hz, 1H, PhCHC=O), 2.96 (ddt, *J* = 10.8, 5.9, 2.4 Hz, 1H, $CHCH_2C=O$), 2.68 (dd, *J* = 17.0, 5.9 Hz, 1H, $CHCH_AH_BC=O$), 2.51 (ddd, *J* = 17.0, 2.6, 1.1 Hz, 1H, $CHCH_AH_BC=O$), 1.18 (t, *J* = 7.0 Hz, 1H, $COCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.2 (ketone C=O), 172.7 (amide C=O), 141.8 (CH=CHC=O), 138.1 (ArC), 136.2 (ArC), 129.2 (CH=CHC=O), 129.2 (ArC, 2C), 128.9 (ArC, 2C), 128.9 (ArC, 2C), 128.3 (ArC, 2C), 128.0 (ArC), 127.8 (ArC), 88.5 ($COCH_2CH_3$), 58.8 ($COCH_2CH_3$), 53.5 (PhCHC=O), 44.0 ($CHCH_2C=O$), 43.1 (NCH_2), 36.2 ($CHCH_2C=O$), 15.3 ($COCH_2CH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_3^+$ $[M+H]^+$: 362.1751, found 362.1746; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1697, 1395, 1078, 760, 702; **$[\alpha]_D^{25}$** = -226.9 (*c* = 3.35, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 13.7 min, $t_{(minor)}$ = 27.7 min.



(3*S*,3a*R*,7a*S*)-7a-(Allyloxy)-1-benzyl-3-phenyl-1,3a,4,7a-tetrahydro-2H-indole-2,5(3*H*)-dione (300) was prepared according to **Procedure 9** with a catalyst loading of 15 mol%. FCC (pentane : EtOAc = 3:1) yielded **300** as a brown oil (35.2 mg, 0.0943 mmol, 95%, 97:3 e.r., >20:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.28 (m, 8H, ArH), 7.24 – 7.17 (m, 2H, ArH), 6.40 (dd, *J* = 10.4, 2.1 Hz, 1H, CH=CHC=O), 6.01 (dd, *J* = 10.4, 1.0 Hz, 1H, CH=CHC=O), 5.83 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1H, $COCH_2CH=CH_2$), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H, $COCH_2CH=CH_AH_B$), 5.21 (dq, *J* = 10.4, 1.4 Hz, 1H, $COCH_2CH=CH_AH_B$), 4.84 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 4.43 (d, *J* = 15.1 Hz, 1H, NCH_AH_B), 4.02 (ddt, *J* = 12.5, 5.4, 1.5 Hz, 1H, $COCH_AH_BCH=CH_2$), 3.91 (ddt, *J* = 12.5, 5.0, 1.6 Hz, 1H, $COCH_AH_BCH=CH_2$), 3.31 (d, *J* = 11.0 Hz, 1H, PhCHC=O), 2.96 (ddt, *J* = 10.9, 5.9, 2.4 Hz, 1H, $CHCH_2C=O$), 2.69 (dd, *J* = 17.0, 5.9 Hz, 1H, $CHCH_AH_BC=O$), 2.50 (ddd, *J* = 17.0, 2.5, 1.0 Hz, 1H, $CHCH_AH_BC=O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.1 (ketone C=O), 172.7 (amide C=O), 141.5

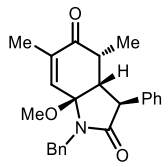
(CH=CHC=O), 138.0 (ArC), 136.0 (ArC), 133.4 ($COCH_2CH=CH_2$), 129.4 (CH=CHC=O), 129.2 (ArC, 2C), 128.9 (ArC, 2C), 128.9 (ArC, 2C), 128.4 (ArC, 2C), 128.0 (ArC), 127.9 (ArC), 117.7 ($COCH_2CH=CH_2$), 88.9 ($COCH_2CH=CH_2$), 64.0 ($COCH_2CH=CH_2$), 53.5 (PhCHC=O), 44.0 ($CHCH_2C=O$), 43.1 (NCH_2), 36.2 ($CHCH_2C=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{24}NO_3^+$ $[M+H]^+$: 374.1751, found 374.1746; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2923, 2853, 1701, 1396, 1078, 738, 702; $[\alpha]_D^{25}$ = -200.0 (c = 3.52, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 15.5 min, $t_{(minor)}$ = 37.9 min.



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-butoxy-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (301) was prepared according to **Procedure 9** with a reaction temperature of 50 °C and a catalyst loading of 15 mol%. FCC (pentane : EtOAc = 4:1) yielded **301** as a brown oil (37.2 mg, 0.0955 mmol, 95%, 94.5:5.5 e.r., >20:1 dr).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.26 (m, 8H, ArH), 7.24 – 7.19 (m, 2H, ArH), 6.37 (dd, J = 10.5, 2.0 Hz, 1H, CH=CHC=O), 6.01 (dd, J = 10.4, 1.0 Hz, 1H, CH=CHC=O), 4.84 (d, J = 15.0 Hz, 1H, NCH_AH_B), 4.42 (d, J = 15.0 Hz, 1H, NCH_AH_B), 3.47 (dt, J = 8.6, 6.7 Hz, 1H, $COCH_AH_BCH_2CH_2CH_3$), 3.36 (dt, J = 8.6, 6.5 Hz, 1H, $COCH_AH_BCH_2CH_2CH_3$), 3.30 (d, J = 11.0 Hz, 1H, PhCHC=O), 2.96 (ddt, J = 10.9, 5.9, 2.4 Hz, 1H, $CHCH_2C=O$), 2.68 (dd, J = 17.0, 6.0 Hz, 1H, $CHCH_AH_BC=O$), 2.52 (ddd, J = 17.0, 2.6, 1.0 Hz, 1H, $CHCH_AH_BC=O$), 1.61 – 1.25 (m, 4H, $COCH_2CH_2CH_2CH_3$ and $COCH_2CH_2CH_2CH_3$), 0.90 (t, J = 7.3 Hz, 3H, $COCH_2CH_2CH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.2 (ketone C=O), 172.7 (amide C=O), 141.9 (CH=CHC=O), 138.2 (ArC), 136.2 (ArC), 129.4 (CH=CHC=O), 129.2 (ArC, 2C), 128.9 (ArC, 2C), 128.9 (ArC, 2C), 128.3 (ArC, 2C), 128.0 (ArC), 127.8 (ArC), 88.4 ($COCH_2CH_2CH_2CH_3$), 63.1 ($COCH_2CH_2CH_2CH_3$), 53.6 (PhCHC=O), 44.1 ($CHCH_2C=O$), 43.1 (NCH_2), 36.4 ($CHCH_2C=O$), 31.9 ($COCH_2CH_2CH_2CH_3$), 19.4 ($COCH_2CH_2CH_2CH_3$), 14.0 ($COCH_2CH_2CH_2CH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{25}H_{28}NO_3^+$ $[M+H]^+$: 390.2064, found 390.2056; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2923, 1694, 1399,

1281, 1159, 1136, 1079, 760, 733, 702; **[α]$_D^{25}$** = -160.2 (*c* =3.72, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 11.5 min, $t_{(minor)}$ = 23.8 min.

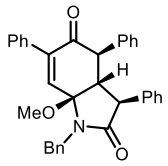


(3*S*,3a*R*,4*R*,7a*R*)-1-Benzyl-7a-methoxy-4,6-dimethyl-3-phenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (302) was prepared according to **Procedure 9.** FCC (pentane : EtOAc = 4:1 – 3:1) yielded **302** as a colourless oil (32.7 mg, 0.0872 mmol, 87%, 99:1 e.r., 3:1 dr).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.39 – 7.26 (m, 8H, ArH), 7.22 – 7.18 (m, 2H, ArH), 6.17 (p, *J* = 1.5 Hz, 1H, CH_3C=CH), 4.66 (d, *J* = 14.9 Hz, 1H, NCH_AH_B), 4.45 (d, *J* = 14.9 Hz, 1H, NCH_AH_B), 3.27 (s, 3H, $COCH_3$), 3.22 (m, 2H, PhCHC=O and CHCH(CH_3)C=O), 2.96 (qdd, *J* = 6.8, 3.5, 1.4 Hz, 1H, CH_3CHC=O), 1.71 (d, *J* = 1.5 Hz, 3H, CH_3C=CH), 0.84 (d, *J* = 6.9 Hz, 3H, CH_3CHC=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 199.4 (ketone C=O), 173.5 (amide C=O), 138.9 (ArC), 138.2 (ArC), 136.4 (CH_3C=CH), 136.0 (CH_3C=CH), 129.1 (ArC, 2C), 128.8 (ArC, 2C), 128.7 (ArC, 2C), 128.6 (ArC, 2C), 127.7 (ArC, 2C), 90.2 ($COCH_3$), 51.7 (PhCHC=O), 50.6 ($COCH_3$), 47.3 (CHCH(CH_3)C=O), 43.3 (NCH_2), 41.0 (CH_3CHC=O), 15.9 (CH_3C=CH), 12.8 (CH_3CHC=O). **HRMS** (ESI+, m/Z): exact mass calculated for $C_{24}H_{26}NO_3^+$ $[M+H]^+$: 376.1907, found 376.1903; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1703, 1400, 1077, 757, 702, 641; **[α]$_D^{25}$ =** -146.5 (*c* = 0.86, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 17.3 min, $t_{(minor)}$ = 14.0 min.

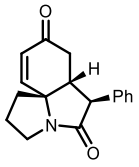
Data for minor diastereomer for NOESY experiments:

^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40 – 7.21 (m, 10H, ArH), 6.23 – 6.20 (m, 1H, CH_3C=CH), 4.83 (d, *J* = 15.2 Hz, 1H, NCH_AH_B), 4.38 (d, *J* = 15.1 Hz, 1H, NCH_AH_B), 3.34 (d, *J* = 8.9 Hz, 1H, PhCHC=O), 3.11 (s, 3H, $COCH_3$), 2.72 (ddd, *J* = 8.9, 4.4, 1.7 Hz, 1H, CHCH(CH_3)C=O), 2.58 (qd, *J* = 7.3, 4.3 Hz, 1H, CH_3CHC=O), 1.69 (d, *J* = 1.5 Hz, 3H, CH_3C=CH), 1.25 (d, *J* = 7.3 Hz, 3H, CH_3CHC=O).



(3*S*,3a*R*,4*R*,7a*R*)-1-Benzyl-7a-methoxy-3,4,6-triphenyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (303) was prepared according to **Procedure 9.** FCC (pentane : EtOAc = 2:1) yielded **303** as a colourless solid (48.3 mg, 0.0967 mmol, 97%, 96.5:3.5 e.r., >20:1 dr).

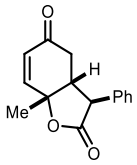
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 – 7.13 (m, 18H, ArH), 6.83 – 6.77 (m, 2H, ArH), 6.57 (d, *J* = 1.1 Hz, 1H, PhC=CH), 5.21 (d, *J* = 15.3 Hz, 1H, NCH_ACH_B), 4.32 (d, *J* = 15.3 Hz, 1H, NCH_ACH_B), 3.93 (d, *J* = 5.7 Hz, 1H, CH(Ph)C(O)CPh), 3.62 (d, *J* = 7.3 Hz, 1H, CH(Ph)C(O)NBn), 3.34 – 3.27 (m, 1H, CHCH(Ph)C=O), 3.11 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.2 (ketone C=O), 173.5 (amide C=O), 140.3 (PhC=CH), 139.2 (PhC=CH), 138.8 (ArC), 137.0 (ArC), 136.8 (ArC), 134.1 (ArC), 129.2 (ArC, 2C), 129.1 (ArC, 2C), 129.0 (ArC, 2C), 128.8 (ArC, 3C), 128.6 (ArC, 2C), 128.5 (ArC, 2C), 128.2 (ArC, 2C), 128.2 (ArC, 2C), 127.9 (ArC), 127.8 (ArC), 127.8 (ArC), 90.0 ($COCH_3$), 56.5 (CH(Ph)C(O)CPh), 54.1 (CH(Ph)C(O)NBn), 49.9 ($COCH_3$), 47.8 (CHCH(Ph)C=O), 42.9 (NCH_2); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{34}H_{30}NO_3^+$ $[M+H]^+$: 500.2220, found 500.2217; **m. p.**: 62 – 64 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1703, 1497, 1399, 1360, 1071, 756, 699; **$[\alpha]_D^{25}$ =** -39.6 (*c* = 4.72, $CHCl_3$); **Chiral HPLC**: CHIRALPAK OD, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 11.1 min, $t_{(minor)}$ = 16.5 min.



