Bifunctional Iminophosphorane Superbase Catalysed Enantioselective Intramolecular Michael Reactions



A thesis submitted in partial fulfilment of the requirement

for the degree of Doctor of Philosophy (DPhil)

Guanglong Su

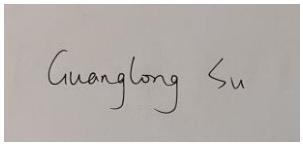
Wolfson College

University of Oxford

Hilary Term 2022

Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2018 until September 2021, under the supervision of Professor Darren J. Dixon. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

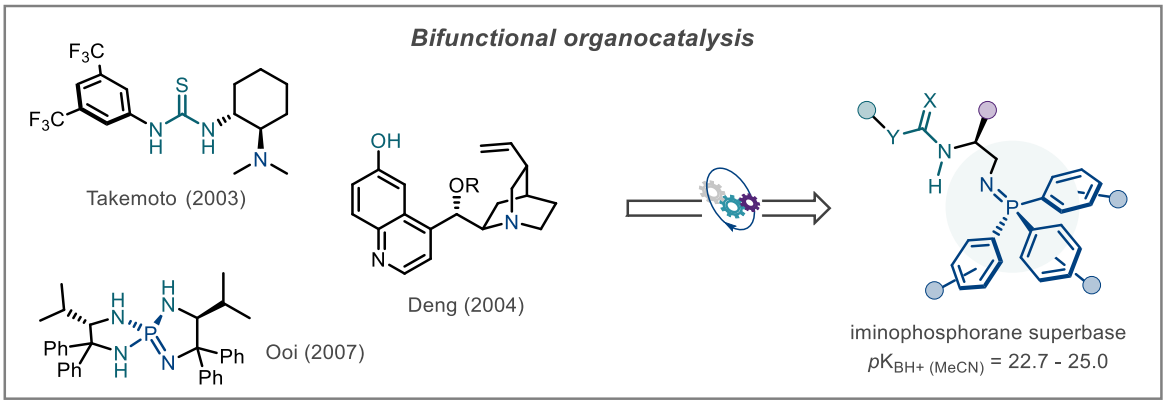


Guanglong Su

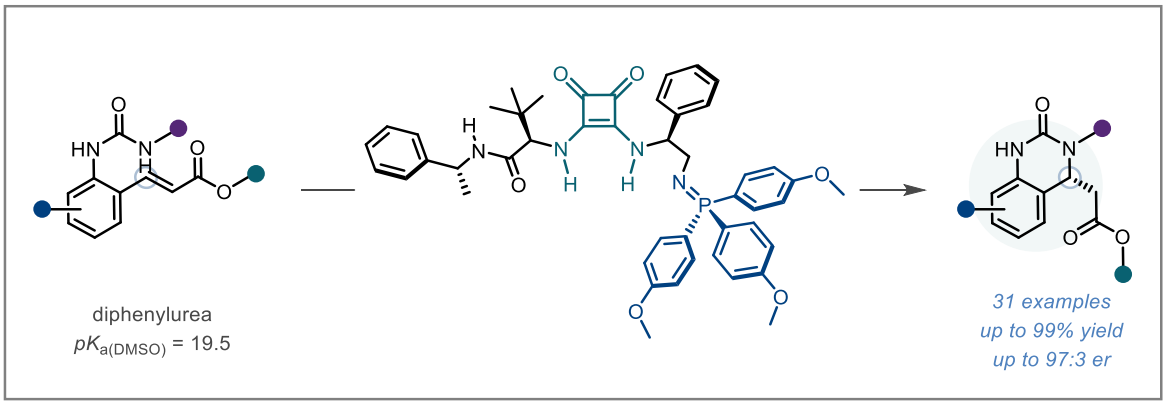
January 2022

Abstract

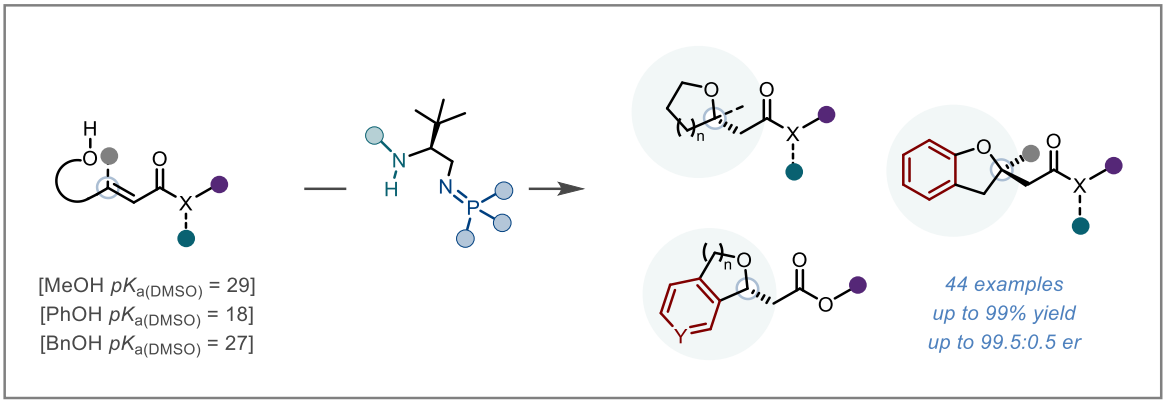
Chapter 1 introduces the strategies to prepare enantioenriched compounds, specifically focusing on tertiary amine-based and superbasic bifunctional organocatalysis. Bifunctional iminophosphorane (BIMP) catalysis will then be detailed in its discovery and applications.



Chapter 2 outlines the development of a squaramide BIMP-catalysed enantioselective intramolecular aza-Michael reaction (IAMR) of both aromatic and aliphatic ureas to tethered α,β-unsaturated esters, furnishing decorated enantioenriched hydroquinazolines.



Chapter 3 demonstrates the enantioselective preparation of structurally diverse enantioenriched cyclic ethers via a BIMP-catalysed intramolecular oxy-Michael reaction (IOMR) of alcohols to tethered α,β-unsaturated esters and amides. The improved efficiency (1 day vs 7 days) and a far broader scope than the previous syntheses will be described. Subsequently, the pronucleophile scope of the IOMR will be extended to phenols and benzylic alcohols, thereby delivering enantioenriched dihydro-(iso)-benzofurans and iso-chromans.



Acknowledgements

People I would like to thank.

Darren, who took me as a DPhil student, generously invited me to his place for Christmas dinner, has been extremely kind, supportive and encouraging to me throughout the whole DPhil and is undoubtedly a great chemist and supervisor, said by GL and many other people he knows; All CRL staff members, who provided timely assistance in acquiring analytical data for me and never sent me angry email when I submitted over 100 MS samples in a week;

Jonny, who is the tallest (but not cutest), very sarcastic and mean but to me always patient, nice and helpful (although did shout at me once when I damaged? the HPLC); Mix, who promoted me from a green hand to a person capable of preparing this PhD thesis independently and is probably the most detailed proof-reader; Connor, who brought me a mac from NYC and a lot of other things in these years; Andrew, who drove me home many many nights, was willing to listen to my complaint and also invited me to an unforgettable Christmas dinner in his place; Ben, who I would regard as the kindest English I have met so far; Yao, who made me feel very warm in the freezing Cortex place and is a person incapable of getting furious; Xing, who gossiped with me in the lab and always sent me not true scandals but only rumours! Tanya, DMR, Ken, Bran, Jamie, Lucia, Thomas, Pete, Philip, Shinya, Yaseen, Tom, Pablo, Big Dan, Roman, Charmaine and all other DJD group members that I had the opportunity to work with, who made my life in the lab so much easier than it ever could be; Yifan, who kindly offered me a temporary shelter during the global pandemic. Jieren, Wula, Ally, Xiaobai, Wenyuan and all my Chinese friends in oxford, who were either my lunchmates or persons I hanged out with. Yuanzhe, who brought so much joy to my life in UK and turned me to a much more confident and brighter man;

My grandma, who brought me up, shaped me who I am today and is the person I love the most; My parents, who always support me, financially and mentally.

Thank you all, my friends or my loves.

Abbreviations

(+)	Dextrorotary
(−)	Levorotatory
D	Dextrorotary
L	Levorotatory
δ	NMR chemical shift
ν_{max}	Infrared absorption maximum
Ac	Acetyl
Ar	Aryl
aq	Aqueous
$BAr^{F}{}_{4}$	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BIMP	Bifunctional IMinoPhosphorane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BQ	Benzoquinone
br	Broad
brs	Broad singlet
BTMG	2-*tert*-Butyl-1,1,3,3-tetramethylguanidine
Bz	Benzoyl
Bu	Butyl
cat	Catalyst
Cbz	Carboxybenzyl

cm	Centimetre
Conc.	Concentrated
COSY	COrrelation SpectroscopY
CPA	Chiral Phosphoric Acid
CPME	Cyclopentyl Methyl Ether
Cy	Cyclohexyl
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
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
ddt	Doublet of doublet of triplets
DFT	Density functional theory
$(DHQ)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppe	1,2-Bis(diphenylphosphino)ethane
dq	Doublet of quartets
dr	Diastereomeric ratio
dt	Doublet of triplets

dtd	Doublet of triplet of doublets
dtdd	Doublet of triplet of doublet of doublets
ee	Enantiomeric excess
ent	Enantiomer
er	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
et al.	*et alia*
equiv.	Equivalents
fac	Facial
FCC	Flash Column Chromatography
FDA	Food and Drug Administration
g	Grams
h	Hour
hept	Heptuplet
HGII	Hoveyda–Grubbs catalyst 2nd generation
HOBt	Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coupling
Hz	Hertz
i-	Iso
i-Pr	Isopropyl
IPA	Isopropyl alcohol
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry

J	Coupling constant
K	Kelvin
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium Diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low resolution mass spectrometry
m	Multiplet
m	Meta
M	Molar concentration
m/*z*	Mass to charge ratio
Me	Methyl
MeCN	Acetonitrile
MHz	Mega hertz
m.p.	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
MVK	Methyl vinyl ketone
n-	Normal
N	Normality
NaHMDS	Sodium bis(trimethylsilyl)amide
NHC	N-Heterocyclic Carbene
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance

nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Np	Naphthyl
Nu	Nucleophile
o	Ortho
p	Para
p	Pentet
Ph	Phenyl
Phth	Phthalimide
Pin	Pinacol
Piv	Pivaloyl
PMP	*para*-Methoxy phenyl
ppm	Parts per million
Pr	Propyl
prep	Preparative
*p*TSA	Para-toluenesulfonic acid
pyr	Pyridine
q	Quartet
qd	Quartet of doublets
qt	Quartet of triplets
quant.	Quantitative
R	Unspecified organic group
RCM	Ring-Closing Metathesis
rr	Regioisomeric ratio
rt	Room temperature
s	Singlet

sat.	Saturated
SCXRD	Single Crystal X-Ray Diffraction
sept	Septuplet
SMA	Sulfa-Michael addition
T	Temperature
T	Triplet
t-	Tert
$t_{1/2}$	Half-life
TBAB	Tert-butyl ammonium bromide
TBAF	Tert-butyl ammonium fluoride
TBME	Tert-butyl methyl ether
TBS	Tert-Butyldimethylsilyl
TBD	Triazabicyclodecene
TBDPS	Tert-Butyldiphenylsilyl
td	Triplet of doublets
tdd	Triplet of doublet of doublets
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMDS	Tetramethyldisiloxane
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
tol	Tolyl
t_R	Retention time

Ts	*para*-Toluenesulfonyl
TS	Transition state
tt	Triplet of triplets
UV	Ultraviolet
w	Weight
WHO	World Health Organization
Z	Zusammen

Table of contents

Chapter 1 Introduction 1
1.1 Chirality: from Single Molecules to Life 1
1.2 Strategies to Prepare Enantioenriched Compounds 2
1.2.1 Chiral resolution or chromatographic separation 3
1.2.2 Synthesis from the chiral pool 3
1.2.3 Diastereoselective synthesis with chiral auxiliaries 3
1.2.4 Enantioselective catalysis 4
1.3 General Introduction to Organocatalysis 6
1.3.1 Organocatalysis in the 20th century 6
1.3.2 Organocatalysis in the beginning of 21st century 9
1.4 Tertiary Amine Brønsted Base Bifunctional Organocatalysis 11
1.4.1 Merging of Brønsted bases and H-bond donor groups 12
1.4.2 *Cinchona* alkaloid derived bifunctional organocatalysts 15
1.4.3 Limitations of the current designs 18
1.5 Superbasic Bifunctional Organocatalysis 20
1.5.1 Superbases definitions 20
1.5.2 Chiral guanidines 21
1.5.3 Chiral cyclopropenimines 25
1.5.4 Chiral phosphazenes 26
1.5.5 Limitations of the current designs 30
1.6 Bifunctional Iminophosphorane Organocatalysis 31
1.6.1 Development of concepts of BIMPs 31
1.6.2 1st generation of BIMPs and their applications 32
1.6.3 2nd generation of BIMPs and their applications 36
1.7 Thesis Aims 39
1.8 References for Chapter 1 40

Chapter 2 Enantioselective Intramolecular *Aza*-Michael Reaction of Ureas to α,β-Unsaturated Esters 50
2.1 Chapter Overview 50
2.2 Introduction 51
2.2.1 Importance of quinazolines and their derivatives 51
2.2.2 Enantioselective preparation of hydroquinazolines 52
2.2.3 Aim of the project 61
2.3 Reaction Discovery and Optimisation 61
2.3.1 Proof of Concept 61

2.3.2 Catalyst Screen....62
2.3.2 Phosphine screen....65
2.3.3 Evaluation of other conjugate acceptors....67
2.4 Substrate Synthesis....67
2.5 Evaluation of Reaction Scope....68
2.5.1 Reaction scope with regards to *NH*-aryl substituents....68
2.5.2 Reaction scope with regards to *N*-aryl substituents....69
2.5.3 Reaction scope with regards to aliphatic ureas....72
2.5.4 Limitations of the reaction scope....73
2.6 Preparative Scale Synthesis and Derivatisation....74
2.7 Computational Studies....77
2.8 Conclusion....81
2.9 References for Chapter 2....82

Chapter 3 Enantioselective Intramolecular *Oxy*-Michael Reaction to α,β-Unsaturated Esters and Amides....89
3.1 Chapter Overview....89
3.2 Introduction....90
3.2.1 Importance of 5- or 6- membered cyclic ethers....90
3.2.2 Enantioselective preparation of 5 or 6 membered cyclic ethers....91
3.2.3 Aim of the project....98
3.3 Reaction Optimisation....99
3.4 Substrate Synthesis....101
3.5 Evaluation of Reaction Scope....102
3.5.1 Reaction scope with regards to Michael acceptors....102
3.5.2 Reaction scope with regards to tether substituents....103
3.5.3 Reaction scope with regards to β-disubstituted benzyl ester....105
3.5.4 Reaction scope with regards to β-oxy-spirocycles....105
3.5.5 Reaction scope with regards to α-oxy-spirocycles....106
3.5.6 Reaction scope with regards to sugars and natural product derivatives....109
3.5.7 Limitations of the reaction scope....110
3.6 Preparative Scale Synthesis and Serivatisation....111
3.7 Extension to Phenol Nucleophiles....114
3.7.1 Reaction re-optimisation....114
3.7.2 Substrate synthesis....115
3.7.3 Evaluation of reaction scope....115
3.7.4 Preparative scale synthesis and derivatisation....116
3.8 Extension to Other Benzene-Fused Cyclic Ethers....119
3.8.1 Reaction optimisation....119
3.8.2 Substrate synthesis....120

3.8.3 Evaluation of reaction scope....121
3.8.4 Derivatisation of enantioenriched 539....122
3.9 Conclusion and Future Work....123
3.10 References for Chapter 3....125

Chapter 4 Experimental Details....134
4.1 General Experimental Details....134
4.2 Experimental Details for Chapter 2....136
4.2.1 Optimisation Results....136
4.2.2 Preparation of Catalyst Precursor and Catalyst....146
4.2.3 Preparation of Starting Materials....155
4.2.4 Preparation of Racemic Compounds....181
4.2.5 Preparation of Enantioenriched Products....181
4.2.6 Scale-up and Derivatisation....213
4.2.7 Single Crystal X-Ray Diffraction Data....219
4.2.8 Computational Studies....222
4.3 Experimental Details for Chapter 3....226
4.3.1 Optimisation Results....226
4.3.2 Preparation of Azide Catalyst Precursor, Phosphines and Catalyst....238
4.3.3 Preparation of Starting Materials....241
4.3.4 Preparation of Racemic Compounds....312
4.3.5 Preparation of Enantioenriched Products....312
4.3.6 Determination of Stereochemical Configuration....355
4.3.7 Scale up and Derivatisation....357
4.4 References for Chapter 4....368

Chapter 1 Introduction

1.1 Chirality: from Single Molecules to Life

In almost all ages, human beings worshipped the beauty of symmetry in aesthetics and architectures. Egyptian pyramids, ancient Chinese gardens as well as the whole forbidden city in Beijing were designed and constructed along a central symmetric line. Chirality, however, is one of the most essential properties of nature. Small organic molecules that function in our body such as cholesterol and epinephrine often have one or more stereo-centres. Macromolecules including nucleic acids, proteins and saccharides that help build life possess their own unique chiral pattern. Furthermore, the flourishment of life also originates from precise recognition of chirality on molecular level.

Importantly, stereo-dependent potency or physiological properties are often exhibited by chiral molecules as a result of *in vivo* diastereomeric interactions.[1] Molecules having different stereochemical configurations can show similar, opposing or even uncorrelated biological activity. While both enantiomers of prilocaine (**1**) show biological activity in treatment of regional nerve block and topical anaesthesia, the (*R*) enantiomer undergoes *in vivo* hydrolysis at a much faster rate than its enantiomer generating toluidine which leads to methemoglobinemia. As a consequence, only the (*S*) enantiomer was used in the clinic (**Figure 1**).[2] Propoxyphene (**2**), which contains two stereogenic centers, demonstrates an uncommon relationship between absolute stereochemical configurations and physiological activity, where the *L*-isomer was used as an antitussive while the *D*-isomer produces an analgesic effect (**Figure 1**).[3] If stereochemical configuration can be considered at the early stage of the drug discovery process, every single isomer can be thoroughly studied in terms of their pharmacologic activity, pharmacokinetic profile, and toxicology. Therefore, preparing molecules in a highly enantioselective manner can help reduce the likelihood of unwanted clinical effects. Moreover, having 3D scaffolds allows for better fit in biologically active pockets and the correct enantiomer can have better binding interactions. In fact, because of this, significant efforts in the pharmaceutical industry have been made to incorporate chiral elements in drug design over the past decades.

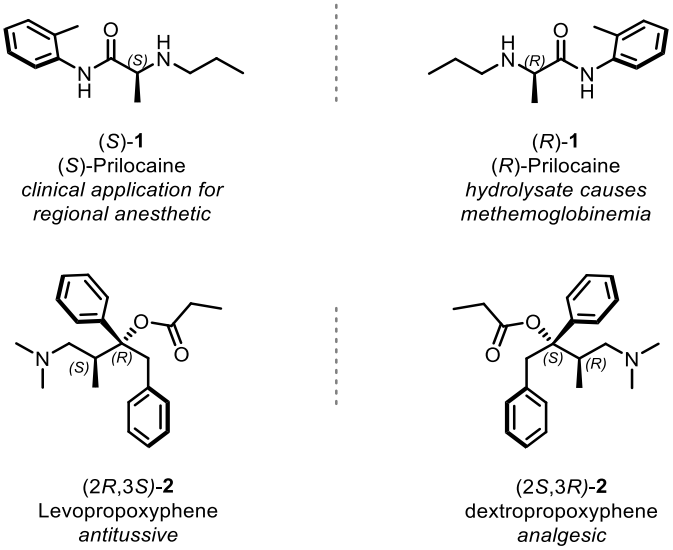


Figure 1. Structures of prilocaine and propoxyphene enantiomers and their biological roles.

1.2 Strategies to Prepare Enantioenriched Compounds

Significant advancements in preparing enantioenriched compounds have been achieved over the past few decades (**Figure 2**). Strategies focus on four aspects: (1) chiral resolution or chromatographic separation, (2) synthesis from the chiral pool, (3) diastereoselective synthesis using chiral auxiliaries and (4) enantioselective synthesis.

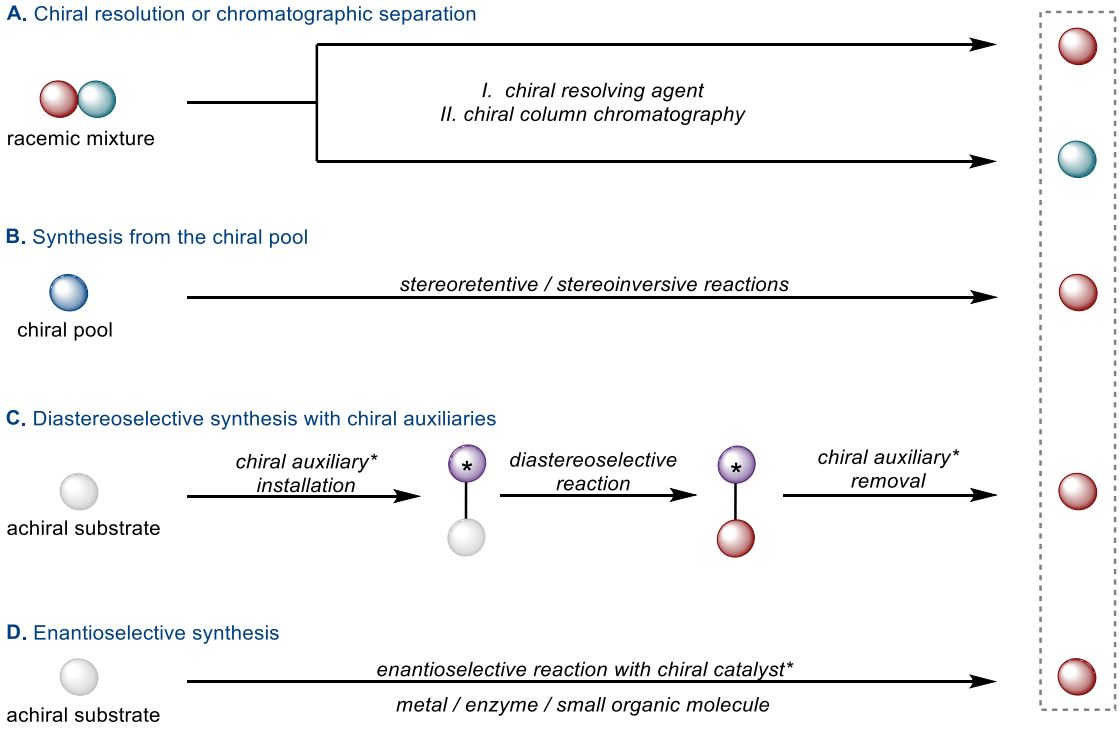


Figure 2. Strategies to prepare enantiomerically enriched material

1.2.1 Chiral resolution or chromatographic separation

Using chiral resolving agents / chiral derivatising agent (CDA) or chiral stationary phases to prepare enantiomerically enriched products has long been the most prevalent method to prepare single enantiomers before the development of sophisticated stereoselective synthetic methods.[4, 5] Chiral resolution techniques normally rely on the solubility difference between the diastereomers (formed by reacting the racemic substrates with CDAs), which is not always high enough for the crystallisation to be efficient. An exception of this is the kinetic resolution process which separates two enantiomers through different reaction rate. Chromatographic separation is seen to be more effective than the former but will typically require large amount of expensive chiral media and is not typically suitable for scale-up synthesis. The greatest shortcoming however, is that both methods can only typically recover 50% desired material from the racemic substrate at best. This is not the case only when dynamic kinetic resolution is employed (100% racemic starting material can be converted to the desired product).

1.2.2 Synthesis from the chiral pool

Another conventional method to access enantiopure scaffolds is the use of starting materials derived from the chiral pool.[6, 7] Abundant chiral molecules are provided as single enantiomers by nature such as amino acids, monosaccharides and terpenes. These building blocks can be highly versatile and valuable for synthetic chemists. The downsides are however also obvious. To preserve the stereochemical integrity, the manipulation of the chiral pool is limited to only configuration retentive / inversive reactions. This can be troublesome especially when the synthetic route is tedious. Besides, the structural diversities of naturally occurring building blocks are relatively limited normally, and hence so is the position of the introduced stereogenic centres. Moreover, nature only provides one enantiomer usually and the unnatural enantiomer can range from being more expensive (amino acids) to ridiculously expensive (sugars or terpenes).

1.2.3 Diastereoselective synthesis with chiral auxiliaries

To overcome these aforementioned problems, the use of chiral auxiliaries in synthesis has provided one solution.[8-10] While being covalently linked to the achiral substrates, chiral auxiliaries can impart influence

to the stereochemical outcome of a reaction. The auxiliaries can later be cleaved to release the desired enantiopure product with in some cases predictable stereochemical configuration. This type of diastereoselective synthesis is still ubiquitous nowadays and greatly contributes to the growth of the drug preparation industries due to their simplicity and robustness. Yet the low atom-economy owing to the use of stoichiometric amounts of auxiliary cannot be neglected.[11] Apart from that, the introduction and removal of the auxiliary add two (or more) extra steps to the synthetic sequence, significantly lessening the isolated yield of target enantiomers as well as vastly increasing waste and lowering overall synthetic efficiency. Exploration of alternative avenues is therefore still highly coveted.

1.2.4 Enantioselective catalysis

Enantioselective catalysis, defined by Bolm and Gladysz [12] as 'the catalytic, selective, and reproducible generation of a given enantiomer of a chiral product from achiral reactants', provides an ideal, direct and highly efficient strategy to generate enantioenriched products. Enantioselective reactions proceed through diastereomeric transition states of different energy and therefore one enantiomer is kinetically favoured. As such, chirality is transferred from the catalysts to the products. Although often a more significant amount of time is invested to optimise a catalytic enantioselective method, the potential cost-savings on industrial scale makes the approach rather appealing. The field can be divided into three branches: organometallic catalysis, biocatalysis and organocatalysis.

1.2.4.1 Transition metal catalysis

Transition metal catalysis / organometallic catalysis, arguably dominates the whole field.[13-15] Its influence was acknowledged with the 2001 Nobel Prize for Chemistry being awarded to Noyori and Knowles, and Sharpless for their work on asymmetric hydrogenation and oxidation, respectively. Combined with a chiral ligand, the active metal species can display extremely high catalytic activity and enable an impressive range of reactions with exceptionally low catalyst loadings. The main drawbacks of metal catalysis normally feature rarity, high cost (Pt, Pd, Rh, Ir) and / or toxicity (Ni, Co, Ru). The latter introduces challenges of thorough removal of residual trace metals from the final drug compounds to meet stringent governmental regulations and overall safety.

1.2.4.2 Biocatalysis

Biocatalysis was developed to avert the toxicity and high cost associated with transition metals and thus be a greener alternative.[16] Enzymatic catalytic processes demonstrate extremely high levels of chemo-, regio- and enantioselectivity. The field remained in its infancy until great advances of directed evolution was developed by Francis Arnold in late 20th century (for which she was awarded the Nobel prize in 2018) whereby enzymes can be engineered to offer improved reactivity and selectivity profiles. Additionally, biocatalyst libraries can be rapidly generated and are becoming more readily available.[17] However, it is quite challenging to have the required complementary skillsets and special equipment for biocatalysis in standard synthetic organic chemistry laboratories. Moreover, enzymatic catalysis is intrinsically substrate dependant and thus not ideal to prepare numerous analogues in a medicinal chemistry campaign. It also typically only functions well in aqueous media in which organic substrates are not always soluble in.

1.2.4.3 Organocatalysis

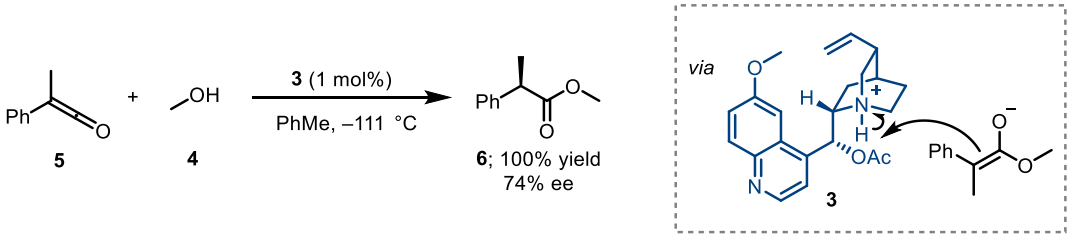
Finally, small organic molecule catalysis, otherwise known as organocatalysis will be discussed. Unlike organometallic catalysts, organocatalytic systems do not normally require rigorous exclusion of moisture and air from the reaction vessels, and are often only a few synthetic steps from commercially available organic building blocks. The advantages of using small organic molecules as catalysts over enzymes include compatibility with organic solvents and improved tolerance to multiple functionalities. Besides, the tuning of organocatalysts to meet optimal performance are less labour intensive than the encoding of active protein sites. Organocatalysis has indeed enabled a vast number of transformations that are unfeasible with metal- / bio-catalysis and has become an essential approach in the catalytic enantioselective synthesis community during the last two decades.[18, 19] Details on the history and current state-of-the-art of organocatalysis will be discussed in the rest of this introduction chapter.

1.3 General Introduction to Organocatalysis

1.3.1 Organocatalysis in the 20th century

Some present-day scientists believe that the origin of enantioselective organocatalysis can be traced back to 1904 when Marckwald and co-workers attempted to use Brucine to catalyse the decarboxylation of malonic acid enantioselectively.[20] Although 10% ee observation was claimed by Marckwald, Kenyon and co-workers failed to reproduce the result in 1951.[21, 22]

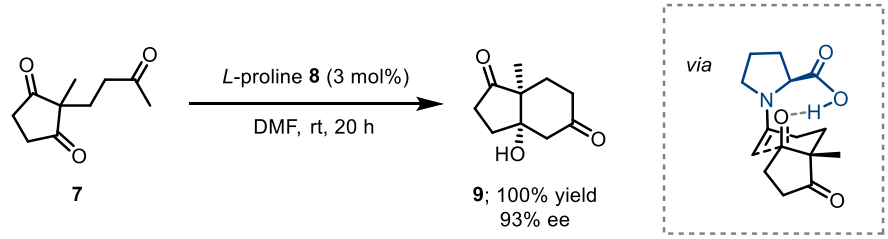
In 1960, Pracejus found an acylated analogue of quinine (**3**) to be very efficient for the addition of methanol (**4**) to phenyl(methyl)ketene (**5**) (using only 1 mol% catalyst loading at –111 ˚C) -- Quantitative yield and 74% ee of the α-methyl branched-methyl ester (**6**) was obtained [23] (**Scheme 1**). It was reasoned that the reaction was initiated by MeOH addition and then one enantiomer was formed preferentially *via* enantioselective re-protonation with the alkaloid catalyst conjugate acid .This work indeed demonstrated the feasibility of enantioselective metal-free catalysis for the first time.



Scheme 1. Pracejus's addition of MeOH to phenyl-(methyl)ketene (1960).

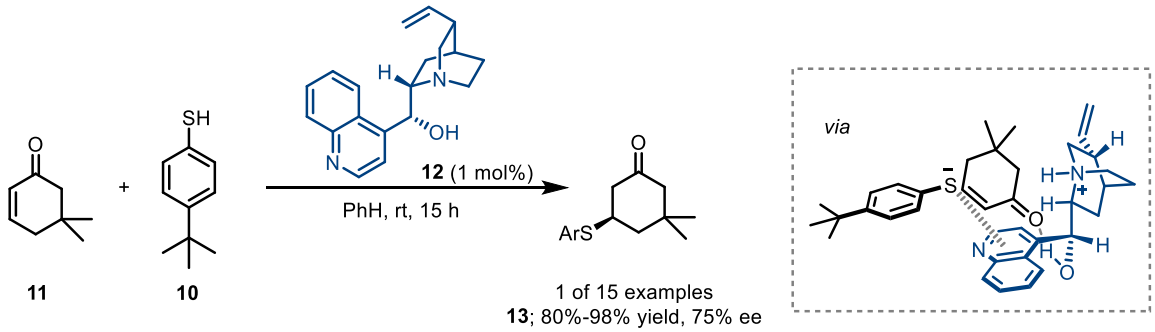
The first example of a highly enantioselective (>90% ee) organocatalytic reaction was the intramolecular cyclisation of triketone (**7**), simultaneously reported by Hajos and Parrish[24] and by Eder, Sauer and Wiechert[25] in 1971 (**Scheme 2**). The direct aldol addition reaction was catalysed by 3 mol% of the naturally occurring amino acid proline (**8**) at room temperature in DMF. The medicinally relevant bicyclic product (**9**) was obtained in 100% yield and 93% ee *via* a proposed chair-like transition state where the pre-formed enamine attacks one of the enantiotopic ketones of the molecules. The differentiation of the two carbonyl moieties and hence the control of the reaction was realised by an intramolecular hydrogen-

bonding interaction, depicted in the scheme. In fact, it is perhaps one of the earliest examples of bifunctional covalent and H-bond donor organocatalysis.



Scheme 2. The Hajos-Parrish-Eder-Sauer-Wiechert reaction (1971).

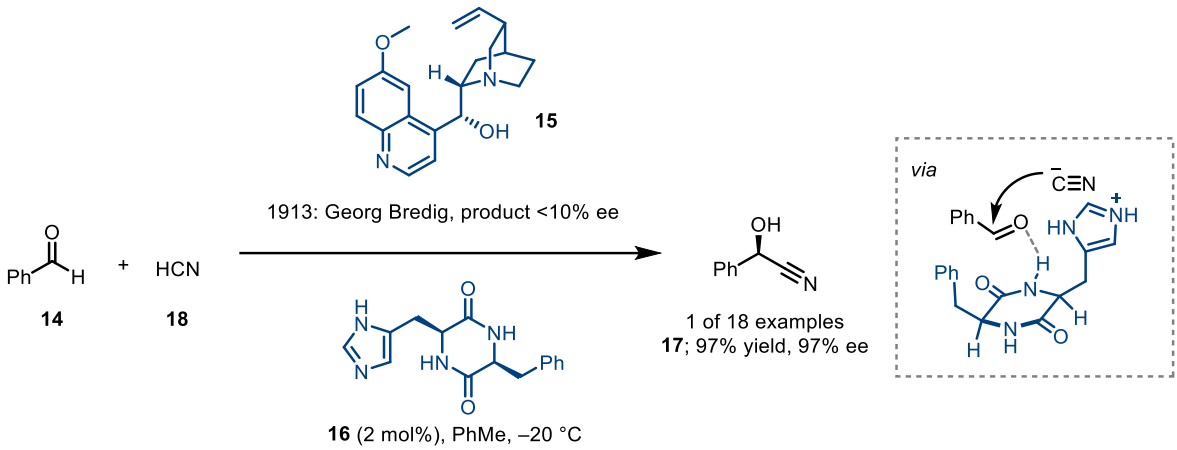
Ten years later, one of the earliest examples of non-covalent bifunctional organocatalysis was reported. Demonstrated by Hiemstra and Wynberg [26] (**Scheme 3**), the enantioselective sulfa Michael addition of aromatic thiols (**10**) to cyclic α,β-unsaturated ketones (**11**) was achieved with sub-stoichiometric amounts of naturally occurring alkaloid cinchonidine (**12**). The author proposed a transition state involving three types of non-covalent interaction to explain the reaction outcome (**Scheme 3**).[26] (1) The hydrogen bonding interaction between the free hydroxyl group of the cinchona alkaloid and the enone – activating the electrophile, (2) the dispersion interaction between the deprotonated thiol anion and cinchonidine's aromatic heterocycle – activating the nucleophile and (3) the ionic interaction between the thiol anion and the ammonium salt – directing the nucleophile.



Scheme 3. Hiemstra & Wynberg's sulfa-Michael addition to enones (1981).

Catalysis governed by non-covalent activation was also investigated in the same year by Inoue on the enantioselective hydrocyanation of benzaldehyde (**14**) [27] (**Scheme 4**). This transformation was known to be catalysed by oxynitrilase in an enantioselective manner although only the (*R*)-isomer of the desired

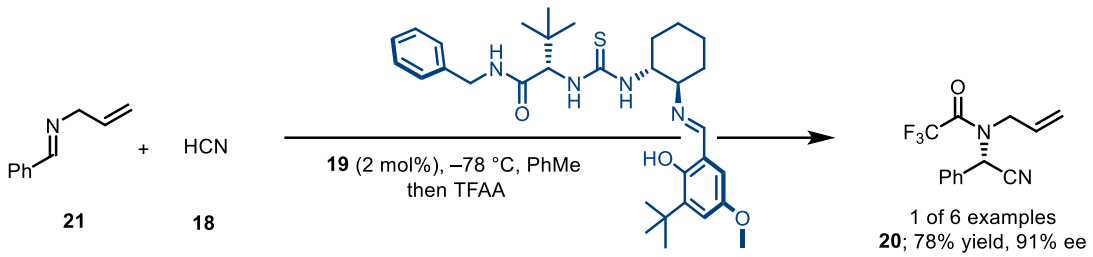
product could be obtained.[27] An organocatalytic version of this reaction was attempted by Bredig in 1913.[28] Quinine (**15**) was used as the catalyst but unfortunately only a very small level of enantioenrichment (<10% ee) was observed. In an effort to obtain better levels of enantiocontrol, Inoue and co-workers developed a novel cyclic diketopiperazine (DKP) catalyst (**16**) (prepared from the condensation of *L*-phenylalanine and *L*-histidine). 2 mol% of this dipeptide successfully delivered the cyanohydrin (**17**) in up to 97% yield and 97% ee. The proposed transition state in the report claimed that the aldehyde substrate fits into the pocket created by the conformationally rigid catalyst *via* H-bonding interactions with the phenyl substituent placed away from the dipeptide. The nucleophilic cyanide group can then attack from the least hindered face. The scope of this reaction was further explored in a follow-up report by the same group in 1990 where aliphatic aldehydes were also found to be compatible with the reaction conditions.[29]



Scheme 4. Inoue's hydrocyanation of benzaldehyde (1981).

Alongside the aforementioned cinchona alkaloids, amino acids and short peptide derived organocatalysts, a new type of catalyst (**19**) bearing a thiourea moiety as the hydrogen bond donor and a Schiff base moiety was proposed by Jacobsen and co-workers in 1998.[30] Its ability to catalyse useful transformations was exemplified by an enantioselective Strecker reaction to afford cyanohydrin (**20**) in 78% yield and 91% ee (**Scheme 5**). The simultaneous activation of both HCN (**18**) and aldimines (**21**) was realised with some nonintuitive synergistic effects demonstrated by the various components of the catalyst. This class of catalyst (with some structural modifications between works) was found to be effective in many

subsequent enantioselective reactions including the addition of HCN to *N*-benzyl imines and ketimines,[31-33] and the addition of phosphites,[34] silyl-ketene acetals,[35] and nitroalkanes[36] to imines.



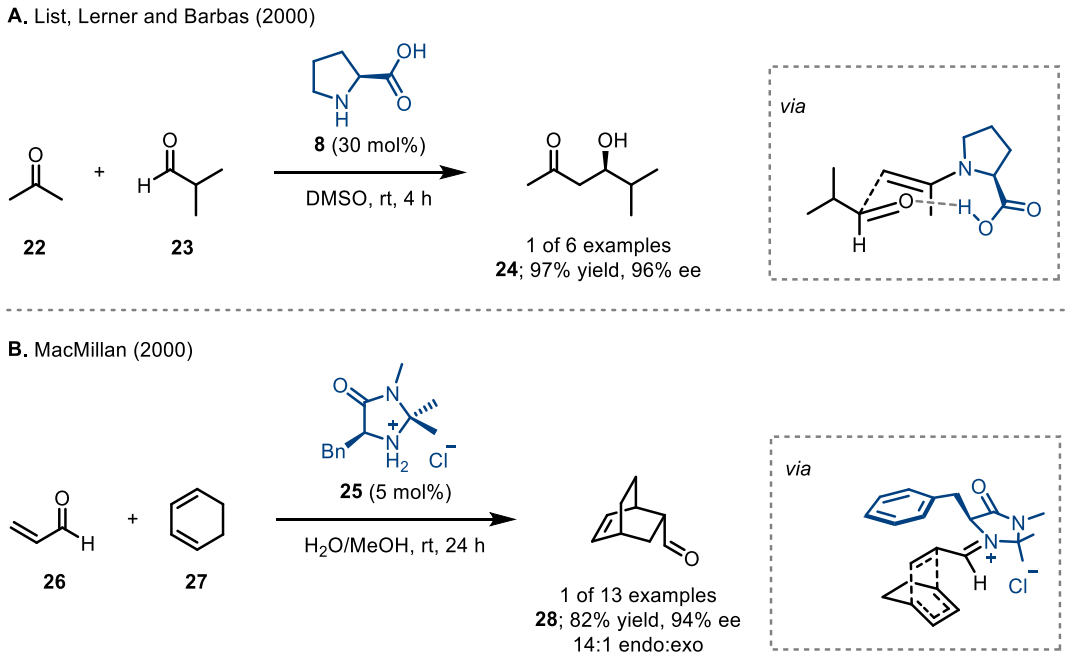
Scheme 5. Jacobsen's enantioselective Strecker reaction (1998).

1.3.2 Organocatalysis in the beginning of 21st century

Despite all the achievements in the 20th century, the field of organocatalysis did not flourish until the beginning of the new millennium (2000) when two landmark works on enamine catalysis and iminium catalysis were published by List, Lerner and Barbas (**Scheme 6A**) and Macmillan (**Scheme 6B**) respectively.

Inspired by the Hajos – Parrish – Eder – Sauer – Wiechert reaction developed in 1971, in 2000 List and co-workers revisited the proline enamine catalysis and applied it to the intermolecular cross-aldol reaction between acetone (**22**) and various *alpha*-branched aldehydes such as **23** or non-enolisable aldehydes such as benzaldehyde **14**.[37] The reaction proceeds *via* condensation of the catalyst and the ketone and a subsequent tautomerisation to an enamine species, thus increasing its nucleophilicity. A nucleophilic attack then occurs between the enamine and aldehyde which is activated and directed *via* a H-bonding interaction with the carboxylic acid residue of proline to afford the cross-aldol product (**24**) in excellent yield and with very high levels of enantioenrichment (up to 97% yield and 96% ee). The transition state of the reaction was believed to proceed *via* Zimmerman-Traxler chair-like transition state – arranged by the enamine species and aldehydes with the bulky *iso*-propyl group occupying a pseudo equatorial position. With proline acting like a micro-aldolase, this work represented the first example of metal-free catalysis on direct intermolecular asymmetric aldol reactions inspiring subsequent enantioselective enamine catalysis.[38]

The first example of highly enantioselective Diels-Alder reaction *via* iminium catalysis was developed by Macmillan and his co-workers in the same year.[39] In their report, the imidazolidinone·HCl catalyst (**25**) underwent an iminium ion forming condensation process with α, β-unsaturated enals (**26**), thus activating the enal by lowering its LUMO energy level towards the cycloaddition by the cyclohexadiene (**27**) – (with a wide range of structural diversity including cyclic (5- and 6-membered rings and heterocycles) and acyclic dienes). This LUMO-lowering strategy was effective even with only 5 mol% of the amine salt and under very mild reaction conditions. The bicyclic aldehyde (**28**) was formed with an excellent yield (82%), enantiocontrol (94%) and high endo : exo selectivity (14 : 1). As indicated by the authors, the high enantioselectivity is proposed to originate from the fact that the vinyl group of the aldehyde is placed away from the *gem*-dimethyl substituent of the catalyst to avoid unfavourable allylic 1,3 interactions. Additionally, the protrusive benzyl group provides steric shielding for the *Si* face of the transition state and allows the cycloaddition to occur from the *Re* face favourably.



Scheme 6. **A.** List, Lerner and Barbas' proline catalysed enantioselective aldol reaction *via* enamine catalysis. **B.** MacMillan's secondary amine catalysed Diels-Alder reaction *via* iminium catalysis.

In this way, the prototype for metal-free enantioselective catalysis had been constructed. The community started to realise the potential of organocatalysis as a complementary approach to transition metal cayalysis and biocatalysis in synthesis. A mass of novel chiral organocatalysts such as chiral phosphoric

acids, phase-transfer ammonium salts and nucleophilic catalyst classes were developed, and with the numerous enantioselective chemical transformations.[40-42] Among the new wave of catalysts being developed, Brønsted base / H-bond donor bifunctional organocatalysts are some of the most successful and most broadly used, and will be further discussed in the remainder of this chapter.

1.4 Tertiary Amine Brønsted Base Bifunctional Organocatalysis

Possessing two types of catalytic sites in the same molecular scaffold, bifunctional metal-free catalysts show increased catalytic activity over the monofunctional ones since they can bring two reaction partners into spacious proximity and provide 'synergistic activation', particularly in activating challenging nucleophiles with high pK_a or electrophiles with low electrophilicity. Among them, the combination of Brønsted base such as tertiary amines and H-bond donor provides impressive outcomes in activating different classes of substrates and organising reaction transition states.[43-46] While the H-bond donor organises and activates the electrophile through non-covalent interactions, the Brønsted basic moiety activates a pro-nucleophile through acid/base equilibria. Representative examples are listed in **Figure 3**.

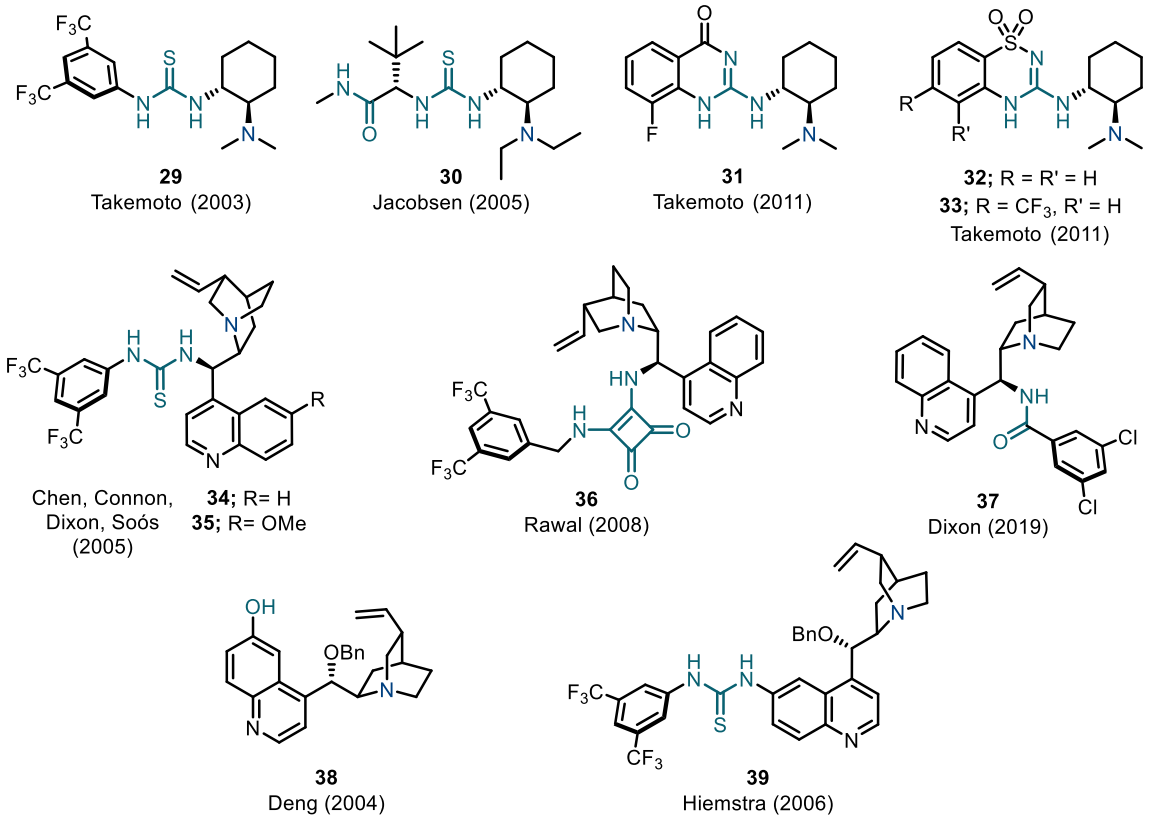


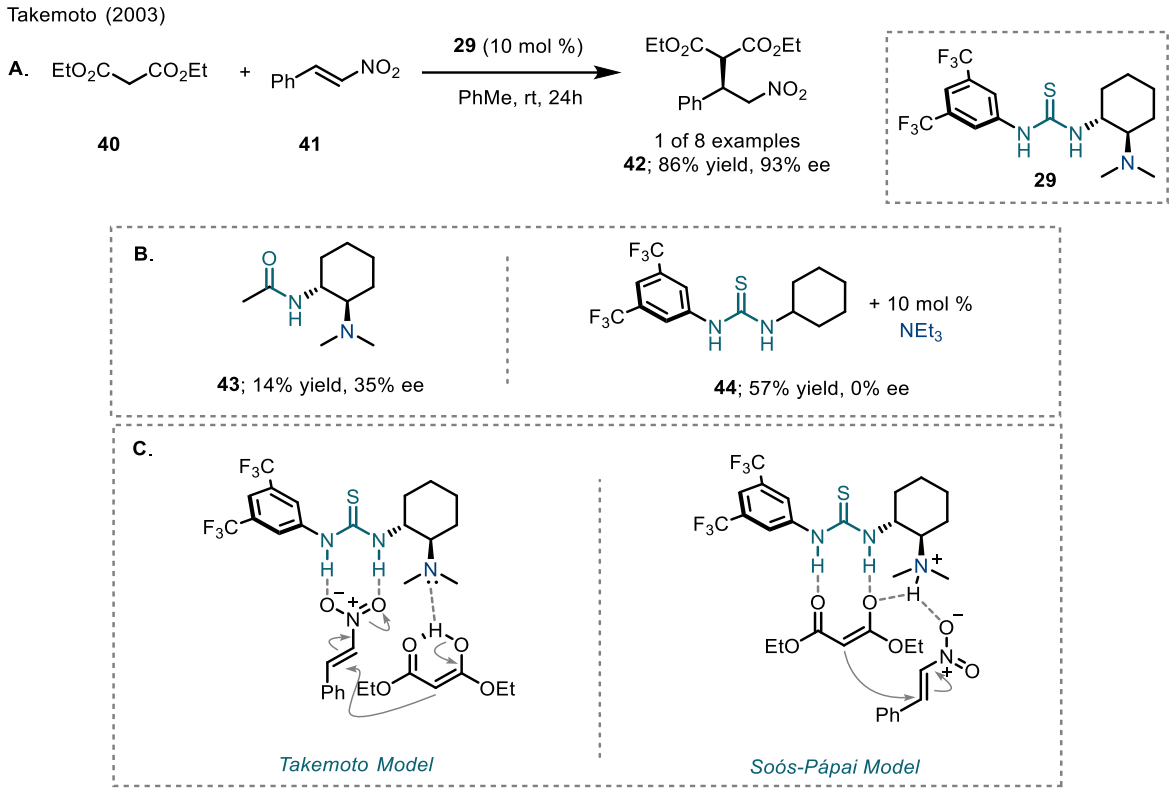
Figure 3. Representative Brønsted base / H-bond donor bifunctional organocatalysts

1.4.1 Merging of Brønsted bases and H-bond donor groups

The first example of bifunctional organocatalyst bearing a highly activated 3,5-$(CF_3)_2C_6H_3$ thiourea as the H-bond donor and a tertiary amine moiety (**29**) was disclosed by Takemoto in 2003 based upon Schreiner's catalyst.[47] Those two key functionalities assembled around a chiral *trans*-diamine backbone were shown to possess very high catalyst activity and enantioselectivity in the Michael addition of malonates (**40**) to nitro-styrenes (**41**) (**Scheme 7A**). The Michael product (**42**) was isolated in 86% yield and 93% ee after 24 hours at room temperature. Two control experiments were conducted to showcase the synergistic effects provided by tethering the tertiary amine Brønsted base and thiourea H-bond donor in the catalyst (**Scheme 7B**). When the thiourea moiety of the catalyst was replaced with an acylated amine H-bond donor (**43**), the reaction yield drastically dropped to 14% and the enantioselectivity decreased to 35% ee. The thiourea (**44**) without a basic site was then attempted together with 10 mol% triethylamine as co-catalyst and as expected only moderate yield (57%) was observed.

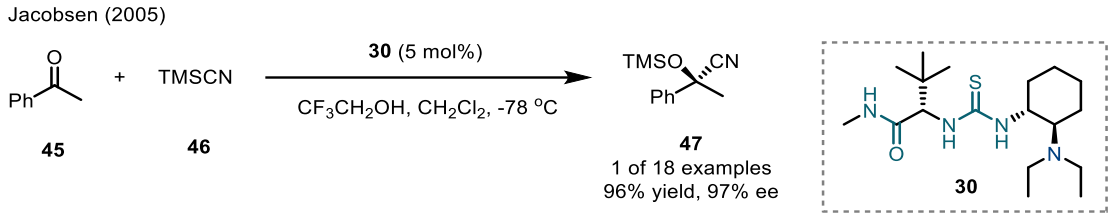
These observations and the origin of enantioselectivity were explained by a transition state model hypothesised by the authors (**Scheme 7C,** left). The nitro-styrenes was bound to the thiourea moiety of the catalyst *via* hydrogen bonding interaction and therefore while the malonate was simultaneously deprotonated by the linked catalyst's dimethylamino moiety. The enantioselectivity can then be explained by the enolate attacking the least sterically hindered face of the olefin. The model also clearly indicates that two activating functionalities existing in a single molecule brings the two substrates into spacious proximity and hence accounts for the enhanced reactivity. Three years later, based on further computational calculations, Soós and Pápai proposed an alternative transition state mechanism whereby the protonated ammonium salt binds the nitro-styrenes and the H-bonding interaction offered by the thiourea occurs with the enol instead [48] (**Scheme 7C**, right). The new model was calculated to be 2.7 kcal/mol more energetically favourable than Takemoto's one while both of them predicted the same enantiomeric outcome of the reaction. As such, it is likely that the actual reaction transition state is more complicated than that has been computed so far. It also indicates that, for reaction transition states involving a Brønsted base / H-bond donor bifunctional organocatalyst, the two models could often both occur simultaneously. Importantly, These works triggered a trend to design novel Brønsted base / H-

bond donor bifunctional organocatalysts for enantioselective synthesis discovery over the coming decades.[43-46]



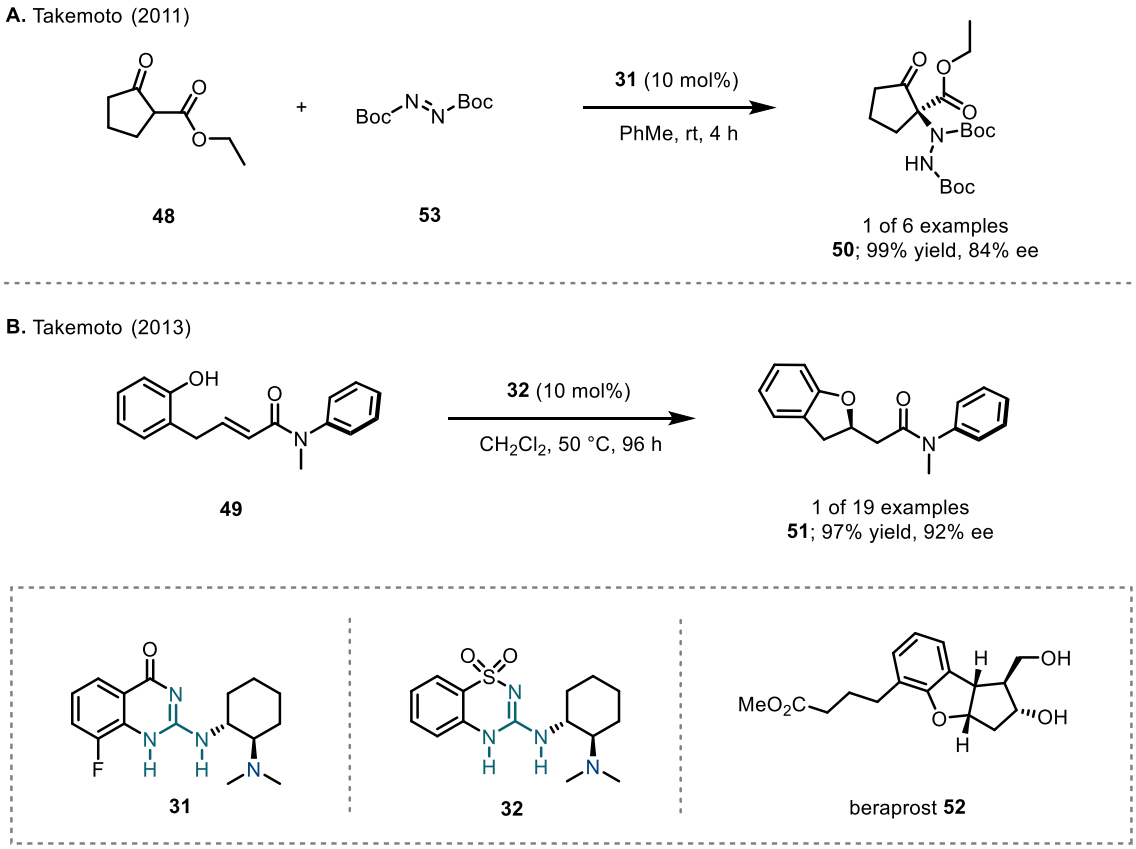
Scheme 7. **A**. Takemoto's enantioselective Michael addition of malonates to nitro-styrenes with a tertiary amine based bifunctional organocatalyst; **B**. Takemoto's investigations on catalysts performance; **C**. Proposed activation modes by Takemoto (left) and Soós and Pápai (right)

Another example of a catalyst merging a Brønsted base and a H-bond donor was Jacobsen's amido-thiourea-tertiary amine catalyst (**30**) bearing two stereo-centres flanking the thiourea, disclosed two years after Takemoto.[49] For the first time, the group derivatised their previous amido-thiourea-Schiff base catalysts by substituting the Schiff base moiety with a more basic tertiary amine Brønsted base. By applying only 5 mol% of this newly designed **30** and stoichiometric amount of trifluoroethanol as additive to generate HCN *in situ*, they managed to deliver a highly enantioselective cyanosilylation of ketones (**45**), affording the cyanosilylation product (**47**) in 96% yield and 97% ee (**Scheme 8**).



Scheme 8. Jacobsen's enantioselective cyanosilylation of ketones with a tertiary amine bifunctional organocatalyst.

In 2011, Takemoto further developed innovative tertiary amine bifunctional organocatalysts (**31** and **32**) [50-53] (**Scheme 9**) bearing a guanidine motif as the H-bond donor. These catalysts incorporate a bridged electron-withdrawing group such as carbonyl or sulfonyl between the guanidine and aryl group of the catalyst to enhance the acidity of the H-bond donor. The authors unveiled their great applicability in useful transformation including enantioselective hydrazination of 1,3-dicarbonyl compound (**48**) (**Scheme 9A**) and enantioselective intramolecular *oxy*-Michael reaction of phenols tethered β-substituted α, β-unsaturated amide (**49**) (**Scheme 9B**).[50 and 52] The hydrazinated product (**50**) and *oxy*-Michael product (**51**) were obtained in good and high enantioselectivity, respectively. Notably, this **32** enabled intramolecular *oxy*-Michael Reaction afforded a key intermediate en route to the synthesis of marketed pharmaceutical beraprost **52**.[53]

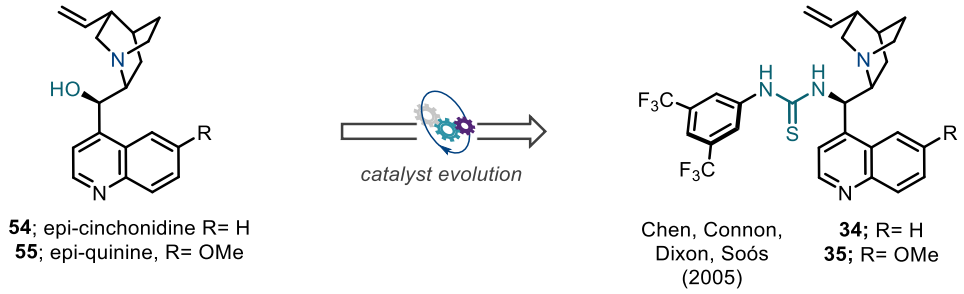


Scheme 9. A. Takemoto's enantioselective hydrazination of 1,3-dicarbonyl compound **48**; **B**. Takemoto's enantioselective intramolecular *oxy*-Michael reaction.

1.4.2 *Cinchona* alkaloid derived bifunctional organocatalysts

With the advancement of the field, the focus shifted towards new creative catalyst designs encompassing alternative H-bond donors, tertiary amines and chiral scaffolds. The derivatisation of naturally abundant alkaloids including quinine, cinchonine, quinidine and cinchonidine provided a pathway towards this end.[54-56] The success of the commercially available alkaloids in enantioselective catalytic chemistry (as described previously in **Chapter 1.3.1**) were believed to come from the strong Brønsted basicity of the quinuclidine cores and the robust chiral environment provided by a rigid molecular architecture. However, using the free hydroxy group as the H-bond donor limited their application to some extent, as it failed to provide adequate and proper organisation for substrates in many cases. Takemoto and Jacobsen's findings of the thiourea H-Bond donor group in the early 2000s promptly gave inspirations for chemists to modify and optimise the parent *Cinchona* alkaloids.[57-59]

Common modifications of *Cinchona* alkaloids involve the free hydroxy group or the quinoline ring. For the former, Chen,[60] Connon,[61] Dixon[62] and Soós[63] independently developed **34** or **35** (**Scheme 10**) in 2005 and found their impressive catalytic capabilities in Michael additions of nitroalkanes or aromatic thiols to numerous electrophiles such as chalcones, unsaturated imides and enones.



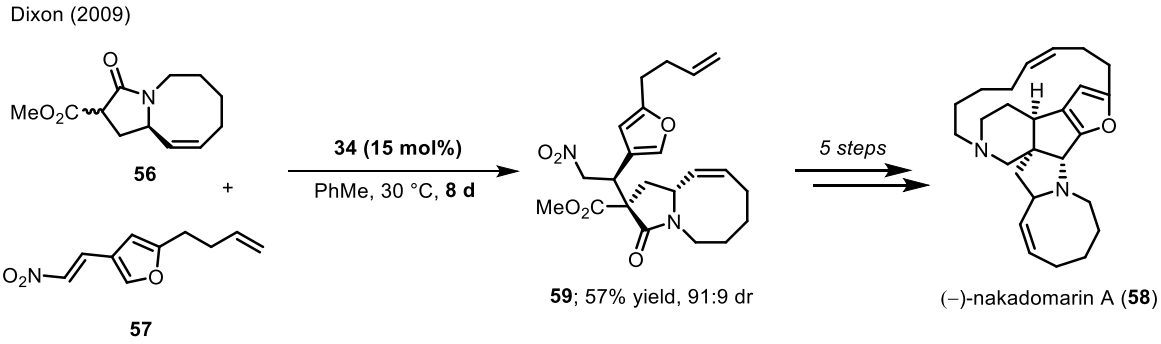
54; epi-cinchonidine R= H
55; epi-quinine, R= OMe

Chen, Connon, Dixon, Soós (2005)

34; R= H
35; R= OMe

Scheme 10. Modifications of *Cinchona* alkaloids to incorporate thiourea H-bond donor group.

The robustness and selectivity of this catalyst class was further exemplified by a diastereoselective addition of malonamide (**56**) to nitro-styrenes (**57**), reported by Dixon and co-workers in 2009 (**Scheme 11**) where more molecular complexities were tolerated and high diastereoselectivity was afforded (91 : 9 d.r.).[64] Demonstrating great applicability in the synthesis of (−)-nakadomarin A (**58**), this report yet revealed some inherent shortcomings which was later found to be quite common in these tertiary amine Brønsted base catalysts including high catalyst loadings (15 mol%) and long reaction time (8 days).



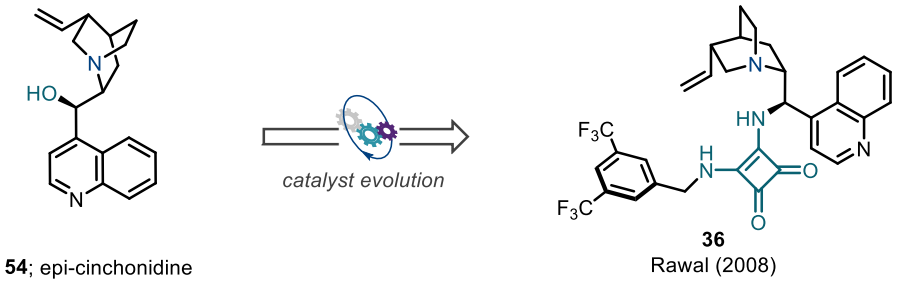
59; 57% yield, 91:9 dr

(−)-nakadomarin A (**58**)

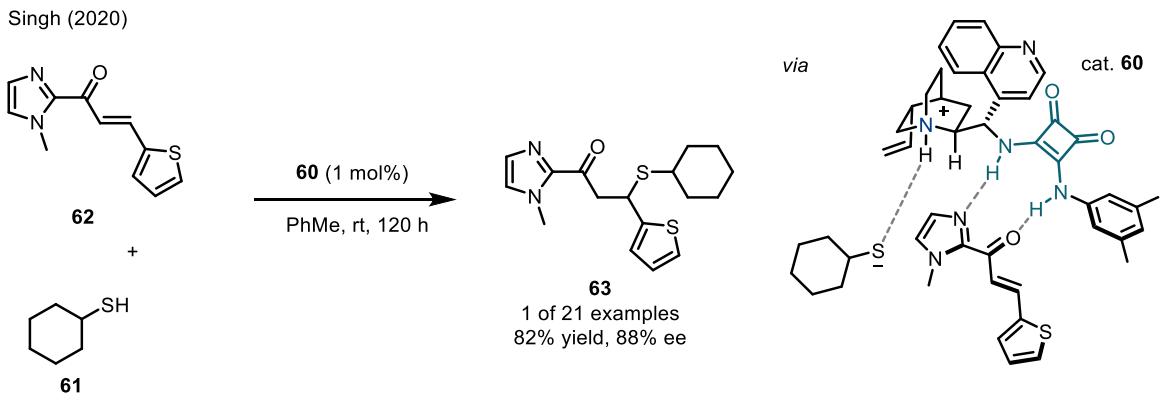
Scheme 11. Dixon's diastereoselective addition of malonamide to nitro-styrenes towards the synthesis of (−)-nakadomarin A with a thiourea based *Cinchona* alkaloid organocatalyst;

In addition to the thiourea / urea, amide [65-66] and squaramide [67-69] modules were also incorporated as a synthetic moiety to replace the alcohol H-bond donor. The resulting bifunctional organocatalysts with

characteristic structure-related activities have functioned remarkably in many useful enantioselective reactions. A pioneered example (**36**) was the one reported by Rawal and co-workers in 2008 (**Scheme 12**), where they innovatively introduce the squaramide to the alkaloid skeleton and found its application in the Michael addition of dione to nitro-styrenes.[70] These catalysts have since become one of the most prominent tools in the organic synthesis community and are still regularly used nowadays. A representative example is the squaramide-based *Cinchona* alkaloid (**60**) catalysed *S* - Michael addition of aliphatic thiols (**61**) to α, β-unsaturated 2-acyl imidazoles (**62**), reported by Singh group in 2020 (**Scheme 13**).[71]



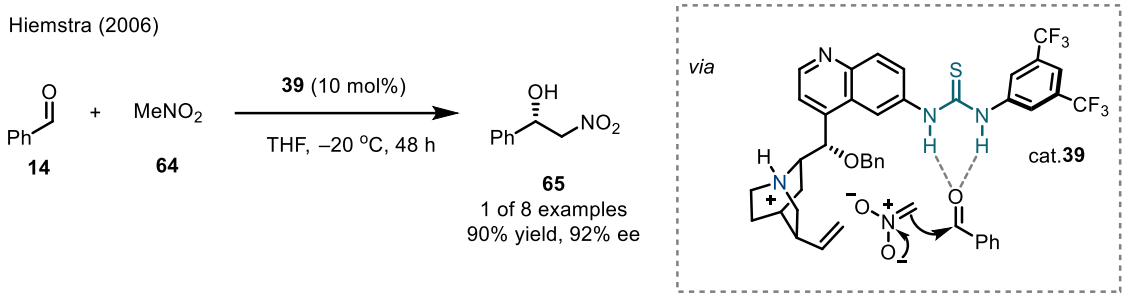
Scheme 12. Modifications of *Cinchona* alkaloids to incorporate squaramide H-bond donor.



Scheme 13. Singh's enantioselective sulfa-Michael addition of aliphatic thiols to α, β-unsaturated 2-acyl imidazoles with a squaramide based *Cinchona* alkaloid organocatalyst.

Modifications to the *Cinchona* alkaloids at the quinoline heterocycle were less common due to the associated synthetic difficulties. Main efforts included the mask of the free hydroxyl group with typically a benzyl group in the parent alkaloids and the relocation of H-bond donor to the quinoline ring. Deng was the first one to adopt this strategy to develop an *O*-benzyl-quinidine (**38**) as an alternative catalyst

for the malonates' enantioselective addition to nitro-styrenes.[72] Two years later, in 2006, Hiemstra and co-workers unveiled a novel quinine-derived organocatalyst (**39**) (prepared by replacing the methoxy group in the quinine with a 3,5-$(CF_3)_2C_6H_3$ thiourea group and masking the native alcohol with a benzyl group) and its application in a highly enantioselective nitro-Henry reaction between aromatic aldehydes (**14**) and nitromethane (**64**) (90% yield, 92% ee) (**Scheme 14**).[73] Although less commonly encountered, this approach serves as an intelligent catalyst design by synthetic chemists contributing to the advancement of organocatalysis.



Scheme 14. Hiemstra's enantioselective nitro-Henry reaction with a thiourea based *Cinchona* alkaloid organocatalyst.

1.4.3 Limitations of the current designs

Despite many impressive applications, tertiary amine Brønsted base bifunctional organocatalysts face some severe limitations. Apart from the aforementioned high catalyst loadings (15 mol%) and long reaction time (8 days)[64] (the diastereoselective addition of malonamide to nitro-styrenes towards the synthesis of (−)-nakadomarin A in **Scheme 11** as a representative example), the other inherent and confessed drawbacks of these catalysts is the relatively narrow range of pronucleophiles that they can activate.[74] More specifically, only pronucleophiles with pK$_a$ value lower than 16.0 (in DMSO) affording corresponding conjugate bases of moderate nucleophilicity are well established.[46, 74] With pK$_a$ of pro-nucleophiles increasing, performance of these catalysts drops drastically indicating insufficient nucleophile activation and precluding access to attractive moieties (such as aliphatic thiols, amides and alcohols (**Figure 4**).[75] A common solution relies on the use of highly activated and non-ubiquitous electrophiles partners including enals, enones, imines, nitro-olefins (**Figure 5**) [76] and reactive carboxylic

acid derivatives (*N*-acyl pyrazoles or aryl esters for example).[77-79] Nevertheless, in a manner akin to diastereoselective synthesis with chiral auxiliary, not only are these approaches inherently of low atom economy, but require extra synthetic steps for the introduction and cleavage of the activating groups.

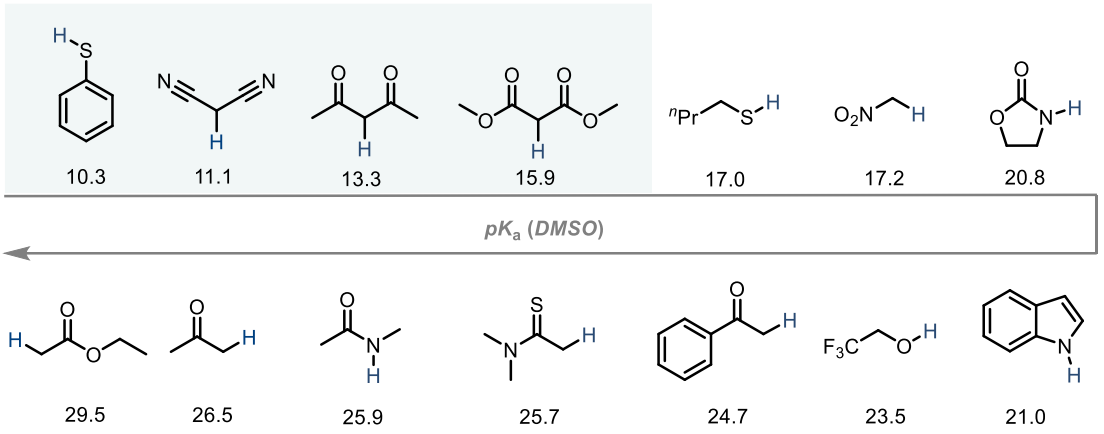


Figure 4. pK_a scale of common pro-nucleophiles in DMSO.

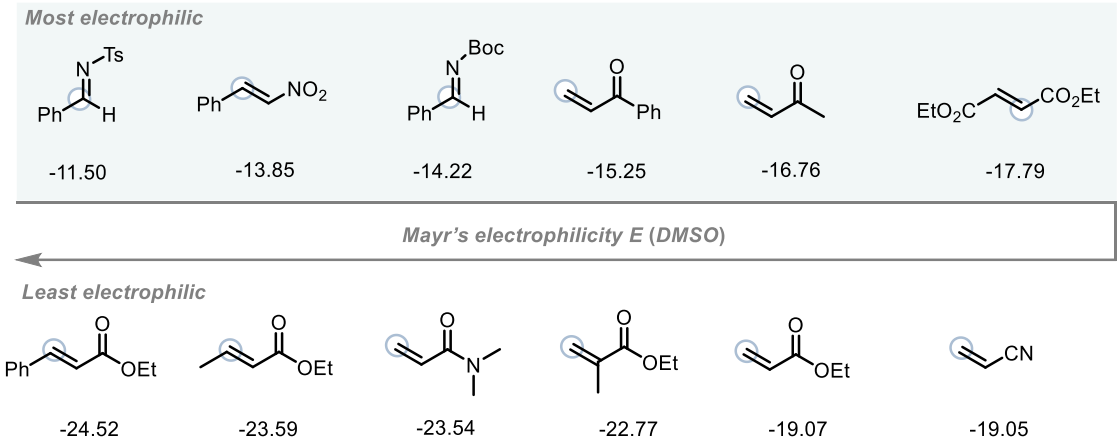


Figure 5. Mayr's electrophilicity scale *E* of common electrophiles in DMSO.

When compared to modifying reaction substrates to improve reaction outcomes, rational design to improve catalyst performance would provide a more general and elegant approach. To this end, incorporating Brønsted superbasic moieties as substitutes for tertiary amines were introduced in an effort to provide enhanced nucleophile activation and thus broaden their applicability in enantioselective organic synthesis. [80]

1.5 Superbasic Bifunctional Organocatalysis

1.5.1 Superbases definitions

Among the most acceptable definition for the term 'superbase' in organic chemistry is the one from Ishikawa and co-workers where they assign this term to encompass any compound with a pK_{BH^+} value higher than that of Proton-sponge® (18.6 in MeCN, 7.5 in DMSO).[80] **Figure 6** shows some representative organosuperbases with their pK_{BH^+} values in acetonitrile.[81] The basicity of organic compounds is typically related to how well the positive charge of the corresponding conjugated acid can be delocalised (i.e. the number of isoelectronic forms after protonation). Compared to tertiary amines, superbases (including guanidines,[82, 83] cyclopropeneimines[84, 85] and phosphazenes [86, 87]) normally have extra *N* atoms and atomic lone pairs to stabilise the positive charge after protonation and therefore display enhanced basicity. **Figure 7** demonstrates these moieties' installation in some representative bifunctional organocatalysts which will be showcased individually in **Chapter 1.5.2** to **1.6.3**.

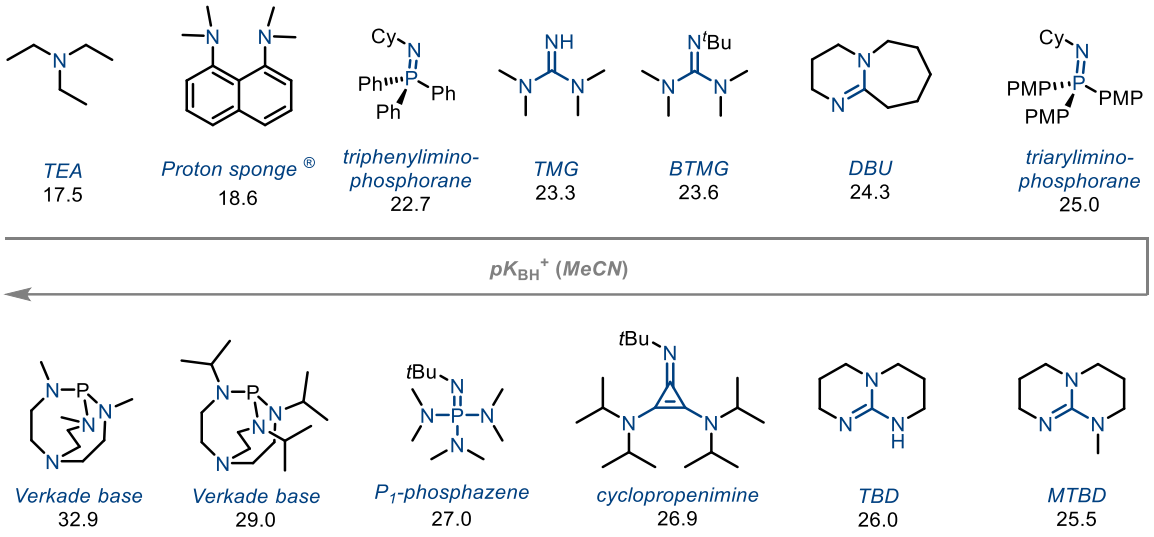


Figure 6. pK_{BH^+} scale of representative organosuperbases in MeCN.

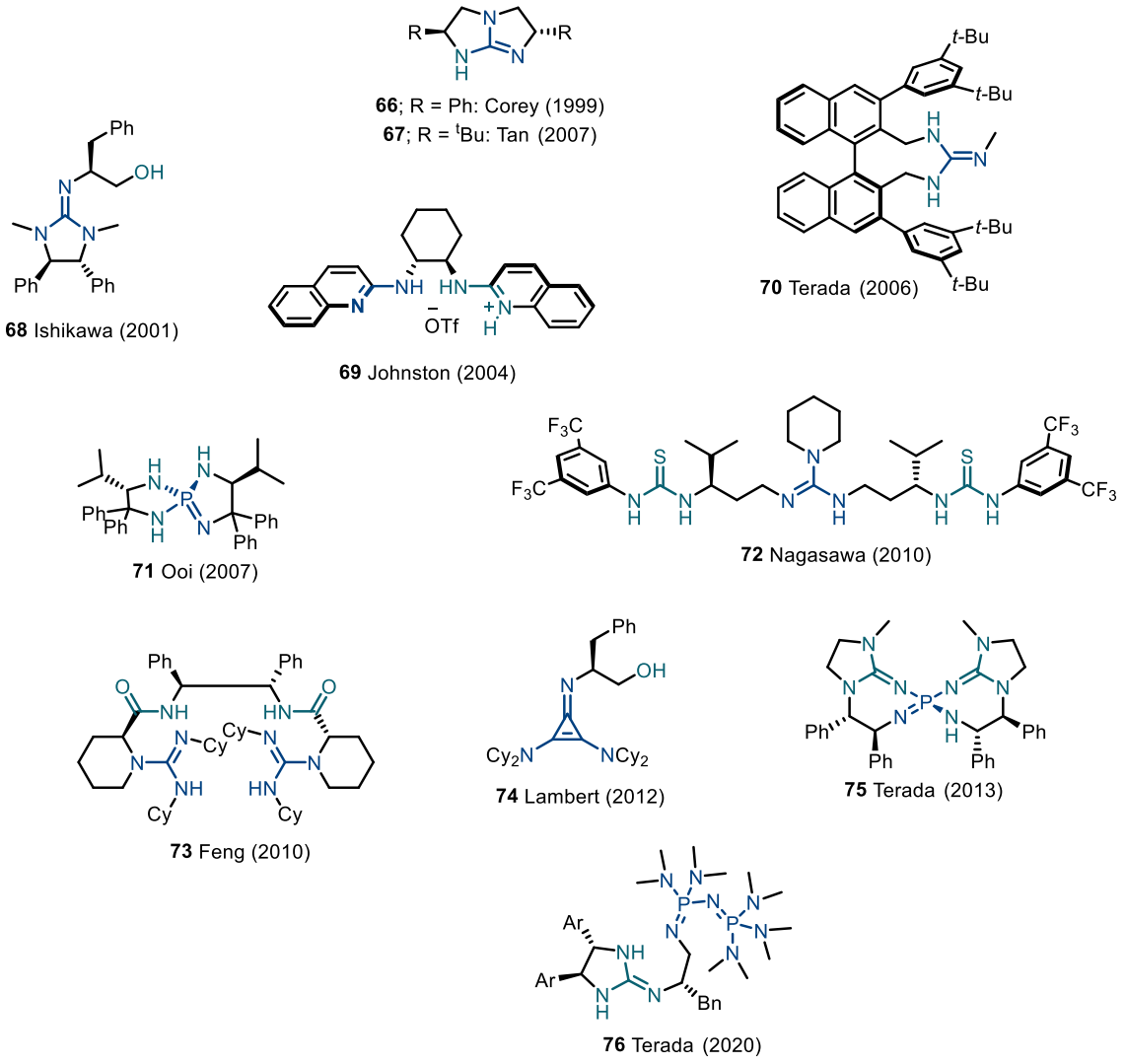
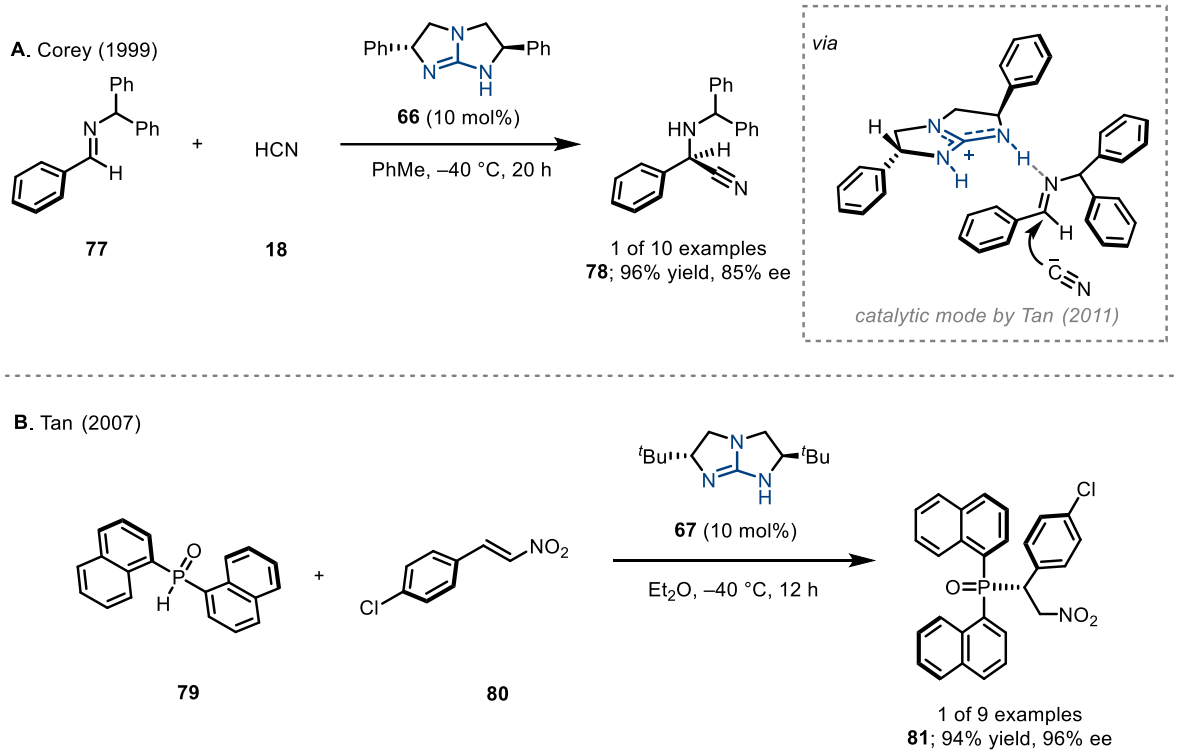


Figure 7. Representative superbasic bifunctional organocatalysts

1.5.2 Chiral guanidines

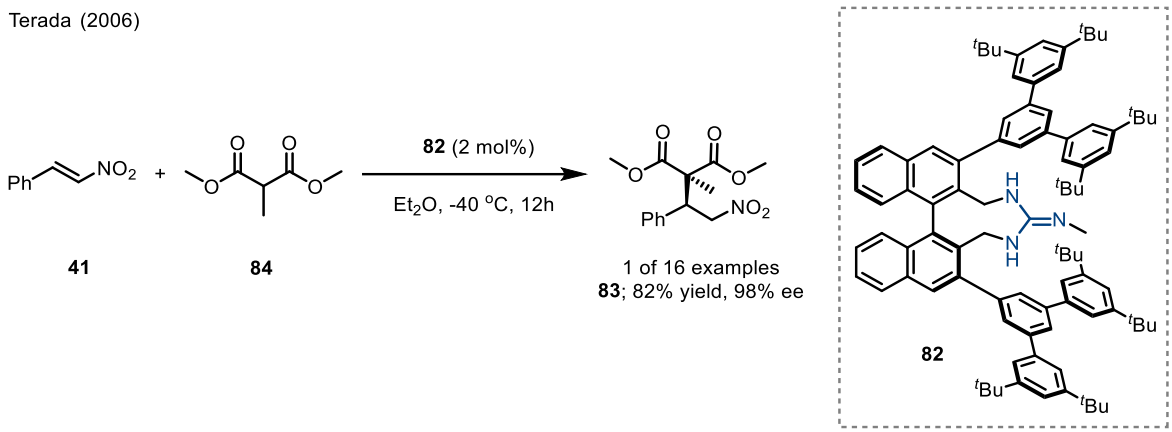
One of the earliest examples of superbasic bifunctional organocatalysis can be traced back to Corey in 1999 when his lab developed a chiral bicyclic C_2-symmetric guanidine catalysts (**66**) for the enantioselective Strecker reaction of hydrogen cyanide (**18**) to aldimines (**77**) [88] (**Scheme 15A**). The desired Strecker product (**78**) was obtained in 96% yield and 85% ee under mild condition (–40 °C). The transition state of this transformation was not clear until a report by Tan in 2011, suggesting that the guanidinium cation resulting from the deprotonation of the hydrogen cyanide can serve as a hydrogen bond donor to guide the nucleophilic attack.[89] Subsequent research on this catalyst system by Tan and co-workers in 2007 further demonstrated its applicability and that the catalyst basicity can be adjusted

by modifying the steric and electronic properties of the two flanking substituents. This fact was demonstrated by their enantioselective Michael addition of secondary phosphine oxides (**79**) to nitro-styrenes (**80**) (**Scheme 15B**).[90]



Scheme 15. **A**. Corey's enantioselective Strecker reaction with a chiral C_2-symmetric guanidine as catalyst; **B**. Tan's enantioselective Michael addition of secondary phosphine oxides to nitro-styrenes.

Seven years after Corey's innovation in guanidine superbasic organocatalysis, in 2006, Terada incorporated the guanidine moiety into an axially chiral binaphthyl backbone bearing aromatic substituents at the 3, 3-positions of the binaphthyl ring.[91] This new class of guanidine organocatalyst (**82**) performed impressively in the enantioselective Michael addition of 1, 3-dicarbonyl compounds to a wide range of conjugated nitroalkenes (**41**) affording a series of chiral nitroalkanes (**83**) of synthetic and medicinal interest in excellent yield (82% yield) and enantioselectivity (98% ee) (**Scheme 16**). This massive catalyst was compatible with sterically hindered and less acidic α-substituted malonate (**84**) and can be quantitatively recovered (96%) as the HCl salt and reused.

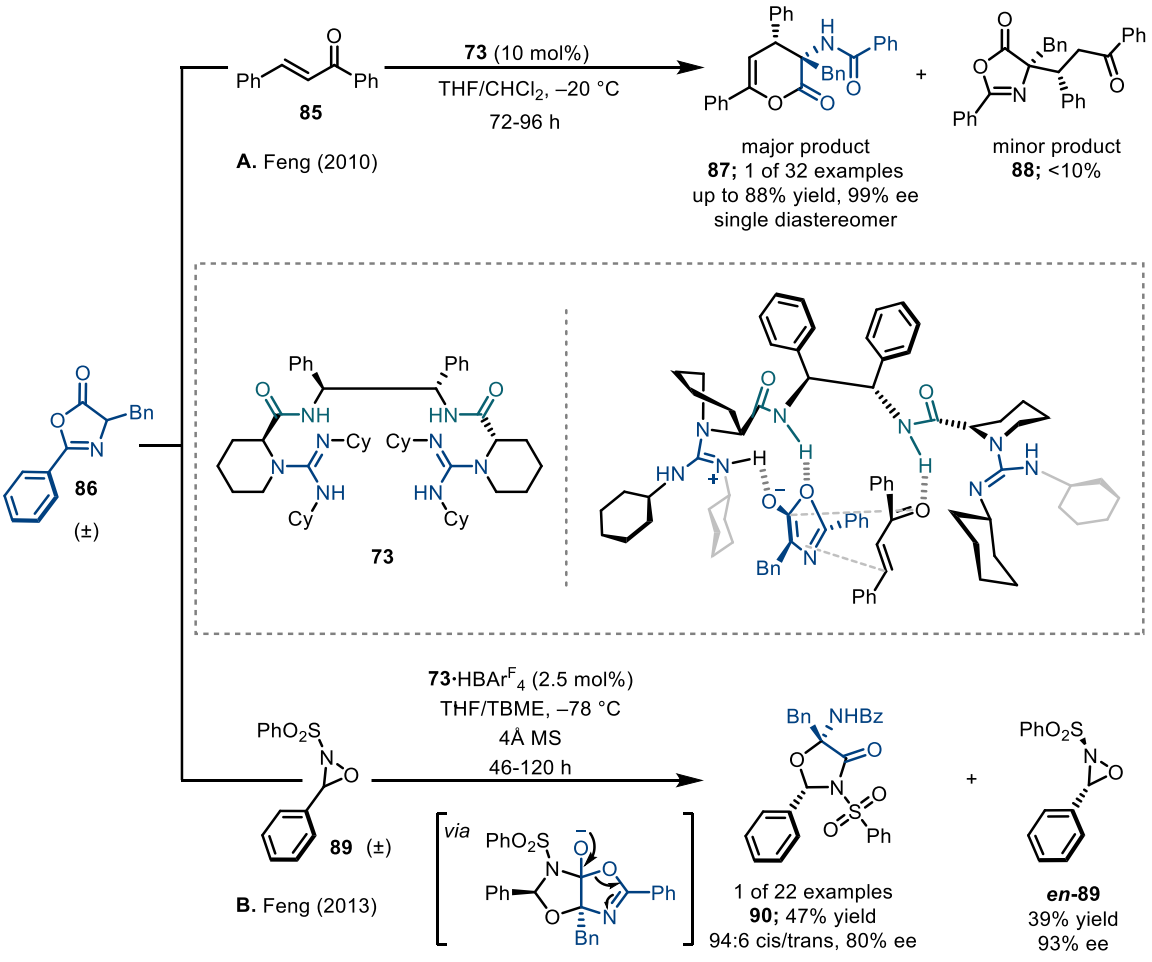


Scheme 16. Terada's enantioselective Michael addition of 1,3-dicarbonyl compounds to nitro-styrenes with a guanidine organocatalyst incorporating an axially chiral binaphthyl backbone.

In 2010, a novel class of C_2-symmetric and easily tuneable chiral superbasic bifunctional organocatalyst (**73**) was developed by Feng.[92] For the first time, Feng and co-workers combined guanidines with amide moieties as H-bond donors in the catalyst scaffold which was found to have impressive application on the enantioselective inverse-electron-demand hetero-Diels-Alder (IEDDA) reaction of chalcones (**85**) and azlactones (**86**) (**Scheme 17A**). The major product (up to 88% yield) of the transformation was a γ, δ-unsaturated δ-lactone (**87**) with α-quaternary-β-tertiary stereo-centres in up to 99% ee while less than 10% of the Michael addition product (**88**) was additionally obtained. Mechanistically, as demonstrated in **Scheme 17** middle right, one of the amide moieties of the catalyst binds to the azlactone *via* a hydrogen bond interaction lowering the azlactone's LUMO energy while the other amide simultaneously activates the chalcones in the same manner. The protonated form of one of the guanidine moieties provides recognition for the enolised azlactone while the other guanidine sterically blocks the top face of the chalcone. The network of intermolecular hydrogen bond interactions within the chiral environment induced by the catalyst's backbone allowed the enolised azlactone to attack almost exclusively from the *Re* face of the chalcone and thus provided excellent stereo-induction.

Further research by the same group was conducted in 2013 to get deeper insight of the workings of this bifunctional catalyst (**Scheme 17B**).[93] The work featured the kinetic resolution of racemic oxaziridines (**89**) by applying the mono $HBAr^F_4$ salt of catalyst **73** delivering enantioenriched oxazolin-4-ones (**90**) in 47% yield / 80% ee and enantioenriched oxaziridines (*en*-84) in 39% yield / 93% ee. The racemic

azlactone substrate can undergo a fast epimerisation process while the *R*-azlactone reacts preferentially with *S*-oxaziridine as a consequence of matched / mismatched substrate-catalyst interactions exerted by **73**·HBAr$^{F}_{4}$. Further studies on the catalyst also showed that free-base bis-guanidine catalyst **73** gave rise to a racemic product while the catalyst HBAr$^{F}_{4}$ double salt failed to deliver any detectable product. Moreover, the activation mode was found to be that the free-guanidine activated the azlactone (**86**) and the guanidinium cation could preferentially recognise and activate one enantiomer of the oxaziridine (**89**). Notably, this is one of the very rare example of triple diastereoselection where three chiral species (racemic azlactone, racemic oxaziridine, and chiral catalyst) were involved and one new stereogenic unit was formed in the transformation.

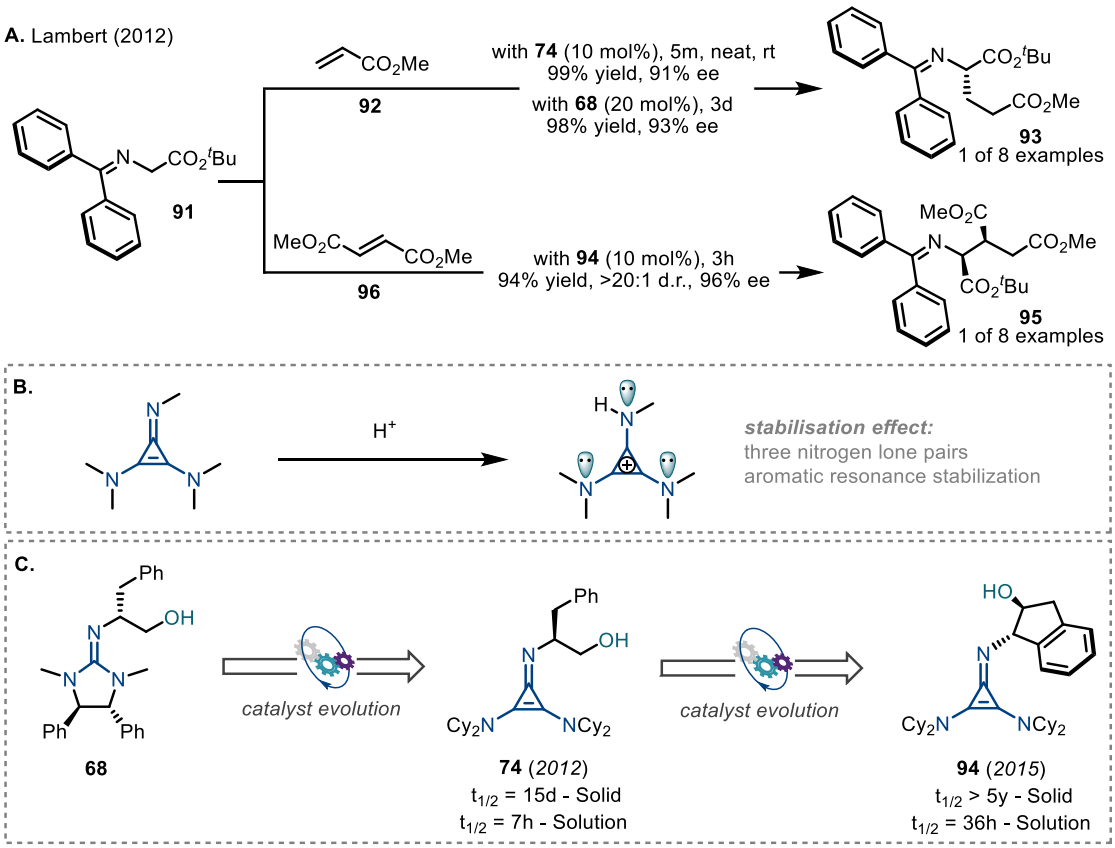


Scheme 17. **A.** Feng's enantioselective inverse-electron-demand hetero-Diels–Alder reaction of chalcones and azlactones with a chiral C_2-symmetric guanidine as catalyst; **B.** Feng's kinetic resolution of oxaziridines with a chiral C_2-symmetric guanidine as catalyst.

1.5.3 Chiral cyclopropenimines

Another example of chiral guanidine bifunctional organocatalysis was reported by Kobayashi and co-workers on the enantioselective Mannich reaction of fluorenone imines with Ishikawa's guanidine-based catalyst (**68**).[94, 95] This catalyst's application to the enantioselective Michael addition of glycine imines (**91**) to acrylate esters (**92**) however suffered from long reaction time (3 days) and a high catalyst loading (20 mol%), revealed by Lambert (**Scheme 18A** top). The authors also hypothesised that the slow reaction rate of this Brønsted base catalysed transformation originates from the inadequate basicity of the catalyst. In designing a novel organocatalyst with stronger Brønsted basicity, the Lambert group considered incorporating cyclopropenimine moiety.[96, 97] The cyclopropenimine species demonstrates a higher basicity than its analogous guanidine mainly because upon protonation of the imino nitrogen, the resulting 2π-electron cyclopropenium ion provides extra aromatic resonance stabilisation as the smallest Hückel's rule-followed ring system (**Scheme 18B**).[84] The combination of tetracyclohexyl cyclopropenimine with an aliphatic alcohol afforded the first chiral cyclopropenimine bifunctional organocatalyst (**74**), reported in 2012 by Lambert.[84, 98] The enhancement of this catalyst over its guanidine analogue was displayed in the same Michael addition (**Scheme 18A** top) where only 10 mol% of **74** was required to deliver the Michael product **93** in 99% yield and 91% ee in 5 mins under neat condition at room temperature.

However, just like other *N*-abundant organosuperbases, **74** has a relatively short experimental half-life (15 days in solid state and 7 hours in solution) which limits its applicability in both laboratory and industrial settings. NMR Analysis unveiled that the catalyst decomposition is due to the rearrangement to an inactive oxazoline.[99] Refinement of the catalyst structure by the same group led to the development of **94** in 2015, successfully lengthening the catalyst half-life to 36 hours in solution and greater than 5 years in the solid state (**Scheme 18C**).[99] The high catalytic efficiency of this 2nd generation cyclopropenimine was demonstrated by its application in a similar reaction to afford Michael adducts (**95**) in excellent yield as well as enantio- and dia-stereoselectivity (**Scheme 18A** bottom).



Scheme 18. **A.** Lambert's enantioselective Michael addition of glycine imines to acrylate esters with a chiral cyclopropenimine catalyst; **B.** Protonation of cyclopropenimine; **C.** Catalyst evolution.

1.5.4 Chiral phosphazenes

Another significant class of bifunctional organosuperbase is the chiral phosphazene, a P(V) species substituted by three amines and one imine group, firstly developed in 1985 by Schwesinger.[100] These molecules are regarded as ones of the strongest non-ionic bases (**Figure 8**) and their basicities can be enhanced by replacement of amine groups with other phosphazene units.[101, 102] This fact is exemplified by the fully substituted ^{t}Bu-P$_4$-phosphazene[I] (**97**) (pK$_{BH^+}$ of 42.7 in MeCN) being much more basic than the P$_1$-phosphazene (**98**) (pK$_{BH^+}$ of 27.0 in MeCN). With such high basicity, the chiral phosphazenes are seen as competitive candidates in the enantioselective organocatalysis field, especially when activating challengingly high pK$_a$ pronucleophiles.

[I] The phosphazene order is determined by the number of phosphorous atoms in the molecule and P$_7$ is the known highest order thus far.[103]

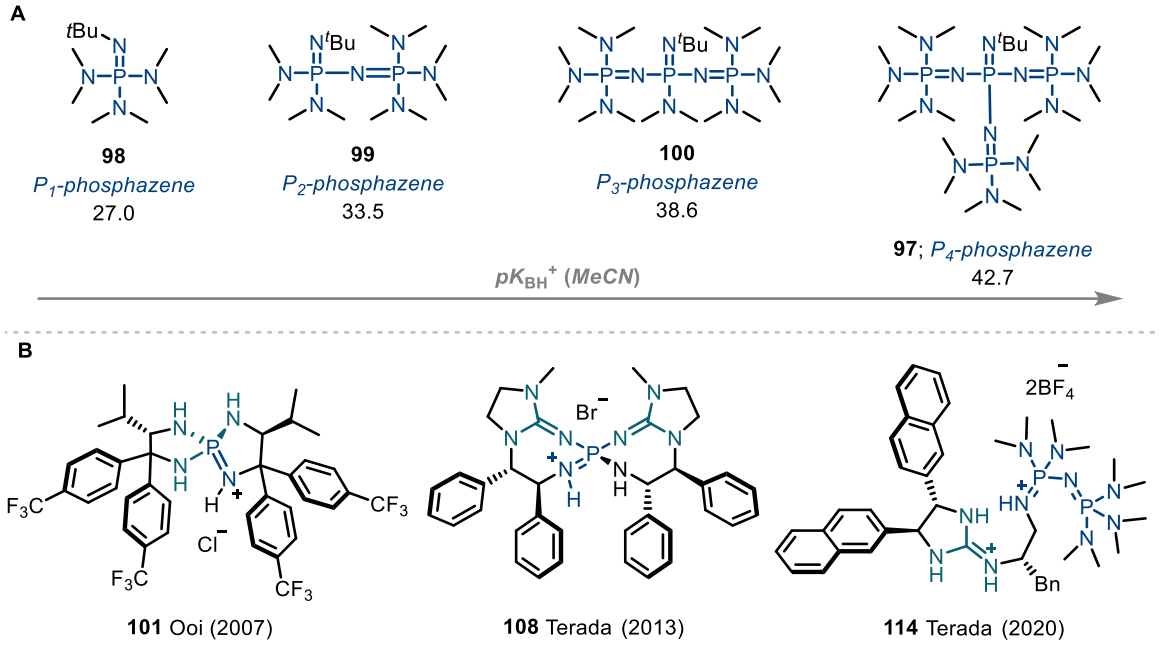
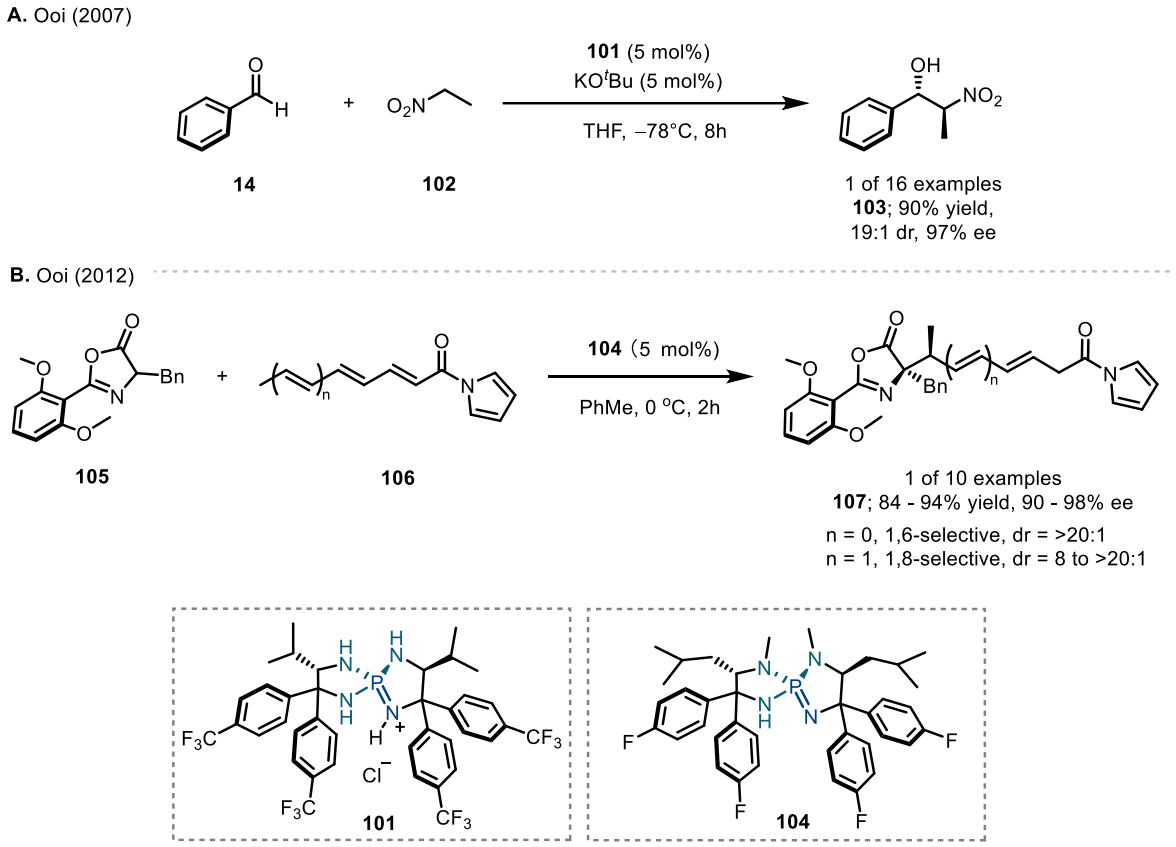


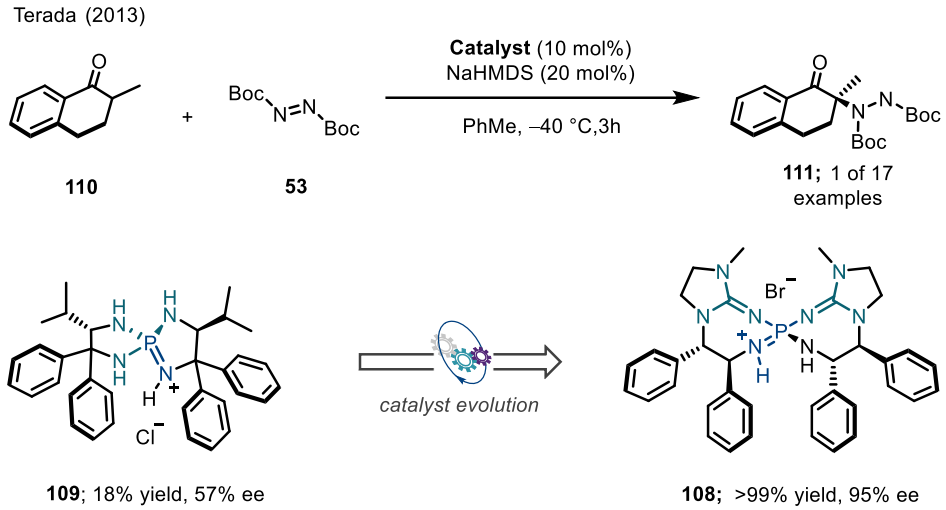
Figure 8. **A.** pK_{BH^+} scale of representative achiral phosphazenes in MeCN; **B.** Representative chiral phosphazenes

They were however not reported until 2007 when Ooi demonstrated the first example of a chiral P_1-spirocyclic structure (**101**) (prepared from a *L*-valine-derived diamine scaffold and PCl_5) to catalyse the enantioselective Henry reaction of benzaldehyde (**14**) and nitroethane (**102**) (**Scheme 19A**).[104] α-Substituted benzyl alcohol (**103**) was obtained in excellent yield (90%), and both enantio- (97%) and diastereoselectivity (19:1) with the new superbasic catalyst. Notably, this chiral phosphazene was applied in its HCl salt form to address problems with stability upon storage and difficulties in purification of the freebase. An equal amount of KO*t*Bu was required to release the active superbasic phosphazene *in situ*. Strong ion-pair hydrogen-bond interactions between the nitroethane and the protonated phosphonium catalyst were proposed to be the origin of the high stereo-induction, hypothesised by the authors first and computationally verified by Paton and co-worker later.[105] In 2012, the same group unveiled similar structured free base triaminoiminophosphorane (**104**) and its application in the diastereo- and enantioselective 1,6 conjugate addition of azlactones (**105**) to δ-substituted dienyl *N*-acylpyrroles (**106**) (**Scheme 19B**).[106] The transformation was later extended to a rare example of enantioselective 1,8-conjugate addition. Methylation of two free amine groups in the basic module were potentially the reason for its higher stability than **101**.



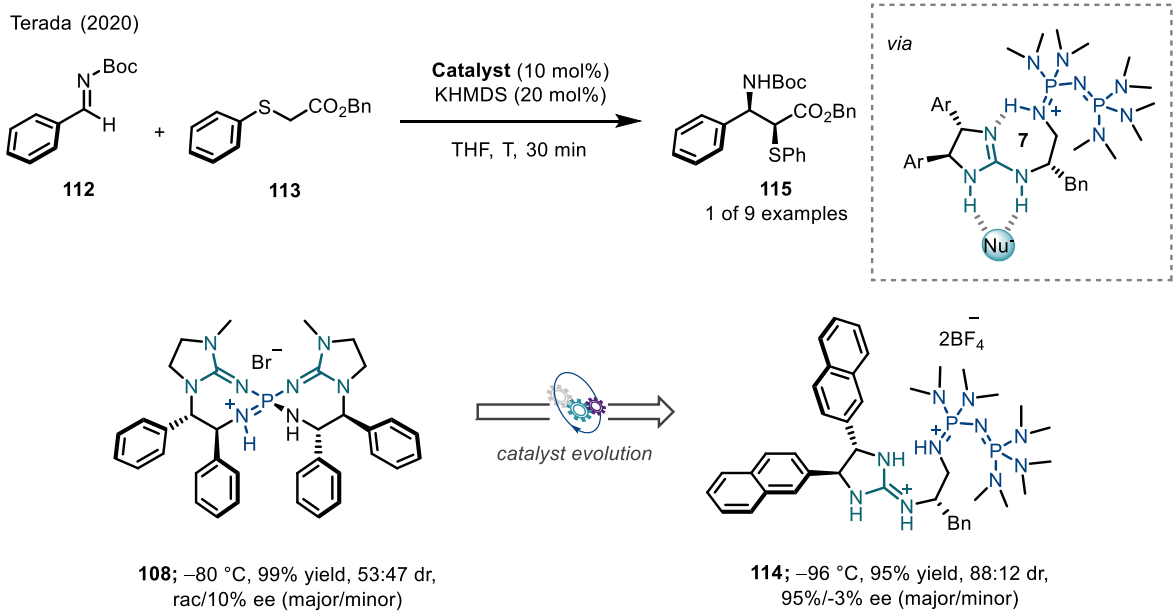
Scheme 19. **A.** Ooi's enantioselective Henry reaction with a chiral phosphazene organocatalyst; **B.** Ooi's enantioselective 1,6- and 1,8-conjugate addition reactions with a chiral phosphazene organocatalyst.

Inspired by Kolomeitsev and Leito's work,[107] Terada modified Ooi's chiral phosphazene scaffolds to a new organosuperbase (**108**) featuring two additional guanidine units around the central P(V) in 2013.[108, 109] The combination of three superbasic moieties indeed gave rise to the most basic chiral Brønsted base catalyst at the time. The superior catalytic efficacy of **108** was showcased in an enantioselective amination reaction of high pK_a tetralone (**110**) with di-*tert*-butyl azodicarboxylate (**53**) as the aminating reagent (**Scheme 20**).[108] While catalysing the reaction in a highly efficient and enantioselective manner (>99% yield and 95% ee), its competitor **109** with a mono- phosphazene unit under identical reaction condition only delivered the aminated products **111** in 18% yield and 57% ee. The versatility of this catalyst class was further displayed by a great number of challenging enantioselective transformations including Mannich reactions with 2-alkyl thionolactones,[110] 2-benzylpyridine *N*-oxides[111] or β,γ-epoxysulfones[112] and a hydrophosphinylation reaction of 1,1-vinyl azaheterocycle N-oxides.[113]



Scheme 20. Terada's enantioselective amination of tetralone with a chiral phosphazene organocatalyst.

Yet, **108** was incapable of imparting high levels of enantioselectivity in a Mannich-type reaction between **112** and high pK$_a$ α-phenylthioacetates (**113**) (pK$_a$ = 21.4 in DMSO), where high yield but only poor diastereoselectivities (53 : 47 dr / rac / 10% ee) were obtained (**Scheme 21**).[114] The demonstration of a new chiral superbase **114** featuring a P$_2$-phosphazene / guanidine scaffold by Terada in 2020 provided a solution to this (88 : 12 dr / 95% ee / -3% ee).[114] It is notable that before this, phosphazene catalysts were typically restricted to the P$_1$ type. The two basic units are linked in the way that a rigid 7-membered ring can be formed *via* intramolecular H-bonding interaction upon deprotonation of the pro-nucleophile. Moreover, the uncovered guanidinium salt can organise and activate substrates *via* an intermolecular H-bonding interaction. The authors also demonstrated the use of a homologous catalyst incorporating a P$_3$ base in the Mannich-type reaction of α-phenylthioacetamide which, whilst promising, only delivered the desired adduct **115** in 58% yield and with modest levels of enantio- and diastereoselectivity.



Scheme 21. Terada's enantioselective Mannich reaction of α-phenylthioacetates with a chiral phosphazene organocatalyst.

1.5.5 Limitations of the current designs

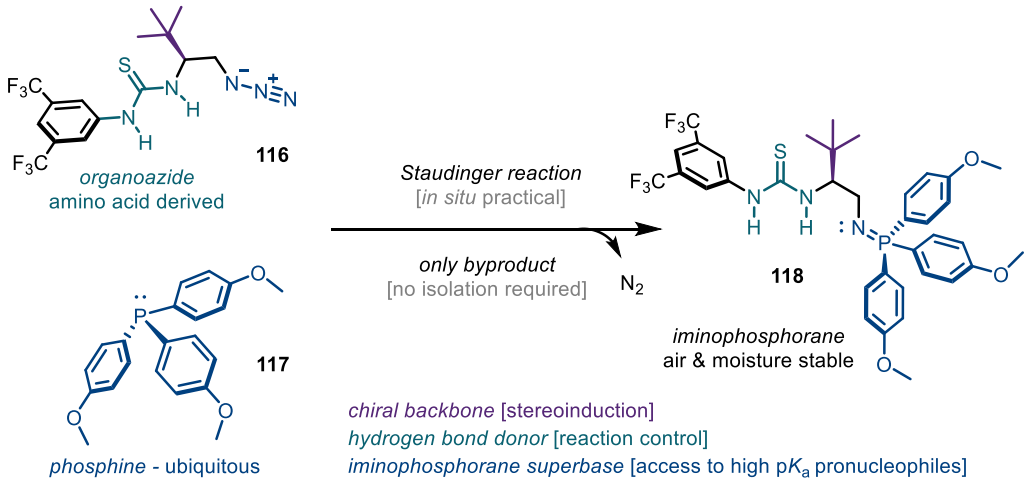
Compared to tertiary amine based bifunctional organocatalysts, these chiral organosuperbases including guanidines, cyclopropeneimines and phosphazenes have indeed managed to activate challenging pronucleophiles with a broader range of pK_a values and thus enabled a huge number of new synthetic methodologies.[115-117] The low basicity-related limitations in catalytic enantioselective synthesis has thus been largely overcome. Yet, their use as commonplace catalysts in organic chemistry is obstructed by their challenging syntheses as well as lack of modularity. Moreover, strongly basic modules such as cyclopropenamines and phosphazines often suffer from issue in handling and storage. Converting such catalysts to their inorganic acid salts form can address this problem occasionally. One example is that the half-life of Lambert's cyclopropenamine catalyst could be extended from 15 days to 5 years upon HCl salt formation.[99] This strategy however demands additional stoichiometric quantity of alkali metal (such as LiHMDS) as the neutralised base to release the active organocatalyst *in situ*.

1.6 Bifunctional Iminophosphorane Organocatalysis

1.6.1 Development of concepts of BIMPs

With the aim of developing a catalyst class that can display both adequate pronucleophile activation and high level of tunability and modularity simultaneously, Dixon and co-workers introduced a fundamentally innovative concept in enantioselective organocatalysis: the combination of H bond donor (such as thiourea and amide) and iminophosphorane fundamentally i.e. bifunctional iminophosphoranes (BIMPs).[118] Triarylphosphine-derived iminophosphorane was found to have a comparable basicity (pK$_{BH^+}$ = 22.7 – 25 in MeCN, firstly measured by Dixon and co-workers[119]) to common achiral organosuperbases such as DBU and TBD and thus is an excellent potential candidate in enantioselective Brønsted superbase catalysis. However, iminophosphoranes are typically thermally unstable and prone to hydrolysis. Therefore, they are normally encountered as intermediates in the synthesis of primary amines from azides *via* Staudinger reduction reaction.[120, 121] Organic chemists would normally not expect the isolation of these labile species and use them as building blocks or catalysts. Dixon group, however, surprisedly found that BIMPs are actually highly air- / moisture-stable and can be isolated and stored for over two years at −20 °C.[122] A potential explanation for this anomaly is the stabilisation of the triaryl-iminophosphorane functionality by an intramolecular hydrogen bonding interaction offered by the adjacent H-bond donor group.

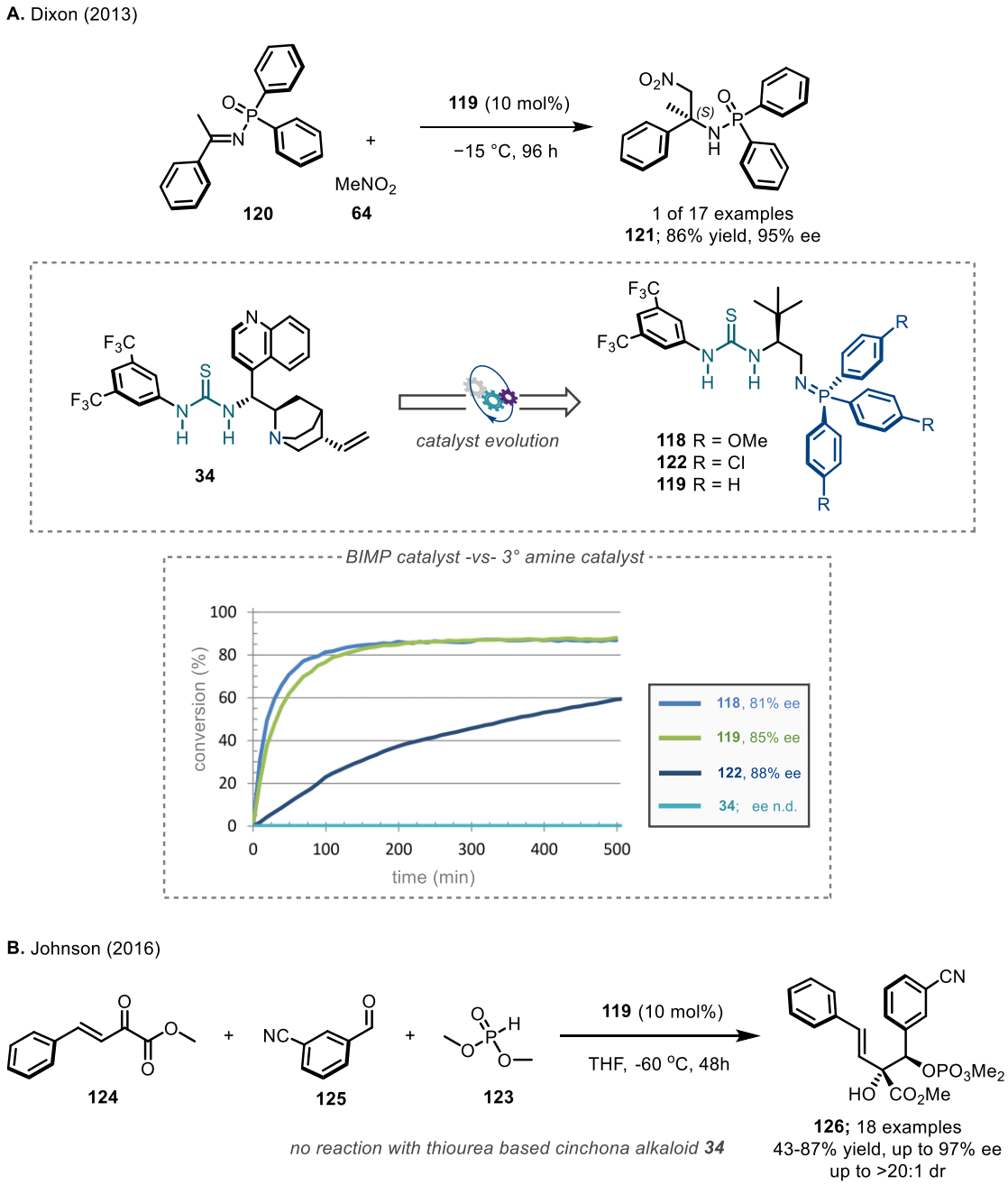
As depicted in **Scheme 22**, active BIMP catalysts (**118**) are normally generated as required from an *in situ* final-stage Staudinger reaction of a chiral organoazide (**116**) and phosphine (**117**). The organoazide precursors are derived from common enantioenriched amino acids displaying highly modular design while the phosphine ligands are normally inexpensive, ubiquitous and easy to handle. In addition, H-bond donors in the BIMP backbone can be conveniently varied to amide or thio(urea) by coupling amino azides with carboxylic acid or iso(thio)cyanate. Based on these facts, BIMPs inherently possess high degree of modularity and tunability which are their key merits over other chiral organosuperbases. Indeed, since their emergence in the early 2010's, BIMPs have come to the forefront of enantioselective bifunctional Brønsted base organocatalysis.



Scheme 22. Representative scheme for the formation of a bifunctional iminophosphorane (BIMP) catalyst.

1.6.2 1st generation of BIMPs and their applications

The very first BIMP catalyst featured one stereogenic center and a highly activated 3,5-$(CF_3)_2C_6H_3$ thiourea H-bond donor. This simple structure (**119**) performed outstandingly in an enantioselective nitro-Mannich reaction of high *p*K_a nitromethane (**64**) to low-electrophilic *N*-DPP protected ketimines (**120**) (**Scheme 23A**).[119] The desired adduct (**121**) was obtained in 86% yield and 95% ee with 10 mol% of **119** while *cinchona* alkaloid (**34**) bearing an identical H-bond donor group failed to deliver any detectable product, even after extended reaction times. This observation highlighted the significant role the strongly basic triphenyl-iminophosphorane moiety played in the transformation. This fact was also illustrated by the appreciably lower reaction rate performed by its *p*-Cl-PPh_3 derived analogue (**122**). Further increasing the Brønsted basicity of the catalyst by using it's $P(PMP)_3$ derived analogue (**118**) resulted in some erosion of the ee and slightly uplifted reaction rate. **119** was therefore chosen as the optimal catalyst for the decagram scale synthesis of 8 grams product where the catalyst loading could be lowered to only 1 mol%.

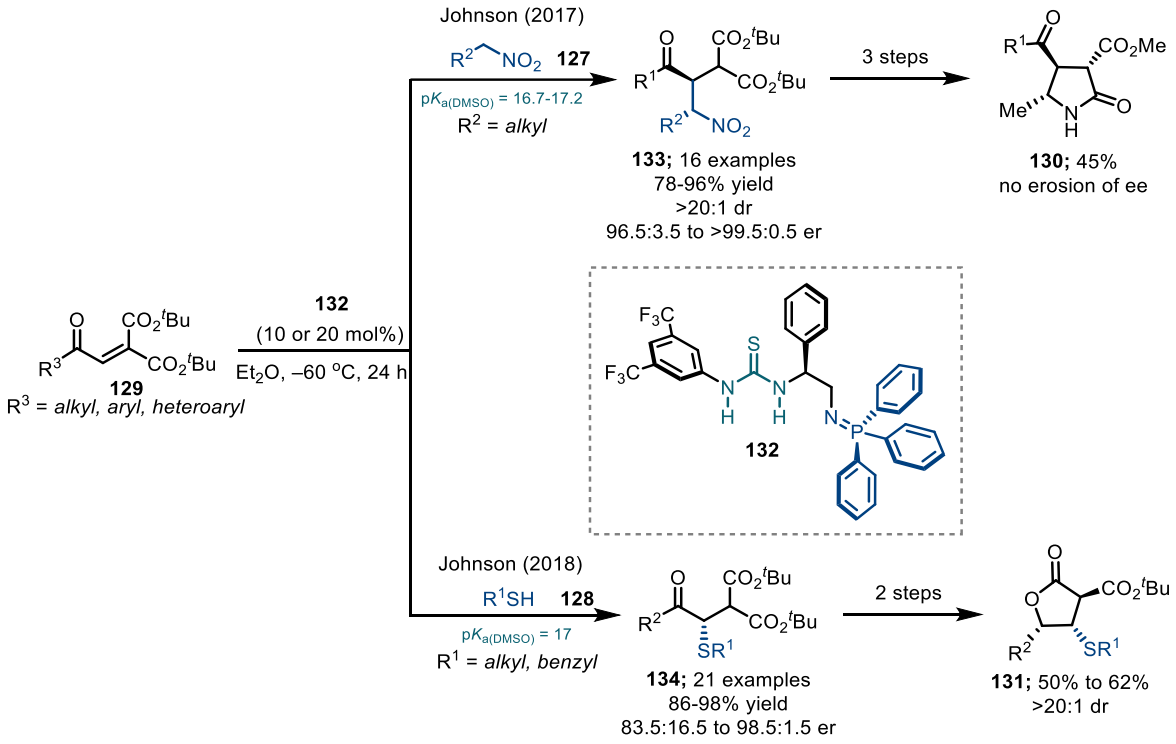


Scheme 23. **A.** Dixon's enantioselective nitro-Mannich reaction to *N*-DPP protected ketimines with a thiourea based 1st generation BIMP catalyst; **B.** Johnson's enantioselective Pudovik addition-Phospha-Brook cascade reaction with a thiourea based 1st generation BIMP catalyst.

Similarly, after experiencing failure in a three-component Pudovik addition-phospha-Brooke cascade reaction with *cinchona* based organocatalysts, Johnson and co-workers in 2016 found that Dixon's BIMP catalyst was the appropriate alternative (**Scheme 23B**).[123] Deprotonation of dialkylphosphites (**123**) was smooth with BIMP catalyst **119**. The resulting phosphorous ion underwent a Pudovik 1, 2-addition into

benzylidene pyruvates (**124**) and subsequently an enantioselective phospha-Brooke rearrangement with benzaldehydes (**125**) to afford the final products (**126**) with multiple functionalities in impressive selectivities (43-87% yield, up to 97% ee and up to >20:1 dr). This work showcases the superior competence of BIMP catalysts in catalysing multicomponent reductive coupling reaction with precise control to build up molecular complexity, particularly vicinal chirality.

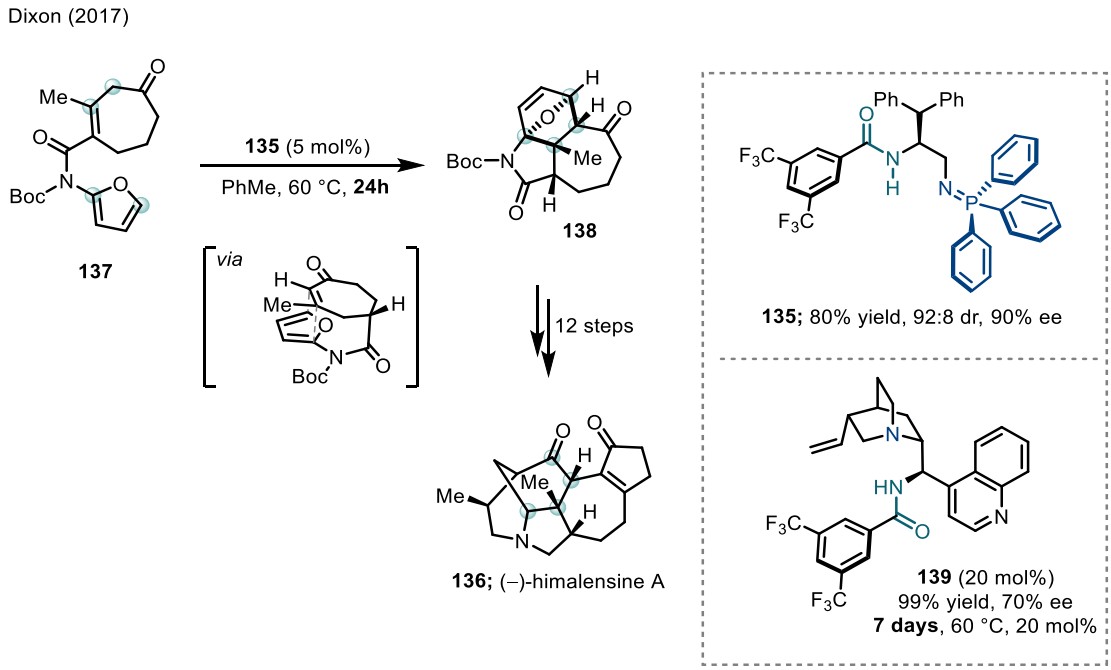
Over the next two years, Johnson also found the application of this BIMP class in the highly enantioselective 1,4-additions of nitroalkanes (**127**)[124] and alkyl thiols (**128**)[125] to enone diesters (**129**) (**Scheme 24**), followed by downstream derivatisations to afford enantioenriched lactams (**130**) and lactones (**131**) respectively.



Scheme 24. Johnson's enantioselective nitro- and sulfa-Michael additions to enone diesters followed by lactamisation or lactonisation with a thiourea based 1st generation BIMP catalyst.

In 2017, the scope of 1st generation BIMP catalyst was extended to **135** bearing an 3,5-$(CF_3)_2C_6H_3$ amide moiety as H-bond donor which demonstrated great catalytic efficacy in the key step of the total synthesis of *Daphniphyllum* alkaloid natural product (−)-himalensine A (**136**).[126] Only 5 mol% **135** was required to enable the enantioselective prototropic shift of **137** and a subsequent intramolecular Diels−Alder

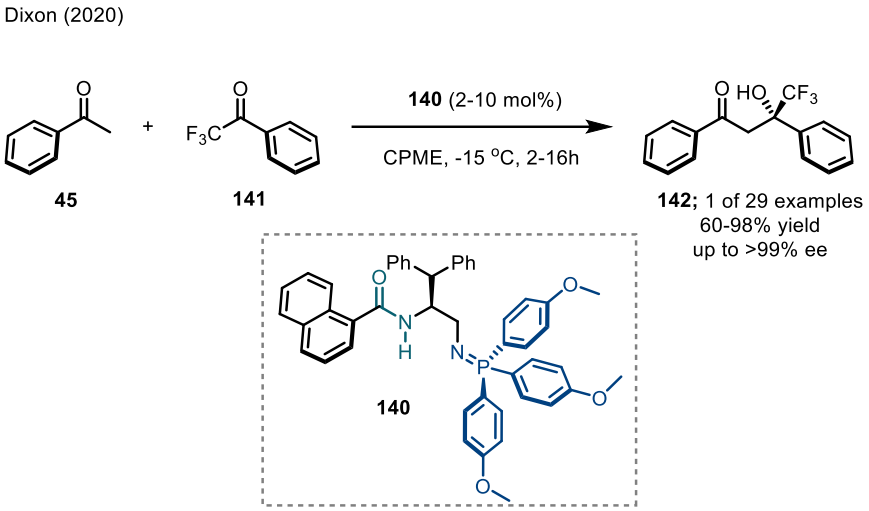
cycloaddition of furan (IMDAF), affording the ACD tricyclic ring (**138**), key intermediate for (−)-himalensine A, rapidly and highly stereoselectively (90% ee and 92 : 8 dr) (**Scheme 25**). By contrast, only modest stereoinduction (70% ee) was observed with amide-based cinchona derivative (**139**) even when 20 mol% catalyst loading and extremely long reaction time (7 days) were applied. Apart from the low catalyst loading and short reaction time, the simplicity and applicability of this BIMP catalysed transformation is also highlighted by the fact that azide precursor and triphenylphosphine can be added directly to the toluene solution of substrate; i.e. no pre-formation of the active BIMP catalyst was required.



Scheme 25. Dixon's enantioselective 1, 3-prototropic shift-intramolecular furan Diels-Alder cascade reaction *en route to* (−)-himalensine A with an amide based 1st generation BIMP catalyst.

An amide-based 1st generation BIMP class (**140**) was also recently demonstrated to be efficient for the activation of high-pK_a aryl methyl ketone pro-nucleophiles (**45**) and subsequent trapping of the resulting enolate species by trifluoromethyl ketones (**141**) in a highly enantioselective direct aldol reaction (**Scheme 26**).[127] The resulting β-hydroxy ketone aldol products (**142**) were obtained in high yield (60-98% yield) and enantiomeric excess (up to >99% ee) and could be used as precursors for 1,3-diols and 1,3-

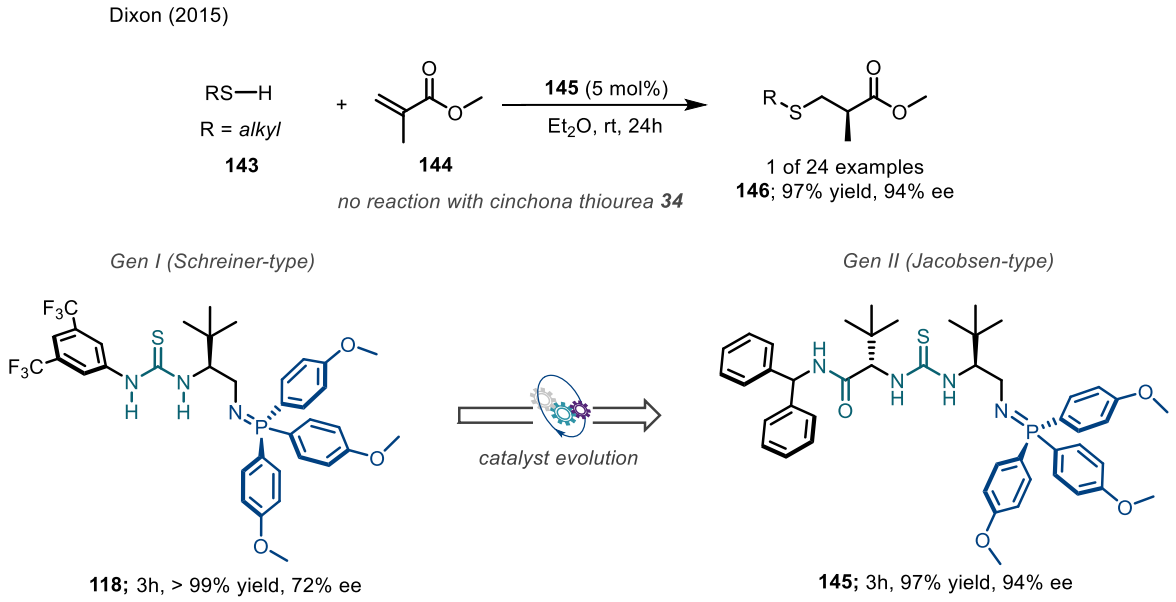
oxime alcohols for example. Notably, aldol reactions using aryl ketones as nucleophilic donors are highly challenging with proline type catalyst due to reluctant formation of aryl enamines.



Scheme 26. Dixon's enantioselective direct aldol reactions with an amide-based 1st generation BIMP catalyst.

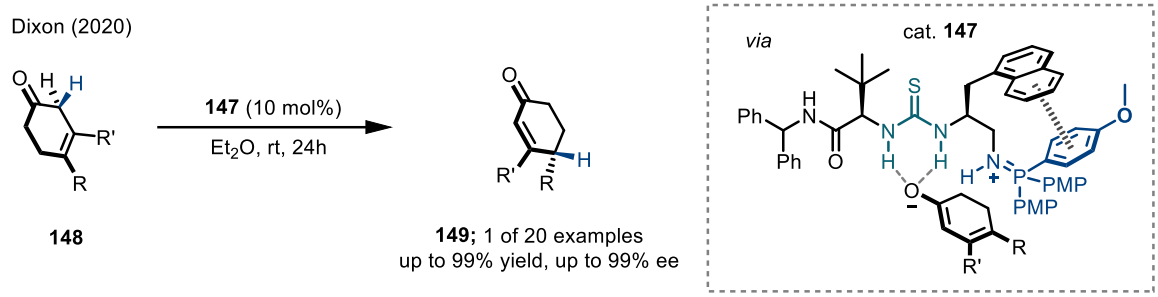
1.6.3 2nd generation of BIMPs and their applications

The limitations of 1st generation BIMP system were made clear when investigating the sulfa-Michael additions (SMA) of aliphatic thiols (**143**) to low electrophilic α-substituted acrylate esters (**144**) [76] where only moderate enantioselectivity (72% ee) was obtained with **118** (**Scheme 27**).[128] Further exhaustive modifications of **118** including variations on chiral substituents, H-bond donor acidity and iminophosphorane basicity failed to give any improvement. Inspired by Jacobsen's catalyst designs,[49] Dixon and co-workers incorporated additional stereo-centres and a remote amide moiety into the BIMP structure attempting to solve this challenging transformation. Indeed, much more impressive enantiocontrol (94% ee) was observed with the newly designed generation II BIMP system (**145**) while comparably excellent reactivity was retained.[128] When the reaction was carried out on 20-gram scale, the catalyst loading could be further reduced to 0.05 mol% (40 milligrams) without any significant loss of reactivity and enantioselectivity. Reaction scope of this SMA reaction was later extended to β-substituted acrylate esters[129] as well as alkenyl benzimidazoles[130] with only small modifications to the catalyst structure.



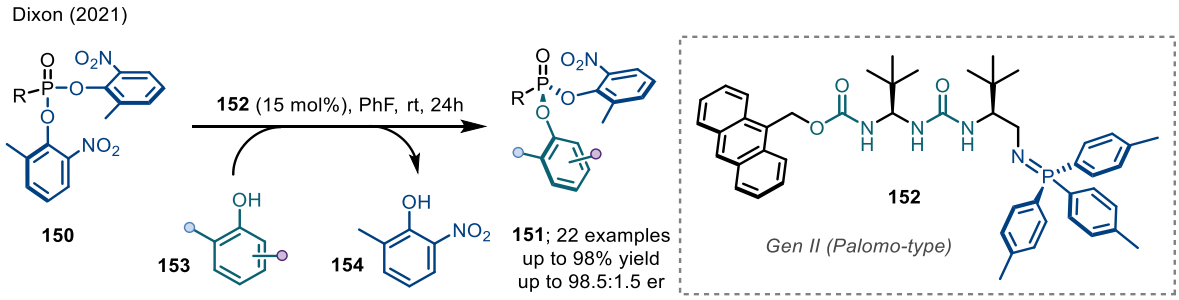
Scheme 27. Dixon's enantioselective sulfa-Michael additions to α-substituted acrylate esters with a 2nd generation BIMP catalyst.

Similarly structured generation II BIMP **147** was found to have application in an enantioselective [1, 3]-prototropic shifts of β, γ-unsaturated cyclohexenones (**148**) towards their chiral conjugated counterparts (**149**) (**Scheme 28**).[131] This reaction type is of great significant in installing key stereo-centres for many drugs or natural products but rarely realised with organocatalysis mainly due to the low acidity of ketone's α-proton. Although generation I BIMP system did manage to catalyse the key prototropic shift step in the synthesis of (−)-himalensine A as shown in **Scheme 25**,[126] the obtained example was a one-off and using an activated starting material. A general enantioselective reprotonation process was not fully developed. To fill this gap and to gain better insight of the versatility of 2nd generation BIMPs, **147** was applied and successfully afforded α, β-unsaturated cyclohexenones (**149**) in up to 99% ee and up to 99% yield which are relevant building blocks for (−)-reserpine and (−)-penitrem D. Stabilised interactions for the transition state structure mainly involved the hydrogen bonding between catalyst's thiourea and enolate intermediate from deprotonation. Through this work, BIMPs have directly proven their utility in installing key stereo-genic centres for known pharmaceutical relevance.



Scheme 28. Dixon's enantioselective 1, 3-prototropic shifts of β, γ-unsaturated cyclohexenones into their chiral conjugated counterparts with a 2nd generation BIMP catalyst.

Another more recent and important example enabled by Gen II BIMP systems was the nucleophilic desymmetrisation of P(V) species with substituted phenols as incoming nucleophiles (**Scheme 29**).[132] Notably, aforementioned 2nd generation BIMPs all feature two stereogenic centers flanking an H-bond donor together with an adjacent amide moiety. These Jacobsen-type BIMPs were yet not sufficiently good in desymmetrising phosphonate esters such as **150**, only affording desired product **151** in 24 - 31% ee. Inspired by a tertiary amine bifunctional catalyst reported by Palomo,[133-135] Dixon group further modified the BIMP structure to incorporate a ureidopeptide skeleton – Gen II Palomo-type BIMPs (**152**). These structures involved two stereo-centres similar to Jacobsen-type but also an additional adjacent *N-H* moiety which can potentially provide different activation pattern and ameliorated reaction outcome. Indeed, with BIMP **152**, the enantioselectivity of the P(V) desymmetrisation reactions was improved significantly (up to 97% ee) while an excellent yield was also obtained (up to 98% yield). Downstream functionalisation of these desymmetrised product to a series of biologically relevant nucleoside-derived species demonstrates the significance of this transformation.



Scheme 29. Dixon's enantioselective nucleophilic desymmetrisation of P(V) Species with a 2nd generation BIMP catalyst

1.7 Thesis Aims

Given all the existing developments with BIMP catalyst systems, we are confident about their capability of enabling challenging reactions, especially the activation of high pK_a pro-nucleophiles and low electrophilic electrophiles. We also believe that work on BIMP catalysis to date has only scratched the surface of the potential enantioselective transformations which could be enabled by this catalyst class. For example, BIMP enabled heteroatom conjugate addtion reactions other than sulphur to Michael acceptors with low reactivity are yet underexplored. Besides, BIMP catalysis has mostly focused on revealing reactivity between two separated partners while intramolecular typed reactions were still unprecedented and could provide attractive opportunities. To this end, throughout this DPhil, we aimed to develop new methodologies centred on the synthesis of useful enantioenriched heterocycles *via* intramolecular heteroatom Michael additions and where necessary explore some new catalyst design.

Initially, we envisioned the superbasic BIMP system was able to promote the intramolecular *aza*-Michael addition of pro-nucleophilic ureas to tethered β-substituted α, β-unsaturated esters. This transformation remains largely unsolved due to the high pK_a of the urea and low electrophilicity of the Michael acceptor. Besides, it would enable the synthesis of enantioenriched hydroquinazoline structures which are commonplace amongst various natural products and potent drug substances used in the clinic. To this end, we aimed to apply known or develop novel BIMP systems to effectively activate both aromatic and aliphatic ureas. The findings are presented in **Chapter 2**.

Next, we recognised the importance and prevalence of α-substituted chiral oxygen-containing heterocycles such as THFs, THPs, dihydro-(iso)-benzofurans and (iso)-chromanes in both natural products and pharmaceuticals. Currently, only very few reports have been published on the synthesis of these molecules *via* intramolecular oxy-Michael additions of pro-nucleophilic alcohols to tethered substituted α, β-unsaturated esters or amides. These works typically featured long reaction times and are of limited scope. We aimed to uncover significant improvements on this specific project with BIMP catalyst systems such as the thorough investigation of all alcohol types as pronucleophiles. Along the

way, we wished to disclose preparation of pharmaceutically relevant molecular complexities. The findings are presented in **Chapter 3**.

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

1.8 References for Chapter 1

[1]. Eichelbaum, M. Side Effects And Toxic Reactions Of Chiral Drugs: A Clinical Perspective. *Arch. Toxicol. Suppl.* **1995**, *17*, 514-521.

[2]. Siluveru, M; Stewart, J. T. Stereoselective Determination Of *R*(-)- And *S*(+)-Prilocaine In Human Serum Using A Brush-Type Chiral Stationary Phase, Solid-Phase Extraction And Uv Detection. *J. Pharm. Biomed.* **1996**, *15*, 389-392.

[3]. Dicpinigaitis, P. V.; Morice, A. H.; Birring, S. S.; Mcgarvey, L.; Smith, J. A.; Canning, B. J.; Page, C. P. Antitussive Drugs--Past, Present, And Future. *Pharmacol Rev.* **2014**, *66*, 468-512.

[4]. Gal, J. The Discovery of Biological Enantioselectivity: Louis Pasteur and the Fermentation of Tartaric Acid, 1857—A Review and Analysis 150 Yr Later. *Chirality* **2008**, *20*, 5–19.

[5]. Subramanian, G. *Chiral Separation Techniques: A Practical Approach, 3rd, Completely Revised and Updated Edition,* Wiley, **2006**.

[6]. Blaser, H. U. The Chiral Pool as a Source of Enantioselective Catalysts and Auxiliaries. *Chem. Rev.* **1992**, *92* (5), 935–952.

[7]. Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **2017**, *117*(18), 11753–11795.

[8]. Evans, D. A.; McGee, L. R.; *J. Am. Chem. Soc.* **1981**, *103*, 2876–2878.

[9]. Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

[10]. Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; de Rezende, D. C.; Alves Nogueira Diaz, M. Use of Chiral Auxiliaries in the Asymmetric Synthesis of Biologically Active Compounds: A Review. *Chirality,* **2019**, *31*, 776–812.

[11]. Trost, B. M. Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chemie Int. Ed. English* **1995**, *34*, 259–281.

[12]. Bolm, C.; Gladysz, J. A. Introduction: Enantioselective Catalysis. *Chem. Rev.* **2003**, *103*, 2761–2762.

[13]. Toste, F. D.; You, S. L. Asymmetric Synthesis Enabled by Organometallic Complexes. *Organometallics* **2019**, *38*, 3899–3901.

[14]. Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture 2001). *Adv. Synth. Catal.* **2003**, *345*, 15–32.

[15]. Knowles, W. S. Asymmetric Hydrogenations (Nobel Lecture 2001). *Adv. Synth. Catal.* **2003**, *345*, 3–13.

[16]. Winkler, C. K.; Schrittwieser, J. H.; Kroutil, W. Power of Biocatalysis for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7*, 55–71.

[17]. Arnold, F. H. Innovation by Evolution: Bringing New Chemistry to Life (Nobel Lecture). *Angew. Chem. Int. Ed.* **2019**, *58*, 14420–14426.

[18]. MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304–308.

[19]. Xiang, S.; Tan, B. Advances in Asymmetric Organocatalysis over the Last 10 Years. *Nat. Commun.* **2020**, *11,* 3786.

[20]. Markwald, W. Ueber asymmetrische Synthese, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349–354.

[21]. Kenyon, J; Ross, W. A. The mechanism of the decarboxylation of substituted malonic acid derivatives, *J. Chem. Soc.,* **1951**, 3407–3411.

[22]. Kenyon, J; Ross, W. A. A new reaction mechanism for the marckwald asymmetric synthesis, *J. Chem. Soc.,* **1952**, 2307–2310.

[23]. Pracejus, H.; Organische Katalysatoren, LXI. Asymmetrische Synthesen mit Ketenen, I. Alkaloid-katalysierte asymmetrische Synthesen von α-Phenyl-propionsäureestern, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.

[24]. Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* **1974**, *39*, 1615–1621.

[25]. Eder, U.; Sauer, G.; Wiechert, R. New Type of Asymmetric Cyclisation to Optically Active Steroid CD Partial Structures. *Angew. Chemie Int. Ed. English* **1971**, *10*, 496–497.

[26]. Hiemstra, H.; Wynberg, H. Addition of Aromatic Thiols to Conjugated Cycloalkenones, Catalysed by Chiral β-Hydroxy Amines. A Mechanistic Study of Homogeneous Catalytic Asymmetric Synthesis. *J. Am. Chem. Soc.* **1981**, *103*, 417–430.

[27]. Oku, J. I.; Inoue, S. Asymmetric Cyanohydrin Synthesis Catalysed by a Synthetic Cyclic Dipeptide. *J. Chem. Soc. Chem. Commun.* **1981**, *5*, 229–230.

[28]. Bredig, G.; Fiske, P. S. Asymmetric synthesis caused by catalyts, *Biochem. Z.* **1913**, *46*, 7–23.

[29]. Tanaka, K. T.; Mori, A.; Inoue, S.; Tanaka, K. The Cyclic Dipeptide Cyclo[(S)-Phenylalanyl-(S)-Histidyl] as a Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehydes. *J. Org. Chem.* **1990**, *55*, 181–185.

[30]. Sigman, M. S.; Jacobsen, E. N. Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimised from Parallel Synthetic Libraries. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

[31]. Vachal, P.; Jacobsen, E. N. Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids. *Org. Lett.* **2000**, *2*, 867–870.

[32]. Sigman, M. S.; Vachal, P. A General Catalyst for Asymmetric Strecker Reaction. Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281.

[33]. Vachal, P.; Jacobsen, E. N. Structure-Based Analysis and Optimisation of a Highly Enantioselective Catalyst for the Strecker Reaction. *J. Am Chem. Soc.* **2002**, *124*, 10012–10014.

[34]. Joly, G. D.; Jacobsen, E. N. Thiourea-Catalysed Enantioselective Hydrophosphonylation of Imines: Practical Access to Enantiomerically Enriched α-Amino Phosphonic Acids. *J. Am Chem. Soc.* **2004**, *126*, 4102–4103.

[35]. Wenzel, A. G.; Jacobsen, E. N. Asymmetric Catalytic Mannich Reactions Catalysed by Urea Derivatives: Enantioselective Synthesis of β-Aryl-β-Amino Acids. *J. Am Chem. Soc.* **2002**, *124*, 12964–12965.

[36]. Yoon, T. P.; Jacobsen, E. N. Highly Enantioselective Thiourea-Catalysed Nitro-Mannich Reactions. *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.

[37]. List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalysed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[38]. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107*, 5471–5569.

[39]. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels - Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[40]. Dalko, P. I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

[41]. Dondoni, A.; Massi, A. Asymmetric Organocatalysis: From Infancy to Adolescence. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660.

[42]. Bertelsen, S.; Jørgensen, K. A. Organocatalysis–after the Gold Rush. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

[43]. Palomo, C.; Oiarbide, M.; Lopez, R. Asymmetric Organocatalysis by Chiral Bronsted Bases: Implications and Applications. *Chem. Soc. Rev.* **2009**, *38* (2), 632–653.

[44]. Odagi, M.; Nagasawa, K. Recent Advances in Natural Products Synthesis Using Bifunctional Organocatalysts Bearing a Hydrogen-Bonding Donor Moiety. *Asian J. Org. Chem.* **2019**, *8* (10), 1766–1774.

[45]. Siau, W. Y.; Wang, J. Asymmetric Organocatalytic Reactions by Bifunctional Amine-Thioureas. *Catal. Sci. Technol.* **2011**, *1* (8), 1298–1310.

[46]. Fang, X.; Wang, C. J. Recent Advances in Asymmetric Organocatalysis Mediated by Bifunctional Amine-Thioureas Bearing Multiple Hydrogen-Bonding Donors. *Chem. Commun.* **2015**, *51* (7), 1185–1197.

[47]. Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalysed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[48]. Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C-C Bond Formation. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

[49]. Fuerst, D. E.; Jacobsen, E. N. Thiourea-Catalysed Enantioselective Cyanosilylation of Ketones. *J. Am. Chem. Soc.* **2005** , *127*, 8964–8965.

[50]. Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. Bifunctional Hydrogen-Bond Donors That Bear a Quinazoline or Benzothiadiazine Skeleton for Asymmetric Organocatalysis. *Chem. Eur. J.* **2011**, *17*, 10470–10477.

[51]. Inokuma, T.; Furukawa, M.; Suzuki, Y.; Kimachi, T.; Kobayashi, Y.; Takemoto, Y. Organocatalysed Isomerisation of α-Substituted Alkynoates into Trisubstituted Allenoates by Dynamic Kinetic Resolution. *Chem. Cat. Chem.* **2012**, *4*, 983–985.

[52]. Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters. *Angew. Chem. Int. Ed.* **2013**, *52*, 11114–11118.

[53]. Kobayashi, Y.; Kuramoto, R.; Takemoto, Y. Catalytic Asymmetric Formal Synthesis of Beraprost. *Beilstein J. Org. Chem.* **2015**, *11*, 2654–2660.

[54]. Tanriver, G.; Dedeoglu, B.; Catak, S.; Aviyente, V. Computational Studies on Cinchona Alkaloid-Catalysed Asymmetric Organic Reactions. *Acc. Chem. Res.* **2016**, *49*, 1250–1262.

[55]. Jiang, L.; Chen, Y. C. Recent Advances in Asymmetric Catalysis with Cinchona Alkaloid-Based Primary Amines. *Catal. Sci. Technol.* **2011**, *1* (3), 354–365.

[56]. Marcelli, T.; Hiemstra, H. Cinchona Alkaloids in Asymmetric Organocatalysis. *Synthesis (Stuttg).* **2010**, No. 8, 1229–1279.

[57]. Connon, S. J. Asymmetric Catalysis with Bifunctional Cinchona Alkaloid-Based Urea and Thiourea Organocatalysts. *Chem. Commun.* **2008**, *22*, 2499–2510.

[58]. Grayson, M. N.; Houk, K. N. Cinchona Urea-Catalysed Asymmetric Sulfa-Michael Reactions: The Bronsted Acid-Hydrogen Bonding Model. *J. Am. Chem. Soc.* **2016**, *138* (29), 9041–9044.

[59]. Boratyński, P. J.; Zielińska-Błajet, M.; Skarżewski, J. Chapter Two - Cinchona Alkaloids—Derivatives and Applications. *Alkaloids. Chem. Biol.* **2019**, *82*, 29–145.

[60]. Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. Asymmetric Michael Addition of Arylthiols to α,β-Unsaturated Carbonyl Compounds Catalysed by Bifunctional Organocatalysts *Synlett.* **2005**, *4*, 603–606.

[61]. McCooey, S. H.; Connon, S. J. Urea- and Thiourea-Substituted Cinchona Alkaloid Derivatives as Highly Efficient Bifunctional Organocatalysts for the Asymmetric Addition of Malonate to Nitroalkenes: Inversion of Configuration at C9 Dramatically Improves Catalyst Performance. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.

[62]. Ye, J.; Dixon, D. J.; Hynes, P. S. Enantioselective Organocatalytic Michael Addition of Malonate Esters to Nitroolefins Using Bifunctional Cinchonine Derivatives. *Chem. Commun.* **2005**, 4481–4483.

[63]. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T.; Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts. *Org. Lett.* **2005**, *7*, 1967–1969.

[64]. Jakubec, P.; Cockfield, D. M.; Dixon, D. J. Total Synthesis of (-)-Nakadomarin A. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

[65]. Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. A New Family of Cinchona-Derived Amino Phosphine Precatalysts: Application to the Highly Enantio- and Diastereoselective Silver-Catalysed Isocyanoacetate Aldol Reaction. *J. Am. Chem. Soc.* **2011**, *133* (6), 1710–1713.

[66]. Hayashi, M.; Shiomi, N.; Funahashi, Y.; Nakamura, S. Cinchona Alkaloid Amides/Dialkylzinc Catalysed Enantioselective Desymmetrisation of Aziridines with Phosphites. *J. Am. Chem. Soc.* **2012**, *134* (47), 19366–19369.

[67]. Zhao, Z. Q.; Zhao, X. L.; Shi, M.; Zhao, M. X. Cinchona Alkaloid Squaramide-Catalysed Asymmetric Ugi-Type Reaction of Isocyanoacetates with C,N-Cyclic Azomethine Imines: Access to Chiral Oxazole-Substituted Tetrahydroisoquinolines. *J. Org. Chem.* **2019**, *84* (22), 14487–14497.

[68]. Guo, J.; Wong, M. W. Cinchona Alkaloid-Squaramide Catalysed Sulfa-Michael Addition Reaction: Mode of Bifunctional Activation and Origin of Stereoinduction. *J. Org. Chem.* **2017**, *82* (8), 4362–4368.

[69]. Ullah, M. S.; Itsuno, S. Cinchona Squaramide-Based Chiral Polymers as Highly Efficient Catalysts in Asymmetric Michael Addition Reaction. *ACS Omega.* **2018**, *3*(4), 4573–4582.

[70]. Malerich, J. P.; Hagihara, K.; Rawal, V. H. Chiral Squaramide Derivatives Are Excellent Hydrogen Bond Donor Catalysts. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[71]. Jha, R. K.; Rout, S.; Joshi, H.; Das, A.; Singh, V. K. An Enantioselective Sulfa-Michael Addition of Alkyl Thiols to α,β-Unsaturated 2-Acyl Imidazoles Catalysed by a Bifunctional Squaramide. *Tetrahedron*. **2020**, *76*, 130800–130806.

[72]. Li, H.; Wang, Y.; Tang, L.; Deng, L. Highly Enantioselective Conjugate Addition of Malonate and β-Ketoester to Nitroalkenes: Asymmetric C-C Bond Formation with New Bifunctional Organic Catalysts Based on Cinchona Alkaloids. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907.

[73]. Marcelli, T.; Van Der Haas, R. N. S.; Van Maarseveen, J. H.; Hiemstra, H. Asymmetric Organocatalytic Henry Reaction. *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.

[74]. Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Cornforth, F. J.; Drucker, G. E.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R.; Bordwell, F. G.; Margolin, Z. Equilibrium Acidities of Carbon Acids. VI. Establishment of an Absolute Scale of Acidities in Dimethyl Sulfoxide Solution. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.

[75]. Shang, M.; Wang, X.; Koo, S. M.; Youn, J.; Chan, J. Z.; Yao, W.; Hastings, B. T.; Wasa, M. Frustrated Lewis Acid/Brønsted Base Catalysts for Direct Enantioselective α-Amination of Carbonyl Compounds. *J. Am. Chem. Soc.* **2017**, *139*, 95–98.

[76]. Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. Quantification and Theoretical Analysis of the Electrophilicities of Michael Acceptors. *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.

[77]. Dong, X. Q.; Fang, X.; Tao, H. Y.; Zhou, X.; Wang, C. J. Highly Efficient Catalytic Asymmetric Sulfa-Michael Addition of Thiols to Trans-4,4,4-Trifluorocrotonoylpyrazole. *Adv. Synth. Catal.* **2012**, *354*, 1141–1147.

[78]. Ortín, I.; Dixon, D. J. Direct Catalytic Enantio- and Diastereoselective Mannich Reaction of Isocyanoacetates and Ketimines. *Angew. Chemie. Int. Ed.* **2014**, *53* (13), 3462–3465.

[79]. Rigby, C. L.; Dixon, D. J. Enantioselective Organocatalytic Michael Additions to Acrylic Acid Derivatives: Generation of All-Carbon Quaternary Stereocentres. *Chem. Commun.* **2008**, *32*, 3798–3800;

[80]. Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts;* John Wiley & Sons, Ltd.: Chichester, UK, **2009**.

[81]. Ishikawa, T.; Harwood, L. M. Organic Superbases: The Concept at a Glance. *Synlett.* **2013**, *24* (19), 2507–2509.

[82]. Leow, D.; Tan, C. H. Chiral Guanidine Catalysed Enantioselective Reactions. *Chem. Asian J.* **2009**, *4*, 488–507.

[83]. Chou, H. C.; Leow, D.; Tan, C. H. Recent Advances in Chiral Guanidine-Catalysed Enantioselective Reactions. *Chem. Asian J.* **2019**, *14*, 3803–3822.

[84]. Bandar, J. S.; Lambert, T. H. Enantioselective Brønsted Base Catalysis with Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2012**, *134*, 5552–5555.

[85]. Bandar, J. S.; Lambert, T. H. Cyclopropenimine-Catalysed Enantioselective Mannich Reactions of tert-Butyl Glycinates with N-Boc-Imines. *J. Am. Chem. Soc.* **2013**, *135* (32) 11799–11802.

[86]. Uraguchi, D.; Sakaki, S.; Ooi, T. Chiral Tetraaminophosphonium Salt-Mediated Asymmetric Direct Henry Reaction. *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393.

[87]. Simón, L.; Paton, R. S. Phosphazene Catalysed Addition to Electron-Deficient Alkynes: The Importance of Nonlinear Allenyl Intermediates upon Stereoselectivity. *J. Org. Chem.* **2017**, *82*, 3855–3863.

[88]. Corey, E. J.; Grogan, M. J. Enantioselective Synthesis of α-Amino Nitriles from *N* -Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst. *Org. Lett.* **1999**, *1*, 157–160.

[89]. Fu, X.; Tan, C.-H. Mechanistic Considerations of Guanidine-Catalysed Reactions. *Chem. Commun.* **2011**, *47*, 8210-8222.

[90]. Fu, X.; Jiang, Z.; Tan, C. H. Bicyclic Guanidine-Catalysed Enantioselective Phospha-Michael Reaction: Synthesis of Chiral β-Aminophosphine Oxides and β-Aminophosphines. *Chem. Commun.* **2007**, *47*, 5058–5060.

[91]. Terada, M.; Ube, H.; Yaguchi, Y. Axially Chiral Guanidine as Enantioselective Base Catalyst for 1,4-Addition Reaction of 1,3-Dicarbonyl Compounds with Conjugated Nitroalkenes. *J. Am. Chem. Soc.* **2006**, *128* (5) 1454–1455.

[92]. Dong, S.; Liu, X.; Chen, X.; Mei, F.; Zhang, Y.; Gao, B.; Lin, L.; Feng, X. Chiral Bisguanidine-Catalysed Inverse-Electron-Demand Hetero-Diels−Alder Reaction of Chalcones with Azlactones. *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651.

[93]. Dong, S.; Liu, X.; Zhu, Y.; He, P.; Lin, L.; Feng, X. Organocatalytic Oxyamination of Azlactones: Kinetic Resolution of Oxaziridines and Asymmetric Synthesis of Oxazolin-4-ones. *J. Am. Chem. Soc.* **2013**, *135*, 10026–10029.

[94]. Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. Modified Guanidines as Chiral Superbases: Application to Asymmetric Michael Reaction of Glycine Imine With Acrylate or Its Related Compounds. *Chem. Commun.* **2001**, 245–246.

[95]. Kobayashi, S.; Yazaki, R.; Seki, K.; Yamashita, Y. The Fluorenone Imines of Glycine Esters and

Their Phosphonic Acid Analogues. *Angew. Chem. Int. Ed.* **2008**, *47*, 5613–5615.

[96]. Maksić, Z. B.; Kovačević, B. Spatial and Electronic Structure of Highly Basic Organic Molecules: Cyclopropeneimines and Some Related Systems. *J. Phys. Chem. A* **1999**, *103*, 6678–6684.

[97]. Gattin, Z.; Kovačević, B.; Maksić, Z. B. Cooperative Intramolecular Hydrogen Bonding Effect and Basicity - An Ab Initio and DFT Study of the Superbasic Properties of N-[(Dimethylamino)Alkyl]-2, 3-Diaminocycloprop-2-Ene-1-Imines. *European J. Org. Chem.* **2005**, *15*, 3206–3213.

[98]. Bandar, J. S.; Sauer, G. S.; Wulff, W. D.; Lambert, T. H.; Vetticatt, M. J. Transition State Analysis of Enantioselective Brønsted Base Catalysis by Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2014**, *136*, 10700–10707.

[99]. Bandar, J. S.; Barthelme, A.; Mazori, A. Y.; Lambert, T. H. Structure-Activity Relationship Studies of Cyclopropenimines as Enantioselective Brønsted Base Catalysts. *Chem. Sci.* **2015**, *6*, 1537–1547.

[100]. Schwesinger, R. Extremely Strong, Non-Ionic Bases: Synthesis and Applications. *Chimia (Aarau).* **1985**, *39*, 269–272.

[101]. Schwesinger, R.; Schlemper, H. Peralkylated Polyaminophosphazenes— Extremely Strong, Neutral Nitrogen Bases. *Angew. Chemie Int. Ed. English* **1987**, *26*, 1167–1169.

[102]. Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G. Z.; Peters, E. M.; Peters, K.; Schnering, H. G. Von.; Walz, L. Extremely Strong, Uncharged Auxiliary Bases; Monomeric and Polymer-Supported Polyaminophosphazenes (P2–P5). *Liebigs Ann.* **1996**, *7*, 1055–1081.

[103]. Ullrich, S.; Kovačević, B.; Xie, X.; Sundermeyer, J. Phosphazenyl Phosphines: The Most Electron-Rich Uncharged Phosphorus Brønsted and Lewis Bases. *Angew. Chem. Int. Ed.* **2019**, *58*, 10335–10339.

[104]. Uraguchi, D.; Sakaki, S.; Ooi, T. Chiral Tetraaminophosphonium Salt-Mediated Asymmetric Direct Henry Reaction. *J. Am. Chem. Soc.* **2007**, *129* (41), 12392–12393.

[105]. Simon, L.; Paton, R. S. Phosphazene Catalysed Addition to Electron-Deficient Alkynes: The Importance of Nonlinear Allenyl Intermediates upon Stereoselectivity. *J. Org. Chem.* **2017**, *82* (7), 3855–3863.

[106]. Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T., Highly Regio-, Diastereo-, and Enantioselective 1,6- and 1,8-Additions of Azlactones to Di- and Trienyl N-Acylpyrroles. *J. Am. Chem. Soc.* **2012**, 134, 19370–19373.

[107]. Kolomeitsev, A. A.; Koppel, I. A.; Rodima, T.; Barten, J.; Lork, E.; Röschenthaler, G. V.; Kaljurand, I.; Kütt, A.; Koppel, I.; Mäemets, V.; et al. Guanidinophosphazenes: Design, Synthesis, and Basicity in THF and in the Gas Phase. *J. Am. Chem. Soc.* **2005**, *127*, 17656–17666.

[108]. Takeda, T.; Terada, M. Development of a Chiral Bis(Guanidino)Iminophosphorane as an Uncharged Organosuperbase for the Enantioselective Amination of Ketones. *J. Am. Chem. Soc.* **2013**, *135*, 15306–15309.

[109]. Takeda, T.; Terada, M. Synthesis of Bulky Aryl Group-Substituted Chiral Bis(Guanidino) Iminophosphoranes as Uncharged Chiral Organosuperbase Catalysts. *Aust. J. Chem.* **2014**, *67*, 1124–1128.

[110]. Takeda, T.; Kondoh, A.; Terada, M. Construction of Vicinal Quaternary Stereogenic Centers by Enantioselective Direct Mannich-Type Reaction Using a Chiral Bis(Guanidino)Iminophosphorane Catalyst. *Angew. Chem. Int. Ed.* **2016**, *55*, 4734–4737.

[111]. Hu, Q.; Kondoh, A.; Terada, M. Enantioselective Direct Mannich-Type Reactions of 2-Benzylpyridine N-Oxides Catalysed by Chiral Bis(Guanidino)Iminophosphorane Organosuperbase. *Chem. Sci.* **2018**, *9*, 4348–4351.

[112]. Kondoh, A.; Akahira, S.; Oishi, M.; Terada, M. Enantioselective Formal [3+2] Cycloaddition of Epoxides with Imines under Brønsted Base Catalysis: Synthesis of 1,3-Oxazolidines with Quaternary Stereogenic Center. *Angew. Chem. Int. Ed.* **2018**, *57*, 6299–6303.

[113]. Das, S.; Hu, Q.; Kondoh, A.; Terada, M. Enantioselective Protonation: Hydrophosphinylation of 1,1-Vinyl Azaheterocycle N-Oxides Catalysed by Chiral Bis(Guanidino)Iminophosphorane Organosuperbase. *Angew. Chem. Int. Ed.* **2021**, *60*, 1417 –1422.

[114]. Kondoh, A.; Oishi, M.; Tezuka, H.; Terada, M. Development of Chiral Organosuperbase Catalysts Consisting of Two Different Organobase Functionalities. *Angew. Chemie Int. Ed.* **2020**, *59*, 7472–7477.

[115]. Teng, B.; Lim, W. C.; Tan, C. H. Recent Advances in Enantioselective Bronsted Base Organocatalytic Reactions. *Synlett* **2017**, *28*, 1272–1277.

[116]. Wang, Y.-H.; Cao, Z.-Y.; Li, Q.-H.; Lin, G.-Q.; Zhou, J.; Tian, P. Activating Low Acidic Pronucleophiles: Chiral Organosuperbases Take Action. *Angew. Chemie Int. Ed.* **2020**, *59*, 8004 – 8014

[117]. Kondoh, A.; Terada, M. Development of Molecular Transformations on the Basis of Catalytic Generation of Anionic Species by Organosuperbase. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 339–356.

[118]. Formica, M.; Rozsar, D.; Su, G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Superbase Catalysis: Applications in Organic Synthesis. *Acc. Chem. Res.* **2020**, *53* (10), 2235–2247.

[119]. Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

[120]. Staudinger, H.; Meyer, J. Uber Neue Organische Phosphorverbindungen III. *Helv. Chim. Acta.* **1919**, *2* (1), 635–646.

[121]. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. The Aza-Wittig Reaction: An Efficient Tool for the Construction of Carbon-Nitrogen Double Bonds. *Tetrahedron.* **2007**, *63* (3), 523–575.

[122]. Farley, A. J. M.; Dixon, D. J. 1-[3,5-Bis(Trifluoromethyl)Phenyl]-3-{(2 S)-3,3-Dimethyl-1-[(Triphenylphosphoranylidene)Amino]Butan-2-Yl}thiourea. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: Chichester, UK, **2016**; 1–4.