(6*S*,6a*R*,10a*R*)-6-Phenyl-2,3,6a,7-tetrahydro-1*H*,5*H*-pyrrolo[2,1-i]indole-5,8(6*H*)-dione (313) was prepared according to **Procedure 9**. FCC (10% EtOAc in CH_2Cl_2) yielded **313** as a yellow oil (14.7 mg, 0.0550 mmol, 55%, 80:20 e.r., >20:1 dr). Analytical data is consistent with the published literature.[18]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.26 (m, 3H), 7.15 – 7.10 (m, 2H), 6.64 (dd, *J* = 10.2, 1.9 Hz, 1H), 6.13 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.68 (d, *J* = 12.1 Hz, 1H), 3.28 – 3.19 (m, 1H),

2.71 – 2.58 (m, 2H), 2.46 (dt, *J* = 17.2, 1.5 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 2.02 (m, 2H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.0, 173.5, 146.9, 135.7, 129.2 (2C), 128.9 (2C), 128.0, 127.8, 65.3, 56.3, 51.5, 42.7, 36.3, 35.6, 26.3; **$[\alpha]_D^{25}$** = -116.3 (*c* = 1.47, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 12.5 min, $t_{(major)}$ = 27.3 min.



7a-Methyl-3-phenyl-3a,7a-dihydrobenzofuran-2,5(3*H*,4*H*)-dione (318) was prepared according to **Procedure 9.** FCC (hexane : EtOAc = 3:2) yielded **318** as a colourless solid (0.1 mmol scale, 40% conversion, 50.5:49.5 e.r.).

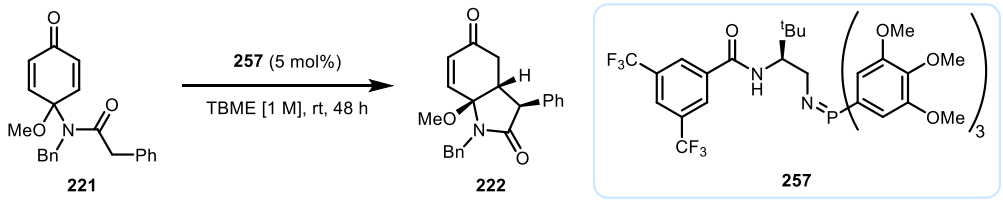
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.22 (m, 3H, Ar<u>H</u>), 7.20 – 7.14 (m, 2H, Ar<u>H</u>), 6.74 (dd, *J* = 10.3, 2.1 Hz, 1H, C<u>H</u>=CHC=O), 6.15 (dd, *J* = 10.3, 1.1 Hz, 1H, CH=C<u>H</u>C=O), 3.58 (d, *J* = 12.7 Hz, 1H, PhC<u>H</u>C=O), 2.89 (ddt, *J* = 12.7, 5.4, 2.1 Hz, 1H, C<u>H</u>CH_2C=O), 2.66 (dd, *J* = 17.6, 5.4 Hz, 1H, CHC<u>H_A</u>H_BC=O), 2.57 (ddd, *J* = 17.6, 2.3, 1.0 Hz, 1H, CHCH_A<u>H_B</u>C=O), 1.76 (s, 3H, CC<u>H_3</u>); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 194.8 (ketone <u>C</u>=O), 174.2 (amide <u>C</u>=O), 146.9 (<u>C</u>H=CHC=O), 134.5 (Ar<u>C</u>), 129.6 (CH=<u>C</u>HC=O), 129.3 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.4 (Ar<u>C</u>), 79.9 (<u>C</u>CH_3), 52.0 (Ph<u>C</u>HC=O), 50.5 (<u>C</u>HCH_2C=O), 35.6 (CH<u>C</u>H_2C=O), 24.4 (C<u>C</u>H_3); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{15}H_{15}O_3^+$ $[M+H]^+$: 243.1016, found 243.1011; **m. p.**: 174 – 176 °C; **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 15.5 min, $t_{(minor)}$ = 18.3 min.

4.2.6 Preparative Scale Synthesis of 222

Azide **S2** (57.3 mg, 0.15 mmol, 5 mol%) and phosphine **S3** (79.9 mg, 0.15 mmol, 5 mol%) were weighed in a 10 mL round-bottom flask, then dissolved in anhydrous THF (3.0 mL, 0.05 M). The solution was stirred for 20 hours at room temperature under a nitrogen atmosphere, after which the volatiles were removed under a stream of nitrogen gas with the reaction mixture kept in a water bath at room temperature. The flask was degassed and refilled with nitrogen using standard Schlenk-technique three times. The substrate **221** (1.04 g, 3 mmol, 1.0 eq.) was added to the crude catalyst followed by TBME

(3.0 mL, 1.0 M). The reaction mixture was stirred for 48 hours, then directly loaded onto a silica column. Product **222** (999 mg, 2.88 mmol, 96%, 96:4 e.r., >20:1 dr) was obtained after FCC (pentane : EtOAc = 2:1). Analytical data is identical with that reported in **4.2.5**. Although it appears as a yellow oil when evaporated in CH_2Cl_2 or $CHCl_3$, it solidifies readily upon addition of methanol and evaporation.

Product **222** was recrystallised in refluxing methanol (11 mL) then cooled and kept at -20 °C overnight. The product was filtered and washed with cold methanol. Product **222** was obtained as a yellow crystalline solid (775 mg, 2.23 mmol, 74%, 99.5:0.5 e.r., >20:1 dr).

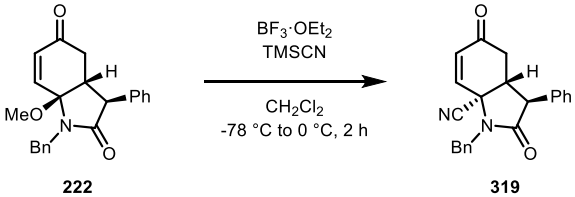


Scheme 72. Preparative scale synthesis of **222**.



Figure 7. Preparative scale synthesis photos. Photos from left to right: evaporating activated crude BIMP catalyst under a stream of nitrogen gas; reaction mixture 10 min after set-up.

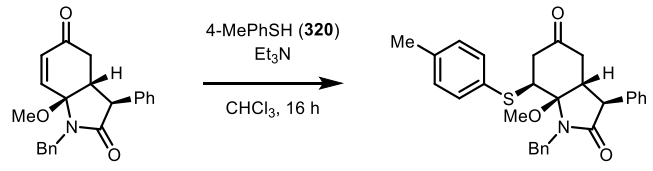
4.2.7 Derivatisations – Specific Procedures and Analytical Data



(3*S*,3a*R*)-1-Benzyl-2,5-dioxo-3-phenyl-1,2,3,3a,4,5-hexahydro-7a*H*-indole-7a-carbonitrile (319) was prepared according to a procedure for nucleophilic substitution with trimethylsilyl cyanide as the

nucleophile. **222** (69 mg, 0.2 mmol, 1.0 eq.) Was dissolved in anhydrous CH_2Cl_2 (2 mL, 0.1 M) under a nitrogen atmosphere. The solution was cooled to -78 °C and trimethylsilyl cyanide (TMSCN, 0.13 mL, 1.0 mmol, 5.0 eq.) and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$, 30 µL, 0.24 mmol, 1.2 eq.) were added. The reaction mixture was warmed to 0 °C and stirred for 2 hours at 0 °C. The reaction was quenched with sat. $NaHCO_3$ (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (CH_2Cl_2 – 5% EtOAc in CH_2Cl_2) yielded **319** as a colourless solid (42.2 mg, 0.123 mmol, 62%, 99:1 e.r., 99% e.s., 3:1 dr). The stereochemical configuration at the quaternary centre of the major diastereomer was determined by X-ray crystallography.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 –7.33 (m, 8H, ArH), 7.28 –7.22 (m, 2H, ArH), 6.84 (d, *J* = 9.9 Hz, 1H, CH=CHC=O), 6.02 (d, *J* = 9.8 Hz, 1H, CH=CHC=O), 5.23 (d, *J* = 15.8 Hz, 1H, NCH_AH_B), 4.41 (d, *J* = 15.8 Hz, 1H, NCH_AH_B), 3.78 (d, *J* = 12.2 Hz, 1H, PhCHC=O), 2.99 –2.73 (m, 3H, CHCH$_2$C=O and CHCH$_2$C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 194.4 (ketone C=O), 174.9 (amide C=O), 139.3 (CH=CHC=O), 136.0 (ArC), 133.8 (ArC), 132.8 (CH=CHC=O), 129.4 (ArC, 2C), 129.4 (ArC, 2C), 128.6 (ArC), 128.6 (ArC, 3C), 127.9 (ArC, 2C), 115.1 (C≡N), 60.5 ($CH_2NCC{\equiv}N$), 51.7 (PhCHC=O), 51.3(CHCH$_2$C=O), 45.8 (NCH_2), 37.9 (CHCH$_2$C=O); **HRMS** (ESI+, m/Z): ion not found; **m. p.**: 163 – 165 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1719, 1697, 1358, 1168, 913, 734, 702; **$[\alpha]_D^{25}$** = +64.9 (*c* =2.48, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 17.6 min, $t_{(major)}$ = 29.4 min.



222 321

(3*S*,3a*R*,7a*R*)-1-Benzyl-7a-methoxy-3-phenyl-7-(p-tolylthio)hexahydro-2*H*-indole-2,5(3*H*)-dione (321) was prepared according to a modified literature procedure.[22] **222** (34.7 mg, 0.1 mmol, 1.0 eq.) Was dissolved in $CHCl_3$. 4-Methylthiophenol **320** (37.3 mg, 0.3 mmol, 3.0 eq.) and triethylamine (3.0 µL, 0.02 mmol, 0.2 eq.) were added. The reaction mixture was stirred at room temperature for 16

hours and the volatiles were then removed *in vacuo*. FCC (pentane : EtOAC = 7:1) and trituration with pentane yielded **321** as a colourless solid (44.0 mg, 0.0932 mmol, 93%, 99.5:0.5 e.r., 99% e.s. for both diastereomers, 1.2:1.0 dr). The configurations of the diastereomers were determined by NOESY NMR spectroscopy.

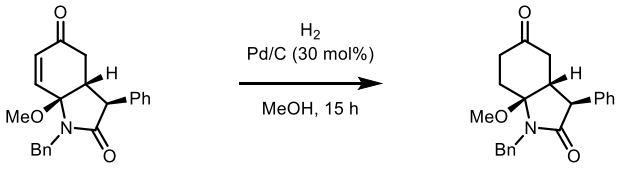
Data for major diastereomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 – 7.49 (m, 2H, ArH), 7.41 – 7.19 (m, 10H, ArH), 7.17 – 7.12 (m, 2H, ArH), 4.72 (d, *J* = 14.6 Hz, 1H, NCH_AH_B), 4.03 – 3.99 (m, 1H, $ArSCHCH_2C{=}O$), 3.98 (d, *J* = 14.7 Hz, 1H, NCH_AH_B), 3.87 (d, *J* = 9.0 Hz, 1H, PhCHC=O), 3.13 – 2.98 (m, 1H, $PhCHCHCH_AH_BC{=}O$), 2.91 (dd, *J* = 18.5, 5.1 Hz, 1H, $ArSCHCH_AH_BC{=}O$), 2.81 – 2.66 (m, 2H, $PhCHCHCH_2C{=}O$ and $PhCHCHCH_AH_BC{=}O$), 2.69 (s, 3H, $COCH_3$), 2.61 (dd, *J* = 18.6, 2.3 Hz, 1H, $ArSCHCH_AH_BC{=}O$), 2.34 (s, 3H, $SArCH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 207.3 (ketone C=O), 173.9 (amide C=O), 139.1 (ArC), 138.2 (ArC), 137.7 (ArC), 133.9 (ArC, 2C), 130.4 (ArC, 2C), 129.9 (ArC, 2C), 129.3 (ArC, 2C), 128.7 (ArC), 128.5 (ArC, 2C), 128.1 (ArC, 2C), 127.8 (ArC), 127.7 (ArC), 94.4 ($COCH_3$), 56.4 (PhCHC=O), 52.1 ($ArSCHCH_2C{=}O$), 49.8 ($COCH_3$), 44.4 (NCH_2), 42.1 ($PhCHCHCH_2C{=}O$), 41.5 ($ArSCHCH_2C{=}O$), 41.1 ($PhCHCHCH_2C{=}O$), 21.3 ($SArCH_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{29}H_{30}NO_3S^+$ $[M+H]^+$: 472.1941, found 472.1931; **m. p.**: 48 – 50 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2920, 1701, 1399, 1069, 911, 813, 732, 702; **$[\alpha]_D^{25}$** = +103.7 (*c* = 1.80, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 16.2 min, $t_{(minor)}$ = 27.5 min.