[123]. Horwitz, M. A.; Zavesky, B. P.; Martinez-Alvarado, J. I.; Johnson, J. S. Asymmetric Organocatalytic Reductive Coupling Reactions between Benzylidene Pyruvates and Aldehydes. *Org. Lett.* **2016**, *18* (1), 36–39.

[124]. Horwitz, M. A.; Fulton, J. L.; Johnson, J. S. Enantio- and Diastereoselective Organocatalytic Conjugate Additions of Nitroalkanes to Enone Diesters. *Org. Lett.* **2017**, *19* (21), 5783–5785.

[125]. Fulton, J. L.; Horwitz, M. A.; Bruske, E. L.; Johnson, J. S. Asymmetric Organocatalytic Sulfa-Michael Addition to Enone Diesters. *J. Org. Chem.* **2018**, *83* (6), 3385–3391.

[126]. Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J. Total Synthesis of (-)-Himalensine A. *J. Am. Chem. Soc.* **2017**, *139*, 17755–17758.

[127]. Thomson, C. J.; Barber, D. M.; Dixon, D. J. Catalytic Enantioselective Direct Aldol Addition of Aryl Ketones to α-Fluorinated Ketones. *Angew. Chem. Int. Ed.* **2020**, *59*, 5359–5364.

[128]. Farley, A. J. M.; Sandford, C.; Dixon, D. J. Bifunctional Iminophosphorane Catalysed Enantioselective Sulfa-Michael Addition to Unactivated α-Substituted Acrylate Esters. *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995.

[129]. Yang, J.; Farley, A. J. M.; Dixon, D. J. Enantioselective Bifunctional Iminophosphorane Catalysed Sulfa-Michael Addition of Alkyl Thiols to Unactivated β-Substituted-α,β-Unsaturated Esters. *Chem. Sci.* **2017**, *8*, 606–610.

[130]. Formica, M.; Sorin, G.; Farley, A. J. M.; Diaz, J.; Paton, R. S.; Dixon, D. J. Bifunctional Iminophosphorane Catalysed Enantioselective Sulfa-Michael Addition of Alkyl Thiols to Alkenyl Benzimidazoles. *Chem. Sci.* **2018**, *9* (34), 6969–6974.

[131]. Golec, J. C.; Carter, E. M.; Ward, J. W.; Whittingham, W. G.; Simón, L.; Paton, R. S.; Dixon, D. J. BIMP-Catalysed 1,3-Prototropic Shift for the Highly Enantioselective Synthesis of Conjugated Cyclohexenones. *Angew. Chemie Int. Ed.* **2020**, *59*, 17417–17422.

[132]. Formica, M.; Rogova, T.; Shi, H.; Sahara, N.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Dixon, D. J. Enantioselective Nucleophilic Desymmetrisation of Phosphonate Esters. *Chem Rxiv* **2021**. DOI: 10.33774/chemrxiv-2021-5714s-v2.

[133]. Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. Catalytic Enantioselective Synthesis of Tertiary Thiols From 5 H -Thiazol-4-Ones and Nitroolefins: Bifunctional Ureidopeptide-Based Brønsted Base Catalysis. *Angew. Chemie Int. Ed.* **2013**, *52*, 11846–11851.

[134]. Lopez, R.; Palomo, C. N,N-Diacylaminals as Emerging Tools in Synthesis: From Peptidomimetics to Asymmetric Catalysis. *Chem. Eur. J.* **2021**, *27*, 20–29.

[135]. Vera, S.; Vázquez, A.; Rodriguez, R.; Pozo, S. del; Urruzuno, I.; Cózar, A. de; Mielgo, A.; Palomo, C. Synthesis of β-Hydroxy α-Amino Acids Through Brønsted Base-Catalysed Syn -Selective Direct Aldol Reaction of Schiff Bases of Glycine o -Nitroanilide. *J. Org. Chem.* **2021**, *86* (11), 7757–7772.

Chapter 2

Enantioselective Intramolecular *Aza*-Michael Reaction of Ureas to α,β-Unsaturated Esters

2.1 Chapter Overview

This chapter outlines the development of a BIMP-catalysed enantioselective intramolecular *aza*-Michael reaction (IAMR) of both aromatic and aliphatic ureas to α,β-unsaturated esters providing decorated hydroquinazolines. Enantioenriched hydroquinazolines and their derivatives are pharmaceutically relevant, finding use as a variety of clinically potent drug substances. Current state-of-the-art methods for their synthesis have relied heavily on the use of activated substrates while organocatalysed IAMR approaches are rare and limited by substrate scope. The method discussed in this chapter provides a simple protocol, through the use of a superbasic BIMP catalyst on providing the hydroquinazoline products in yields of up to 99% and enantiomeric ratios of up to 97:3 er. Additionally, detailed computational studies were carried out by Dr. Trevor A. Hamlin and Ken Yamazaki to investigate the origin of enantioselectivity as well as rationalisation of the catalyst design.

2.2 Introduction

2.2.1 Importance of quinazolines and their derivatives

Heterocyclic organic compounds containing a quinazoline core or its derivatives are commonplace amongst natural products and potent drug substances used in the clinic.[1-10] Considerable research has been done to explore their broad range of biological and medicinal activities including anti-microbial, anti-malarial, anti-inflammatory, anti-convulsant, anti-hypertensive, anti-oxidant, anti-viral, anti-HIV and anti-cancer.[1] Some of the representative structural diversity found in these species and their related activities are illustrated in **Figure 9A**. Branching at the C_4 position is particularly prevalent and highlights the importance of methods able to effect stereoselectivity at this position.[11-14] They include, for instance, DPC 963, a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV treatment,[11] fungicidal 2-azolyl-3,4-dihydroquinazolines compounds[12] and the anti-human cytomegalovirus drug, letermovir (**Figure 9B**).[13-14]

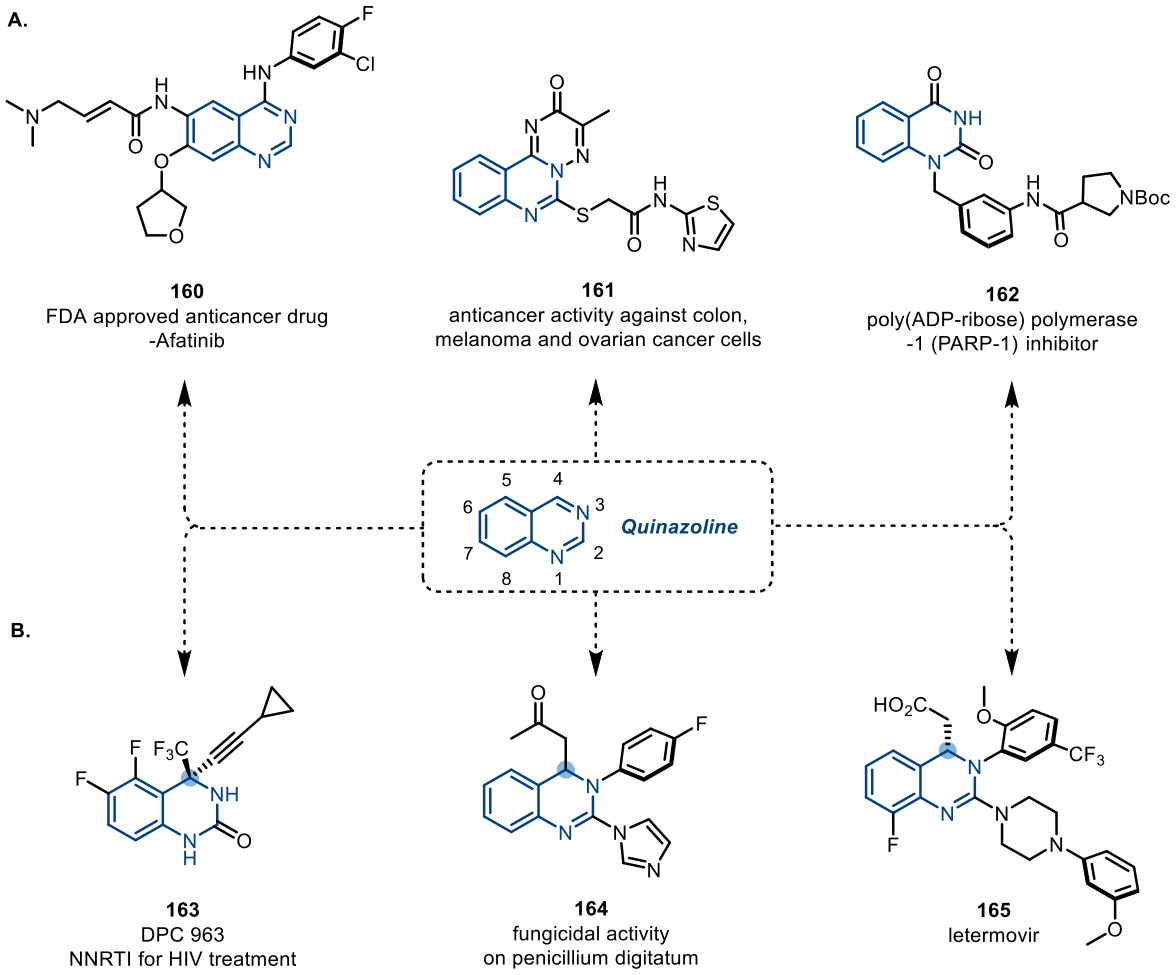


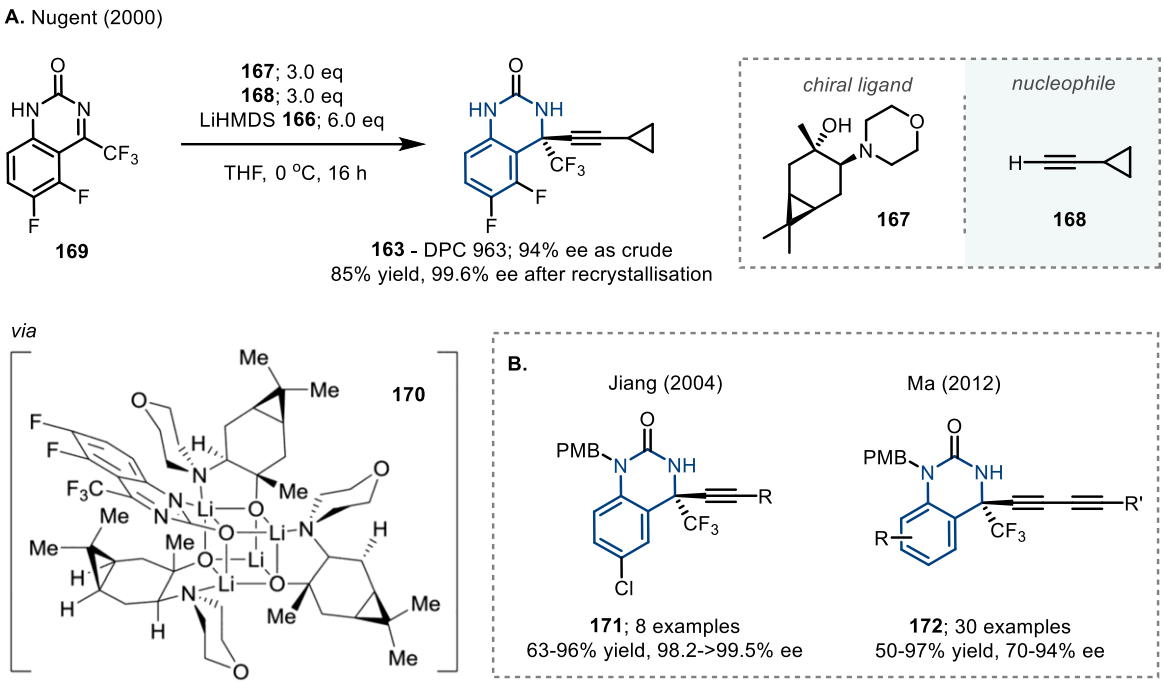
Figure 9. **A.** Representative pharmaceutically active compounds containing a quinazoline core or derivatives thereof; **B.** Representative pharmaceutically active hydroquinazolines bearing a sp^3 carbon at C_4 position.

2.2.2 Enantioselective preparation of hydroquinazolines

2.2.2.1 Nucleophilic additions to cyclic-CF_3 ketimines

Although much effort has been directed towards the synthesis of hydroquinazoline compounds,[15-20] highly enantioselective catalytic methods are still rare. To the best of our knowledge, the first example of enantioselective preparation of an hydroquinazoline core was reported by Nugent and co-workers at DuPont in 2000 (**Scheme 30A**).[21] The authors applied 3.0 equivalents of LiHMDS (**166**) as a strong base together with a chiral amino alcohol (**167**) additives to promote the addition of ethynylcyclopropane (**168**) to a cyclic ketimine (**169**) en route to DPC 963 (**163**). The NNRTI inhibitor was obtained with high yield and 94% ee while a single recrystallisation could further improve its enantiomeric excess to 99.6%. Later

mechanistic studies (NMR spectroscopic analysis and DFT calculations) by Collum and co-workers demonstrated a tetramer intermediate **170** consisting of chiral ligand **167** and ketimine **169** (3 : 1) which was prone to the external attack of lithium cyclopropylacetylide.[22, 23] The reaction scope of this transformation was subsequently expanded to enable use of various alkyl alkynes and diynes as nucleophiles by Jiang[24] in 2004 and Ma[25] in 2012 respectively (**Scheme 30B**). In both cases, excellent reactivity and enantioselectivity were achieved by applying Zn(II) salt together with chiral additives.



Scheme 30. **A.** Nugent's enantioselective addition of ethynylcyclopropane to cyclic ketimine; **B.** Jiang and Ma's preparation of chiral hydroquinazolines by enantioselective additions of alkynes to cyclic ketimines.

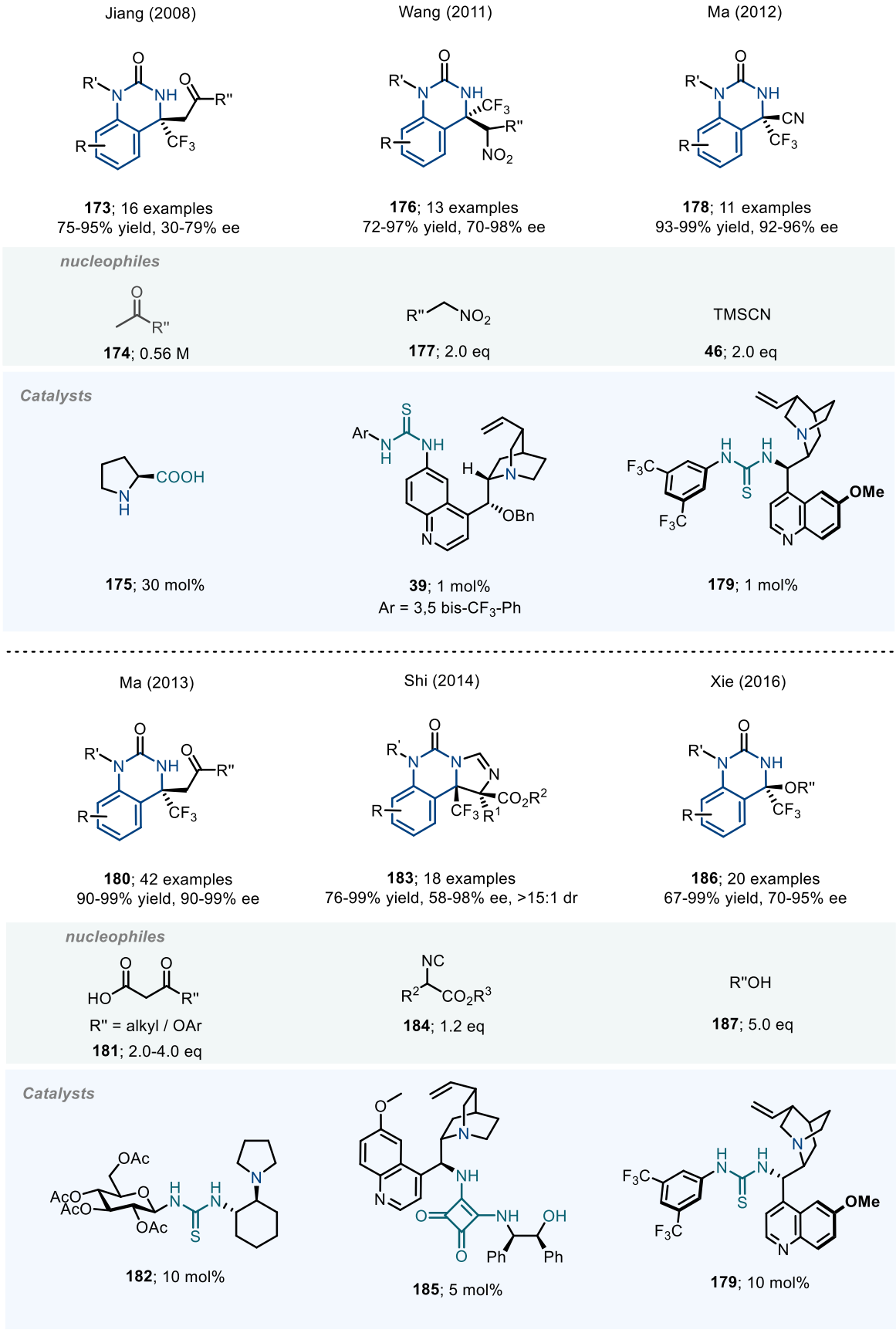
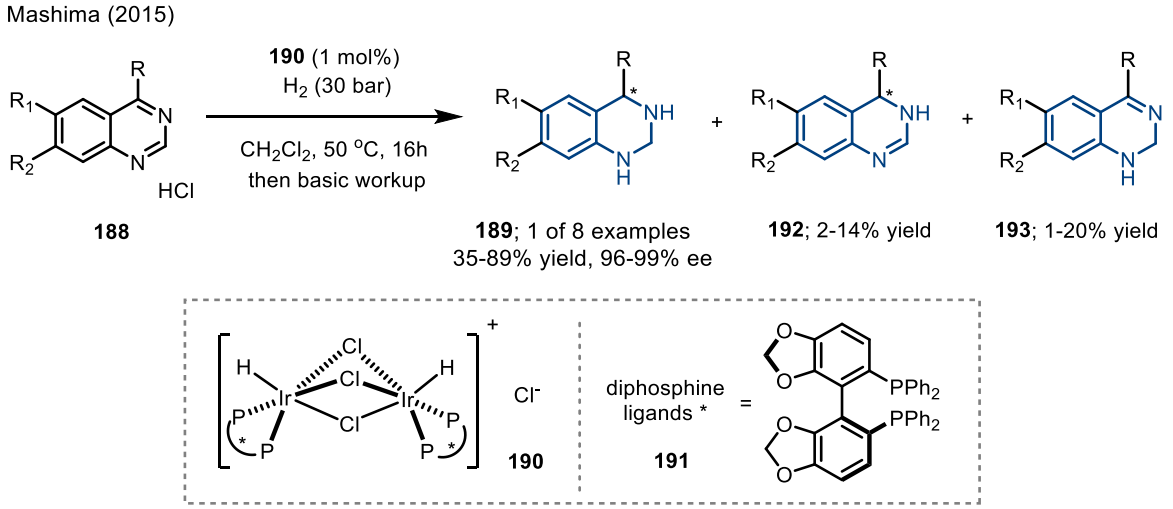


Figure 10. Enantioselective addition of various nucleophiles to cyclic ketimines with metal free catalysis. R' = PMB / H

Inspired by Nugent's seminal report, an extensive range of organo-catalysed highly enantioselective addition reactions to reactive cyclic ketimines using ketones[26] (**174**), nitroalkanes[27] (**177**), nitriles[28] (**46**), beta-keto acids[29, 30] (**181**), isocyanoacetates[31] (**184**) and alcohols[32] (**187**) nucleophiles, were developed in the following 20 years (**Figure 10**). Typically, these transformations relied on 1-10 mol% Brønsted base / H bond donor bifunctional organocatalysts. It is worth noting that all these chiral dihydroquinazolines bearing a trifluoromethyl group in the newly generated quaternary carbon centre could serve as key precursors to access the anti-HIV agent DPC 963 (**163**) or close analogues and have indeed enabled the preparation process for these drugs in the clinical, launch and sale quantities.[33]

2.2.2.2 Enantioselective hydrogenation of quinazolinium salts

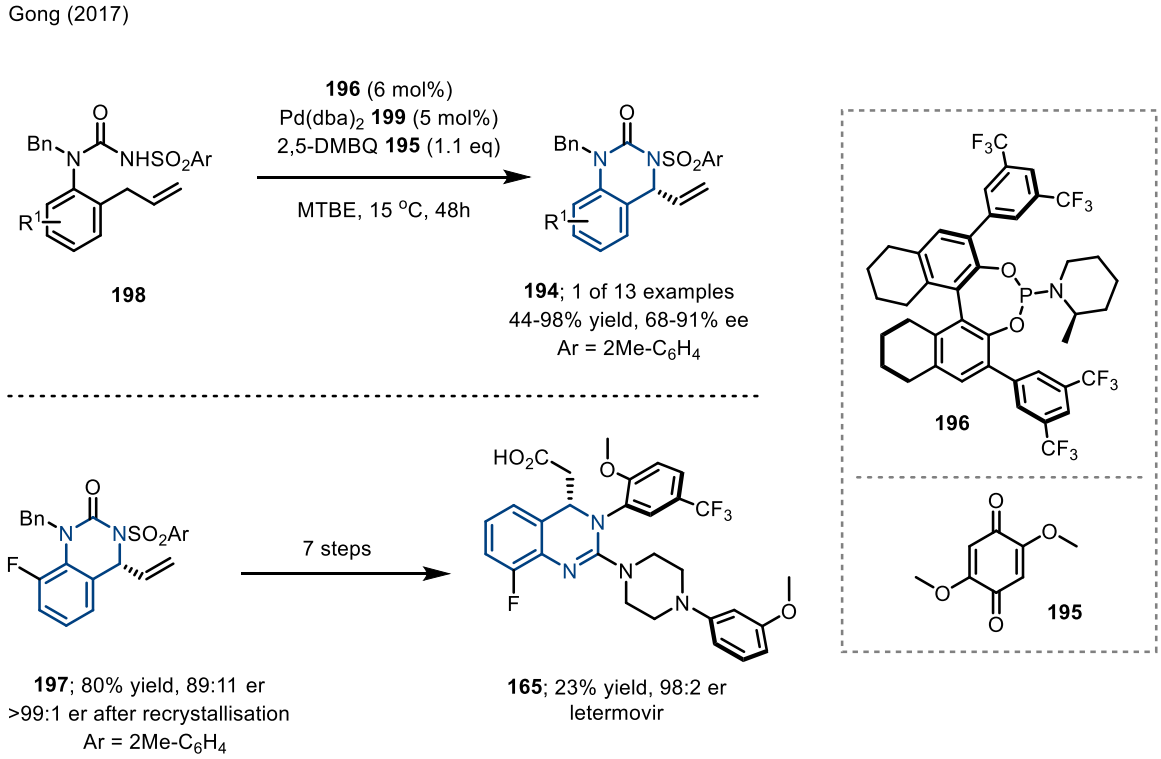
In 2015, the Mashima group developed an enantioselective hydrogenation of quinazolinium salts **188** to yield tetrahydroquinazolines **189** with excellent enantioselectivity using a chiral iridium catalyst.[34] (**Scheme 31**) A halide-bridged dinuclear iridium complex **190** bearing (*S*)-SEGPHOS **191** as chiral ligands accounted for the high enantioselectivity (96-99% ee) of the desired fully reduced product. This transformation featured some limitations such as a) 1-20% of semi-reduced dihydroquinazolines **192** and **193** as minor products; b) requirement of high hydrogen pressure (30 bar); c) the fully reduced *N*-six membered ring could impose some restrictions on the late-functionalisation. It was, however, a rare example furnishing enantioenriched hydroquinazoline skeletons other than the aforementioned anti-HIV drug analogues.



Scheme 31. Mashima's Ir-catalysed enantioselective hydrogenation of quinazolinium salts.

2.2.2.3 Enantioselective intramolecular allylic C-H amination

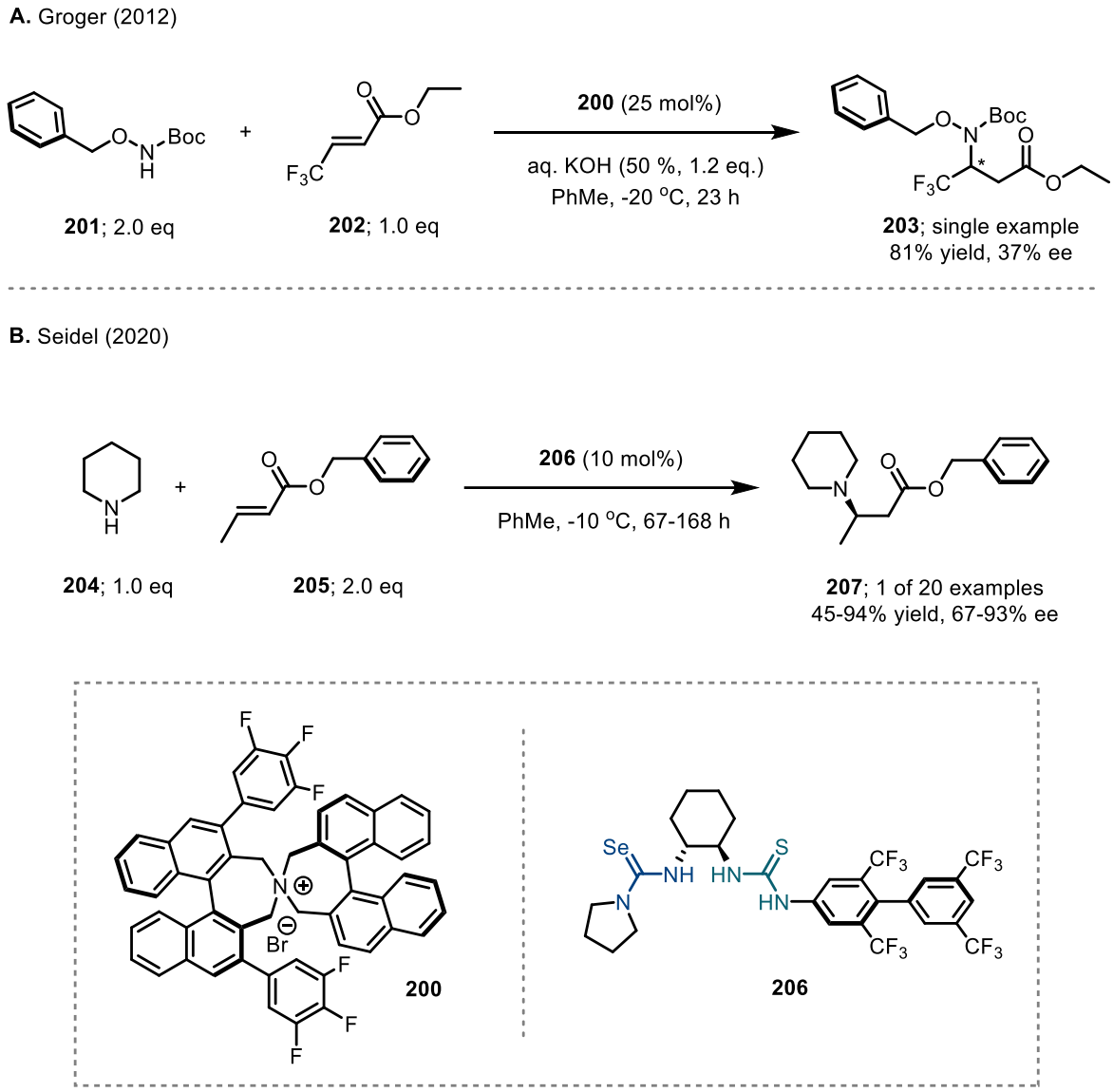
Another metal catalysed synthesis of a chiral hydroquinazoline core was reported by Gong and co-workers in 2017 (**Scheme 32**).[35] A palladium-catalysed enantioselective intramolecular allylic C–H amination to generate the chiral hydroquinazoline **194** in good yield and high enantioselectivity was demonstrated. The method relied on using 2,5-DMBQ **195** as an external oxidant for the palladium catalytic cycle and a tethered aryl-sulfonyl urea species as the aminating reagent. A BINOL-derived phosphoramidite ligand **196** was found to provide a suitable chiral environment and accelerate the amination process of the activated allylic C–H. The aminated product **197** could be recrystallised to enantiopure materials, and the benzyl or arenesulfonamide protecting groups could be later removal to enable further downstream modification. Potential applications of this work in the pharmaceutical chemistry was demonstrated by an enantioselective preparation of letermovir **165** from enantiopure **197** *via* a seven-step synthesis without significant loss in enantiomeric purity.



Scheme 32. Gong's enantioselective allylic C-H amination by with chiral palladium catalysis.

2.2.2.4 Enantioselective *aza*-Michael reaction

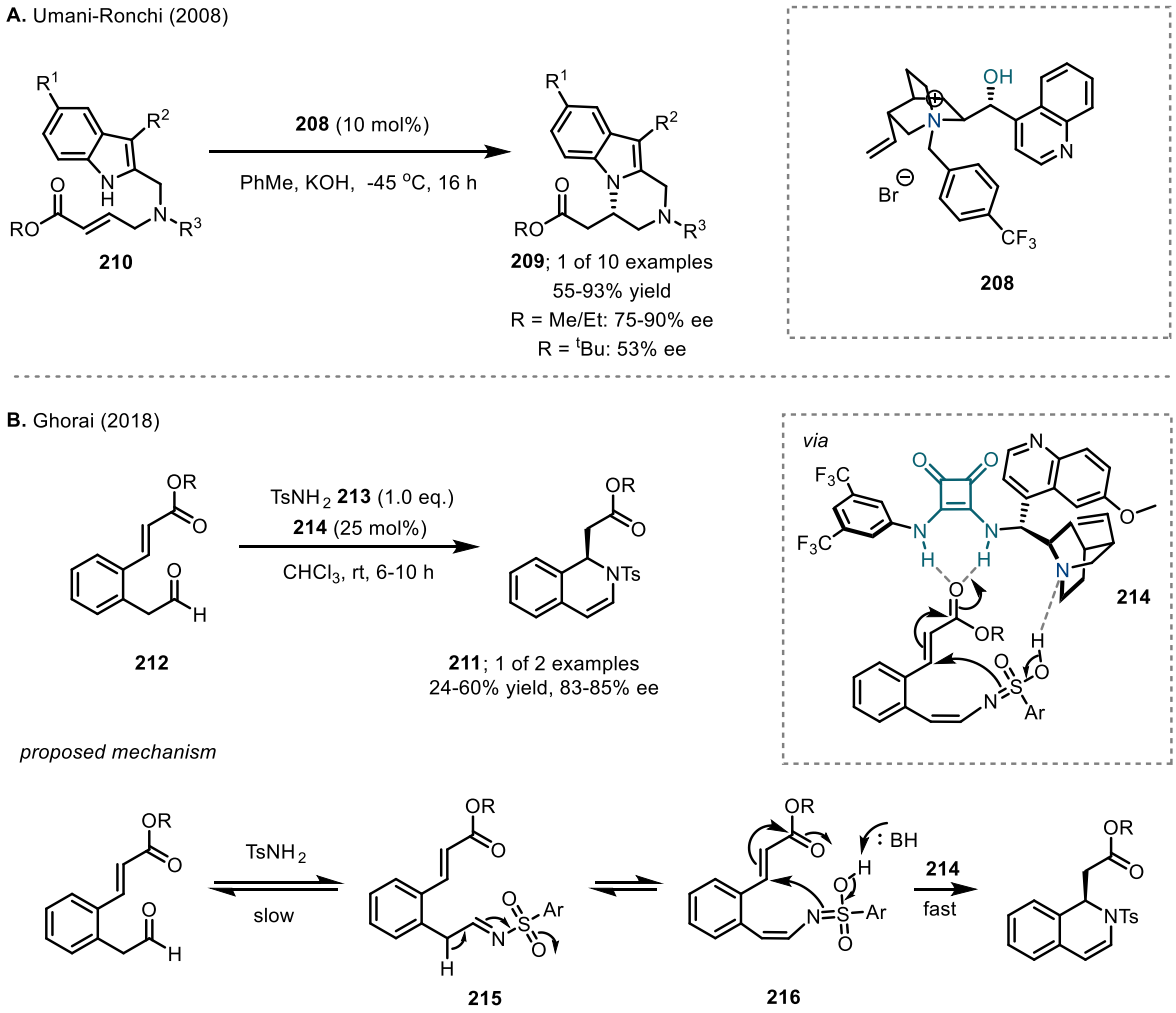
Enantioselective *aza*-Michael reaction enabled by metal-free catalysts is one of the most powerful and promising approaches to enable stereoselective *C-N* bond formation and furnish valuable synthetic intermediates for natural product and active pharmaceutical ingredients synthesis.[36-42] Representative examples include addition of *N*-silyloxycarbamates to α,β-unsaturated aldehydes[43]; primary amines to nitroalkenes[44, 45] and indolines to α,β-unsaturated ketones[46]. Relevant intermolecular *aza*-Michael reactions involving unbiased/unactivated Michael acceptors such as α,β-unsaturated esters yet remains largely unsolved due to their low electrophilicity.[47] To the best of our knowledge, only two such examples have been reported to date. Groger and co-workers reported in 2012 the first enantioselective intermolecular *aza*-Michael addition to α,β-unsaturated esters with metal-free catalysis.[48] (**Scheme 33A**) A chiral phase-transfer catalyst (PTC) **200** together with aqueous KOH were suitable to promote the addition of benzyloxycarbamate **201** to an activated CF_3 ethyl crotonate **202**. Although satisfactory yield of the desired β-amino ester **203** was obtained (up to 81% yield), only moderate level of enantioselectivity was observed (37% ee). A more recent and impressive example was demonstrated by Seidel in 2020 (**Scheme 33B.**)[49]. The authors disclosed the first enantioselective conjugate addition of cyclic amines **204** to unactivated α,β-unsaturated esters **205** catalysed by an unprecedented bifunctional selenourea-thiourea organocatalyst **206**. This transformation featured excellent yield and enantioselectivity (up to 94% yield and 93% ee) albeit with very long reaction time (67-168 h).



Scheme 33. **A.** Groger's enantioselective intermolecular *aza*-Michael addition of benzyloxycarbamate to CF_3 ethyl crotonate with chiral phase-transfer catalyst. **B.** Seidel's enantioselective intermolecular *aza*-Michael addition of cyclic amines to unactivated α,β-unsaturated esters with a bifunctional selenourea-thiourea organocatalyst.

Intramolecular versions are also known.[50] In 2008, Umani-Ronchi and co-workers developed an enantioselective synthesis of 3,4-dihydropyrazino[1,2-*a*]indol-1(*2H*)-ones *via* an *N*-benzylcinchonidinium bromide **208** catalysed ring-closing intramolecular *aza*-Michael reaction (IAMR) of indolyl ester **210** (**Scheme 34A**).[51] Under a phase-transfer regime, in combination with KOH, catalyst **208** delivered the desired pyrazinoindol-1-ones **209** in up to 93% yield and up to 90% ee. The electron-withdrawing CF_3 substituent on the benzyl group of the catalyst was found to be crucial for high

enantioselectivity as it strengthened the contact ion pairing substrate–catalyst interaction. Substrates **210** bearing both electron- donating and withdrawing substituents on the indolyl scaffold underwent the cyclisation with good yield and enantiocontrol while the limitation of this transformation was indicated by the intolerance of sterically demanding esters (R = ^{t}Bu: 53% ee).

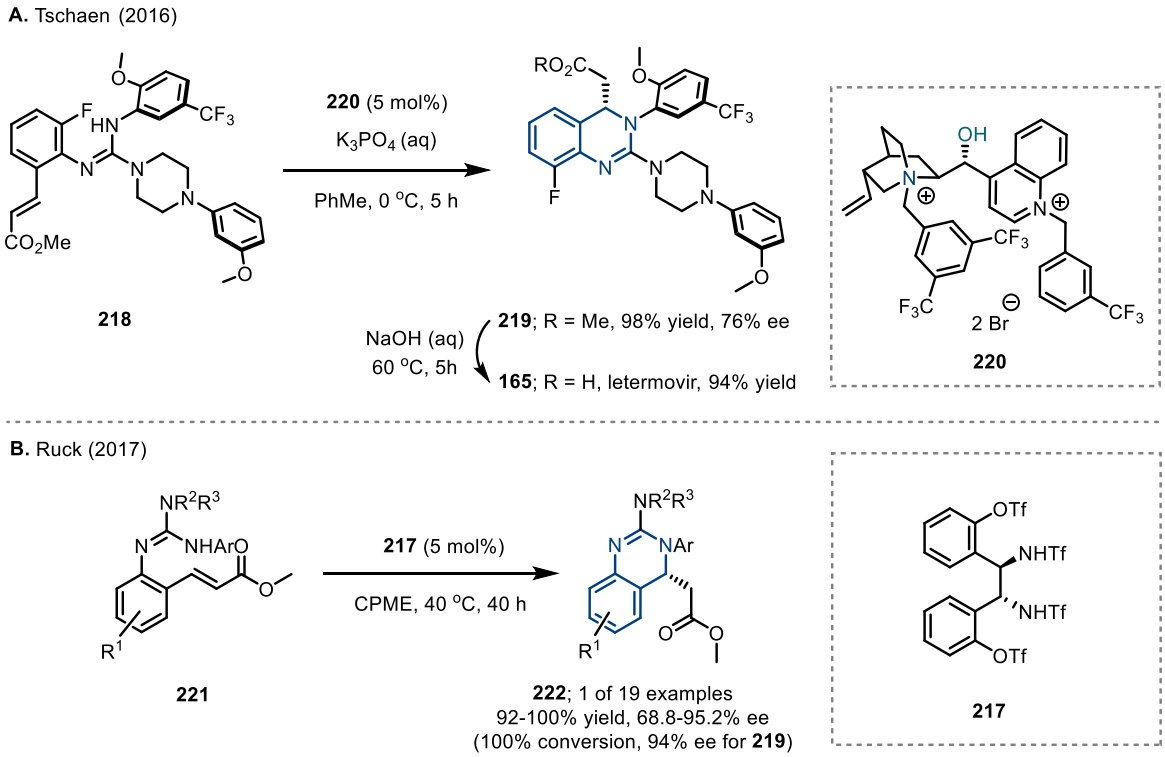


Scheme 34. **A.** Umani-Ronchi's enantioselective intramolecular *aza*-Michael additions of indoles to α,β-unsaturated esters. **B.** Ghorai's enantioselective intramolecular *aza*-Michael additions of *in-situ* generated enamines to α,β-unsaturated esters.

Another organocatalysed enantioselective intramolecular *C-N* bond formation through *aza*-Michael addition to α,β-unsaturated esters was described by the Ghorai group in 2018.[52] (**Scheme 34B**) The authors demonstrated the synthesis of enantiomerically enriched dihydroisoquinolines **211** *via in-situ* enamine generation from *ortho*-homoformyl cinnamate **212** / $TsNH_2$ **213** condensation and a subsequent chiral cinchona-derived squaramide **214** catalysed IAMR reaction. The ring closure outcome can be

rationalised by the faster **214** catalysed enantioselective *N*-cyclisation process compared to the formation of either imine **215** or enamine **216**. The ester moiety was effectively activated by the catalyst's squaramide moiety towards the conjugate addition of the enamine nucleophile *via* substrate-catalyst hydrogen bonding interaction. Notably, this work represents the very first enantioselective *aza*-Michael reaction of enamines with hydrogen-bond-donor catalysts.

Specifically, the application of such powerful IAMR reactions for the preparation of chiral hydroquinazoline cores is rather undeveloped. There are only two reports of catalytic enantioselective addition of *N*-based pronucleophiles to α,β-unsaturated esters to construct these pharmaceutically and biologically relevant skeletons. In 2016, moderately enantioselective (76% ee) phase-transfer-catalysed IAMR reaction was described by Tschaen and coworkers en route to letermovir **165** (**Scheme 35A**).[53] This transformation was further explored in 2017 by Ruck and co-workers with significant improvement (higher enantioselectivity across a broader substrate scope) with a C_2-symmetric, dual hydrogen-bond donating bistriflamide **217** (**Scheme 35B**).[54] However, only *N*-aryl nucleophiles were compatible and transformation is limited to guanidine-containing products.



Scheme 35. Enantioselective intramolecular *aza*-Michael additions of pronucleophilic guanidines to tethered α,β-unsaturated esters with metal-free catalysis towards the synthesis of chiral hydroquinazoline cores.

2.2.3 Aim of the project

Despite these elegant advances in the field, new and more versatile synthetic methods to access such optically active hydroquinazoline-based molecular skeletons are still highly attractive owing to their tremendous therapeutic potential, especially for unactivated systems and under metal free catalysis. Among the most powerful approach is the direct organocatalysed enantioselective IAMR reaction. The rather high pK_a of *N*-based pronucleophiles is the main challenge of this approach and only highly electrophilic Michael acceptors such as α,β- unsaturated ketones or aldehydes have been fully exploited to date. As a consequence, identification of new catalyst systems that are capable of effectively activating challenging nitrogen-centred pronucleophiles and α,β- unsaturated esters towards Michael addition chemistry would significantly advance the field.

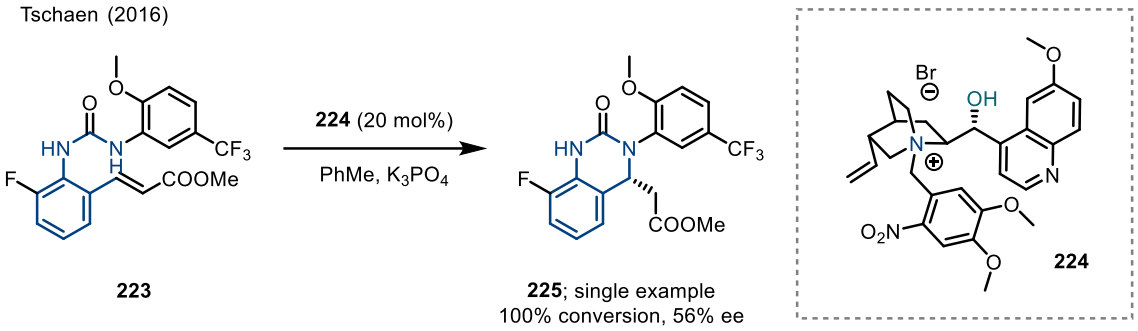
Against this backdrop, we envisaged that the enhanced Brønsted basicity and broadly tunable structure of the bifunctional iminophosphorane (BIMP) superbase catalyst system developed by Dixon and co-workers, (such as those described in **Chapter 1.6**) could provide the solution to the challenging pK_a related reactivity and modest stereocontrol in the IAMR, allowing the expeditious synthesis of enantioenriched hydroquinazoline cores. Additionally, this would represent the first example of an enantioselective *aza*-Michael addition to α,β-unsaturated esters enabled by BIMP catalysis.

2.3 Reaction Discovery and Optimisation

2.3.1 Proof of Concept

Instead of guanidines, we considered a urea moiety (pK_a of diphenylurea= 19.5 in DMSO) as the pronucleophile in the IAMR reaction towards the synthesis of enantioenriched hydroquinazolines. Notably, there appears to be only one single report of activating ureas in the IAMR reaction involving α,β-unsaturated esters as Michael acceptors reported by Tschaen and co-workers prior to development of the herein reported method.[53] With the attempt of accessing enantioenriched letermovir, the authors treated urea **223** with a biphasic toluene and aqueous K_3PO_4 mixture and 20 mol% phase transfer catalyst **224** which afforded the Michael product **225** smoothly (100% conversion) yet only in moderate

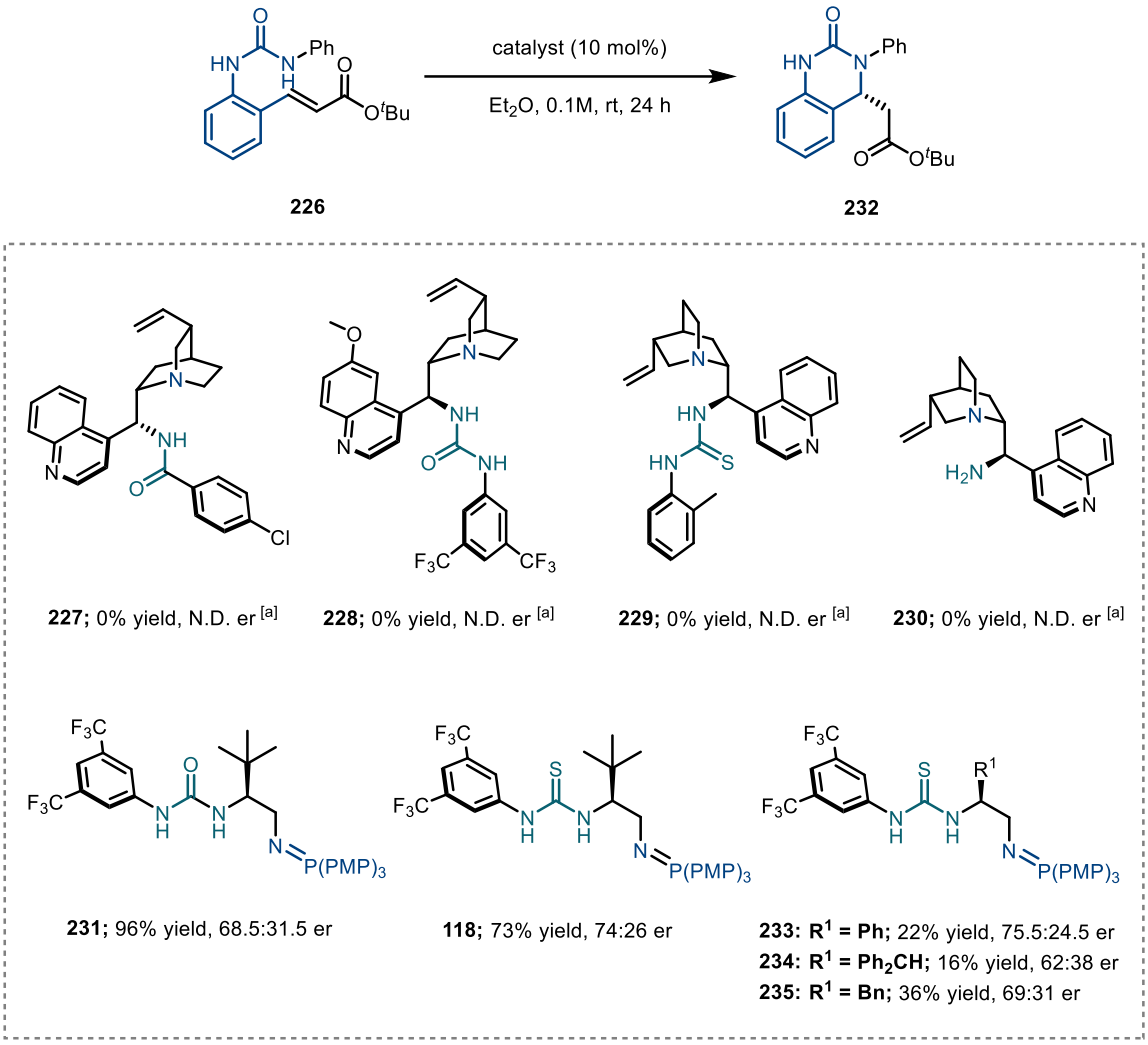
enantioselectivity (56% ee) (**Scheme 36**). The incompetence of the *cinchona*-derived catalytic system in the Michael reaction was seen to be caused by the moderate basicity of the *in-situ* generated Brønsted base, encouraging our consideration of super-Brønsted basic BIMP system in the following investigation.



Scheme 36. Tschaen's enantioselective intramolecular *aza*-Michael additions of pronucleophilic urea to tethered α,β unsaturated ester with phase-transfer catalysis towards the synthesis of chiral hydroquinazoline core.

2.3.2 Catalyst Screen

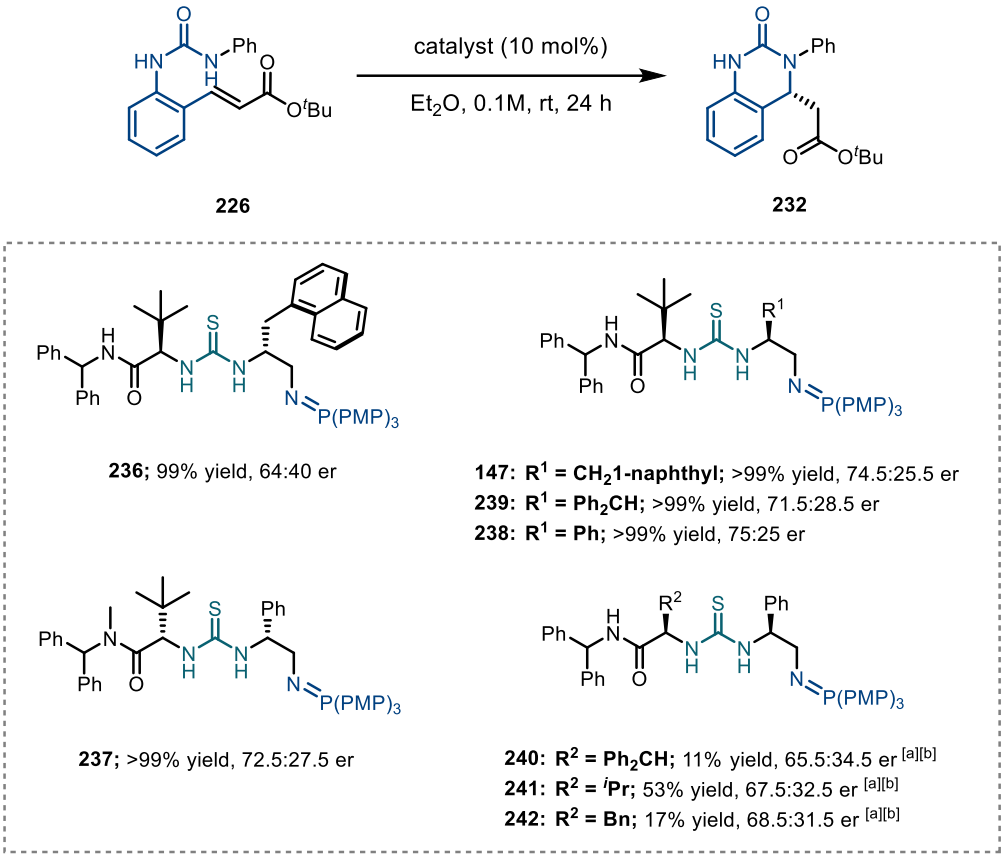
A similarly structured urea **226** bearing an α,β-unsaturated *tert*-butyl ester was chosen as the model substrate for the IAMR reaction. We began our studies by assessing various *cinchona*-based bifunctional organocatalysts possessing different H-bond donors including amide **227**, urea **228**, thiourea **229** and primary amine **230** (**Scheme 37** top). Expectedly, all of them failed to deliver any detectable product in toluene at room temperature after 24 hours. By contrast, the 1st generation BIMP catalyst **231** smoothly provided the desired hydroquinazoline **232** in 96% isolated yield and 68.5:31.5 er under similar conditions, highlighting the role of the superbasic iminophosphorane moiety in the transformation. (**Scheme 37** bottom). Having identified excellent reactivity, we then performed a series of modifications to the BIMP catalyst structure to optimise the IAMR reaction. Altering the H-bond donor from a urea to the more acidic thiourea **118** improved the enantioselectivity to 74:26 er but reduced the isolated yield to 73%. Further variation of the substituents adjacent to the iminophosphorane only slightly uplifted the enantioselectivity to 75.5:24.5 er but demonstrating poor reactivity. (**233** to **235**)



Scheme 37. Screening of *Cinchona*-based bifunctional organocatalysts and 1st generation BIMP catalysts; Reactions were carried out with 0.05 mmol **226**; All yields are isolated yields; er determined by HPLC analysis on a chiral stationary phase; N.D. = not determined; rt = room temperature; PMP = *para*-methoxy phenyl; [a] = reaction carried out in toluene.

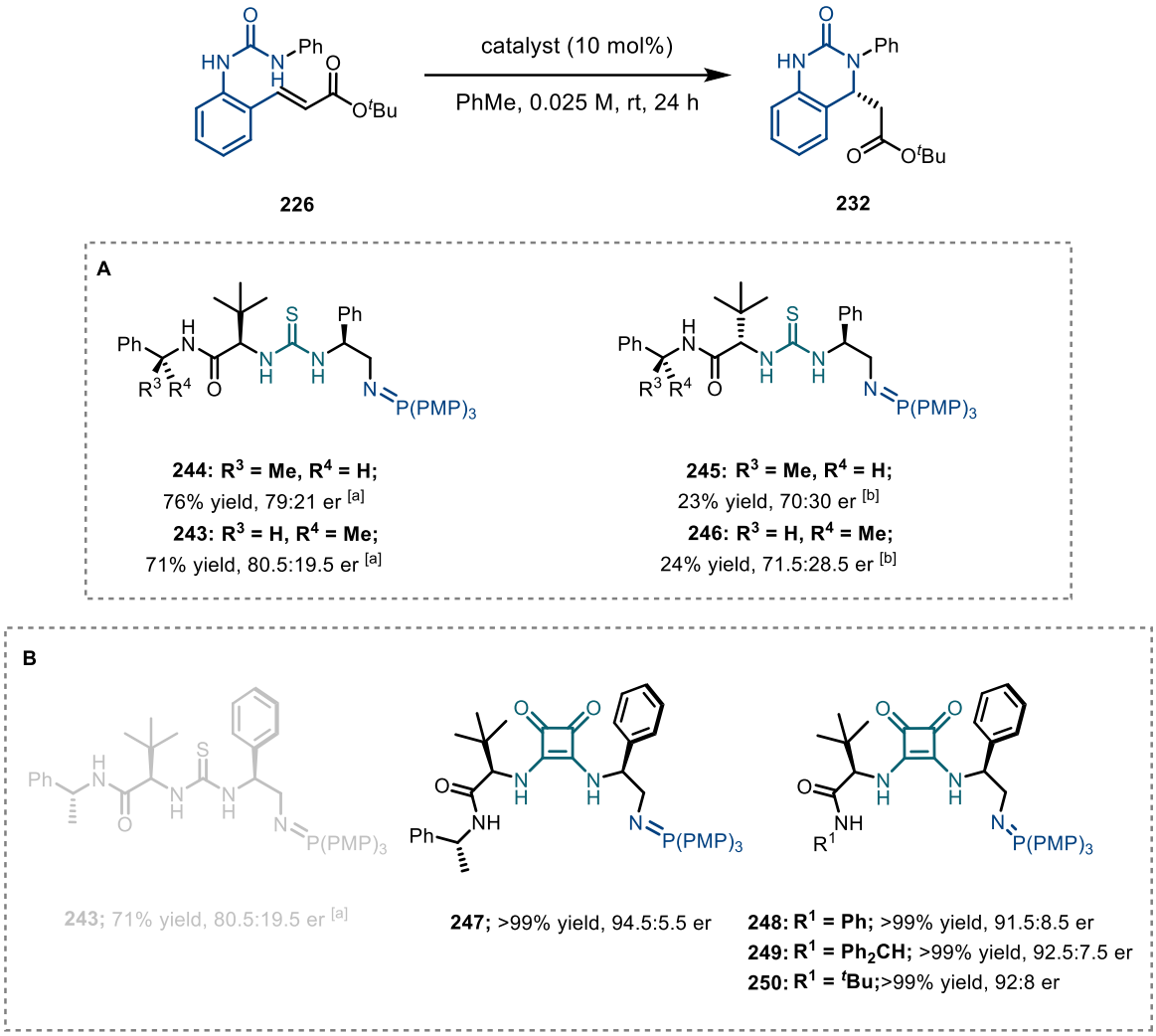
Without any further improvement realised by 1st generation BIMPs, we then considered the introduction of a second distal stereogenic centre adjacent to the thiourea motif in the catalyst which allowed for a rapid library generation. These 2nd generation BIMPs systems solved the issue of poor reactivity from previous optimisation studies, typically giving the Michael adduct in quantitative yield after 24 hours. **Scheme 38** presents the data from out catalyst structure performance study. Notably: A) Catalyst bearing phenyl and *t*Bu-substituted stereo-centres was found to be the optimal skeleton; B) *Cis*-configuration of substituents as drawn on the two stereogenic centre displayed better performance than

the *trans*-one (comparing **147** and **236**); C) The LHS amide H bond donor of BIMP also played a role in the substrate-catalyst binding process (comparing **237** and **238**), albeit with only a moderate effect.



Scheme 38. Screening of 2nd generation BIMP catalysts. Reactions were carried out with 0.05 mmol **226**; all yields are isolated yields; er determined by HPLC analysis on a chiral stationary phase; PMP = *para*-methoxy phenyl; [a] = reaction carried out in 0.025M toluene; [b] = 4 hours reaction time.

A third stereogenic centre adjacent to the amide moiety led to an increase in the enantioselectivity to 80.5:19.5 er with catalyst **243** slightly outcompeting other diastereomeric catalysts **244**, **245** and **246** **(Scheme 39A)**. Pleasingly, with the chiral backbone of the catalyst untouched, a squaramide substitution for the thiourea H bond donor (catalyst **247**) greatly improved the enantio-induction to 94.5:5.5 er, together with quantitative yield (>99%) **(Scheme 39B)**. This major selectivity enhancement is potentially owing to the squaramide's higher acidity and thus stronger hydrogen bonding interaction with substrates and/or its differing bond angle and thus modified 3D structure.[55-60] Additional fine-tuning of the amide moiety did not lead to any improvements on the reaction stereoselectivity. (see **Chapter 4.2.1** for optimisation details).

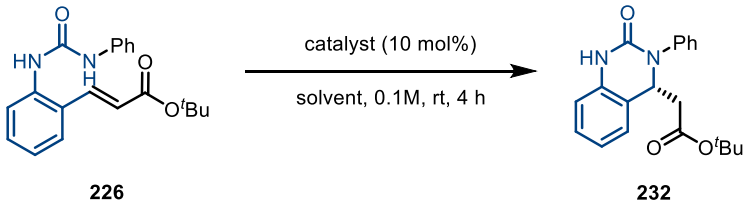


Scheme 39. Further screening of 2nd generation BIMP catalysts. Reactions were carried out with 0.05 mmol **226**; all yields are isolated yields; er determined by HPLC analysis on a chiral stationary phase; PMP = *para*-methoxy phenyl; [a] = 10 hours reaction time; [b] = 4 hours reaction time.

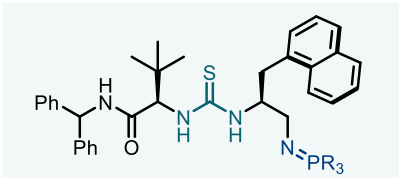
2.3.2 Phosphine screen

During the optimisation process, we also carried out some phosphine screening studies to showcase how basicity and steric environment of the iminophosphorane catalyst component affected the IAMR reaction. (**Scheme 40**) This was achieved by simply varying the electronic and steric parameters of the phosphine candidates used in the BIMP preparation process. With a PPh_3 **251** derived BIMP the yield dropped to 24% while ee remained similar. With *para*-Cl PPh_3 **252**, no reaction was observed. With other tri-aryl-phosphine ligands including **253**, **254** and **255**, ee was decreased by 11%, 23% and 18% respectively. Finally, alkyl phosphines such as $P(^nBu)_3$ **256** and **257** or ferrocene-incorporated phosphine

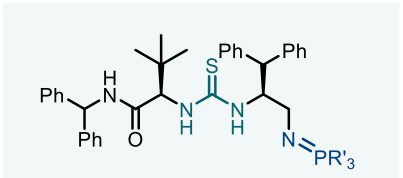
258 did not lead to any improvement in enantioselectivity. Hence, $P(PMP)_3$ was selected as the optimal phosphine component during the reaction condition investigation including solvent, concentration, catalyst loading and temperature. (see **Chapter 4.2.1** for optimisation details).



226 **232**

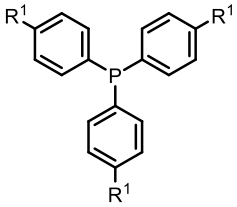


147: **R = PMP;** >99% yield, 76.5:23.5 er [a]

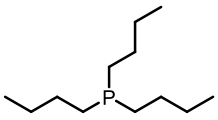


239: R' = PMP; >99% yield, 71.5:28.5 er [b]

PR_3 = [c]

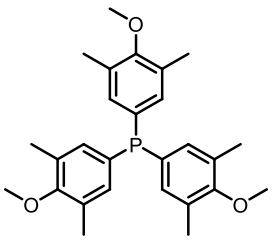


251: R^1 = H; 24% yield, 76:24 er
252: R^1 = Cl; 0% yield, N.D.

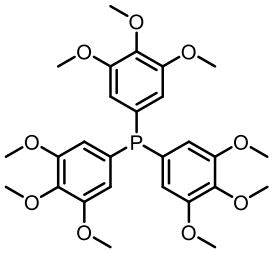


256; >99% yield
65:35 er [b]

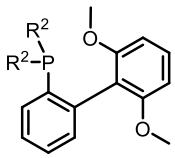
PR'_3 = [d]



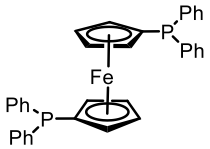
253; 76% yield, 66:34 er



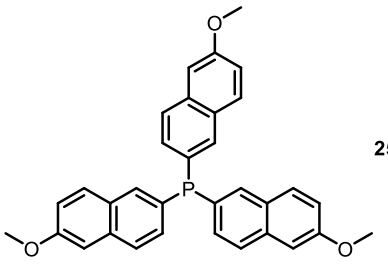
254; 31% yield, 60:40 er



257: R^2 = Cy
>99% yield, 60:40 er



258; (dppf) 44% yield
69:31 er

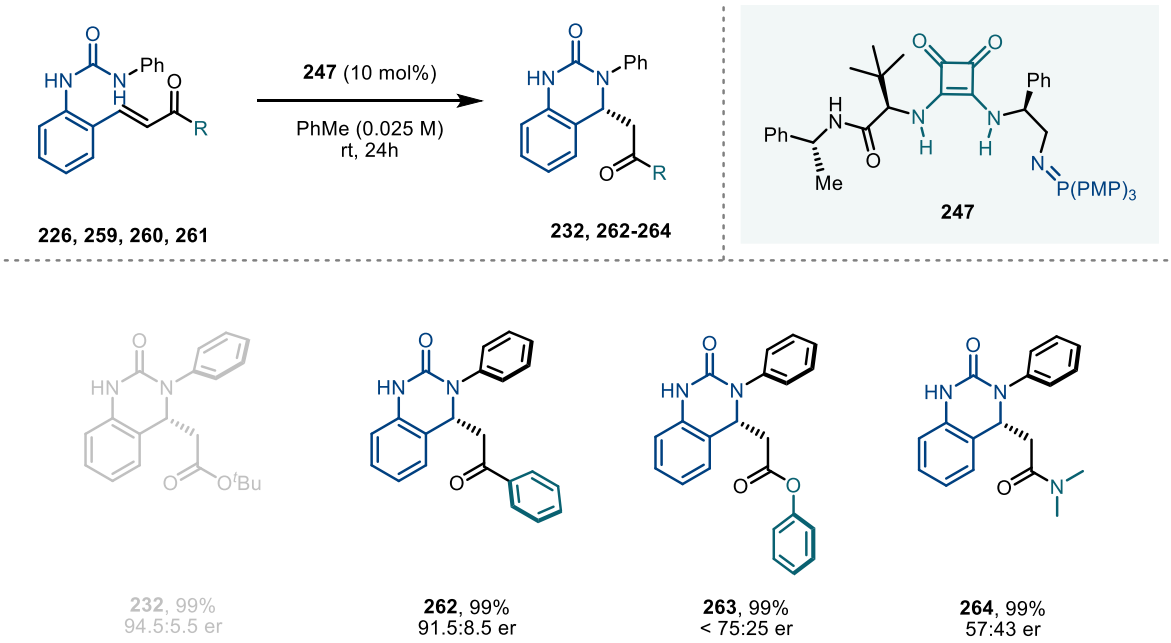


255; 24% yield
62.5:37.5 er

Scheme 40. Screening of phosphines. Reactions were carried out with 0.05 mmol **226**; all yields are isolated yields; er determined by HPLC analysis on a chiral stationary phase; PMP = *para*-methoxy phenyl; dppf = 1,1'-Bis(diphenylphosphino)ferrocene; [a] 9 hours reaction time; [b] 24 hours reaction time; [c] = reaction carried out in toluene; [d] = reaction carried out in Et_2O;

2.3.3 Evaluation of other conjugate acceptors

In addition to the α,β-unsaturated *tert*-butyl ester, we also examined other conjugate acceptors in the IAMR reaction (**Scheme 41**). Urea **259** and **260** bearing more activated electrophiles including enone and phenyl ester were assessed first.[47] Disappointingly, although almost quantitative yields were obtained in both cases, the IAMR reactions failed to feature satisfactory stereo-induction (91.5:8.5 er and less than 75:25 er respectively). We then examined a less electrophilic *N*, *N*-dimethylacrylamide as the Michael acceptor (**261**).[47] Surprisingly, BIMP **247** still catalysed the IAMR reaction efficiently, albeit with low enantioselectivities (57:43 er).

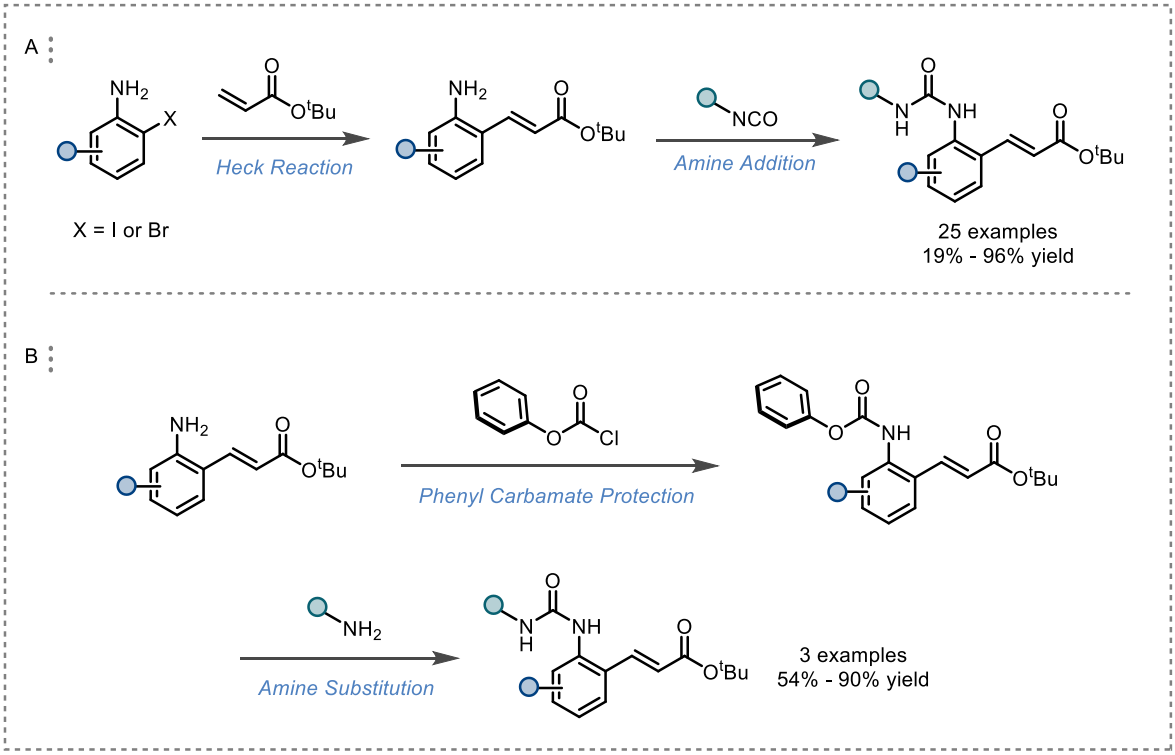


Scheme 41. Evaluation of other conjugate acceptors in the BIMP-catalysed intramolecular *aza*-Michael reaction to α,β-unsaturated ester.

2.4 Substrate Synthesis

With the optimised conditions in hand, we proceeded to prepare an array of urea substrates to explore the scope of the IAMR. General synthetic routes are outlined in **Scheme 42** (see chapter **4.2.3** for full details of experimental conditions and reaction yields). We relied on the palladium-catalysed Heck reaction between 2-iodo / bromo aniline and *tert*-butyl acrylate to construct the *E*-alkene in excellent

yield. The urea functionality was then installed either *via* a direct amine addition (**Scheme 42A**) or a phenyl carbamate protection followed by an amine substitution. (**Scheme 42B**)



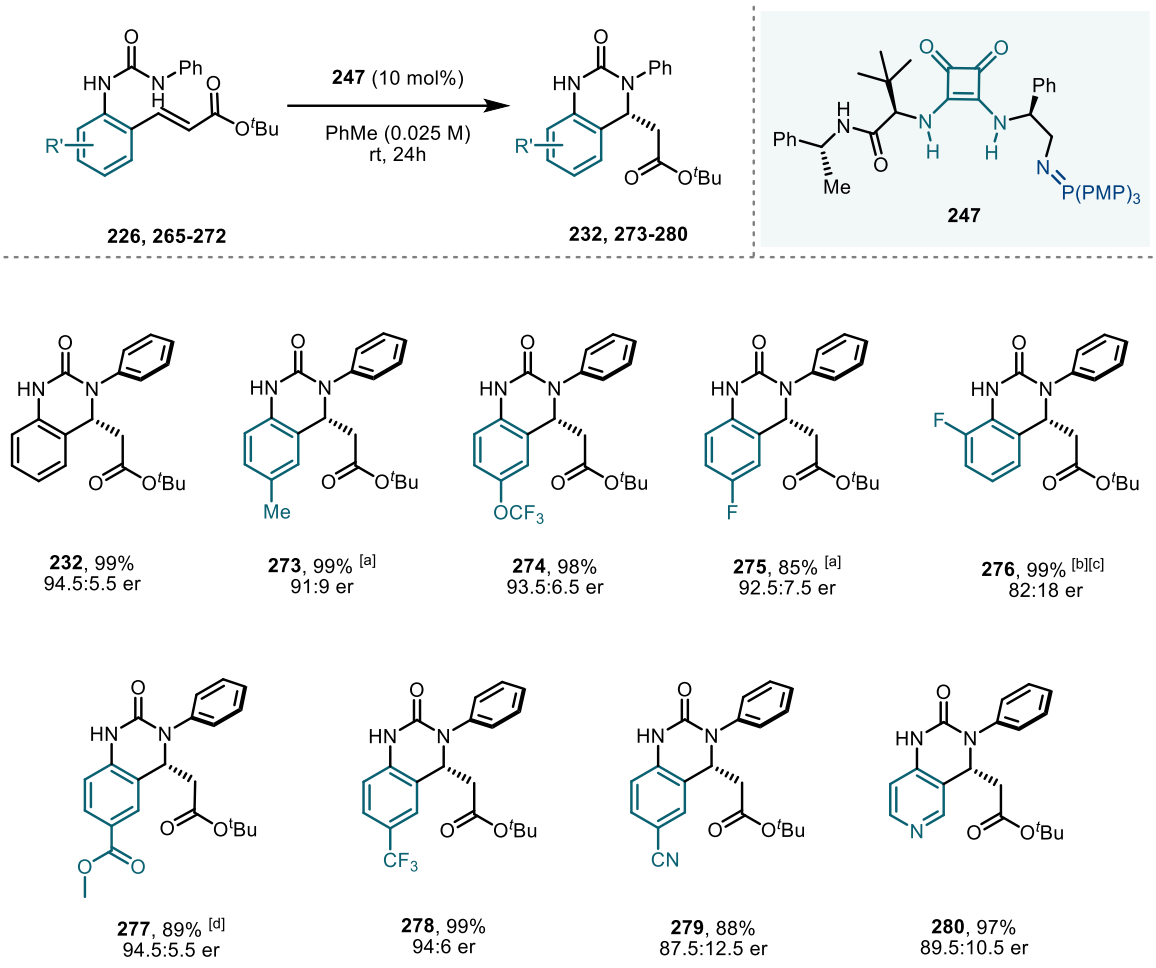
Scheme 42. Representative substrate synthetic routes

2.5 Evaluation of Reaction Scope

2.5.1 Reaction scope with regards to *NH*-aryl substituents

With the optimal catalyst – 10 mol% **247**, conjugate acceptor – α,β-unsaturated *tert* butyl ester and reaction conditions – toluene (0.025 M) at room temperature in hand, the scope of the enantioselective IAMR reaction with regards to *NH*-aryl substituents was then explored (**Scheme 43**). It is worth noting that minimal effort was required to exclude moisture or oxygen from the reaction system. Varying functionalities on the *NH*-aryl core typically resulted in insignificant fluctuation in enantioselectivity. Compatible substituents varied from electron-donating groups such as *para*-methyl (**265**, 99% yield, 91:9 er) and *para*-trifluoromethoxyl (**266**, 98% yield, 93.5:6.5 er) to electron-withdrawing groups such as *para*-fluorine atom (**267**, 85% yield, 92.5:7.5 er), *para*-carboxylic methyl ester (**269**, 89% yield, 94.5:5.5 er), *para*-trifluoromethyl (**270**, 99% yield, 94:6 er) and *para*-cyano (**271**, 88% yield, 87.5:12.5 er). Product with

an *ortho*-fluorine atom substituent was obtained in only moderate ee (**276**, 99% yield, 82:18 er). A pyridine-based aromatic core was also tolerated furnishing the desired Michael adduct **280** in excellent yield (97% yield) and enantioselectivity (89.5:10.5 er) under the standard reaction conditions. It is also worth noting that raised reaction temperatures of up to 80 °C were necessary in some cases (**265** and **266**) to ensure solubility of these urea-based substrates.



Scheme 43. Reaction scope with regards to *NH*-Aryl substituents. Reactions were carried out with 0.2 mmol substrate; [a] 80 °C. [b] 40 °C. [c] 30 hours. [d] 48 hours.

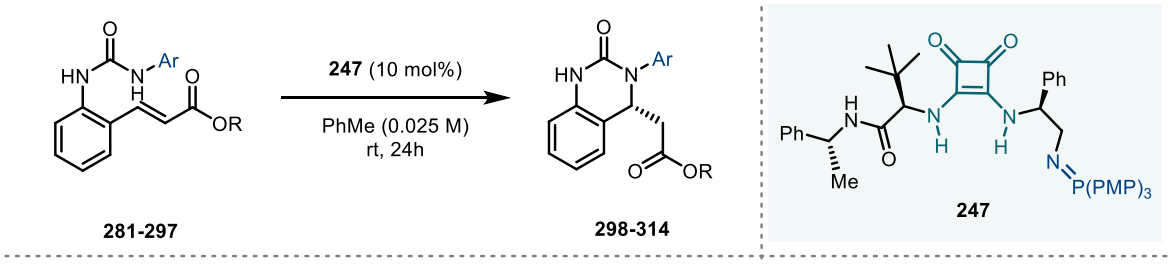
2.5.2 Reaction scope with regards to *N*-aryl substituents

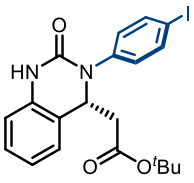
Following the successful evaluation of reaction scope with respect to *NH*-aryl substituents, we then turned our attention to investigate the substituent effect on the *N*-aryl ring (**Scheme 44**). Substrates bearing a single iodine or bromine atom at various ring positions including *para*- and *ortho*-, performed well furnishing the targeted hydroquinazoline core in excellent yield (91% – 99% yield) and high er (92:8

– 93:7 er) (**281** to **283**). Varying position of the electronegative fluorine atom on the *N*-aryl ring gave rise to minimum fluctuation in enantioselectivity of product (**301** to **303**). 3,5-dichloro example **287** was also very efficient (98% yield in 24 hours) with a moderate decrease in stereoinduction (87.5:12.5 er).

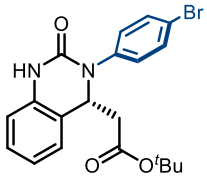
We next assessed the effect of electron-donating substituents on the *N*-aryl ring. IAMR reactions of enhanced electron-rich *N*-aryl rings were found to be slower than usual. This is potentially due to the higher pK_a of the urea protons and thus higher transition state energy barrier in these examples. To preserve the high yield, we applied additional reaction time or elevated temperature of 50 °C for substrates **288** to **291** and pleasingly did not observe any compromising enantio-control. Varying the position of the electro-donating methoxyl group on the *N*-aryl ring led to negligible fluctuation in stereoselectivity of product (**309** to **310**). Interestingly, we observed a slight enhancement of enantioselectivity (96:4 – 97:3 er) with *ortho*-substituents including thiomethyl, *tert*-butyl and ethynyl (**311** to **313**). It is most likely that these sterically bulky functional groups provided an appropriate and positive influence on catalyst-substrate binding, thereby furnishing one enantiomer more preferentially.

Finally, the methyl ester acceptor **297** also proved to be an appropriate substrate. Hydroquinazoline product **314** was obtained in 48 hours under identical reaction conditions in almost quantitative yield and high enantioselectivity (92:8 er).

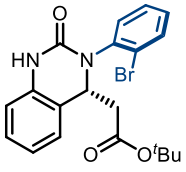




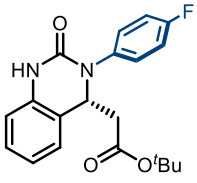
298, 96%
93:7 er



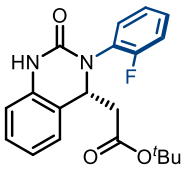
299, 99%
92:8 er



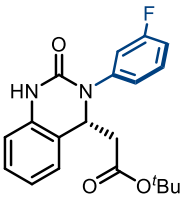
300, 91% [a][b]
93:7 er



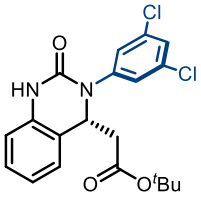
301, 95%
92:8 er



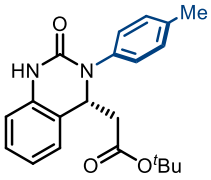
302, 96%
93.5:6.5 er



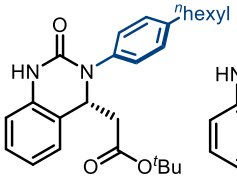
303, 97%
91.5:8.5 er



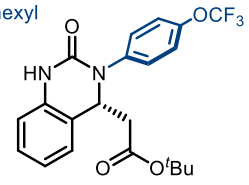
304, 98%
87.5:12.5 er



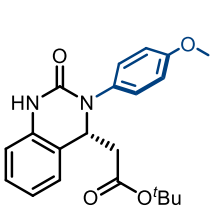
305, 88% [c]
94:6 er



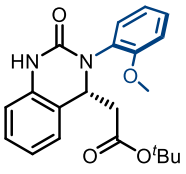
306, 91% [c]
95:5 er



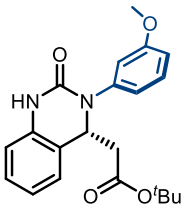
307, 99%
90:10 er



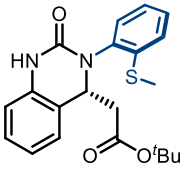
308, 99% [d][e]
92:8 er



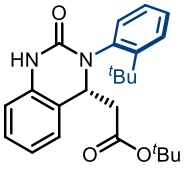
309, 80% [e]
91:9 er



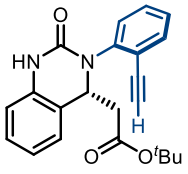
310, 97% [e]
93:7 er



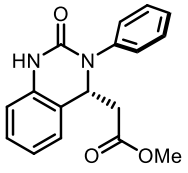
311, 98% [e]
96:4 er



312, 90% [e]
97:3 er



313, 91% [c]
96:4 er

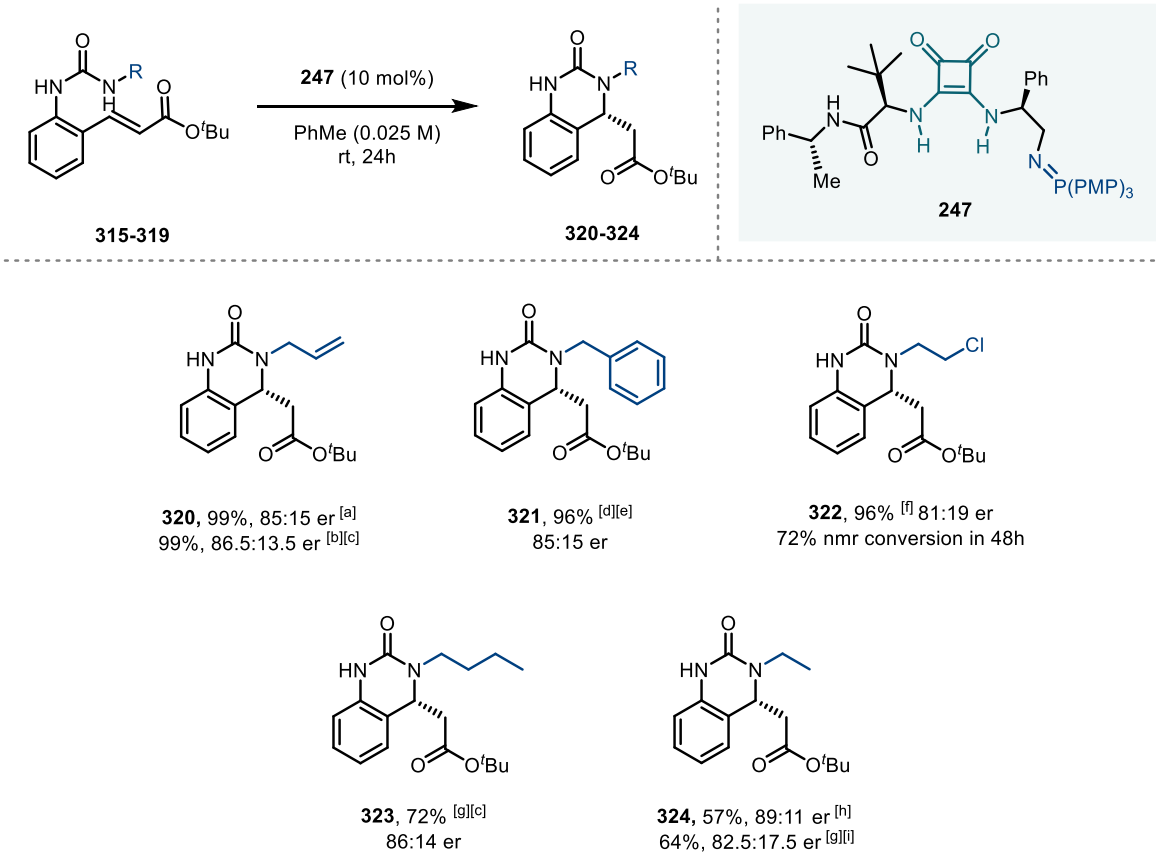


314, 99% [c]
92:8 er

Scheme 44. Reaction scope with regards to *N*-Aryl substituents. Reactions were carried out with 0.2 mmol substrate; [a] 72 hours reaction time. [b] 5 mol% cat. **247** was used. [c] 48 hours reaction time. [d] 30 hours reaction time. [e] Reaction carried out at 50 °C.