Data for minor diastereomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 – 7.36 (m, 4H, ArH), 7.35 – 7.26 (m, 4H, ArH), 7.24 – 7.19 (m, 2H, ArH), 7.07 – 7.01 (s, 4H, ArH), 5.18 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 4.30 (d, *J* = 15.0 Hz, 1H, NCH_AH_B), 3.74 (dd, *J* = 5.3, 4.0 Hz, 1H, $ArSCHCH_2C{=}O$), 3.33 (d, *J* = 8.9 Hz, 1H, PhCHC=O), 3.23 (s, 3H, $COCH_3$), 3.20 (dd, *J* = 17.1, 6.2 Hz, 1H, $PhCHCHCH_AH_BC{=}O$), 2.89 (ddd, *J* = 9.2, 6.2, 3.2 Hz, 1H, $PhCHCHCH_2C{=}O$), 2.50 (dd, *J* = 17.1, 3.2 Hz, 1H, $PhCHCHCH_AH_BC{=}O$), 2.31 (s, 3H, $SArCH_3$), 2.22 (dd, *J* = 18.2, 5.3 Hz, 1H, $ArSCHCH_AH_BC{=}O$), 2.14 (dd, *J* = 18.1, 4.0 Hz, 1H,

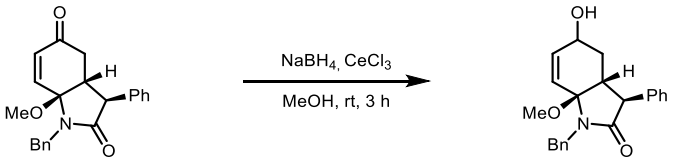
ArSCHCH$_A$H$_B$C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 207.3 (ketone C=O), 174.0 (amide C=O), 138.5 (ArC), 138.2 (ArC), 137.1 (ArC), 133.6 (ArC, 2C), 130.2 (ArC, 2C), 129.4 (ArC, 2C), 129.2 (ArC), 129.0 (ArC, 2C), 128.3 (ArC, 4C), 128.0 (ArC), 127.9 (ArC), 94.6 ($COCH_3$), 54.0 (PhCHC=O), 50.1 (ArSCHCH$_2$C=O), 49.7 ($COCH_3$), 43.6 (NCH_2), 42.1 (PhCHCHCH$_2$C=O), 40.9 (ArSCHCH$_2$C=O), 40.0 (PhCHCHCH$_2$C=O), 21.3 (SArCH$_3$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{29}H_{30}NO_3S^+$ $[M+H]^+$: 472.1941, found 472.1930; **m. p.**: 48 – 50 °C; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2922, 1701, 1399, 1076, 911, 732, 700; **$[\alpha]_D^{25}$** = -20.3 (*c* = 1.20, $CHCl_3$); **Chiral HPLC**: CHIRALPAK IA, hexane/isopropanol = 80/20, 1 ml/min, λ = 210 nm, $t_{(major)}$ = 24.3 min, $t_{(minor)}$ = 49.5 min.



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-phenylhexahydro-2*H*-indole-2,5(3*H*)-dione (322) was prepared according to a procedure for hydrogenation with Pd/C catalyst. **222** (34.7 mg, 0.1 mmol, 1.0 eq.) Was dissolved in anhydrous methanol (5 mL, 0.02 M) under a positive pressure of hydrogen gas. Pd/C (3.2 mg, 0.03 mmol, 30 mol%) was added and the reaction was stirred for 15 hours at room temperature. The mixture was then filtered through silica and FCC (pentane : EtOAc = 2:1) and trituration with pentane yielded **322** as a colourless oil (35.0 mg, 0.1 mmol, 99%, 99.5:0.5 e.r., 100% e.s.).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 – 7.20 (m, 10H, ArH), 4.92 (d, *J* = 14.9 Hz, 1H, NCH$_A$H$_B$), 4.13 (d, *J* = 14.8 Hz, 1H, NCH$_A$H$_B$), 3.34 (d, *J* = 8.4 Hz, 1H, PhCHC=O), 3.10 (s, 3H, $COCH_3$), 2.79 – 2.71 (m, 1H, PhCHCHCH$_2$C=O), 2.70 (dd, *J* = 16.4, 7.2 Hz, 1H, PhCHCHCH$_A$H$_B$C=O), 2.48 (dd, *J* = 15.2, 4.6 Hz, 1H, PhCHCHCH$_A$H$_B$C=O), 2.29 – 2.18 (m, 1H, $CH_3OCCH_AH_B$ or $CH_3OCCH_2CH_AH_BC$=O), 2.17 – 2.06 (m, 1H, $CH_3OCCH_AH_B$ or $CH_3OCCH_2CH_AH_BC$=O), 2.04 – 1.88 (m, 2H, $CH_3OCCH_AH_B$ and $CH_3OCCH_2CH_AH_BC$=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 209.9 (ketone C=O), 173.7 (amide C=O), 138.1 (ArC), 137.6 (ArC), 129.2 (ArC, 2C), 128.8 (ArC, 2C), 128.5 (ArC, 2C), 128.2 (ArC, 2C), 127.8 (ArC), 127.8 (ArC), 93.4 ($COCH_3$), 53.9 (PhCHC=O), 48.9 ($COCH_3$), 43.0 (NCH_2), 41.8 (PhCHCHCH$_2$C=O), 41.3 (PhCHCHCH$_2$C=O), 34.7 (CH_3OCCH_2), 31.2 ($CH_3OCCH_2CH_2$C=O);

HRMS (ESI+, m/Z): exact mass calculated for $C_{22}H_{24}NO_3^+$ $[M+H]^+$: 350.1751, found 350.1743; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 2924, 1697, 1404, 1078, 759, 702; **$[\alpha]_D^{25}$** = -123.3 (c = 3.50, $CHCl_3$); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 210 nm, $t_{(major)}$ = 20.5 min, $t_{(minor)}$ = 59.3 min.

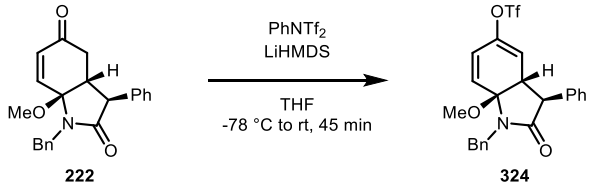


222 323

(3*S*,3a*R*,7a*S*)-1-Benzyl-5-hydroxy-7a-methoxy-3-phenyl-1,3,3a,4,5,7a-hexahydro-2*H*-indol-2-one (323) was prepared according to a procedure for the selective reduction of the ketone in **222**. The amide **222** (34.7 mg, 0.1 mmol, 1.0 eq.) and $CeCl_3 \cdot 7H_2O$ (37.2 mg, 0.1 mmol, 1.0 eq.) were dissolved in methanol (1 mL, 0.1 M). The reaction mixture was cooled to 0 °C and sodium borohydride ($NaBH_4$, 6.0 mg, 0.15 mmol, 1.5 eq.) was added. The mixture was stirred for 3 hours and then quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. FCC on basic alumina (pentane : EtOAc = 1:1) yielded **323** as a colourless viscous oil (25.6 mg, 0.0733 mmol, 73%, 1.2:1.0 d.r., 98.5:1.5 e.r. and 95.5:4.5 e.r., 98% and 92% e.s., 1.2:1 dr). For NMR assignments, the major and minor diastereomer are referred to as *A* and *B* respectively.

^{1}H NMR (CD_3OD, 600 MHz) δ 7.41 –7.19 (m, 10H, Ar$\underline{H}$, *A* + *B*), 6.05 (dd, *J* = 10.4, 2.6 Hz, 1H, CH=C$\underline{H}$CH(OH), *A*), 5.93 (ddd, *J* = 10.5, 2.5, 1.2 Hz, 1H, CH=C$\underline{H}$CH(OH), *B*), 5.67 – 5.60 (m, 1H, C$\underline{H}$=CHCH(OH), *A* + *B*), 4.74 (d, *J* = 15.7 Hz, 1H, NC$\underline{H}_A$H$_B$, *A*), 4.69 (d, *J* = 15.4 Hz, 1H, NC$\underline{H}_A$H$_B$, *B*), 4.45 – 4.40 (m, 1H, C$\underline{H}$(OH), *B*), 4.42 (d, *J* = 15.6 Hz, 1H, NCH$_A\underline{H}_B$, *A*), 4.41 (d, *J* = 15.4 Hz, 1H, NCH$_A\underline{H}_B$, *B*), 4.28 – 4.22 (m, 1H, C$\underline{H}$(OH), *A*), 3.82 (d, *J* = 5.4 Hz, 1H, PhC$\underline{H}$C=O, *A*), 3.59 (d, *J* = 9.5 Hz, 1H, PhC$\underline{H}$C=O, *B*), 3.17 (s, 3H, COC$\underline{H}_3$, *B*), 3.09 (s, 3H, COC$\underline{H}_3$, *A*), 2.79 – 2.74 (m, 1H, C$\underline{H}$CH$_2$CH(OH), *B*), 2.65 (dt, *J* = 9.1, 5.1 Hz, 1H, C$\underline{H}$CH$_2$CH(OH), *A*), 2.14 (dt, *J* = 13.4, 4.8 Hz, 1H, CHC$\underline{H}_A$H$_B$CH(OH), *A*), 2.02 – 1.95 (m, 1H, CHC$\underline{H}_A$H$_B$CH(OH), *B*), 1.75 (ddd, *J* = 13.8, 9.4, 4.9 Hz, 1H, CHCH$_A\underline{H}_B$CH(OH), *B*), 1.66 (ddd, *J* = 13.5, 9.1, 7.0 Hz, 1H, CHCH$_A\underline{H}_B$CH(OH), *A*); **^{13}C NMR**

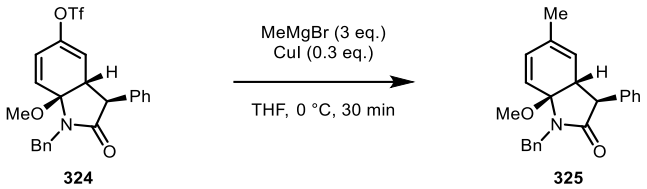
(CD_3OD, 151 MHz) δ 177.1 (C=O, *A*), 176.1 (C=O, *B*), 140.2 (ArC), 139.5 (ArC), 139.4 (ArC), 139.4 (ArC), 137.8 (CH=CHCH(OH), *A*), 136.5 (CH=CHCH(OH), *B*), 129.9 (ArC, 2C), 129.8 (ArC, 2C), 129.8 (ArC, 2C), 129.7 (ArC, 2C), 129.4 (ArC, 2C), 129.4 (ArC, 2C), 129.0 (ArC, 2C), 128.7 (ArC, 2C), 128.5 (ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (ArC), 126.7 (CH=CHCH(OH), *B*), 125.8 (CH=CHCH(OH), *A*), 92.5 ($COCH_3$, *A*), 91.2 ($COCH_3$, *B*), 65.0 (CH(OH), *A*), 63.2 (CH(OH), *B*), 55.4 (PhCHC=O, *A*), 52.6 (PhCHC=O, *B*), 51.0 ($COCH_3$, *B*), 50.5 ($COCH_3$, *A*), 44.1 (NCH_2, *A* or *B*), 44.0 (NCH_2, *A* or *B*), 43.6 ($CHCH_2CH(OH)$, *B*), 42.7 ($CHCH_2CH(OH)$, *A*), 35.5 ($CHCH_2CH(OH)$, *A*), 31.7 ($CHCH_2CH(OH)$, *B*); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{22}H_{24}NO_3^+$ $[M+H]^+$: 350.1751, found 350.1747; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 3421, 2829, 1676, 1408, 1076, 1030, 701; **$[\alpha]_D^{25}$** = -19.4 (*c* = 8.25, MeOH); **Chiral HPLC**: CHIRALPAK AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 12.2 min, $t_{(minor)}$ = 16.3 min, $t_{(major)}$ = 17.7 min, $t_{(minor)}$ = 47.0 min.



(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-2-oxo-3-phenyl-2,3,3a,7a-tetrahydro-1*H*-indol-5-yl trifluoromethanesulfonate (324) was prepared according to a modified literature procedure.[23] Enone **222** (104 mg, 0.3 mmol, 1.0 eq.) and *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhNTf_2$, 146 mg, 0.409 mmol, 1.36 eq.) were dissolved in anhydrous THF (2 mL, 0.15 M) under a nitrogen atmosphere. The solution was cooled to -78 °C and LiHMDS (1 M in THF, 0.33 mL, 0.33 mmol, 1.1 eq.) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 45 min before quenching with sat. $NaHCO_3$ (5 mL) and extracting with Et_2O (2 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. FCC on basic alumina (pentane : Et_2O 2:1 – 1:1) yielded **324** as a pale-yellow oil (137 mg, 0.286 mmol, 95%, 99.5:0.5 e.r., 100% e.s.).

^{1}H NMR (CD_3OD, 400 MHz) δ 7.43 – 7.23 (m, 10H, ArH), 6.20 (dd, *J* = 10.4, 2.4 Hz, 1H, CH_3OCCH=CH), 6.05 (ddd, *J* = 5.8, 2.4, 0.8 Hz, 1H, TfOC=CHCH), 5.81 (dt, *J* = 10.4, 0.9 Hz, 1H,

$CH_3OCC\underline{H}$=CH), 4.76 (d, *J* = 15.5 Hz, 1H, $NC\underline{H}_AH_B$), 4.49 (d, *J* = 15.5 Hz, 1H, $NCH_A\underline{H}_B$), 3.65 (d, *J* = 9.8 Hz, 1H, PhC<u>H</u>C=O), 3.37 (ddd, *J* = 9.8, 5.7, 0.9 Hz, 1H, TfOC=CHC<u>H</u>), 3.24 (s, 3H, $COC\underline{H}_3$); **^{13}C NMR** (CD_3OD, 101 MHz) δ 175.4 (<u>C</u>=O), 145.4 (<u>C</u>OTf), 139.1 (Ar<u>C</u>), 138.0 (Ar<u>C</u>), 130.1 (Ar<u>C</u>, 2C), 129.8 (Ar<u>C</u>, 2C), 129.6 (Ar<u>C</u>, 2C), 129.0 (Ar<u>C</u>), 128.8 (Ar<u>C</u>, 2C), 128.4 ($CH_3OC\underline{C}H$=CH), 128.1 (Ar<u>C</u>), 124.4 ($CH_3OCCH=\underline{C}H$), 119.9 (q, J^1_F = 319.9 Hz, $\underline{C}F_3$,), 119.4 (TfOC=<u>C</u>HCH), 90.5 (<u>C</u>OCH_3), 56.3 (Ph<u>C</u>HC=O), 50.4 ($CO\underline{C}H_3$), 48.2 (TfOC=CH<u>C</u>H), 44.2 ($N\underline{C}H_2$); **^{19}F NMR** (CD_3OD, 377 MHz) δ -75.1; **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{21}F_3NO_5S^+$ $[M+H]^+$: 480.1087, found 480.1082; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1705, 1424, 1406, 1248, 1213, 1141, 1103, 874, 762, 700; **$[\alpha]_D^{25}$** = -75.3 (*c* = 8.89, $CHCl_3$); **Chiral HPLC**: CHIRALPAK OD, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 8.3 min, $t_{(major)}$ = 10.6 min.



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(3*S*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-5-methyl-3-phenyl-1,3,3a,7a-tetrahydro-2*H*-indol-2-one (325) was prepared according to a modified literature procedure.[24] Dienyl triflate **324** (48 mg, 0.1 mmol, 1.0 eq.) was dissolved in anhydrous THF (1 mL) and added to CuI (6 mg, 0.03 mmol, 0.3 eq.) dissolved in anhydrous THF (1 mL, 0.05 M overall) under a nitrogen atmosphere at 0 °C. MeMgBr (3 M in Et_2O, 0.1 mL, 0.3 mmol, 3.0 eq.) was added to the solution dropwise and the reaction mixture was stirred for 30 min before quenching with sat. NH_4Cl (5 mL). Et_2O (5 mL) and water (2 mL) were added, and the clear layers formed were separated. The aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo*. FCC on basic alumina (pentane : Et_2O = 3:1) yielded **325** as a colourless oil (28.6 mg, 0.0828 mmol, 83%, 99.5:0.5 e.r., 100% e.s.).

^{1}H NMR (CD_3OD, 400 MHz) δ 7.41 – 7.21 (m, 10H, Ar<u>H</u>), 6.06 (dd, *J* = 10.0, 1.7 Hz, 1H, $CH_3OCC\underline{H}$=CH), 5.67 (dtd, *J* = 5.3, 1.7, 1.0 Hz, 1H, $C(CH_3)$=C<u>H</u>), 5.54 (d, *J* = 10.0 Hz, 1H, $CH_3OCCH=C\underline{H}$), 4.73 (d, *J* = 15.5 Hz, 1H, $NC\underline{H}_ACH_B$), 4.47 (d, *J* = 15.5 Hz, 1H, $NCH_AC\underline{H}_B$), 3.47

(d, *J* = 9.4 Hz, 1H, PhC<u>H</u>C=O), 3.08 – 3.02 (m, 1H, C<u>H</u>PhCHC=O), 1.80 (t, *J* = 1.6 Hz, 1H, C(C<u>H</u>$_3$)=CH); **^{13}C NMR** (CD_3OD, 101 MHz) δ 176.5 (<u>C</u>=O), 139.5 (Ar<u>C</u>), 139.2 (Ar<u>C</u>), 131.7 (CH_3OC<u>C</u>H=CH), 130.6 (<u>C</u>(CH_3)=CH), 129.9 (Ar<u>C</u>, 2C), 129.8 (Ar<u>C</u>, 2C), 129.4 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.6 (Ar<u>C</u>), 128.2 (Ar<u>C</u>), 123.8 (C(CH_3)=<u>C</u>H), 123.1 (CH_3OCCH=<u>C</u>H), 91.3 (<u>C</u>OCH_3), 57.2 (Ph<u>C</u>HC=O), 50.1 (CO<u>C</u>H_3), 48.7 (<u>C</u>HPhCHC=O), 44.1 (N<u>C</u>H_2), 21.4 (C(<u>C</u>H_3)=CH); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{23}H_{24}NO_2^+$ $[M+H]^+$: 346.1802, found 346.1796; **FT-IR** (thin film): ν_{max} (cm^{-1}) = 1698, 1406, 1262, 1099, 1066, 805, 700; **$[\alpha]_D^{25}$** = -54.0 (*c* =2.45, MeOH); **Chiral HPLC**: CHIRALPAK OD, hexane/isopropanol = 90/10, 1 ml/min, λ = 220 nm, $t_{(minor)}$ = 7.5 min, $t_{(major)}$ = 9.0 min.

4.2.8 X-ray Crystal Structures of 222 and 319

Low temperature single crystal X-ray diffraction data for **222** and **319** were collected using a Rigaku Oxford Diffraction SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip' before refinement with CRYSTALS (CIF).[25]

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC **222**: 2289921; **319**: 2295083) and can be obtained via www.ccdc.cam.ac.uk/data_request

Compound **222**

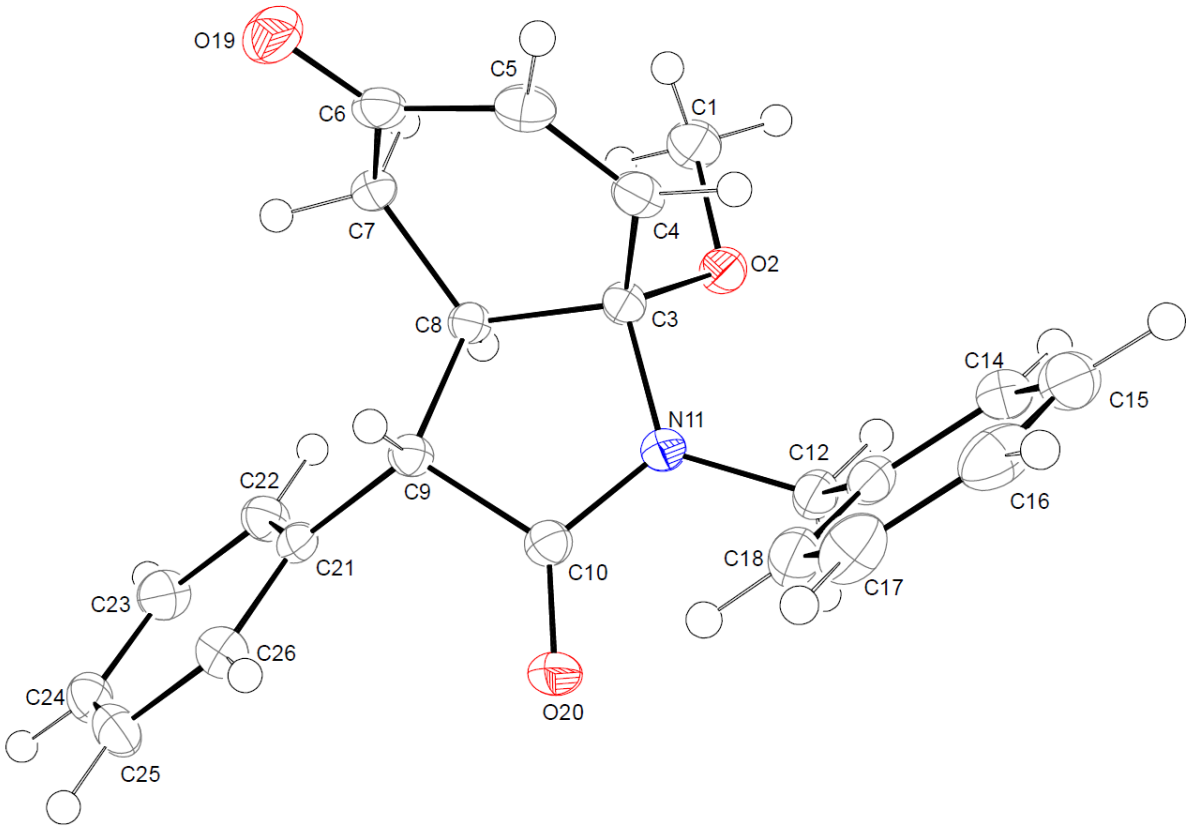


Table 5. Crystal data and structure refinement for **222** – 7624.

Identification code	7624	
Empirical formula	C22 H21 N O3	
Formula weight	347.41	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 7.65570(10) Å	α= 90°.
	b = 11.5145(2) Å	β= 90°.
	c = 19.6191(4) Å	γ = 90°.
Volume	1729.45(5) Å^3	

Z	4
Density (calculated)	1.334 Mg/m^3
Absorption coefficient	0.712 mm^{-1}
F(000)	736
Crystal size	0.22 x 0.19 x 0.08 mm^3
Theta range for data collection	4.452 to 76.375°.
Index ranges	-9<=h<=9, -14<=k<=9, -24<=l<=24
Reflections collected	12430
Independent reflections	3596 [R(int) = 0.035]
Completeness to theta = 74.847°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.94 and 0.79
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3596 / 0 / 236
Goodness-of-fit on F^2	1.0050
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0785
R indices (all data)	R1 = 0.0351, wR2 = 0.0807
Absolute structure parameter	-0.09(9)
Largest diff. peak and hole	0.15 and -0.18 $e.Å^{-3}$

Compound **319**

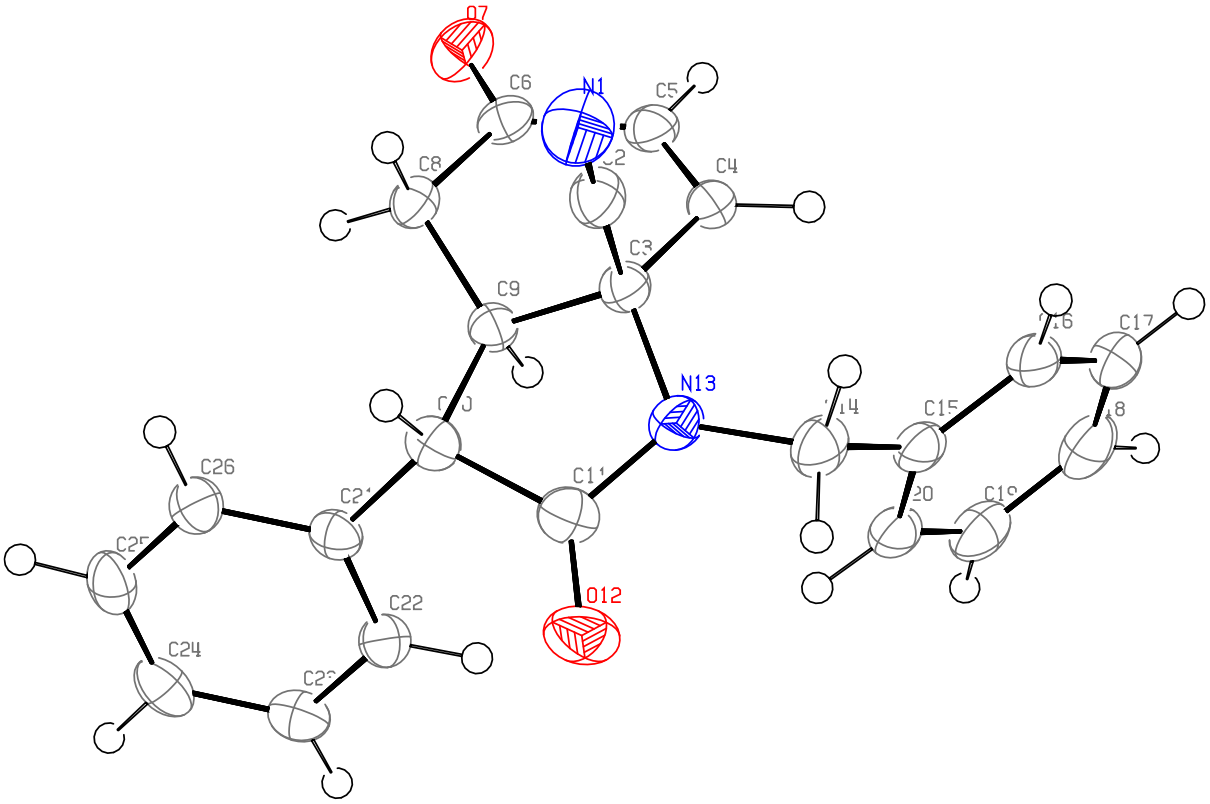


Table 6. Crystal data and structure refinement for **319** – 011tad23.