2.5.3 Reaction scope with regards to aliphatic ureas

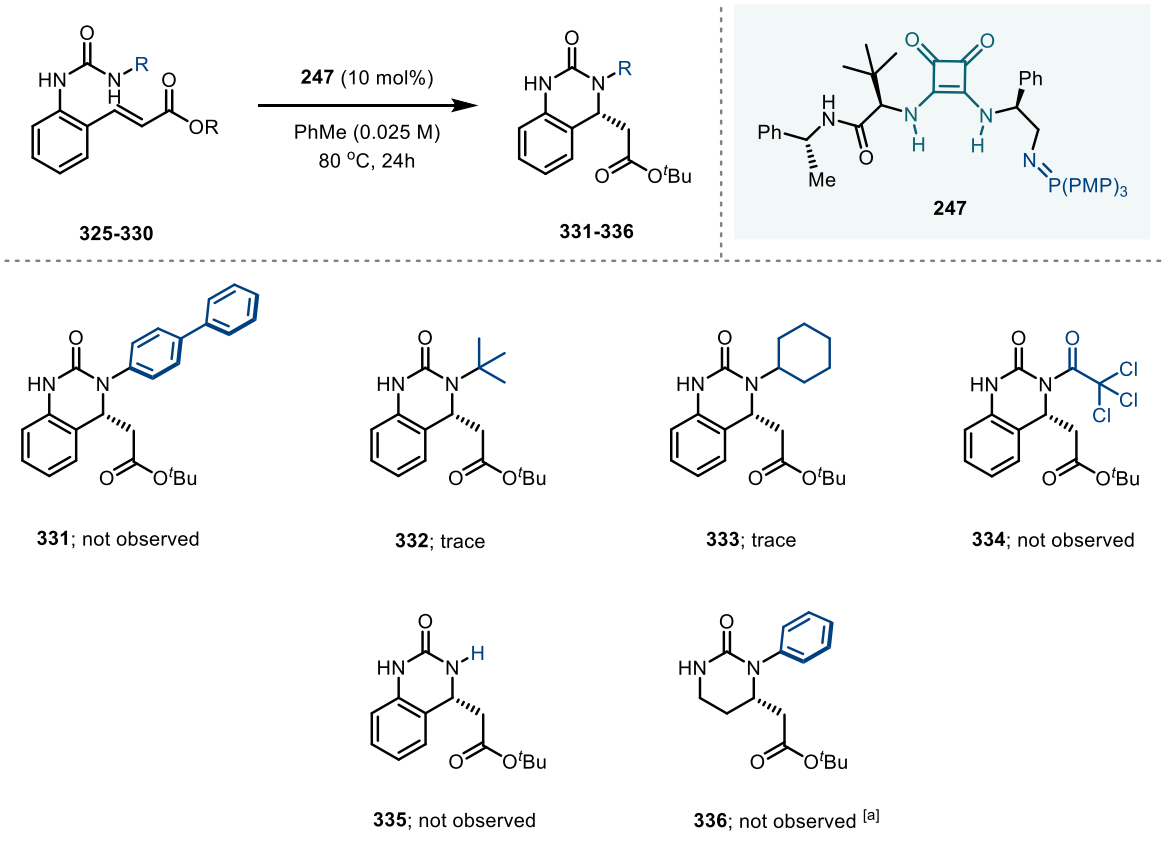
Having showcased a wide scope with respect to aromatic ureas, we were interested to assess if the methodology is applicable to higher pK_a, less activated, alkyl-substituted ureas. (**Scheme 45**) Firstly, *N*-allyl and *N*-benzyl substituted ureas were attempted. Thanks to the high Brønsted basicity of the BIMP catalyst system, hydroquinazolines **320** and **321** were furnished in almost quantitative yield and good er (85:15) only with an increased reaction temperature to 50 °C or 60 °C. Notably, for substrates **315**, decreasing temperature from 60 °C to 40 °C only resulted in an insignificant enantioselectivity enhancement (3%) but a much prolonged reaction time to three days. Encouraged by the success of these non-aromatic ureas, we then assessed even less activated ureas (**317** to **319**). Cyclised product **322** to **324** with moderate to excellent yield and good er were obtained albeit with harsher reaction conditions such as longer reaction time up to nine days and additional heating.



Scheme 45. Reaction scope with regards to aliphatic ureas. Reactions were carried out with 0.2 mmol substrate; [a] 60 °C. [b] 40 °C. [c] 72 hours reaction time. [d] 30 hours reaction time. [e] 50 °C. [f] 120 hours reaction time. [g] 80 °C. [h] 216 hours reaction time. [i] 48 hours reaction time.

2.5.4 Limitations of the reaction scope

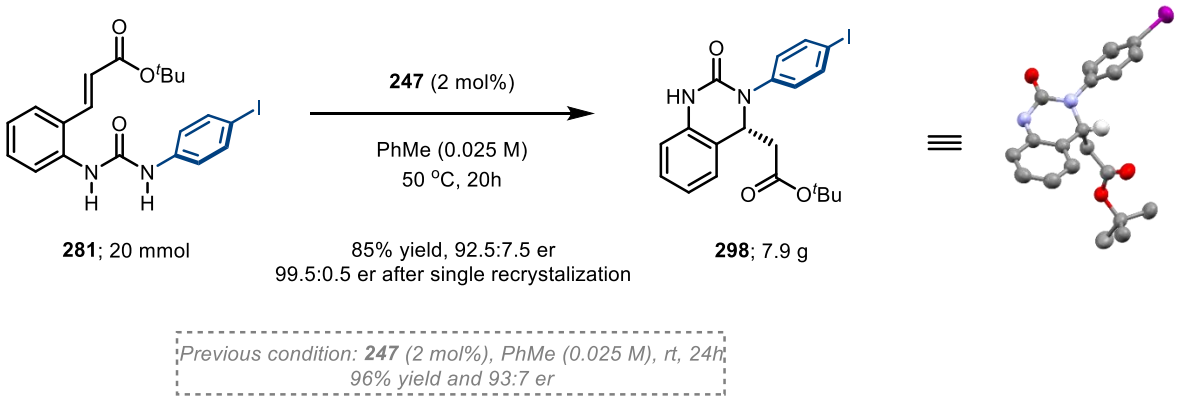
The IAMR reactions were found to generally feature rather clean reaction profiles with only unreacted starting materials, BIMP catalyst and products observed in the crude reaction mixture. While the scope with regards to *NH*-aryl substituents, *N*-aryl substituents as well as aliphatic ureas displayed in this chapter marks a clear improvement from the previously developed enantioselective synthesis of hydroquinazoline cores *via* IAMR reactions, several limitations exist (**Scheme 46**). Urea bearing a 1,1'-biphenyl **325** or trichloroacetyl substituent **328** failed to afford any product, possibly due to the insufficient nucleophilicity resulted from the delocalisation of nitrogen negative charge or lone pair in the extended conjugate system. Sterically hindered *tert*-butyl or cyclohexyl based ureas **326** and **327** proved to be unsuccessful. Furthermore, high pK_a substrates such as unsubstituted urea **329** (pK_a of unsubstituted urea= 26.9 in DMSO) and urea **330** with a non-aromatic backbone are beyond the activating power of BIMP catalyst **247**.



Scheme 46. Unsuccessful examples of the BIMP-catalysed intramolecular *aza*-Michael reaction to α,β-unsaturated ester. [a] Reaction carried out with 30 mol% cat. **247**.

2.6 Preparative Scale Synthesis and Derivatisation

After demonstrating the wide scope and limitations for the enantioselective IAMR reaction, we wanted to substantiate the scalability of this new method and elaborate potential downstream applications. To this end, we performed the reaction of urea **281** with catalyst **247** on a 20 mmol scale under similar conditions to the previous 0.2 mmol scale (**Scheme 47**). Catalyst loading was reduced to 2 mol% to limit costs and waste. Upon lowering the catalyst loading, a higher reaction temperature of 50 °C was required to deliver good yield (7.9 g, 85%) without compromising enantioselectivity (92.5:7.5 er). Pleasingly, only a single recrystallisation could afford essentially enantiopure **298** (99.5:0.5 er). Absolute stereochemical configuration was determined on the crystalline hydroquinazoline **298** by single crystal X-ray diffraction and all other products were assigned by analogy. Notably, crystal preparation under air led to decomposition of **298**. The benzylic proton was prone to oxidation which resulted in a complex mixture and complication in the X-ray diffraction analysis. Anhydrous and degassed CH_2Cl_2 and pentane were thus demanded during the X-ray crystal preparation. (see **Chapter 4.2.7** for crystal preparation details).

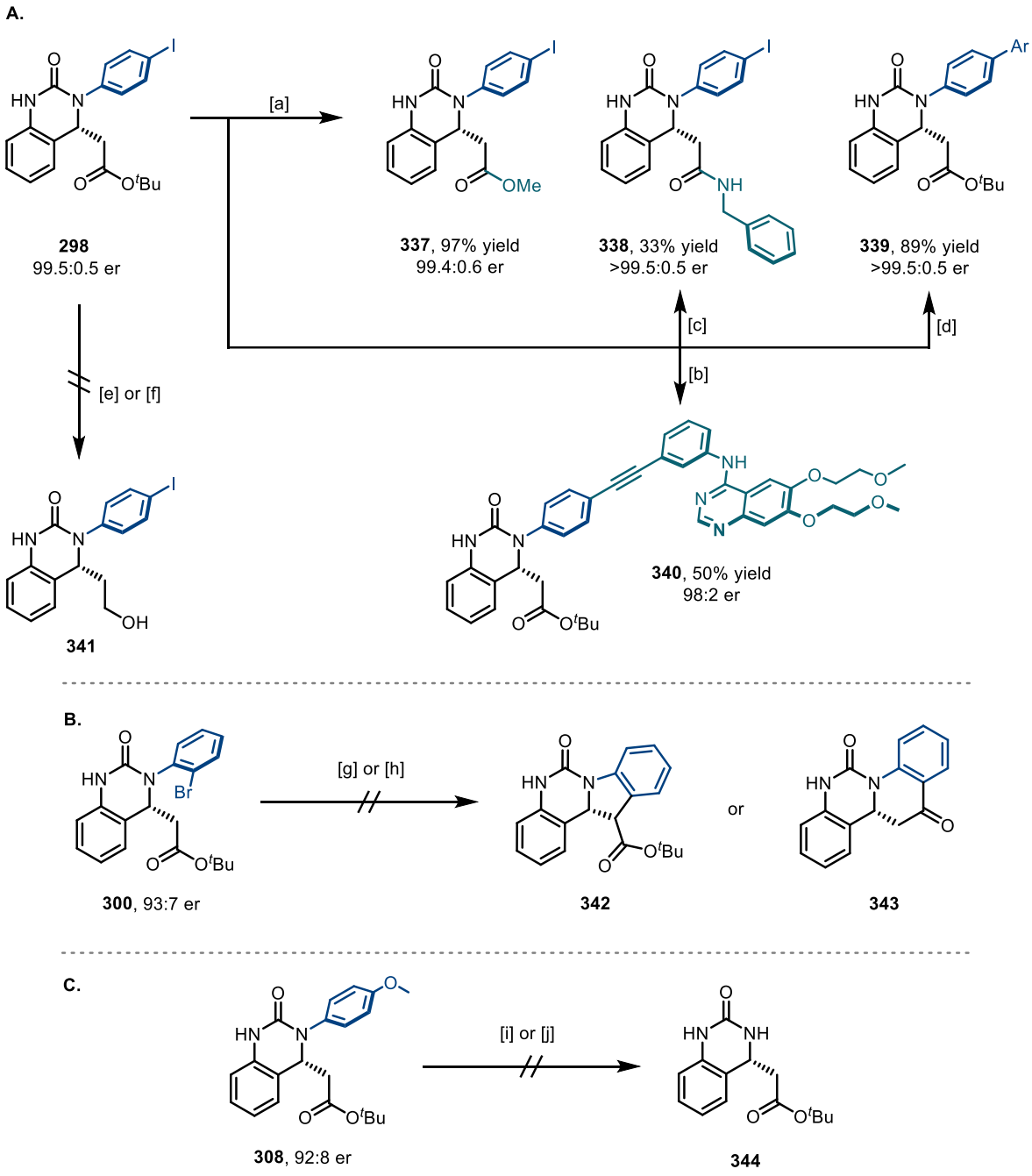


Scheme 47. Preparative scale synthesis of **298**; Single crystal X-ray structure of (*R*)-**298.**

To showcase potential industrial applicability of the cyclisation methodology, enantiopure **298** – obtained from the scale-up reaction described above – was selected as a model scaffold for late-stage functionalisation (**Scheme 48A**). Firstly, we performed removal of the *tert*-butyl carboxylate ester using TFA, activation as the acid chloride, and subsequent treatment with methanol or benzyl amine to give the methyl ester (**337**) or amide (**338**) in excellent or moderate yield, respectively. Secondly, we wanted

to see if the IAMR reaction product is stable towards some industrially common metal-catalysed coupling reaction conditions. To this end, Suzuki coupling with an *N*-methyl substituted pyrazole boronic acid and Sonogashira coupling with erlotinib under standard conditions were carried out and various functionalities in the *para*-position of the *N*-aryl ring were successfully installed (**339** and **340**).

We also found some unsuccessful late-stage transformations with these hydroquinazolines. The reduction of the ester moiety of **298** to furnish primary alcohol **341** proved to be challenging. We failed to observe any reaction with DIBAl-H toluene solution while Red-Al toluene solution gave a complex mixture of products. It is very likely that the C–I bond was prone to metal hydride attack as well since we noticed some formation of the de-iodinated structure **232** through NMR analysis. Unsuccessful derivatisations also included an attempt to make fused rings **342** or **343** *via* palladium catalysed coupling reactions (**Scheme 48B**) and a removal of PMP group with CAN or DDQ reagents (**Scheme 48C**).



Scheme 48. Derivatisation of enantioenriched **298**. [a] (i) TFA, CH_2Cl_2, 0 °C to RT, 5 hours. (ii) $SOCl_2$, MeOH, 20 hours. [b] Erlotinib (HCl complex), $PdCl_2(PPh_3)_2$, CuI, PPh_3, Et_3N, 18 hours. [c] (i) TFA, CH_2Cl_2, 0 °C to RT, 5 hours. (ii) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 2 hours. (iii) $BnNH_2$, Et_3N, CH_2Cl_2, 18 hours. [d] 1-Methyl-1H-pyrazole-3-boronic acid pinacol ester, $Pd(dppf)Cl_2$-CH_2Cl_2, Cs_2CO_3, 1,4-dioxane, H_2O, 23 hours. [e] DIBAl-H solution in toluene, –60 °C to RT, 4 hours. [f] Red-Al solution in toluene, 0 °C to RT, 4.5 hours. [g] $Pd(OAc)_2$, Ligand, LiHMDS, toluene, 16 hours. [h] $Pd(PPh_3)_4$, K_3PO_4, Et_3N, toluene, 110 °C, 16 hours. [i] CAN, MeCN / H_2O, 0 °C to RT, 3 hours. [j] DDQ, CH_2Cl_2, Phosphate buffer *p*H = 7.41, 3 hours.

2.7 Computational Studies

The work in this section was done in collaboration with Dr. Trevor A. Hamlin and one of our group member Ken Yamazaki (it was included in this thesis for completeness). Further details can be found in the published work.

Having developed a highly enantioselective BIMP-catalysed IAMR reaction, details of the reaction mechanism remained unclear. Further computational studies would provide understanding on the origin of the enantio-discrimination and explanation towards the observation that the squaramide motif in the BIMP catalyst demonstrated advantages over urea and thiourea H-bond donor groups. Towards this end, they firstly performed a state-of-the-art DFT study. All possible TSs for the enantio-determining Michael reaction step of substrate **297** were computed and compared. (see **Chapter 4.2.8** for further details) The most energetically favoured transition structures that give rise to either (*R*)- or (*S*)- Michael adduct are selectively displayed in **Figure 11** where **TS–ModeA–LA1–RA1–*R*** towards the (*R*)-product was found to be favoured by 1.2 kcal mol^{-1}. This computational prediction agrees with the experimentally confirmed absolute stereochemical configuration by single crystal X-ray diffraction studies. Several weak stabilising interactions were involved to account for the energy difference. **A)**. The squaramide moiety interacts with the ester carbonyl group *via* hydrogen bonding and with the urea carbonyl group *via* CO–π interaction to activate both the electrophile and the nucleophile. **B)**. The "*left arm*" of the BIMP catalyst possessing the amide group additionally interacts with the aromatic scaffold of the substrate *via* CH–π, and CO–π interactions. **C)**. The "*right arm*" of the BIMP catalyst possessing the iminophosphorane moiety provides additional hydrogen bonding interaction with the urea carbonyl group and CH–π interactions between the PPh_3 and the aromatic ring on the *N* atom. **D)**. Besides these catalyst/substrate interactions, the hydrogen bonding and the CH– π interactions within the catalyst also enhances the rigidity of this particular lowest energy transition structure.[61-63] Overall, this conformation creates an ideal-fit pocket (within which the substrate can perfectly fit) that maximises stabilising interactions and minimises steric repulsion during the *C–N* bond forming step of the Michael reaction. Analysis of non-covalent interaction (NCI) plots allows for qualitative visualisation of these weak interactions (**Chapter 4.2.8**).[64, 65]

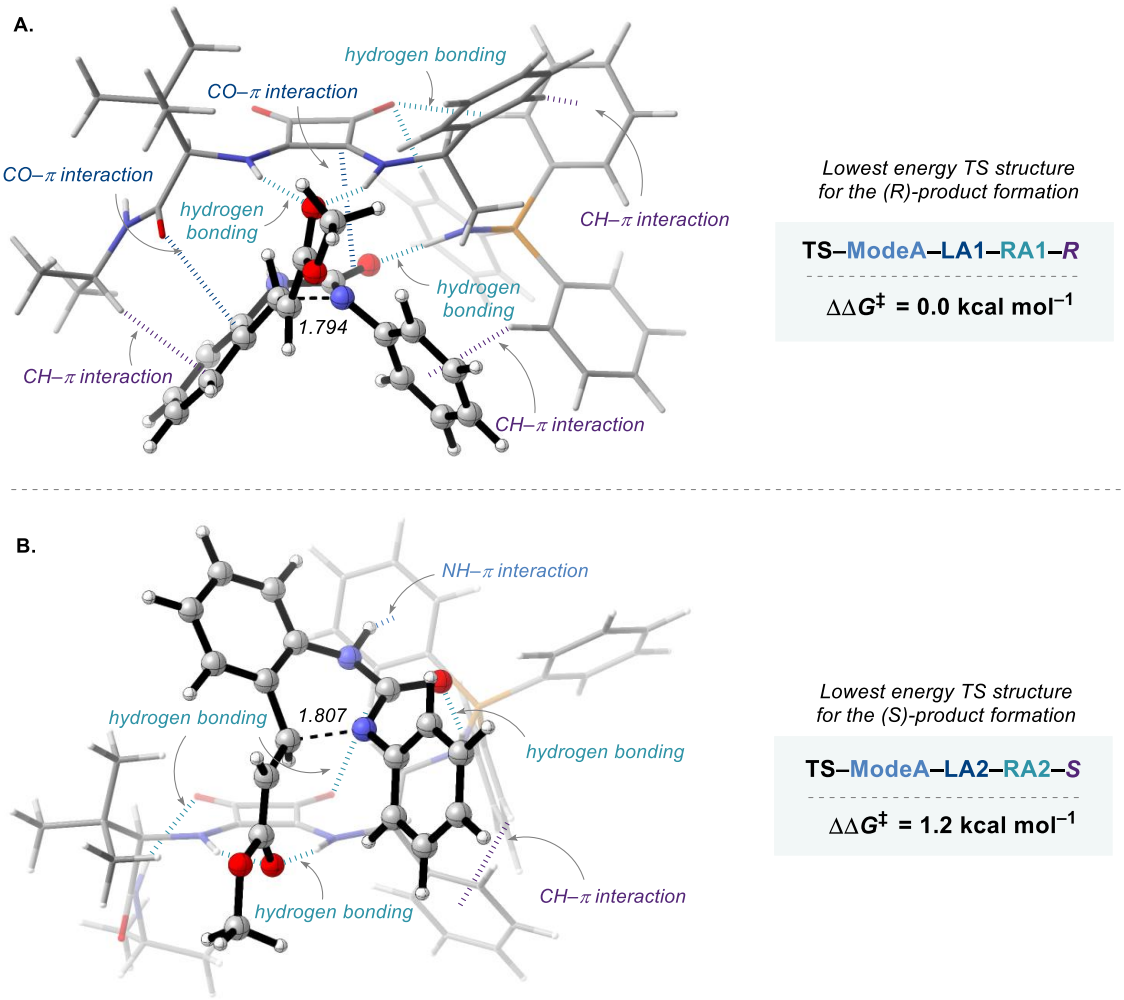


Figure 11. **A.** Lowest energy TS structure for the formation of (*R*)-product and **B.** lowest energy TS structure for the formation of (*S*)-product of the BIMP squaramide-catalysed intramolecular *aza*-Michael reaction computed at COSMO(toluene)-ZORA-M06-2X/TZ2P//COSMO(toluene)-ZORA-BLYP-D3(BJ)/DZP.

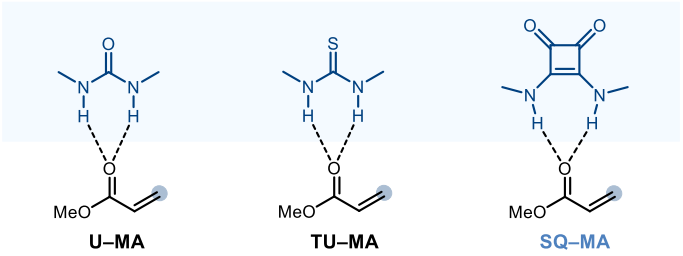
With the aim of obtaining deeper insight into the origin of the catalytic activity imparted by the squaramide motif of the BIMP catalyst, they then carried out an activation strain analysis (ASA) and an energy decomposition analysis (EDA) on archetypal model systems hydrogen bond donor (HB) and methyl acrylate (MA). The ASM involves breaking the electronic energy ΔE into **A)**. the strain energy ΔE_{strain} related to the structural deformation of HB and MA from their equilibrium geometry and **B)**. the interaction energy ΔE_{int} between the deformed reactants HB and MA [eqn (1)].[66-70] The EDA decomposes the interaction energy (ΔE_{int}) into three terms: classical electrostatic interaction (ΔV_{elstat}), Pauli repulsion (ΔE_{Pauli}) between closed-shell orbitals which accounts for steric repulsion, and stabilising orbital interaction (ΔE_{oi}) that accounts, among others, for HOMO–LUMO interactions [eqn (2)].[71]

$$\Delta E = \Delta E_{strain} + \Delta E_{int} \qquad \text{[eqn (1)]}$$

$$\Delta E_{int} = \Delta V_{elstat} + \Delta E_{Pauli} + \Delta E_{oi} \qquad \text{[eqn (2)]}$$

Firstly, they performed modelling of the interaction between HB (urea, thiourea, and squaramide) and MA in the form of complexes **U–MA**, **TU–MA** and **SQ–MA** (**Scheme 49**). As the scheme shows, the stabilising interaction becomes stronger from **U–MA** to **TU–MA** to **SQ–MA** (ΔE_{int} = -9.0 to -10.1 to -11.5 kcal mol^{-1}) which is mainly owing to a more stabilising ΔV_{elstat} term (as a result of the electrostatic nature of hydrogen bonds). The ΔE_{oi} term also plays a very important role and involves significant charge transfer from the lone pair of the **MA** oxygen atom to the two **HB** $\sigma^*_{N\text{-}H}$ orbitals. This charge flow from substrate to catalyst results in a polarisation of the π–MO away from the C=C bond (importance of this polarisation would be explained below). In short, the enhanced stabilising interactions ΔV_{elstat} and ΔE_{oi} provided by the squaramide catalyst contribute significantly to the hydrogen bonding stabilisation, which is affirmed by the shorten H···O=C bond length in **SQ–MA** compared to **U–MA** and **TU–MA**.

Interaction between H-bond donor and substrate



U–MA **TU–MA** **SQ–MA**

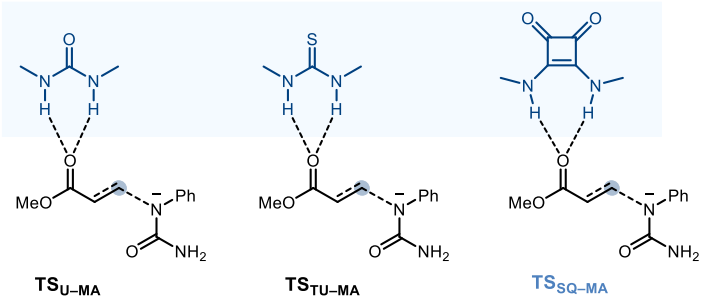
	ΔE_{int}	ΔE_{Pauli}	ΔV_{elstat}	ΔE_{oi}	ε_{LUMO}	r_{avg} (H•••O=C)
U–MA	–9.0	8.6	–12.7	–4.8	–1.1	2.138
TU–MA	–10.1	9.7	–14.1	–5.7	–1.3	2.079
SQ–MA	–11.5	11.3	–15.9	–6.9	–1.6	2.007

Scheme 49. Interaction energies and the energy decomposition analysis (EDA) of the hydrogen bond donor–methyl acrylate complexes (HB–MA).

Secondly, they calculated the energy barriers towards transition structures for the IAMR reaction (**Scheme 50**). The uncatalysed reaction goes with the highest reaction barrier ($\Delta G^{\ddagger}$ = 16.3 kcal mol^{-1}). The urea, thiourea, and squaramide catalysed reactions go with barriers of 12.0, 11.2, and 8.9 kcal mol^{-1}, respectively. In order to demonstrate the reactivity trend, they carried out an ASA study on the transition

structures. It should be noticed that the trend in Gibbs free energy activation barriers is identical to that in electronic activation energy barriers. The lower, more favourable, energy barrier for the squaramide catalysed reaction compared to the uncatalysed one ($\Delta E^{\ddagger}$ = -8.8 vs. 2.9 kcal mol^{-1}) originates from a more stabilising interaction energy ($\Delta E^{\ddagger}_{int}$ = -29.2 *vs* -20.0 kcal mol^{-1}). The $\Delta E^{\ddagger}_{strain}$ differences also make a contribution to the trend but less decisively for the overall reactivity trends ($\Delta E^{\ddagger}_{strain}$ = 20.4 *vs* 23.0 kcal mol^{-1}). Next, by using the EDA method, the trend in the more stabilising $\Delta E^{\ddagger}_{int}$ was computed which successfully identified the Pauli repulsion reduction between reactants being the main reason for the more enhanced reactivity of the catalysed reactions.

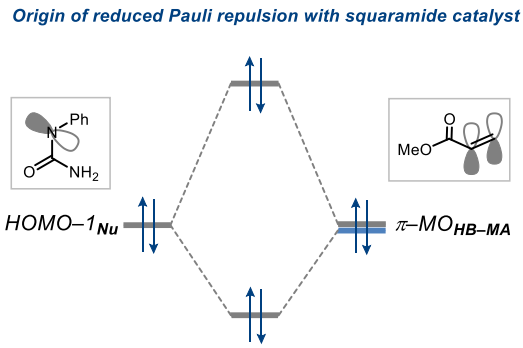
Transition structures of H-bond donor-catalysed aza-Michael addition



	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{strain}$	$\Delta E^{\ddagger}_{int}$	$\Delta E^{\ddagger}_{int,gas}$	$\Delta E^{\ddagger}_{Pauli}$	$\Delta V^{\ddagger}_{elstat}$	$\Delta E^{\ddagger}_{oi}$
TS$_{uncatalysed}$	16.3	2.9	23.0	–20.0	–27.6	146.3	–81.6	–92.2
TS$_{U-MA}$	12.0	–4.5	21.9	–26.4	–39.5	114.8	–75.2	–79.1
TS$_{TU-MA}$	11.2	–5.7	21.5	–27.2	–41.4	109.4	–73.8	–77.0
TS$_{SQ-MA}$	8.9	–8.8	20.4	–29.2	–46.9	102.7	–76.1	–73.5

Scheme 50. Energy barriers of the *aza*-Michael reaction transition structures and the activation strain analysis (ASA) and the energy decomposition analysis (EDA).

Lastly, a Kohn–Sham molecular orbital (KS–MO) analysis was performed to quantify the origin of the less destabilising Pauli repulsion ($\Delta E^{\ddagger}_{Pauli}$) for the transformation (**Scheme 51**). Pauli repulsion extent is represented by the orbital overlap extent *S* between the occupied π–MO$_{\mathbf{HB-MA}}$ (2_p atomic orbitals on the reacting C=C double bonds) and the lone pair of the nucleophile HOMO-1$_{Nu}$. The computed orbital overlap extent *S* decreases from 0.141 for TS$_{uncatalysed}$ to 0.106 for TS$_{\mathbf{SQ-MA}}$, which originates from the aforementioned polarisation of π–MO$_{\mathbf{HB-MA}}$ away from the reacting carbon centre of the C=C bond through charge transfer interaction with the hydrogen bond donor catalyst.



TS	π–$MO_{HB–MA}$	Orbital Overlap *S*
$TS_{uncatalysed}$	*HOMO*	0.141
$TS_{U–MA}$	*HOMO–2*	0.118
$TS_{TU–MA}$	*HOMO–2*	0.111
$TS_{SQ–MA}$	*HOMO–2*	**0.106**

Scheme 51. Molecular orbital diagram and the most significant occupied orbital overlaps computed at COSMO(toluene)-ZORA-M06-2X/TZ2P//COSMO(toluene)-ZORA-BLYP-D3(BJ)/DZP.

In short, these systematic computational analyses[72-75] simultaneously disclose the origin of reactivity and enantioselectivity in this BIMP squaramide catalysed IAMR reaction. The squaramide catalyst emerging as the best BIMP class in this study can be explained by its ability to weaken the destabilising Pauli repulsion between reactants and therefore furnish the greatest reactivity enhancement.

2.8 Conclusion

In summary, this chapter describes a highly efficient and enantioselective BIMP-catalysed intramolecular *aza*-Michael reaction delivering decorated hydroquinazoline scaffolds with excellent yields and enantiomeric ratios. To this end, we have developed a novel BIMP squaramide system which proved to be effective in activating challenging nucleophiles (including both aromatic and aliphatic ureas) and electrophiles (α,β-unsaturated esters). DFT calculations were subsequently performed in collaboration with Dr. Trevor A. Hamlin and Ken Yamazaki to identify that the optimal squaramide catalyst conformation furnished a pocket-like binding site for the substrate to impart enantioselectivity. They also carried out combined ASM and EDA studies to mechanistically show that the squaramide motif exhibited advantages over urea and thiourea H-bond donors by decreasing the destabilizing Pauli repulsion between the reactants. The catalytic ring closing approach displayed wide functional group compatibility including tolerance to esters, nitriles, pyridine-based heterocycle, alkenes, and alkynes while catalyst loading could be reduced down to 2 mol% in a multi-gram scale synthesis. Furthermore, the hydroquinazoline *aza*-Michael adducts were stable towards a set of late-stage functionalisation conditions

therefore demonstrating high pharmaceutical relevance. Although, unfortunately, the developed protocol could not be extended to more challenging and attractive synthesis of chiral hydropyrimidine, it represents one of the very rare example of an enantioselective addition of nitrogen-based nucleophiles to unactivated α,β-unsaturated esters electrophiles.

2.9 References for Chapter 2

[1]. Shagufta; Ahmad, I. An Insight Into the Therapeutic Potential of Quinazoline Derivatives as Anticancer Agents. *Med. Chem. Commun.* **2017**, *8*, 871–885.

[2]. Patterson, S.; Alphey, M. S.; Jones, D. C.; Shanks, E. J. Street, I. P.; Frearson, J. A.; Wyatt, P. G. Gilbert I. H.; Fairlamb, A. H. Dihydroquinazolines as a Novel Class of Trypanosoma brucei Trypanothione Reductase Inhibitors: Discovery, Synthesis, and Characterisation of their Binding Mode by Protein Crystallography. *J. Med. Chem.* **2011**, *54*, 6514–6530.

[3]. Hemalatha, K.; Madhumitha, G. Synthetic Strategy with Representation on Mechanistic Pathway Forthe Therapeutic Applications of Dihydroquinazolinones. *Eur. J. Med. Chem.* **2016**, *123*, 596–630.

[4]. Tiwary, B. K.; Pradhan, K.; Nanda, A. K.; Chakraborty, R. Implication of Quinazoline-4(3H)-ones in Medicinal Chemistry: A Brief Review. *J. Chem. Biol. Ther.* **2015**, *1*, 1–7.

[5]. Prajapat, P.; Talesara, G. L.; Agarwal, S. Synthetic and Pharmacophoric Utility of Quinazoline Motif in Drug Design. *Der. Pharma. Chemica.* **2018**, *10*, (7), 38–45.

[6]. Wang, J.; Zhang, M. M.; Wang, X. S. Structurally Diversified Synthesis of 2,3-Dihydroquinazolin-4-(1H)-Ones from 2-Aminobenzamides and 1,2-Dicarbonyl Compounds in Ionic Liquids Catalysed by Iodine. *Res. Chem. Intermed.* **2017**, *43*, 2985–3005.

[7]. Reddy A, G.; Babu V, H.; Rao Y, J. P.; Reddy P, S.; Manga, V. Docking Studies of Piperazine Propyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate Derivatives. *Der. Pharma. Chemica.* **2017**, *9*, (10), 13–15.

[8]. Heo, J. H.; Seo, H. N.; Choe, Y. J.; Kim, S.; Oh, C. R.; Kim, Y. D.; Rhim, H.; Choo, D. J.; Kim, J.; Lee, J. Y. T-Type Ca^{2+} Channel Blockers Suppress the Growth of Human Cancer Cells. *Bioorg. Med. Chem. Lett.* **2008**, *18*, (14), 3899–3901.

[9]. Thanigaimalai, P.; Lee, K. C.; Bang, S. C.; Lee, J. H.; Yun, C. Y.; Roh, E.; Hwang, B. Y.; Kim, Y.; Jung, S. H. Evaluation of 3,4-dihydroquinazoline-2(1H)-thiones as Inhibitors of α-MSH-Induced Melanin Production in Melanoma B16 Cells. *Bioorg. Med. Chem.* **2010**, *18*, 1555–1562.

[10]. Schlegel, K. A. S.; Yang, Z. Q.; Reger, T. S.; Shu, Y.; Cube, R.; Rittle, K. E.; Bondiskey, P.; Bock, M. G.; Hartman, G. D.; Tang, C.; Ballard, J.; Kuo, Y.; Prueksaritanont, T.; Nuss, C. E.; Doran, S. M.; Fox, S. V.; Garson, S. L.; Kraus, R. L.; Li, Y.; Uebele, V. N.; Renger, J. J.; Barrow, J. C. Discovery and expanded SAR of 4,4-disubstituted quinazolin-2-ones as potent T-type calcium channel antagonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5147–5152.

[11]. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K.; Inhibition of Clinically Relevant Mutant Variants of HIV-1 by Quinazolinone Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Med. Chem.* **2000**, *43*, 2019–2030.

[12]. Li, W. J.; Li, Q.; Liu, D. L.; Ding, M. W. Synthesis, Fungicidal Activity, and Sterol 14α-Demethylase Binding Interaction of 2-Azolyl-3,4-dihydroquinazolines on Penicillium digitatum. *J. Agric. Food Chem.* **2013**, *61*, 1419–1426.

[13]. Verghese, P. S.; Schleiss, M. R. Letermovir Treatment of Human Cytomegalovirus Infection Antiinfective Agent. *Drugs Future.* **2013**, *38*, 291–298.

[14]. Goldner, T.; Hewlett, G.; Ettischer, N.; Ruebsamen-Schaeff, H.; Zimmermann, H.; Lischka, P. The Novel Anticytomegalovirus Compound AIC246 (Letermovir) Inhibits Human Cytomegalovirus Replication through a Specific Antiviral Mechanism That Involves the Viral Terminase. *J. Virol.* **2011**, *85*, 10884–10893.

[15]. Pandey, V. K.; Kumar, M. A.; Trivedi, N.; An Investigation Leading to Preparation of Tetrahydro-quinazoline Derivatives Involving Ureidoalkylation and α-Amidoalkylation Reactions. *Indian J. Chem. Sec. B.* **2008**, *47B*, 1910–1914.

[16]. Rhim, H.; Lee, Y. S.; Park, S. J.; Chung, B. Y.; Lee, J. Y. Synthesis and Biological Evaluation of Novel T-Type Calcium Channel Blockers. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 283–286.

[17]. Xie, T.; Xiao, Y.; Zhao, S.; Hu, X. Q.; Xu, P. F. Catalyst-Free Chemoselective Synthesis of 3,4-Dihydroquinazoline-2-thiones and 2-Imino[1,3]benzothiazines. *J. Org. Chem.* **2016**, *81*, 10499−10505.

[18]. Willwacher, J.; Rakshit, S.; Glorius, F. Investigating *N*-Methoxy-*N*-Aryl Ureas in Oxidative C–H Olefination Reactions: an Unexpected Oxidation Behavior. *Org. Biomol. Chem.* **2011**, *9*, 4736–4740.

[19]. Xin, Z.; Pei, Z.; Geldem, T. V.; Jirousek, M. A Practical and Efficient Intramolecular Michael Addition of Ureas to α,β-Unsaturated Esters. *Tetrahedron Lett.* **2000**, *41*, 1147–1150.

[20]. Gruber, N.; Díaz, J. E.; Orelli, L. R.; Synthesis of Dihydroquinazolines from 2-Aminobenzylamine: N3-Aryl Derivatives with Electron-Withdrawing Groups. *Beilstein. J. Org. Chem.* **2018**, *14*, 2510–2519.

[21]. Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. An Efficient Chiral Moderator Prepared from Inexpensive (+)-3-Carene: Synthesis of the HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor DPC 963. *Org. Lett.* **2000**, *2*, 3119–3121.

[22]. Parsons, R. L.; Fortunak, J. M.; Dorow, R. L.; Harris, G. D.; Kauffman, G. S.; Nugent, W. A.; Winemiller, M. D.; Briggs, T. F.; Xiang, B.; Collum, D. B. NMR Spectroscopic Investigations

of Mixed Aggregates Underlying Highly Enantioselective 1,2-Additions of Lithium Cyclopropylacetylide to Quinazolinones. *J. Am. Chem. Soc.* **2001**, *123*, 37, 9135–9143.

[23]. Bruneau, A. M.; Liou, L.; Collum, D. B. Solution Structures of Lithium Amino Alkoxides Used in Highly Enantioselective 1,2-Additions. *J. Am. Chem. Soc.* **2014**, *136*, 7, 2885–2891.

[24]. Si, Y. G.; Jiang, B. Highly Enantioselective Construction of a ChiralTertiary Carbon Center by Alkynylation of aCyclic N-Acyl Ketimine: An Efficient Preparationof HIV Therapeutics. *Angew. Chem. Int. Ed.* **2004**, *43*, 216–218.

[25]. Zhang, F. G.; Ma, H.; Nie, J.; Zheng, Y.; Gao, Q.; Ma, J. A. Enantioselective Diynylation of Cyclic N-Acyl Ketimines: Access to Chiral Trifluoromethylated Tertiary Carbinamines. *Adv. Synth. Catal.* **2012**, *354*, 1422–1428.

[26]. Jiang, B.; Dong, J. J.; Si, Y. G.; Zhao, X. L.; Huang, Z. G.; Xu, M. Highly Enantioselective Construction of a Quaternary CarbonCenter of Dihydroquinazoline by Asymmetric Mannich Reactionand Chiral Recognition. *Adv. Synth. Catal.* **2008**, *350*, 1360–1366.

[27]. Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. Bifunctional Cinchona Alkaloid Thiourea Catalysed Highly Efficient, Enantioselective *Aza*-Henry Reaction of Cyclic Trifluoromethyl Ketimines: Synthesis of Anti-HIV Drug DPC 083. *Angew. Chem. Int. Ed.* **2011**, *50*, 11773–11776.

[28]. Zhang, F. G.; Zhu, X. Y.; Li, S.; Nie, J.; Ma, J. A. Highly Enantioselective Organocatalytic Strecker Reaction of Cyclic *N*-Acyl Trifluoromethylketimines: Synthesis of Anti-HIV Drug DPC 083. *Chem. Commun.* **2012**, *48*, 11552–11554.

[29]. Yuan, H. N.; Li, S.; Nie, J.; Zheng, Y.; Ma, J. A. Highly Enantioselective Decarboxylative Mannich Reaction of Malonic AcidHalf Oxyesters with Cyclic Trifluoromethyl Ketimines: Synthesis of b-AminoEsters and Anti-HIV Drug DPC 083. *Chem. Eur. J.* **2013**, *19*, 15856–15860.

[30]. Yuan, H. N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J. A. Hydrogen-Bond-Directed Enantioselective Decarboxylative Mannich Reaction of β-Ketoacids with Ketimines: Application to the Synthesis of Anti-HIV Drug DPC 083. *Angew. Chem. Int. Ed.* **2013**, *52*, 3869–3873.

[31]. Zhao, M. X.; Bi, H. L.; Jiang, R. H.; Xu, X. W.; Shi, M. Cinchona Alkaloid Squaramide/AgOAc Cooperatively Catalysed Diastereo- and Enantioselective Mannich/Cyclisation Cascade Reaction of Isocyanoacetates and Cyclic Trifluoromethyl Ketimines. *Org. Lett.* **2014**, *16*, 17, 4566–4569.

[32]. Zhou, D.; Yu, X.; Zhang, J.; Wang, W.; Xie, H. Organocatalytic Asymmetric Addition of Alcohols to Cyclic Trifluoromethyl Ketimines: Highly Enantioselective Synthesis of Chiral *N*,*O*-Ketals. *Org. Biomol. Chem.* **2016**, *14*, 6193–6196.

[33]. Li, S.; Ma, J. Core-Structure-Inspired Asymmetric Addition Reactions: Enantioselective Synthesis of Dihydrobenzoxazinone and Dihydroquinazolinonebased Anti-HIV Agents. *Chem. Soc. Rev.* **2015**, *44*, 7439–7448.

[34]. Kita, Y.; Higashida, K.; Yamaji, K.; Iimuro, A.; Mashima, K.; Asymmetric Hydrogenation of Quinazolinium Salts Catalysed by Halide-Bridged Dinuclear Iridium Complexes Bearing Chiral Diphosphine Ligands. *Chem. Commun.* **2015**, *51*, 4380–4382.

[35]. Wang, P.; Shen, M.; Wang, T.; Lin, H.; Gong, L.; Access to Chiral Hydropyrimidines through Palladium-Catalyzed Asymmetric Allylic C-H Amination. *Angew. Chem. Int. Ed.* **2017**, *56*, 16032–16036; *Angew.Chem.* **2017**, *129*, 16248–16252.

[36]. Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. Recent Advances in the Asymmetric Synthesis of Pharmacology-Relevant Nitrogen Heterocycles *via* Stereoselective *Aza*-Michael Reactions. *Org. Biomol. Chem.* **2019**, *17*, 3670–3708.

[37]. Nayak, S.; Panda, P.; Bhakta, S.; Mishra, S. K.; Mohapatra, S. Current Advances of Organocatalytic Michael–Michael Cascade Reaction in the Synthesis of Highly Functionalised Cyclic Molecules. *RSC Adv.* **2016**, *6*, 96154–96175.

[38]. Bhanja, C.; Jena, S.; Nayak, S.; Mohapatra, S. Organocatalytic Tandem Michael Addition Reactions: A Powerful Access to the Enantioselective Synthesis of Functionalised Chromenes, Thiochromenes and 1,2-Dihydroquinolines. *Beilstein J. Org. Chem.* **2012**, *8*, 1668–1694.

[39]. Enders, D.; Wang, C.; Liebich, J. X. Organocatalytic Asymmetric *Aza*-Michael Additions. *Chem. Eur. J.* **2009**, *15*, 11058–11076.

[40]. Wang, J.; Li, P.; Choy, P. Y.; Chan, A. S. C.; Kwong, F. Y. Advances and Applications in Organocatalytic Asymmetric *aza*-Michael Addition. *Chem. Cat. Chem.* **2012**, *4*, 917–925.

[41]. Krishna, P. R.; Sreeshailam, A.; Srinivas, R. Recent Advances and Applications in Asymmetric *Aza*-Michael Addition Chemistry. *Tetrahedron*, **2009**, *65*, 9657–9672.

[42]. Reyes, E.; Ferna´ndez, M.; Urı´a, U.; Vicario, J. L.; Badı´a, D.; Carrillo, L. Organocatalytic Enantioselective *aza*-Michael Reactions. *Curr. Org. Chem.* **2012**, *16*, 521–546.

[43]. Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. Enantioselective Organocatalytic Amine Conjugate Addition. *J. Am. Chem. Soc.* **2006**, *128*, 9328−9329.

[44]. Uraguchi, D.; Nakashima, D.; Ooi, T. Chiral Arylaminophosphonium Barfates as a New Class of Charged Brønsted Acid for the Enantioselective Activation of Nonionic Lewis Bases. *J. Am. Chem. Soc.* **2009**, *131*, 7242−7243.

[45]. Wang, L.; Chen, J.; Huang, Y. Highly Enantioselective *Aza*-Michael Reaction between Alkyl Amines and βTrifluoromethyl β-Aryl Nitroolefins. *Angew. Chem., Int. Ed.* **2015**, *54*, 15414−15418.

[46]. Ghosh, A. K.; Zhou, B. Bifunctional Cinchona Alkaloidsquaramide-Catalyzed Highly Enantioselective *Aza*-Michael Addition of Indolines to A,B-Unsaturated Ketones. *Tetrahedron Lett.* **2013**, *54*, 3500−3502.

[47]. Allgauer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. Quantification and Theoretical Analysis of the Electrophilicities of Michael Acceptors. *J. Am. Chem. Soc.* **2017**, *139*, 13318−13329.

[48]. Weiß, M.; Borchert, S.; Remond, E.; Juge´ , S.; Gro´ger, H. Asymmetric Addition of A Nitrogen Nucleophile to an Enoate in the Presence of A Chiral Phase-Transfer Catalyst: A Novel Approach Toward Enantiomerically Enriched Protected B-Amino Acids. *Heteroat. Chem.* **2012**, *23*, 202−209.

[49]. Lin, Y.; Hirschi, W. J.; Kunadia, A.; Paul, A.; Ghiviriga, I.; Abboud, K. A.; Karugu, R. W.; Vetticatt, M. J.; Hirschi, J. S.; Seidel, D. A Selenourea-Thiourea Brønsted Acid Catalyst

Facilitates Asymmetric Conjugate Additions of Amines to α,β-Unsaturated Esters *J. Am. Chem. Soc.* **2020**, *142*, 5627–5635.

[50]. Sánchez-Roselló, M.; Aceña, J. L.; Simón-Fuentesa, A.; Pozo, C. D. A General Overview of the Organocatalytic Intramolecular *Aza*-Michael Reaction. *Chem. Soc. Rev.* **2014**, *43*, 7430–7453.

[51]. Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. Enantioselective Phase-Transfer-Catalysed Intramolecular *Aza*-Michael Reaction: Effective Route to Pyrazino-Indole Compounds. *Angew. Chem. Int. Ed.* **2008**, *47*, 3238 –3241.

[52]. Roy, T. K.; Parhi, B.; Ghorai, P. Cinchonamine Squaramide Catalysed Asymmetric *aza*-Michael Reaction: Dihydroisoquinolines and Tetrahydropyridines. *Angew. Chem. Int. Ed.* **2018**, *57*, 9397–9401.

[53]. Humphrey, G. R.; Dalby, S. M.; Andreani, T.; Xiang, B.; Luzung, M. R.; Song, Z. J.; Shevlin, M.; Christensen, M.; Belyk, K. M.; Tschaen, D. M.; Asymmetric Synthesis of Letermovir Using a Novel Phase-Transfer Catalysed *Aza*-Michael Reaction. *Org. Process Res. Dev.* **2016**, *20*, 1097–1103.

[54]. Chung, C. K.; Liu, Z.; Lexa, K. W.; Andreani, T.; Xu, Y.; Ji, Y.; DiRocco, D. A.; Humphrey, G. R.; Ruck, R. T. Asymmetric Hydrogen Bonding Catalysis for the Synthesis of Dihydroquinazoline-Containing Antiviral, Letermovir. *J. Am. Chem. Soc.* **2017**, *139*, 10637–10640.

[55]. Malerich, J. P.; Hagihara, K.; Rawal, V. H. Chiral Squaramide Derivatives are Excellent Hydrogen Bond Donor Catalysts. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[56]. Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. Enantioselective α-Amination of 1,3-Dicarbonyl Compounds Using Squaramide Derivatives as Hydrogen Bonding Catalysts. *Org. Lett.* **2010**, *12*, 2028–2031.

[57]. Yang, K. S.; Nibbs, A. E.; T¨urkmen, Y. E.; Rawal, V. H. Squaramide-Catalysed Enantioselective Michael Addition of Masked Acyl Cyanides to Substituted Enones. *J. Am. Chem. Soc.* **2013**, *135*, 16050–16053.

[58]. Banik, S. M.; Levina, A.; Hyde, A. M.; Jacobsen, E. N. Lewis Acid Enhancement by Hydrogen-Bond Donors for Asymmetric Catalysis. *Science*, **2017**, *358*, 761–764.

[59]. Alemμn, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. Squaramides: Bridging from Molecular Recognition to Bifunctional Organocatalysis. *Chem. Eur. J.* **2011**, *17*, 6890–6899.

[60]. X. Ni, X. Li, Z. Wang, J. Cheng, Squaramide Equilibrium Acidities in DMSO. *Org. Lett.* **2014**, *16*, 1786−1789.

[61]. Lubbe, S. C. C. van der; Guerra, C. F. The Nature of Hydrogen Bonds: A Delineation of the Role of Different Energy Components on Hydrogen Bond Strengths and Lengths. *Chem. Asian J.* **2019**, *14*, 2760–2769.

[62]. Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. The Magnitude of the CH/π Interaction between Benzene and Some Model Hydrocarbons. *J. Am. Chem. Soc.* **2000**, *122*, 3746–3753.

[63]. Nishio, M. The CH/π Hydrogen Bond in Chemistry. Conformation, Supramolecules, Optical Resolution and Interactions Involving Carbohydrates *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873–13900.

[64]. Johnson, E. R.; Keinan, S.; Mori-S´anchez, P.; Contreras-Garc´ıa, J.; Cohen, A. J.; Yang, W. Revealing Noncovalent Interactions. *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506.

[65]. Contreras-Garc´ıa, J.; Johnson, E. R.; Keinan, S.; Chaudret, R.; Piquemal, J. P.; Beratan, D. N.; Yang, W. NCIPLOT: a Program for Plotting Non-Covalent Interaction Regions. *J. Chem. Theory Comput.* **2011**, *7*, 625–632.

[66]. Vermeeren, P.; Lubbe, Guerra, S. C. C. van der; C. F.; Bickelhaupt, F. M.; Hamlin, T. A. Understanding Chemical Reactivity Using the Activation Strain Model. *Nat. Protoc.* **2020**, *15*, 649–667.

[67]. Bickelhaupt, F. M.; Houk, K. N.; Analysing Reaction Rates with the Distortion/Interaction-Activation Strain Model. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070–10086.

[68]. Wolters, L. P.; Bickelhaupt, F. M. The Activation Strain Model and Molecular Orbital Theory. *WIRES Comput. Mol. Sci.* **2015**, *5*, 324–343.

[69]. Fern´andez, I.; Bickelhaupt, F. M. The Activation Strain Model and Molecular Orbital Theory: Understanding and Designing Chemical Reactions. *Chem. Soc. Rev.* **2014**, *43*, 4953–4967.

[70]. Zeist, W. J. v.; Bickelhaupt, F. M. The Activation Strain Model of Chemical Reactivity. *Org. Biomol. Chem.* **2010**, *8*, 3118–3127.

[71]. Bickelhaupt, F. M.; Baerends, E. J. *In Reviews in Computational Chemistry,* ed. Lipkowitz, K. B.; Boyd, D. B. Wiley, Hoboken, **2000**, 1–86.

[72]. T. A.; Hamlin, I.; Fernandez, F. M. Bickelhaupt, How Dihalogens Catalyse Michael Addition Reactions. *Angew. Chem. Int. Ed.* **2019**, *58*, 8922–8926.

[73]. Vermeeren, P.; Hamlin, T. A.; Fernandez, I.; Bickelhaupt, F. M. How Lewis Acids Catalyse Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2020**, *59*, 6201–6206.

[74]. Vermeeren, P.; Brinkhuis, F.; Hamlin, T. A.; Bickelhaupt, F. M. How Alkali Cations Catalyse Aromatic Diels-Alder Reactions. *Chem. Asian J.* **2020**, *15*, 1167–1174.

[75]. Vermeeren, P.; Hamlin, T. A.; Bickelhaupt, F. M.; Fernandez, I. Bifunctional Hydrogen Bond Donor-Catalysed Diels–Alder Reactions: Origin of Stereoselectivity and Rate Enhancement. *Chem. Eur. J.* **2021**, *27*, 5180 –5190.

Chapter 3

Enantioselective Intramolecular *Oxy*-Michael Reaction to α,β-Unsaturated Esters and Amides

3.1 Chapter Overview

This chapter outlines the development of a BIMP-catalysed enantioselective intramolecular oxy-Michael reaction (IOMR) of alcohols to tethered α,β-unsaturated esters and amides furnishing structurally diverse enantioenriched cyclic ethers. Of high pharmaceutical relevance, chiral oxygenated heterocycles have been attracting the interest of synthetic chemists and medicinal scientists for decades. The preparation *via* metal-free catalysed IOMR involving α,β-unsaturated esters or amides are conceptually straightforward and appealing but to date are limited by poor reactivity and substrate scope. Current efforts on this majorly rely on the use of lower pK_a tethered pronucleophiles such as phenols, to circumvent the reactivity issue. The new chemistry discussed in this chapter provides effective activation of primary, secondary and tertiary alcohols by a superbasic BIMP catalyst furnishing tether substituted THFs/THPs, oxy-spirocycles and also sugar and natural product derivatives in yields of up to 99% and enantiomeric ratios of up to 99:1 er. The IOMR was also extended to phenols and benzylic alcohols, thereby delivering dihydro-(iso)-benzofurans and iso-chromans with excellent yield and enantioselectivity.

3.2 Introduction

3.2.1 Importance of 5 or 6 membered cyclic ethers

Saturated and semi-saturated oxygen-containing systems constitute one of the most significant and abundant classes of heterocycle, appearing in a large variety of natural resources, agrochemicals and particularly therapeutically active compounds, as supported by the many FDA-approved cyclic ether-containing drug molecules.[1-4] In addition, thousands of marine products that contain oxy-cyclic skeletons are isolated each year, offering abundant sources for potential drug molecules development.[5] With unique electronic and physicochemical properties, most cyclic ether heterocycles demonstrate promising pharmacological and biological properties including antibiotic, antibacterial and antitumor activities, which provides fertile ground for drug candidate selection and optimisation.[2]

Specifically, chiral α-substituted 5- or 6- membered rings such as THFs,[6-10] THPs,[11-13] dihydro-(iso)-benzofurans[14-20] and (iso)-chromans [21-24] represent some of the most common pharmaceutically relevant cyclic ether containing motifs (**Figure 12**). **Figure 13** showcases some of the representative structural diversities. They include bioactive natural products such as (+) egenine **350** (Ca^{2+} current blocker),[25] (+)-fragransin A2 **351** (cytotoxic activity against several human cancer cell lines) [26] and rocaglamide **352** (antileukemic activity),[27] herbicides such as tefuryltrione **353** [28] and a dopamine D4 antagonist (–)-sonepiprazole **354** [29] and also the carbohydrates family such as salicin **355** (anti-inflammatory agent).[30] There is therefore a high demand for new and sophisticated synthetic methodologies towards these cyclic ether frameworks due to their intrinsic biological properties and the enormous therapeutic potential that has been achieved thus far. Specifically, the development of enantioselective approaches towards optically active cyclic ethers is highly desirable and of great importance to further leverage their applications in efficient ways.

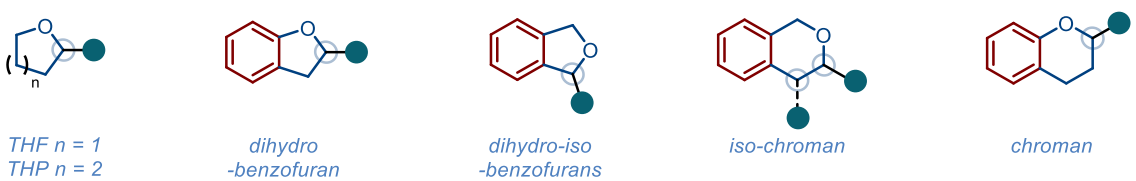


Figure 12. Chiral α-substituted 5- or 6- membered oxygen-containing heterocycles.

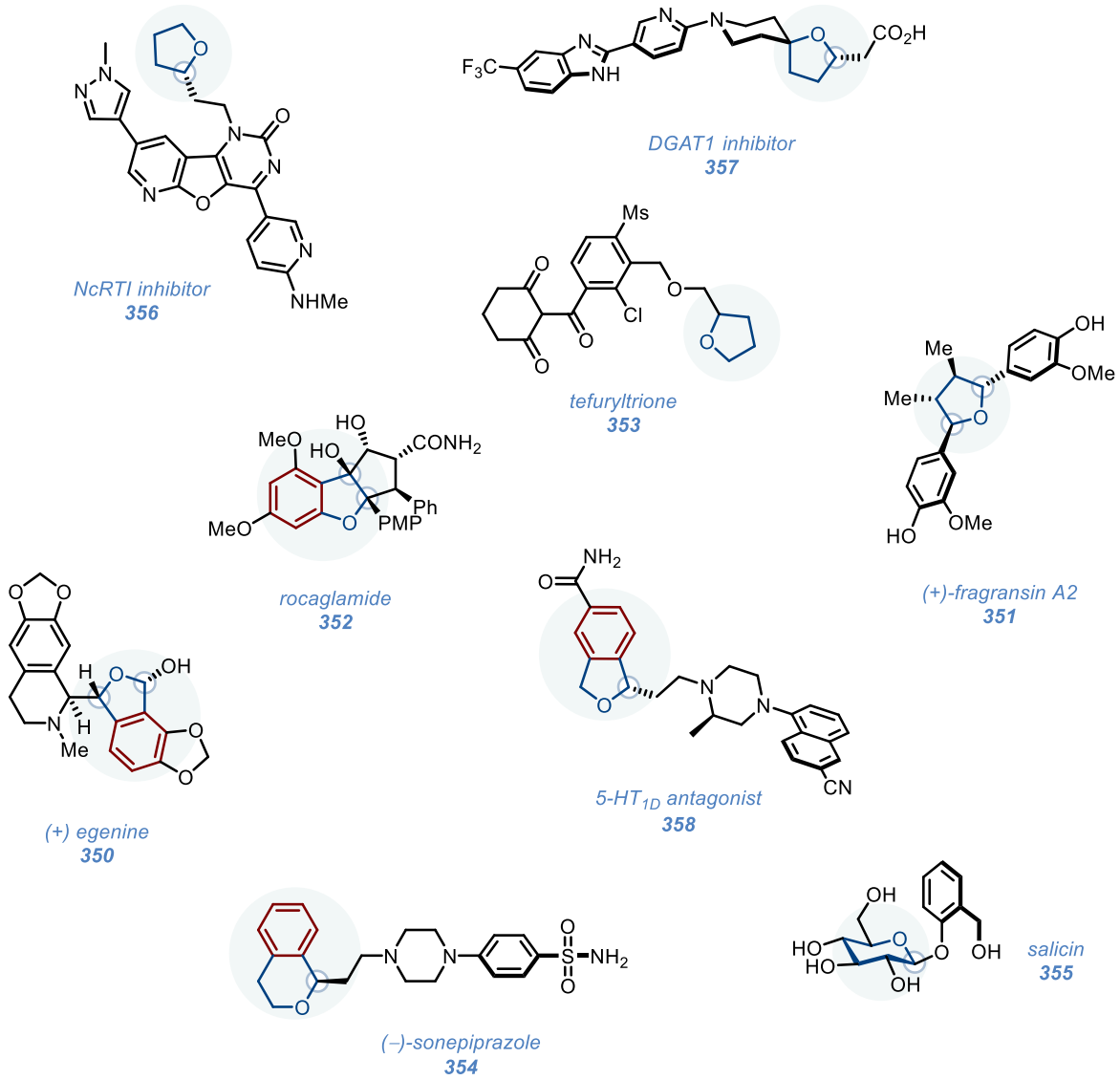


Figure 13. Representative pharmaceutically active 5- or 6- membered oxygen-containing heterocycles.

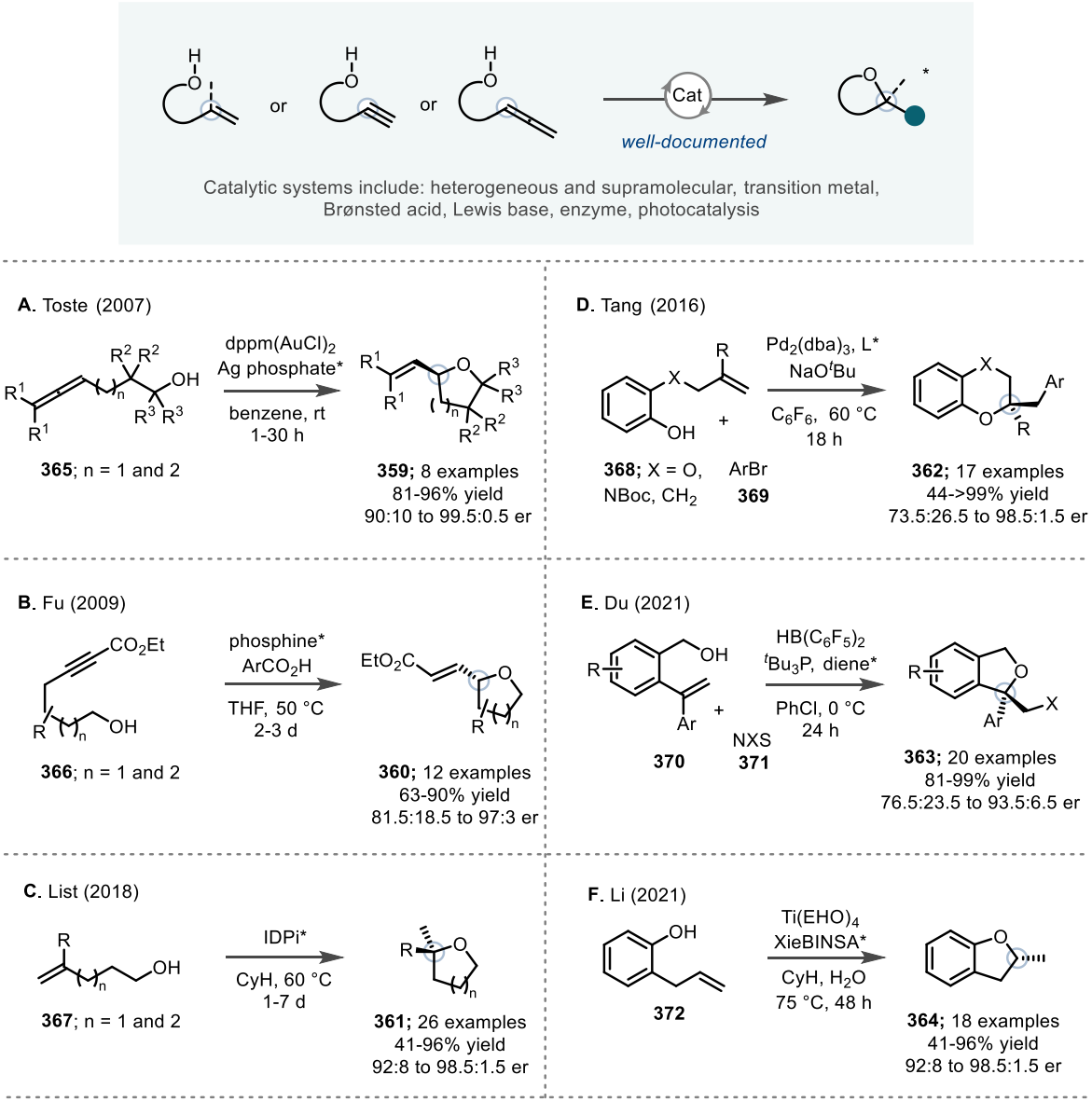
3.2.2 Enantioselective preparation of 5- or 6- membered cyclic ethers

3.2.2.1 Intramolecular hydroalkoxylation of non-activated C−C multiple bonds

Indeed, significant effort has been invested into the enantioselective preparation of 5- or 6- membered cyclic oxygenated building blocks. One of the most predominant approaches is the direct enantioselective intramolecular hydroalkoxylation of non-activated C−C multiple bonds which provides a redox-neutral, atom- and step-economical strategy to prepare substituted cyclic ether skeletons.[31] To date, this type of transformation has evolved considerably, enabled by almost all classes of catalytic modes including transition metal catalysis, photocatalysis, organocatalysis, enzyme catalysis, and

heterogeneous catalysis. For enantioselective synthesis of THFs and THPs *via* this approach, alkenes, alkynes and allenes prone to the addition of alcohols have all been utilised.[31] For example, enantioenriched THFs or THPs bearing a vicinal olefin functionality **359** and **360** could be prepared by an intramolecular hydroalkoxylation of tethered allene [32] or alkyne functionality,[33] as reported by Toste group in 2007 (**Scheme 52A**) and Fu group in 2008 (**Scheme 52B**) respectively. While a cationic achiral Au precatalyst together with a chiral silver phosphate counteranion accounting for the activation of the allene species in Toste's report, a chiral Lewis basic phosphine was responsible for the highly enantioselective hydroalkoxylation of alkynes in Fu's work. Another more recent work by List and co-workers in 2018 demonstrated a chiral imidodiphosphorimidate catalysed high yielding (41−96%) and enantioselective (92:8 to 98.5:1.5 er) hydroalkoxylation of simple alkenols to furnish THFs and THPs **361** bearing a quaternary stereo-centre (**Scheme 52C**).[34] Notably, unlike the aforementioned examples, this approach does not rely on the Thorpe−Ingold effect from the tether of the substrates to assist the cyclisation. In fact, an alkenol bearing a gem-dimethyl motif along the chain proved less reactive than the non-substituted one (7 days reaction time *vs* 1 day). Acid-sensitive functionalities were however not compatible with this elegant transformation due to the strongly acidic nature of the catalyst.

For the enantioselective preparation of benzene fused cyclic ether structures such as dihydro-(iso)-benzofurans and (iso)-chromans *via* hydroalkoxylation of alkenes, aryl-halides or halogenating reagents such as NBS or NIS were involved sometimes to assist the ring formation and install aryl or halogen functionalities proximal to the newly generated stereo-centres. Such cases were illustrated by Tang group in 2016 (**Scheme 52D**) [35] and Du group in 2021 (**Scheme 52E**),[36] for example. In Tang's work, a variety of enantioenriched *O*-containing heterocycles including 1,4-benzodioxanes, 1,4-benzooxazines, and chromans **362** (up to 98.5:1.5 er) were prepared by a palladium catalysed addition of phenol to tethered terminal alkenes. The other case disclosed by Du and co-workers utilised a chiral frustrated Lewis pair (FLP) which consists of a Lewis acidic chiral diene-derived borane complex and a Lewis basic ^{t}Bu$_3$P to furnish dihydro iso-benzofurans **363** in high yield (81-99% yield) and moderate to good enantioselectivity (76.5:23.5 to 93.5:6.5 er). In addition, optically active α-methyl substituted dihydro-benzofurans **364** can also be prepared *via* a hydroalkoxylation of 2-allylphenols mediated by Ti(IV) and chiral ligand BINSA, reported by Li in 2021 (**Scheme 52F**).[37]

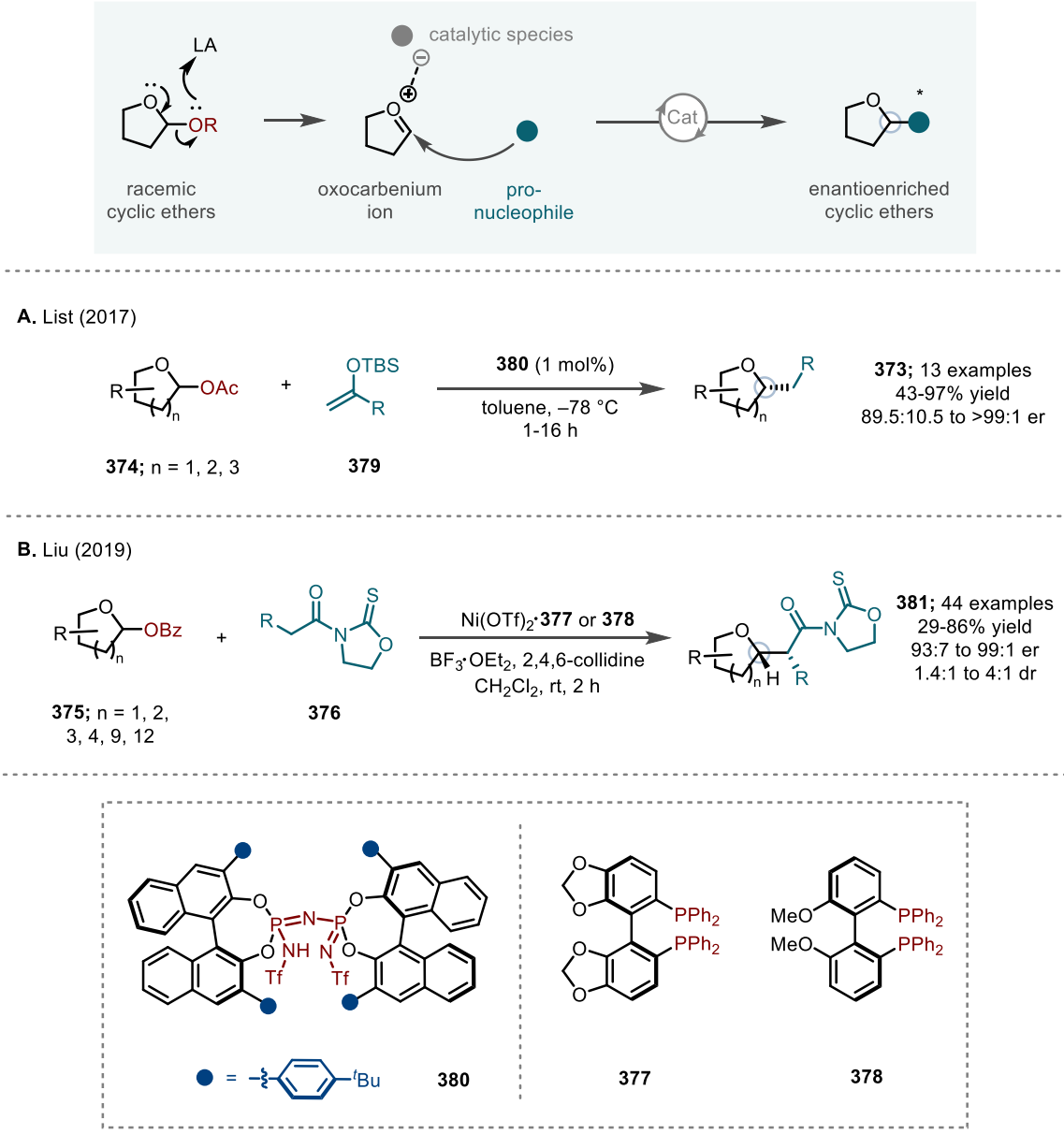


Scheme 52. Representative enantioselective intramolecular hydroalkoxylations towards cyclic ethers. * = chiral species; IDPi = imidodiphosphorimidate; CyH = cyclohexane; NXS = *N*-Bromosuccinimide or *N*-Iodosuccinimide; EHO = 2-ethylhexyloxy; BINSA = 1,1' binaphthyl-2,2'-disulfonic acid.

3.2.2.2 Enantioselective functionalisation of cyclic oxocarbenium ions

Enantioselective alkylation of cyclic oxocarbenium ions represents another novel and increasingly appealing approach towards chiral oxygenated heterocycle synthesis.[38] In 2017, List and co-workers reported the metal-free IDPi catalysis mediated construction of enantioenriched THF, THP and oxepane **373** *via* the enantioselective alkylation of racemic lactol acetate **374** where the cyclic oxocarbenium ion was generated from an acetate abstraction process by a silicon-centred Lewis acid, followed by a stereo-

determining enol silane nucleophile addition (**Scheme 53A**).[39] Two years later, *via* a similar reaction concept, the Liu group realised the efficient coupling of achiral lactol benzoate **375** and acetyloxazolidinethione **376** under nickel catalysis in the presence of chiral diphosphine ligands **377** or **378** and under very mild condition (**Scheme 53B**).[40] Notably, their method not only furnished prevalent THFs and THPs, but also covered medium (7 and 8) to large-sized (13 and 16) cyclic ethers, all in high enantioselectivity (up to 99:1 er) albeit with moderate diastereoselectivity (1.0:1 to 4:1 dr).



Scheme 53. Representative examples of enantioselective alkylation of racemic cyclic ethers.

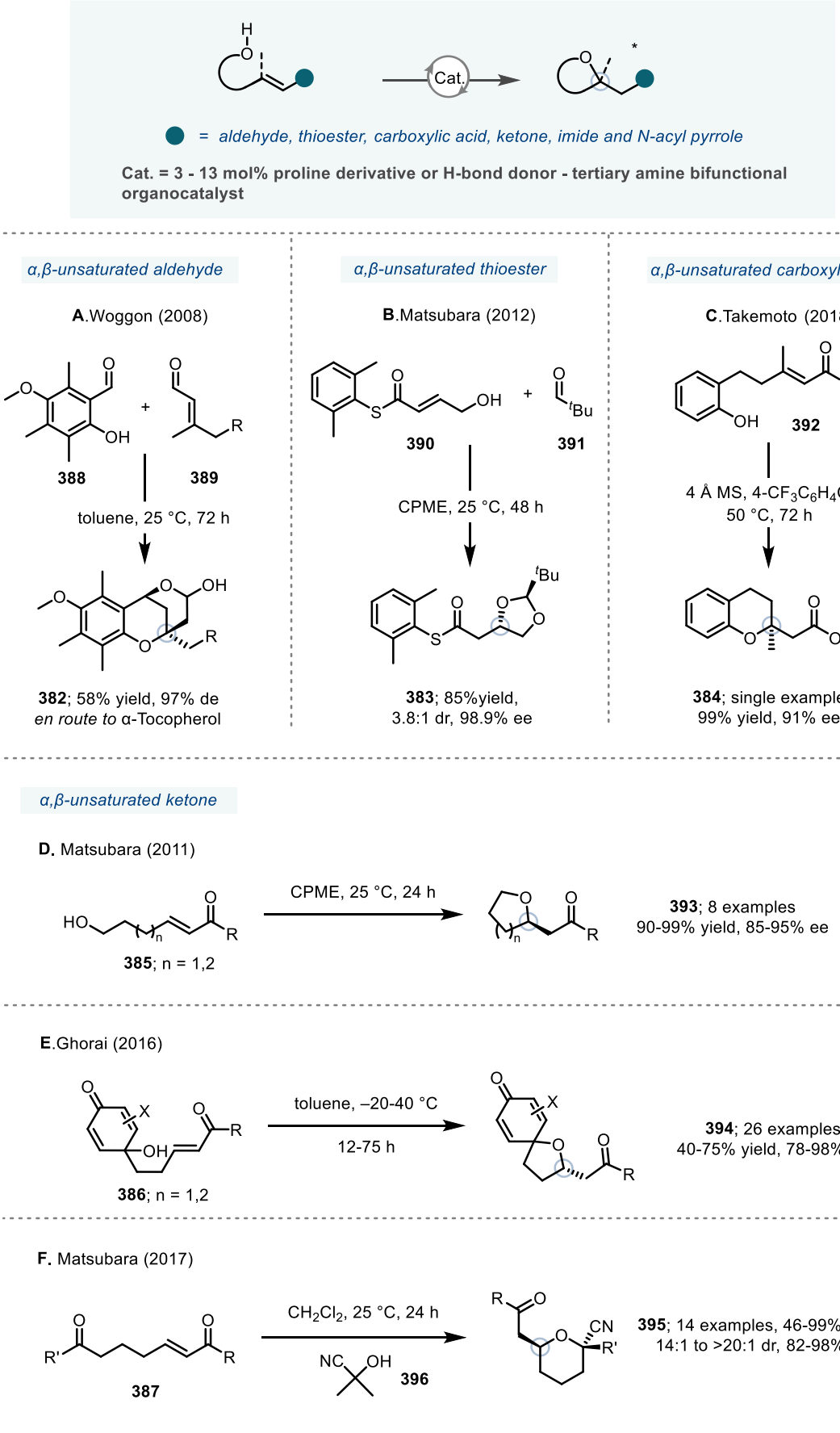
Collectively the reported protocols outlined above represent a valuable toolkit for the synthesis of enantioenriched cyclic ethers based on the *in situ* generation of tight ion-pairs to discriminate the

prochiral plane of the oxocarbenium intermediates. As such, great advances in the development of direct catalytic enantio-controlled additions of nucleophiles to *in situ*-generated (a)cyclic oxocarbenium ions in recent years has greatly expanded their respective substrate scopes. Importantly, compatible pronucleophiles has been expanded from *C*-based to *O*-based species such as H_2O and alcohol to prepare optically active lactols [41] and spiroketals.[42-43] However, there remains ample room for broadening the structural diversity of coupling reactants.[38]

3.2.2.3 Enantioselective intramolecular oxy-Michael reactions

Among the most attractive approaches to chiral cyclic ethers are organocatalysed enantioselective intramolecular oxy-Michael reactions (IOMRs).[44-49] These transformations are redox-neutral, atom- and step-economical and, yet, typically highly challenging because of the poor nucleophilicity and the high *p*K_a of the alcohol pro-nucleophile when compared to their corresponding *C*-, *N*- and *S*- counterparts. One solution targeting this challenge is to involve amines, Lewis acids or transition metal complexes to activate the Michael acceptors by lowering their LUMO level.[47] For example, Woggon in 2008 proposed a chiral proline derivative catalysed highly diastereoselective IOMR of phenol to an α,β-unsaturated aldehyde to furnish a chroman intermediate **382** en route to α-Tocopherol (**Scheme 54A**).[50] This method is however not always effective as it fails to provide direct activation to the hydroxyl nucleophiles which normally lack an appropriate substituent nearby.[47] Instead, the use of bifunctional organocatalysts bearing hydrogen bond donor moiety and a basic tertiary amino group is a complementary and more suitable activation mode.[51]

In this specific field, the addition of pronucleophilic aliphatic alcohols or phenols to tethered activated β-substituted α,β-unsaturated ketones,[52-64] thioesters,[65-66] imides/*N*-acyl pyrroles,[67] and carboxylic acids [68-69] are well documented. Synthesis of chiral 1,3-dioxolane **383** [65] and α-di-substituted chroman **384** [69] are selected examples for using α,β-unsaturated thioester and carboxylic acid in IOMRs respectively (**Scheme 54B-C**). For ketone acceptors, pronucleophiles including primary alcohols **385** [53] and cyclohexadienone- [62] or cyano- [57] bearing tertiary alcohols **386** or **387** were smoothly activated to undergo the enantioselective additions, affording highly enantioenriched THFs or THPs (**Scheme 54D-F**).

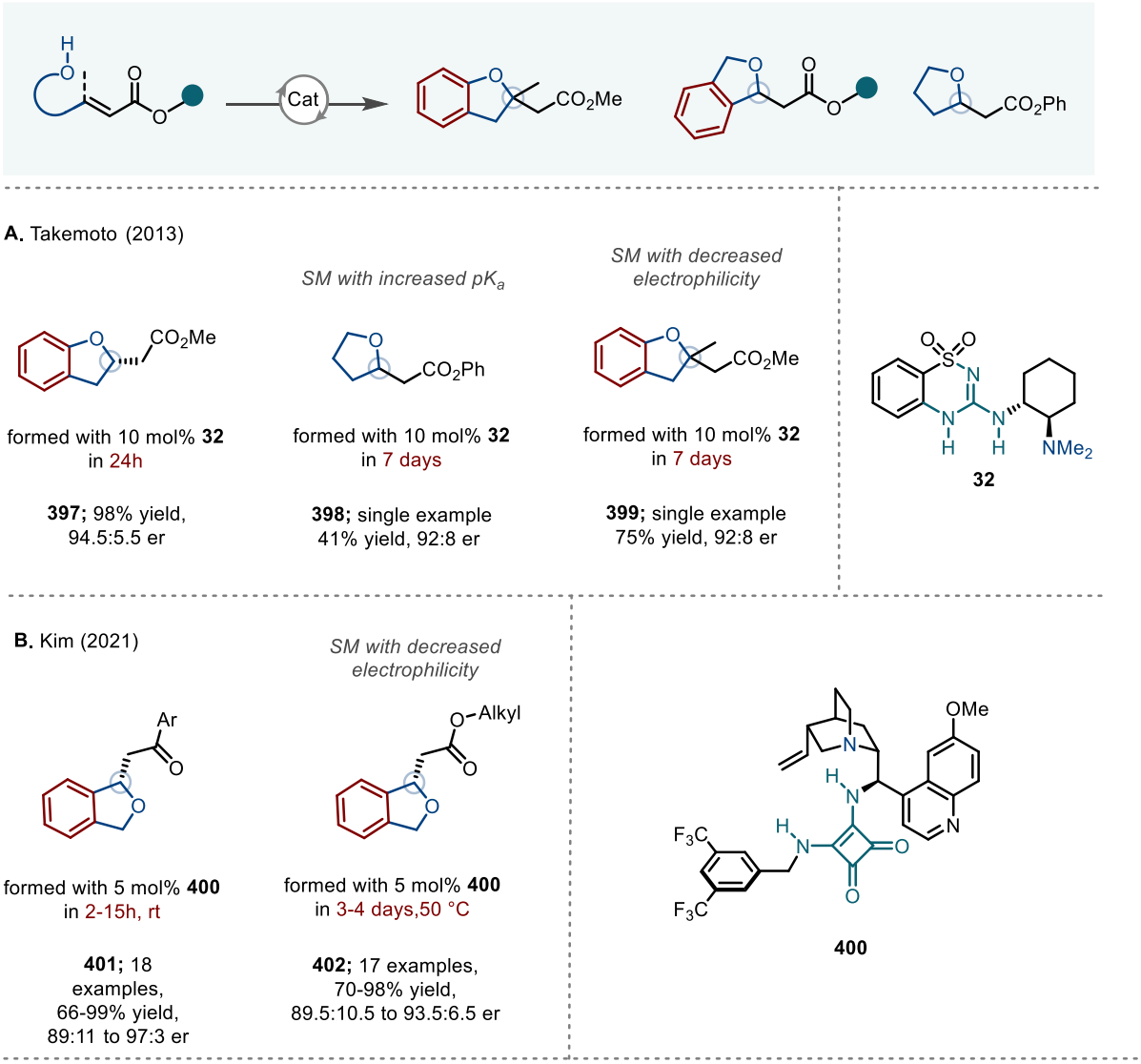


Scheme 54. Representative enantioselective intramolecular oxy-Michael reactions.

Notably, the chiral oxygenated frameworks obtained from IOMRs are well-known to undergo retro-Michael process in the presence of base which could result in potential racemisation.[70-71] Instead of converting carbonyl groups to other functionalities that are inert to the reversible process (through extensive functional group manipulation), corresponding IOMRs to α,β-unsaturated esters or amides could realise more robust chirality installation and thus circumvent the issue of reversibility. Although being highly attractive, they remain largely undeveloped due to the much weaker electrophilicity of the Michael acceptors.[72]

Current suppressing reactivity state-of-the-art methods for enantioselective IOMRs to α,β-unsaturated esters or amides relied heavily on the use of lower pK_a tethered pronucleophiles such as phenols to circumvent the reactivity issue. [71, 73-77] An example of this was reported by Takemoto in 2013 (**Scheme 55A**),[71] where a novel bifunctional tertiary amine catalyst **32** consisting of a highly acidic guanidine-based H-bond donor could direct rapid access towards a wide range of enantioenriched benzofurans (**397**, 98% yield and 94.5:5.5 er in 24 hours). By contrast, activation of aliphatic alcohol with increased pK_a to afford THF product **398** proved to be rather challenging, only leading to 41% yield after 7 days. Apart from that, 7 days of reaction time were also demanded in the case of β-substituted benzofuran **399** due to the low electrophilicity of the β,β'-disubstituted Michael acceptor.

An analogous scenario reported by Kim group in 2021 also highlighted the difficulty of such enantioselective IOMRs when involving α,β-unsaturated esters as Michael acceptors (**Scheme 55B**).[77] Bifunctional cinchona catalyst **400** bearing squaramide H-bond donor rapidly promoted the enantioselective IOMRs of benzylic alcohols to α,β-unsaturated ketones furnishing enantioenriched α-substituted dihydro-iso-benzofurans **401** under mild reaction condition. Extended reaction times to 4 days at 50 °C were however typical when the tethered α,β-unsaturated ketone Michael acceptor was replaced with an α,β-unsaturated ester **402**. This work also exposed the inefficient activation that tertiary amine based bifunctional catalysts afford to provide when dealing with such transformations. With a full awareness that the bifunctional iminophosphorane (BIMP) superbase catalysts often greatly outcompete tertiary amine bifunctional catalysts owing to the increased basicity of the iminophosphorane moiety, we were confident that it is very likely this catalyst class could promote these challenging enantioselective transformations in only a fraction of the time, while maintaining high enantioselectivity.



Scheme 55. Challenging enantioselective intramolecular oxy-Michael reactions.

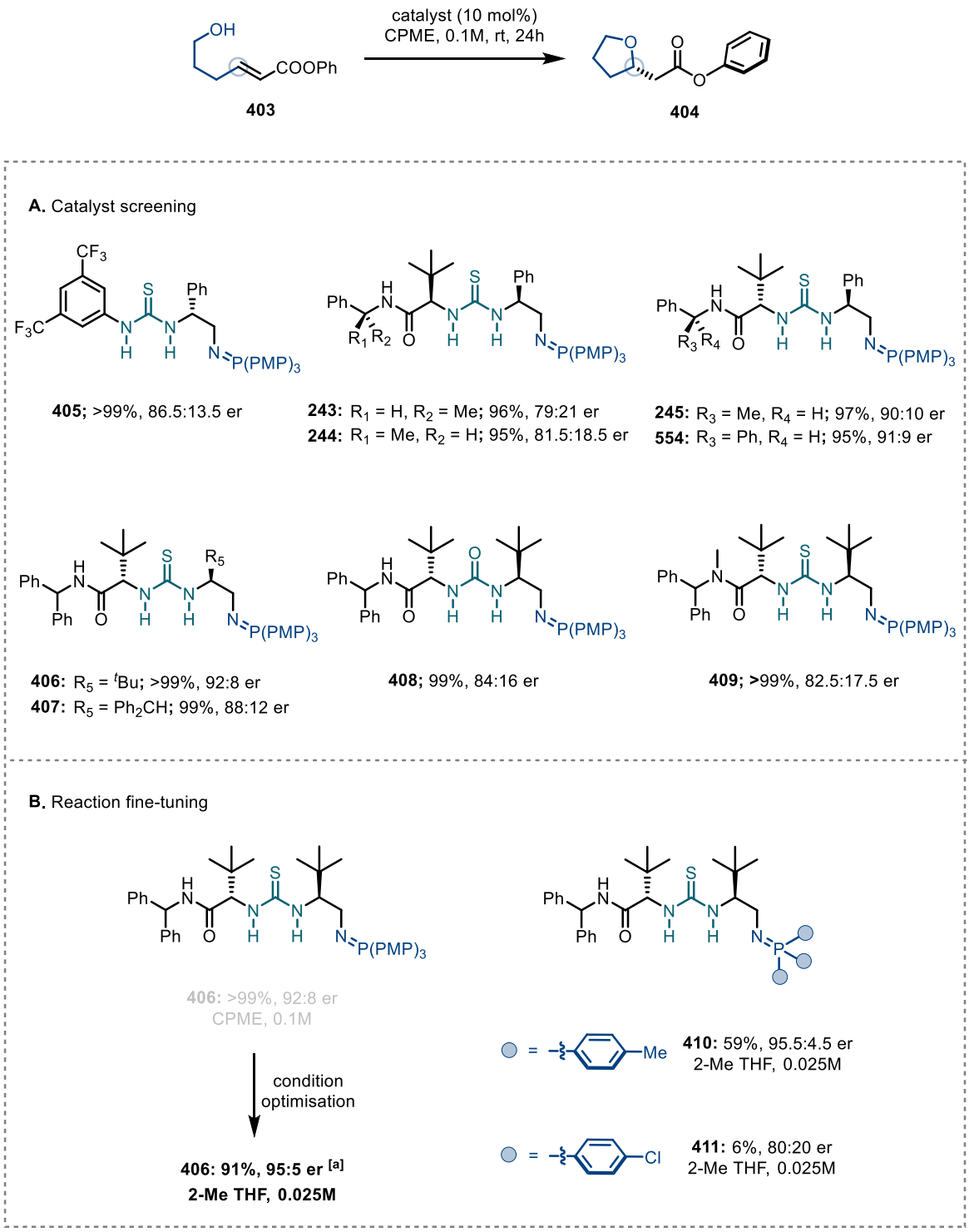
3.2.3 Aim of the project

While enabling faster reactions was already a worthwhile goal, the true challenge was in enabling intramolecular oxy-Michael reactions far beyond the reach of current methods. Against this backdrop, we wished to develop an unified methodology to enable the synthesis of a broad range of chiral cyclic ethers efficiently and highly enantioselectively. We envisaged the enhanced Brønsted basicity of the BIMP system could potentially provide synergistic activation for much less reactive and more hindered pronucleophiles such as secondary and tertiary alcohols, low electrophilicity β-substituted α,β-unsaturated amide and ester acceptors and tethers of varying length. Additionally, we believed the tuneability and modularity of the BIMP catalyst system could be the key for assessing challenging

enantioselective oxy-Michael reactions across a wide range of substrate classes. The aim of the work described in this chapter was to explore the capabilities of the BIMP catalyst family in a wide range of IOMRs.

3.3 Reaction Optimisation

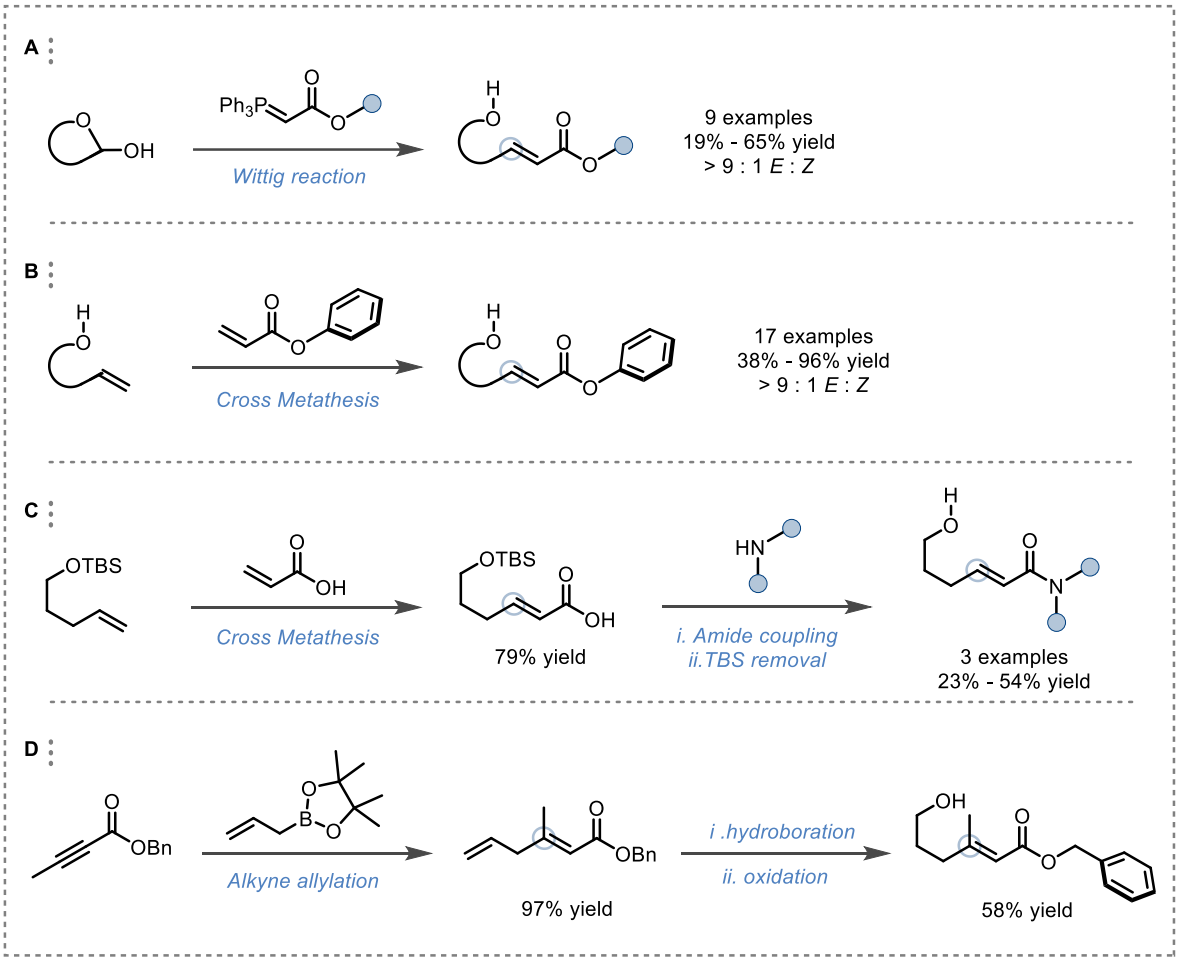
Our study began with the investigation of the IOMR of model substrate **403** bearing a primary alcohol tethered α,β-unsaturated phenyl ester. In Takemoto's study, only moderate yield (41%) of the desired product was obtained after 7 days employing a bespoke chiral tertiary amine catalyst.[71] We were very pleased to find that first-generation BIMP catalyst **405** could smoothly promote the cyclisation of precursor **403** to enantioenriched THF **404** with full conversion and good enantioselectivity (86.5:13.5 er) in only 24 h (**Scheme 56**). Further catalyst optimisation was carried out by investigating the incorporation of an additional stereogenic centre flanking the thiourea moiety within the BIMP scaffold. The furthest stereogenic centre from the superbasic iminophosphorane motif proved to be insignificant for the enantiofacial control (catalyst **243** and **244**). In contrast, the trans/cis configuration of the two stereogenic centres adjacent to the thiourea was found to be important with trans-configured catalyst **245** outperforming diastereomeric cis-configured catalyst **244**. Further variation of the chiral backbone revealed that catalyst **406** smoothly gave the desired product in full conversion and 92:8 er in 24 h. Deploying a less acidic urea **408** as the H-bond donor or methylating the amide hydrogen (**409**) were detrimental to the enantioselectivity, indicating the appropriate combination of the thiourea and the amide for substrate binding (see chapter **4.3.1** for full details of catalyst screening). Following the identification of catalyst **406** as the optimal catalyst, a systematic screening of solvent, temperature and reaction concentration was carried out (see chapter **4.3.1** for full details of condition optimisation). We were delighted to find that when the reaction was carried out in 2-Me THF at 0.025 M concentration, **404** could be obtained in 91% isolated yield and 95:5 er. We also attempted to fine-tune the basicity of the BIMP catalyst to acquire better reaction control. The IOMRs were unfortunately found to be much less efficient with derivatives of catalyst **406** carrying a less Brønsted basic iminophosphorane motif (**410** and **411**, with only 59% and 6% yield obtained respectively in 24 hours). This fact nonetheless highlighted the importance and advantages of employing a catalyst bearing a superbasic site.



Scheme 56. **A**. Screening of BIMP catalysts; **B**. Reaction fine-tuning. Reactions were carried out with 0.05 mmol **403**; Conversion was determined by ^{1}H NMR analysis of crude reaction mixture; er was determined by HPLC analysis on chiral stationary phase; rt = room temperature; CPME = cyclopentyl methyl ether; PMP = *para*-methoxy phenyl. [a] Reaction was carried out with 0.2 mmol **403** and yield of isolated product is presented.

3.4 Substrate Synthesis

With the optimised conditions in hand, we proceeded to prepare an array of alcohol substrates to explore the scope of the IOMR. General synthetic routes are outlined in **Scheme 57** (see chapter **4.3.3** for full details of experimental conditions and reaction yields). We typically relied on the Wittig reaction between hemiacetals and phosphonium ylides or a Hoveyda–Grubbs catalyst promoted cross metathesis between substituted 4-pentenols/5-hexenols and phenyl acrylate to construct the alkene in high *E*-selectivity and satisfactory yield (**Scheme 57A** and **B**).



Scheme 57. Representative substrate synthetic routes

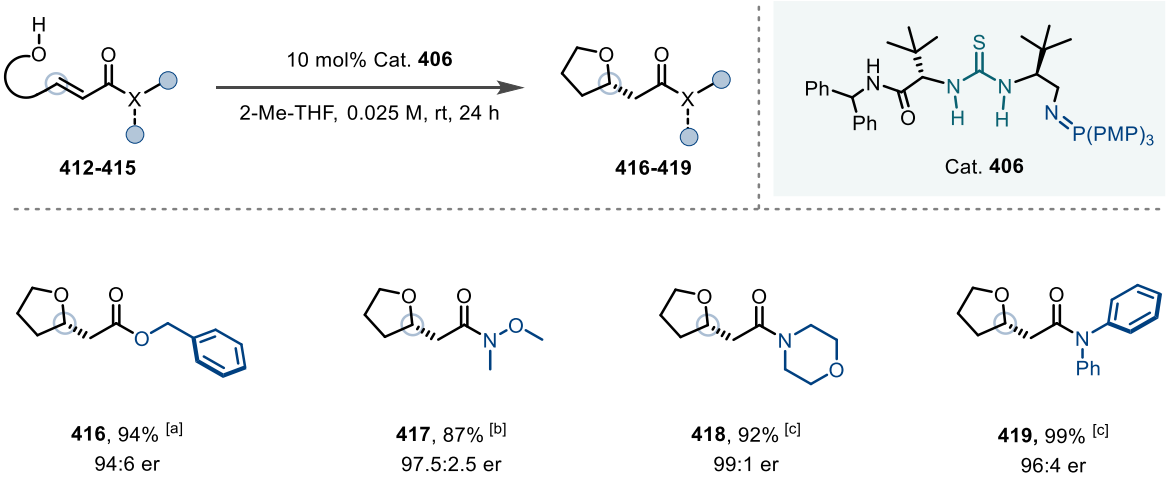
For substrates bearing an amide motif, the cross-metathesis approach proved to be typically inefficient potentially due to coordination of the electron pair on the nitrogen atom with metal-alkylidene and thus deactivation of the catalyst.[78] The Wittig reaction was also not ideal because of the tedious preparation of amide bearing phosphonium ylides. As such, we prepared the amide bearing substrates *via* a cross

metathesis between TBS-protected 4-pentenols and acrylic acid, followed by a typical amide coupling reaction and a methanol/camphorsulfonic acid-catalysed TBS deprotection process (**Scheme 57C**). For a substrate carrying a β,β'-disubstituted α,β-unsaturated ester, we failed to obtain a satisfactory amount of this substrate class *via* Wittig reaction or cross metathesis approach. Pleasingly, we then found a smooth three-step synthetic sequence towards this tri-substituted alkene species (**Scheme 57D**). It started from a copper-catalysed highly *E*-selective conjugate allylation of electron-deficient benzyl but-2-ynoate with allylboronate, followed by hydroboration and a subsequent oxidation to afford the final alcohol starting material for the IOMR.[79]

3.5 Evaluation of Reaction Scope

3.5.1 Reaction scope with regards to Michael acceptors

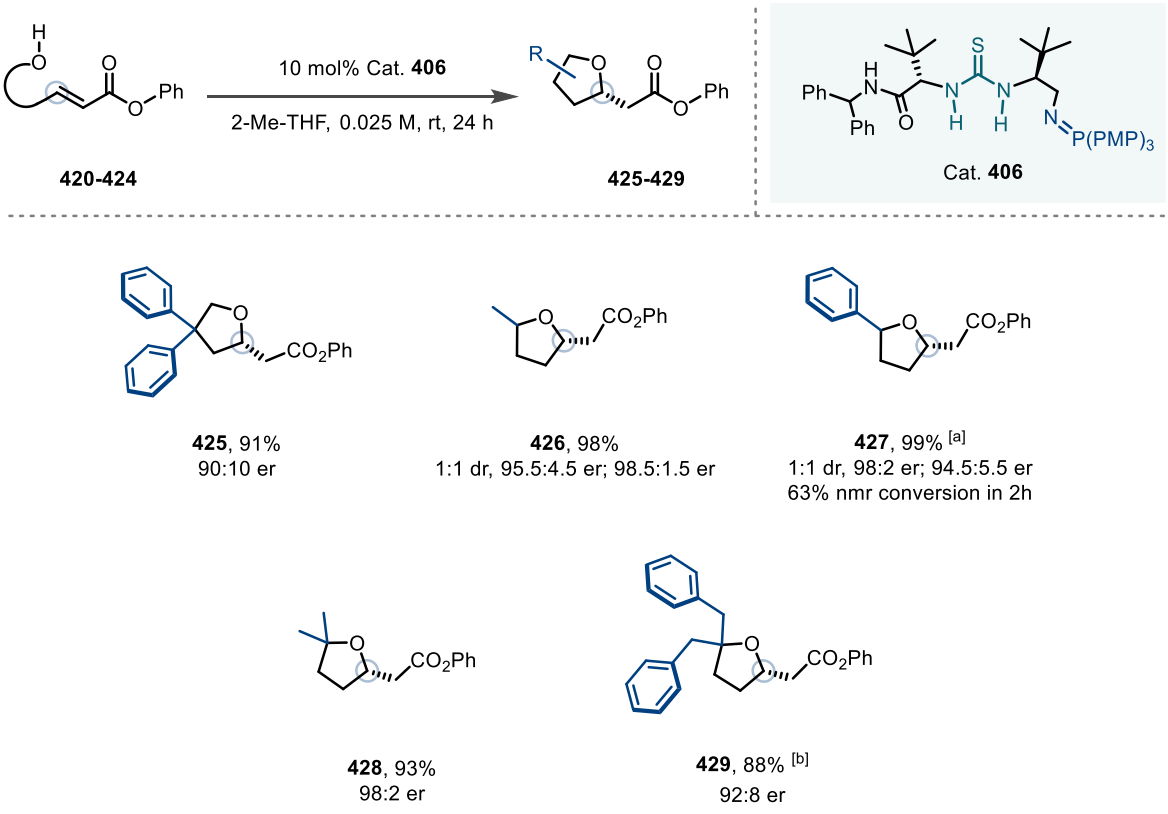
To evaluate the reaction scope of the IOMR, variations to the Michael acceptor were first explored (**Scheme 58**). We found that the reaction concentration is of great significance to the ring closure outcome. Compared to phenyl ester, less activated Michael acceptors including benzyl ester **412** and amides **413** required an increase in concentration (to 0.2 M and 0.1 M respectively) to realise a satisfactory reaction yield while maintaining high enantioselectivity. Specifically, 15 mol% cat. **406** was demanded for more challenging morpholine amide **414** and diphenyl amide **415**.



Scheme 58. Reaction scope with regards to Michael acceptors. Reactions were carried out with 0.2 mmol substrates; variations from standard conditions: [a] 0.2 M 2-Me-THF; [b] 0.1 M CPME for 48 hours; [c] 15 mol% cat. **406** in 0.1 M CPME for 48 hours.

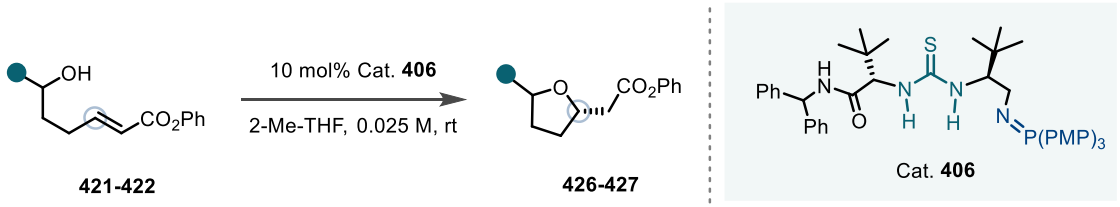
3.5.2 Reaction scope with regards to tether substituents

Having explored modifications in the Michael acceptor, the effect of substituents on the alcohol tether were investigated (**Scheme 59**). Pleasingly, β-disubstituted alcohol **420** underwent smooth cyclisation under the optimised conditions, furnishing **425** in 91% yield and 90:10 er. α-Mono-substitution on the alcohol tether demonstrated a positive influence on the enantioselectivity — α-methyl (**421**) and α-phenyl secondary (**422**) alcohols substrates afforded the corresponding enantioenriched cyclic ethers **426** and **427** in quantitative yields and excellent enantioselectivity (up to 98.5:1.5 er) as a 1:1 mixture of diastereomers. To our delight, even more hindered α-disubstituted tertiary alcohols were compatible with the method. Sterically hindered THFs preparation through IOMR of α-tertiary alcohols typically represent a rather daunting challenge due to their α-crowding and thus reduced nucleophilicity. With 10% cat. **406** and under mild conditions, gem dimethyl (**428**) and dibenzyl (**429**) enantioenriched THFs were furnished in excellent yield and 98:2 and 92:8 er respectively.



Scheme 59. Reaction scope with regards to tether substituents. Reactions were carried out with 0.2 mmol substrates; variations from standard conditions: [a] 8 hours reaction time; [b] 0.2 M 2-Me-THF for 48 hours.

We also wished to examine if an effective kinetic resolution of racemic alcohol starting materials could be developed with the BIMP system. As depicted in **scheme 60**, for substrate **421**, the enantiomeric ratio of the remaining starting material increased as the reaction proceeded, which indicated a difference in the rate of IOMR of the two enantiomers. We however only witnessed an unsatisfactory maximum diastereomeric ratio of 1.58:1, suggesting an inefficient kinetic resolution. We envisioned that increasing α-crowding could enhance the efficiency of the resolution. Indeed, substrate **422** bearing an α-phenyl substituent featured a better diastereomeric ratio in high conversion (1.55:1 for substrate **421** *vs* 1.21:1 for substrate **422** in around 60% conversion). Although the catalyst selectivity of the two enantiomers prevents an effective kinetic resolution, the constant ee values for both substrates demonstrated an absence of racemisation of the IOMR during the reaction profile.



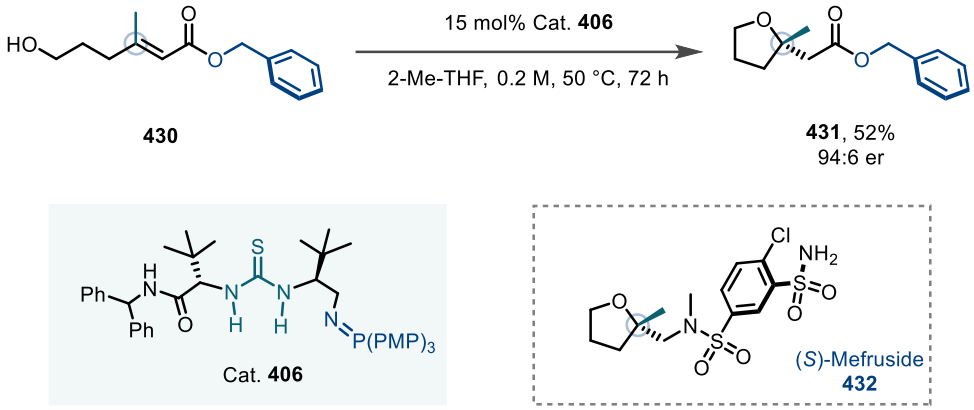
● = Me, **421**	Time (h)	Conv. (%)	ee (major)	ee (minor)	ee (SM)	dr
1	1	17	97	91	5	1.58:1
2	2	36	97	91	9	1.43:1
3	5.6	65	97.4	92	23	1.21:1
4	24	>99	97.6	91	-	1:1
5 [a]	**24**	**98**	**97**	**91**	**-**	**1:1**

● = Ph, **422**	Time (h)	Conv. (%)	ee (major)	ee (minor)	ee (SM)	dr
1	2	63	96	88	42	1.55:1
2	8	>99	96	89	-	1:1
3	26.5	>99	95	88	-	1:1
4 [a]	**8**	**99**	**96**	**89**	**-**	**1:1**

Scheme 60. Final tuning of reaction condition for substrate **421** and **422**. Reactions were carried out with 0.2 mmol substrates; aliquot was taken and quenched with 1 M AcOH in CH_2Cl_2 in designated time for analysis; Conversion and dr were determined by ^1H NMR analysis of crude reaction mixture; ee was determined by HPLC analysis on chiral stationary phase; rt = room temperature; [a] reaction was quenched with 1 M AcOH in CH_2Cl_2 in designated time and yield of isolated product was presented.

3.5.3 Reaction scope with regards to β-disubstituted benzyl ester

The effect of β,β'-disubstitution on the Michael acceptor was then investigated (**Scheme 61**). While low conversion of **430** was observed under standard conditions, increasing catalyst loading to 15 mol% and re-optimising the reaction conditions (0.2 M concentration at 50 °C for 72 h) was sufficient to overcome the reactivity issue, affording **431** bearing a quaternary stereo-centre in 52% yield and 94:6 er. Notably, THF **431** could serve as a precursor en route to the marketed pharmaceutical Mefruside **432** – – an effective diuretic and anti-hypertensive drug.[80]



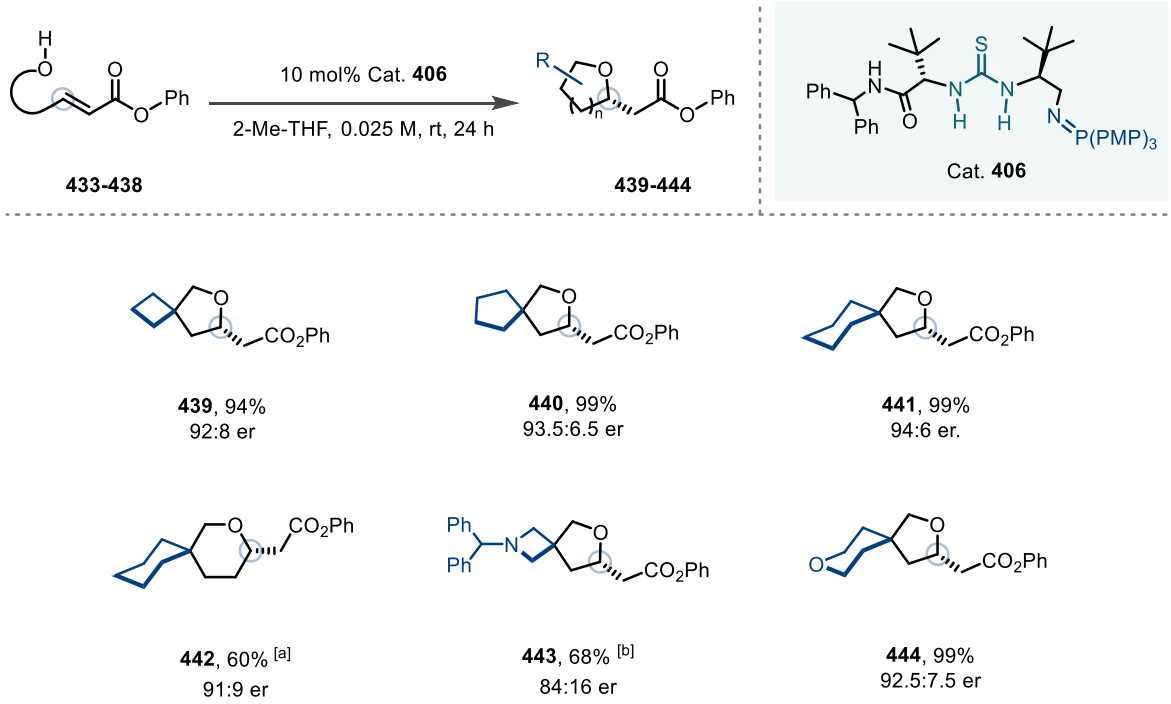
Scheme 61. Reaction scope with regards to β-disubstituted benzyl ester; reaction were carried out with 0.2 mmol substrate; structure of (*S*)-Mefruside **432**.

3.5.4 Reaction scope with regards to β-oxy-spirocycles

Since Lovering proposed the concept of 'escape from flatland' in 2009, medicinal chemists have progressively realised the importance of increasing the F(sp^3)-richness (F(sp^3) = (number of sp^3 hybridised carbons/total carbon number) in the molecules of their research.[81-83] Saturated spirocycles were demonstrated to possess enhanced physico-chemical characteristics including lipophilicity, aqueous solubility and stability against metabolic degradation compared to their common monocyclic counterparts.[83] Oxy-spirocycles, as a new generation in the family discovered only recently, were found to be much more soluble than their all-carbon counterparts and incorporates a further H-bond acceptor to modulate pharmacological properties.[83] To date, catalytic enantioselective methods towards these oxygen-containing compounds have remained rare and nonsystematic.[62, 64, 84-86] Against this backdrop,

we envisaged that our newly developed methodology could be applied to the synthesis of medicinally relevant, yet largely underexplored, enantioenriched oxy-spirocycles.

We firstly evaluated the IOMR scope with regards to β-oxy-spirocycles (**Scheme 62**). β-Spiro-cyclobutane (**439**), pentane (**440**) and hexane (**441**) products were all obtained in excellent yields and enantioselectivities while for spirocyclic enantioenriched THP **442**, only 60% yield could be obtained under similar conditions even after a lengthened reaction time to 72 h. We witnessed slightly diminished enantioselectivity in the IOMR of substate **437** bearing a β-spiroaziridine motif. Only 68% yield and moderate enantioselectivity (84:16 er) was afforded after 48 hours. We envisioned that this selectivity drop originated from the interruption of discreet hydrogen bonding interaction (crucial for efficient enantioselectivity to occur) between the BIMP thiourea and substrate, by the new free amine. Pleasingly, β-spiro-THP **444** was obtained in 99% yield and 92.5:7.5 er without the need for any re-optimisation.

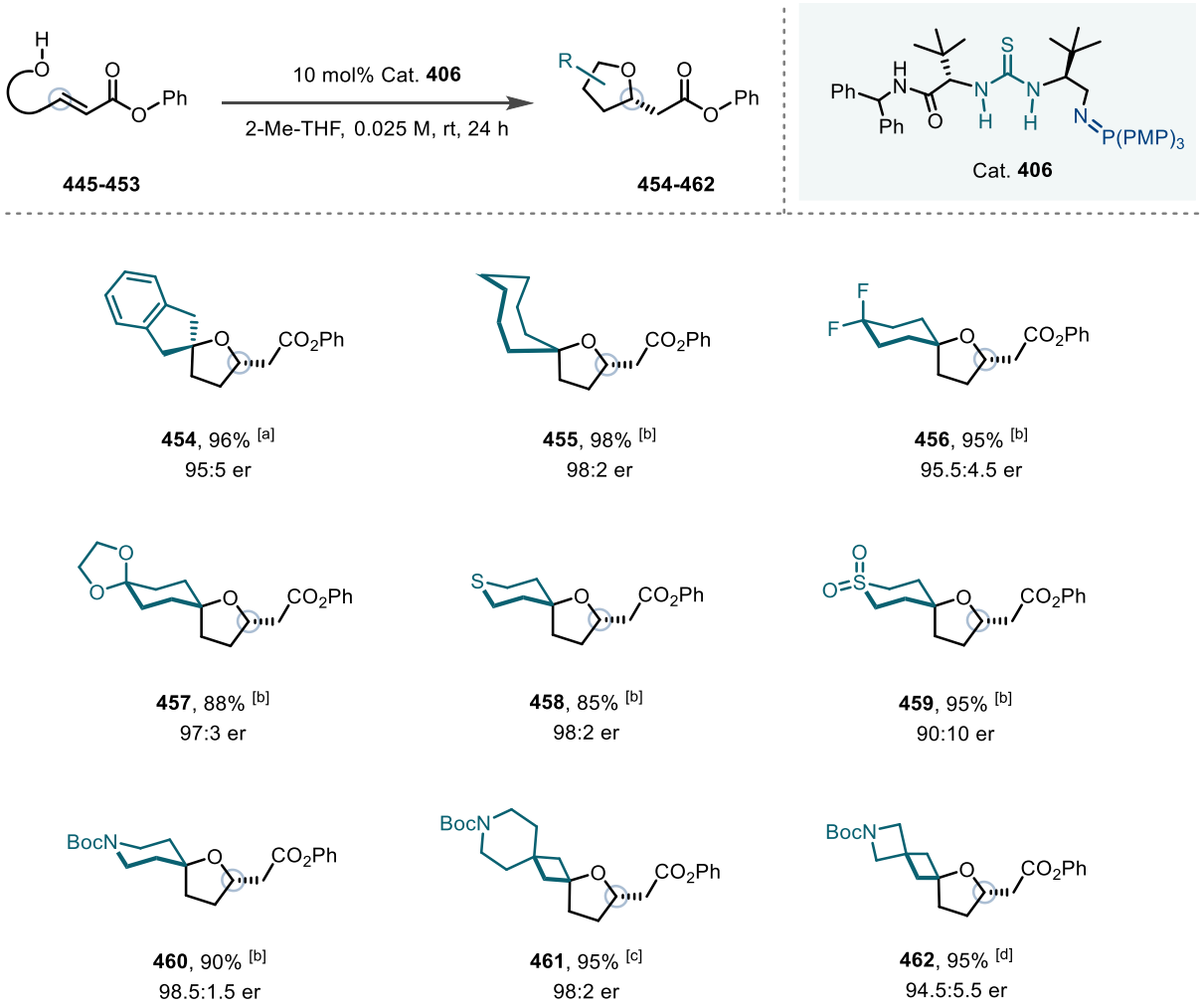


Scheme 62. Reaction scope with regards to β-oxy-spirocycles. Reactions were carried out with 0.2 mmol substrates; variations from standard conditions: [a] 8 mol% cat. **406** for 72 hours; [b] 48 hours reaction time.

3.5.5 Reaction scope with regards to α-oxy-spirocycles

Following the successful evaluation of reaction scope with respect to β-oxy-spirocycles, we proceeded to investigate the use of spirocyclic tertiary alcohols as substrates for IOMR to generate enantioenriched

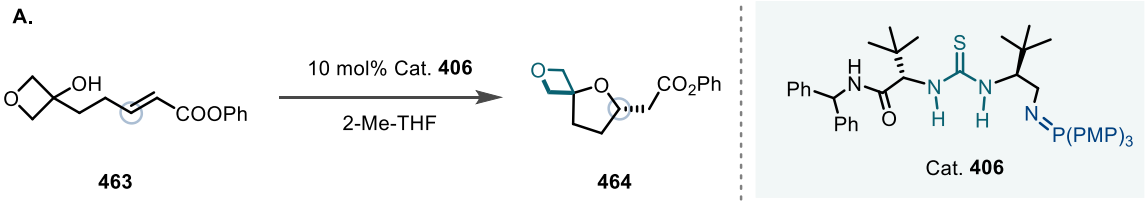
α-oxy-spirocycles (**Scheme 63**). Products **454**-**457** bearing 5-, 6- or 8- membered carbocyclic spirocycles were all obtained in excellent yield (88% – 98% yield) and enantioselectivity (95:5 – 98:2 er) with both gem-difuoro **456** and acetal **457** groups being tolerated. Products carrying spiro-heterocycles **458**-**460** were also obtained in good to excellent yields with >90:10 er with thioethers **458** and acid sensitive functionalities including sulfones **459** and *N*-Boc piperidine **460** all being compatible. We were also delighted to observe that the new BIMP-catalysed IOMR was amenable to substrates bearing bis-spirocylic moieties **452** and **453**. Both *N*-Boc 7-azaspiro[3.5]nonane **461** and 2-azaspiro[3.3]heptane Michael products **462** were afforded in 95% yield and 98:2 and 94.5:5.5 er respectively with minor variations in reaction conditions.



Scheme 63. Reaction scope with regards to α-oxy-spirocycles. Reactions were carried out with 0.2 mmol substrates; variations from standard conditions: [a] 2-Me-THF (0.1 M) for 48 hours; [b] 2-Me-THF (0.2 M) for 48 hours; [c] 2-Me-THF (0.05 M) for 48 hours; [d] 2-Me-THF (0.05 M) solvent system.

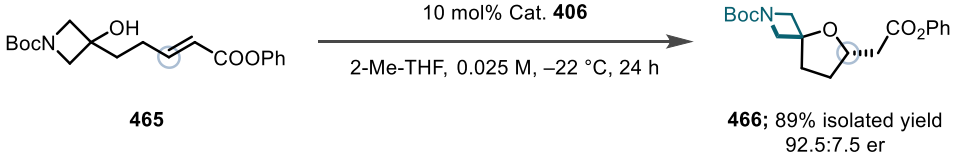
Oxetanes, as strained oxygenated heterocycles broadly adopted in therapeutics, have received enormous interest as bio-isosteres for carbonyl groups and gem-dimethyl with improved "druglike" properties recently.[87-90] We wished to incorporate this intriguing entity into molecular scaffolds that can be prepared by our BIMP enabled IOMR. Interestingly, unlike α-methyl substituted alcohol starting material **421**, substrate **463** bearing an α-oxetane ring was found to suffer from a significant retro-Michael process and a consequent racemisation. As depicted in **Scheme 64A**, 83% conversion of product **464** in 74:26 er was obtained in 0.2 M 2-Me THF at rt after 24 hours while an improved enantiomeric ratio and conversion was furnished in a shorter reaction time under identical conditions (entry 1-2). We then noticed reaction temperature is of greater significance to the IOMR enantioselectivity over solvent concentration (entry 3-4). Finally, 77% yield of oxetane-spiro THF **464** in 91:9 er was furnished in 0.2 M 2-Me THF at –22 °C after 10 hours (entry 5). Pleasingly, an α-*N*-Boc azetidine-spiro THF **466** was also successfully prepared (**Scheme 64B**).

A.



Entry	[C]	T (°C)	Reaction time (h)	conversion (%)	er
1	0.2 M	rt	24	83	74:26
2	0.2 M	rt	2	94	85:15
3	0.2 M	–22	16	95	90.5:9.5
4	0.025 M	rt	16	97	85.5:14.5
5 [a]	**0.2 M**	**–22**	**10**	**77**	**91:9**

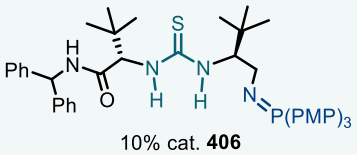
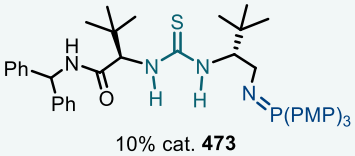
B.



Scheme 64. **A**. Final tuning of reaction condition for substrate **463**. Reactions were carried out with 0.05 mmol **463**; conversion was determined by ^{1}H NMR analysis of crude reaction mixture; er was determined by HPLC analysis on chiral stationary phase; rt = room temperature; [a] reaction was carried out with 0.2 mmol **463** and yield of isolated product was presented; **B**. IOMR of *N*-Boc azetidine bearing substrate **465**.

3.5.6 Reaction scope with regards to sugars and natural product derivatives

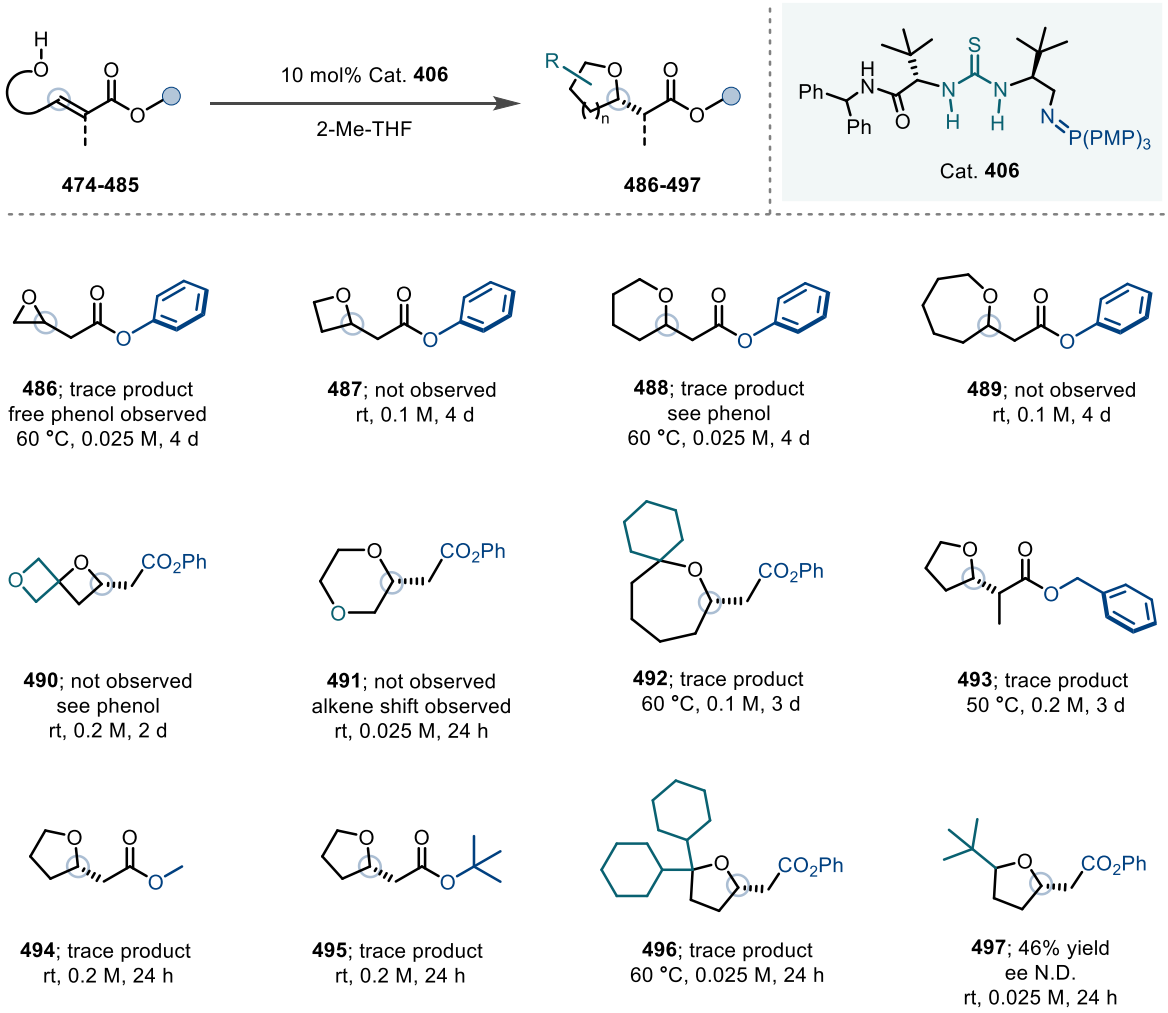
Having demonstrated a wide scope with respect to oxy-spirocycles, we were intrigued to see if the BIMP catalysed stereo-centres installation in the IOMR would be affected by the existing stereo-centres of the substrates (**Scheme 65**). As such, enantioenriched substrate **468** bearing an acetonide motif was selected as the investigated object. While 56:44 ratio of anomers was observed with 10% BEMP (an achiral superbase), BIMP catalyst **406** was able to smoothly deliver pyranose **467** in high yield and excellent diastereoselectivity (93% yield and 94:6 dr). Pleasingly, the two anomers were readily separable by silica gel chromatography, affording the optically pure carbosugar product **469** in 85% yield. It is worth noting that the diastereoselectivity dropped significantly to 70:30 dr with enantiomer of catalyst **473**, indicating a mis-match effect of substrate-catalyst binding. Similarly, optically pure anomer of pyranose **467** was obtained by chromatography purification in 75% yield. Scope of this highly diastereoselective IOMR was extended to furanose **469** and natural product sclareolide derivative **471** in 94% yield, 97.5:2.5 dr and 92% yield, 99:1 dr respectively.

IOMR product / *Catalyst*	*[carbosugar synthesis]* **467** (substrate **468**)	*[carbosugar synthesis]* **469** (substrate **470**)	*[sclareolide derivative]* **471** (substrate **472**)
 10% cat. **406**	**93%, 94:6 dr** [a] **85%, >99.5:0.5 dr** [b] *2-Me THF, 0.025 M* *rt, 24 h*	98% yield 64:36 dr	**92% yield** **99:1 dr** *2-Me THF, 0.025 M* *rt, 24 h*
 10% cat. **473**	99%, 30:70 dr [a] 75%, >0.5:99.5 dr [b]	**94% yield** **97.5:2.5 dr** *2-Me THF, 0.1 M* *rt, 24 h*	61% yield 60:40 dr
10% BEMP	54%, 44:56 dr	99%, 53.5:46.5 dr [c]	60%, 1:1 dr

Scheme 65. Reaction scope with regards to sugars and natural product derivatives. Reactions were carried out with 0.2 mmol substrates; [a] crude reaction mixture analysis; [b] purified product analysis; [c] 10% DBU.

3.5.7 Limitations of the reaction scope

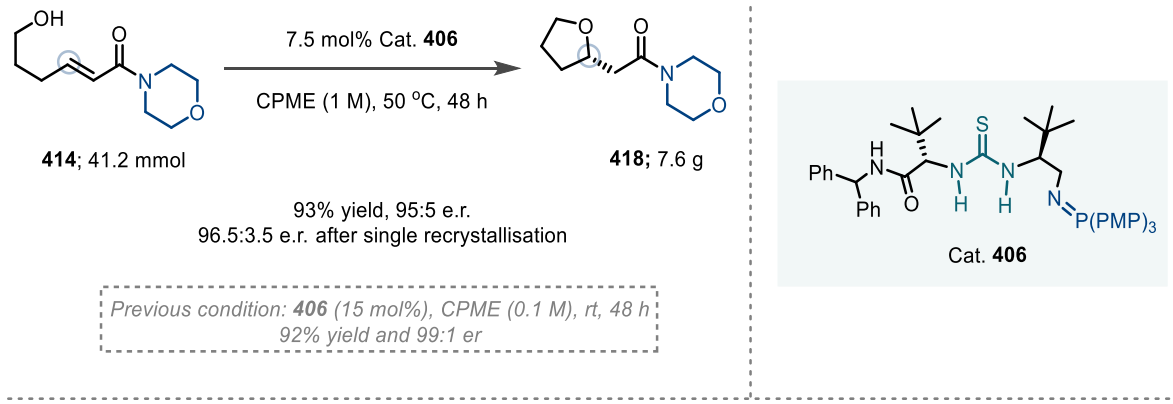
While the broad scope with regards to Michael acceptors, tether substituents, oxy-spirocycles and sugar/natural product derivatives demonstrated thus far marks a clear improvement from the previously developed enantioselective synthesis of aliphatic cyclic ethers *via* IOMR reactions, certain limitations indeed exist (**Scheme 66**). Our BIMP catalytic system mainly provided access to enantioenriched THF rings but failed to produce oxirane **486**, oxetane **487**, non-substituted THP **488** and oxepane **489**. Even Thorpe-Ingold effect-assisted IOMR to prepare 4-, 6-, and 7-membered ethers **490** to **492** were unsuccessful. Moreover, Michael acceptors including α-substituted α,β-unsaturated ester **481**, methyl ester **482** and *tert*-butyl ester **483**, nucleophiles including α,α'-dicyclohexyl **484** or α-*tert*-butyl **485** substituted alcohols were disappointingly not compatible with this method.



Scheme 66. Unsuccessful example of the BIMP-catalysed IOMR to α,β-unsaturated ester.

3.6 Preparative Scale Synthesis and Derivatisation

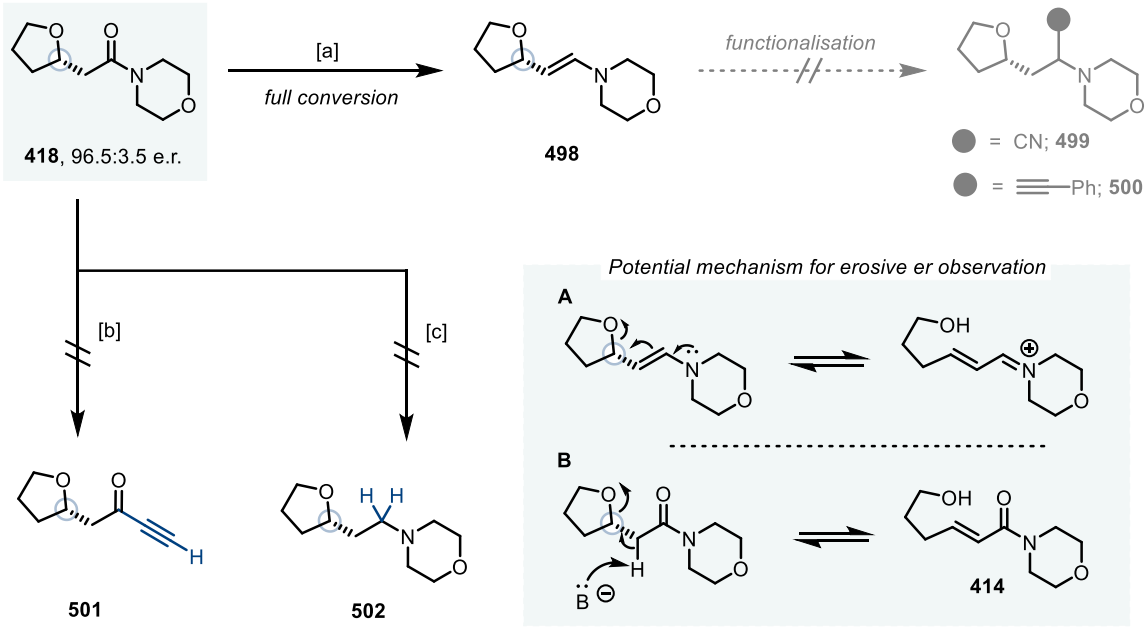
Having established the scope of the IOMR over three distinct substrate classes and demonstrating examples that are beyond the activation of our BIMP system, we wish to substantiate the scalability of the method and illustrate potential downstream applications. To this end, cyclisation of alcohol **414** on a 41.2 mmol scale was carried out with loading of catalyst **406** lowered to 7.5 mol% (**Scheme 67**). Upon reducing the catalyst loading, a higher reaction temperature of 50 °C and a CPME concentration increase to 1 M were demanded to deliver good yield (7.6 g, 93%). Pleasingly, only a small compromise with respect to the level of enantioselectivity was observed with the re-optimised conditions (95:5 er). Unfortunately, we failed to find effective recrystallisation conditions to uplift the enantiomeric ratio of cyclised product **418** — only a slight increase to 96.5:3.5 er was obtained by recrystallising from hot hexane.



Scheme 67. Preparative scale synthesis of **418.**

To showcase the synthetic utility of the Michael product and elaborate potential chiral 'drug-like' molecules preparation, enantioenriched **418** — obtained from the scale-up reaction described above — was selected as a model scaffold for late-stage derivatisation. Tertiary amides, although typically inert in nature, can undergo a wide range of downstream C–C bond formation reactions *via* reductive activation through hydrosilylation with Vaska's complex ($IrCl(CO)(PPh_3)_2$), for example.[91] Indeed, we observed a full conversion of morpholine amide **418** to enamine species **498** with 1 mol % Vaska's complex and 2 equiv TMDS. Following attempted C-C bond formations including alkynylation and Strecker reaction, however, only delivered desired products **499** and **500** with significantly erosive enantiomeric ratio values,

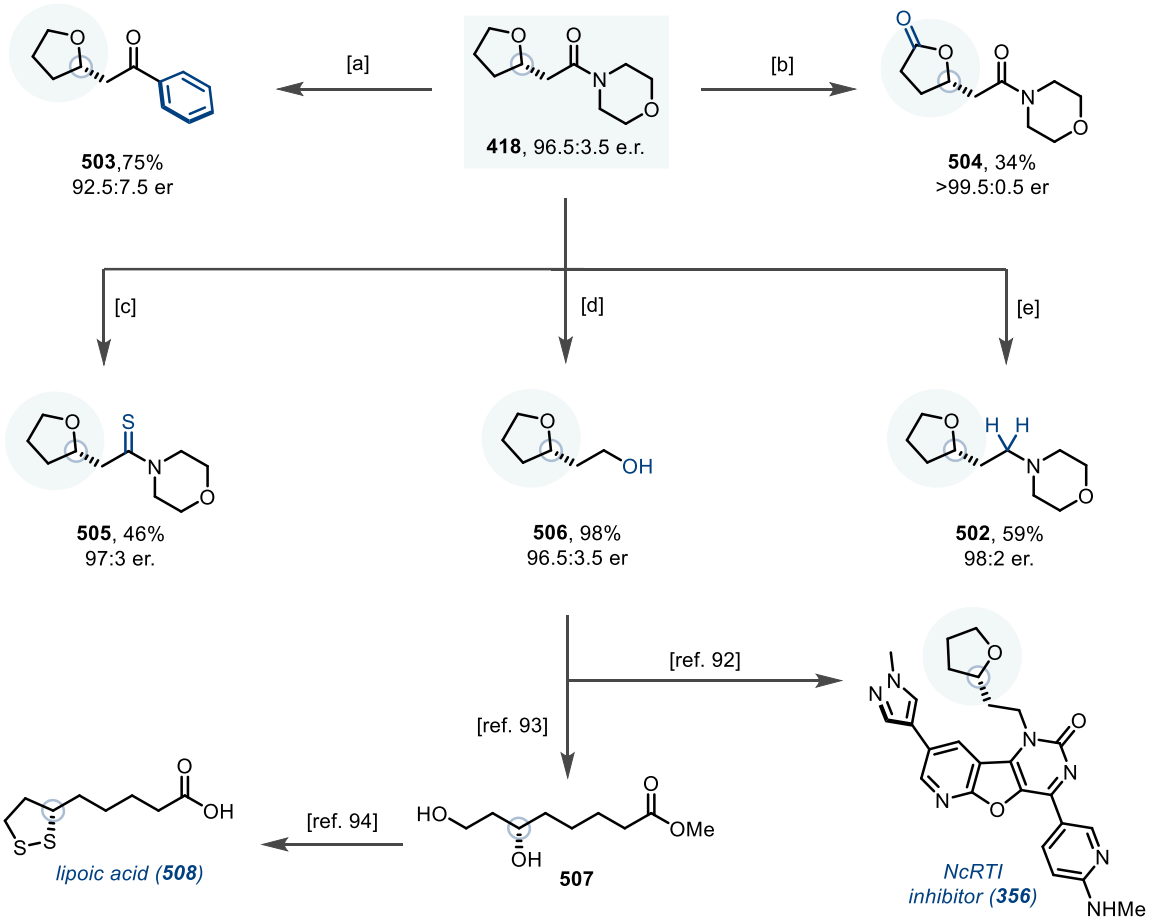
which, we speculated, was owing to a reversible ring opening process of the enamine species, illustrating in **Scheme 68A**. We then attempted to derivatise the morpholine amide **418** to alkyne species **501** and tertiary amine **502** *via* Grignard addition with 1.2 equiv ethynylmagnesium bromide and metal-hydride reduction by 4 equiv $LiAlH_4$, respectively. Unfortunately, no desired functionalised product was furnished while recovered starting material **418** and ring opening product **414** were mainly observed, indicating a retro-Michael process (**Scheme 68B**) was dominant in the present of a strong base (Grignard reagent or metal-hydride complex).



Scheme 68. Unsuccessful derivatisation of enantioenriched **418**. [a] $IrCl(CO)(PPh_3)_2$ (Vaska's complex), TMDS, THF, rt, 10 min; [b] ethynylmagnesium bromide, 78 °C to rt, 16 h; [c] $LiAlH_4$, THF, 0 °C to rt, 4 h.

To our delight, application of alternative strong base-free functionalisation conditions allowed us to prepare a wide range of attractive chiral building blocks and drug precursors from enantioenriched morpholine amide **418** (**Scheme 69**). Firstly, **418** was converted to the corresponding ketone **503** using non-basic organocerium reagent $PhCeCl_2$ in 75% yield with a slight erosion in optical purity. Next, treating **418** with 2 mol% $RuCl_3 \cdot 3H_2O$ and 8 equiv sodium periodate furnished lactone product **504** in moderate yield and >99.5:0.5 er. Moreover, the amide moiety could be fully reduced to corresponding amine **502** with Hantzsch ester and Tf_2O or transformed to thioamide **505** using Lawesson's reagent. Both products were obtained in moderate yield with no racemisation being observed. Synthetic utility of

the Michael product was further showcased by a direct conversion to medicinally useful alcohol **506** in 98% yield using 8 equiv SmI_2 and Et_3N. Transformation of enantioenriched primary alcohol **506** to pharmaceutical intermediates are well-documented, such as providing access to NcRTI inhibitor (**356**) [92] — an analogue of potent HIV-1 nucleotide competing reverse transcriptase inhibitor (NcRTI) and diol precursor **507** [93] for *S*-lipoic acid (**508**) [94] — pivotal protein-bound coenzyme and growth factor produced in animal tissues as well as plants.[95]

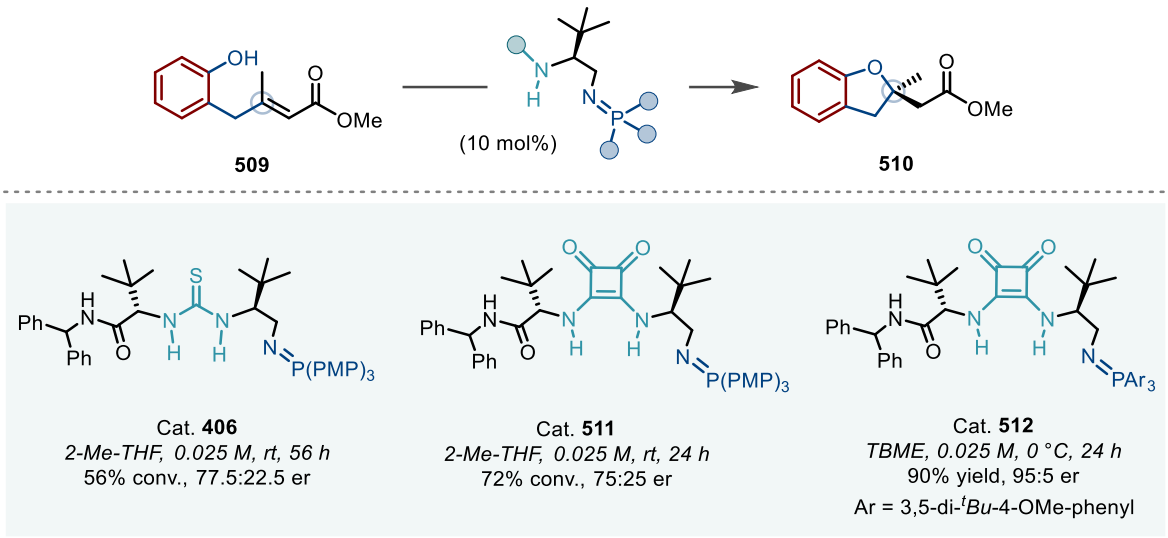


Scheme 69. Derivatisation of enantioenriched **418**. [a] $PhCeCl_2$, THF, -78 °C, 2 h; [b] $RuCl_3 \cdot 3H_2O$, $NaIO_4$, MeCN, H_2O, CCl_4, rt, 16 h; [c] Lawesson's reagent, THF, 60 °C, 72 h; [d] SmI_2, Et_3N, H_2O, rt, 16 h; [e] Hantzsch ester, Tf_2O, DCM, 0 °C to rt, 16 h.

3.7 Extension to Phenol Nucleophiles

3.7.1 Reaction re-optimisation

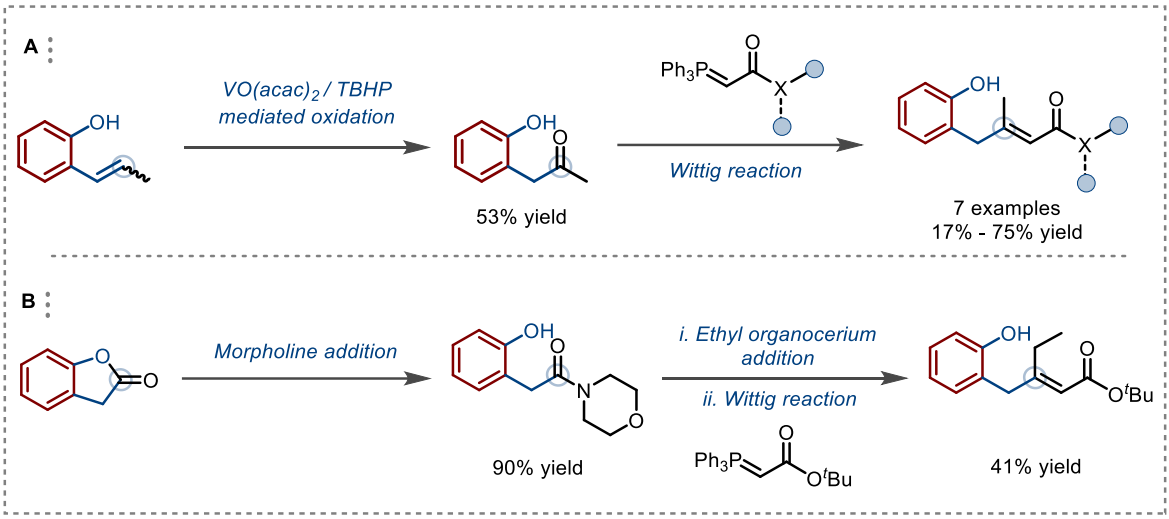
Having established a broad-scope transformation of aliphatic primary, secondary and tertiary alcohols into enantioenriched THF and THP rings, we wished to extend the IOMR to substrates bearing a phenolic nucleophile tethered to β-substituted, α,β-unsaturated esters and amides and thus for the enantioselective synthesis of dihydro-benzofurans carrying a fully substituted stereo-centre. To our knowledge, only the Takemoto group provided access to such unique building block in a highly enantioselective manner *via* IOMR,[71] albeit with only 75% yield after 7 days of reaction time. Our optimal BIMP catalyst **406**, identified in the IOMR of aliphatic alcohols, however only delivered an unsatisfactory 56% conversion of the same adduct product **510** in a moderate 77.5:22.5 er after 56 hours (**Scheme 70**). Pleasingly, this issue of reactivity was soon circumvented by employing catalyst **511**, which incorporates a more acidic squaramide H-bond donor motif in place of a thiourea and furnished the desired product in 75% conversion and 75:25 er after 24 hours. Catalyst **512** bearing bulkier aryl substituents on the iminophosphorane moiety proved to further enhance the enantioselectivity, affording **510** in 90% yield and 95:5 er when paired with a decreased temperature to 0 °C and the use of TBME as solvent (see chapter **4.3.1** for full details of optimisation).



Scheme 70. Selected BIMP catalysts screening and condition fine-tuning; Reactions were carried out with 0.05 mmol **509**; conversion was determined by ^{1}H NMR analysis of the crude reaction mixture; er was determined by HPLC analysis on a chiral stationary phase;

3.7.2 Substrate synthesis

An array of phenol-bearing substrates were then synthesised to explore variations in the Michael acceptor. General synthetic routes are outlined in **Scheme 71** (see chapter **4.3.3** for full details of experimental conditions and reaction yields). Preparation of *o*-hydroxyaryl/methyl/ketones followed a mild oxidation of commercially available *o*-alkenyl phenol *via* a $VO(acac)_2$/TBHP (2 mol %/1.2 equiv) system, reported by Scettri and co-workers.[96] Notably, this Vanadium catalysed oxidative transformation was compatible with both isomers of starting materials yet not with any additional substituents on the phenol rings. Therefore, synthesis of substituted *o*-hydroxyaryl/methyl/ketones was found to be rather challenging. The construction of the tri-substituted alkene final product was then achieved by a smooth highly *E*-selective Wittig reaction. For phenol substrate bearing a β-ethyl-substituted, α,β-unsaturated ester, the preparation of corresponding *o*-hydroxyaryl/methyl/ketones followed firstly a morpholine amide synthesis and then an ethyl organocerium addition. It is worth noting that non-basic organocerium reagent was necessary for the ketone synthesis in the presence of an acidic α-proton.

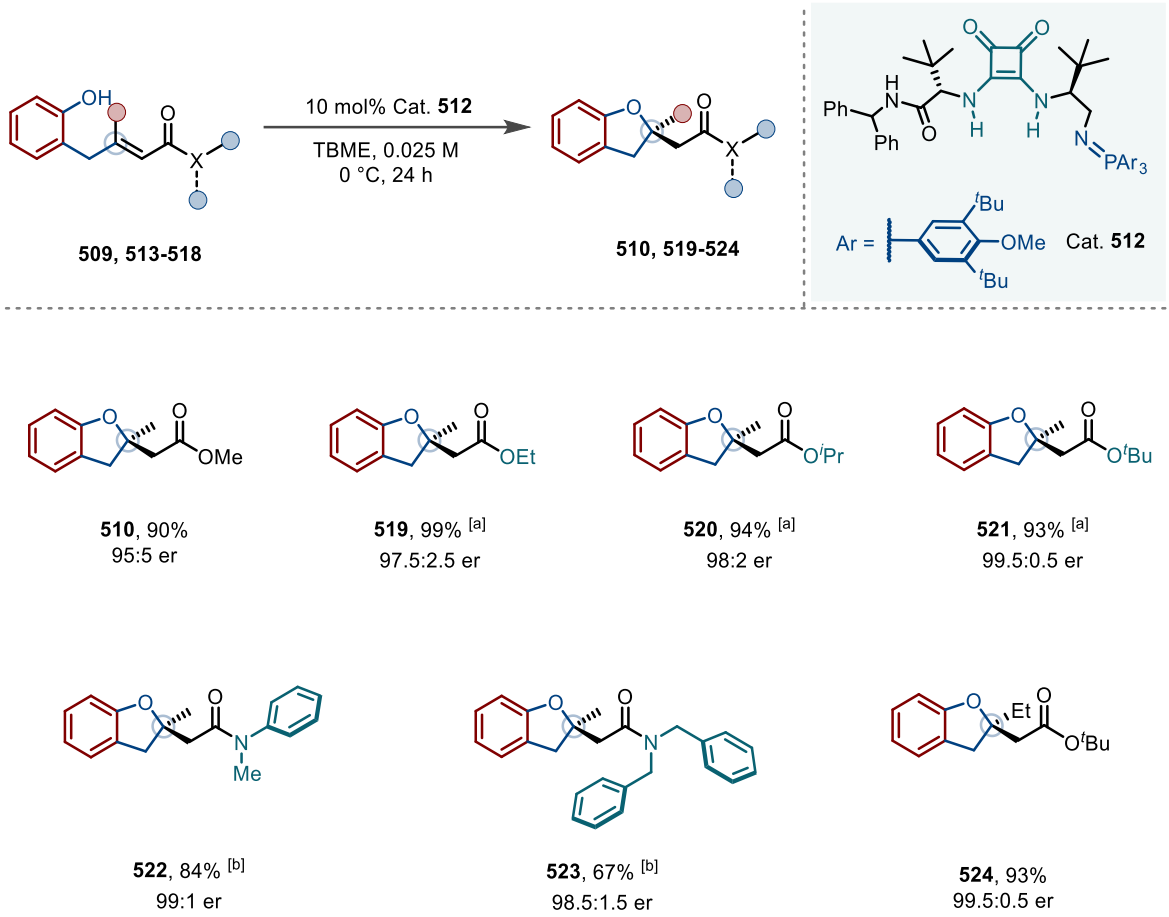


Scheme 71. Representative synthetic routes for substrates bearing phenol nucleophiles.

3.7.3 Evaluation of reaction scope

Under the optimised reaction conditions, products bearing more sterically hindered esters (**519**-**521**) were obtained in excellent yield and enantioselectivity in only 17 h (**Scheme 72**). Aligned to our expectations, the level of enantioselectivity was uplifted with increased ester steric bulkiness. Pleasingly, even much

less reactive substrates bearing amide Michael acceptors (**516** and **517**) or a β-ethyl substituent (**518**) underwent the desired 1,4-addition to furnish dihydro-benzofurans **522** to **524** in good yield and excellent enantioselectivity. A reaction temperature of 40 °C and 96 h were necessary to deliver satisfactory level of cyclisation for substrates carrying amide acceptors, however.

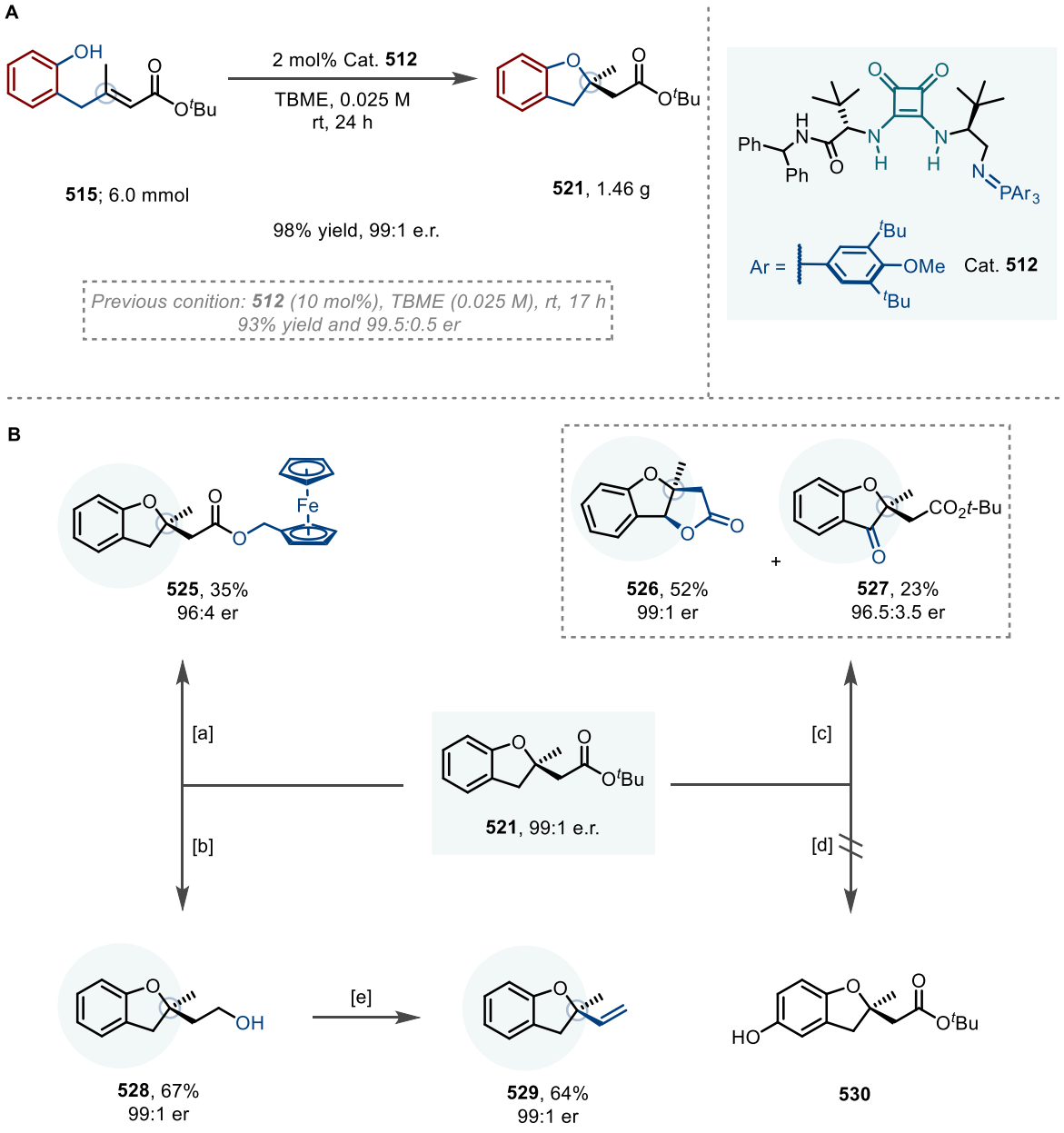


Scheme 72. Reaction scope with respects to the Michael acceptors. Reactions were carried out with 0.2 mmol substrates; variations from standard conditions: [a] 17 hours reaction time; [b] 40 °C for 96 hours.

3.7.4 Preparative scale synthesis and derivatisation

When the reaction was carried out on gram-scale, the catalyst loading could be reduced to as little as 2 mol% to deliver **521** in 98% yield and 99:1 er with the only varied reaction condition being an increase in reaction temperature to room temperature (**Scheme 73A**). We then endeavoured to explore potential further functionalisation of compound **521** (**Scheme 73B**). Firstly, transesterification with ferrocenemethanol was smoothly achieved *via* ester hydrolysis followed by conversion to the

corresponding acyl chloride. Next, reduction to primary alcohol **528** in 67% yield was realised using $LiAlH_4$ with no erosion of optical purity. Surprisingly, based promoted retro-Michael reaction did not outcompete the metal-hydride insertion into the carbonyl moiety as described in chapter **3.6**, indicating a more robust chirality installation. Alcohol **528** was then converted to the corresponding terminal olefin **529** *via* Grieco elimination to determine the absolute configuration of compounds **510** and **519**-**524** by optical rotation and comparison to literature data. Interestingly, oxidation of the benzylic position with potassium persulfate and $CuSO_4$ led to an easily separable mixture of lactone product **526** and desired ketone **527** in 52% and 23% yield respectively.[97] Finally, we also hoped that the ether moiety could serve as a directing group for *o*-hydroxylation via Ruthenium catalysis,[80] disappointingly, however, no desired product **530** was observed.



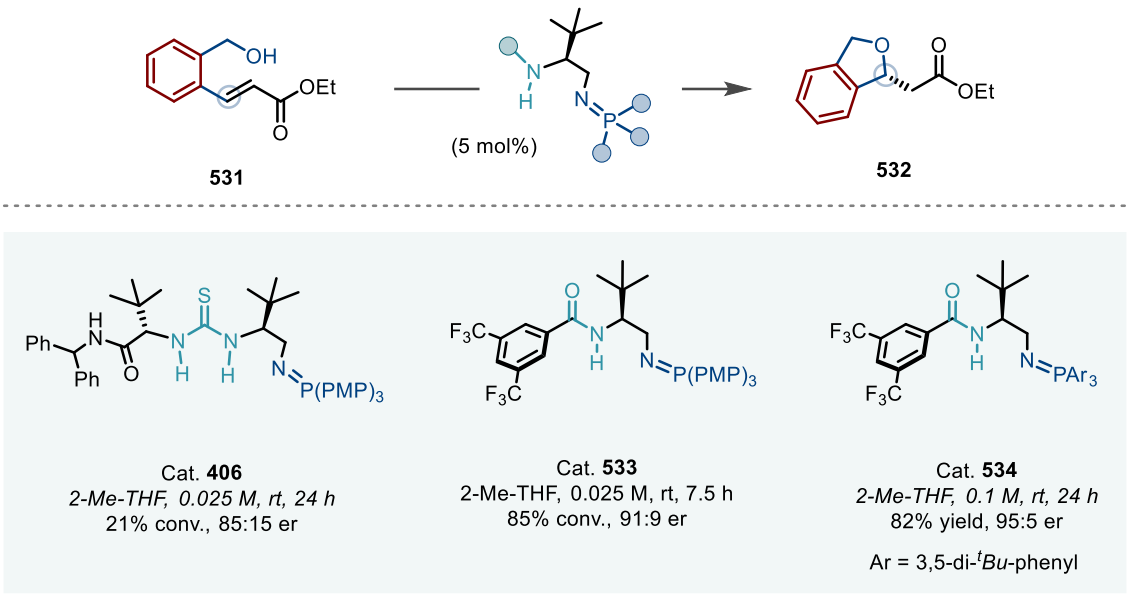
Scheme 73. **A**. Preparative scale synthesis of **521**; **B**. Derivatisation of enantioenriched **521**. [a] (i) TFA, DCM, 0 °C to rt, 2 hours. (ii) $SOCl_2$, DMF (cat.), DCM, 0 °C to rt, 2 hours. (iii) Ferrocenemethanol, Et_3N, DCM, 0 °C to rt, 2 hours; [b] $LiAlH_4$, THF, 0 °C to rt, 4 hours; [c] $K_2S_2O_8$, $CuSO_4$, MeCN, H_2O, 80 °C, 1 hours; [d] $[RuCl_2(p\text{-cymene})]_2$, $PhI(TFA)_2$, DCE, 80 °C, 4 hours; [e] (i) 1-nitro-2-selenocyanatobenzene, $P(n\text{-Bu})_3$, THF, 0 °C, 4 hours. (ii) 30% H_2O_2, THF, 0 °C, 5 hours.

3.8 Extension to Other Benzene-Fused Cyclic Ethers

3.8.1 Reaction optimisation

Thus far, we have successfully developed BIMP enabled IOMR of numerous aliphatic alcohols and extended the methodology to phenol bearing substrates. A good diverse range of enantioenriched THFs, THPs and dihydro-benzofurans with various structural diversities were smoothly furnished. We wished to further extend the BIMP catalysed IOMR to the preparation of other benzene-fused cyclic ethers such as dihydro-iso-benzofuran and iso-chroman. IOMR of substrates carrying tethered benzylic alcohols as nucleophiles to α,β-unsaturated esters were also regarded as a challenging transformation type. As described in **chapter 3.2.2.3**, it has only been investigated by Kim and co-workers while unsatisfactory reaction outcome was obtained — 96 hours and 50 °C were typically required to achieve a pleasing reaction outcome.[77] We therefore initiated our exploration with the preparation of dihydro-iso-benzofuran **532** from benzylic alcohol **531**.

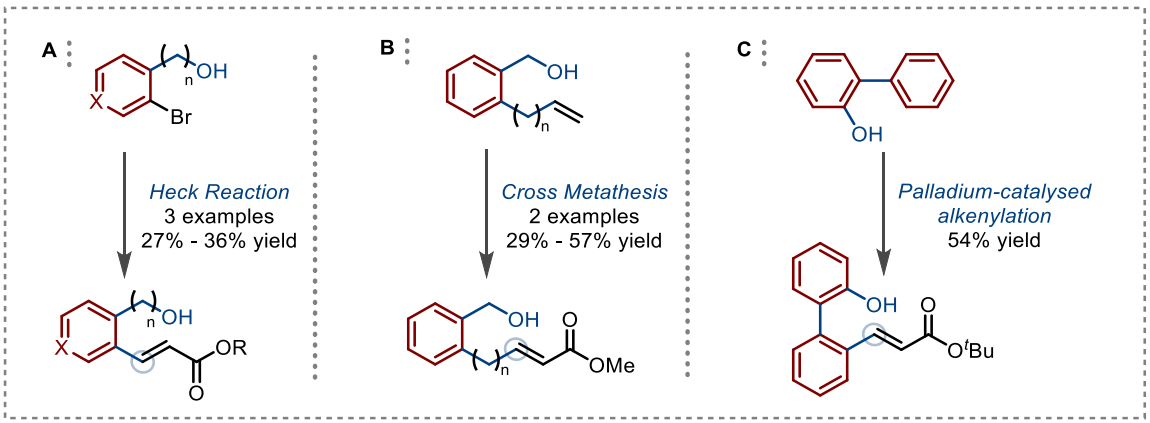
Unfortunately, the optimal catalyst **406** (for aliphatic alcohols substrates) incorporating a thiourea H-bond donor proved to be very inefficient with this substrate, affording the desired Michael product **532** in only 21% conversion and 85:15 er after 24 h. Thanks to the modular nature of the BIMP catalyst family however, we quickly identified a superior amide derived catalyst **533**, furnishing **532** in 85% conversion and 91:9 er after 7.5 h at rt (*vs* 96 hours at 50 °C using Kim's protocol). Replacement of the PMP phosphine with a sterically bulkier 3,5-di-*tert*-butyl-triphenyl phosphine further improved enantioselectivity to 95:5 er when paired with concentrated solvent system to 0.1 M (**Scheme 74**) (see **chapter 4.3.1** for full details of optimisation). Notably, 24 hours was necessary for 82% yield isolation.



Scheme 74. Selected BIMP catalysts screening and condition fine-tuning; reactions scale: 0.05 mmol **531**.

3.8.2 Substrate synthesis

Having re-optimised the IOMR conditions and identified amide catalyst **534** for model substrate benzylic alcohol **531**, we endeavoured to prepare a series of benzene-fused alcohol substrates. The general synthetic routes applied to this end are outlined in **Scheme 75** (see chapter **4.3.3** for full details of experimental conditions and reaction yields). Heck reactions of aryl bromides with acrylic acid derivatives smoothly delivered substrates bearing tethered phenyl-conjugated Michael acceptors (**Scheme 75A**) while benzylic alcohols bearing a tethered non-conjugated Michael acceptors were prepared *via* a Hoveyda–Grubbs catalyst promoted cross metathesis (**Scheme 75B**). We also prepared a biaryl-phenol substrate *via* a palladium-catalysed alkenylation using the phenol as directing group (**Scheme 75C**).[99]

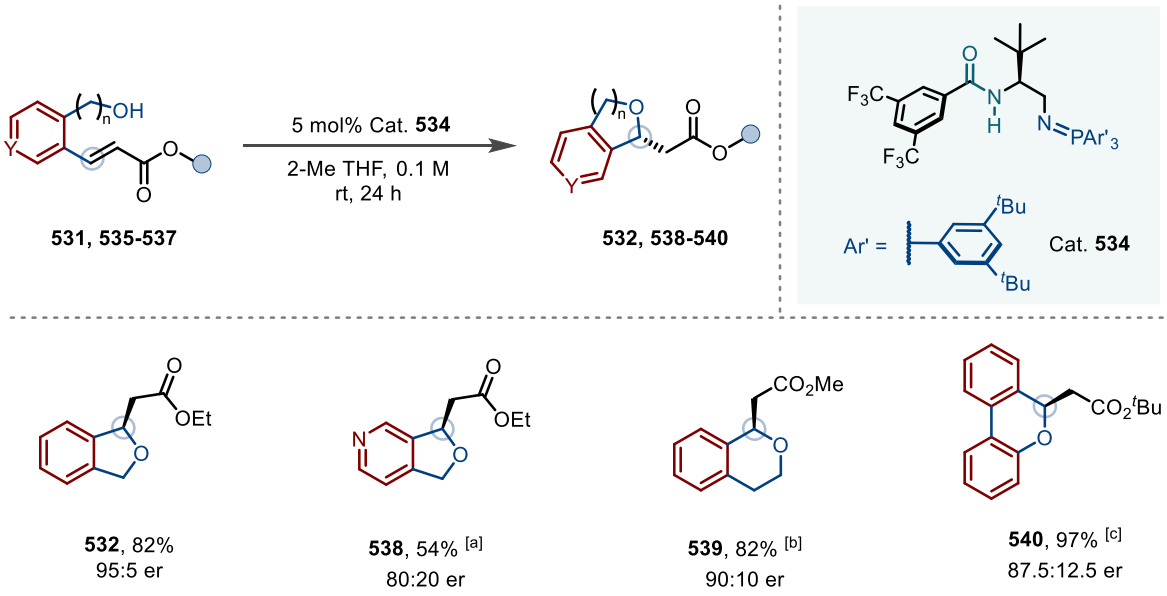


Scheme 75. Representative substrate synthetic routes

3.8.3 Evaluation of reaction scope

3.8.3.1 Reaction scope with regards to phenyl-conjugated Michael acceptors

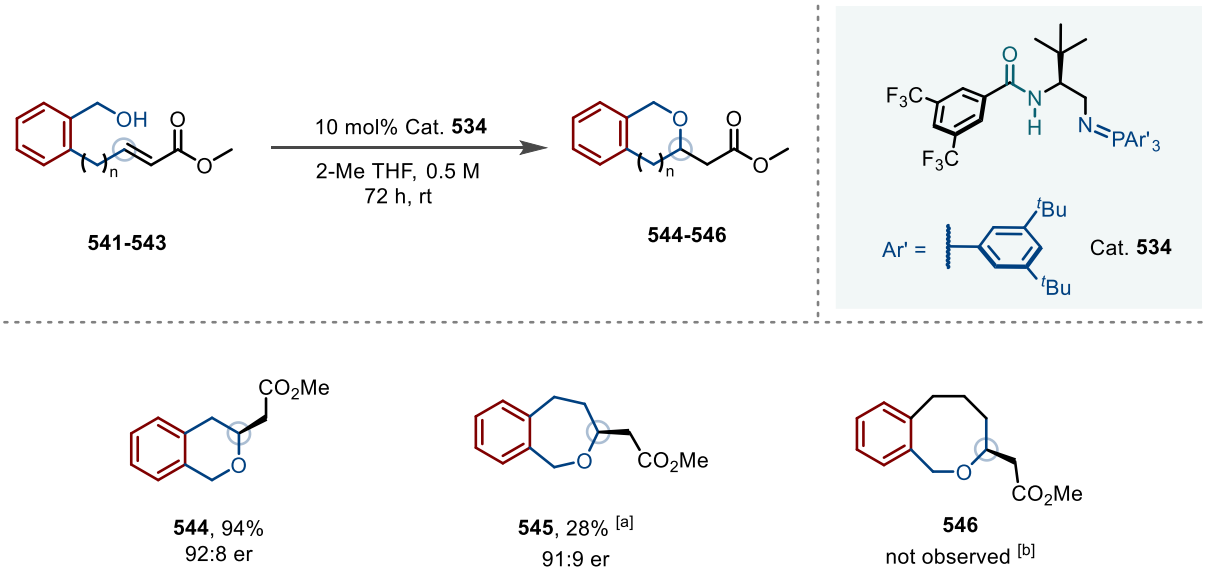
The scope for benzene-fused cyclic ethers started from substrates bearing phenyl-conjugated Michael acceptors. We soon recognised that reaction conditions were determined on a case by case basis for optimal performance of catalyst **534** within this substrate class (**Scheme 76**). For substrate **535** bearing a pyridine linker, potentially owing to an inappropriate substrate-catalyst H-bonding interaction, product **538** was obtained in only 54% yield and moderate 80:20 er even when more forcing reaction conditions were applied. 10 mol% cat. **534**, 50 °C and 72 hours reaction time were demanding for a good-yielding and enantioselective preparation of iso-chroman **539**. Benzo[*d*]chromenes represent a valuable structural class found in a vast number of naturally and biologically active compounds such as cannabinol — demonstrating anticonvulsant, antiemetic, analgesic, antibiotic, and psychotropic activities.[100-102] To the best of our knowledge, enantioselective preparation of these biaryl-THP rings has not been disclosed previously. While formation of biaryl product **540** was highly efficient with catalyst **534** (97% yield after 24 hours), the enantioselectivity could only be improved to 87.5:12.5 er even with a lower reaction temperature of –22 °C.



Scheme 76. Reaction scope with regards to phenyl conjugated Michael acceptors. Reactions were carried out with 0.2 mmol substrates; variations from standard conditions: [a] 50 °C for 72 hours; [b] 10 mol% cat. **534** in 2-Me-THF (0.5 M) at 50 °C for 72 hours; [c] 10 mol% cat. **534** in 2-Me-THF (0.025 M) at –22 °C.