Identification code	011tad23	
Empirical formula	C22 H18 N2 O2	
Formula weight	324.40	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 2_1	
Unit cell dimensions	a = 10.49110(10) Å	α= 90°.
	b = 7.80970(10) Å	β= 106.1452(12)°.
	c = 11.15760(10) Å	γ = 90°.
Volume	878.114(17) Å^3	
Z	2	

Density (calculated)	1.295 Mg/m^3
Absorption coefficient	0.670 mm^{-1}
F(000)	359.998
Crystal size	0.30 x 0.16 x 0.10 mm^3
Theta range for data collection	4.125 to 76.235°.
Index ranges	-13<=h<=13, -9<=k<=9, -13<=l<=13
Reflections collected	53997
Independent reflections	3650 [R(int) = 0.021]
Completeness to theta = 76.235°	99.6 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3650 / 1 / 237
Goodness-of-fit on F^2	1.0021
Final R indices [I>2sigma(I)]	R1 = 0.0245, wR2 = 0.0664
R indices (all data)	R1 = 0.0248, wR2 = 0.0668
Absolute structure parameter	-0.07(15)

4.2.9 General Procedure for pK_{BH+} Determination of Catalyst 257 in CD_3CN

According to a modified literature procedure,[26] **257** (26.6 mg, 0.03 mmol) was prepared from its corresponding azide **S2** (11.5 mg, 0.03 mmol, 1.0 eq.) and phosphine **S3** (16 mg, 0.03 mmol, 1.0 eq.) according to **Procedure 8**. The ^1H, ^{13}C and ^{31}P NMR spectra of the freebase catalyst was obtained in CD_3CN. After transferring the mixture into a round-bottomed flask and evaporating the CD_3CN, catalyst **257** was dissolved in 2 mL of TBME and 2 mL of glacial AcOH was added. The mixture was stirred at room temperature under a nitrogen atmosphere for one hour before the removal of solvent *in vacuo*. The resulting residue was dissolved in approximately 2 mL of CH_2Cl_2 and around 15 mL of cold pentane was quickly added to induce precipitation. The mixture was chilled in a freezer overnight, and then filtered and dried *in vacuo* to yield catalyst **257**-AcOH salt. The ^1H, ^{13}C and ^{31}P NMR spectra of this salt in were obtained in 0.6 mL CD_3CN. *N*, *N'*, *N'* tetramethylguanidine (TMG, 3.76 μL, 0.03 mmol,

1.0 eq.) was then added to the NMR tube and the ^{1}H, ^{13}C and ^{31}P NMR spectra of this mixture were obtained. The chemical shifts of specific peaks in the ^{13}C and ^{31}P NMR spectra were tabulated in a Microsoft excel sheet (**Table 7**) which was used as a tool to facilitate the calculations of x_{AH+} (column F), K_1 (column H) and the estimated pK_{BH+} of catalyst **257** in CD_3CN (column I).

	A	B	C	D	E	F	G	H	I
2	31P	chemical shift NPR3 (with TMG)	31P NMR for cat-salt	31P NMR for free base catalyst	pKBH+ TMG	xAH+	1-xAH+	K1	pKBH+
3		36.806	39.303	10.227	23.3	0.91412161	0.08587839	0.008825916	25.3542402
4	13C	chemical shift CH2NP (with TMG)	13C NMR for cat-salt	13C NMR for free base catalyst	pKBH+ TMG	xAH+	1-xAH+	K1	pKBH+
5		41.119	41.328	45.506	23.3	1.05002393	-0.0500239	0.002269642	25.9440427
6									
7								Average pKBH+	25.6491414

Table 7. Calculations performed to estimate the pK_{BH+} of **257** in CD_3CN.

Equations for cells (same applies for cells in row 5):

F3: =(B3-D3)/(C3-D3) (from equation **[2]**)

G3: =1-F3

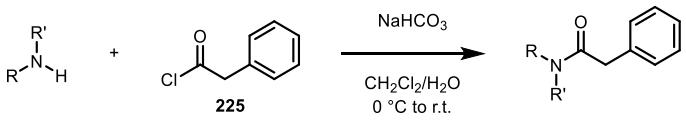
H3: =POWER(G3,2)/POWER(F3,2) (from equation **[3]**)

I3: =23.3-LOG10(H3) (from equation **[1]**)

4.3 Experimental Details for Chapter 3

4.3.1 Synthesis of Starting Materials – General Procedures

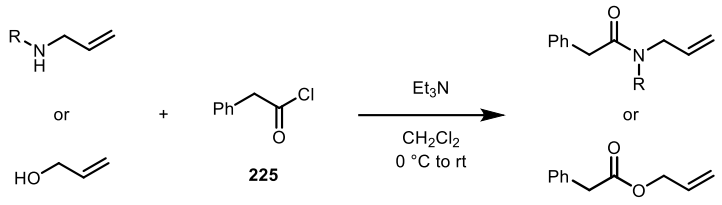
Procedure 2 – Schotten-Baumann amide formation



The amine (1.0 eq.) was dissolved in a biphasic mixture containing CH_2Cl_2 (0.36 M) and water (1.14 M). After cooling to 0 °C, $NaHCO_3$ (2.0 eq.) and 2-phenylacetyl chloride **225** (1.05 eq.) were added to the reaction mixture. The mixture was warmed to room temperature and stirred until consumption of the amine as indicated by TLC (19 hours). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL / 1 mmol SM). The organic layer was dried over anhydrous $MgSO_4$, and the

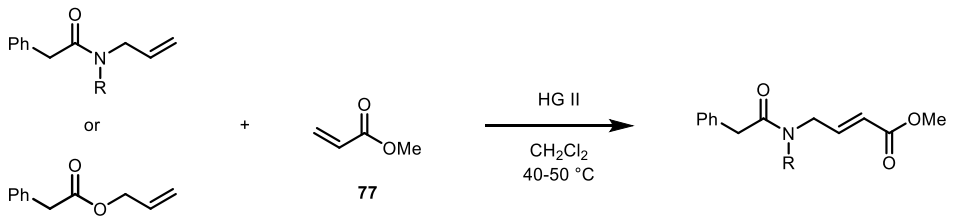
volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

Procedure 11 – Amide or ester formation with organic base Et_3N



The amine or alcohol (1.0 eq.) was dissolved in CH_2Cl_2 (0.3 M) and triethylamine (1.5 eq.) was added. The reaction mixture was cooled to 0 °C and 2-phenylacetyl chloride **225** (1.2 eq.) was added dropwise. The reaction was slowly warmed to room temperature and stirred until consumption of the amine as indicated by TLC (2 hours). The mixture was then extracted with sat. $NaHCO_3$ (2 x 3 mL / 1 mmol SM) and brine (3 mL / 1 mmol SM). The organic layer was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

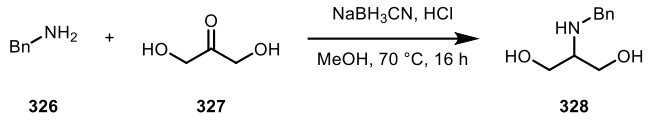
Procedure 12 – Alkene metathesis



According to a modified literature procedure,[27] the amide or alcohol (1.0 eq.) was dissolved in degassed methyl acrylate **77** (10.0 eq.) under a nitrogen atmosphere and heated to 40 - 50 °C. Hoveyda-Grubs catalyst 2nd generation (2.5 mol %) was dissolved in a few drops of degassed CH_2Cl_2 under a nitrogen atmosphere and added to the hot reaction mixture slowly dropwise (10 min – 1 h). The reaction was stirred at 40 - 50 °C for 24 hours or until consumption of the limiting reagent as indicated by TLC. Another portion of Hoveyda-Grubs catalyst 2nd generation (2.5 mol %) was added if the reaction was no longer progressing and limiting reagent still can be observed on TLC. The resulting solution was

then filtered through a short silica pad and the volatiles were removed *in vacuo*. Products were purified by FCC using conditions specified in each individual experiment.

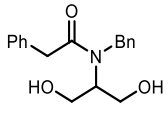
4.3.2 Synthesis of Starting Materials – Specific Procedures and Analytical Data



326 **327** **328**

2-(Benzylamino)propane-1,3-diol (328) was prepared according to the following procedure. 2 M HCl (1.8 mL) and $NaBH_3CN$ (2.26 g, 36 mmol) were added successively to a solution of benzylamine **326** (1.0 mL, 9 mmol, 1.0 eq.) and 1,3-dihydroxyacetone **327** (3.23 g, 36 mmol, 4.0 eq.) in methanol (100 mL, 0.09 M) at 0 °C. The mixture was heated for 16 hours at 70 °C with stirring and then cooled to room temperature. $NaHCO_3$ (10 mL) was added to the mixture to reach pH 7, the white precipitate formed was filtered out and the mixture was evaporated. Water (50 mL) was added to the residue, which was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$, and the volatiles were removed *in vacuo* to afford crude **328** as a colourless oil (1.37 g, 7.56 mmol, 83 %). Analytical data is consistent with the published literature.[28]

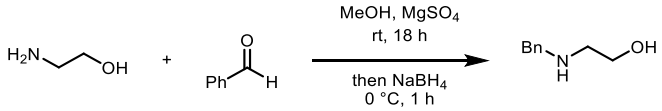
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 – 7.26 (m, 5H), 3.85 (s, 2H), 3.73 (dd, J = 11.9, 4.4 Hz, 2H), 3.60 (dd, J = 11.1, 4.9 Hz, 2H), 2.82 (m, 1H), 2.51 (br s, 3H); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{10}H_{16}NO_2$ $[M+H]^+$: 182.1181, found 182.1184.



***N*-Benzyl-*N*-(1,3-dihydroxypropan-2-yl)-2-phenylacetamide (329)** was prepared according to **Procedure 2**. FCC (EtOAc) yielded **329** as a colourless solid (396 mg, 1.33 mmol, 37 %). The ^{1}H NMR spectrum of **329** in DMSO-d_6 shows different signals for the two rotamers of the amide, which are not shown in $CDCl_3$.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.38 – 7.11 (m, 10H, Ar<u>H</u>, both rotamers), 4.79 (t, J = 5.2 Hz, 2H, C<u>H</u>$_2$OH), 4.69 (t, J = 5.4 Hz, 2H, C<u>H</u>$_2$OH), 4.64 (s, 2H, C<u>H</u>$_2$C=O), 4.48 (s, 2H, C<u>H</u>$_2$C=O), 4.21 (p, J =

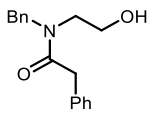
6.4 Hz, 1H, C<u>H</u>CH$_2$OH), 4.12 (p, *J* = 6.5 Hz, 1H, C<u>H</u>CH$_2$OH), 3.88 (s, 2H, NC<u>H$_2$</u>), 3.56 (s, 2H, NC<u>H$_2$</u>), 3.52 (m, 2H, C<u>H$_2$</u>OH), 3.43 (m, 2H, C<u>H$_2$</u>OH); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38 – 7.22 (m, 8H, Ar<u>H</u>), 7.15 (d, *J* = 6.8 Hz, 2H, Ar<u>H</u>), 4.57 (s, 2H, C<u>H$_2$</u>C=O), 3.96 (dd, *J* = 11.7, 4.8 Hz, 2H, C<u>H$_2$</u>OH), 3.84 (m, 2H, C<u>H$_2$</u>OH), 3.77 (s, 2H, NC<u>H$_2$</u>), 3.53 (p, *J* = 5.6 Hz, 2H, C<u>H</u>CH$_2$OH overlapping with br s, 1H, O<u>H</u>); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 173.9 (<u>C</u>=O), 136.4 (Ar<u>C</u>), 134.6 (Ar<u>C</u>), 129.2 (Ar<u>C</u>, 2C), 129.0 (Ar<u>C</u>, 2C), 128.8 (Ar<u>C</u>, 2C), 128.2 (Ar<u>C</u>), 127.3 (Ar<u>C</u>), 126.8 (Ar<u>C</u>, 2C), 63.5 (<u>C</u>HCH$_2$OH), 61.5 (<u>C</u>H$_2$OH, 2C), 54.3 (<u>C</u>H$_2$C=O), 42.1 (NCH$_2$); **LRMS** (ESI+, m/Z): exact mass calculated for - $C_{18}H_{21}NNaO_3$ $[M+Na]^+$: 322.1, found 322.2.



334 27 335

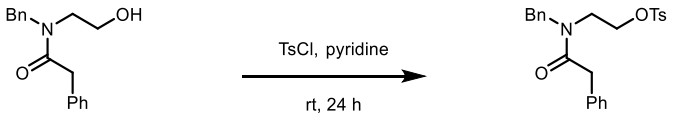
2-(Benzylamino)ethan-1-ol (335) was prepared according to a literature procedure.[29] Ethanolamine **334** (0.3 mL, 5 mmol, 1.0 eq.) was dissolved in methanol (9 mL, 0.55 M). $MgSO_4$ (1.2 g, 10 mmol, 2.0 eq.) and benzaldehyde **27** (0.5 mL, 5 mmol, 1.0 eq.) were successively added to this solution. The resulting mixture was stirred at room temperature overnight for 18 hours. The solution was then cooled to 0 °C and $NaBH_4$ (189 mg, 5 mmol, 1.0 eq.) was added portionwise. The mixture was stirred at 0 °C for one hour before quenching with water (10 mL). The mixture was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo* to yield **335** as a yellow oil (470 mg, 3.1 mmol, 62%). Analytical data is consistent with the published literature.[29]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 – 7.21 (m, 5H), 3.81 (s, 2H), 3.71 – 3.61 (m, 2H), 2.86 – 2.78 (m, 2H), 1.95 (br s, 2H).



***N*-Benzyl-*N*-(2-hydroxyethyl)-2-phenylacetamide (336)** was prepared according to **Procedure 2**. FCC (pentane : EtOAc = 1:1) yielded **336** as a colourless solid and as a 3:1 mixture of rotamers *A*:*B* (650 mg, 2.41 mmol, 85%). Analytical data is consistent with the published literature.[30]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.19 (m, 8H, *A* and 10H, *B*), 7.13 (d, *J* = 7.0 Hz, 2H, *A*), 4.67 (s, 2H, *B*), 4.60 (s, 2H, *A*), 3.90 (s, 2H, *B*), 3.76 (s, 2H, *A*), 3.74 (t, *J* = 5.0 Hz, 2H, *A*), 3.63 (t, *J* = 5.0 Hz, 2H, *B*), 3.58 (t, *J* = 5.0 Hz, 2H, *A*), 3.41 (t, *J* = 5.6 Hz, 2H, *B*), 3.31 (br s, 1H, *A* + *B*).

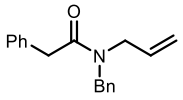


336 **338**

2-(*N*-Benzyl-2-phenylacetamido)ethyl 4-methylbenzenesulfonate (338) was prepared according to a modified literature procedure.[31] *p*-Toluenesulfonyl chloride (269 mg, 1.41 mmol, 3.0 eq.) was added to a solution of **336** (127 mg, 0.47 mmol, 1.0 eq.) dissolved in pyridine (1.2 mL, 0.4 M). The resulting mixture was stirred at room temperature for 24 hours before quenching with water (7 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with water (14 mL) and brine (14 mL), dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 9:1) yielded **338** as a yellow oil (52.2 mg, 0.123 mmol, 26% with impurities).

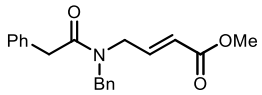
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.18 (m, 13H, Ar<u>H</u>), 7.13 – 7.08 (m, 2H, Ar<u>H</u>), 4.67 (s, 2H, NC<u>H</u>$_2$), 4.01 (t, *J* = 5.9 Hz, 2H, NCH$_2$C<u>H</u>$_2$OTs), 3.87 (s, 2H, C<u>H</u>$_2$C=O), 3.36 (t, *J* = 5.9 Hz, 2H, NC<u>H</u>$_2$CH$_2$OTs), 2.44 (s, 3H, OSO$_2$PhC<u>H</u>$_3$).

Synthesis of **340**:



***N*-Allyl-*N*-benzyl-2-phenylacetamide (S56)** was prepared according to **Procedure 11**. FCC (pentane : EtOAc = 9:1) yielded **S56** as a yellow oil and a 1.4:1 mixture of rotamers *A*:*B* (567 mg, 2.14 mmol, quant.). Analytical data is consistent with the published literature.[32]

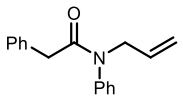
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.19 (m, 10H, *A* and 8H, *B*), 7.13 (d, *J* = 7.0 Hz, 2H, *B*), 5.78 (ddt, *J* = 16.1, 10.1, 6.0 Hz, 1H, *B*), 5.65 (ddt, *J* = 17.1, 10.1, 5.0 Hz, 1H, *A*), 5.22 (dd, *J* = 10.4, 1.5 Hz, 1H, *A*), 5.17 (dd, *J* = 17.1, 1.4 Hz, 1H, *A*), 5.14 (dd, *J* = 10.1, 1.5 Hz, 1H, *B*), 5.05 (dd, *J* = 17.1, 1.6 Hz, 1H, *B*), 4.62 (s, 2H, *A*), 4.50 (s, 2H, *B*), 4.03 (d, *J* = 6.0 Hz, 2H, *B*), 3.82 (d, *J* = 5.0 Hz, 2H, *A*), 3.77 (s, 2H, *A*), 3.74 (s, 2H, *B*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.5 (*A*), 171.4 (*B*), 137.6 (*A*), 136.8 (*B*), 135.3 (*A*), 135.1 (*B*), 133.0 (*B*), 132.8 (*A*), 129.0 (2C, *B*), 129.0 (2C, *A*), 128.9 (2C, *B*), 128.8 (2C, *B*), 128.8 (2C, *A*), 128.7 (2C, *A*), 128.4 (2C, *A*), 127.7 (*B*), 127.5 (*A*), 127.0 (*A* + *B*), 126.5 (2C, *B*), 117.7 (*B*), 117.2 (*A*), 50.5 (*B*), 49.5 (*A*), 48.3 (*A*), 48.2 (*B*), 41.1 (*B*), 40.9 (*A*).



Methyl (*E*)-4-(*N*-benzyl-2-phenylacetamido)but-2-enoate (340) was prepared according to **Procedure 12**. FCC (pentane : EtOAc = 9:1) yielded **340** as a brown oil and a 1.2:1 mixture of rotamers *A*:*B* (167 mg, 0.515 mmol, 26%).

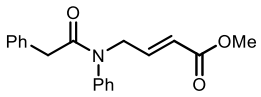
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.22 (m, 8H, ArH, *A* + *B*), 7.22 – 7.17 (m, 2H, ArH, *B*), 7.12 – 7.06 (m, 2H, ArH, *A*), 6.82 (dt, *J* = 15.8, 5.5 Hz, 1H, CH_2CH=CH, *A*), 6.75 (dt, *J* = 15.8, 4.6 Hz, 1H, CH_2CH=CH, *B*), 5.88 (dt, *J* = 15.8, 1.9 Hz, 1H, CH_2CH=CH, *B*), 5.77 (dt, *J* = 15.7, 1.7 Hz, 1H, CH_2CH=CH, *A*), 4.61 (s, 2H, NCH_2Ph, *B*), 4.50 (s, 2H, NCH_2Ph, *A*), 4.14 (dd, *J* = 5.6, 1.5 Hz, 1H, CH_2CH=CH, *A*), 3.95 (dd, *J* = 4.6, 2.0 Hz, 2H, CH_2CH=CH, *B*), 3.77 (s, 2H, CH_2C=O, *B*), 3.76 (s, 2H, CH_2C=O, *A*), 3.72 (s, 3H, CO_2CH_3, *A* + *B*).

Synthesis of **341**:



***N*-Allyl-*N*,2-diphenylacetamide (S57)** was prepared according to **Procedure 11**. FCC (pentane : EtOAc = 9:1 – 4:1) yielded **S57** as a yellow oil (340 mg, 1.35 mmol, 68%). Analytical data is consistent with the published literature.[32]

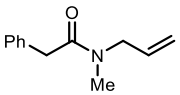
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 – 7.31 (m, 3H), 7.30 – 7.16 (m, 3H), 7.12 – 7.01 (m, 4H), 5.86 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.09 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.30 (dt, *J* = 6.4, 1.4 Hz, 2H), 3.45 (s, 2H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.7, 142.5, 135.5, 133.1, 129.6 (2C), 129.2 (2C), 128.7 (2C), 128.4 (2C), 128.2, 126.7, 118.1, 52.6, 41.3.



Methyl (*E*)-4-(*N*,2-diphenylacetamido)but-2-enoate (341) was prepared according to **Procedure 12**. FCC (pentane : EtOAc = 3:1) yielded **341** as a brown oil (124 mg, 0.400 mmol, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 – 7.35 (m, 3H, ArH), 7.30 – 7.17 (m, 3H, ArH), 7.13 – 7.07 (m, 2H, ArH), 7.07 – 7.02 (m, 2H, ArH), 6.92 (dt, *J* = 15.8, 6.0 Hz, 1H, CH_2CH=CH), 5.85 (dt, *J* = 15.8, 1.8 Hz, 1H, CH_2CH=CH), 4.45 (dd, *J* = 6.0, 1.6 Hz, 2H, CH_2CH=CH), 3.71 (s, 3H, CO_2CH_3), 3.48 (s, 2H, CH_2C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.9 (amide C=O), 166.4 (ester C=O), 142.8 (CH_2CH=CH), 142.2 (ArC),135.0 (ArC), 129.9 (ArC, 2C), 129.1 (ArC, 2C), 128.5 (ArC, 3C), 128.4 (ArC, 2C), 126.8 (ArC), 123.1 (CH_2CH=CH), 51.7 (CO_2CH_3), 50.7 (CH_2CH=CH), 41.1 (CH_2C=O).

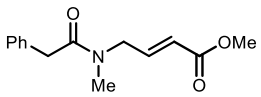
Synthesis of **342**:



***N*-Allyl-*N*-methyl-2-phenylacetamide (S58)** was prepared according to **Procedure 11**. FCC (pentane : EtOAc = 2:1) yielded **S58** as a yellow oil and a 1:1 mixture of rotamers *A*:*B* (469 mg, 2.48 mmol, 83%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 – 7.21 (m, 5H, ArH, *A* + *B*), 5.81 – 5.61 (m, 1H, CH_2CH=CH_2, *A* + *B*), 5.23 – 5.07 (m, 2H, CH_2CH=CH_2, *A* + *B*), 4.02 (dt, *J* = 6.0, 1.6 Hz, 2H, CH_2CH=CH_2, *A*), 3.89 (dt, *J* = 5.0, 1.8 Hz, 2H, CH_2CH=CH_2, *B*), 3.74 (s, 2H, CH_2C=O, *A*), 3.70 (s, 2H, CH_2C=O, *B*), 2.94 (s, 3H, NCH_3, *B*), 2.93 (s, 3H, NCH_3, *A*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.3 (C=O, *B*), 170.9 (C=O, *A*), 135.3 (ArC, *B*), 135.1 (ArC, *A*), 133.0 (CH_2CH=CH_2, *A*), 132.6 (CH_2CH=CH_2, *B*), 128.9 (ArC, 2C, *A* + *B*), 128.8 (ArC, 2C, *A* or *B*), 128.7 (ArC, 2C, *A* or *B*), 126.9 (ArC, *A* or *B*), 126.8 (ArC, *A* or *B*),

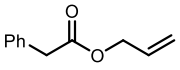
117.4 ($CH_2CH=\underline{C}H_2$, *A*), 117.0 ($CH_2CH=\underline{C}H_2$, *B*), 52.6 ($\underline{C}H_2CH=CH_2$, *B*), 50.2 ($\underline{C}H_2CH=CH_2$, *A*), 41.3 ($\underline{C}H_2C=O$, *A*), 40.8 ($\underline{C}H_2C=O$, *B*), 35.2 ($N\underline{C}H_3$, *A*), 33.8 ($N\underline{C}H_3$, *B*).



Methyl (*E*)-4-(*N*-methyl-2-phenylacetamido)but-2-enoate (342) was prepared according to **Procedure 12**. FCC (pentane : EtOAc = 2:1 – 1:1) yielded **342** as a brown oil and a 1.6:1 mixture of rotamers *A*:*B* (23.8 mg, 0.0962 mmol, 16%).