3.8.3.1 Reaction scope with regards to ring sizes

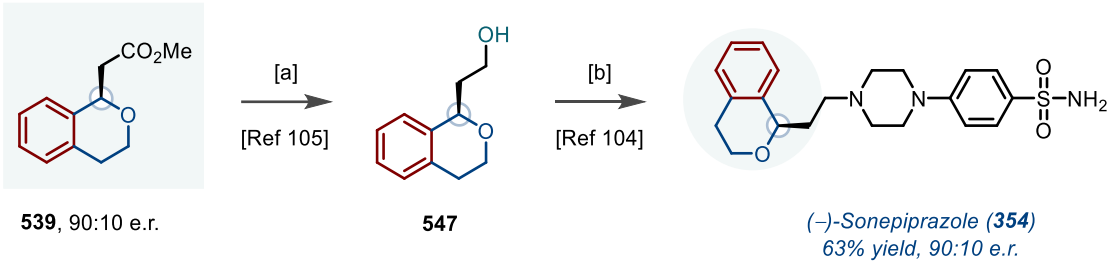
Attention then turned to benzylic alcohol substrates bearing non-conjugated Michael acceptors (**Scheme 77**). While isochroman **544** was obtained in excellent yield (94%) and good enantioselectivity (92:8 er) after 3 days, an uncommon benzo[*c*]oxepane product **545** could also be afforded in 91:9 enantiomeric ratio. It is worth noting that this is the first example of a highly enantiocontrolled direct synthesis of benzene-fused 7-membered ring albeit with only modest 28% yield at 60 °C for 3 days. We also made an attempt at the construction of 8-membered benzene fused cyclic ether **546**. However, disappointingly, no reaction occurred presumably due to the unconquered ring strain.



Scheme 77. Reaction scope with regards to ethers' ring sizes. Reactions were carried out with 0.2 mmol substrates; [a] 60 °C; [b] 50 °C.

3.8.4 Derivatisation of enantioenriched 539

Demonstrating diverse therapeutically related applications, isochromans are one of the most well recognised oxygen-containing heterocycles in pharmaceuticals.[103] One representative example is Sonepiprazole which displays highly specific binding to the D4 dopamine receptor and are of great importance in drug discovery research for schizophrenia and psychotic-typed diseases in general.[29, 104] By using $LiAlH_4$, enantioenriched isochroman **539** obtained from our BIMP catalysed IOMR could be converted to primary alcohol **547** (with no erosion of enantiopurity) which previously has served as a key precursor for (–)-Sonepiprazole **354**, reported by Nakai [105] and Smith (**Scheme 78**).[104]

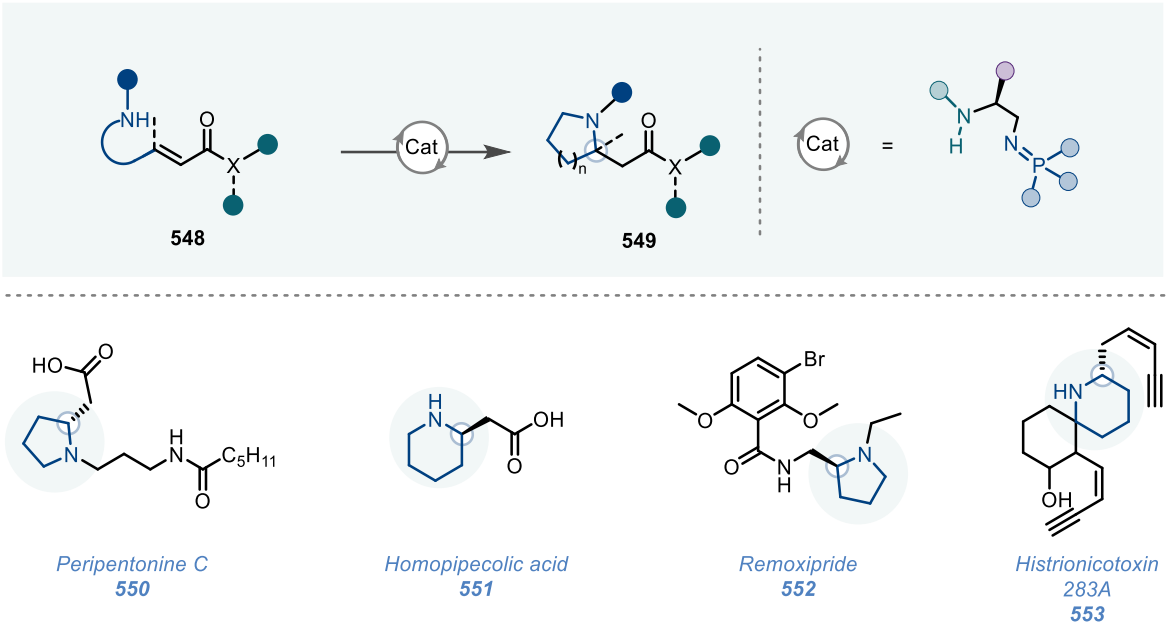


Scheme 78. Derivatisation of enantioenriched 539. [a] $LiAlH_4$, THF, 0 °C to rt, 4 h; [b] (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h. (ii) 4-(piperazin-1-yl)benzenesulfonamide, ethylene glycol, DIPEA, CH_2Cl_2, rt to 80 °C, 3.5 h.

Stereochemical configurations of all IOMR products described in this chapter were assigned by comparing their optical rotations with literature known compounds (see **Chapter 4.3.6** for full details).

3.9 Conclusion and Future Work

In summary, this chapter describes a highly efficient and enantioselective thiourea BIMP-catalysed intramolecular oxy-Michael reaction furnishing decorated THFs/THPs with excellent yields (up to 99%) and enantiomeric ratios (up to 99:1 er). An intramolecular Michael transformation involving challenging pronucleophiles (primary, secondary and tertiary alcohols) and unactivated electrophiles (tethered α,β-unsaturated esters and amides) was developed and demonstrated improved efficiency (1 day *vs* 7 days) and a far broader scope than any previously described method. Importantly, we have enabled an enantioselective synthesis of oxy-spirocycles including oxetane and azetidine bearing ones which have not yet been realised previously. The catalytic ring closing approach was scaled up to 41.2 mmol and the final Michael product was further derivatised to an array of useful building blocks, providing access to biologically active 'drug-like' molecules and natural product. The IOMR cannot be extended to alkyl ester bearing substrates or preparation of 3, 4 and 7-membered oxygenated heterocycles disappointingly. However, we have achieved rapid activations of phenols and benzylic alcohols using a squaramide BIMP and amide BIMP respectively. Addition of these oxy-pronucleophiles to unactivated tethered β-disubstituted α,β-unsaturated esters or amides resulted in a series of chiral benzene-fused cyclic ethers including dihydro-(iso)-benzofurans, iso-chromans, benzo[*d*]chromene and benzo[*d*]oxepane in moderate to excellent yield and consistently high enantioselectivity.



Scheme 79. Top: BIMP catalysed intramolecular aza-Michael reactions to prepare enantioenriched nitrogen heterocycles; Bottom: representative pharmaceutically active 5 or 6 membered nitrogen heterocycles.

Apart from cyclic ethers, nitrogen-bearing heterocycles are also one of the most important structural components found in pharmaceuticals and natural products (**Scheme 79**).[106-108] A report from Njardarson Group in 2014 demonstrated that piperidine ranks the 1st of the top 25 most frequent nitrogen heterocycles in U.S. FDA approved drugs while pyrrolidine ranks the 5th.[109] Enantioselective intramolecular aza-Michael reactions enabled by metal-free catalysts are among the most powerful and appealing approaches to prepare such skeletons,[110] while ones involving unbiased/unactivated Michael acceptors such as α,β-unsaturated esters and amides remains largely unsolved due to their low electrophilicity,[72] as described in **Chapter 2**. Against this backdrop, future work will focus on the investigation of the analogous BIMP catalysed intramolecular aza-Michael reactions of amines **548**, towards the rapid and divergent synthesis of enantioenriched nitrogen-containing heterocycles **549** (**Scheme 79**).

3.10 References for Chapter 3

[1]. E. J. Kang, E. Lee, Total Synthesis of Oxacyclic Macrodiolide Natural Products, *Chem. Rev.* **2005**, *105*, 4348-4378.

[2]. Q. Lu, D. S. Harmalkar, Y. Choi, K. Lee, An Overview of Saturated Cyclic Ethers: Biological Profiles and Synthetic Strategies, *Molecules.* **2019**, *24*, 3778-3800.

[3]. M. C. Elliott, E. Williams, Saturated Oxygen Heterocycles, *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 2303-2340.

[4]. A. K Ghosh, D. D. Anderson, Tetrahydrofuran, Tetrahydropyran, Triazoles and Related Heterocyclic Derivatives as HIV Protease Inhibitors, *Future Med. Chem.* **2011**, *9*, 1181-1197.

[5]. J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munroa, M. R. Prinsep, Marine Natural Products, *Nat. Prod. Rep.* **2016**, *33*, 382-431.

[6]. A. de la Torre, C. Cuyamendous, V. Bultel-Ponce, T. Durand, J. M. Galano, C. Oger, Recent Advances in the Synthesis of Tetrahydrofurans and Applications in Total Synthesis, *Tetrahedron.* **2016**, *72*, 5003-5025.

[7]. A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez, Tetrahydrofuran-Containing Macrolides: A Fascinating Gift from the Deep Sea, *Chem. Rev.* **2013**, *113*, 4567-4610.

[8]. R. A. Fernandes, R. S. Pathare, D. A. Gorve, Advances in Total Synthesis of Some 2,3,5-Trisubstituted Tetrahydrofuran Natural Products, *Chem. Asian. J.* **2020**, *15*, 2815-283.

[9]. M. Hattori, S. Hada, Y. Kawata, Y. Tezuka, T. Kikuchi, T. Namba, New 2,5-Bis-aryl-3,4-dimethyltetrahydrofuran Lignans from the Aril of Myristica Fragrans, *Chem. Pharm. Bull.* **1987**, *35*, 3315-3322.

[10]. J. S. Song, Y. S. Park, M. W. Park, J. D. Lee, D. S. Kim, Selectivity of Tefuryltrione between Rice and Eleocharis Kuroguwai, *Weed Turf. Sci.* **2016**, *5*, 191-195.

[11]. N. M. Nasir, K. Ermanis, P. A. Clarke, Strategies for the Construction of Tetrahydropyran Rings in the Synthesis of Natural Products, *Org. Biomol. Chem.* **2014**, *12*, 3323-3335.

[12]. F. Vetica, P. Chauhan, S. Dochain, D. Enders, Asymmetric Organocatalytic Methods for the Synthesis of Tetrahydropyrans and Their Application in Total Synthesis, *Chem. Soc. Rev.* **2017**, *46*, 1661-1674.

[13]. M. A. Perry, S. D. Rychnovsky, N. Sizemore, Synthesis of Saturated Tetrahydropyrans, *Top. Heterocycl. Chem.* **2014**, *35*, 43-95.

[14]. R. Karmakar, P. Pahari, D. Mal, Phthalides and Phthalans: Synthetic Methodologies and Their Applications in the Total Synthesis. *Chem. Rev.* **2014**, *114*, 6213-6284.

[15]. G. Albano, L. A. Aronica, Cyclization Reactions for the Synthesis of Phthalans and Isoindolines, *Synthesis.* **2018**, *50*, 1209-1227.

[16]. E. Ilya, L. Kulikova, E. V. Van der Eycken, L. Voskressensky, Recent Advances in Phthalan and Coumaran Chemistry, *ChemistryOpen.* **2018**, *7*, 914-929.

[17]. T. D. Sheppard, Strategies for the Synthesis of 2,3-Dihydrobenzofurans, *J. Chem. Res.* **2011**, *7*, 377-385.

[18]. F. Bertolini, M.Pineschi, Recent Progress in the Synthesis of 2,3-Dihydrobenzofurans, *New J. Chem.* **2009**, *41*, 385-418.

[19]. B. Gözler, T. Gözler, M. Shamma, Egenine: a Possible Intermediate in Phthalide Isoquinoline Biogenesis, *Tetrahedron.* **1983**, *39*, 577-580.

[20]. G. Schulz, C. Victoria, A. Kirschning, E. Steinmann, Rocaglamide and Silvestrol: a Long Story from Antitumor to Anti-coronavirus Compounds, Nat. Prod. Rep. **2021**, *38*, 18-23.

[21]. A. Goel, A. Kumar, A. Raghuvanshi, Synthesis, Stereochemistry, Structural Classification, and Chemical Reactivity of Natural Pterocarpans, *Chem. Rev.* **2013**, *113*, 1614-1640.

[22]. P. Acosta-Guzmán, A. Rodríguez-López, D. Gamba-Sánchez, Pummerer Synthesis of Chromanes Reveals a Competition between Cyclization and Reductive Chlorination, *Org. Lett.* **2019**, 21, 6903-6908.

[23]. X. H. Li, X. H. Han, L. L. Qin, J. L. He, Z. X. Cao, Y. C. Gu, D. L. Guo, Y. Deng, Isochromanes from Aspergillus Fumigatus, an Endophytic Fungus from Cordyceps Sinensis, Nat. Prod. Res. **2019**, *33*, 1870-1875.

[24]. R. E. TenBrink, C. L. Bergh, J. N. Duncan, D. W. Harris, R. M. Huff, R. A. Lahti, C. F. Lawson, B. S. Lutzke, I. J. Martin, S. A. Rees, S. K. Schlachter, J. C. Sih, M. W. Smith, (*S*)-(-)-4-[4-[2-(Isochroman-1-yl)ethyl]-piperazin-1-yl]benzenesulfonamide, a Selective Dopamine D4 Antagonist, *J. Med. Chem.* **1996**, *39*, 2435-2437.

[25]. B. Gözler, T. Gözler, M. Shamma, Egenine: a Possible Intermediate in Phthalide Isoquinoline Biogenesis, *Tetrahedron.* **1983**, *39*, 577-580.

[26]. M. Hattori, S. Hada, Y. Kawata, Y. Tezuka, T. Kikuchi, T. Namba, New 2,5-Bis-aryl-3,4-dimethyltetrahydrofuran Lignans from the Aril of Myristica Fragrans, *Chem. Pharm. Bull.* **1987**, *35*, 3315-3322.

[27]. G. Schulz, C. Victoria, A. Kirschning, E. Steinmann, Rocaglamide and Silvestrol: a Long Story from Antitumor to Anti-coronavirus Compounds, *Nat. Prod. Rep.* **2021**, *38*, 18-23.

[28]. J. S. Song, Y. S. Park, M. W. Park, J. D. Lee, D.-S. Kim, Selectivity of Tefuryltrione between Rice and Eleocharis Kuroguwai, *Weed Turf. Sci.* **2016**, *5*, 191-195.

[29]. R. E. TenBrink, C. L. Bergh, J. N. Duncan, D. W. Harris, R. M. Huff, R. A. Lahti, C. F. Lawson, B. S. Lutzke, I. J. Martin, S. A. Rees, S. K. Schlachter, J. C. Sih, M. W. Smith, (*S*)-(-)-4-[4-[2-(Isochroman-1-yl)ethyl]-piperazin-1-yl]benzenesulfonamide, a Selective Dopamine D4 Antagonist, *J. Med. Chem.* **1996**, *39*, 2435-2437.

[30]. J. M. Pasteels, M. Rowell-Rahier, J. C. Braekman, A. Dupont, Salicin from Host Plant as Precursor of Salicylaldehyde in Defensive Secretion of Chrysomeline Larvae, *Physiol. Entomol.* **1983**, *8*, (*3*), 307-314.

[31]. J. L. Kennemur, R. Maji, M. J. Scharf, B. List, Catalytic Asymmetric Hydroalkoxylation of C−C Multiple Bonds, *Chem. Rev.* **2021**, *121*, 24, 14649-14681.

[32]. G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, A Powerful Chiral Counterion Strategy for Asymmetric Transition Metal Catalysis. *Science.* **2007**, *317*, 496-499.

[33]. Y. K. Chung, G. C. Fu, Phosphine-Catalysed Enantioselective Synthesis of Oxygen Heterocycles. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225-2227.

[34]. N. Tsuji, J. L. Kennemur, T. Buyck, S. Lee, S. Prévost, P. S. J. Kaib, D. Bykov, C. Fares, B. List, Activation of Olefins Via Asymmetric Brønsted Acid Catalysis. *Science*. **2018**, *359*, 1501-1505.

[35]. N. Hu, K. Li, Z. Wang, W. Tang, Synthesis of Chiral 1,4-Benzodioxanes and Chromans by Enantioselective Palladium-Catalysed Alkene Aryloxyarylation Reactions, *Angew. Chem.* **2016**, *128*, 5128-5132.

[36]. C. Han, X. Feng, H. Du, Asymmetric Halocyclizations of 2-Vinylbenzyl Alcohols with Chiral FLPs, *Org. Lett.* **2021**, *23*, 7325-7329.

[37]. W. B. Xie, Z. Li, Bis(μ-oxo)−Dititanium(IV)−Chiral Binaphthyldisulfonate Complexes for Highly Enantioselective Intramolecular Hydroalkoxylation of Nonactivated Alkenes, *ACS Catal.* **2021**, *11*, 6270-6275.

[38]. C. W. Lei, B. S. Mu, F. Zhou, J. S. Yu, Y. Zhou, J. Zhou, Organocatalytic Enantioselective Reactions Involving Prochiral Carbocationic Intermediates. ***Chem. Commun.*** **2021**, ***57***, 9178-9191.

[39]. S. Lee, P. S. J. Kaib, B. List, Asymmetric Catalysis via Cyclic, Aliphatic Oxocarbenium Ions, *J. Am. Chem. Soc.* **2017**, *139*, 2156-2159.

[40]. G. Wang, X. Xin, Z. Wang, G. Lu, Y. Ma, L. Liu, Catalytic Enantioselective Oxidative Coupling of Saturated Ethers with Carboxylic Acid Derivatives. *Nat. Commun.* **2019**, *10*, 559, 1-9.

[41]. Y. Liu, J. A. Izzo, D. McLeod, S. Ricˇko, E. B. Svenningsen, T. B. Poulsen, K. A. Jørgensen, Organocatalytic Asymmetric Multicomponent Cascade Reaction for the Synthesis of Contiguously Substituted Tetrahydronaphthols. *J. Am. Chem. Soc.* **2021**, *143*, 8208-8220.

[42]. I. Cˇoric´, B. List, Asymmetric Spiroacetalization Catalysed by Confined Brønsted Acids. *Nature*, **2012**, *483*, 315-319.

[43]. Z. Sun, G. A. Winschel, A. Borovika, P. Nagorny, Chiral Phosphoric Acid-Catalysed Enantioselective and Diastereoselective Spiroketalisations. *J. Am. Chem. Soc.* **2012**, *13*4, 8074-8077.

[44]. C. F. Nising, S. Brase, The Oxa-Michael Reaction: from Recent Developments to Applications in Natural Product Synthesis, *Chem. Soc. Rev.* **2008**, *37*, 1218-1228.

[45]. C. F. Nising, S. Brase, Recent Developments in the Field of Oxa-Michael Reactions, *Chem. Soc. Rev.* **2012**, *41*, 988-999.

[46]. K. Asano, Multipoint Recognition of Molecular Conformations with Organocatalysts for Asymmetric Synthetic Reactions, *Bull. Chem. Soc. Jpn.* **2021**, *94*, 694-712.

[47]. T. Ahmad, N. Ullah, The Oxa-Michael Reaction in the Synthesis of 5- and 6-membered Oxygen-containing Heterocycles, *Org. Chem. Front.* **2021**, *8*,1329-1344.

[48]. L. N. Chavan, P. S. Mainkar, S. Chandrasekhar, Organocatalytic Asymmetric Synthesis of Tetrahydrofuran and 1,2-Dihydrobenzofuran Scaffolds, *Eur. J. Org. Chem.* **2019**, *41*, 6890-6910.

[49]. Y. Wang, D.-M. Du, Recent Advances in Organocatalytic Asymmetric Oxa-Michael Addition Triggered Cascade Reactions, *Org. Chem. Front.* **2020**, *7*, 3266-3283.

[50]. K. Liu, A. Chougnet, W.-D. Woggon, A Short Route to α-Tocopherol, *Angew. Chem.* **2008**, *120*, 5911-5913; *Angew. Chem. Int. Ed.* **2008**, *47*, 5827-5829.

[51]. T. Okamura, K. Asano, S. Matsubara, Asymmetric Cycloetherifications by Bifunctional Aminothiourea Catalysts: The Importance of Hydrogen Bonding. *Synthesis.* **2013**, *45*, 1627-1634.

[52]. N. Yoneda, Y. Fukata, K. Asano, S. Matsubara, Asymmetric Synthesis of Spiroketals with Aminothiourea Catalysts, *Angew. Chem.* **2015**, *127*, 15717-15720; *Angew. Chem. Int. Ed.* **2015**, *54*, 15497-15500.

[53]. K. Asano, S. Matsubara, Asymmetric Catalytic Cycloetherification Mediated by Bifunctional Organocatalysts, *J. Am. Chem. Soc.* **2011**, *133*, 16711-16713.

[54]. A. Matsumoto, K. Asano, S. Matsubara, Kinetic Resolution of Acylsilane Cyanohydrins via Organocatalytic Cycloetherification, *Chem. Asian J.* **2019**, *14*,116-120.

[55]. R. Murata, A. Matsumoto, K. Asano, S. Matsubara, Desymmetrisation of Gem-diols via Water-assisted Organocatalytic Enantio- and Diastereoselective Cycloetherification, *Chem. Commun.* **2020**, *56*, 12335-12338.

[56]. A. Matsumoto, K. Asano, S. Matsubara, A Chiral Phosphoric Acid Catalyst for Asymmetric Construction of 1,3-dioxanes, *Chem. Commun.* **2015**, *51*, 11693-11696.

[57]. N. Yoneda, Y. Fujii, A. Matsumoto, K. Asano, S. Matsubara, Organocatalytic Enantio- and Diastereoselective Cycloetherification via Dynamic Kinetic Resolution of Chiral Cyanohydrins, *Nat. Commun.* **2017**, *8*, 1397 (1-7).

[58]. A. P. Jadhav, J.-A. Oh, I.-S. Hwang, H. Yan, C. E. Song, Organocatalytic Enantioselective Cycloetherifications Using a Cooperative Cation-Binding Catalyst, *Org. Lett.* **2018**, *20*, 5319-5322.

[59]. B. Ravindra, S. Maity, B. G. Das, P. Ghorai, Organocatalytic, Enantioselective Synthesis of 1- and 3-Substituted Isochromans via Intramolecular Oxa-Michael Reaction of Alkoxyboronate: Synthesis of (+)-Sonepiprazole, *J. Org. Chem.* **2015**, *80*, 7008-7018.

[60]. N. Yoneda, A. Matsumoto, K. Asano, S. Matsubara, Asymmetric Cycloetherification via the Kinetic Resolution of Alcohols Using Chiral Phosphoric Acid Catalysts, *Chem. Lett.* **2016**, *45*, 1300-1303.

[61]. A. Matsumoto, K.Asano, S. Matsubara, Organocatalytic Enantio- and Diastereoselective Construction of syn-1,3-Diol Motifs via Dynamic Kinetic Resolution of In Situ Generated Chiral Cyanohydrins, *Org. Lett.* **2019**, *21*, 2688-2692.

[62]. R. R. Reddy, S. S. Gudup, P. Ghorai, Organocatalytic, Enantioselective Synthesis of Cyclohexadienone Containing Hindered Spirocyclic Ethers through an Oxidative Dearomatisation/Oxa-Michael Addition Sequence*, Angew. Chem.* **2016**, *128*, 15339-15343; *Angew. Chem. Int. Ed.* **2016**, *55*, 15115-15119.

[63]. Y. Lu, G. Zou, G. Zhao, Asymmetric Intramolecular Oxa-Michael Reactions to Tetrahydrofurans/2H-Pyrans Catalyzed by Primary−Secondary Diamines, *ACS Catal.* **2013**, *3*, 1356-1359.

[64]. R. R. Reddy, S. Panda, P. Ghorai, Enantioselective Synthesis of Cyclohexadienone Containing Spiroketals via DyKat Ketalisation/oxa-Michael Addition Cascade, *J. Org. Chem.* **2019**, *84*, 5357-5368.

[65]. T. Okamura, K. Asano, S. Matsubara, Organocatalytic Asymmetric Oxy-Michael Addition to a γ-hydroxy-α,β-unsaturated Thioester via Hemiacetal Intermediates, *Chem. Commun.* **2012**, *48*, 5076-5078.

[66]. Y. Fukata, R. Miyaji, T. Okamura, K. Asano, S. Matsubara, Asymmetric Cycloetherifications by Bifunctional Aminothiourea Catalysts: The Importance of Hydrogen Bonding Synthesis, **2013**, *45*, 1627-1634.

[67]. H. Fuwa, N. Ichinokawa, K. Noto, M. Sasaki, Stereoselective Synthesis of 2,6-Cis-Substituted Tetrahydropyrans: Brønsted Acid-Catalyzed Intramolecular Oxa-Conjugate Cyclization of α,β-Unsaturated Ester Surrogates, *J. Org. Chem.* **2012**, *77*, 2588-2607 and references cited therein.

[68]. T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma, Y. Takemoto, A Dual Arylboronic Acid−Aminothiourea Catalytic System for the Asymmetric Intramolecular Hetero-Michael Reaction of α,β-Unsaturated Carboxylic Acids, *Org. Lett.* **2014**, *16*, 4256-4259.

[69]. N. Hayama, R. Kuramoto, T. Földes, K. Nishibayashi, Y. Kobayashi, I. Pápai, Y. Takemoto, Mechanistic Insight into Asymmetric Hetero-Michael Addition of α,β-Unsaturated Carboxylic Acids Catalyzed by Multifunctional Thioureas, *J. Am. Chem. Soc.* **2018**, *140*, 12216-12225.

[70]. J. A. Pesti, J. Yin, L.-H. Zhang, L. Anzalone, R. E. Waltermire, P. Ma, E. Gorko, P. N. Confalone, J. Fortunak, C. Silverman, O. J. Black- well, J. C. Chung, M. D. Hrytsak, M. Cooke, L. Powell, C. Ray, Efficient Preparation of a Key Intermediate in the Synthesis of Roxifiban by Enzymatic Dynamic Kinetic Resolution on Large Scale. *Org. Process Res. Dev.* **2004**, *8*, 22-27.

[71]. Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters. *Angew. Chem. Int. Ed.* **2013**, *52*, 11114-11118.

[72]. Allgauer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. Quantification and Theoretical Analysis of the Electrophilicities of Michael Acceptors. *J. Am. Chem. Soc.* **2017**, *139*, 13318−13329.

[73]. D. X. Zhu, J. G. Liu, M. H. Xu, Stereodivergent Synthesis of Enantioenriched 2,3-Disubstituted Dihydrobenzofurans via a One-Pot C−H Functionalization/Oxa-Michael Addition Cascade, *J. Am. Chem. Soc.* **2021**, *143*, 23, 8583-8589.

[74]. Y. Kurimoto, T. Nasu, Y. Fujii, K. Asano, S. Matsubara, Asymmetric Cycloetherification of in Situ Generated Cyanohydrins through the Concomitant Construction of Three Chiral Carbon Centers, *Org. Lett.* **2019**, *21*, 2156-2160;

[75]. N. Saito, A. Ryoda, W. Nakanishi, T. Kumamoto, T. Ishikawa, Guanidine-Catalyzed Asymmetric Synthesis of 2,2-Disubstituted Chromane Skeletons by Intramolecular Oxa-Michael Addition, *Eur. J. Org. Chem.* **2008**, *16*, 2759-2766;

[76]. Y. Kobayashi, R. Kuramoto, Y. Takemoto, Catalytic Asymmetric Formal Synthesis of Beraprost, *Beilstein J. Org. Chem.* **2015**, *11*, 2654-2660;

[77]. E. C. Son, S. Y. Kim, S. G. Kim, Squaramide-Catalyzed Asymmetric Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Carbonyls Containing Benzyl Alcohol: Construction of Chiral 1-Substituted Phthalans, *J. Org. Chem.* **2021**, *86*, 6826-6839;

[78]. P. Compain, Olefin Metathesis of Amine-Containing Systems: Beyond the Current Consensus. *Adv. Synth. Catal.* **2007**, *349*, 1829-1846.

[79]. Y. Yamamoto, S. Yamada, H. Nishiyama, Copper-Catalysed Regio- and Stereoselective Conjugate Allylation of Electron-Deficient Alkynes with Allyl boronates under Mild Conditions. *Chem. Eur. J.* **2012**, *18*, 3153-3156.

[80]. H. B. Allen, D. A. Lee, A General Practice Assessment of Mefruside ('Baycaron') in the Treatment of Oedema and Hypertension. *Curr. Med. Res. Opin.* **1973**, *1*, 547-553.

[81]. F. Lovering, J. Bikker, C. Humblet, Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752-6756.

[82]. F. Lovering, Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Comm.* **2013**, *4*, 515-519.

[83]. K. Fominova, T. Diachuk, D. Granat, T. Savchuk, V. Vilchynskyi, O. Svitlychnyi, V. Meliantsev, I. Kovalchuk, E. Litskan, V. V. Levterov, V. R. Badlo, R. I. Vaskevych, A. I. Vaskevych, A. V. Bolbut, V. V. Semeno, R. Iminov, K. Shvydenko, A. S. Kuznetsova, Y. V. Dmytriv, D. Vysochyn, V. Ripenko, A. A. Tolmachev, O. Pavlova, H. Kuznietsova, I. Pishel, P. Borysko, P. K. Mykhailiuk, Oxa-Spirocycles: Synthesis, Properties and Applications. *Chem. Sci.* **2021**, *12*, 11294-11305.

[84]. G. Zhu, Y. Li, G. Bao, W. Sun, L. Huang, L. Hong, R. Wang, Catalytic Kinetic Resolution of Spiro-Epoxyoxindoles with 1-Naphthols: Switchable Asymmetric Tandem Dearomatization/Oxa-Michael Reaction and Friedel−Crafts Alkylation of 1-Naphthols at the C4 Position. *ACS Catal.* **2018**, *8*, 1810-1816.

[85]. W. Yang, X. Wang, X. Jin, H. Sun, R. Guo, W. Xu, Q. Cai, Copper-Catalysed Double O-Arylation for Enantioselective Synthesis of oxa-Spirocycles. *Adv. Synth. Catal.* **2019**, *361*, 562-568.

[86]. Y. Kim, S. T. Kim, D. Kang, T. Sohn, E. Jang, M. H. Baik, S. Hong, Stereoselective Construction of Sterically Hindered Oxaspirocycles via Chiral Bidentate Directing Groupmediated C(Sp3)–O Bond Formation. *Chem. Sci.* **2018**, *9*, 1473-1480.

[87]. J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 12150-12233.

[88]. G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. M€uller, Oxetanes in Drug Discovery: Structural and Synthetic Insights. *J. Med. Chem.* **2010**, *53*, 3227-3246.

[89]. E. M. Carreira, T. C. Fessard, Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257-8322.

[90]. G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Marki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Muller, E. M. Carreira, Spirocyclic Oxetanes: Synthesis and Properties. *Angew. Chem. Int. Ed.* **2008**, *47*, 4512-4515.

[91]. D. Matheau-Raven, P. Gabriel, J. A. Leitch, Y. A. Almehmadi, K. Yamazaki, D. J. Dixon, Catalytic Reductive Functionalization of Tertiary Amides using Vaska's Complex: Synthesis of Complex Tertiary Amine Building Blocks and Natural Products. *ACS Catal.* **2020**, *10*, *15*, 8880-8897.

[92]. C. A. James, P. DeRoy, M. Duplessis, P. J. Edwards, T. Halmos, J. Minville, L. Morency, S. Morin, B. Simoneau, M. Tremblay, R. Bethell, M. Cordingley, J. Duan, L. Lamorte, A. Pelletier, D. Rajotte, P. Salois, S. Tremblay, C. F. Sturino, Nucleotide Competing Reverse Transcriptase Inhibitors: Discovery of a Series of Non-Basic Benzofurano[3,2-D]Pyrimidin-2-One Derived Inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2781-2786.

[93]. Y. R. S. Laxmi, D. S. Iyengar, Chemoenzymatic Synthesis of Methyl (6S)-(–)-6,8-Dihydroxyoctanoate: A Precursor to (R)-(+)-α-Lipoic Acid. *Synthesis.* **1995**, *5*, 594-596.

[94]. B. Adger, M. T. Bes, G. Grogan, R. McCague, S. Pedragosa-Moreau, S. M. Roberts, R. Villa, P. W. H. Wan, A. J. Willetts, Application of Enzymic Baeyer-Villiger Oxidations of 2-Substituted Cycloalkanones to the Total Synthesis of (*R*)-(+)-Lipoic Acid. *J. Chem. Soc., Chem. Commun.* **1995**, 1563-1564.

[95]. J. Teichert, R. Hermann, P. Ruus, R. Preiss, Plasma Kinetics, Metabolism, and Urinary Excretion of Alpha-Lipoic Acid Following Oral Administration in Healthy Volunteers. *J. Clin. Pharmacol.* **2003**, *43* (11), 1257-1267.

[96]. A. Lattanzi, A. Senatore, A. Massa, A. Scettri, Novel Highly Regioselective $VO(acac)_2$/TBHP Mediated Oxidation of o-Alkenyl Phenols to o-Hydroxybenzyl Ketones. *J. Org. Chem.* **2003**, *68*, 9, 3691-3694.

[97]. S. Banerjee, S. Sathyamoorthi, J. D. Bois, R. N. Zare, Mechanistic Analysis Of A Copper-Catalyzed C–H Oxidative Cyclization Of Carboxylic Acids. *Chem. Sci.,* **2017**, *8*, 7003-7008.

[98]. W. Liu, L. Ackermann, Ortho- and Para-Selective Ruthenium-Catalysed C(sp2)–H Oxygenations of Phenol Derivatives. *Org. Lett.* **2013**, *15*, *13*, 3484-3486.

[99]. C. Zhang, J. Ji, P. Sun, Palladium-Catalyzed Alkenylation via sp2 C–H Bond Activation Using Phenolic Hydroxyl as the Directing Group. *J. Org. Chem*. **2014**, *79*, 7, 3200-3205.

[100]. A. Ahmed, Y. Nuree, J. K. Ray, Aerobic Ligand-Free Domino Suzuki Coupling—Michael Addition Reaction Catalysed by in situ Generated Palladium Nanoparticles in Water: a General Method for the Synthesis of Benzo[C]Chromene Derivatives. *Tetrahedron Lett.* **2013**, *54*, 665-668.

[101]. D. D. Guo, B. Li, D. Y. Wang, Y. R. Gao, S. H. Guo, G. F. Pan, Y. Q. Wang, Synthesis of 6H-Benzo[c]chromenes via Palladium-Catalyzed Intramolecular Dehydrogenative Coupling of Two Aryl C–H Bonds. *Org. Lett.* **2017**, *19*, *4*, 798-801.

[102]. Q. Zhu, X. Wang, Y. Xu, Palladium-Catalysed Tandem Reactions ofβ-(2-Bromophenyl)-α,β-Unsaturated Carbonyl Compounds with 2-Hydroxyphenylboronic Acid: A New Route toBenzo[c]chromenes. *Eur. J. Org. Chem.* **2012**, *6*, 1112-1114.

[103]. Z. Zhao, K. Kang, J. Yue, X. Ji, H. Qiao, P. Fan, X. Zheng, Research Progress in Biological Activities of Isochroman Derivatives. *Eur. J. Med. Chem.* **2021**, *210*, 113073-113086.

[104]. R. E. TenBrink, C. L. Bergh, J. N. Duncan, D. W. Harris, R. M. Huff, R. A. Lahti, C. F. Lawson, B. S. Lutzke, I. J. Martin, S. A. Rees, S. K. Schlachter, J. C. Sihr, M. W. Smith, (S)-(-)-4-[4-[2-(Isochroman-1-Yl)Ethyl]-Piperazin-1-Yl]Benzenesulfonamide, a Selective Dopamine D4 Antagonist. *J. Med. Chem.* **1996**, *39*, *13*, 2435-2437.

[105]. K. Tomooka, L. F. Wang, F. Okazaki, T. Nakai, External Chiral Ligand-Induced Enantioselective Lithiation/SE2 Reactions of Isochroman and Phthalan. *Tetrahedron Lett.* **2000**, *41*, 6121-6125.

[106]. D. O. Hagan, Pyrrole, Pyrrolidine, Pyridine, Piperidine and Tropane Alkaloids. *Nat. Prod. Rep.,* **2000**, *17*, 435-446.

[107]. A. Hager, N. Vrielink, D. Hager, J. Lefranc, D. Trauner, Synthetic Approaches Towards Alkaloids Bearing A-Tertiary Amines. *Nat. Prod. Rep.,* **2016**, *33*, 491-522.

[108]. Z. F. Zhang, Z. H. Gao, C. L. Zhang, S. Ye, N-Heterocyclic Carbene-Catalyzed Intramolecular Aza-Michael Addition of Alkyl Amines to A,B-Unsaturated Carboxylic Acid: Synthesis of Pyrrolidines and Piperidines. *Tetrahedron.* **2021**, *94*, 132337-132346.

[109]. E. Vitaku, D. T. Smith, J. T. Njardarson, Analysis Of The Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.,* **2014**, *57*, 10257-10274.

[110]. M. Sánchez-Roselló, J. L. Aceña, A. Simón-Fuentesa, C. d. Pozo, A General Overview of the Organocatalytic Intramolecular Aza-Michael Reaction. *Chem. Soc. Rev.,* **2014**, *43*, 7430-7453.

Chapter 4 Experimental Details

4.1 General Experimental Details

Reagents and solvents were purchased at reagent-grade from Acros Organics, Sigma-Aldrich, Alfa Aeser, and Fluorochem and used without further purification unless stated. Solvents for extraction or column chromatography were of technical quality. All water used was purified via a Merck Millipore reverse osmosis purification system prior to use. All reactions were performed under N_2 atmosphere if not stated otherwise. Anhydrous solvents (tetrahydrofuran, toluene, dichloromethane, and diethyl ether) were dried by filtration through activated alumina (Sigma-Aldrich, 58 Å pore size, powder 150 mesh, basic) columns and stored under N_2 atmosphere prior to use. Solvents were removed under reduced pressure using Büchi Rotavapor apparatus.

Thin-layer chromatography was performed on SiO_2-60 UV_{254} coated aluminium sheets from Merck (silica gel 60 F254). Visualisation was achieved with a UV lamp at a wavelength of 254 nm, or with a $KMnO_4$ solution.

Flash column chromatography was carried out on silica gel 60 (VWR, 40-63 μm). Solvents for extraction and chromatography were of technical quality. Solvent mixtures are individually reported in parenthesis.

Proton, Carbon, and Fluorine nuclear magnetic resonance (^{1}H, ^{13}C, and ^{19}F NMR) spectra were recorded on Bruker DPX200 (200 MHz) Bruker AVG400 (400/101 MHz), Bruker AVH400 (400/101 MHz), Bruker AVC500 (500/126 MHz) and Bruker AVB500 (500/126 MHz) NMR spectrometers at 25 °C. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), pentet (p), or a combination e.g. doublet of doublets, or as a multiplet over a peak range. Some peaks are described as broad (b). The residual deuterated solvent was used as

internal standard ($CDCl_3$: δ_H = 7.26 ppm; CD_3OD: δ_H = 3.31 ppm; $(CD_3)_2SO$: δ_H = 2.50 ppm). HSQC, COSY and HMBC experiments were used for ^1H and ^{13}C NMR signals assignment where required.

Melting points (m.p.) were determined with a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported uncorrected.

Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film.

High-resolution mass spectrometry (HR-MS-ESI) was performed on a Bruker μTOF mass spectrometer. The molecular ion (M^+) is reported in m/z units.

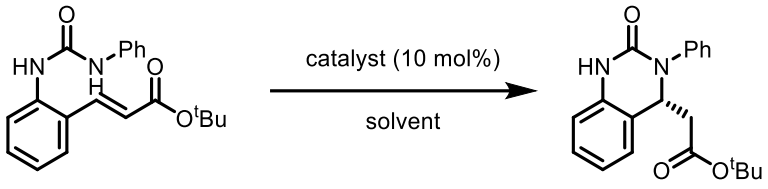
Chiral HPLC The enantiomeric excesses were determined by HPLC analysis on an Agilent 1200 Series instrument employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures.

$[\alpha]_D^T$ Optical rotations were recorded using a Perkin Elmer 341 polarimeter; $[\alpha]_D^T$ values are reported in 10^{-1} deg·cm^2 g^{-1} ; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C). (+) and (–) compound number prefixes indicate the sign of the optical rotation.

4.2 Experimental Details for Chapter 2

4.2.1 Optimisation Results

General procedure for optimisation of model reaction:



226 **232**

Urea **226** (16.9 mg, 0.05 mmol, 1.0 eq) was added to a solution of catalyst (0.005 mmol, 0.1 eq) in the appropriate solvent under N_2 at room temperature. The reaction mixture was stirred at the specified temperature for 24 hours unless otherwise indicated. Purification by silica gel chromatography (pentane/EtOAc) afforded the pure products, which were taken the isolated yield and analysed by chiral HPLC. (Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 220 nm, t_R (major) = 36.6 min, t_R (minor) = 57.4 min)

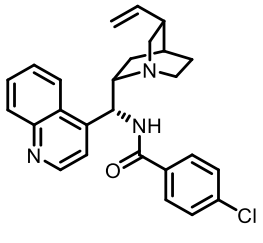
Table 1: Catalyst Screen

entry	cat. X	Conc.	temp/°C	solvent	reaction time	Yield (%)[a]	er[b]
1	**227**	0.1M	rt	toluene	24h	0	N.D.
2	**228**	0.1M	rt	toluene	24h	0	N.D.
3	**229**	0.1M	rt	toluene	24h	0	N.D.
4	**230**	0.1M	rt	toluene	24h	0	N.D.
5	**E1**	0.1M	rt	toluene	24h	0	N.D.
6	**231**	0.1M	rt	Et_2O	24h	96	68.5:31.5
7	**E2**	0.1M	rt	Et_2O	24h	95	63:37

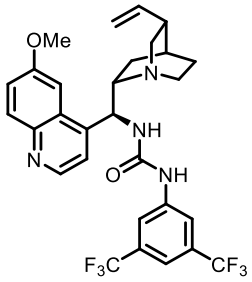
entry	cat. X	Conc.	temp/^{o}C	solvent	reaction time	Yield (%)[a]	er[b]
8	**118**	0.1M	rt	Et_2O	24h	73	74:26
9	**233**	0.1M	rt	Et_2O	24h	22	75.5:24.5
10	**E3**	0.1M	rt	Et_2O	24h	51	71:29
11	**234**	0.1M	rt	Et_2O	24h	16	62:38
12	**E4**	0.1M	rt	Et_2O	24h	32	66.5:33.5
13	**235**	0.1M	rt	Et_2O	24h	36	69:31
14	**E5**	0.1M	rt	Et_2O	24h	99	53.5:46.5
15	**E6**	0.1M	rt	Et_2O	24h	99	60:40
16	**236**	0.1M	rt	Et_2O	24h	99	60:40
17	**147**	0.1M	rt	Et_2O	24h	>99	74.5:25.5
18	**239**	0.1M	rt	Et_2O	24h	>99	71.5:28.5
19	**E7**	0.1M	rt	Et_2O	24h	0	N.D.
20	**238**	0.1M	rt	Et_2O	24h	>99	75:25
21	**237**	0.1M	rt	Et_2O	24h	>99	72.5:27.5
22	**240**	0.025M	rt	toluene	4h	11	65.5:34.5
23	**241**	0.025M	rt	toluene	4h	53	67.5:32.5
24	**E8**	0.025M	rt	toluene	4h	36	70:30
25	**242**	0.025M	rt	toluene	4h	17	68.5:31.5
26	**244**	0.025M	rt	toluene	10h	76	79:21
27	**243**	0.025M	rt	toluene	10h	71	80.5:19.5
28	**245**	0.025M	rt	toluene	4h	23	70:30

entry	cat. X	Conc.	temp/^{o}C	solvent	reaction time	Yield (%)[a]	er[b]
29	**246**	0.025M	rt	toluene	4h	24	71.5:28.5
30	**E29**	0.025M	rt	toluene	4h	62	80:20
31	**E9**	0.1M	rt	Et_2O	24h	10	67:33
32	**E10**	0.025M	rt	toluene	24h	91	54.5:45.5
33	**248**	0.025M	rt	toluene	24h	>99	91.5:8.5
34	**247**	**0.025M**	**rt**	**toluene**	**24h**	**>99**	**94.5:5.5**
35	**E11**	0.025M	rt	toluene	24h	>99	83.5:16.5
36	**249**	0.025M	rt	toluene	24h	>99	92.5:7.5
37	**250**	0.025M	rt	toluene	24h	>99	92:8

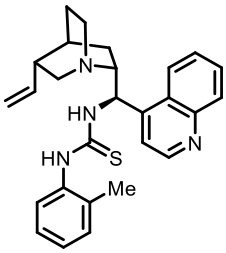
Table 1. Detailed catalyst screen results for the intramolecular aza-Michael reaction of urea **226**. [a] determined by ^{1}H NMR analysis of crude reaction mixture. [b] determined by HPLC analysis on chiral stationary phase. rt = room temperature. N.D. = not determined.



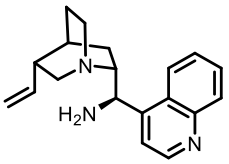
227



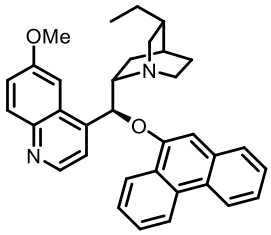
228



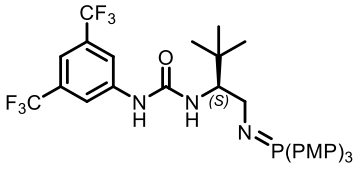
229



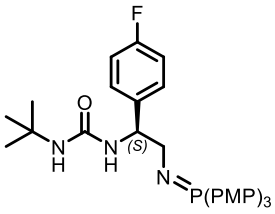
230



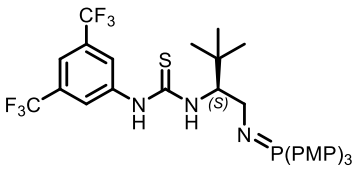
E1



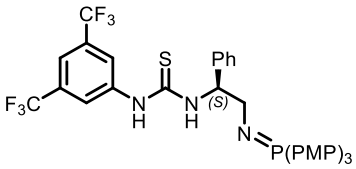
231



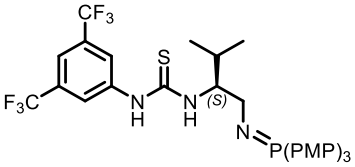
E2



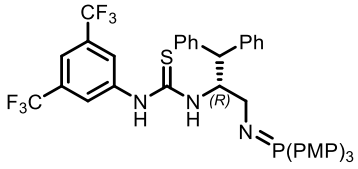
118



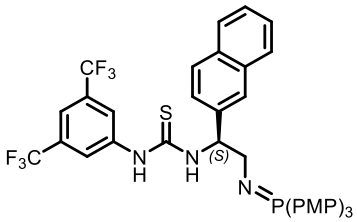
233



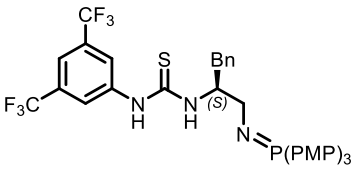
E3



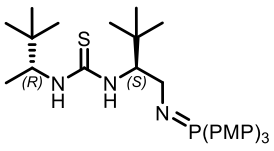
234



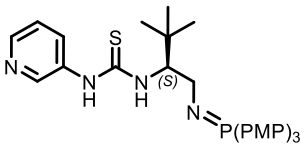
E4



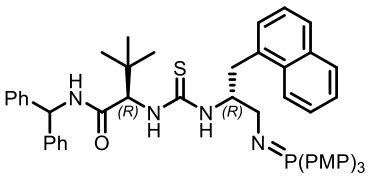
235



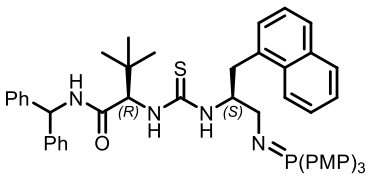
E5



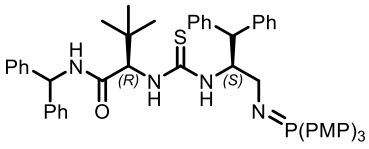
E6



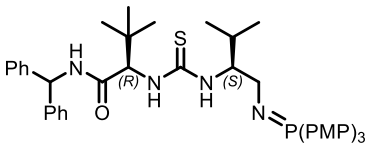
236



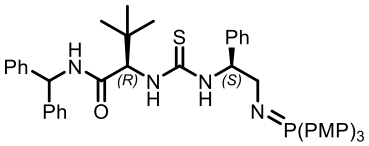
147



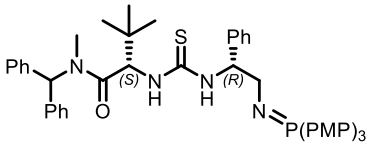
239



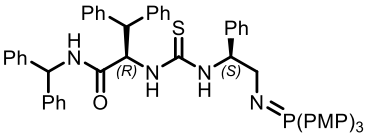
E7



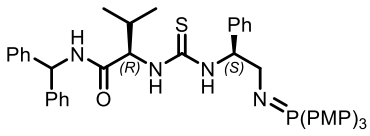
238



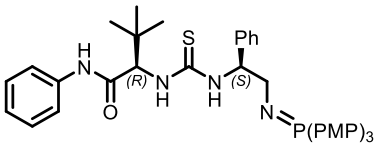
237



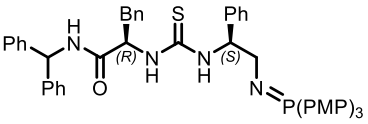
240



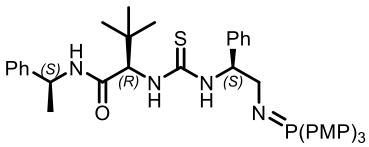
241



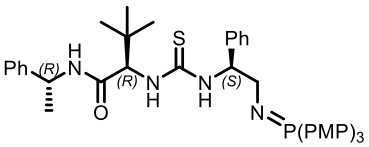
E8



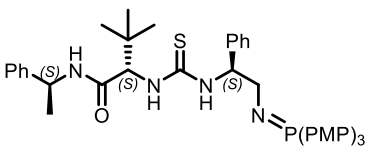
242



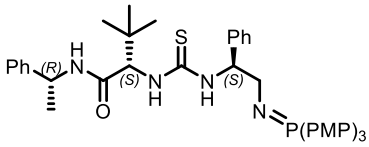
244



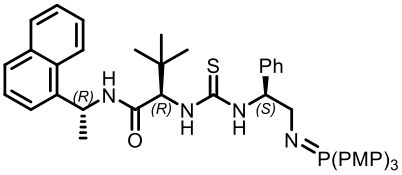
243



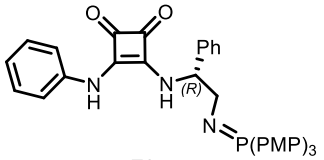
245



246



E29



E9

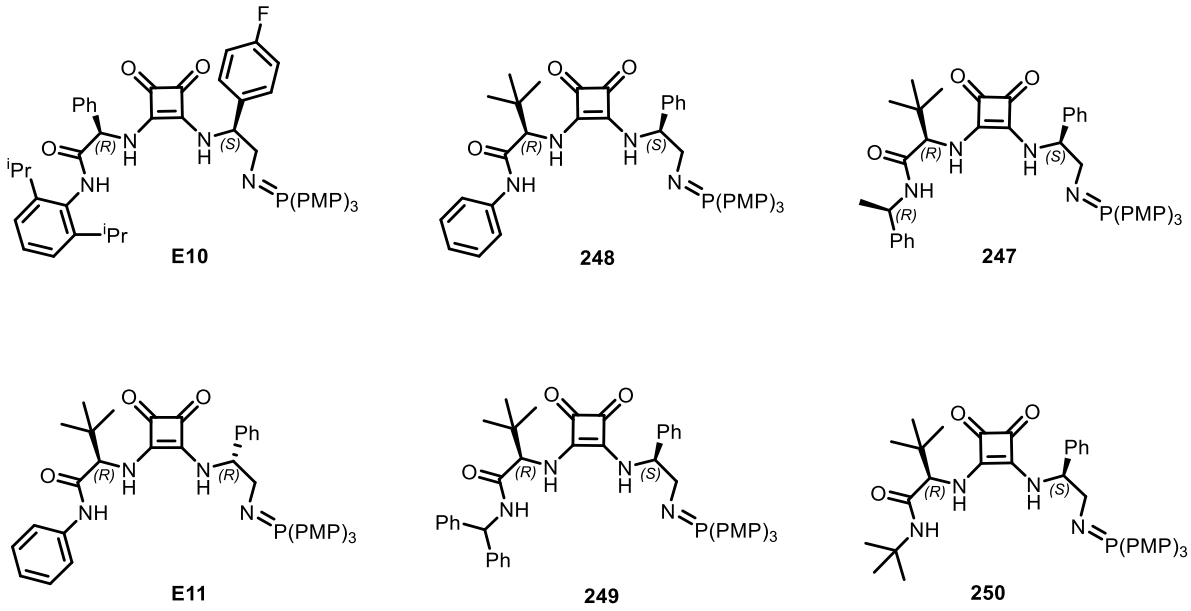


Figure 14. Selected catalysts studied in the optimisation of the intramolecular aza-Michael reaction of urea **226**.

Table 2: Solvent and Conditions Optimisation

entry	cat. X	Conc.	temp/^{o}C	solvent	reaction time	Yield (%)[a]	er[b]
1	**147**	0.1M	rt	Et_2O	4h	>99	74.5:25.5
2	**147**	0.1M	rt	Et_2O	9h	97	75:25
3	**147**	0.1M	rt	Et_2O	24h	>99	74.5:25.5
4	**147**	0.1M	rt	EtOAc	9h	60	67.5:32.5
5	**147**	0.1M	rt	TBME	9h	>99	76:24
6	**147**	0.1M	rt	dioxane	9h	51	77.5:22.5
7	**147**	0.1M	rt	toluene	9h	>99	76.5:23.5
8	**147**	0.1M	rt	THF	9h	73	70:30
9	**147**	0.1M	rt	CPME	9h	>99	76:24
10	**147**	0.1M	rt	PhF	4h	>99	69.5:30.5
11	**147**	0.1M	rt	2-methyl THF	4h	64	74:26
12	**147**	0.1M	-15	toluene	4h	47	63.5:36.5
13	**147**	0.1M	10	toluene	4h	67	70.5:29.5
14	**147**	0.1M	35	toluene	4h	>99	77.5:22.5
15	**147**	0.1M	55	toluene	4h	>99	77.5:22.5
16	**147**	0.3M	rt	toluene	4h	98	74.5:25.5
17	**147**	0.025M	rt	toluene	4h	99	78:22
18	**147**	0.025M	55	toluene	4h	>99	78.5:21.5
19	**147**	0.025M	75	toluene	4h	>99	77.5:22.5
20	**147**	0.025M	95	toluene	4h	>99	77:23
21	**248**	0.1M	rt	toluene	24h	>99	90.5:9.5
22	**248**	0.025M	rt	toluene	24h	>99	91.5:8.5
23	**248**	0.025M	-15	toluene	24h	trace	N.D.
24	**248**	0.025M	50	toluene	24h	>99	90.5:9.5
25	**248**	0.025M	5	toluene	24h	22	91.5:8.5
26	**248**	0.025M	rt	$PhCF_3$	24h	0	N.D.
27	**248**	0.025M	rt	MeCN	24h	>99	56:44
28	**248**	0.025M	rt	EtOAc	24h	77	80.5:19.5
29	**248**	0.025M	rt	DCM	24h	>99	72.5:27.5
30	**248**	0.025M	rt	CPME	24h	79	85.5:14.5
31	**248**	0.025M	rt	THF	24h	>99	66.5:33.5
32	**247**	**0.025M**	**rt**	**toluene**	**24h**	**>99**	**94.5:5.5**
33	**247**	0.025M	rt	PhF	24h	91	89:11

entry	cat. X	Conc.	temp/^{o}C	solvent	reaction time	Yield (%)[a]	er[b]
34	**247**	0.025M	rt	*o*-xylene	24h	>99	94.2:5.8
35	**247**	0.025M	rt	*p*-xylene	24h	87	91.5:8.5
36	**247**	0.025M	rt	*m*-xylene	24h	92	94.5:5.5

Table 2. Detailed solvent and conditions optimisation results for the intramolecular aza-Michael reaction of urea **226**. [a] yields of isolated products. [b] determined by HPLC analysis on chiral stationary phase. rt = room temperature. N.D. = not determined. TBME = *tert*-butyl methyl ether. CPME = cyclopentyl methyl ether.

Table 3: Phosphine Screen[a]

entry	cat. X	Conc.	PR_3	solvent	Yield (%)[b]	er[c]
1[d]	**147**	**0.1M**	**$P(PMP)_3$**	**toluene**	**>99**	**76.5:23.5**
2	**147**	0.1M	PPh3	toluene	24	76:24
3	**147**	0.1M	$P(4\text{-Cl-Ph})_3$	toluene	0	N.D.
4[e]	**147**	0.1M	$P(^{n}Bu)_3$	toluene	>99	65:35
5	**147**	0.1M	dppf	toluene	44	69:31
6	**147**	0.1M	dppe	toluene	34	65:35
7	**147**	0.1M	dppm	toluene	>99	67:33
8	**147**	0.1M	257	toluene	>99	60:40
9	**147**	0.1M	E12	toluene	>99	64:36
10	**147**	0.1M	E13	toluene	0	N.D.
11[e]	**239**	0.1M	$P(PMP)_3$	Et_2O	>99	71.5:28.5
12	**239**	0.1M	253	Et_2O	76	66:34
13	**239**	0.1M	255	Et_2O	24	62.5:37.5
14	**239**	0.1M	E14	Et_2O	0	N.D.
15	**239**	0.1M	254	Et_2O	31	60:40
16	**239**	0.1M	E15	Et_2O	0	N.D.

Table 3. Detailed phosphine screen results for the intramolecular aza-Michael reaction of urea **226**. [a] reaction was carried out at room temperature for 4 hours unless otherwise indicated. [b] yields of isolated products. [c] determined by HPLC analysis on chiral stationary phase. [d] reaction was carried out for 9 hours. [e] reaction was carried out for 24 hours. N.D. = not determined. PMP = *para*-methoxy phenyl. dppm = 1,1-Bis(diphenylphosphino)methane. dppf = 1,1'-Bis(diphenylphosphino)ferrocene. dppe = 1,2-Bis(diphenylphosphino)ethane.

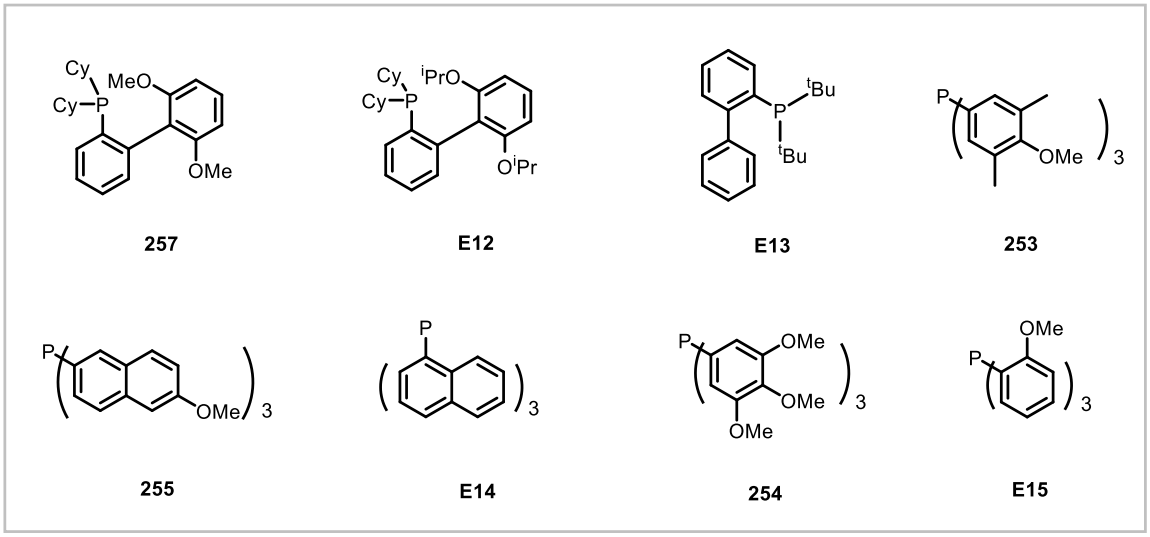
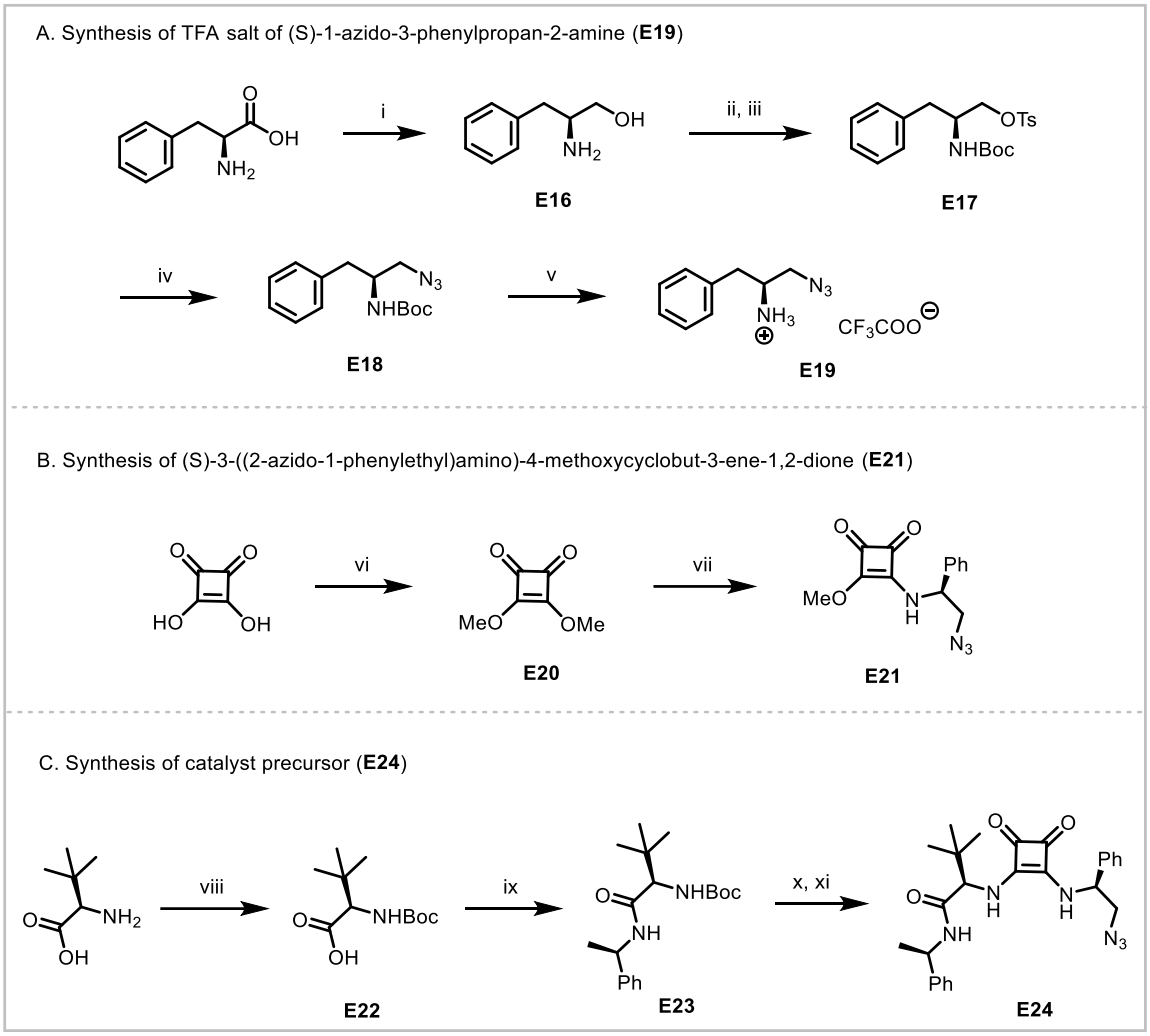


Figure 15. Selected phosphines studied in the optimisation of the intramolecular aza-Michael reaction of urea **226**.

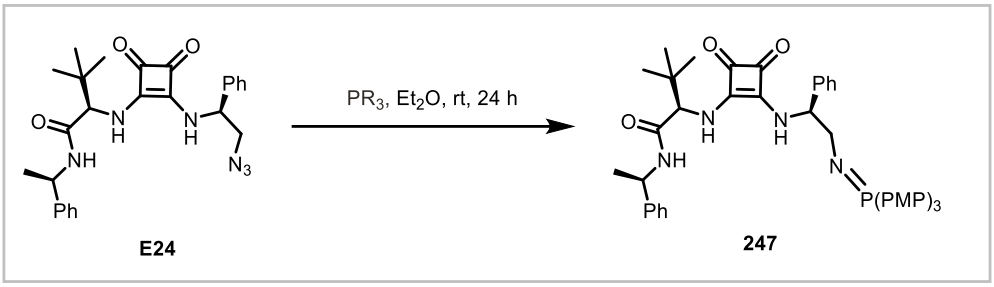
4.2.2 Preparation of Catalyst Precursor and Catalyst

Synthesis of catalyst precursor



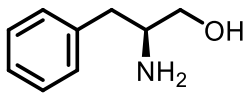
Scheme 80. A). Synthesis of (*S*)-1-azido-3-phenylpropan-2-amine (**E19**). i. $NaBH_4$, I_2, THF, reflux, 20 h, 75%; ii. Et_3N, $(Boc)_2O$, DCM, rt, 8 h; iii. Et_3N, TsCl, DCM, rt, 16 h, 59% over ii and iii; iv. NaN_3, DMF, 45 °C, 14 h, 46%; v. TFA, 0 °C to rt, 2 h, 99%. **B).** Synthesis of (S)-3-((2-azido-1-phenylethyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**E21**). vi. trimethyl orthoformate, MeOH, reflux, 24 h, 82%; vii. compound **E19**, Et_3N, MeOH, rt, 16 h, 51%. **C).** Synthesis of catalyst precursor (**E24**). viii. $(Boc)_2O$, Na_2CO_3, MeOH/H_2O, rt, 24 h, 96%; ix. (*R*)-1-phenylethan-1-amine, HATU, Et_3N, DCM, rt, 20 h, 94%; x. TFA, 0 °C to rt, 2 h; xi. compound **S6**, Et_3N, MeOH, 50 °C, 20 h, 80%.

Synthesis of catalyst



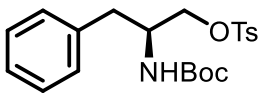
E24 247

Staudinger reaction for *in-situ* generation of the active BIMP catalysts: Et_2O (0.025 M) was added to the BIMP catalysts precursors (1.0 eq) and the appropriate phosphine (1.0 eq) in a mass spectrometry vial under N_2 at room temperature. The reaction mixture was stirred for 24 hours before evaporating to dryness under a stream of nitrogen gas. The iminophosphorane product was confirmed by LRMS and TLC. The resulting mixture was used as crude for enantioselective reactions without any purification.



(*S*)-2-amino-3-phenylpropan-1-ol (E16) was prepared according to the literature procedure reported by S. Ruppenthal *et. al.* [1] A solution of I_2 (15.37 g, 60.54 mmol, 1.0 eq) in THF (40 mL) was added dropwise to a solution of $NaBH_4$ (5.50 g, 145.30 mmol, 2.4 eq) and *L*-phenylalanine (10.00 g, 60.54 mmol, 1.0 eq) in THF (160 mL) over 30 mins under N_2 at 0 °C. The reaction mixture was heated to reflux for 20 hours. After cooled back to room temperature, methanol (25 mL) was added dropwise to the mixture. The resulting clear solution was stirred for 30 mins and evaporated to dryness under reduced pressure. 20% KOH solution (200 mL) was then added and stirring was maintained for 4 hours. The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by recrystallisation from toluene afforded the title compound as a white solid (6.86 g, 75%). Data is consistent with the published literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.16 (m, 5H, Ar-H), 3.63 (dd, *J* = 10.7, 3.8 Hz, 1H, CH_2OH), 3.39 (dd, *J* = 10.7, 7.2 Hz, 1H, CH_2OH), 3.12 (m, 1H, $CHNH_2$), 2.79 (dd, *J* = 13.4, 5.2 Hz, 1H, $PhCH_2$), 2.52 (dd, *J* = 13.4, 8.7 Hz, 1H, $PhCH_2$), 2.12 (brs, 3H, NH_2 and OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 138.8 (ArC), 129.3 (*m*-ArCH), 128.7 (*o*-ArCH), 126.5 (*p*-ArCH), 66.4 (CH_2OH), 54.3 (NH_2CH), 40.9 ($PhCH_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_9H_{14}NO$ ($[M+H]^+$) 152.10699, found 152.10725.

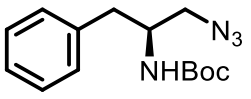


(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl 4-methylbenzenesulfonate (E17) was prepared according to the literature procedure reported by S. Bera, *et. al.* [2] Triethylamine (3.95 g, 39.02 mmol, 1.2 eq) was added to a solution of (*S*)-2-amino-3-phenylpropan-1-ol (**E16**) (5.00 g, 33.07 mmol, 1.0 eq) in CH_2Cl_2 (116 ml) under N_2 at room temperature. The reaction mixture was cooled to 0 °C and di-*tert*-butyl decarbonate (8.52 g, 39.02 mmol, 1.2 eq) was added. The stirring was maintained at 0 °C for

1 hour and then room temperature for 8 hours. The mixture was washed with water (100 mL) and brine (100 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAC = 3/2 then 2/3) afforded the *N*-boc protected amino alcohol as a white solid (7.32 g, 88%).

Triethylamine (3.1 g, 30.64 mmol, 1.1 eq) and *p*-toluenesulfonyl chloride (5.31g, 27.85 mmol, 1.0 eq) were added sequentially to a solution of the *N*-boc protected amino alcohol (7.00 g, 27.85 mmol, 1.0 eq) in CH_2Cl_2 (103 mL) under N_2 at room temperature. The reaction mixture was stirred for 16 hours and partitioned by the addition of H_2O (100mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAC = 9/1) afforded the title compound as a pale yellow solid (7.56 g, 67%). Data is consistent with the published literature.

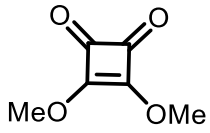
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.0 Hz, 2H, $C_6\underline{H}_4CH_3$), 7.35 (d, *J* = 8.0 Hz, 2H, $C_6\underline{H}_4CH_3$), 7.25 – 7.15 (m, 3H, $C_6\underline{H}_5CH_2$), 7.12 – 7.04 (m, 2H, $C_6\underline{H}_5CH_2$), 4.76 – 4.70 (brs, 1H, N<u>H</u>), 4.06 – 3.85 (m, 3H, NHC<u>H</u> and C$\underline{H}_2$O), 2.93 – 2.72 (m, 2H, PhC$\underline{H}_2$), 2.46 (s, 3H, $C_6H_4C\underline{H}_3$), 1.38 (s, 9H, C(C$\underline{H}_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.1 (O<u>C</u>(O)N), 145.2 (SO_2Ar<u>C</u>), 136.9 (Ar<u>C</u>), 132.7 (SO_2Ar<u>C</u>CH_3), 130.1 (*m*-SO_2Ar<u>C</u>H), 129.4 (*m*-Ar<u>C</u>H), 128.7 (*o*-Ar<u>C</u>H), 128.1 (*o*-SO_2Ar<u>C</u>H), 126.9 (*p*-Ar<u>C</u>H), 80.0 (<u>C</u>($CH_3)_3$), 70.1 (<u>C</u>H_2O), 50.9 (NH<u>C</u>H), 37.3 (Ph<u>C</u>H_2), 28.4 (C(<u>C</u>$H_3)_3$), 21.8 ($C_6H_4\underline{C}H_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{27}NO_5{}^{23}Na^{32}S$ ([M+Na]$^+$) 428.15021, found 428.14987.



***tert*-Butyl (*S*)-(1-azido-3-phenylpropan-2-yl) carbamate (E18)** was prepared according to the literature procedure reported by S. Bera, *et. al.* [2] Sodium azide (1.30 g, 19.96 mmol, 1.1 eq) was added to a solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl 4-methylbenzenesulfonate (**E17**) (7.36 g, 18.15 mmol, 1.0 eq) in DMF (61 mL) under N_2 at room temperature. The reaction mixture was

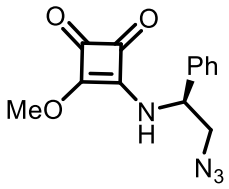
warmed to 45 °C and stirred for 14 hours. The mixture was cooled to room temperature and diluted with water (100 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 9/1 then 4/1) afforded the title compound as a white solid (2.33 g, 46%). Data is consistent with the published literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.17 (m, 5H, Ar-H), 4.65 (brs, 1H, NH), 3.97 (brs, 1H, NHCH), 3.46 – 3.27 (m, 2H, CH_2N_3), 2.94 – 2.74 (m, 2H, $PhCH_2$), 1.43 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.2 (OC(O)N), 137.3 (ArC), 129.4 (*m*-ArCH), 128.8 (*o*-ArCH), 126.9 (*p*-ArCH), 79.9 ($C(CH_3)_3$), 53.3 (CH_2N_3), 51.5 (NHCH), 38.3 ($PhCH_2$), 28.5 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{20}N_4O_2{}^{23}Na$ ($[M+Na]^+$) 299.14785, found 299.14781.



3,4-dimethoxycyclobut-3-ene-1,2-dione (E20) was prepared according to the literature procedure reported by M. Lu *et. al.* [3] Trimethyl orthoformate (13.70 g, 129.00 mmol, 2.1 eq) was added to a solution of 3,4-Dihydroxy-3-cyclobutene-1,2-dione (7.00 g, 61.40 mmol, 1.0 eq) in anhydrous MeOH (62 mL) under N_2 at room temperature. The reaction mixture was heated to reflux for 24 hours. After cooled back to room temperature, the mixture was evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc= 2/1) afforded the title compound as a white solid (7.11 g, 82%). Data is consistent with the published literature.

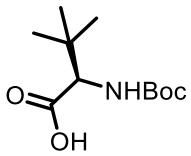
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (s, 6H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 189.3 (C=O), 184.6 ($COCH_3$), 61.1 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_6H_7O_4$ ($[M+H]^+$) 143.0339, found 143.0340.



(*S*)-3-((2-azido-1-phenylethyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (E21) was prepared according to the following procedure. According to the modified literature procedure reported by D. M. Rotstein *et. al.*, [4] trifluoroacetic acid (7.8 mL) was added to the *tert*-butyl (*S*)-(1-azido-3-phenylpropan-2-yl) carbamate **(E18)** (2.03 g, 7.74 mmol, 1.0 eq) under N_2 at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C, before warming to room temperature. Volatiles were removed under a stream of nitrogen gas behind a blast shield to afford TFA salt of (*S*)-1-azido-3-phenylpropan-2-amine (**E19**) which was used as crude for next step without any purification.

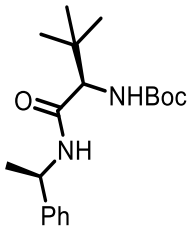
A solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (**E20**) (2.21 g, 15.50 mmol, 2.0 eq) and triethylamine (5.48 g, 54.20 mmol, 7.0 eq) in anhydrous MeOH (39 mL) was added to a solution of the TFA salt of (*S*)-1-azido-3-phenylpropan-2-amine (**E19**) in anhydrous MeOH (116 mL) over 2h under N_2 at room temperature. The reaction mixture was stirred for 24 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/MeCN = 9/1) afforded the title compound as a pale yellow oil (1.07 g, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (brs, 1H, NH), 7.43 – 7.32 (m, 5H, Ar-H), 4.87 (brs, 1H, CH), 4.41 (s, 3H, CH_3), 3.83 (dd, J = 12.7, 8.2 Hz, 1H, CH_2), 3.71 (brs, 1H, CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 179.1 (CO), 171.7 (CO), 137.9 (ArC), 129.4 (ArCH), 129.0 (ArCH), 126.6 (ArCH), 61.0 (CH_3), 59.1 (CH), 55.6 (CH_2) ppm. (C=C not observed); **HRMS** (ESI) m/z calcd. for $C_{13}H_{13}N_4O_3$ ($[M+H]^+$) 273.0982, found 273.0981.



(*R*)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (E22) was prepared according to the literature procedure reported by M. S. Manna, *et. al.* [5] Na_2CO_3 (4.55 g, 42.90 mmol, 1.1 eq) was added to a solution of (*D*)-tert-leucine (5.13 g, 39.00 mmol, 1.0 eq) in MeOH/H_2O (1:1) (156 mL) under N_2 at room temperature. Di-*tert*-butyl decarbonate (9.37 g, 42.90 mmol, 1.1 eq) was added and the resulting mixture was stirred at room temperature for 20 h. MeOH was evaporated under reduced pressure. The aqueous mixture was acidified to pH = 4 with saturated aqueous solution of citric acid (200 mL) and then extracted with CH_2Cl_2 (4 × 100 mL) and Et_2O (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to afford title compound as a white foam (4:1 (**A**:**B**) mixture of rotamers), (8.71 g, 96%) which was used as crude for next step without any purification. Data is consistent with the published literature.

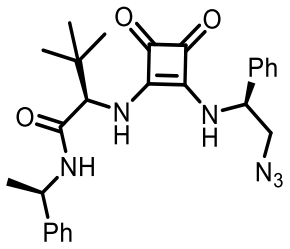
^{1}H NMR (400 MHz, CD_3OD): δ 3.95 (s, 0.8H, C<u>H</u> (**A**)), 3.83 (s, 0.2H, C<u>H</u> (**B**)), 1.45 (s, 9H, OC(C<u>H</u>$_3$)$_3$), 1.00 (s, 9H, CHC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, CD_3OD)** δ 174.8 (<u>C</u>O_2), 158.0 (NH<u>C</u>O_2), 80.5 (O<u>C</u>(CH$_3$)$_3$), 63.4 (<u>C</u>HC(CH$_3$)$_3$), 34.9 (CH<u>C</u>(CH$_3$)$_3$), 28.7 (OC(<u>C</u>H$_3$)$_3$), 27.1 (CHC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{11}H_{21}NO_4{}^{23}Na([M+Na]^+)$ 254.1374, found 254.1364.



***tert*-Butyl ((*R*)-3,3-dimethyl-1-oxo-1-(((*R*)-1-phenylethyl)amino)butan-2-yl)carbamate (E23)** was prepared according to the following procedure. Triethylamine (0.90 g, 8.80 mmol, 2.0 eq) was added to a solution of (*R*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid **(E22)** (1.02 g, 4.40 mmol, 1.0 eq), (*R*)-1-phenylethan-1-amine (1.07 g, 8.80 mmol, 2.0 eq) and HATU (2.01 g, 5.28 mmol, 1.2 eq)

in CH_2Cl_2 (22 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours before quenching with a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Purification by silica gel chromatography (pentane/EtOAc= 9/1) afforded the title compound as a white solid (1.39 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.22 (m, 5H, Ar-H), 5.88 (d, *J* = 7.5 Hz, 1H, NHCO), 5.32 – 5.19 (m, 1H, $NHCO_2$), 5.11 (p, *J* = 7.0 Hz, 1H, $CHCH_3$), 3.76 (d, *J* = 9.3 Hz, 1H, $CHC(CH_3)_3$), 1.49 (d, *J* = 7.0 Hz, 3H, $CHCH_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 0.93 (s, 9H, $CHC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.1 (NHCO), 156.0 ($NHCO_2$), 143.1 (ArC), 128.8 (*m*-ArCH), 127.6 (*p*-ArCH), 126.4 (*o*-ArCH), 79.8 ($OC(CH_3)_3$), 62.7 ($CHC(CH_3)_3$), 49.1 ($CHCH_3$), 34.8 ($CHC(CH_3)_3$), 28.5 ($OC(CH_3)_3$), 26.7 ($CHC(CH_3)_3$), 21.7 ($CHCH_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{30}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 357.2149, found 357.2149; **FT-IR (thin film)** ν_{max} 3312, 2972, 2524, 2160, 2030, 1977, 1685, 1648, 1523, 1454, 1391, 1366, 1322, 1246, 1173, 1128, 1062, 1009, 913, 863, 759, 700 cm^{-1}; **m .p.**: 141-142 °C; **$[\alpha]_D^{25}$** = +47.5 (c=0.99, $CHCl_3$).



Catalyst Precursor (*R*)-2-((2-(((*S*)-2-azido-1-phenylethyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl-*N*-((*R*)-1-phenylethyl)butanamide (E24) was prepared according to the following procedure. According to the modified literature procedure reported by D. M. Rotstein *et. al.,* [4] trifluoroacetic acid (2.7 mL) was added to the *tert*-butyl ((*R*)-3,3-dimethyl-1-oxo-1-(((*R*)-1-phenylethyl)amino)butan-2-yl)carbamate **(E23)** (0.89 g, 2.67 mmol, 1.0 eq) under N_2 at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C, before warming to room temperature. Volatiles were

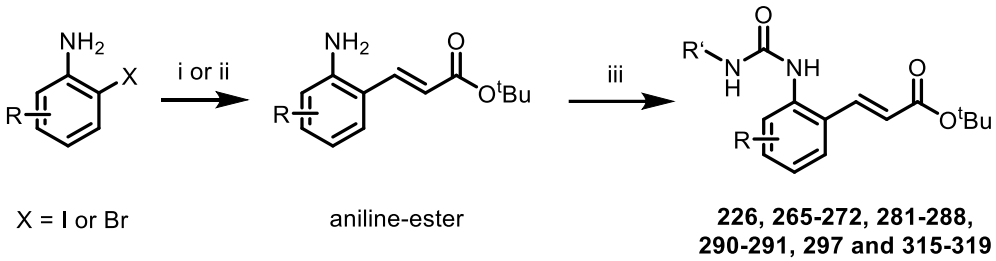
removed under a stream of nitrogen gas behind a blast shield to afford TFA salt of (*R*)-2-amino-3,3-dimethyl-*N*-((*R*)-1-phenylethyl)butanamide which was used as crude for next step without any purification.

A solution of the TFA salt of (*R*)-2-amino-3,3-dimethyl-*N*-((*R*)-1-phenylethyl)butanamide in anhydrous MeOH (5.7 mL) was added to a solution of (*S*)-3-((2-azido-1-phenylethyl)amino)-4-methoxycyclobut-3-ene-1,2-dione **(E21)** (0.73 g, 2.67 mmol, 1.0 eq) and triethylamine (1.89 g, 18.70 mmol, 7.0 eq) in anhydrous MeOH (3.2 mL) under N_2 at room temperature. The reaction mixture was heated to 50 °C and stirred for 20 hours. The reaction mixture was cooled to room temperature and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/MeCN = 4/1) afforded the title compound as a white solid (1.02 g, 80%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.93 (d, *J* = 8.2 Hz, 1H, NHCO), 8.33 (d, *J* = 9.1 Hz, 1H, NHCHCH$_2$), 7.95 (d, *J* = 10.0 Hz, 1H, NHCHCO), 7.47 – 7.39 (m, 4H, Ar-H), 7.38 – 7.29 (m, 5H, Ar-H), 7.25 – 7.19 (m, 1H, Ar-H), 5.46 – 5.25 (m, 1H, NHCHCH$_2$), 4.98 (p, *J* = 7.0 Hz, 1H, NHCHCH$_3$), 4.51 (d, *J* = 10.0 Hz, 1H, NHCHCO), 3.94 – 3.74 (m, 2H, NHCHCH$_2$), 1.37 (d, *J* = 7.0 Hz, 3H, NHCHCH$_3$), 0.82 (s, 9H, CHC(CH$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 182.31 (CCO), 182.25 (CCO), 168.2 (NHCO), 167.5 (CCO), 166.7 (CCO), 144.3 (ArCCHCH$_3$), 139.1 (ArCCHCH$_2$), 128.8 (*m*-ArCH), 128.2 (*m*-ArCH), 128.0 (*p*-ArCH), 126.7 (*p*-ArCH), 126.6 (*o*-ArCH), 126.2 (*o*-ArCH), 63.6 (CHC(CH$_3$)$_3$), 56.4 (NHCHCH$_2$), 55.6 (NHCHCH$_2$), 48.1 (CHCH$_3$), 35.5 (CHC(CH$_3$)$_3$), 26.0 (CHC(CH$_3$)$_3$), 22.5 (CHCH$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{26}H_{31}N_6O_3$ ([M+H]$^+$) 475.2452, found 475.2452; **FT-IR (thin film)** ν_{max} 3448, 2996, 2913, 2360, 2160, 1978, 1665, 1437, 1407, 1311, 1043, 1024, 953, 932, 898, 698, 668 cm^{-1}; **m.p.**: 235-237 °C; **[α]D^{25}** = +1.7 (c=0.65, $(CH_3)_2SO$).

4.2.3 Preparation of Starting Materials

General procedure A for preparation of starting materials 226, 265-272, 281-288, 290-291, 297 and **315-319**



Scheme 81. Synthesis of starting materials **226, 265-272, 281-288, 290-291, 297** and **315-319**. i. $PdCl_2(PPh_3)_2$, *tert*-butyl acrylate, triethylamine, 100 °C, 24 h; ii. $Pd(OAc)_2$, *tert*-butyl acrylate, triethylamine, tris(*o*-tolyl)phosphine, acetonitrile, 120 °C, 24 h; iii. Isocyanate, toluene, rt, 16 h.