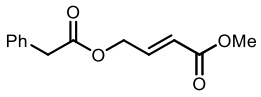
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.20 (m, 5H, Ar$\underline{H}$), 6.84 (dt, *J* = 15.8, 5.4 Hz, 1H, $CH_2C\underline{H}=CH$, *A*), 6.78 (dt, *J* = 15.8, 4.6 Hz, 1H, $CH_2C\underline{H}=CH$, *B*), 5.86 (dt, *J* = 15.0, 1.9 Hz, 1H, $CH_2CH=C\underline{H}$, *B*), 5.82 (dt, *J* = 15.8, 1.8 Hz, 1H, $CH_2CH=C\underline{H}$, *A*), 4.17 (dd, *J* = 5.4, 1.8 Hz, 2H, $C\underline{H}_2CH=CH$, *A*), 4.05 (dd, *J* = 4.6, 2.0 Hz, 2H, $C\underline{H}_2CH=CH$, *B*), 3.76 (s, 2H, $C\underline{H}_2C=O$, *A*), 3.75 (s, 3H, $CO_2C\underline{H}_3$, *B*), 3.73 (s, 3H, $CO_2C\underline{H}_3$, *A*), 3.67 (s, 2H, $C\underline{H}_2C=O$, *B*), 2.97 (s, 3H, $NC\underline{H}_3$, *A*), 2.96 (s, 3H, $NC\underline{H}_3$, *B*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.2 (amide $\underline{C}=O$, *B*), 171.1 (amide $\underline{C}=O$, *A*), 166.4 (ester $\underline{C}=O$, *A*), 166.1 (ester $\underline{C}=O$, *B*), 143.0 ($CH_2\underline{C}H=CH$, *A*), 142.4 ($CH_2\underline{C}H=CH$, *B*), 134.8 (Ar$\underline{C}$, *B*), 134.7 (Ar$\underline{C}$, *A*), 128.9 (Ar$\underline{C}$, 2C, *A* + *B*), 128.9 (Ar$\underline{C}$, 2C, *A*), 128.8 (Ar$\underline{C}$, 2C, *B*), 127.0 (Ar$\underline{C}$, *B*), 127.0 (Ar$\underline{C}$, *A*), 122.3 ($CH_2CH=\underline{C}H$, *A*), 122.2 ($CH_2CH=\underline{C}H$, *B*), 51.9 ($CO_2\underline{C}H_3$), 51.7 ($CO_2\underline{C}H_3$), 51.0 ($\underline{C}H_2CH=CH$, *B*), 48.6 ($\underline{C}H_2CH=CH$, *A*), 41.1 ($\underline{C}H_2C=O$, *A*), 40.9 ($\underline{C}H_2C=O$, *B*), 35.8 ($N\underline{C}H_3$, *A*), 34.2 ($N\underline{C}H_3$, *B*).

Synthesis of **343**:



Allyl 2-phenylacetate (S59) was prepared according to **Procedure 11**. Crude **S59** was obtained as a yellow oil and used in the next step without purification (462 mg, 2.62 mmol, 89%). Analytical data is consistent with the published literature.[33]

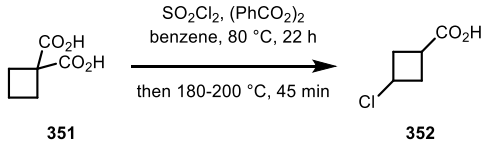
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.23 (m, 5H), 5.90 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.60 (dt, *J* = 5.7, 1.5 Hz, 2H), 3.66 (s, 2H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.4, 134.1, 132.2, 129.4 (2C), 128.7 (2C), 127.2, 118.4, 65.6, 41.5.



Methyl (*E*)-4-(2-phenylacetoxy)but-2-enoate (343) was prepared according to **Procedure 12**. FCC (pentane : EtOAc = 19:1 – 9:1) yielded **343** as a yellow oil (102 mg, 0.435 mmol, 69%).

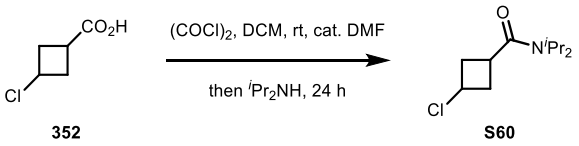
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.26 (m, 5H, ArH), 6.92 (dt, *J* = 15.8, 4.6 Hz, 1H, CH_2CH=CH), 5.96 (dt, *J* = 15.8, 2.0 Hz, 1H, CH_2CH=CH), 4.76 (dd, *J* = 4.6, 2.0 Hz, 2H, CH_2CH=CH), 3.75 (s, 3H, CO_2CH_3), 3.69 (s, 2H, CH_2C=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.9 (CH_2C=O), 166.3 (CO_2CH_3), 141.3 (CH_2CH=CH), 133.6 (ArC), 129.4 (ArC, 2C), 128.8 (ArC, 2C), 127.4 (ArC), 122.0 (CH_2CH=CH), 63.0 (CH_2CH=CH), 51.8 (CO_2CH_3), 41.3 (CH_2C=O).

Synthesis of **356** (obtained up to **353**):



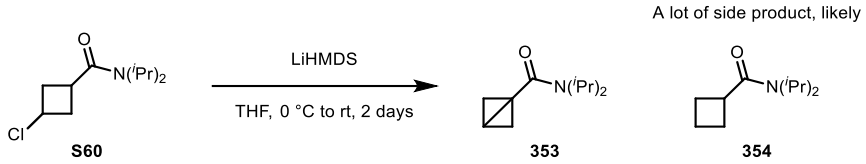
3-Chlorocyclobutane-1-carboxylic acid (352) was prepared according to a literature procedure.[34] Cyclobutane-1,1-dicarboxylic acid **351** (721 g, 5 mol, 1.0 eq.) was dissolved in benzene (4 mL, 0.8 M). A reflux condenser was fitted, and this solution was heated to 80 °C. Sulfuryl chloride (0.5 mL, 5.25 mol, 1.05 eq.) was added dropwise to this solution, and benzoyl peroxide (12 mg, 0.05 mmol, 1 mol%) was added at the same time from the top of the condenser. The reflux condenser was fitted with a drying tube and stirred at 80 °C for 22 hours. The reaction mixture was cooled and concentrated to yield a colourless solid, which was heated to 180-200 °C in air for 45 min, yielding crude **352** as a dark brown oil and a 1:1 mixture of diastereomers *A*:*B* which was used in the next step without purification. Analytical data is consistent with the published literature.[34]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.65 – 4.56 (m, 1H, *A* or *B*), 4.32 (tt, *J* = 8.7, 7.3 Hz, 1H, *A* or *B*), 3.38 – 3.29 (m, 1H, *A* or *B*), 3.24 – 3.12 (m, 1H, *A* or *B*), 2.97 – 2.77 (m, 2H, *A* + *B*), 2.66 – 2.53 (m, 2H, *A* + *B*).



352 S60

3-Chloro-*N*,*N*-diisopropylcyclobutane-1-carboxamide (S60) was prepared according to a literature procedure.[34] **352** (670 mg, 5 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (12.5 mL, 0.4 M). Oxalyl chloride (0.5 mL, 6 mmol, 1.2 eq.) and DMF (1 drop) were added. The reaction was stirred for 1.5 hours at room temperature before concentrating *in vacuo* and placing under vacuum (250 mbar) for 5 min. The crude acyl chloride was dissolved in CH_2Cl_2 (9.4 mL) and diisopropylamide (0.8 mL, 5.5 mmol, 1.1 eq.) in CH_2Cl_2 (3.1 mL) was added slowly at room temperature. The solution was stirred at room temperature for 24 hours followed by washing with 1 M HCl (15 mL) and sat. $NaHCO_3$ (15 mL). The organic phase was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. Filtration through a silica pad (Pentane : Et_2O = 1:1) yielded **S60** as a yellow oil and as a 1:1 mixture of diastereomers *A*:*B* which was used in the next step without further purification (454 mg, 1.73 mmol, 35% from **351**).



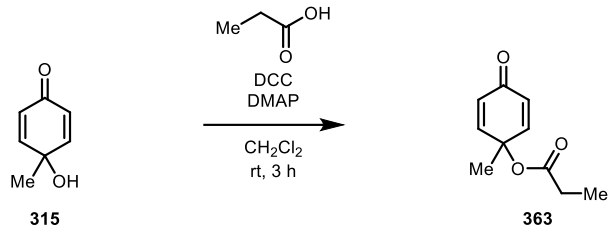
S60 353 354

***N*,*N*-Diisopropylbicyclo[1.1.0]butane-1-carboxamide (353)** was prepared according to a literature procedure.[34] **S60** (454 mg, 1.73 mmol, 1.0 eq.) was dissolved in in THF (8 mL, 0.2 M) under a nitrogen atmosphere. The solution was cooled to 0 °C and LiHMDS (1 M in THF, 1.9 mL, 1.9 mmol, 1.1 eq.) was added. The reaction was warmed to room temperature and stirred for 43 h before diluting with Et_2O (10 mL) and quenching with a few drops of water. The organic phase was washed with water (10 mL) and the aqueous phase was extracted with Et_2O (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane : EtOAc = 9:1, 1%, NEt_3) yielded **353** as a colourless solid (65 mg, 0.359 mmol, 7% from **351**). Analytical data is consistent with the published literature.[34]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.79 (br s, 1H), 3.35 (br s, 1H), 2.09 (d, J = 3.3 Hz, 2H), 1.80 (tt, J = 3.4, 2.2 Hz, 1H), 1.40 – 1.26 (m, 6H), 1.20 – 1.10 (m, 6H), 0.98 (d, J = 2.2 Hz, 2H).

***N,N*-Diisopropylcyclobutanecarboxamide (354)** was likely obtained as a major side product of the above reaction.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (hept, *J* = 6.7 Hz, 1H, $(CH_3)_2C\underline{H}$, *A*), 3.45 – 3.25 (m, 1H, $(CH_3)_2C\underline{H}$, *B*), 3.18 (pt, *J* = 8.7, 1.5 Hz, 2H, C<u>H</u>C=O), 2.39 – 2.26 (m, 2H, $C\underline{H}_AH_BC$=O, *A* + *B*), 2.13 – 2.01 (m, 2H, $CH_A\underline{H}_BC$=O), 1.99 – 1.86 (m, 1H, $C\underline{H}_AH_BCH_2CHC$=O), 1.87 – 1.74 (m, 1H, $CH_A\underline{H}_BCH_2CHC$=O), 1.38 (dq, *J* = 6.9, 1.7 Hz, 6H, $(C\underline{H}_3)_2CH$, *B*), 1.13 (dq, *J* = 6.8, 1.7 Hz, 6H, $(C\underline{H}_3)_2CH$, *A*); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{11}H_{22}NO^+$ $[M+H]^+$: 184.1696, found 184.1736.

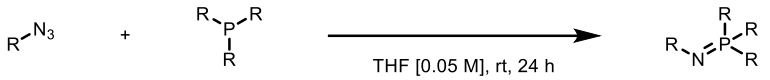


1-Methyl-4-oxocyclohexa-2,5-dien-1-yl propionate (363) was prepared according to a modified literature procedure.[19] *N*,*N*'-Dicyclohexylcarbodiimide (619 mg, 3 mmol, 3.0 eq.) was added to a solution of **315** (124 mg, 1 mmol, 1.0 eq., see **4.2.3** for preparation), propionic acid (0.3 mL, 4 mmol, 4.0 eq.), and 4-dimethylaminopyridine (12 mg, 0.1 mmol, 10 mol%) in CH_2Cl_2 (2.5 mL, 0.4 M). The mixture was stirred for 3 hours until consumption of **315** as indicated by TLC, then filtered and concentrated. FCC (pentane : EtOAc = 9:1 – 4:1) yielded **363** as a yellow solid (83.6 mg, 0.464 mmol, 46% after 2 steps).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, *J* = 10.3 Hz, 2H, C<u>H</u>C(CH_3)C<u>H</u>), 6.22 (d, *J* = 10.1 Hz, 2H, C<u>H</u>C(O)C<u>H</u>), 2.32 (q, *J* = 7.6 Hz, 2H, $CH_3C\underline{H}_2C$=O), 1.54 (s, 3H, $CC\underline{H}_3$), 1.11 (t, *J* = 7.6 Hz, 3H, $C\underline{H}_3CH_2C$=O); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 185.2 (ketone <u>C</u>=O), 173.2 (ester <u>C</u>=O), 149.4 (<u>C</u>HC(CH_3)CH), 128.2 (<u>C</u>HC(O)CH), 74.1 (<u>C</u>CH_3), 27.8 ($CH_3\underline{C}H_2C$=O), 26.4 ($C\underline{C}H_3$), 9.0 ($\underline{C}H_3CH_2C$=O); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{10}H_{13}O_3^+$ $[M+H]^+$: 181.0859, found 181.0858; **m. p.**: 46 – 48 °C.

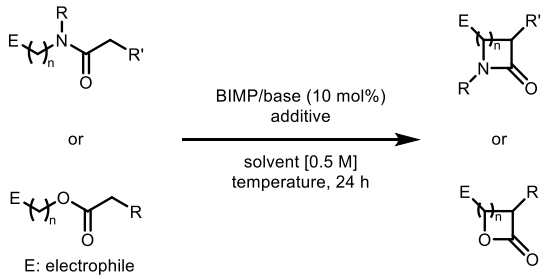
4.3.3 Reactions with BIMP and Other Superbases – General Procedures

Procedure 8 – *in situ* generation of iminophosphorane/BIMP catalysts



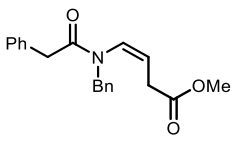
According to a literature procedure,[21] the organoazide (0.01 mmol, 1.0 eq.) and trivalent phosphine (0.01 mmol, 1.0 eq.) were dissolved in anhydrous THF (0.2 mL, 0.05 M) and the reaction mixture was stirred at room temperature for 12 to 24 hours. Volatiles were removed under a stream of nitrogen yielding the crude iminophosphorane or BIMP catalyst which was used without purification.

Procedure 13 – reaction with BIMP or another base



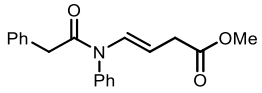
For a catalyst generated using **Procedure 8**, the amide or ester (0.1 mmol, 1.0 eq.) and any additives if required (1.0 eq. $CsCO_3$, 5.0 eq. D_2O or MeOD) was added to the catalyst (0.01 mmol, 10 mol%), which were then dissolved in the intended reaction solvent (0.2 mL, 0.5 M). For other bases, the amide or ester (0.1 mmol, 1.0 eq.) was dissolved in the intended reaction solvent (0.2 mL, 0.5 M) and the intended base (0.01 mmol, 10 mol%) was added to this solution. The reaction mixture was left to stir at room temperature or heated to the intended reaction temperature. After 24 hours of vigorous stirring, crude products were isolated by passing the reaction mixture through a short silica plug eluting with 1:1 pentane : EtOAc.

4.3.4 Reactions with BIMP and Other Superbases – Analytical Data



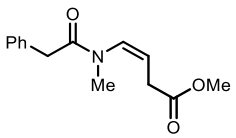
Methyl (*Z*)-4-(*N*-benzyl-2-phenylacetamido)but-3-enoate (345) was deduced to be the most likely structure of the major side product prepared according to **Procedure 13** with **340** and BIMP catalyst **259** or BEMP **344**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 – 7.20 (m, 10H, ArH), 6.12 (dt, *J* = 7.8, 1.8 Hz, 1H, NCH=$CHCH_2$), 5.71 (q, *J* = 7.5 Hz, 1H, NCH=CHCH$_2$), 4.62 (s, 2H, NCH_2), 3.65 (s, 2H, $PhCH_2C$=O), 3.62 (s, 3H, CO_2CH_2), 2.72 (dd, *J* = 7.3, 1.9 Hz, 2H, NCH=CHCH_2).



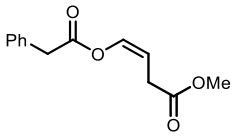
Methyl (*E*)-4-(*N*,2-diphenylacetamido)but-3-enoate (346) was deduced to be the most likely structure of the major side product prepared according to **Procedure 13** with **341** and BIMP catalyst **259** (78% conversion).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, *J* = 14.4 Hz, 1H, NCH=$CHCH_2$), 7.48 – 7.35 (m, 3H, ArH), 7.27 – 7.16 (m, 3H, ArH), 7.12 – 7.07 (m, 2H, ArH), 7.04 – 6.96 (m, 2H, ArH), 4.49 (dt, *J* = 14.5, 7.3 Hz, 1H, NCH=CHCH$_2$), 3.61 (s, 3H, CO_2CH_3), 3.43 (s, 2H, $PhCH_2C$=O), 3.01 (dd, *J* = 7.3, 1.3 Hz, 2H, NCH=CHCH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.4 (amide C=O), 169.2 (ester C=O), 138.9 (ArC), 134.6 (ArC), 131.5 (NCH=$CHCH_2$), 130.1 (ArC, 2C), 129.4 (ArC), 129.1 (ArC, 4C), 128.5 (ArC, 2C), 126.9 (ArC), 106.1 (NCH=CHCH$_2$), 51.9 (CO_2CH_3), 41.8 ($PhCH_2C$=O), 35.4 (NCH=CHCH_2).



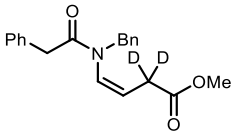
Methyl (*Z*)-4-(*N*-methyl-2-phenylacetamido)but-3-enoate (347) was deduced to be the most likely structure of the major side product prepared according to **Procedure 13** with **342** and BEMP **344**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.20 (m, 5H, ArH), 6.34 (dt, *J* = 7.9, 1.8 Hz, 1H, NCH=$CHCH_2$), 5.59 (q, *J* = 7.3 Hz, 1H, NCH=CHCH$_2$), 3.67 (s, 3H, CO_2CH_3), 3.64 (s, 2H, $PhCH_2C$=O), 3.04 (s, 3H, NCH_3), 3.00 (dd, *J* = 7.3, 1.8 Hz, 2H, NCH=CHCH_2).



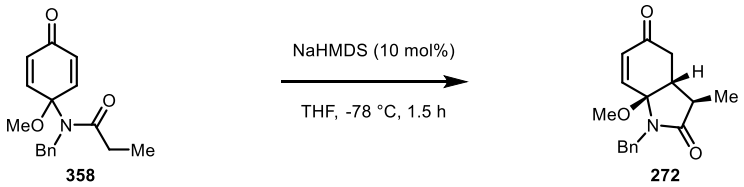
Methyl (*Z*)-4-(2-phenylacetoxy)but-3-enoate (348) was deduced to be the most likely structure of the major side product prepared according to **Procedure 13** with **343** and BEMP **344**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.25 (m, 5H, ArH), 7.18 (dt, *J* = 6.4, 1.8 Hz, 1H, NCH=$CHCH_2$), 5.12 (td, *J* = 7.2, 6.4 Hz, 1H, NCH=CHCH_2), 3.72 (s, 2H, $PhCH_2C$=O), 3.70 (s, 3H, CO_2CH_3), 3.18 (dd, *J* = 7.2, 1.8 Hz, 2H, NCH=CHCH_2).



Methyl (*Z*)-4-(*N*-benzyl-2-phenylacetamido)but-3-enoate-2,2-d_2 (350) was deduced to be the most likely structure of the product prepared according to **Procedure 13** with **340**, BIMP catalyst **259** and 5 eq. of either D_2O or MeOD.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 – 7.20 (m, 10H, ArH), 6.12 (d, *J* = 7.7 Hz, 1H, NCH=$CHCD_2$), 5.69 (d, *J* = 7.8 Hz, 1H, , NCH=CHCD_2), 4.62 (s, 2H, NCH_2), 3.65 (s, 2H, CH_2C=O), 3.62 (s, 3H, CO_2CH_3).

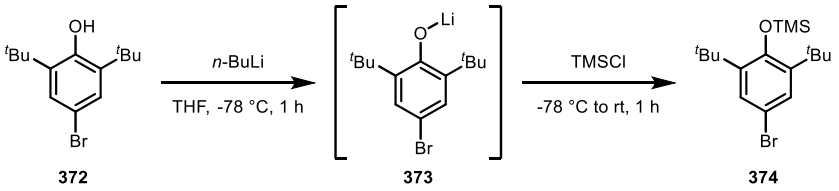


(3*R*,3a*R*,7a*S*)-1-Benzyl-7a-methoxy-3-methyl-1,3a,4,7a-tetrahydro-2*H*-indole-2,5(3*H*)-dione (272) was prepared according to a modified literature procedure.[35] **358** (28.5 mg, 0.1 mmol, 1.0 eq.) was dissolved in in anhydrous THF (1 mL, 0.1 M) under a nitrogen atmosphere. After cooling to -78 °C, NaHMDS (1 M in THF, 0.15 mL, 0.15 mmol, 1.5 eq.) was added to this solution. The reaction was stirred at this temperature for 1.5 hours. The reaction mixture was then warmed to 0 °C and quenched with sat. NH_4Cl (0.3 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were

washed with brine (5 mL), dried over anhydrous Na_2SO_4, and the volatiles were removed *in vacuo* to yield crude **272** as a yellow oil (83% conversion).

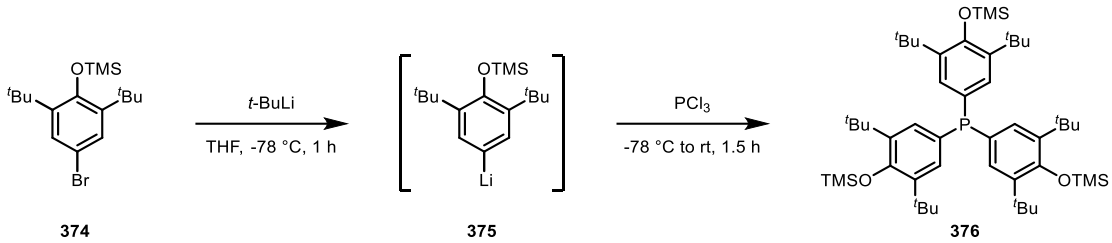
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 – 7.20 (m, 5H, ArH), 6.30 (dd, *J* = 10.4, 1.8 Hz, 1H, CH=CHC=O), 5.91 (dd, *J* = 10.4, 0.9 Hz, 1H, CH=CHC=O), 4.76 (d, *J* = 15.2 Hz, 1H, NCH_AH_B), 4.26 (d, *J* = 15.2 Hz, 1H, NCH_AH_B), 3.19 (s, 3H, $COCH_3$), 2.73 (dd, *J* = 17.3, 6.4 Hz, 1H, $CHCH_AH_BC=O$), 2.57 – 2.49 (m, 2H, $CHCH_2C=O$ and $CHCH_AH_BC=O$), 2.24 – 2.13 (m, 1H, $CH_3CHC=O$), 1.29 (d, *J* = 7.0 Hz, 3H, $CH_3CHC=O$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.2 (ketone C=O), 175.0 (amide C=O), 141.9 (CH=CHC=O), 138.0 (ArC), 129.2 (CH=CHC=O), 128.8 (ArC, 2C), 128.2 (ArC, 2C), 127.7 (ArC), 89.2 ($COCH_3$), 50.4 ($COCH_3$), 42.7 (NCH_2), 41.6 ($CH_3CHC=O$), 41.4 ($CHCH_2C=O$), 36.9 ($CHCH_2C=O$), 13.7 ($CH_3CHC=O$); **HRMS** (ESI+, m/Z): exact mass calculated for $C_{17}H_{20}NO_3^+$ $[M+H]^+$: 286.1438, found 286.1432.

4.3.5 Synthesis of Phosphines



(4-Bromo-2,6-di-*tert*-butylphenoxy)trimethylsilane (374) was prepared according to a literature procedure.[36] 2,6-Di-*tert*-butyl-4-bromophenol **372** (5.0 g, 17.5 mmol, 1.0 eq.) was dissolved in THF (60 mL, 0.3 M) under a nitrogen atmosphere and cooled to -78 ºC. *n*-Butyllithium (1.6 M in hexanes, 16.4 mL, 26.25 mmol, 1.5 eq.) was added dropwise and the resulting solution was stirred at -78 ºC for one hour. Trimethylsilyl chloride (3.8 mL, 29.6 mmol, 1.7 eq.) was added *via* syringe and the reaction mixture was stirred and allowed to warm to room temperature over one hour. Water (8 mL) was added *via* syringe to quench the reaction, and the mixture was stirred for another 30 min. The layers were separated, and the aqueous layer was extracted with pentane (2 x 50 mL). The combined organic layers were washed with water (50 mL) and dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. FCC (pentane) yielded **374** as a yellow solid (6.23 g, 17.4 mmol, >99%). Analytical data is consistent with the published literature.[36]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (s, 2H), 1.38 (s, 18H), 0.40 (s, 9H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 152.6, 143.3 (2C), 128.8 (2C), 113.9, 35.4 (2C), 31.2 (6C), 4.0 (3C).



374 375 376

Tris(3,5-di-*tert*-butyl-4-((trimethylsilyl)oxy)phenyl)phosphane (376) was prepared according to a modified literature procedure.[37] **374** (1.2 g, 3.36 mmol, 3.0 eq.) was dissolved in degassed THF (4 mL, 0.28 M) under a nitrogen atmosphere. The solution was cooled to −78 °C for 10 min with stirring and commercial ^{t}BuLi (1.7 M in pentane, 4 mL, 6.72 mmol, 6.0 eq.) was added dropwise. The resulting mixture was stirred for 1.5 hours, after which PCl_3 (98 µL, 1.12 mmol, 1.0 eq.) was added dropwise over 10 min. The resulting mixture was stirred for one hour at −78 °C and then for another hour at room temperature. After removing all volatiles *in vacuo*, the residue was dissolved in degassed pentane (15 mL) and the resulting solution was stirred for 30 min. Thereafter, the suspension of lithium chloride was removed by filtration under a nitrogen atmosphere. Pentane was removed *in vacuo* and FCC (pentane : CH_2Cl_2 = 9:1) yielded **376** as a colourless solid (244 mg, 0.283 mmol, 25%). Analytical data is consistent with the published literature.[37]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, J = 8.1 Hz, 6H), 1.29 (s, 54H), 0.39 (s, 27H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 153.8 (3C), 140.6 (d, J = 6.8 Hz, 6C), 131.6 (d, J = 20.3 Hz, 6C), 129.2 (3C), 35.4 (6C), 31.4 (18C), 4.00 (9C); **^{31}P NMR** ($CDCl_3$, 162 MHz) δ -9.11.

The remaining phosphines mentioned in **Chapter 3** were prepared according to the procedure for the synthesis of **S3**.

4.4 References for Chapter 4

[1] Rozsar, D.; Formica, M.; Yamazaki, K.; Hamlin, T. A.; Dixon, D. J. Bifunctional Iminophosphorane-Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α,β-Unsaturated Amides. *J. Am. Chem. Soc.* **2022**, *144*, 1006–1015.

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