Aniline-ester

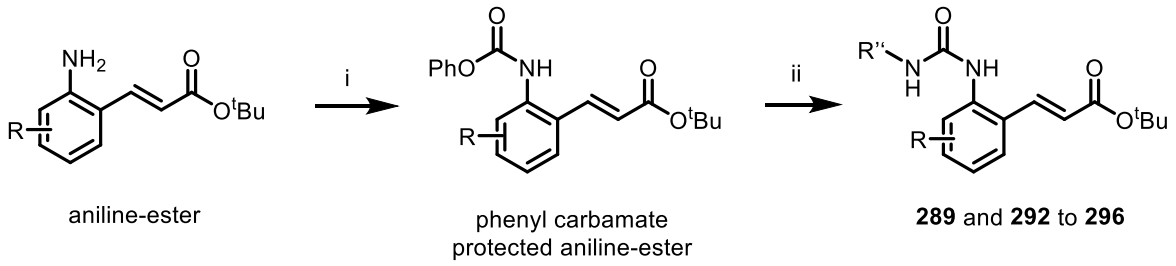
i. (for starting materials **1b** to **1i**) According to the modified literature procedure reported by M. M. Ahire *et. al.,* [6] *tert*-butyl acrylate (1.2 eq) was added to a solution of 2-halogen-aniline (1.0 eq) and $PdCl_2(PPh_3)_2$ (0.05 eq) in triethylamine (1.2M) in a sealed tube under N_2 at room temperature. The sealed tube was flushed twice with argon gas before sealed with a screw cap. The reaction mixture was heated to 100 °C and stirred for 24 hours. After cooled back to room temperature, the resulting mixture was diluted with H_2O (50 mL) and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The resulting paste was flushed through silica gel with (pentane/Et_2O = 4/1) to afford the aniline-ester as a yellow solid which was used as crude for next step without any further purification.

ii. (for starting materials **226, 265-272, 281-288, 290-291, 297** and **315-319**) According to the modified literature procedure reported by Yamanaka *et. al.,* [7] *tert*-butyl acrylate (2.0 eq) and triethylamine (2.0 eq) were added to a solution of 2-halogen-aniline (1.0 eq), tris(*o*-tolyl)phosphine (0.06 eq) and $Pd(OAc)_2$ (0.03 eq) in acetonitrile (0.42M) in a sealed tube under N_2 at room temperature. The sealed tube was

flushed twice with argon gas before sealed with a screw cap. The reaction mixture was heated to 120 °C and stirred for 24 hours. After cooled back to room temperature, the resulting mixture was diluted with H_2O (50 mL), made alkaline with K_2CO_3 and then extracted with $CHCl_3$ (4 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The resulting paste was flushed through silica gel with (CH_2Cl_2/MeOH = 95/5) to afford the aniline-ester as a yellow solid which was used as crude for next step without any further purification.

Starting materials 226, 265-272, 281-288, 290-291, 297 and **315-319.** According to the modified literature procedure reported by S. J. Park *et. al.,* [8] the corresponding isocyanate (2.0 eq) was added to a solution of the aniline-ester (1.0 eq) in toluene (0.24M) under N_2 at room temperature. The reaction mixture was stirred for 20 hours, filtered and washed with pentane (2 x 100 mL) to afford starting materials **226, 265-272, 281-288, 290-291, 297** and **315-319** as an off-white solid.

General Procedure B for Preparation of Starting Materials 289 and 292 to 296

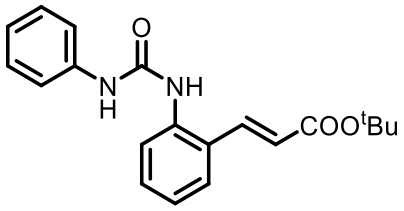


Scheme 82. Synthesis of starting materials **289** and **292** to **296**. i. Phenyl chloroformate, Na_2HPO_4, EtOAc/H_2O, 12 h at rt then 2 h at 60 °C; ii. Amine, triethylamine, THF, reflux, 7 h.

Phenyl carbamate aniline-ester. According to the modified literature procedure reported by G. R. Humphrey *et. al.,* [9] Na_2HPO_4 (1.5 eq) and H_2O (1.1M) were added to a solution of the aniline-ester (1.0 eq) in EtOAc (0.35M) at room temperature, followed by dropwise addition of phenyl chloroformate (1.25 eq). The reaction mixture was stirred for 12h at room temperature and then 2h at 60 °C. More EtOAc was added at 60 °C until all solids were dissolved and the layer was then separated. The organic

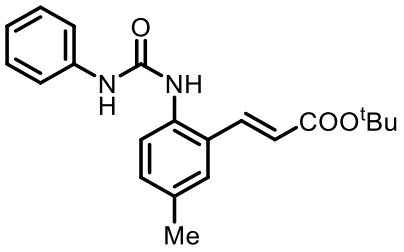
layer was washed with H_2O (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The resulting paste was flushed through silica gel with (pentane/EtOAc = 9/1) to afford the phenyl carbamate protected aniline-ester as an orange solid which was used as crude for next step without any further purification.

Starting materials 289 and 292 to 296. Amine (2.0 eq) was added to a solution of the phenyl carbamate protected aniline-ester (1.0 eq) and triethylamine (2.0 eq) in THF (0.5M) in a sealed tube under N_2 at room temperature. The sealed tube was flushed twice with argon gas before sealed with a screw cap. The reaction mixture was heated to 50 °C and stirred for 7 hours. After cooled back to room temperature, the resulting mixture was evaporated to dryness under reduced pressure. Purification by silica gel chromatography (EtOAc in pentane) afforded the starting materials **289** and **292** to **296** as an off-white solid.



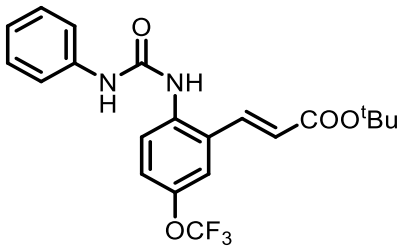
***tert*-Butyl (*E*)-3-(2-(3-phenylureido)phenyl)acrylate (226)** was prepared following **General Procedure A**, using 2-iodoaniline (1.70 g, 7.75 mmol, 1.0 eq) and phenyl isocyanate (1.85 g, 15.50 mmol, 2.0 eq) to afford the title compound as an off-white powder (2.32 g, 89%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.95 (s, 1H, NH), 8.46 (s, 1H, NH), 7.83 (d, *J* = 15.8 Hz, 1H, CH), 7.77 (dd, *J* = 8.3, 1.3 Hz, 1H, CH=CHAr-H), 7.73 (dd, *J* = 7.9, 1.6 Hz, 1H, CH=CHAr-H), 7.52 – 7.44 (m, 2H, Ar-H), 7.38 (ddd, *J* = 8.3, 7.3, 1.6 Hz, 1H, CH=CHAr-H), 7.33 – 7.25 (m, 2H, Ar-H), 7.11 (tdd, *J* = 7.3, 1.3, 0.6 Hz, 1H, CH=CHAr-H), 6.98 (tt, *J* = 7.3, 1.3 Hz, 1H, Ar-H), 6.47 (d, *J* = 15.8 Hz, 1H, CH), 1.49 (s, 9H, OC(CH_3)$_3$) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 165.6 (C(O)O), 152.7 (C(O)NH), 139.6 (ArC), 138.9 (CH), 137.7 (CH=CHArC), 130.4 (CH=CHArCH), 128.75 (ArCH), 127.0 (CH=CHArC), 126.1 (CH=CHArCH), 123.8 (CH=CHArCH), 123.7 (CH=CHArCH), 121.9 (ArCH), 120.7 (CH), 118.2 (ArCH), 80.0 (OC(CH_3)$_3$), 27.8 (OC(CH_3)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}N_2O_3{}^{23}Na$ ([M+Na]$^+$) 361.15226, found 361.15231; **FT-IR (thin film)** ν_{max} 3319, 2978, 2160, 2027, 1707, 1650, 1600, 1581, 1553, 1499, 1444, 1392, 1367, 1320, 1235, 1150, 981, 873, 752, 693 cm^{-1}; **m.p.**: 181-184 °C.



***tert*-Butyl (*E*)-3-(5-methyl-2-(3-phenylureido)phenyl)acrylate (265)** was prepared following **General Procedure A**, using 2-bromo-4-methylaniline (1.86 g, 10.00 mmol, 1.0 eq) and phenyl isocyanate (2.39 g, 20.00 mmol, 2.0 eq) to afford the title compound as a white powder (1.03 g, 76%).

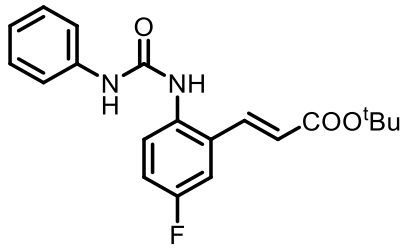
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 7.50 (d, *J* = 8.2 Hz, 1H, Ar-<u>H</u>), 7.45 – 7.30 (m, 3H, N<u>H</u> and Ar-<u>H</u>), 7.22 – 7.19 (m, 4H, Ar-<u>H</u>), 7.15 – 7.08 (m, 1H, Ar-<u>H</u>), 7.01 (qd, *J* = 4.6, 3.7 Hz, 1H, Ar-<u>H</u>), 6.31 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 2.28 (s, 3H, C<u>H</u>$_3$), 1.45 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.7 (<u>C</u>(O)OC(CH$_3$)$_3$), 154.4 (<u>C</u>(O)NH), 138.8 (<u>C</u>H), 138.3 (Ar<u>C</u>), 135.5 (Ar<u>C</u>), 134.1 (Ar<u>C</u>), 131.8 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>), 127.5 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 123.9 (Ar<u>C</u>H), 121.8 (<u>C</u>H), 121.1 (Ar<u>C</u>H), 81.0 (O<u>C</u>(CH$_3$)$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$), 21.0 (<u>C</u>H$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_3{}^{23}Na$ ([M+Na]$^+$) 375.1679, found 375.1680; **FT-IR (thin film)** ν_{max} 3323, 2977, 2160, 2032, 1707, 1648, 1598, 1553, 1498, 1443, 1392, 1367, 1317, 1240, 1151, 981 864, 752, 693 cm^{-1}; **m.p.**: 201-202 °C.



***tert*-Butyl (*E*)-3-(2-(3-phenylureido)-5-(trifluoromethoxy)phenyl)acrylate (266)** was prepared following **General Procedure A**, using 2-bromo-4-(trifluoromethoxy)aniline (0.72 g, 2.80 mmol, 1.0 eq) and phenyl isocyanate (0.58 g, 4.88 mmol, 2.00 eq) to afford the title compound as a white powder (0.84 g, 72%).

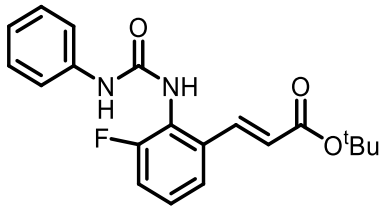
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 2H, C<u>H</u> and N<u>H</u>), 7.71 – 7.64 (m, 2H, N<u>H</u> and Ar-<u>H</u>), 7.32 – 7.28 (m, 1H, Ar-<u>H</u>), 7.20 – 7.12 (m, 4H, Ar-<u>H</u>), 7.10 (dq, *J* = 8.9, 1.1 Hz, 1H, Ar-<u>H</u>), 7.00 (ddt, *J* = 7.4, 6.4, 1.7 Hz, 1H, Ar-<u>H</u>), 6.26 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 1.43 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 (<u>C</u>(O)OC(CH$_3$)$_3$), 154.3 (<u>C</u>(O)NH), 146.1 (Ar<u>C</u>), 137.8 (Ar<u>C</u>), 137.3 (<u>C</u>H), 135.3 (Ar<u>C</u>), 129.5 (Ar<u>C</u>), 129.2 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 124.4 (Ar<u>C</u>H), 123.3 (<u>C</u>H), 123.2 (Ar<u>C</u>H), 121.8 (<u>C</u>F$_3$), 121.4 (Ar<u>C</u>H), 119.3 (Ar<u>C</u>H), 81.5 (O<u>C</u>(CH$_3$)$_3$), 28.2 (OC(<u>C</u>H$_3$)$_3$) ppm. (C-F coupling not observed); **^{19}F NMR (377 MHz, $CDCl_3$)** δ -58.07 (s) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{21}F_3N_2O_4{}^{23}Na$ ([M+Na]$^+$) 445.1346, found 445.1346; **FT-IR (thin film)** ν_{max} 3689, 3308, 2980,

2519, 2362, 2160, 2028, 1978, 1711, 1652, 1601, 1557, 1498, 1445, 1369, 1324, 1259, 1221, 1154, 977, 752, 693, 625 cm^{-1}; **m.p.**: 192-193 °C.



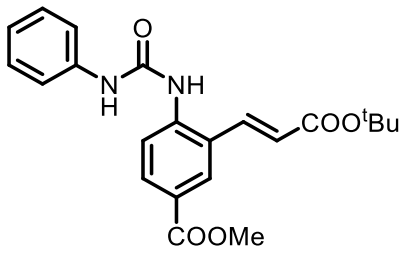
***tert*-Butyl (*E*)-3-(5-fluoro-2-(3-phenylureido)phenyl)acrylate (267)** was prepared following **General Procedure A**, using 2-bromo-4-fluoroaniline (0.67 g, 3.53 mmol, 1.0 eq) and phenyl isocyanate (0.72, 6.00 mmol, 2.0 eq) to afford the title compound as an off-white powder (1.00 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 15.8, 1.6 Hz, 1H, ArC<u>H</u>=CH), 7.64 (brs, 2H, N<u>H</u>), 7.46 (dd, *J* = 8.9, 5.3 Hz, 1H, Ar-<u>H</u>), 7.14 (qt, *J* = 8.5, 3.4 Hz, 5H, Ar-<u>H</u>), 7.03 – 6.95 (m, 1H, Ar-<u>H</u>), 6.91 (ddd, *J* = 8.9, 7.7, 2.9 Hz, 1H, Ar-<u>H</u>), 6.22 (d, *J* = 15.8 Hz, 1H, ArCH=C<u>H</u>), 1.44 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 (<u>C</u>(O)OC(CH$_3$)$_3$), 160.3 (d, *J* = 245.6 Hz, <u>C</u>F), 154.8 (<u>C</u>(O)NH), 138.0 (Ar<u>C</u>), 137.6 (d, *J* = 2.2 Hz, Ar<u>C</u>H=CH), 132.6 (d, *J* = 2.7 Hz, CH=CHAr<u>C</u>), 130.9 (d, *J* = 7.8 Hz, CH=CHAr<u>C</u>), 129.1 (Ar<u>C</u>H), 128.1 (d, *J* = 8.3 Hz, CH=CHAr<u>C</u>H), 124.1 (Ar<u>C</u>H), 122.9 (ArCH=<u>C</u>H), 121.2 (Ar<u>C</u>H), 117.7 (d, *J* = 22.7 Hz, CH=CHAr<u>C</u>H), 113.0 (d, *J* = 23.4 Hz, CH=CHAr<u>C</u>H), 81.2 (O<u>C</u>(CH$_3$)$_3$), 28.2 (OC(<u>C</u>H$_3$)$_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -116.17 (s) ppm. (H-F coupling not observed); **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}FN_2O_3{}^{23}Na$ ([M+Na]$^+$) 379.1428, found 379.1429; **FT-IR (thin film)** ν_{max} 3310, 2519, 2364, 2160, 2029, 1977, 1709, 1648, 1599, 1556, 1491, 1444, 1368, 1319, 1245, 1154, 980, 860, 752, 693 cm^{-1}; **m.p.**: 177-179 °C.



***tert*-Butyl (*E*)-3-(3-fluoro-2-(3-phenylureido)phenyl)acrylate (268)** was prepared following **General Procedure A**, using 2-bromo-6-fluoroaniline (0.40 g, 2.10 mmol, 1.0 eq) and phenyl isocyanate (0.50 g, 4.20 mmol, 2.0 eq) to afford the title compound as an off-white powder (0.40 g, 50%).

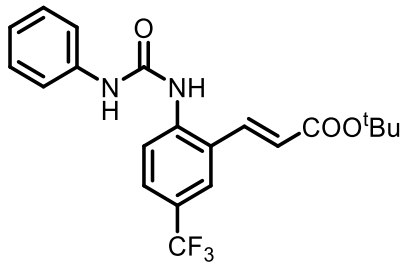
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 16.0 Hz, 1H, C<u>H</u>), 7.55 – 7.38 (m, 2H, Ar-<u>H</u>), 7.35 – 7.27 (m, 3H, Ar-<u>H</u>), 7.25 – 7.19 (m, 1H, Ar-<u>H</u>), 7.18 – 7.10 (m, 1H, Ar-<u>H</u>), 7.10 – 7.02 (m, 1H, Ar-<u>H</u>), 6.91 (s, 1H, N<u>H</u>), 6.54 (s, 1H, N<u>H</u>), 6.40 (d, *J* = 16.0 Hz, 1H, C<u>H</u>), 1.49 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -120.45 (t, *J* = 7.8 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}FN_2O_3{}^{23}Na$ ([M+Na]$^+$) 379.1428, found 379.1428; **FT-IR (thin film)** ν_{max} 3310, 2529, 2160, 2031, 1977, 1709, 1651, 1600, 1556, 1499, 1476, 1444, 1368, 1321, 1252, 1153, 984, 753, 693, 620 cm^{-1}; **m.p.**: 209-210 °C.



Methyl (*E*)-3-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-4-(3-phenylureido)benzoate (269) was prepared following **General Procedure A**, using methyl 4-amino-3-bromobenzoate (0.53 g, 2.29 mmol, 1.0 eq) and phenyl isocyanate (0.44 g, 3.70 mmol, 2.0 eq) to afford the title compound as an off-white powder (0.37 g, 41%).

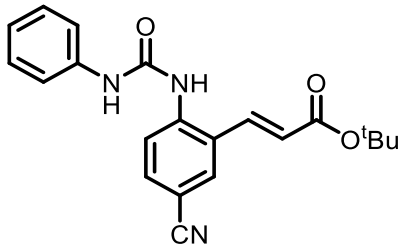
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.0 Hz, 1H, CH=CHAr-<u>H</u>), 8.03 (d, *J* = 8.6 Hz, 1H, CH=CHAr-<u>H</u>), 7.95 (dd, *J* = 8.6, 2.0 Hz, 1H, CH=CHAr-<u>H</u>), 7.82 (d, *J* = 15.7 Hz, 1H, C<u>H</u>), 7.67 (s, 1H, N<u>H</u>), 7.64 (s, 1H, N<u>H</u>), 7.28 – 7.25 (m, 4H, Ar-<u>H</u>), 7.08 (ddd, *J* = 5.6, 4.4, 2.7 Hz, 1H, Ar-<u>H</u>), 6.41 (d, *J*

= 15.7 Hz, 1H, C<u>H</u>), 3.91 (s, 3H, OC<u>H</u>$_3$), 1.48 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 166.6 (<u>C</u>(O)OCH$_3$), 166.4 (<u>C</u>(O)OC(CH$_3$)$_3$), 153.3 (<u>C</u>(O)NH), 141.0 (CH=CHAr<u>C</u>), 137.8 (<u>C</u>H), 137.7 (Ar<u>C</u>), 131.9 (CH=CHAr<u>C</u>H), 129.4 (Ar<u>C</u>H), 129.1 (CH=CHAr<u>C</u>H), 126.0 (CH=CHAr<u>C</u>), 125.8 (CH=CHAr<u>C</u>), 124.6 (Ar<u>C</u>H), 123.6 (<u>C</u>H), 122.9 (CH=CHAr<u>C</u>H), 121.5 (Ar<u>C</u>H), 81.5 (O<u>C</u>(CH$_3$)$_3$), 52.3 (O<u>C</u>H$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{24}N_2O_5{}^{23}Na$ ([M+Na]$^+$) 419.1577, found 419.1577; **FT-IR (thin film)** ν_{max} 3345, 2979, 2518, 2364, 2160, 2030, 1977, 1711, 1655, 1602, 1585, 1552, 1499, 1438, 1368, 1289, 1252, 1196, 1152, 982, 849, 758, 693, 626 cm^{-1}; **m.p.**: 187-189 °C



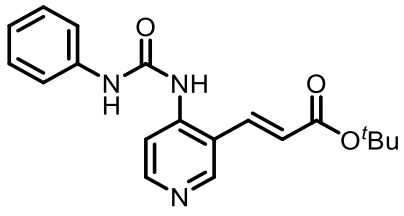
***tert*-Butyl (*E*)-3-(2-(3-phenylureido)-5-(trifluoromethyl)phenyl)acrylate (270)** was prepared following **General Procedure A**, using 2-iodo-4-(trifluoromethyl)aniline (0.70 g, 2.43 mmol, 1.0 eq) and phenyl isocyanate (0.58 g, 4.86 mmol, 2.00 eq) to afford the title compound as a white powder (0.49 g, 50%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 8.6 Hz, 1H, CH=CHAr-<u>H</u>), 7.79 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 7.72 (brs, 1H, N<u>H</u>), 7.70 (brs, 1H, N<u>H</u>), 7.68 (d, *J* = 1.6 Hz, 1H, CH=CHAr-<u>H</u>), 7.50 (dd, *J* = 8.6, 2.1 Hz, 1H, CH=CHAr-<u>H</u>), 7.25 – 7.19 (m, 4H, Ar-<u>H</u>), 7.10 – 7.01 (m, 1H, Ar-<u>H</u>), 6.34 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 1.46 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ δ 166.4 (<u>C</u>(O)OC(CH$_3$)$_3$), 153.5 (<u>C</u>(O)NH), 139.8 (Ar<u>C</u>), 137.6 (Ar<u>C</u>), 137.5 (<u>C</u>H), 129.4 (Ar<u>C</u>H), 127.4 (q, *J* = 3.3 Hz, Ar<u>C</u>H), 126.6 (Ar<u>C</u>), 125.8 (q, *J* = 103.8 Hz, Ar<u>C</u>), 125.7 (q, *J* = 198.2 Hz, Ar<u>C</u>F$_3$), 124.7 (Ar<u>C</u>H), 124.3 (q, *J* = 3.9 Hz, Ar<u>C</u>H), 123.9 (<u>C</u>H), 123.7 (Ar<u>C</u>H), 121.5 (Ar<u>C</u>H), 81.7 (O<u>C</u>(CH$_3$)$_3$), 28.2 (OC(<u>C</u>H$_3$)$_3$) ppm; **^{19}F NMR (377 MHz, CDCl$_3$)** δ -62.40 (s) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{20}F_3N_2O_3$ ([M - H]$^+$) 405.1432, found 405.1426; **FT-IR (thin film)** ν_{max} 3020, 2360, 2161, 2032, 1699, 1593, 1541, 1499, 1445, 1370, 1322, 1293, 1215, 1153, 1127, 1080, 980, 908, 844, 747, 668 cm^{-1}; **m.p.**: 203-205 °C



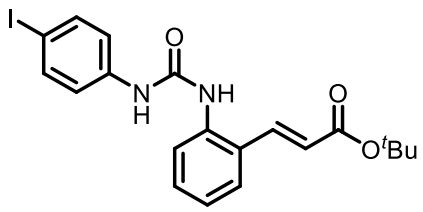
***tert*-Butyl (*E*)-3-(5-cyano-2-(3-phenylureido)phenyl)acrylate (271)** was prepared following **General Procedure A**, using 4-amino-3-iodobenzonitrile (0.81 g, 3.31 mmol, 1.0 eq) and phenyl isocyanate (0.79 g, 6.62 mmol, 2.0 eq) to afford the title compound as a white powder (0.48 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.95 (s, 1H, NH), 7.88 (s, 1H, NH), 7.74 (d, *J* = 15.7 Hz, 1H, CH), 7.70 (d, *J* = 1.9 Hz, 1H, Ar-H), 7.51 (dd, *J* = 8.6, 1.9 Hz, 1H, Ar-H), 7.37 – 7.28 (m, 1H, Ar-H), 7.25 – 7.20 (m, 3H, Ar-H), 7.13 – 7.05 (m, 1H, Ar-H), 6.31 (d, *J* = 15.7 Hz, 1H, CH), 1.49 (s, 9H, OC(CH_3)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 (C(O)OC(CH_3)$_3$), 152.9 (C(O)NH), 141.1 (ArC), 137.5 (ArC), 136.6 (CH), 133.9 (ArCH), 131.4 (ArCH), 129.5 (ArCH), 129.3 (ArC), 126.2 (ArCH), 125.0 (CH), 122.8 (ArCH), 121.4 (ArCH), 118.5 (ArCN), 107.2 (ArC), 82.0 (OC(CH_3)$_3$), 28.2 (OC(CH_3)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{21}N_3O_3{}^{23}Na$ ([M+Na]$^+$) 386.1475, found 386.1475; **FT-IR (thin film)** ν_{max} 3649, 3340, 2980, 2360, 2228, 2161, 2033, 1710, 1659, 1607, 1583, 1557, 1500, 1445, 1393, 1369, 1299, 1239, 1153, 979, 851, 754, 694 cm^{-1}; **m.p.**: 146-150 °C.



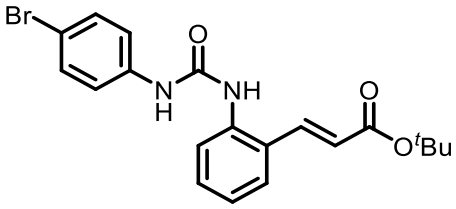
***tert*-Butyl (*E*)-3-(4-(3-phenylureido)pyridin-3-yl)acrylate (272)** was prepared following **General Procedure A**, using 3-bromopyridin-4-amine (0.76 g, 4.40 mmol, 1.0 eq) and phenyl isocyanate (1.05 g, 8.80 mmol, 2.0 eq). Purification by silica gel chromatography (50% EtOAc in CH_2Cl_2) afforded the title compound as a white powder (0.29 g, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar(N)-H), 8.43 (d, *J* = 5.8 Hz, 1H, Ar(N)-H), 8.17 (d, *J* = 5.8 Hz, 1H, Ar(N)-H), 7.84 (s, 1H, NH), 7.78 (s, 1H, NH), 7.66 (d, *J* = 15.8 Hz, 1H, CH), 7.35 – 7.27 (m, 4H, Ar-H), 7.16 – 7.06 (m, 1H, Ar-H), 6.34 (d, *J* = 15.8 Hz, 1H, CH), 1.48 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 ($C(O)OC(CH_3)_3$), 152.4 (C(O)NH), 151.4 (ArCH), 148.9 (ArCH), 144.4 (ArC), 137.6 (ArC), 135.9 (CH), 129.5 (ArCH), 124.9 (ArCH), 124.4 (CH), 121.2 (ArCH), 120.2 (ArC), 114.6 (ArCH), 81.9 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{22}N_3O_3$ $([M+H]^+)$ 340.1656, found 340.1655; **FT-IR (thin film)** ν_{max} 3323, 2979, 2360, 2160, 2030, 1707, 1636, 1601, 1579, 1556, 1516, 1498, 1445, 1419, 1393, 1368, 1314, 1288, 1247, 1199, 1149, 1067, 1025, 979, 871, 841, 752, 692, 646 cm^{-1}; **m.p.**: 167-170 °C.



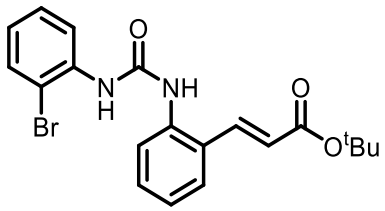
***tert*-Butyl (*E*)-3-(2-(3-(4-iodophenyl)ureido)phenyl)acrylate (281)** was prepared following **General Procedure A**, using 2-iodoaniline (0.42 g, 1.90 mmol, 1.0 eq) and 1-iodo-4-isocyanatobenzene (0.93 g, 3.80 mmol, 2.0 eq) to afford the title compound as a white powder (0.64 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.6 Hz, 1H, CH), 7.64 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.58 (brs, 1H, NH), 7.55 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 7.47 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.46 (brs, 1H, NH), 7.33 (td, *J* = 7.3, 1.5 Hz, 1H, Ar-H), 7.15 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.96 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.33 (d, *J* = 15.6 Hz, 1H, CH), 1.45 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.8 ($C(O)OC(CH_3)_3$), 153.9 (C(O)NH), 138.7 (CH), 138.06 (ArC), 138.03 (ArCH), 136.5 (ArC), 131.0 (ArCH), 128.5 (ArC), 127.2 (ArCH), 125.8 (ArCH), 125.6 (ArCH), 122.5 (ArCH), 122.1 (CH), 87.1 (ArC), 81.3 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}{}^{127}IN_2O_3{}^{23}Na$ $([M+Na]^+)$ 487.0489, found 487.0490; **FT-IR (thin film)** ν_{max} 3853, 3734, 3649, 3295, 2360, 2341, 2161, 2031, 1977, 1705, 1649, 1584, 1542, 1486, 1457, 1392, 1367, 1321, 1235, 1151, 982, 770, 669 cm^{-1}; **m.p.**: 216-217 °C.



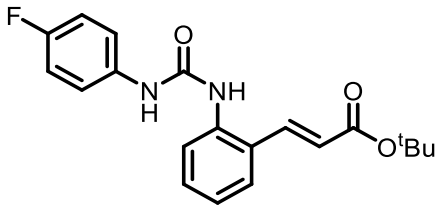
***tert*-Butyl (*E*)-3-(2-(3-(4-bromophenyl)ureido)phenyl)acrylate (282)** was prepared following **General Procedure A**, using 2-iodoaniline (0.47 g, 2.15 mmol, 1.0 eq) and 1-bromo-4-isocyanatobenzene (0.85 g, 4.30 mmol, 2.0 eq) to afford the title compound as a white powder (0.65 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 7.69 (brs, 1H, N<u>H</u>), 7.63 – 7.57 (m, 2H, N<u>H</u> and Ar-<u>H</u>), 7.53 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-<u>H</u>), 7.32 – 7.27 (m, 1H, Ar-<u>H</u>), 7.27 – 7.23 (m, 2H, Ar-<u>H</u>), 7.12 (t, *J* = 7.6 Hz, 1H, Ar-<u>H</u>), 7.07 – 6.99 (m, 2H, Ar-<u>H</u>), 6.31 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 1.45 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.8 (<u>C</u>(O)OC(CH$_3$)$_3$), 154.1 (<u>C</u>(O)NH), 138.7 (<u>C</u>H), 137.3 (Ar<u>C</u>), 136.4 (Ar<u>C</u>), 132.0 (Ar<u>C</u>H), 131.0 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>), 127.2 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 122.3 (Ar<u>C</u>H), 122.0 (<u>C</u>H), 116.6 (Ar<u>C</u>), 81.2 (O<u>C</u>(CH$_3$)$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}{}^{80}BrN_2O_3{}^{23}Na$ ([M+Na]$^+$) 439.0628, found 439.0628; **FT-IR (thin film)** ν_{max} 3323, 2361, 2161, 2031, 1706, 1650, 1591, 1544, 1488, 1456, 1395, 1367, 1321, 1235, 1151, 1073, 1009, 982, 871, 757, 668 cm^{-1}; **m.p.**: 199-200 °C.



***tert*-Butyl (*E*)-3-(2-(3-(2-bromophenyl)ureido)phenyl)acrylate (283)** was prepared following **General Procedure A**, using 2-iodoaniline (0.52 g, 2.38 mmol, 1.0 eq) and 1-bromo-2-isocyanatobenzene (0.94 g, 4.76 mmol, 2.0 eq). Purification by silica gel chromatography (10% EtOAc in pentane) afforded the title compound as an off-white powder (0.86 g, 87%).

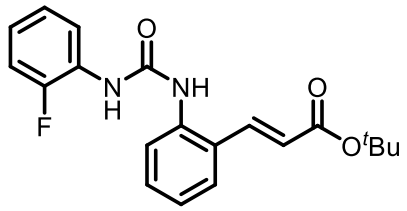
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H, NH), 8.04 (dd, *J* = 8.2, 1.6 Hz, 1H, Ar-H), 7.95 (d, *J* = 15.8 Hz, 1H, CH), 7.66 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.55 – 7.48 (m, 2H, Ar-H and NH), 7.35 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 7.30 (td, *J* = 7.7, 1.5 Hz, 1H, Ar-H), 7.13 (dddd, *J* = 9.5, 6.4, 3.8, 1.8 Hz, 2H, Ar-H), 6.78 (ddd, *J* = 7.7, 1.6 Hz, 1H, Ar-H), 6.30 (d, *J* = 15.8 Hz, 1H, CH), 1.44 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.7 ($C(O)OC(CH_3)_3$), 153.5 (C(O)NH), 138.9 (CH), 136.4 (ArC), 136.3 (ArC), 132.4 (ArCH), 131.0 (ArCH), 129.3 (ArC), 128.3 (ArCH), 127.4 (ArCH), 126.2 (ArCH), 126.1 (ArCH), 124.5 (ArCH), 122.45 (CH), 122.40 (ArCH), 114.1 (ArC), 81.2 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}BrN_2O_3{}^{23}Na$ ($[M+Na]^+$) 439.0628, found 439.0628; **FT-IR (thin film)** ν_{max} 3297, 2977, 2161 2024, 1707, 1650, 1584, 1551, 1477, 1455, 1437, 1391, 1367, 1322, 1297, 1259, 1233, 1151, 1027, 980, 875, 752, 668 cm^{-1}; **m.p.**: 87-92 °C.



***tert*-Butyl (*E*)-3-(2-(3-(4-fluorophenyl)ureido)phenyl)acrylate (284)** was prepared following **General Procedure A**, using 2-iodoaniline (0.33 g, 1.50 mmol, 1.0 eq) and 1-fluoro-4-isocyanatobenzene (0.42 g, 3.00 mmol, 2.0 eq) to afford the title compound as a white powder (0.33 g, 61%).

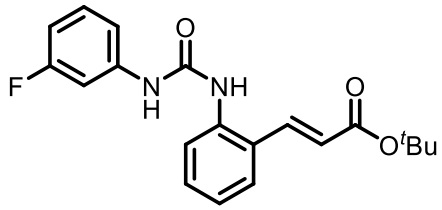
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 15.8 Hz, 1H, CH), 7.65 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.61 – 7.47 (brs, 2H, NH), 7.53 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.33 – 7.27 (m, 1H, Ar-H), 7.21 – 7.07 (m, 3H, Ar-H), 6.93 – 6.82 (m, 2H, Ar-H), 6.31 (d, *J* = 15.8 Hz, 1H, CH), 1.45 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.7 ($C(O)OC(CH_3)_3$), 159.6 (d, *J* = 243.4 Hz, ArCF), 154.3 (C(O)NH), 138.6 (CH), 138.0 (ArC), 134.0 (d, *J* = 2.7 Hz, ArC), 131.0 (ArCH), 128.3 (ArC), 127.2 (ArCH), 125.6 (ArCH), 125.5 (ArCH), 123.2 (d, *J* = 8.0 Hz, ArCH), 122.1 (CH), 115.8 (d, *J* = 22.5 Hz, ArCH), 81.2 ($OC(CH_3)_3$), 28.2 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -118.58 (s) ppm. (H-F coupling not observed); **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}FN_2O_3{}^{23}Na$ ($[M+Na]^+$) 379.1428, found 379.1430;

FT-IR (thin film) ν_{max} 3309, 2980, 2551, 2160, 2032, 1977, 1707, 1648, 1558, 1509, 1455, 1408, 1368, 1322, 1213, 1152, 982, 835, 760, 619 cm^{-1}; **m.p.**: 116-118 °C.



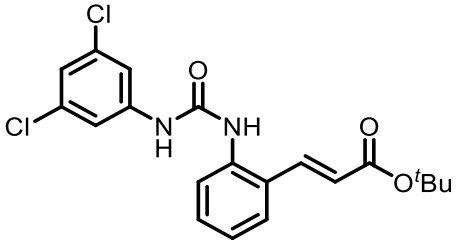
***tert*-Butyl (*E*)-3-(2-(3-(2-fluorophenyl)ureido)phenyl)acrylate (285)** was prepared following **General Procedure A**, using 2-iodoaniline (0.50 g, 2.25 mmol, 1.0 eq) and 1-fluoro-2-isocyanatobenzene (0.62 g, 4.50 mmol, 2.0 eq) to afford the title compound as an off-white powder (0.65 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (td, *J* = 8.1, 1.5 Hz, 1H, Ar-H), 7.94 (d, *J* = 15.8 Hz, 1H, CH), 7.79 (s, 1H, NH), 7.75 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.52 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar-H), 7.48 (d, *J* = 2.9 Hz, 1H, NH), 7.34 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H, Ar-H), 7.13 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.05 – 6.99 (m, 1H, Ar-H), 6.99 – 6.93 (m, 1H, Ar-H), 6.93 – 6.87 (m, 1H, Ar-H), 6.33 (d, *J* = 15.8 Hz, 1H, CH), 1.45 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.0 ($C(O)OC(CH_3)_3$), 153.5 (C(O)NH), 153.1 (d, *J* = 244.1 Hz, ArCF), 139.1 (CH), 136.6 (ArC), 130.9 (ArCH), 128.3 (ArC), 127.3 (ArCH), 126.9 (d, *J* = 10.3 Hz, ArC), 125.4 (ArCH), 125.2 (ArCH), 124.5 (d, *J* = 3.6 Hz, ArCH), 123.6 (d, *J* = 7.4 Hz, ArCH), 122.2 (CH), 122.1 (ArCH), 114.9 (d, *J* = 19.4 Hz, ArCH), 81.3 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -130.44 (s) ppm. (H-F coupling not observed); **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}FN_2O_3{}^{23}Na$ ($[M+Na]^+$) 379.1428, found 379.1428; **FT-IR (thin film)** ν_{max} 3326, 2979, 2160, 2032, 1707, 1655, 1620, 1583, 1546, 1488, 1456, 1392, 1368, 1322, 1250, 1186, 1150 1098, 1034, 982, 872, 753, 668 cm^{-1}; **m.p.**: 163-164 °C.



***tert*-Butyl (*E*)-3-(2-(3-(3-fluorophenyl)ureido)phenyl)acrylate (286)** was prepared following **General Procedure A**, using 2-iodoaniline (0.47 g, 2.12 mmol, 1.0 eq) and 1-fluoro-3-isocyanatobenzene (0.58 g, 4.24 mmol, 2.0 eq) to afford the title compound as an off-white powder (0.51 g, 67%).

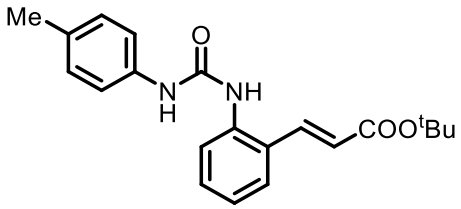
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 7.74 (s, 1H, N<u>H</u>), 7.71 (s, 1H, N<u>H</u>), 7.61 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-<u>H</u>), 7.51 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar-<u>H</u>), 7.32 – 7.27 (m, 1H, Ar-<u>H</u>), 7.14 – 7.07 (m, 2H, Ar-<u>H</u>), 7.06 – 7.00 (m, 1H, Ar-<u>H</u>), 6.87 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H, Ar-<u>H</u>), 6.65 (tdd, *J* = 8.3, 2.6, 0.9 Hz, 1H, Ar-<u>H</u>), 6.31 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 1.44 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.9 (<u>C</u>(O)OC(CH$_3$)$_3$), 163.1 (d, *J* = 244.8 Hz, Ar<u>C</u>F), 154.1 (<u>C</u>(O)NH), 139.9 (d, *J* = 10.9 Hz, Ar<u>C</u>), 138.7 (<u>C</u>H), 136.4 (Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 130.1 (d, *J* = 9.5 Hz, Ar<u>C</u>H), 128.5 (Ar<u>C</u>), 127.1 (Ar<u>C</u>H), 125.73 (Ar<u>C</u>H), 125.71 (Ar<u>C</u>H), 121.9 (<u>C</u>H), 115.8 (d, *J* = 2.8 Hz, Ar<u>C</u>H), 110.4 (d, *J* = 21.2 Hz, Ar<u>C</u>H), 107.8 (d, *J* = 25.5 Hz, Ar<u>C</u>H), 81.2 (O<u>C</u>(CH$_3$)$_3$), 28.2 (OC(<u>C</u>H$_3$)$_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -111.80 (dt, *J* = 11.0, 7.6 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}FN_2O_3{}^{23}Na$ ([M+Na]$^+$) 379.1428, found 379.1429; **FT-IR (thin film)** ν_{max} 3734, 3649, 2978, 2501, 2359, 2160, 2032, 1977, 1707, 1653, 1609, 1556, 1492, 1456, 1393, 1368, 1322, 1282, 1251, 1220, 1149, 976, 863, 771, 682 cm^{-1}; **m.p.**: 167-168 °C.



***tert*-Butyl (*E*)-3-(2-(3-(3,5-dichlorophenyl)ureido)phenyl)acrylate (287)** was prepared following **General Procedure A**, using 2-iodoaniline (0.33 g, 1.50 mmol, 1.0 eq) and 1,3-dichloro-5-

isocyanatobenzene (0.57 g, 3.00 mmol, 2.0 eq) to afford the title compound as a white powder (0.59 g, 96%).

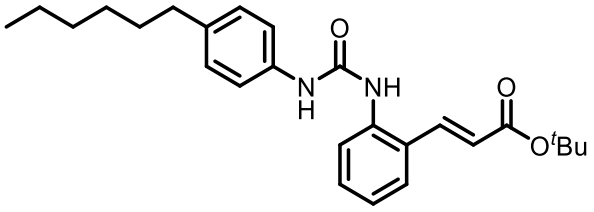
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.28 (s, 1H, NH), 8.65 (s, 1H, NH), 7.78 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.77 – 7.73 (m, 1H, CH), 7.64 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.54 (d, *J* = 1.9 Hz, 2H, Ar-H), 7.44 – 7.35 (m, 1H, Ar-H), 7.23 – 7.13 (m, 2H, Ar-H), 6.48 (d, *J* = 15.8 Hz, 1H, CH), 1.48 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 165.6 ($C(O)OC(CH_3)_3$), 152.7 (C(O)NH), 142.2 (ArC), 138.9 (CH), 137.1 (ArC), 134.1 (ArC), 130.5 (ArCH), 127.2 (ArCH or ArC), 127.0 (ArCH or ArC), 124.7 (ArCH), 124.6 (ArCH), 121.0 (ArCH), 120.8 (CH), 116.4 (ArCH), 80.1 ($OC(CH_3)_3$), 27.8 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{20}Cl_2N_2O_3{}^{23}Na$ ($[M+Na]^+$) 429.0743, found 429.0744; **FT-IR (thin film)** ν_{max} 3323, 2979, 2360, 2161, 2031, 1706, 1653, 1584, 1544, 1487, 1448, 1410, 1368, 1322, 1249, 1213, 1151, 1113, 981, 845, 758, 670 cm^{-1}; **m.p.**: >250 °C.



***tert*-Butyl (*E*)-3-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (288)** was prepared following **General Procedure A**, using 2-iodoaniline (0.33 g, 1.50 mmol, 1.0 eq) and *p*-tolyl isocyanate (0.40 g, 3.00 mmol, 2.0 eq) to afford the title compound as a white powder (0.48 g, 91%).

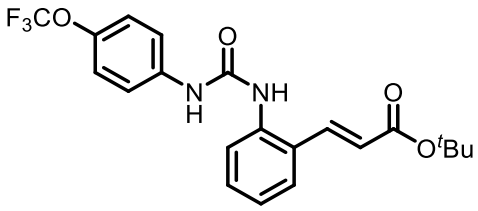
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 15.8 Hz, 1H, CH), 7.72 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.54 (dd, *J* = 7.9, 1.6 Hz, 1H, Ar-H), 7.34 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H, Ar-H), 7.31 – 7.16 (m, 2H, NH), 7.15 – 7.10 (m, 3H, Ar-H), 7.05 (d, *J* = 8.2 Hz, 2H, Ar-H), 6.32 (d, *J* = 15.8 Hz, 1H, CH), 2.27 (s, 3H, CH_3), 1.47 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.5 ($C(O)OC(CH_3)_3$), 154.2 (C(O)NH), 138.7 (CH), 136.7 (ArC), 135.3 (ArC), 134.2 (ArC), 130.9 (ArCH), 129.9 (ArCH), 128.2 (ArC), 127.3 (ArCH), 125.39 (ArCH), 125.37 (ArCH), 122.3 (CH), 121.9 (ArCH), 81.1 ($OC(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 21.0 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 375.1679, found

375.1680; **FT-IR (thin film)** ν_{max} 3313, 2979, 2160, 2026, 1707, 1647, 1603, 1581, 1548, 1515, 1481, 1455, 1392, 1367, 1319, 1295, 1236, 1150, 981, 873, 816, 759 cm^{-1}; **m.p.**: 219 °C.



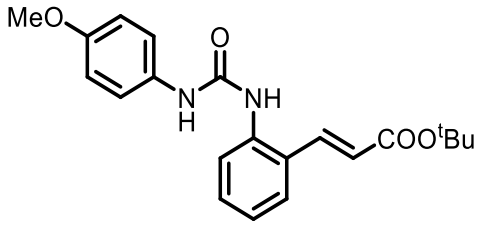
***tert*-Butyl (*E*)-3-(2-(3-(4-hexylphenyl)ureido)phenyl)acrylate (289)** was prepared following **General Procedure B**, using 2-iodoaniline (0.40 g, 1.84 mmol, 1.0 eq) and 4-hexylaniline (0.66 g, 3.68 mmol, 2.0 eq). Purification by silica gel chromatography (20% Et_2O in pentane) afforded the title compound as a white powder (0.42 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 7.72 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-<u>H</u>), 7.53 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar-<u>H</u>), 7.39 (brs, 1H, N<u>H</u>), 7.32 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H, Ar-<u>H</u>), 7.29 (brs, 1H, N<u>H</u>), 7.19 – 7.08 (m, 3H, Ar-<u>H</u>), 7.08 – 7.00 (m, 2H, Ar-<u>H</u>), 6.32 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 2.56 – 2.47 (m, 2H, ArC<u>H</u>$_2$), 1.64 – 1.47 (m, 2H, ArCH$_2$C<u>H</u>$_2$), 1.46 (s, 9H, OC(C<u>H</u>$_3$)$_3$), 1.36 – 1.22 (m, 6H, ArCH$_2$CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.92 – 0.82 (m, 3H, C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.6 (<u>C</u>(O)OC(CH$_3$)$_3$), 154.2 (<u>C</u>(O)NH), 139.1 (Ar<u>C</u>), 138.7 (<u>C</u>H), 136.9 (Ar<u>C</u>), 135.6 (Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>), 127.2 (Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 122.1 (<u>C</u>H), 121.7 (Ar<u>C</u>H), 81.0 (O<u>C</u>(CH$_3$)$_3$), 35.5 (Ar<u>C</u>H$_2$), 31.9 (ArCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 31.6 (ArCH$_2$<u>C</u>H$_2$), 29.1 (ArCH$_2$CH$_2$<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$), 22.8 (ArCH$_2$CH$_2$CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 14.2 (<u>C</u>H$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{26}H_{34}N_2O_3{}^{23}Na$ ([M+Na]$^+$) 445.2462, found 445.2462; **FT-IR (thin film)** ν_{max} 3734, 3324, 2927, 2360, 2161, 2031, 1707, 1648, 1605, 1550, 1456, 1367, 1320, 1237, 1151, 982, 772 cm^{-1}; **m.p.**: 180-183 °C.



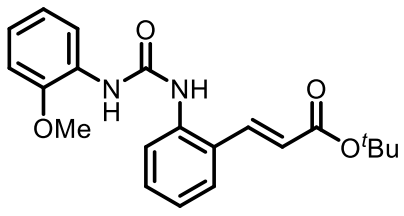
***tert*-Butyl (*E*)-3-(2-(3-(4-(trifluoromethoxy)phenyl)ureido)phenyl)acrylate (290)** was prepared following **General Procedure A**, using 2-iodoaniline (0.48 g, 2.20 mmol, 1.0 eq) and 1-isocyanato-4-(trifluoromethoxy)benzene (0.89 g, 4.40 mmol, 2.0 eq) to afford the title compound as a white powder (0.58 g, 63%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.15 (s, 1H, NH), 8.51 (s, 1H, NH), 7.80 (d, *J* = 15.7 Hz, 1H, CH), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 7.72 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.61 – 7.52 (m, 2H, Ar-H), 7.38 (ddd, *J* = 8.4, 7.3, 1.6 Hz, 1H, Ar-H), 7.33 – 7.25 (m, 2H, Ar-H), 7.13 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-H), 6.47 (d, *J* = 15.7 Hz, 1H, CH), 1.48 (s, 9H, OC(CH_3)$_3$) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 165.6 (C(O)OC(CH_3)$_3$), 152.8 (C(O)NH), 142.6 (ArCO), 139.0 (ArC), 138.9 (CH), 137.5 (ArC), 130.5 (ArCH), 127.0 (ArCH), 126.5 (ArC), 124.13 (ArCH), 123.95 (ArCH), 121.7 (ArCH), 121.5 (CF_3), 120.8 (CH), 119.4 (ArCH), 80.0 (OC(CH_3)$_3$), 27.8 (OC(CH_3)$_3$) ppm. (C-F coupling not observed); **^{19}F NMR (377 MHz, $(CD_3)_2SO$)** δ -56.89 (s)(assigned to self-cyclised product in $(CD_3)SO$ during nmr measurement), -57.11 (s) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{21}F_3N_2O_4{}^{23}Na$ ($[M+Na]^+$) 445.1346, found 445.1347; **FT-IR (thin film)** ν_{max} 3325, 2980, 2360, 2161, 2032, 1708, 1652, 1610, 1557, 1509, 1457, 1411, 1369, 1323, 1263, 1238, 1202, 1154, 982, 849, 761, 670 cm^{-1}; **m.p.**: 180 °C.



***tert*-Butyl (*E*)-3-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate (291)** was prepared following **General Procedure A**, using 2-iodoaniline (0.32 g, 1.43 mmol, 1.0 eq) and 4-Methoxyphenyl isocyanate (0.34 g, 2.86 mmol, 2.0 eq) to afford the title compound as a white powder (0.43 g, 82%).

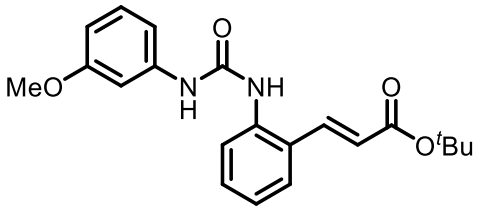
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 7.70 (dd, *J* = 8.3, 1.2 Hz, 1H, CH=CHAr-<u>H</u>), 7.52 (dd, *J* = 7.9, 1.6 Hz, 1H, CH=CHAr-<u>H</u>), 7.42 (brs, 1H, N<u>H</u>), 7.35 (brs, 1H, N<u>H</u>), 7.30 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H, CH=CHAr-<u>H</u>), 7.14 – 7.06 (m, 3H, CH=CHAr-<u>H</u> and Ar-<u>H</u>), 6.85 – 6.67 (m, 2H, Ar-<u>H</u>), 6.30 (d, *J* = 15.8 Hz, 1H, C<u>H</u>), 3.74 (s, 3H, OC<u>H</u>$_3$), 1.45 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.6 (<u>C</u>(O)OC(CH$_3$)$_3$), 156.9 (<u>C</u>OCH$_3$ or <u>C</u>(O)NH), 154.7 (<u>C</u>OCH$_3$ or <u>C</u>(O)NH), 138.7 (<u>C</u>H), 136.9 (CH=CHAr<u>C</u> or Ar<u>C</u>), 130.9 (CH=CHAr<u>C</u>H), 130.8 (CH=CHAr<u>C</u> or Ar<u>C</u>), 128.0 (CH=CHAr<u>C</u> or Ar<u>C</u>), 127.2 (CH=CHAr<u>C</u>H), 125.3 (CH=CHAr<u>C</u>H), 125.2 (CH=CHAr<u>C</u>H), 124.2 (Ar<u>C</u>H), 122.0 (<u>C</u>H), 114.5 (Ar<u>C</u>H), 81.0 (O<u>C</u>(CH$_3$)$_3$), 55.6 (O<u>C</u>H$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_4{}^{23}Na$ ([M+Na]$^+$) 391.1628, found 391.1629; **FT-IR (thin film)** ν_{max} 3628, 3309, 2520, 2364, 2160, 2028, 1978, 1707, 1646, 1555, 1511, 1367, 1322, 1233, 1151, 982, 832, 760, 626 cm^{-1}; **m.p.**: 208-210 °C.



***tert*-Butyl (*E*)-3-(2-(3-(2-methoxyphenyl)ureido)phenyl)acrylate (292)** was prepared following **General Procedure B**, using 2-iodoaniline (0.29 g, 1.31 mmol, 1.0 eq) and 2-methoxyaniline (0.33 g,

2.62 mmol, 2.0 eq). Purification by silica gel chromatography (15% EtOAc in pentane) afforded the title compound as an off-white powder (0.44 g, 90%).

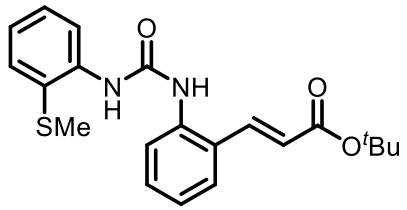
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.9 Hz, 1H, Ar-H), 7.93 (d, *J* = 15.8 Hz, 1H, CH), 7.77 (dd, *J* = 8.3, 1.2 Hz, 1H, Ar-H), 7.54 (dd, *J* = 7.9, 1.6 Hz, 1H, Ar-H), 7.50 (brs, 1H, NH), 7.48 (brs, 1H, NH), 7.36 (ddd, *J* = 8.3, 7.3, 1.6 Hz, 1H, Ar-H), 7.19 – 7.10 (m, 1H, Ar-H), 6.95 (td, *J* = 7.6, 1.9 Hz, 1H, Ar-H), 6.90 (td, *J* = 7.6, 1.7 Hz, 1H, Ar-H), 6.79 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar-H), 6.34 (d, *J* = 15.8 Hz, 1H, CH), 3.73 (s, 3H, OCH_3), 1.46 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.7 ($C(O)OC(CH_3)_3$), 153.4 (C(O)NH), 148.5 (ArC), 139.1 (CH), 137.0 (ArC), 130.8 (ArCH), 128.25 (ArC), 128.19 (ArC), 127.3 (ArCH), 125.3 (ArCH), 125.2 (ArCH), 123.0 (ArCH), 122.2 (CH), 121.3 (ArCH), 119.9 (ArCH), 110.2 (ArCH), 81.1 ($OC(CH_3)_3$), 55.7 (OCH_3), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_4{}^{23}Na$ ($[M+Na]^+$) 391.1628, found 391.1629; **FT-IR (thin film)** ν_{max} 3649, 3333, 2979, 2916, 2850, 2360, 2341, 2161, 2031, 1707, 1654, 1635, 1602, 1582, 1542, 1489, 1459, 1435, 1367, 1323, 1291, 1248, 1217, 1151, 1122, 1029, 982, 871, 749, 669 cm^{-1}; **m.p.**: 191-192 °C.



***tert*-Butyl (*E*)-3-(2-(3-(3-methoxyphenyl)ureido)phenyl)acrylate (293)** was prepared following **General Procedure B**, using 2-iodoaniline (0.29 g, 1.30 mmol, 1.0 eq) and 3-methoxyaniline (0.32 g, 2.60 mmol, 2.0 eq). Purification by silica gel chromatography (20% EtOAc in pentane) afforded the title compound as an off-white powder (0.29 g, 60%).

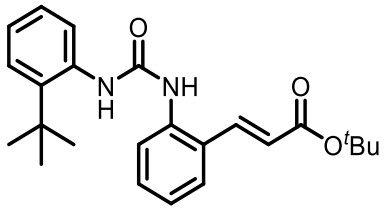
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 15.8 Hz, 1H, CH), 7.69 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-H), 7.57 – 7.50 (m, 2H, Ar-H and NH), 7.42 (brs, 1H, NH), 7.33 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H, Ar-H), 7.15 – 7.10 (m, 1H, Ar-H), 7.10 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.01 (t, *J* = 2.2 Hz, 1H, Ar-H), 6.69 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H, Ar-H), 6.57 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H, Ar-H), 6.33 (d, *J* = 15.8 Hz, 1H, CH), 3.72

(s, 3H, OC<u>H</u>$_3$), 1.45 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 166.7 (<u>C</u>(O)OC(CH$_3$)$_3$), 160.4 (Ar<u>C</u>O), 154.0 (<u>C</u>(O)NH), 139.5 (Ar<u>C</u>), 138.7 (<u>C</u>H), 136.7 (Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>), 127.2 (Ar<u>C</u>H), 125.54 (Ar<u>C</u>H), 125.50 (Ar<u>C</u>H), 122.2 (<u>C</u>H), 113.2 (Ar<u>C</u>H), 110.1 (Ar<u>C</u>H), 106.6 (Ar<u>C</u>H), 81.1 (O<u>C</u>(CH$_3$)$_3$), 55.4 (O<u>C</u>H$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_4{}^{23}Na$ ([M+Na]$^+$) 391.1628, found 391.1629; **FT-IR (thin film)** ν_{max} 3317, 2978, 2553, 2160, 2031, 1706, 1650, 1603, 1582, 1553, 1494, 1455, 1429, 1392, 1367, 1322, 1289, 1252, 1221, 1155, 1042, 981, 858, 760, 689 cm^{-1}; **m.p.**: 177-179 °C.



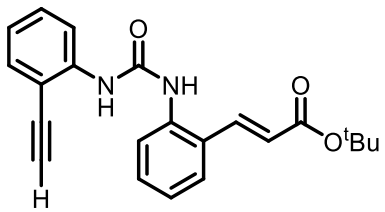
***tert*-Butyl (*E*)-3-(2-(3-(2-(methylthio)phenyl)ureido)phenyl)acrylate (294)** was prepared following **General Procedure B**, using 2-iodoaniline (0.43 g, 1.93 mmol, 1.0 eq) and 2-(methylthio)aniline (0.54 g, 3.86 mmol, 2.0 eq). Purification by silica gel chromatography (20% EtOAc in pentane) afforded the title compound as an off-white powder (0.51 g, 69%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.07 (dd, *J* = 8.2, 1.4 Hz, 1H, Ar-<u>H</u>), 7.92 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 7.73 (s, 1H, N<u>H</u>), 7.70 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-<u>H</u>), 7.59 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar-<u>H</u>), 7.39 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H, Ar-<u>H</u>), 7.35 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar-<u>H</u>), 7.29 (s, 1H, N<u>H</u>), 7.22 (ddt, *J* = 9.7, 7.5, 1.6 Hz, 2H, Ar-<u>H</u>), 6.99 (td, *J* = 7.6, 1.4 Hz, 1H, Ar-<u>H</u>), 6.35 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 2.21 (s, 3H, SC<u>H</u>$_3$), 1.47 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 166.4 (<u>C</u>(O)OC(CH$_3$)$_3$), 153.7 (<u>C</u>(O)NH), 138.7 (<u>C</u>H), 138.4 (Ar<u>C</u>), 136.3 (Ar<u>C</u>), 132.2 (Ar<u>C</u>H), 130.9 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.8 (Ar<u>C</u>), 126.4 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 124.1 (Ar<u>C</u>H), 122.6 (<u>C</u>H), 121.4 (Ar<u>C</u>H), 81.0 (O<u>C</u>(CH$_3$)$_3$), 28.3 (OC(<u>C</u>H$_3$)$_3$), 18.4 (S<u>C</u>H$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}{}^{32}SN_2O_3{}^{23}Na$ ([M+Na]$^+$) 407.1400, found 407.1400; **FT-IR (thin film)** ν_{max} 3298, 2978, 2360, 2160, 2031, 1707, 1652, 1578, 1534, 1479, 1455, 1437, 1392, 1367, 1322, 1295, 1259, 1228, 1150, 1039, 981, 871, 755, 668 cm^{-1}; **m.p.**: 171-172 °C.



***tert*-Butyl (*E*)-3-(2-(3-(2-(tert-butyl)phenyl)ureido)phenyl)acrylate (295)** was prepared following **General Procedure B**, using 2-iodoaniline (0.27 g, 1.22 mmol, 1.0 eq) and 2-(*tert*-butyl)aniline (0.37 g, 2.44 mmol, 2.0 eq). Purification by silica gel chromatography (40% Et_2O in pentane) afforded the title compound as an off-white powder (0.37 g, 77%).

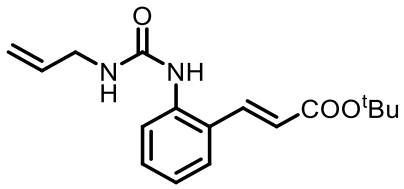
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 7.67 (d, *J* = 15.9 Hz, 1H, CH), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar-H), 7.43 (td, *J* = 7.8, 1.8 Hz, 2H, Ar-H), 7.32 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H, Ar-H), 7.30 – 7.20 (m, 2H, Ar-H), 7.20 – 7.09 (m, 1H, Ar-H), 6.67 (s, 1H, NH), 6.56 (s, 1H, NH), 6.22 (d, *J* = 15.9 Hz, 1H, CH), 1.49 (s, 9H, OC(CH_3)$_3$), 1.37 (s, 9H, ArC(CH_3)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.9 (C(O)OC(CH_3)$_3$), 154.8 (C(O)NH), 146.4 (ArC), 138.5 (CH), 136.4 (ArC), 135.2 (ArC), 130.7 (ArCH), 130.3 (ArCH), 128.7 (ArC), 127.64 (ArCH), 127.62 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 125.5 (ArCH), 125.4 (ArCH), 122.9 (CH), 80.8 (OC(CH_3)$_3$), 35.2 (ArC(CH_3)$_3$), 30.8 (ArC(CH_3)$_3$), 28.3 (OC(CH_3)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{30}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 417.2149, found 417.2149; **FT-IR (thin film)** ν_{max} 3271, 2966, 2555, 2160, 2025, 1977, 1708, 1631, 1599, 1550, 1485, 1366, 1320, 1288, 1236, 1151, 983, 866, 755 cm^{-1}; **m.p.**: 182-184 °C.



***tert*-Butyl (*E*)-3-(2-(3-(2-ethynylphenyl)ureido)phenyl)acrylate (296)** was prepared following **General Procedure B**, using 2-iodoaniline (0.32 g, 1.46 mmol, 1.0 eq) and 2-ethynyl aniline (0.30 g, 2.54

mmol, 2.0 eq). Purification by silica gel chromatography (25% Et_2O in pentane) afforded the title compound as an off-white powder (0.42 g, 79%).

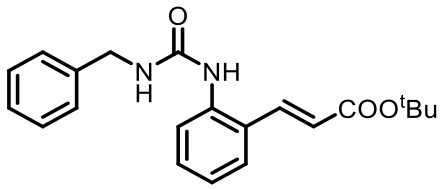
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar-H), 7.92 (d, *J* = 15.9 Hz, 1H, CH), 7.63 (ddd, *J* = 8.0, 6.7, 1.5 Hz, 2H, Ar-H), 7.52 (s, 1H, NH), 7.41 (td, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 7.37 – 7.23 (m, 3H, Ar-H), 7.18 (s, 1H, NH), 6.93 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 6.37 (d, *J* = 15.9 Hz, 1H, CH), 3.16 (s, 1H, C≡CH), 1.47 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.3 ($C(O)OC(CH_3)_3$), 153.3 (C(O)NH), 140.5 (ArC), 138.4 (CH), 136.0 (ArC), 132.2 (ArCH), 131.0 (ArCH), 130.3 (ArCH), 127.6 (ArCH), 127.1 (ArCH), 126.7 (ArC), 122.9 (CH), 122.5 (ArCH), 119.2 (ArCH), 110.9 (ArC), 84.0 (C≡CH), 81.1 ($OC(CH_3)_3$ or C≡CH), 79.4 ($OC(CH_3)_3$ or C≡CH), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{22}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 385.1523, found 385.1523; **FT-IR (thin film)** ν_{max} 3278, 2977, 2511, 2160, 2032, 1977, 1707, 1648, 1608, 1580, 1546, 1480, 1448, 1391, 1367, 1322, 1298, 1239, 1152, 1043, 979, 876, 755, 668, 629 cm^{-1}; **m.p.**: 160-162 °C.



***tert*-Butyl (*E*)-3-(2-(3-allylureido)phenyl)acrylate (315)** was prepared following **General Procedure A**, using 2-iodoaniline (0.22 g, 1.00 mmol, 1.0 eq) and 3-isocyanatoprop-1-ene (0.17 g, 2.00 mmol, 2.0 eq) to afford the title compound as a white powder (0.25 g, 82%).

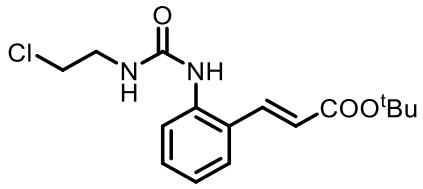
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.9 Hz, 1H, CHCH), 7.63 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 7.55 (dd, *J* = 7.9, 1.6 Hz, 1H, Ar-H), 7.34 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H, Ar-H), 7.21 (brs, 1H, NH), 7.18 – 7.10 (m, 1H, Ar-H), 6.33 (d, *J* = 15.9 Hz, 1H, CHCH), 5.83 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H, $CH=CH_2$), 5.68 - 4.57 (brs, 1H, NH), 5.17 (dq, *J* = 17.2, 1.6 Hz, 1H, $CH=CH_2$), 5.09 (dq, *J* = 10.3, 1.6 Hz, 1H, $CH=CH_2$), 3.83 (dt, *J* = 5.5, 1.6 Hz, 2H, $NHCH_2$), 1.47 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.5 ($C(O)OC(CH_3)_3$), 156.3 (C(O)NH), 138.8 (CHCH), 137.2 (ArC), 135.1

(CH=CH_2), 131.0 (ArCH), 128.6 (ArC), 127.3 (ArCH), 125.7 (ArCH), 125.4 (ArCH), 122.2 (CHCH), 116.1 (CH=CH_2), 81.0 ($OC(CH_3)_3$), 43.0 ($NHCH_2$), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{22}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 325.1523, found 325.1523; **FT-IR (thin film)** ν_{max} 3333, 2978, 2160, 2031, 1707, 1637, 1556, 1476, 1455, 1392, 1367, 1322, 1242, 1150, 985, 918, 872, 760, 668 cm^{-1}; **m.p.**: 136-138 °C.



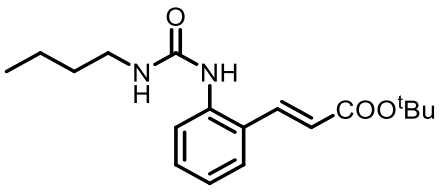
***tert*-Butyl (*E*)-3-(2-(3-benzylureido)phenyl)acrylate (316)** was prepared following **General Procedure A**, using 2-iodoaniline (0.31 g, 1.42 mmol, 1.0 eq) and 1-isocyanatobutane (0.38 g, 2.84 mmol, 2.0 eq) to afford the title compound as a white powder (0.38 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 15.9 Hz, 1H, CH), 7.63 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 7.53 (dd, *J* = 7.9, 1.6 Hz, 1H, Ar-H), 7.35 – 7.28 (m, 2H, NH and Ar-H), 7.27 – 7.17 (m, 5H, Ar-H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 6.31 (d, *J* = 15.9 Hz, 1H, CH), 5.57 (t, *J* = 5.7 Hz, 1H, CH_2NH), 4.29 (d, *J* = 5.7 Hz, 2H, CH_2), 1.46 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.5 (C(O)$OC(CH_3)_3$), 156.4 (C(O)NH), 138.9 (CH), 138.8 (ArC), 137.2 (ArC), 131.0 (ArCH), 128.7 (ArCH), 128.6 (ArC), 127.5 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 125.7 (ArCH), 125.4 (ArCH), 122.0 (CH), 81.0 ($OC(CH_3)_3$), 44.4 (CH_2), 28.3 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 375.1679, found 375.1680; **FT-IR (thin film)** ν_{max} 3333, 2980, 2531, 2359, 2161, 2027, 1977, 1707, 1639, 1558, 1455, 1367, 1322, 1250, 1150, 983, 761, 698 cm^{-1}; **m.p.**: 123-124 °C.



***tert*-Butyl (*E*)-3-(2-(3-(2-chloroethyl)ureido)phenyl)acrylate (317)** was prepared following **General Procedure A**, using 2-iodoaniline (0.22 g, 1.00 mmol, 1.0 eq) and 1-chloro-2-isocyanatoethane (0.21 g, 2.00 mmol, 2.0 eq) to afford the title compound as a white powder (0.26 g, 78%).

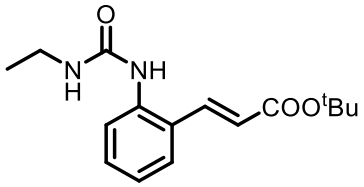
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 7.52 (ddd, *J* = 13.8, 7.9, 1.5 Hz, 2H, Ar-<u>H</u>), 7.29 (td, *J* = 7.9, 1.5 Hz, 1H, Ar-<u>H</u>), 7.14 – 7.08 (m, 1H, Ar-<u>H</u>), 7.06 (brs, 1H, N<u>H</u>), 6.27 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 5.45 (brs, 1H, N<u>H</u>), 3.60 – 3.53 (m, 2H, C<u>H</u>$_2$), 3.50 (td, *J* = 5.0, 4.5, 1.3 Hz, 2H, C<u>H</u>$_2$), 1.41 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.5 (<u>C</u>(O)OC(CH$_3$)$_3$), 156.1 (<u>C</u>(O)NH), 138.6 (<u>C</u>H), 136.7 (Ar<u>C</u>), 131.0 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>), 127.4 (Ar<u>C</u>H), 125.84 (Ar<u>C</u>H), 125.78 (Ar<u>C</u>H), 122.4 (<u>C</u>H), 81.1 (O<u>C</u>(CH$_3$)$_3$), 44.7 (<u>C</u>H$_2$), 42.3 (<u>C</u>H$_2$), 28.3 (OC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}ClN_2O_3{}^{23}Na$ ([M+Na]$^+$) 347.1133, found 347.1133; **FT-IR (thin film)** ν_{max} 3334, 2978, 2161, 2032, 1705, 1640, 1556, 1476, 1455, 1392, 1368, 1322, 1248, 1150, 983, 871, 759, 658 cm^{-1}; **m.p.**: 128-129 °C.



***tert*-Butyl (*E*)-3-(2-(3-butylureido)phenyl)acrylate (318)** was prepared following **General Procedure A**, using 2-iodoaniline (0.30 g, 1.35 mmol, 1.0 eq) and 1-isocyanatobutane (0.27 g, 2.70 mmol, 2.0 eq) to afford the title compound as a white powder (0.33 g, 76%).

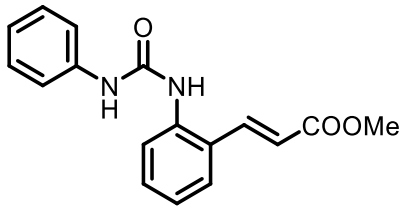
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.9 Hz, 1H, C<u>H</u>), 7.61 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar-<u>H</u>), 7.54 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar-<u>H</u>), 7.32 (ddd, *J* = 8.1, 7.2, 1.5 Hz, 1H, Ar-<u>H</u>), 7.27 (s, 1H, N<u>H</u>), 7.16 –

7.07 (m, 1H, Ar-H), 6.32 (d, *J* = 15.9 Hz, 1H, CH), 5.24 (s, 1H, NH), 3.18 (t, *J* = 7.3 Hz, 2H, CH_2), 1.49 – 1.39 (m, 11H, $OC(CH_3)_3$ and CH_2), 1.36 – 1.23 (m, 2H, CH_2), 0.88 (t, *J* = 7.3 Hz, 3H, CH_2CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.6 (C(O)$OC(CH_3)_3$), 156.5 (C(O)NH), 138.9 (CH), 137.5 (ArC), 130.9 (ArCH), 128.4 (ArC), 127.2 (ArCH), 125.6 (ArCH), 125.1 (ArCH), 121.9 (CH), 80.9 ($OC(CH_3)_3$), 40.3 (CH_2), 32.3 (CH_2), 28.3 ($OC(CH_3)_3$), 20.2 (CH_2), 13.9 (CH_2CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{26}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 341.1836, found 341.1836; **FT-IR (thin film)** ν_{max} 3329, 2961, 2931, 2161, 2025, 1709, 1639, 1560, 1476, 1455, 1392, 1367, 1321, 1244, 1149, 983, 759 cm^{-1}; **m.p.**: 127-129 °C.



***tert*-Butyl (*E*)-3-(2-(3-ethylureido)phenyl)acrylate (319)** was prepared following **General Procedure A**, using 2-iodoaniline (0.23 g, 1.02 mmol, 1.0 eq) and isocyanatoethane (0.15 g, 2.04 mmol, 2.0 eq) to afford the title compound as a white powder (0.23 g, 76%).

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.18 (s, 1H, NH), 7.75 (d, *J* = 15.7 Hz, 1H, CH), 7.68 (ddd, *J* = 7.8, 5.1, 1.5 Hz, 2H, Ar-H), 7.31 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H, Ar-H), 7.03 (td, *J* = 7.8, 1.0 Hz, 1H, Ar-H), 6.47 – 6.35 (m, 2H, CH and NH), 3.11 (qd, *J* = 7.2, 5.5 Hz, 2H, CH_2), 1.49 (s, 9H, $OC(CH_3)_3$), 1.06 (t, *J* = 7.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 165.7 (C(O)$OC(CH_3)_3$), 155.3 (C(O)NH), 139.3 (CH), 138.7 (ArC), 130.4 (ArCH), 126.9 (ArCH), 125.5 (ArC), 123.3 (ArCH), 123.0 (ArCH), 120.1 (CH), 79.9 ($OC(CH_3)_3$), 34.1 (CH_2), 27.9 ($OC(CH_3)_3$), 15.4 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{22}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 313.1523, found 313.1523; **FT-IR (thin film)** ν_{max} 3327, 2979, 2161, 2026, 1707, 1640, 1557, 1476, 1455, 1367, 1322, 1243, 1149, 982, 876, 759, 668 cm^{-1}; **m.p.**: 111-113 °C.



Methyl (*E*)-3-(2-(3-phenylureido)phenyl)acrylate (297) was prepared following **General Procedure A**, using 2-iodoaniline (8.18 g, 37.35 mmol, 1.0 eq) and phenyl isocyanate (8.90 g, 74.70 mmol, 2.0 eq) to afford the title compound as a white powder (10.09 g, 91%). Data is consistent with the published literature.[8]

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.94 (s, 1H, NH), 8.49 (s, 1H, NH), 7.89 (d, *J* = 15.8 Hz, 1H, CH), 7.76 (dd, *J* = 8.2, 1.3 Hz, 2H, CH=CHAr-H), 7.49 – 7.44 (m, 2H, Ar-H), 7.40 (ddd, *J* = 8.6, 7.3, 1.3 Hz, 1H, CH=CHAr-H), 7.32 – 7.26 (m, 2H, Ar-H), 7.16 – 7.11 (m, 1H, CH=CHAr-H), 7.02 – 6.95 (m, 1H, Ar-H), 6.59 (d, *J* = 15.8 Hz, 1H, CH), 3.74 (s, 3H, OCH_3) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 166.7 (C(O)O), 152.7 (C(O)NH), 139.8 (ArC), 139.6 (CH), 137.8 (CH=CHArC), 130.7 (CH=CHArCH), 128.8 (ArCH), 127.5 (CH=CHArC), 127.1(CH=CHArCH), 123.8 (CH=CHArCH), 123.7 (CH=CHArCH), 121.9 (ArCH), 118.8 (CH), 118.2 (ArCH), 51.5 (OCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{17}N_2O_3$ ($[M+H]^+$) 297.12337, found 297.12327; **FT-IR (thin film)** ν_{max} 3280, 2950, 2555, 2160, 2024, 1977, 1718, 1642, 1599, 1582, 1552, 1498, 1445, 1322, 1275, 1235, 1195, 1171, 976, 760, 749, 693 cm^{-1}; **m.p.**: 181-182 °C.

4.2.4 Preparation of Racemic Compounds

DBU (0.2 eq) was added to a solution of starting materials (0.20 mmol, 1.0 eq) in THF (0.1M) under N_2 at room temperature. The reaction was stirred at room temperature for 16 hours. before diluting with CH_2Cl_2 (10 mL). The resulting mixture was then washed with 1M HCl aqueous solution (20 mL) and H_2O (20 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to afford the pure samples of racemic compounds for HPLC analysis.

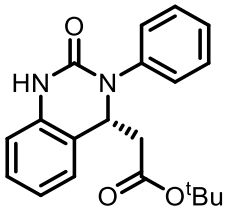
4.2.5 Preparation of Enantioenriched Products

General procedure C for the intramolecular aza-Michael reaction

Et_2O (0.0125 M, 1.6 mL) was added to the BIMP catalysts precursors **E24** (9.5 mg, 0.02 mmol, 0.1 eq) and tris(4-methoxyphenyl)phosphine (7.2 mg, 0.02 mmol, 0.1 eq) in a sealed mass spectrometry vial under N_2 at room temperature. The reaction mixture was stirred for 24 hours before evaporating to dryness under a stream of nitrogen gas. The iminophosphorane product was confirmed by HRMS and TLC and used as crude for enantioselective reactions without any purification.

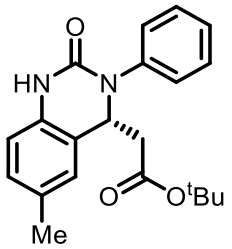
Active BIMP catalyst HRMS (ESI) m/z calcd. for $C_{47}H_{52}N_4O_6P$ ($[M+H]^+$) 799.3619, found 799.3615.

Corrsponding urea (0.2 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst (0.02 mmol, 0.1 eq) in toluene (0.025M, 8 mL) unless otherwise indicated under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours unless otherwise indicated before loaded directly onto silica gel. Purification by silica gel chromatography (pentane/EtOAc) afforded the pure intramolecular aza-Michael reaction products, which were taken the isolated yield and analysed by chiral HPLC.



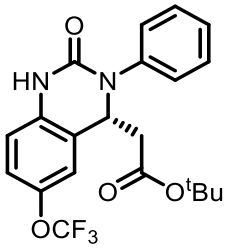
***tert*-Butyl (*R*)-2-(2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (232)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-phenylureido)phenyl)acrylate (226)** (16.9 mg, 0.05 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (9:1 (**A**:**B**) mixture of rotamers) (16.7 mg, 99%, 94.5:5.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 0.1H, NH (**B**)), 8.08 (s, 0.9H, NH (**A**)), 7.48 – 7.39 (m, 4H, Ar-H), 7.30 (ddt, *J* = 5.7, 4.6, 3.8 Hz, 1H, Ar-H), 7.19 (ddd, *J* = 15.9, 7.9, 1.4 Hz, 2H, Ar-H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.81 (dd, *J* = 7.9, 1.1 Hz, 0.1H, Ar-H, (**B**)), 6.77 (dd, *J* = 7.9, 1.1 Hz, 0.9H, Ar-H, (**A**)), 5.23 (dd, *J* = 8.5, 4.6 Hz, 1H, CH), 2.84 – 2.66 (m, 2H, CH_2), 1.32 (s, 8.1H, $OC(CH_3)_3$ (**A**)), 1.31 (s, 0.9H, (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 ($C(O)OC(CH_3)_3$), 153.9 (C(O)NH), 141.0 (ArC), 136.6 (ArC), 129.3 (ArCH), 128.8 (ArCH), 127.6 (ArCH), 126.9 (ArCH), 126.0 (ArCH), 122.1 (ArCH), 121.3 (ArC), 114.5 (ArCH), 81.3 ($OC(CH_3)_3$), 60.1 (CH), 41.2 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{23}N_2O_3$ ($[M+H]^+$) 339.1703, found 339.1704; **FT-IR (thin film)** ν_{max} 3020, 2453, 2160, 2030, 1977, 1677, 1422, 1215, 909, 745, 669, 628 cm^{-1}; **m.p.**: 200-202 °C; **[α]D^{25}** = −2.5 (c=2.00, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 254 nm, t_R (major) = 36.6 min, t_R (minor) = 57.4 min.



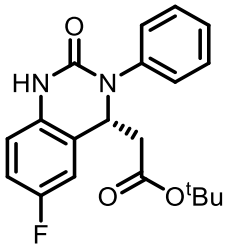
***tert*-Butyl (*R*)-2-(6-methyl-2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (273)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out at 80 °C), using ***tert*-butyl (*E*)-3-(5-methyl-2-(3-phenylureido)phenyl)acrylate (265)** (70.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as an off-white solid (69.8 mg, 99%, 91:9 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, NH), 7.44 – 7.36 (m, 4H, Ar-H), 7.28 (ddd, *J* = 5.7, 4.5, 2.6 Hz, 1H, Ar-H), 7.00 – 6.89 (m, 2H, Ar-H), 6.71 – 6.61 (m, 1H, Ar-H), 5.15 (dd, *J* = 8.6, 4.5 Hz, 1H, CH), 2.82 – 2.62 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 1.30 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 ($C(O)OC(CH_3)_3$), 154.0 (C(O)NH), 141.1 (ArC), 134.0 (ArC), 131.5 (ArC), 129.3 (s, 2 non-equivalent C, ArCH), 127.6 (ArCH), 126.9 (ArCH), 126.3 (ArCH), 121.1 (ArC), 114.3 (ArCH), 81.3 ($OC(CH_3)_3$), 60.2 (CH), 41.2 (CH_2), 28.0 ($OC(CH_3)_3$), 20.8 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{25}N_2O_3$ ($[M+H]^+$) 353.1860, found 353.1861; **FT-IR (thin film)** ν_{max} 3020, 2402, 2161, 2029, 1721, 1673, 1516, 1445, 1369, 1296, 1215, 1143, 1030, 928, 745, 668, 628 cm^{-1}; **m.p.**: 200-201 °C; **$[\alpha]D^{25}$** = −96.1 (c=0.55, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 240 nm, t_R (major) = 19.0 min, t_R (minor) = 14.8 min.



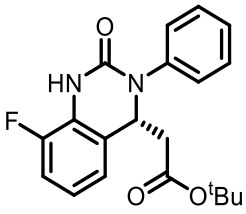
***tert*-Butyl (*R*)-2-(2-oxo-3-phenyl-6-(trifluoromethoxy)-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (274)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-phenylureido)-5-(trifluoromethoxy)phenyl)acrylate (266)** (84.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (9:1 (**A**:**B**) mixture of rotamers) (82.6 mg, 98%, 93.5:6.5 er).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 0.1H, NH (**B**)), 9.37 (s, 0.9H, NH (**A**)), 7.49 – 7.39 (m, 4H, NAr-H), 7.33 (tt, *J* = 6.5, 1.7 Hz, 1H, NAr-H), 7.08 (d, *J* = 2.6 Hz, 1H, NHAr-H), 7.06 – 6.99 (m, 1H, NHAr-H), 6.81 (d, *J* = 8.7 Hz, 0.1H, NHAr-H (**B**)), 6.74 (d, *J* = 8.7 Hz, 0.9H, NHAr-H (**B**)), 5.21 (dd, *J* = 8.9, 4.3 Hz, 1H, CH), 2.80 (dd, *J* = 15.2, 4.3 Hz, 1H, CH_2), 2.73 (dd, *J* = 15.2, 8.9 Hz, 1H, CH_2), 1.33 (s, 8.1H, $OC(CH_3)_3$ (**A**)), 1.31 (s, 0.9H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2 ($C(O)OC(CH_3)_3$), 153.9 (C(O)NH), 143.8 (q, *J* = 2.0 Hz, $ArCOCF_3$), 140.6 (NArC), 135.6 (NHArC), 129.5 (NArCH), 127.7 (NArCH), 127.3 (NArCH), 122.4 (NHArC), 121.9 (NHArCH), 120.6 (q, *J* = 257.1 Hz, CF_3)119.3 (NHArCH), 115.6 (NHArCH), 81.7 ($OC(CH_3)_3$), 59.7 (CH), 40.7(CH_2), 27.9 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -58.27 (s) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{22}F_3N_2O_4$ ($[M+H]^+$) 423.1526, found 423.1526; **FT-IR (thin film)** ν_{max} 3235, 2981, 2160, 2032, 1726, 1680, 1596, 1510, 1480, 1457, 1397, 1369, 1254, 1215, 1162, 1075, 1008, 914, 827, 755, 698, 620 cm^{-1}; **m.p.**: 96-99 °C; **[α]D^{25}** = −119.5 (c=0.47, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 37.4 min, t_R (minor) = 28.6 min.



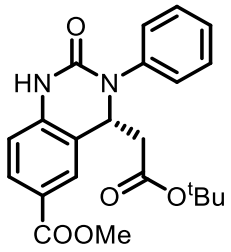
***tert*-Butyl (*R*)-2-(6-fluoro-2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (275)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out at 80 °C for 16 hours), using ***tert*-butyl (*E*)-3-(5-fluoro-2-(3-phenylureido)phenyl)acrylate (267)** (71.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (60.9 mg, 85%, 92.5:7.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H, NH), 7.47 – 7.38 (m, 4H, NAr-H), 7.32 (ddt, *J* = 6.9, 4.6, 1.8 Hz, 1H, NAr-H), 6.98 – 6.86 (m, 2H, NHAr-H), 6.80 – 6.67 (m, 1H, NHAr-H), 5.17 (dd, *J* = 8.8, 4.5 Hz, 1H, CH), 2.83 – 2.66 (m, 2H, CH_2), 1.33 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.2 ($C(O)OC(CH_3)_3$), 158.2 (d, *J* = 240.9 Hz, CF), 153.7 (C(O)NH), 140.7 (NArC), 132.8 (d, *J* = 2.3 Hz, NHArC), 129.5 (NArCH), 127.6 (NArCH), 127.2 (NArCH), 122.7 (d, *J* = 7.6 Hz, NHArC), 115.6 (d, *J* = 23.1 Hz, NHArCH), 115.5 (d, *J* = 7.9 Hz, NHArCH), 113.1 (d, *J* = 24.2 Hz, NHArCH), 81.7 ($OC(CH_3)_3$), 59.9 (d, *J* = 1.8 Hz, CH), 40.8 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -121.25 (td, *J* = 8.5, 4.6 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}FN_2O_3$ ($[M+H]^+$) 357.1609, found 357.1610; **FT-IR (thin film)** ν_{max} 3020, 2402, 2160, 2028, 1721, 1675, 1509, 1446, 1370, 1298, 1243, 1215, 1138, 1030, 925, 745, 668, 625 cm^{-1}; **m.p.**: 131-135 °C; **[α]D^{25}** = −129.9 (c=0.83, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 220 nm, t_R (major) = 91.0 min, t_R (minor) = 75.2 min.



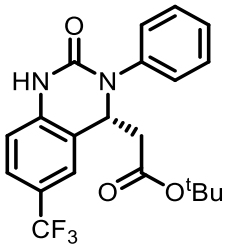
***tert*-Butyl (*R*)-2-(8-fluoro-2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (276)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out at 40 °C for 30h), using ***tert*-butyl (*E*)-3-(3-fluoro-2-(3-phenylureido)phenyl)acrylate (268)** (71.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 4/1) afforded the title compound as a white solid (70.6 mg, 99%, 82:18 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 5H, Ar-H and NH), 7.30 (ddt, *J* = 6.8, 5.7, 2.6 Hz, 1H, Ar-H), 7.03 (ddd, *J* = 10.0, 8.0, 1.4 Hz, 1H, Ar-H), 7.00 – 6.97 (m, 1H, Ar-H), 6.92 (td, *J* = 8.0, 5.0 Hz, 1H, Ar-H), 5.26 (dd, *J* = 8.4, 4.4 Hz, 1H, CH), 2.83 – 2.66 (m, 2H, CH_2), 1.33 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.1 ($C(O)OC(CH_3)_3$), 152.5 (C(O)NH), 149.2 (d, *J* = 243.9 Hz, CF), 140.6 (ArC), 129.5 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 125.1 (d, *J* = 13.6 Hz, ArC), 123.6 (d, *J* = 2.1 Hz, ArC), 122.2 (d, *J* = 6.8 Hz, ArCH), 121.5 (d, *J* = 3.6 Hz, ArCH), 114.9 (d, *J* = 17.5 Hz, ArCH), 81.6 ($OC(CH_3)_3$), 60.0 (d, *J* = 2.1 Hz, CH), 41.0 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -135.54 (td, *J* = 12.5, 10.0, 5.0 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}FN_2O_3$ ($[M+H]^+$) 357.1609, found 357.1610; **FT-IR (thin film)** ν_{max} 3220, 2160, 2032, 1723, 1675, 1632, 1595, 1511, 1422, 1367, 1292, 1256, 1145, 1074, 1007, 922, 757, 703 621 cm^{-1}; **m.p.**: 56-58 °C; **[α]D^{25}** = −42.9 (c=0.42, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 29.9 min, t_R (minor) = 35.9 min.



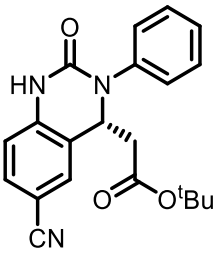
Methyl (*R*)-4-(2-(*tert*-butoxy)-2-oxoethyl)-2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate (277) was prepared following **General Procedure C** (variation from standard conditions: reaction carried out for 48 hours), using **methyl (*E*)-3-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)-4-(3-phenylureido)benzoate (269)** (79.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/2) afforded the title compound as a white solid (70.6 mg, 89%, 94.5:5.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H, NH), 7.87 (d, *J* = 8.0 Hz, 2H, NHAr-H), 7.49 – 7.39 (m, 4H, NAr-H)), 7.36 – 7.31 (m, 1H, NAr-H)), 6.87 – 6.73 (m, 1H, NHAr-H), 5.26 (dd, *J* = 8.4, 4.5 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 2.92 – 2.53 (m, 2H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.9 (C(O)), 166.5 (C(O)), 153.4 (C(O)NH), 140.7 (ArC), 140.5 (ArC), 130.8 (NHArCH), 129.5 (NArCH), 127.9 (NHArCH), 127.8 (NArCH), 127.4 (NArCH), 124.0 (ArC), 120.9 (ArC), 114.3 (NHArCH), 81.8 ($OC(CH_3)_3$), 60.0 (CH), 52.1 (OCH_3), 41.4 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{25}N_2O_5$ ($[M+H]^+$) 397.1758, found 397.1758; **FT-IR (thin film)** ν_{max} 3218, 3066, 2950, 2545, 2161, 2029, 1977, 1719, 1679, 1617, 1606 1494, 1456, 1434, 1399, 1368, 1290, 1262, 1199, 1144, 1104, 1009, 958, 915, 844, 758, 698, 652, 615 cm^{-1}; **m.p.**: 174-176 °C; **$[\alpha]D^{25}$** = −79.9 (c=0.85, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 220 nm, t_R (major) = 40.0 min, t_R (minor) = 48.3 min.



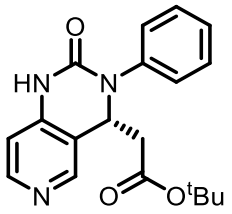
***tert*-Butyl (*R*)-2-(2-oxo-3-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (278)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-phenylureido)-5-(trifluoromethyl)phenyl)acrylate (270)** (81.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc =7/3) afforded the title compound as a white solid (81.2 mg, 99%, 94:6 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H, NH), 7.52 – 7.32 (m, 7H, Ar-H), 6.81 (d, *J* = 8.3 Hz, 1H, Ar-H), 5.26 (dd, *J* = 9.1, 4.3 Hz, 1H, CH), 2.82 (dd, *J* = 14.9, 4.3 Hz, 1H, CH_2), 2.72 (dd, *J* = 14.9, 9.1 Hz, 1H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.0 ($C(O)OC(CH_3)_3$), 153.8 (C(O)NH), 140.5 (ArC), 139.7 (ArC), 129.5 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 126.1 (q, *J* = 3.7 Hz, ArCH), 124.3 (q, *J* = 32.7 Hz, $ArCCF_3$), 124.25 (q, *J* = 272.3 Hz, CF_3), 123.4 (q, *J* = 4.0 Hz, ArCH), 121.4 (ArC), 114.8 (ArCH), 81.8 ($OC(CH_3)_3$), 59.9 (CH), 40.9 (CH_2), 27.9 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -61.74 (s) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{22}F_3N_2O_3$ ($[M+H]^+$) 407.1577, found 407.1577; **FT-IR (thin film)** ν_{max} 3020, 2161, 2035, 1977, 1722, 1681, 1626, 1496, 1455, 1406, 1370, 1330, 1295, 1215, 1165, 1145, 1128, 1074, 924, 837, 746, 697, 668 cm^{-1}; **m.p.**: 80-83 °C; **$[\alpha]D^{25}$** = −115.6 (c=0.50, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 35.1 min, t_R (minor) = 26.5 min.



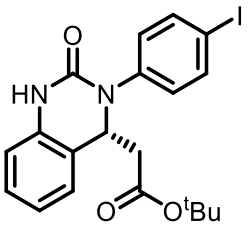
***tert*-Butyl (*R*)-2-(6-cyano-2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (279)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(5-cyano-2-(3-phenylureido)phenyl)acrylate (271)** (72.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 13/7) afforded the title compound as an off-white solid (6:1 (**A**:**B**) mixture of rotamers) (64.0 mg, 88%, 87.5:12.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 0.14H, NH (**B**)), 9.62 (s, 0.86H, NH (**A**)), 7.52 – 7.44 (m, 3H, Ar-H), 7.43 – 7.34 (m, 4H, Ar-H), 6.81 (d, *J* = 8.3 Hz, , 0.14H, Ar-H (**B**)), 6.74 (d, *J* = 8.3 Hz, 0.86H, Ar-H (**A**)), 5.21 (dd, J = 8.6, 4.4 Hz, 1H, CH), 2.77 (dd, *J* = 15.0, 4.4 Hz, 1H, CH_2), 2.69 (dd, *J* = 15.0, 8.6 Hz, 1H, CH_2), 1.33 (s, 7.7H, $OC(CH_3)_3$ (**A**)), 1.31 (s, 1.3H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.8 ($C(O)OC(CH_3)_3$), 153.3 (C(O)NH), 140.7 (ArC), 140.1 (ArC), 133.1 (ArCH), 130.2 (ArCH), 129.6 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 121.8 (ArC), 118.9 (ArC), 115.3 (ArCH), 105.2 (ArCN), 82.0 ($OC(CH_3)_3$), 59.5 ($CHCH_2$), 40.9 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{22}N_3O_3$ ($[M+H]^+$) 364.1656, found 364.1656; **FT-IR (thin film)** ν_{max} 3242, 2978, 2934, 2533, 2224, 2160, 2032, 1977, 1722, 1680, 1615, 1597, 1498 1456, 1402, 1367, 1295, 1146, 1030, 959, 900, 836, 756, 699, 627 cm^{-1}; **m.p.**: 95-97 °C; **$[\alpha]D^{25}$** = −88.2 (c=0.69, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 220 nm, t_R (major) = 19.1 min, t_R (minor) = 25.1 min.



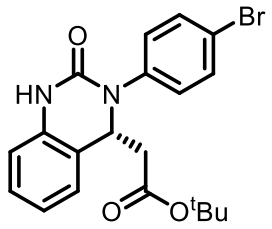
***tert*-Butyl (*R*)-2-(2-oxo-3-phenyl-1,2,3,4-tetrahydropyrido[4,3-d]pyrimidin-4-yl)acetate (280)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(4-(3-phenylureido)pyridin-3-yl)acrylate (272)** (67.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/7) afforded the title compound as a white solid (8:1 (**A**:**B**) mixture of rotamers) (66.1 mg, 97%, 89.5:10.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 0.11H, NH (**B**)), 9.66 (s, 0.89H, NH (**A**)), 8.33 (s, 1H, Ar-H), 8.24 (d, *J* = 5.4 Hz, 1H, Ar-H), 7.51 – 7.37 (m, 4H, Ar-H), 7.34 (ddt, *J* = 8.5, 6.8, 1.5 Hz, 1H, Ar-H), 6.65 (d, *J* = 5.4 Hz, 0.11H, Ar-H (**B**)), 6.58 (d, *J* = 5.4 Hz, 0.89H, Ar-H (**A**)), 5.24 (dd, *J* = 8.1, 4.4 Hz, 1H, CH), 2.80 – 2.60 (m, 2H, CH_2), 1.31 (s, 8H, $OC(CH_3)_3$ (**A**)), 1.28 (s, 1H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.8 ($C(O)OC(CH_3)_3$), 153.2 (C(O)NH), 149.8 (ArCH), 146.7 (ArCH), 143.8 (ArC), 140.2 (ArC), 129.5 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 116.9 (ArC), 109.2 (ArCH), 81.8 ($OC(CH_3)_3$), 57.9 ($CHCH_2$), 41.3 ($CHCH_2$), 27.9 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{22}N_3O_3$ ($[M+H]^+$) 340.1656, found 340.1657; **FT-IR (thin film)** ν_{max} 3243, 3063, 2977, 2513, 2160, 2029, 1977, 1723, 1682, 1601, 1494, 1446, 1410, 1367, 1319, 1291, 1141, 1057, 955, 840, 755, 699, 642 cm^{-1}; **m.p.**: 108-110 °C; **[α]D^{25}** = −120.1 (c=0.74, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 280 nm, t_R (major) = 23.5 min, t_R (minor) = 16.7 min.



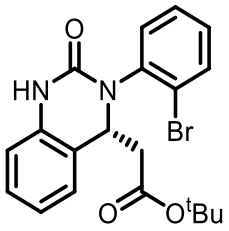
***tert*-Butyl (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (298)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(4-iodophenyl)ureido)phenyl)acrylate (281)** (92.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (88.5 mg, 96%, 93:7 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H, NH), 7.78 – 7.70 (m, 2H, Ar-H), 7.23 – 7.14 (m, 4H, Ar-H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.76 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-H), 5.21 (dd, *J* = 8.2, 4.7 Hz, 1H, CH), 2.79 – 2.61 (m, 2H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.2 ($C(O)OC(CH_3)_3$), 153.6 (C(O)NH), 140.8 (ArC), 138.4 (ArCH), 136.3 (ArC), 129.4 (ArCH), 129.0 (ArCH), 126.0 (ArCH), 122.4 (ArCH), 121.2 (ArC), 114.5 (ArCH), 91.7 (CI), 81.5 ($OC(CH_3)_3$), 60.0 ($CHCH_2$), 41.2 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}{}^{127}IN_2O_3$ ($[M+H]^+$) 465.0670, found 465.0669; **FT-IR (thin film)** ν_{max} 3247, 3064, 2978, 2932, 2543, 2361, 2341, 2161, 2025, 1977, 1721, 1675, 1605, 1504, 1485, 1449, 1413, 1394, 1368, 1280, 1207, 1145, 1075, 1009, 948, 828, 804, 756, 724 cm^{-1}; **m.p.**: 102-105 °C; **[α]D^{25}** = −23.0 (c=1.12, CH_3OH); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 70/30, 1.0 ml/min, λ = 220 nm, t_R (major) = 9.8 min, t_R (minor) = 11.0 min.



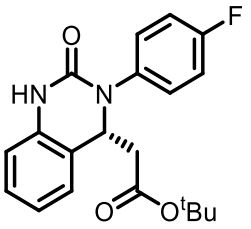
***tert*-Butyl (*R*)-2-(3-(4-bromophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (299)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(4-bromophenyl)ureido)phenyl)acrylate (282)** (83.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (83.0 mg, 99%, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, NH), 7.59 – 7.51 (m, 2H, Ar-H), 7.37 – 7.29 (m, 2H, Ar-H), 7.20 (td, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 7.16 (dd, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 7.01 – 6.92 (m, 1H, Ar-H), 6.76 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-H), 5.21 (dd, *J* = 8.2, 4.7 Hz, 1H, CH), 2.78 – 2.63 (m, 2H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 ($C(O)OC(CH_3)_3$), 153.6 (C(O)NH), 140.0 (ArC), 136.4 (ArC), 132.4 (ArCH), 129.2 (ArCH), 129.0 (ArCH), 126.0 (ArCH), 122.4 (ArCH), 121.2 (ArC), 120.4 (ArC), 114.5 (ArCH), 81.5 ($OC(CH_3)_3$), 60.0 ($CHCH_2$), 41.2 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}{}^{80}BrN_2O_3$ ($[M+H]^+$) 417.0808, found 417.0809; **FT-IR (thin film)** ν_{max} 3236, 3065, 2979, 2929, 2544, 2360, 2341, 2161, 2031, 1977, 1722, 1674, 1604, 1489, 1452, 1418, 1398, 1367, 1294, 1256, 1142, 1071, 1034, 1013, 956, 831, 804, 756, 726, 624 cm^{-1}; **m.p.**: 72-74 °C; **$[\alpha]D^{25}$** = −59.51 (c=0.79, CH_3OH); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 70/30, 1.0 ml/min, λ = 240 nm, t_R (major) = 8.8 min, t_R (minor) = 10.5 min.



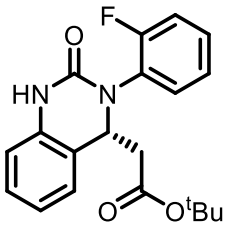
***tert*-Butyl (*R*)-2-(3-(2-bromophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (300)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out with 5 mol% **Cat.AH** for 72h), using ***tert*-butyl (*E*)-3-(2-(3-(2-bromophenyl)ureido)phenyl)acrylate (283)** (167.0 mg, 0.4 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 1/1) afforded the title compound as an off-white solid (6.8:1 (**A**:**B**) rotamers) (151.2 mg, 91%, 93:7 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 0.88H, Ar-H (**A**)), 7.86 (s, 0.12H, Ar-H (**B**)), 7.69 (dt, *J* = 8.0, 2.5 Hz, 1H, Ar-H), 7.57 (dd, *J* = 8.0, 1.7 Hz, 1H, Ar-H), 7.46 – 7.31 (m, 1H, Ar-H), 7.25 – 7.13 (m, 2H, Ar-H), 6.98 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 6.83 – 6.66 (m, 1H, Ar-H), 5.26 (dd, *J* = 9.1, 4.6 Hz, 0.12H, CH (**B**)), 5.12 (dd, *J* = 7.3, 5.3 Hz, 0.88H, CH (**A**)), 3.02 (dd, *J* = 15.5, 4.6 Hz, 0.12H, CH_2 (**B**)), 2.79 – 2.65 (m, 1.88H, CH_2 (**A**)), 1.31 (s, 7.8H, $OC(CH_3)_3$ (**A**)), 1.30 (s, 1.2H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 ($C(O)OC(CH_3)_3$), 153.4 (C(O)NH), 139.0 (ArC), 136.3 (ArC), 134.0 (ArCH), 133.0 (ArCH), 129.6 (ArCH), 128.8 (ArCH), 128.2 (ArCH), 126.3 (ArCH), 122.8 (ArC), 122.5 (ArCH), 121.2 (ArC), 114.4 (ArCH), 81.4 ($OC(CH_3)_3$), 58.9 ($CHCH_2$), 41.2 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}BrN_2O_3$ ($[M+H]^+$) 417.0808, found 417.0807; **FT-IR (thin film)** ν_{max} 3020, 2161, 2027, 1978, 1722, 1678, 1603, 1476, 1450, 1369, 1287, 1215, 1143, 1029, 929, 745, 668, 627 cm^{-1}; **m.p.**: 80-82 °C; **[α]D^{25}** = −190.9 (c=0.45, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 240 nm, t_R (major) = 21.1 min, t_R (minor) = 35.6 min.



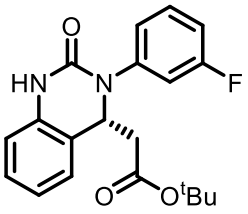
***tert*-Butyl (*R*)-2-(3-(4-fluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (301)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(4-fluorophenyl)ureido)phenyl)acrylate (284)** (71.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 13/7) afforded the title compound as an off-white solid (67.3 mg, 95%, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, NH), 7.45 – 7.36 (m, 2H, Ar-H), 7.24 – 7.06 (m, 4H, Ar-H), 6.95 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.83 – 6.72 (m, 1H, Ar-H), 5.18 (dd, *J* = 8.0, 4.7 Hz, 1H, CH), 2.79 – 2.61 (m, 2H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 ($C(O)OC(CH_3)_3$), 161.3 (d, *J* = 246.5 Hz, CF), 154.0 (C(O)NH), 136.9 (d, *J* = 3.2 Hz, ArC), 136.5 (ArC), 129.6 (d, *J* = 8.5 Hz, ArCH), 128.8 (ArCH), 125.9 (ArCH), 122.2 (ArCH), 121.0 (ArC), 116.2 (d, *J* = 22.6 Hz, ArCH), 114.5 (ArCH), 81.4 ($OC(CH_3)_3$), 60.3 (CH), 41.2 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -114.80 (ddd, *J* = 13.1, 8.5, 4.9 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}FN_2O_3$ ($[M+H]^+$) 357.1609, found 357.1609; **FT-IR (thin film)** ν_{max} 3699, 3236, 3071, 2929, 2552, 2160, 2032, 1977, 1722, 1675, 1602, 1509, 1453, 1412, 1368, 1294, 1217, 1143, 1016, 841, 755, 661, 616 cm^{-1}; **m.p.**: 68-72 °C; **[α]D^{25}** = −80.5 (c=0.55, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 254 nm, t_R (major) = 19.3 min, t_R (minor) = 24.8 min.



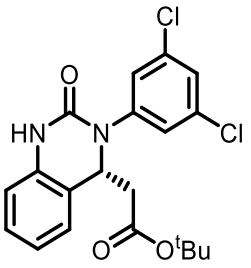
***tert*-Butyl (*R*)-2-(3-(2-fluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (302)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(2-fluorophenyl)ureido)phenyl)acrylate (285)** (71.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (68.8 mg, 96%, 93.5:6.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H, NH), 7.47 (td, *J* = 7.6, 1.8 Hz, 1H, Ar-H), 7.39 – 7.29 (m, 1H, Ar-H), 7.26 – 7.11 (m, 4H, Ar-H), 6.95 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 6.85 – 6.70 (m, 1H, Ar-H), 5.13 (dd, *J* = 8.2, 4.9 Hz, 1H, CH), 2.82 – 2.75 (m, 1H, CH_2), 2.70 (dd, *J* = 15.0, 8.2 Hz, 1H, CH_2), 1.31 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 ($C(O)OC(CH_3)_3$), 158.7 (d, *J* = 250.4 Hz, CF), 153.5 (C(O)NH), 136.5 (ArC), 131.1 (ArCH), 129.3 (d, *J* = 8.0 Hz, ArCH), 128.8 (ArCH), 128.3 (d, *J* = 12.2 Hz, ArC), 126.0 (ArCH), 124.7 (d, *J* = 3.7 Hz, ArCH), 122.2 (ArCH), 121.1 (ArC), 116.8 (d, *J* = 20.3 Hz, ArCH), 114.6 (ArCH), 81.3 ($OC(CH_3)_3$), 59.8 (d, *J* = 1.8 Hz, CH), 41.5 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -118.90 (s) ppm (H-F coupling not observed); **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}FN_2O_3$ ($[M+H]^+$) 357.1609, found 357.1609; **FT-IR (thin film)** ν_{max} 3219, 3069, 2978, 2554, 2160, 2029, 1723, 1680, 1603, 1501, 1453, 1420, 1367, 1289, 1257, 1216, 1143, 1106, 1034, 960, 846, 824, 754, 686 cm^{-1}; **m.p.**: 168-170 °C; **[α]D^{25}** = −112.7 (c=0.75, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 240 nm, t_R (major) = 10.6 min, t_R (minor) = 14.7 min.



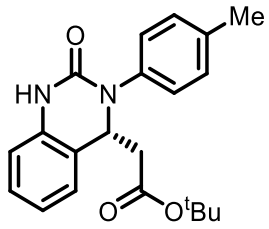
***tert*-Butyl (*R*)-2-(3-(3-fluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (303)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(3-fluorophenyl)ureido)phenyl)acrylate (286)** (71.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/1) afforded the title compound as a white solid (69.8 mg, 97%, 91.5:8.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H, NH), 7.46 – 7.34 (m, 1H, Ar-H), 7.28 – 7.20 (m, 2H, Ar-H), 7.20 – 7.14 (m, 2H, Ar-H), 7.05 – 6.92 (m, 2H, Ar-H), 6.80 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-H), 5.26 (dd, *J* = 8.2, 4.6 Hz, 1H, CH), 2.78 (dd, *J* = 14.9, 4.7 Hz, 1H, CH_2), 2.70 (dd, *J* = 14.9, 8.2 Hz, 1H, CH_2), 1.33 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 ($C(O)OC(CH_3)_3$), 162.9 (d, *J* = 246.5 Hz, ArC), 153.8 (C(O)NH), 142.5 (d, *J* = 9.9 Hz, ArC), 136.3 (ArC), 130.3 (d, *J* = 9.2 Hz, ArCH), 128.9 (ArCH), 125.9 (ArCH), 122.6 (d, *J* = 3.2 Hz, ArCH), 122.3 (ArCH), 121.2 (ArC), 114.9 (d, *J* = 23.3 Hz, ArCH), 114.6 (ArCH), 113.8 (d, *J* = 20.9 Hz, ArCH), 81.5 ($OC(CH_3)_3$), 60.0 (CH), 41.3 (CH_2), 28.0 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -111.62 (td, *J* = 10.4, 9.7, 7.0 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{22}FN_2O_3$ ($[M+H]^+$) 357.1609, found 357.1609; **FT-IR (thin film)** ν_{max} 3233, 3068, 2978, 2930, 2539, 2160, 2031, 1977, 1723, 1678, 1605, 1487, 1454, 1416, 1368, 1288, 1209, 1141, 1038, 1014, 870, 844, 755, 697, 634 cm^{-1}; **m.p.**: 134-139 °C; **[α]D^{25}** = −83.2 (c=0.66, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 13.4 min, t_R (minor) = 18.8 min.



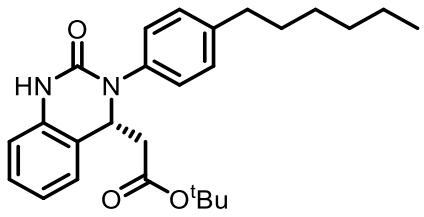
***tert*-Butyl (*R*)-2-(3-(3,5-dichlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (304)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(3,5-dichlorophenyl)ureido)phenyl)acrylate (287)** (81.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 17/3) afforded the title compound as a white solid (6:1 (**A**:**B**) mixture of rotamers) (79.9 mg, 98%, 87.5:12.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H, NH), 7.38 (d, *J* = 1.8 Hz, 2H, Ar-H), 7.29 (t, *J* = 1.8 Hz, 1H, Ar-H), 7.25 – 7.20 (m, 1H, Ar-H), 7.17 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar-H), 7.00 (tdd, *J* = 7.5, 2.7, 1.1 Hz, 1H, Ar-H), 6.79 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar-H), 5.23 (dd, *J* = 8.0, 4.8 Hz, 1H, CH), 2.80 – 2.61 (m, 2H, CH_2), 1.34 (s, 7.75H, $OC(CH_3)_3$ (**A**)), 1.33 (s, 1.25H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.1 ($C(O)OC(CH_3)_3$), 153.4 (C(O)NH), 142.9 (ArC), 136.0 (ArC), 135.3 (ArC), 129.2 (ArCH), 127.1 (ArCH), 126.0 (ArCH), 125.96 (ArCH), 122.7 (ArCH), 121.1 (ArC), 114.6 (ArCH), 81.8 ($OC(CH_3)_3$), 60.0 ($CHCH_2$), 41.4 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}Cl_2N_2O_3$ ($[M+H]^+$) 407.0924, found 407.0924; **FT-IR (thin film)** ν_{max} 3229, 3074, 2979, 2930, 2361, 2160, 2031, 1977, 1725, 1681, 1605, 1586, 1570, 1504, 1453, 1414, 1368, 1302, 1142, 1036, 847, 804, 756, 684 cm^{-1}; **m.p.**: 62-64 °C; **[α]D^{25}** = −74.7 (c=0.69, CH_3OH); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 25.4 min, t_R (minor) = 14.1 min.



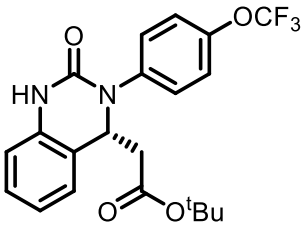
***tert*-Butyl (*R*)-2-(2-oxo-3-(p-tolyl)-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (305)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out for 48 hours), using ***tert*-butyl (*E*)-3-(2-(3-(*p*-tolyl)ureido)phenyl)acrylate (288)** (70.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 13/7) afforded the title compound as a white solid (62.3 mg, 88%, 94:6 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H, NH), 7.35 – 7.28 (m, 2H, Ar-H), 7.26 – 7.21 (m, 2H, Ar-H), 7.21 – 7.12 (m, 2H, Ar-H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.77 (dt, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 5.18 (dd, *J* = 8.5, 4.5 Hz, 1H, CH), 2.82 – 2.64 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 ($C(O)OC(CH_3)_3$), 154.1 (C(O)NH), 138.3 (ArC), 136.8 (ArC), 136.7 (ArC), 129. (ArCH)9, 128.7 (ArCH), 127.5 (ArCH), 125.9 (ArCH), 122.0 (ArCH), 121.2 (ArC), 114.5 (ArCH), 81.2 ($OC(CH_3)_3$), 60.2 (CH), 41.1 (CH_2), 28.0 ($OC(CH_3)_3$), 21.2 (CH_3)ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{25}N_2O_3$ ($[M+H]^+$) 353.1860, found 353.1861; **FT-IR (thin film)** ν_{max} 3225, 2160, 2031, 1722, 1675, 1603, 1514, 1454, 1367, 1291, 1144, 1076, 1007, 914, 754, 659 cm^{-1}; **m.p.**: 88-91 °C; **[α]D^{25}** = −89.3 (c=0.35, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 21.4 min, t_R (minor) = 30.0 min.



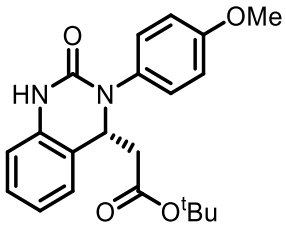
***tert*-Butyl (*R*)-2-(3-(4-hexylphenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (306)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out for 48h), using ***tert*-butyl (*E*)-3-(2-(3-(4-hexylphenyl)ureido)phenyl)acrylate (289)** (84.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 4/1) afforded the title compound as a white solid (76.7 mg, 91%, 95:5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H, NH), 7.37 – 7.29 (m, 2H, Ar-H), 7.26 – 7.22 (m, 2H, Ar-H), 7.16 (dd, *J* = 8.5, 6.8 Hz, 2H, Ar-H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 6.84 – 6.73 (m, 1H, Ar-H), 5.20 (dd, *J* = 8.5, 4.5 Hz, 1H, CHCH$_2$), 2.83 – 2.67 (m, 2H, CHCH$_2$), 2.67 – 2.59 (m, 2H, ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.70 – 1.58 (m, 2H, ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.43-1.29 (m, 15H, OC(CH$_3$)$_3$ and ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 0.98 – 0.87 (m, 3H, CH$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (C(O)OC(CH$_3$)$_3$), 154.0 (C(O)NH), 141.7 (ArC), 138.5 (ArC), 136.7(ArC), 129.3 (ArCH), 128.7 (ArCH), 127.4 (ArCH), 126.0 (ArCH), 122.0 (ArCH), 121.4 (ArC), 114.5 (ArCH), 81.2 (OC(CH$_3$)$_3$), 60.2 (CHCH$_2$), 41.1 (CHCH$_2$), 35.7 (ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.8 (ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 31.4 (ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 29.1 (ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 28.0 (OC(CH$_3$)$_3$), 22.7 (ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 14.2 (ArCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{26}H_{35}N_2O_3$ ([M+H]$^+$) 423.2642, found 423.2642; **FT-IR (thin film)** ν_{max} 3216, 2928, 2857, 2160, 2031, 1724, 1676, 1604, 1512, 1451, 1413, 1367, 1282, 1143, 846, 754 cm^{-1}; **m.p.**: 42-45 °C; **[α]D^{25}** = −64.5 (c=1.28, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 254 nm, t_R (major) = 8.9 min, t_R (minor) = 11.4 min.



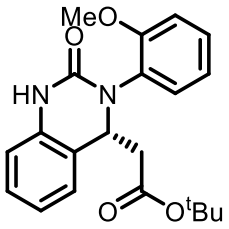
***tert*-Butyl (*R*)-2-(2-oxo-3-(4-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (307)** was prepared following **General Procedure C**, using ***tert*-butyl (*E*)-3-(2-(3-(4-(trifluoromethoxy)phenyl)ureido)phenyl)acrylate (290)** (84.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/1) afforded the title compound as a white solid (83.7 mg, 99%, 90:10 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H, NH), 7.53 – 7.45 (m, 2H, Ar-H), 7.32 – 7.25 (m, 2H, Ar-H), 7.24 – 7.14 (m, 2H, Ar-H), 7.07 – 6.93 (m, 1H, Ar-H), 6.87 – 6.73 (m, 1H, Ar-H), 5.24 (dd, *J* = 8.0, 4.8 Hz, 1H, CH), 2.76 (dd, *J* = 14.7, 4.8 Hz, 1H, CH_2), 2.69 (dd, *J* = 14.7, 8.0 Hz, 1H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 ($C(O)OC(CH_3)_3$), 153.9 (C(O)NH), 147.5 (d, *J* = 2.1 Hz, ArC), 139.5 (ArC), 136.4 (ArC), 128.9 (s, 2 non-equivalent C, ArCH), 125.9 (ArCH), 122.4 (ArCH), 121.8 (ArCH), 121.1 (ArC), 120.6 (q, *J* = 257.5 Hz, CF_3), 114.6 (ArCH), 81.5 ($OC(CH_3)_3$), 60.2 (CH), 41.3 (CH_2), 27.9 ($OC(CH_3)_3$) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -57.87 (s) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{22}F_3N_2O_4$ ($[M+H]^+$) 423.1526, found 423.1526; **FT-IR (thin film)** ν_{max} 3241, 2512, 2160, 2032, 1977, 1724, 1677, 1605, 1509, 1451, 1413, 1369, 1260, 1222, 1206, 1164, 1020, 845, 755 cm^{-1}; **m.p.**: 124-126 °C; **[α]D^{25}** = −37.4 (c=0.61, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 70/30, 1.0 ml/min, λ = 230 nm, t_R (major) = 6.5 min, t_R (minor) = 8.7 min.



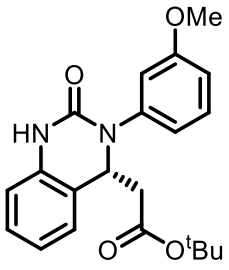
***tert*-Butyl (*R*)-2-(3-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (308)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out at 50 °C for 29 hours), using ***tert*-butyl (*E*)-3-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate (291)** (73.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 1/1) afforded the title compound as a white solid (73.4 mg, 99%, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H, NH), 7.37 – 7.29 (m, 2H, Ar-H), 7.24 – 7.11 (m, 2H, Ar-H), 7.01 – 6.90 (m, 3H, Ar-H), 6.75 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-H), 5.14 (dd, *J* = 8.2, 4.6 Hz, 1H, CH), 3.83 (s, 3H, OCH_3), 2.76 (dd, *J* = 14.7, 4.6 Hz, 1H, CH_2), 2.69 (dd, *J* = 14.7, 8.2 Hz, 1H, CH_2), 1.32 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (C(O)$OC(CH_3)_3$), 158.5 (C(O)NH or ArCO), 154.1 (C(O)NH or ArCO), 136.7 (ArC), 133.7 (ArC), 129.2 (ArCH), 128.8 (ArCH), 126.0 (ArCH), 122.1 (ArC), 121.2 (ArCH), 114.7 (ArCH), 114.4 (ArCH), 81.3 ($OC(CH_3)_3$), 60.4 (CH), 55.6 (OCH_3), 41.1(CH_2), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{25}N_2O_4$ ($[M+H]^+$) 369.1809, found 369.1810; **FT-IR (thin film)** ν_{max} 2857, 2160, 1675, 1605, 1581, 1495, 1450, 1380, 1305, 1249, 1188, 1117, 1035, 996, 975, 933, 889, 840, 761, 687, 666, 646 cm^{-1}; **m.p.**: 66-89 °C; **[α]D^{25}** = −98.8 (c=0.63, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 280 nm, t_R (major) = 33.3 min, t_R (minor) = 46.6 min.



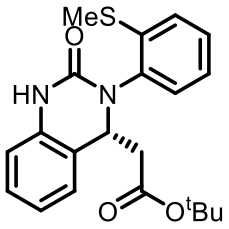
***tert*-Butyl (*R*)-2-(3-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (309)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out at 50 °C), using ***tert*-butyl (*E*)-3-(2-(3-(2-methoxyphenyl)ureido)phenyl)acrylate (292)** (73.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 1/1) afforded the title compound as a white solid (8:1 (**A**:**B**) mixture of rotamers) (58.9 mg, 80%, 91:9 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 0.11H, NH (**B**)), 8.46 (s, 0.88H, NH (**A**)), 7.41 (brs, 1H, Ar-H), 7.32 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H, Ar-H), 7.20 – 7.10 (m, 2H, Ar-H), 7.06 – 6.96 (m, 2H, Ar-H), 6.96 – 6.87 (m, 1H, Ar-H), 6.78 (dd, *J* = 8.0, 1.1 Hz, 0.11H, Ar-H (**B**)), 6.73 (dd, *J* = 8.3, 1.2 Hz, 0.88H, Ar-H (**A**)), 5.10 (dd, *J* = 8.3, 4.7 Hz, 1H, CH), 3.80 (d, *J* = 3.4 Hz, 3H, OCH_3), 2.86 – 2.60 (m, 2H, CH_2), 1.31 (s, 8H, $OC(CH_3)_3$ (**A**)), 1.29 (s, 1H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 ($C(O)OC(CH_3)_3$), 155.3 (C(O)NH or ArCO), 153.7 (C(O)NH or ArCO), 136.8 (ArC), 131.2 (ArC), 131.1 (ArCH), 129.0 (ArCH), 128.5 (ArCH), 126.0 (ArCH), 121.9 (ArCH), 121.5 (ArCH), 120.9 (ArC), 114.3 (ArCH), 112.4 (ArCH), 81.1 ($OC(CH_3)_3$), 58.0 ($CHCH_2$), 55.8 (OCH_3), 41.6 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{25}N_2O_4$ ($[M+H]^+$) 369.1809, found 369.1809; **FT-IR (thin film)** ν_{max} 3791, 3213, 3068, 2932, 2161, 2035, 1978, 1723, 1676, 1601, 1502, 1454, 1423, 1367, 1288, 1259, 1143, 1116, 1027, 847, 752, 692 cm^{-1}; **m.p.**: 70-73 °C; **[α]D^{25}** = −147.4 (c=0.63, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 240 nm, t_R (major) = 15.1 min, t_R (minor) = 13.3 min.



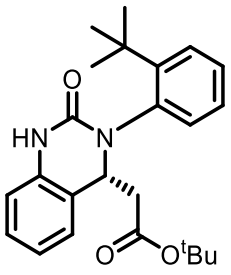
***tert*-Butyl (*R*)-2-(3-(3-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (310)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out at 50 °C), using ***tert*-butyl (*E*)-3-(2-(3-(3-methoxyphenyl)ureido)phenyl)acrylate (293)** (73.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/2) afforded the title compound as a white solid (71.4 mg, 97%, 93:7 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H, NH), 7.34 (ddd, *J* = 8.3, 7.4, 0.9 Hz, 1H, Ar-H), 7.17 (dd, *J* = 8.0, 6.6 Hz, 2H, Ar-H), 7.07 – 6.99 (m, 2H, Ar-H), 6.94 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-H), 6.86 (ddd, *J* = 8.3, 2.3, 1.2 Hz, 1H, Ar-H), 6.82 – 6.75 (m, 1H, Ar-H), 5.23 (dd, *J* = 8.4, 4.5 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 2.84 – 2.65 (m, 2H, CH_2), 1.33 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 ($C(O)OC(CH_3)_3$), 160.3 (ArCO), 153.9 (C(O)NH), 142.1 (ArC), 136.6 (ArC), 129.9 (ArCH), 128.7 (ArCH), 125.9 (ArCH), 122.0 (ArCH), 121.3 (ArC), 119.7 (ArCH), 114.5 (ArCH), 113.5 (ArCH), 112.8 (ArCH), 81.3 ($OC(CH_3)_3$), 60.1 ($CHCH_2$), 55.5 (OCH_3), 41.2 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{25}N_2O_4$ ($[M+H]^+$) 369.1809, found 369.1810; **FT-IR (thin film)** ν_{max} 3221, 3068, 2978, 2161, 2027, 1977, 1722, 1674, 1604, 1489, 1453, 1416, 1368, 1289, 1207, 1142, 1045, 844, 755, 697 cm^{-1}; **m.p.**: 54-57 °C; **[α]D^{25}** = −92.1 (c=0.92, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 240 nm, t_R (major) = 20.5 min, t_R (minor) = 12.1 min.



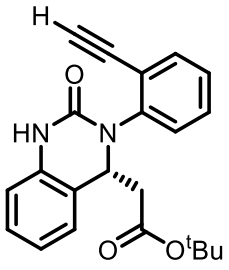
***tert*-Butyl (*R*)-2-(3-(2-(methylthio)phenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (311)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out at 50 °C), using ***tert*-butyl (*E*)-3-(2-(3-(2-(methylthio)phenyl)ureido)phenyl)acrylate (294)** (76.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 1/1) afforded the title compound as a white solid (74.8 mg, 98%, 96:4 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H, NH), 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 7.39 – 7.30 (m, 1H, Ar-H), 7.28 – 7.20 (m, 2H, Ar-H), 7.18 – 7.09 (m, 2H, Ar-H), 6.93 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-H), 6.74 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar-H), 5.11 (dd, *J* = 7.3, 5.5 Hz, 1H, CH), 2.83 – 2.67 (m, 2H, CH_2), 2.33 (s, 3H, SCH_3), 1.31 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (C(O)$OC(CH_3)_3$), 153.8 (C(O)NH), 137.6 (ArC), 137.0 (ArC), 136.5 (ArC), 131.6 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 126.1 (ArCH), 125.8 (ArCH), 125.0 (ArCH), 122.0 (ArCH), 121.2 (ArC), 114.6 (ArCH), 81.1 ($OC(CH_3)_3$), 58.0 (CH), 41.2 (CH_2), 27.9 ($OC(CH_3)_3$), 14.5 (SCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{25}{}^{32}SN_2O_3$ ($[M+H]^+$) 385.1580, found 385.1581; **FT-IR (thin film)** ν_{max} 3019, 2161, 2026, 1722, 1675, 1603, 1473, 1447, 1369, 1295, 1215, 1143, 929, 745, 668, 628 cm^{-1}; **m.p.**: 85-87 °C; **[α]D^{25}** = −261.9 (c=0.70, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 240 nm, t_R (major) = 15.2 min, t_R (minor) = 20.8 min.



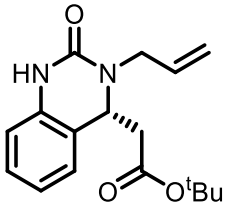
***tert*-Butyl (*R*)-2-(3-(2-(*tert*-butyl)phenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (312)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out at 50 °C), using ***tert*-butyl (*E*)-3-(2-(3-(2-(tert-butyl)phenyl)ureido)phenyl)acrylate (295)** (78.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (71.1 mg, 90%, 97:3 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H, NH), 7.60 – 7.53 (m, 1H, Ar-H), 7.40 – 7.28 (m, 3H, Ar-H), 7.14 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 7.09 (dd, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 6.91 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 6.72 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-H), 4.89 (dd, *J* = 9.5, 4.3 Hz, 1H, CH), 2.99 (dd, *J* = 14.2, 4.3 Hz, 1H, CH_2), 2.80 (dd, *J* = 14.2, 9.5 Hz, 1H, CH_2), 1.305 (s, 9H, $C(CH_3)_3$), 1.296 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 ($C(O)OC(CH_3)_3$), 155.1 (C(O)NH), 147.5 (ArC), 138.8 (ArC), 136.6 (ArC), 133.7 (ArCH), 128.9 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 127.0 (ArCH), 126.3 (ArCH), 122.1 (ArCH), 121.2 (ArC), 114.6 (ArCH), 81.2 ($OC(CH_3)_3$), 60.6 ($CHCH_2$), 40.1 ($CHCH_2$), 35.7 ($ArC(CH_3)_3$), 31.6 ($C(CH_3)_3$), 28.0 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{31}N_2O_3$ ($[M+H]^+$) 395.2329, found 395.2329; **FT-IR (thin film)** ν_{max} 3214, 3065, 2972, 2513, 2160, 2028, 1978, 1724, 1677, 1602, 1503, 1486, 1447, 1418, 1367, 1289, 1140, 1092, 1054, 960, 847, 755, 725, 667, 630 cm^{-1}; **m.p.**: 178-180 °C; **$[\alpha]D^{25}$** = −147.7 (c=0.71, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 17.3 min, t_R (minor) = 18.9 min.



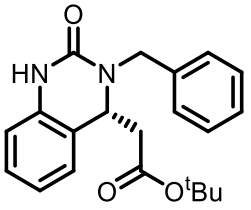
***tert*-Butyl (*R*)-2-(3-(2-ethynylphenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (313)** was prepared following **General Procedure C**, (variation from standard conditions: reaction carried out for 48h), using ***tert*-butyl (*E*)-3-(2-(3-(2-ethynylphenyl)ureido)phenyl)acrylate (296)** (72.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/2) afforded the title compound as a white solid (65.8 mg, 91%, 96:4 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, NH), 7.60 (dd, *J* = 7.7, 1.6 Hz, 1H, Ar-H), 7.52 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.44 (td, *J* = 7.7, 1.6 Hz, 1H, Ar-H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H, Ar-H), 7.14 (dtd, *J* = 8.0, 3.9, 1.3 Hz, 2H, Ar-H), 6.92 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-H), 6.74 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar-H), 5.33 (dd, *J* = 8.2, 4.9 Hz, 1H, CH), 3.10 (s, 1H), 2.83-2.74 (m, 1H, CH_2), 2.69 (dd, *J* = 14.8, 8.3 Hz, 1H, CH_2), 1.31 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 ($C(O)OC(CH_3)_3$), 153.6 (C(O)NH), 142.8 (ArC), 136.6 (ArC), 134.0 (ArCH), 130.8 (ArCH), 129.6 (ArCH), 128.6 (ArCH), 127.5 (ArCH), 125.8 (ArCH), 122.1 (ArCH), 121.6 (ArC), 121.4 (ArC), 114.5 (ArCH), 82.9 (C≡CH), 81.2 ($OC(CH_3)_3$), 80.3 (C≡CH), 59.6 ($CHCH_2$), 41.4 ($CHCH_2$), 28.0 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{23}N_2O_3$ ($[M+H]^+$) 363.1703, found 363.1703; **FT-IR (thin film)** ν_{max} 3019, 2160, 2031, 1721, 1675, 1604, 1485, 1451, 1422, 1369, 1287, 1215, 1143, 929, 745, 668, 628 cm^{-1}; **m.p.**: 76-78 °C; **[α]D^{25}** = −306.6 (c=0.68, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 254 nm, t_R (major) = 24.2 min, t_R (minor) = 36.5 min.



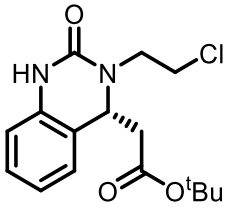
***tert*-Butyl (*R*)-2-(3-allyl-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (320)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out at 60 °C), using ***tert*-butyl (*E*)-3-(2-(3-allylureido)phenyl)acrylate (315)** (60.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 7/13) afforded the title compound as a colorless oil (60.4 mg, 99%, 85:15 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, NH), 7.17 (tt, *J* = 7.7, 2.1 Hz, 1H, Ar-H), 7.08 (dd, *J* = 7.7, 1.5 Hz, 1H, Ar-H), 6.99 – 6.86 (m, 1H, Ar-H), 6.86 – 6.78 (m, 1H, Ar-H), 5.83 (dddd, *J* = 17.0, 10.1, 6.7, 4.8 Hz, 1H, CH=CH_2), 5.24 (dd, *J* = 17.3, 1.6 Hz, 1H, CH=CH_2), 5.19 (dd, *J* = 10.3, 1.5 Hz, 1H, CH=CH_2), 4.83 (dd, *J* = 8.4, 4.8 Hz, 1H, CH), 4.66 (ddt, *J* = 15.8, 5.1, 1.7 Hz, 1H, NCH_2), 3.68 (dd, *J* = 15.7, 6.7 Hz, 1H, NCH_2), 2.69 (dd, *J* = 14.8, 4.8 Hz, 1H, CH_2), 2.55 (dd, *J* = 14.8, 8.4 Hz, 1H, CH_2), 1.38 (s, 9H, OC(CH_3)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9 (C(O)OC(CH_3)$_3$), 155.0 (C(O)NH), 136.7 (ArC), 133.4 (CH=CH_2), 128.6 (ArCH), 125.7 (ArCH), 122.0 (ArCH), 121.3 (ArC), 117.7 (CH=CH_2), 114.3 (ArCH), 81.3 (OC(CH_3)$_3$), 55.2 (CH), 47.8 (NCH_2), 41.1 (CH_2), 28.1 (OC(CH_3)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{23}N_2O_3$ ([M+H]$^+$) 303.1703, found 303.1704; **FT-IR (thin film)** ν_{max} 3211, 3067, 2977, 2930, 2535, 2160, 2028, 1722, 1669, 1605, 1466, 1416, 1368, 1289, 1259, 1147, 995, 925, 846, 755 cm^{-1}; **[α]D^{25}** = +38.1 (c=1.83, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 254 nm, t_R (major) = 20.1 min, t_R (minor) = 22.2 min.



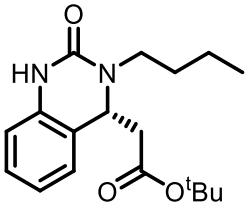
***tert*-Butyl (*R*)-2-(3-benzyl-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (321)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out at 50 °C for 30 hours), using ***tert*-butyl (*E*)-3-(2-(3-benzylureido)phenyl)acrylate (316)** (70.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as a white solid (5:1 (**A**:**B**) mixture of rotamers) (67.7 mg, 96%, 85:15 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 0.8H, NH (**A**)), 8.77 (s, 0.2H, NH (**B**)), 7.35 – 7.24 (m, 5H, Ar-H), 7.17 (td, J = 7.7, 1.5 Hz, 0.2H (**B**)), 7.14 (td, J = 7.7, 1.5 Hz, 0.8H (**A**)), 6.99 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 6.89 (td, J = 7.6, 1.1 Hz, 0.2H (**B**)), 6.87 (td, J = 7.6, 1.1 Hz, 0.8H (**A**)), 6.83 (dd, *J* = 8.0, 1.1 Hz, 0.2H (**B**)), 6.77 (dd, *J* = 8.0, 1.1 Hz, 0.8H, Ar-H (**A**)), 5.31 (d, *J* = 15.4 Hz, 1H, NCH_2), 4.79 (dd, *J* = 8.2, 4.9 Hz, 1H, CH), 4.23 (dd, *J* = 15.4, 1.5 Hz, 1H, NCH_2), 2.72 – 2.51 (m, 2H, CH_2), 1.38 (s, 7.5H, $OC(CH_3)_3$ (**A**)), 1.37 (s, 1.5H, $OC(CH_3)_3$ (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 ($C(O)OC(CH_3)_3$), 155.6 (C(O)NH), 137.1 (ArC), 129.0 (ArC), 128.8 (ArCH), 128.7 (ArC), 128.5 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 125.8 (ArCH), 122.3 (ArCH), 114.4 (ArCH), 81.4 ($OC(CH_3)_3$), 55.4 (CH), 48.7 (NCH_2), 44.2, 41.2 (CH_2), 28.1 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{24}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 375.1679, found 375.1680; **FT-IR (thin film)** ν_{max} 3204, 3064, 2977, 2929, 2534, 2160, 2032, 1977, 1715, 1666, 1605, 1493, 1467, 1454, 1367, 1294, 1259, 1151, 1074, 1030, 958, 845, 756, 714 cm^{-1}; **m.p.**: 43-46 °C; **$[\alpha]D^{25}$** = +43.6 (c=0.93, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 20.7 min, t_R (minor) = 13.1 min.



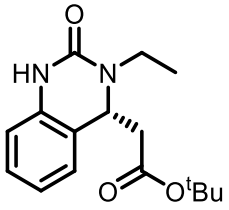
***tert*-Butyl *(R)*-2-(3-(2-chloroethyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (322)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out for 120h), using ***tert*-butyl *(E)*-3-(2-(3-(2-chloroethyl)ureido)phenyl)acrylate (317)** (65.0 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 13/7) afforded the title compound as a colorless oil (62.0 mg, 96%, 81:19 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H, NH), 7.19 (tt, *J* = 7.6, 1.6 Hz, 1H, Ar-H), 7.10 (dd, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 6.93 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-H), 6.86 – 6.78 (m, 1H, Ar-H), 4.93 (dd, *J* = 7.7, 5.5 Hz, 1H, CH), 4.27 (ddd, *J* = 14.2, 6.3, 5.1 Hz, 1H, CH_2CH_2), 3.78 – 3.62 (m, 2H, CH_2CH_2), 3.41 – 3.30 (m, 1H, CH_2CH_2), 2.74 – 2.63 (m, 1H, $CHCH_2$), 2.55 (dd, *J* = 15.0, 7.7 Hz, 1H, $CHCH_2$), 1.39 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.7 ($C(O)OC(CH_3)_3$), 155.0 ($C(O)NH$), 136.5 (ArC), 128.7 (ArCH), 125.8 (ArCH), 122.3 (ArCH), 121.3 (ArC), 114.3 (ArCH), 81.5 ($OC(CH_3)_3$), 58.0 (CH), 48.5 (CH_2CH_2), 42.0 (CH_2CH_2), 41.9 ($CHCH_2$), 28.1 ($OC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}ClN_2O_3{}^{23}Na$ ($[M+Na]^+$) 347.1133, found 347.1134; **FT-IR (thin film)** ν_{max} 3019, 2160, 2031, 1715, 1667, 1605, 1466, 1369, 1294, 1259, 1215, 1150, 1012, 929, 844, 745, 668, 626 cm^{-1}; **[α]D^{25}** = +44.6 (c=1.89, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 280 nm, t_R (major) = 16.0 min, t_R (minor) = 11.0 min.



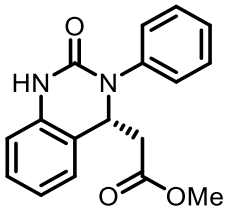
***tert*-Butyl *(R)*-2-(3-butyl-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (323)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out at 80 °C for 72 hours), using ***tert*-butyl (*E*)-3-(2-(3-butylureido)phenyl)acrylate (318)** (63.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 3/1) afforded the title compound as a colorless oil (45.9 mg, 72%, 86:14 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H, NH), 7.17 (tt, *J* = 7.9, 1.4 Hz, 1H, Ar-H), 7.10 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 6.90 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.79 (ddd, *J* = 7.9, 4.1, 1.1 Hz, 1H, Ar-H), 4.80 (dd, *J* = 8.5, 4.8 Hz, 1H, CH), 4.05 – 3.92 (m, 1H, CH_2), 2.97 (ddd, *J* = 14.0, 7.9, 6.2 Hz, 1H, CH_2), 2.71 – 2.61 (m, 1H, $CH_2C(O)O$), 2.59 – 2.48 (m, 1H, $CH_2C(O)O$), 1.66 – 1.52 (m, 2H, CH_2), 1.38 (s, 9H, $OC(CH_3)_3$), 1.36 – 1.29 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** 170.0 ($C(O)OC(CH_3)_3$), 162.6, 152.3 (C(O)NH), 138.8 (ArC), 135.0 (ArCH), 128.5 (ArCH), 123.4 (ArCH), 122.3 (ArC), 115.1 (ArCH), 81.5 ($OC(CH_3)_3$), 56.2 (CH), 41.0 ($CH_2C(O)O$), 30.2 (CH_2), 28.2 (CH_2), 28.1 ($OC(CH_3)_3$), 20.4 (CH_2), 14.0 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{26}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 341.1836, found 341.1836; **FT-IR (thin film)** ν_{max} 3207, 2960, 2932, 2873, 2160, 2028, 1714, 1663, 1607, 1493, 1454, 1409, 1370, 1287, 1149, 1077, 949, 845, 757, 693 cm^{-1}; **$[\alpha]D^{25}$** = +22.8 (c=1.41, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 11.6 min, t_R (minor) = 8.3 min.



***tert*-Butyl (*R*)-2-(3-ethyl-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (324)** was prepared following **General Procedure C** (variation from standard conditions: reaction carried out for 216 hours), using ***tert*-butyl (*E*)-3-(2-(3-ethylureido)phenyl)acrylate (319)** (58.1 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 7/13) afforded the title compound as an off-white solid (33.1 mg, 57%, 89:11 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H, NH), 7.17 (td, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 7.11 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar-H), 6.91 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-H), 6.82 – 6.75 (m, 1H, Ar-H), 4.84 (dd, *J* = 8.4, 4.9 Hz, 1H, CH), 3.99 (dq, *J* = 14.2, 7.1 Hz, 1H, NCH_2), 3.10 (dq, *J* = 14.2, 7.1 Hz, 1H, NCH_2), 2.72 – 2.62 (m, 1H, CH_2), 2.55 (dd, *J* = 14.9, 8.4 Hz, 1H, CH_2), 1.39 (s, 9H, $OC(CH_3)_3$), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.0 ($C(O)OC(CH_3)_3$), 154.8 (C(O)NH), 136.8 (ArC), 128.6 (ArCH), 125.8 (ArCH), 121.9 (ArCH), 121.6 (ArC), 114.1 (ArCH), 81.4 ($OC(CH_3)_3$), 55.7 (CH), 41.6 (CH_2), 40.7 (NCH_2), 28.1 ($OC(CH_3)_3$), 13.8 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{22}N_2O_3{}^{23}Na$ ($[M+Na]^+$) 313.1523, found 313.1523; **FT-IR (thin film)** ν_{max} 3020, 2402, 2161, 2028, 1666, 1605, 1471, 1215, 1148, 929, 745, 668, 627 cm^{-1}; **m.p.**: 51-53 °C; **[α]D^{25}** = +23.1 (c=0.47, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 254 nm, t_R (major) = 10.2 min, t_R (minor) = 6.6 min.



Methyl (*R*)-2-(2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (314) was prepared following **General Procedure C** (variation from standard conditions: reaction carried out for 48 hours), using **methyl (*E*)-3-(2-(3-phenylureido)phenyl)acrylate (297)** (59.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded the title compound as an off-white solid (10:1 (**A**:**B**) mixture of rotamers) (58.5 mg, 99%, 92:8 er). Data is consistent with the published literature. [10]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 0.1H, NH (**B**)), 8.94 (s, 1H, NH (**A**)), 7.49 – 7.40 (m, 4H, Ar-H), 7.36 – 7.27 (m, 1H, Ar-H), 7.23 – 7.11 (m, 2H, Ar-H), 6.95 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 6.84 (d, *J* = 8.0, 0.1H, Ar-H (**B**)), 6.78 (d, *J* = 8.0, 1H, Ar-H (**A**)), 5.29 (dd, *J* = 8.4, 4.9 Hz, 1H, CH), 3.52 (s, 3H, CH_3 (**A**)), 3.50 (s, 0.3H, CH_3 (**B**)) 2.90 (dd, *J* = 15.0, 4.9 Hz, 1H, CH_2), 2.79 (dd, *J* = 15.0, 8.4 Hz, 1H, CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.5 (C(O)OCH_3), 154.0 (C(O)NH), 140.9 (ArC), 136.6 (ArC), 129.3 (ArCH), 128.9 (ArCH), 127.6 (ArCH), 127.0 (ArCH), 125.6 (ArCH), 122.2 (ArCH), 121.2 (ArC), 114.6 (ArCH), 60.0 (CH), 51.8 (CH_3), 40.0 (CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{17}N_2O_3$ ($[M+H]^+$) 297.1234, found 297.1235; **FT-IR (thin film)** ν_{max} 3280, 2950, 2555, 2160, 2024, 1977, 1718, 1642, 1599, 1582, 1552, 1498, 1445, 1322, 1275, 1235, 1195, 1171, 976, 760, 749, 693 cm^{-1}; **m.p.**: 52-54 °C; **[α]D^{25}** = −113.6 (c=0.28, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 70/30, 1.0 ml/min, λ = 240 nm, t_R (major) = 12.5 min, t_R (minor) = 15.8 min.

4.2.6 Scale-up and Derivatisation

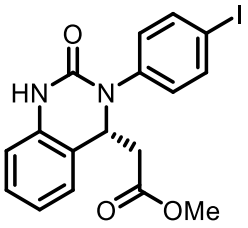
Scale-up

CPME (0.0125 M, 32 mL) was added to the BIMP catalysts precursors **S9** (189.8 mg, 0.4 mmol, 0.02 eq) and tris(4-methoxyphenyl)phosphine (141.0 mg, 0.4 mmol, 0.02 eq) in a 100 mL RBF under N_2 at room temperature. The reaction mixture was stirred for 24 hours before transferring to a 1000 mL RBF and evaporating to dryness under reduced pressure. The iminophosphorane product was confirmed by HRMS and TLC and used as crude for enantioselective reactions without any purification.

Urea **1j** (9.29 g, 20 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst (0.4 mmol, 0.02 eq) in toluene (0.025M, 800 mL) under N_2 at 50 °C. The reaction mixture was stirred at room temperature for 20 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc = 7/3) afforded **2j** as an off-white solid (7.90 g, 85%, 92.5:7.5 er).

Material was dissolved in the minium volume of CH_2Cl_2 before carefully layering with pentane in a RBF. The flask was sealed with a suba-seal. A needle was placed in the seal to allow slow evaporation. The crushed out solid after several days was filtered out. The combined filtrate was concentrated under reduced pressure to afford colourless crystal of enantioenriched **2j** (99.5:0.5 er).

Derivatisation

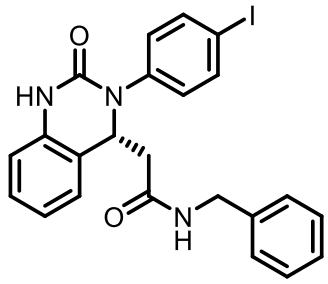


Methyl (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (337) was prepared according to the following procedure. Trifluoroacetic acid (3 mL, 7 mL/mmol) was added dropwise to a solution of the *tert*-butyl (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (**2j**) (200 mg, 0.43 mmol, 1.0 eq, 99.5:0.5 er) in CH_2Cl_2 (6 mL, 2 x Volume of trifluoroacetic acid) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 hours. Volatiles were removed under a stream of nitrogen gas to afford (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid which was used as crude for next step without any purification.

Thionyl chloride (112.6 mg, 0.95 mmol, 2.2 eq) was added dropwise to a solution of the (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid in MeOH (11 mL, 0.04M) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 21 hours before quenching with a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to afford the title compound as an off-white solid (176.7 mg, 97%, 99.4:0.6 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, NH), 7.78 – 7.70 (m, 2H, Ar-H), 7.24 – 7.13 (m, 4H, Ar-H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.78 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar-H), 5.26 (dd, *J* = 8.2, 5.0 Hz, 1H, CH), 3.53 (s, 3H, CH_3), 2.85 (dd, *J* = 15.1, 5.0 Hz, 1H, CH_2), 2.76 (dd, *J* = 15.1, 8.2 Hz, 1H, CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.4 (C(O)OCH_3), 153.5 (C(O)NH), 140.6 (ArC), 138.5 (ArCH), 136.3 (ArC), 129.4 (ArCH), 129.2 (ArCH), 125.8 (ArCH), 122.7 (ArCH), 121.1 (ArC), 114.6 (ArCH), 91.8(CI), 59.9 ($CHCH_2$), 52.0 (CH_3), 40.0 ($CHCH_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{16}IN_2O_3$ ($[M+H]^+$) 423.0200, found 423.0198; **FT-IR (thin film)** ν_{max} 3213, 3064, 2950, 2544, 2160, 2032, 1734, 1677, 1603, 1503, 1485, 1449, 1419, 1396, 1358, 1296, 1251, 1207, 1148, 1059, 1037, 1009, 919, 828, 755,

722 cm^{-1}; **m.p.**: 57-59 °C; **[α]D^{25}** = −92.6 (c=0.94, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 70/30, 1.0 ml/min, λ = 254 nm, t_R (major) = 10.3 min, t_R (minor) = 8.2 min.



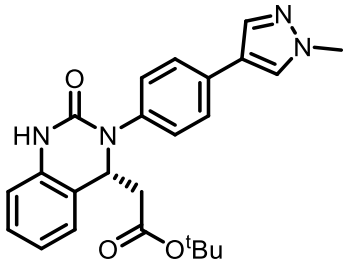
(*R*)-*N*-benzyl-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetamide (338) was prepared according to the following procedure. Trifluoroacetic acid (3 mL, 7 mL/mmol) was added dropwise to a solution of the *tert*-butyl (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (**2j**) (200 mg, 0.43 mmol, 1.0 eq, 99.5:0.5 er) in CH_2Cl_2 (6 mL, 2 x Volume of trifluoroacetic acid) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 hours. Volatiles were removed under a stream of nitrogen gas to afford (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid which was used as crude for next step without any purification.

Oxalyl chloride (81.9 mg, 0.65 mmol, 1.5 eq) and a few drops of DMF was added dropwise to a solution of the (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetic acid in CH_2Cl_2 (0.9 mL, 0.5M) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 2 hours. Volatiles were removed under a stream of nitrogen gas to afford (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetyl chloride which was used as crude for next step without any purification.

Benzylamine (3 mL) and Et_3N (3.8 mL) was added to a solution of the afford (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetyl chloride in CH_2Cl_2 (5 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours before quenching with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with 1M HCl aqueous solution (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (50 mL). The resulting mixture was dried over Na_2SO_4, filtered and evaporated to dryness under reduced

pressure. Purification by silica gel chromatography (pentane/EtOAc = 2/3) afforded the title compound as an off-white solid (77.3 mg, 36%, >99.5:0.5 er).

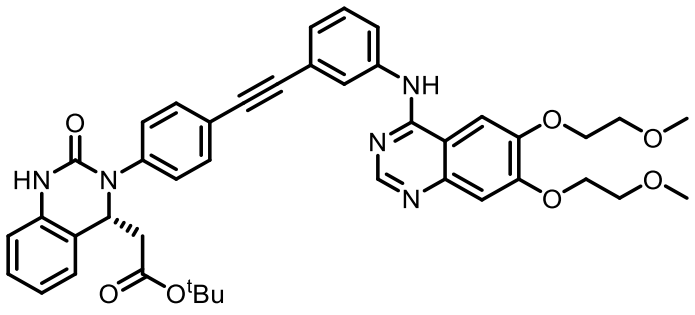
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H, ArNH), 7.68 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.30 – 7.11 (m, 7H, Ar-H), 7.08 – 7.00 (m, 2H, Ar-H), 6.94 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.73 (d, *J* = 7.9 Hz, 1H, Ar-H), 5.78 (t, *J* = 5.7 Hz, 1H, NHCH$_2$), 5.30 (dd, *J* = 9.1, 4.0 Hz, 1H, CH), 4.29 (dd, *J* = 14.7, 4.9 Hz, 1H, NHCH$_2$), 4.17 (dd, *J* = 14.6, 4.3 Hz, 1H, NHCH$_2$), 2.75 (dd, *J* = 13.7, 4.3 Hz, 1H, CHCH$_2$), 2.52 (dd, *J* = 13.6, 9.1 Hz, 1H, CHCH$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.6 (C(O)NH), 153.7 (NC(O)NH), 140.6 (ArC), 138.4 (ArCH), 137.7 (ArC), 136.0 (ArC), 129.0 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 126.2 (ArCH), 122.7 (ArCH), 121.4 (ArC), 114.4 (ArCH), 91.6 (CI), 60.0 (CH), 43.7 (NHCH$_2$), 41.9 (CHCH$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{23}H_{21}IN_3O_2$ ([M+H]$^+$) 498.0673, found 498.0673; **FT-IR (thin film)** ν_{max} 3020, 2542, 2160, 2032, 1978, 1676, 1602, 1485, 1451, 1215, 1009, 929, 745, 669, 629 cm^{-1}; **m.p.**: 108-112 °C; **[α]D^{25}** = −124.2 (c=0.27, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 80/20, 1.0 ml/min, λ = 240 nm, t_R = 17.2 min, (minor enantiomer not observed), >99.5:0.5 er.



***tert*-Butyl (*R*)-2-(3-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (339)** was prepared according to the following procedure. To an oven-dried screw-cap vial equipped with a magnetic stirrer bar was added *tert*-butyl (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (**2j**) (200 mg, 0.43 mmol, 1.0 eq, 99.5:0.5 er), 1-methyl-1H-pyrazole-3-boronic acid pinacol ester (107.4 mg, 0.52 mmol, 1.2 eq), Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (17.6 mg, 0.02 mmol, 0.05 eq), Cs_2CO_3 (280.2 mg, 0.86 mmol, 2.0 eq), 1,4-dioxane (3.5 mL, 0.13M) and H_2O (0.6 mL, 0.7M). The reaction mixture was stirred under air at 110 °C for 23 hours. After cooled to room temperature, the

mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL). The resulting mixture was dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc = 3:7 to EtOAc) afforded the title compound as an off-white solid (159.4 mg, 89%, >99.5:0.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, NH), 7.76 (s, 1H, NNCH), 7.61 (s, 1H, NNCH), 7.51 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.24 – 7.15 (m, 2H, Ar-H), 6.97 (td, *J* = 7.5, 0.9 Hz, 1H, Ar-H), 6.77 (d, *J* = 7.8 Hz, 1H, Ar-H), 5.23 (dd, *J* = 8.5, 4.5 Hz, 1H, NCHCH$_2$), 3.96 (s, 3H, CH$_3$), 2.79 (dd, *J* = 14.8, 4.5 Hz, 1H, NCHCH$_2$), 2.71 (dd, *J* = 14.8, 8.5 Hz, 1H, NCHCH$_2$), 1.32 (s, 9H, OC(CH$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 (C(O)OC(CH$_3$)$_3$), 153.6 (C(O)NH), 139.1 (ArC), 136.7 (N-ArCH), 136.5 (ArC), 131.3 (ArC), 128.9 (ArCH), 128.0 (ArCH), 127.4 (N-ArCH), 126.5 (ArCH), 126.1 (ArCH), 122.8 (ArC), 122.3 (ArCH), 121.4 (ArC), 114.3 (ArCH), 81.4 (OC(CH$_3$)$_3$), 60.1 (NCHCH$_2$), 41.2 (NCHCH$_2$), 39.3 (CH$_3$), 28.0 (OC(CH$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{27}N_4O_3$ ([M+H]$^+$) 419.2078, found 419.2073; **FT-IR (thin film)** ν_{max} 3221, 2978, 2528, 2161, 2034, 1977, 1722, 1673, 1604 1572, 1505, 1452, 1416, 1367, 1301, 1213, 1142, 987, 956, 840, 755, 626 cm^{-1}; **m.p.**: 87-89 °C; **[α]D^{25}** = −89.2 (c=0.58, $CHCl_3$); **Chiral HPLC:** Chiralcel OJ, 98/2 to 70/30 gradient hexane/isopropanol, 1.0 ml/min, λ = 280 nm, t_R = 38.7 min, (minor enantiomer not observed), >99.5:0.5 er.



***tert*-Butyl (*R*)-2-(3-(4-((3-((6,7-bis(2-methoxyethoxy)quinazolin-4-yl)amino)phenyl)ethynyl)phenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (340)** was prepared according to the following procedure. To an oven-dried screw-cap vial equipped with a magnetic stirrer bar was added *tert*-butyl (*R*)-2-(3-(4-iodophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (**2j**) (200 mg, 0.43 mmol, 1.0 eq, 99.5:0.5 er), erlotinib (HCl complex) (172.7 mg, 0.43 mmol,

1.0 eq), copper iodide (16.4 mg, 0.09 mmol, 0.2 eq), bis(triphenylphosphine) palladium dichloride (30.2 mg, 0.043 mmol, 0.1 eq), triphenylphosphine (56.4 mg, 0.22 mmol, 0.5 eq) and anhydrous triethylamine (1.5 mL, 0.3M). The vial was closed, evacuated and back-filled with nitrogen three times before heating to 90 °C for 18 hours. After cooled to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/MeOH = 95:5) afforded the title compound as a pale yellow solid (155.1 mg, 50%, 98:2 er).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H, NC<u>H</u>N), 8.39 (s, 1H, N<u>H</u>), 8.18 (s, 1H, N<u>H</u>), 7.90 (s, 1H, Ar-<u>H</u>), 7.72 – 7.61 (m, 2H, Ar-<u>H</u>), 7.57 – 7.49 (m, 1H, Ar-<u>H</u>), 7.44 (ddd, *J* = 8.8, 7.1, 3.0 Hz, 1H, Ar-<u>H</u>), 7.38 (d, *J* = 8.1 Hz, 2H, Ar-<u>H</u>), 7.32 – 7.27 (m, 2H, Ar-<u>H</u>), 7.25 – 7.18 (m, 2H, Ar-<u>H</u>), 7.16 (d, *J* = 7.5 Hz, 1H, Ar-<u>H</u>), 7.00 – 6.94 (m, 1H, Ar-<u>H</u>), 6.81 (d, *J* = 8.0 Hz, 1H, Ar-<u>H</u>), 5.21 (dd, *J* = 8.1, 4.6 Hz, 1H, NC<u>H</u>), 4.28 (t, *J* = 4.8 Hz, 2H, OC<u>H</u>$_2$CH$_2$O), 4.19 (d, *J* = 5.3 Hz, 2H, OCH$_2$C<u>H</u>$_2$O), 3.78 (dq, *J* = 19.7, 6.3, 5.0 Hz, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.42 (s, 3H, C<u>H</u>$_3$), 3.41 (s, 3H, C<u>H</u>$_3$), 2.69 (qd, *J* = 14.9, 6.3 Hz, 2H, NCHC<u>H</u>$_2$), 1.30 (s, 9H, OC(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (126 MHz, $CDCl_3$)** δ 169.2 (<u>C</u>(O)OC(CH$_3$)$_3$), 156.7 (NH<u>C</u>=N or Ar<u>C</u>), 154.6 (NH<u>C</u>=N or Ar<u>C</u>), 153.5 (<u>C</u>(O)NH), 153.3 (N<u>C</u>HN), 148.8 (Ar<u>C</u>), 140.4 (Ar<u>C</u>), 139.0 (Ar<u>C</u>), 136.2 (Ar<u>C</u>), 132.5 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>H), 132.1 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 123.6 (Ar<u>C</u>), 122.5 (Ar<u>C</u>H), 122.4 (Ar<u>C</u>H), 121.9 (Ar<u>C</u>), 121.1 (Ar<u>C</u>), 114.3 (Ar<u>C</u>H), 109.4 (Ar<u>C</u>), 103.5 (Ar<u>C</u>H), 90.1 (C≡<u>C</u>), 88.8 (<u>C</u>≡C), 81.5 (O<u>C</u>(CH$_3$)$_3$), 70.9 (O<u>C</u>H$_2$CH$_2$O), 70.5 (O<u>C</u>H$_2$CH$_2$O), 69.2 (OCH$_2$<u>C</u>H$_2$O), 68.4 (OCH$_2$<u>C</u>H$_2$O), 59.9 (N<u>C</u>HCH$_2$), 59.344 (<u>C</u>H$_3$), 59.336 (<u>C</u>H$_3$), 41.2 (NCH<u>C</u>H$_2$), 28.0 (OC(<u>C</u>H$_3$)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{42}H_{44}N_5O_7$ ([M+H]$^+$) 730.3235, found 730.3227; **FT-IR (thin film)** ν_{max} 3019, 2452, 2160, 2032, 1977, 1722, 1671, 1622, 1602, 1578, 1510, 1434, 1369, 1291, 1215, 1143, 1033, 931, 843, 748, 668, 630 cm^{-1}.

m.p.: 148-152 °C; **[α]D^{25}** = −32.0 (c=0.60, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 220 nm, t_R (major) = 27.1 min, t_R (minor) = 26.0 min.

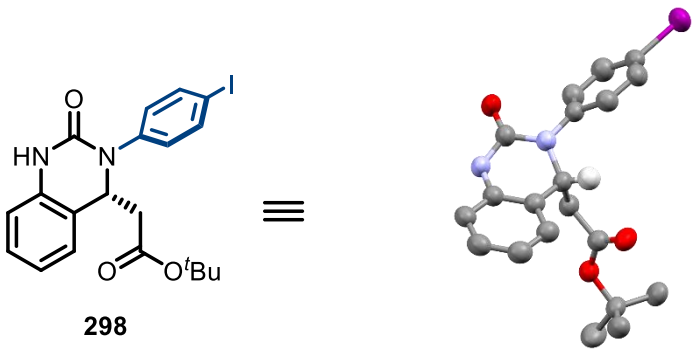
4.2.7 Single Crystal X-Ray Diffraction Data

X-ray diffraction data has been made available in the Cambridge Crystallographic Data Centre as **CCDC 2054508**

Preparation of single crystal sample: crystal preparation under air led to decomposition of **2j**. Anhydrous CH_2Cl_2 and pentane were degassed under N_2 for 30 minutes before being used for the crystal preparation. Material **2j** (99.5:0.5 er) was dissolved in minimum volume of CH_2Cl_2 under N_2 before carefully layering with pentane (approximately 3 x volume of CH_2Cl_2) in a vial equipped with a suba seal. The vial was closed, wrapped with aluminum foil and left at room temperature for a few hours to afford colourless crystal of enantiopure **2j** for single crystal X-ray diffraction experiment.

General X-ray Crystallography Methods

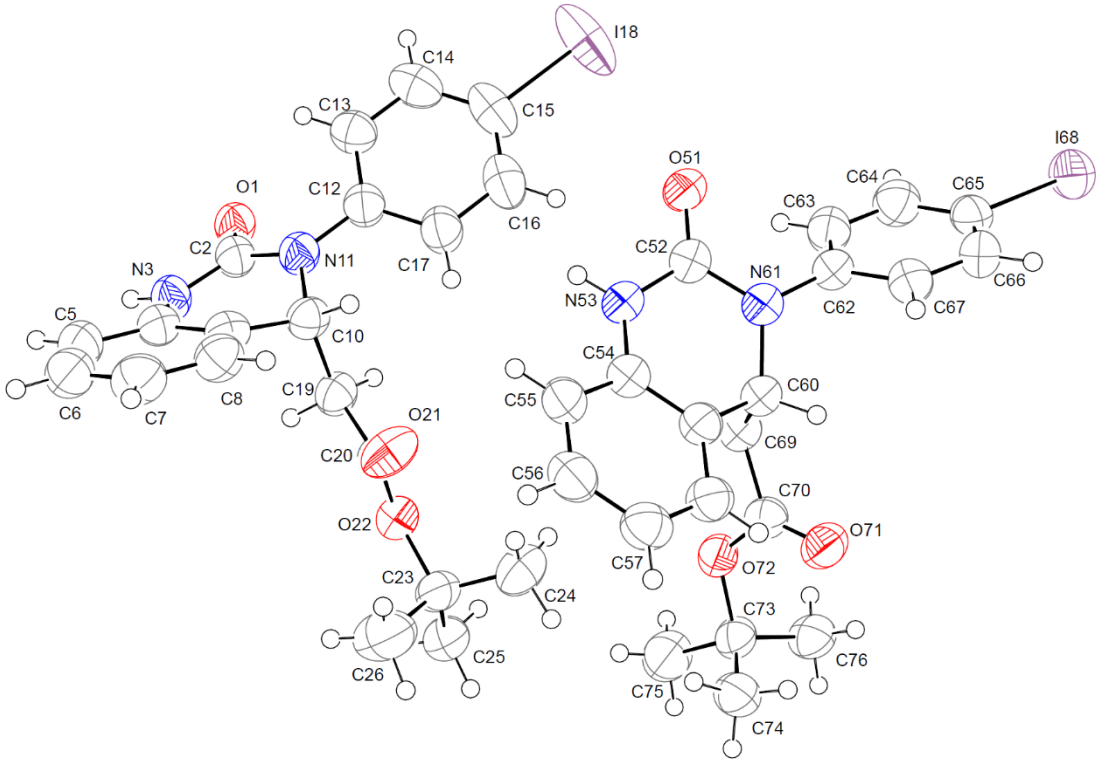
Single crystal X-ray diffraction data were collected using an Rigaku Oxford Diffraction SuperNova diffractometer fitted with an Oxford Cryosystems Cryostream 700 plus open flow nitrogen cooling device.[11] The CrysAlisPro software was used for data collection and integration. The structure was solved using charge flipping[12, 13] with SuperFlip method[14] within the CRYSTALS suite.[15, 16] The structures were then modified, improved and optimised by full-matrix least squares on F2 as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2054508) and can be obtained via www. ccdc.cam.ac.uk/data_request/cif.



298

Table 4. Crystal data and structure refinement for 7355.

Identification code	7355	
Empirical formula	C20 H21 I N2 O3	
Formula weight	464.30	
Temperature	K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 13.46500(10) Å	α = 90°.
	b = 9.55400(10) Å	β = 93.8204(9)°.
	c = 15.72860(10) Å	γ = 90°.
Volume	2018.90(3) $Å^3$	
Z	4	
Density (calculated)	1.527 Mg/m^3	
Absorption coefficient	12.635 mm^{-1}	
F(000)	928	
Crystal size	0.23 x 0.10 x 0.08 mm^3	
Theta range for data collection	2.816 to 76.574°.	
Index ranges	-16<=h<=16, -11<=k<=11, -19<=l<=19	
Reflections collected	22597	
Independent reflections	8251 [R(int) = 0.031]	
Completeness to theta = 75.043°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.36 and 0.03	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8251 / 1 / 470	
Goodness-of-fit on F^2	1.0586	
Final R indices [I>2sigma(I)]	R1 = 0.0748, wR2 = 0.1730	
R indices (all data)	R1 = 0.0752, wR2 = 0.1746	
Absolute structure parameter	0	
Largest diff. peak and hole	1.58 and -0.66 $e.Å^{-3}$	


I18
C14
C13
C15
O1
C12
C16
C2
N11
C17
N3
C5
C10
C6
C7
C8
C19
O21
C20
O22
C23
C24
C26
C25
O51
C64
C65
I68
C63
C52
C66
N61
N53
C62
C67
C54
C55
C60
C69
C56
C70
O71
C57
O72
C73
C76
C75
C74

4.2.8 Computational Studies

Details of TS studies

The highly flexible nature of the BIMP squaramide catalyst prompted us to perform a conformational analysis on model substrates of the catalyst (**Figure 16**). For this purpose, we explored the conformation spaces of the "*left arm – LA*" (side containing the amide moiety with the *tert*-butyl group) and "*right arm – RA*" (side with the iminophosphorane moiety with phenyl group) of the organocatalyst. Regarding the *left arm*, two conformations are possible which form a hydrogen bonding between the amide and the squaramide, and the model substrate **LA-1** with O(amide)–H(squaramide) interaction was preferred over **LA-2** with O(squaramide)–H(amide) (ΔG = 1.6 kcal mol^{-1}). On the other hand, the *right arm* of the catalyst can have the iminophosphorane located either on the top or bottom side of the squaramide plane. Similar energies between **RA-1** and **RA-2** were observed (ΔG = 0.1 kcal mol^{-1}). Taken altogether, these findings indicate that the various conformations of the catalyst are likely assessable. Below we detail the reactivity for every possible conformation of the BIMP squaramide catalyst.

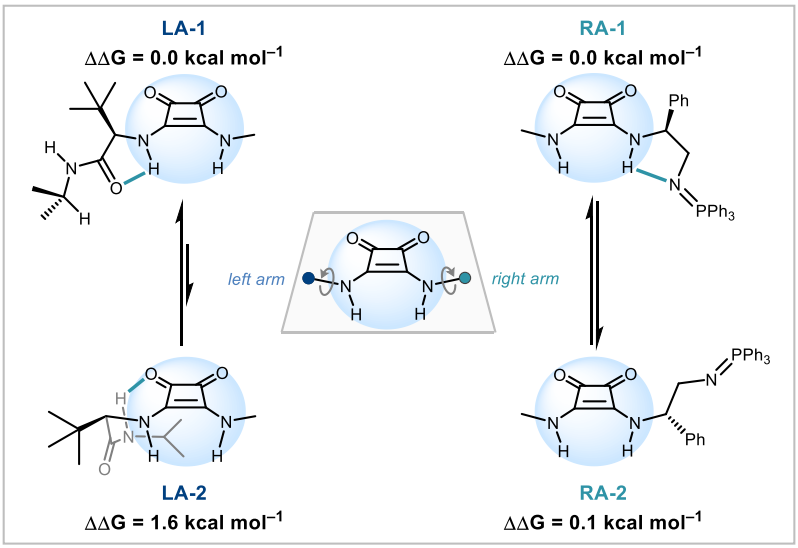


Figure 16. Relative stability of the model squaramide catalyst computed at COSMO(toluene)-ZORA-M06-2X/TZ2P//COSMO(toluene)-ZORA-BLYP-D3(BJ)/DZP. Energies (kcal mol^{-1}) are provided in the insert.

In general, there are two modes for which the substrate may bind to the substrate in the transition structures (TSs, Mode A and Mode B) as originally hypothesised by Pápai (**Figure 17**).[17-20] In the mode

A, the squaramide coordinates to the electrophile (ester) and the protonated iminophosphorane coordinates to the nucleophile (urea). In the mode B, the squaramide coordinates to the nucleophile (urea) and the protonated iminophosphorane coordinates to the electrophile (ester). Both activation modes were considered in the calculations of the TSs described below.

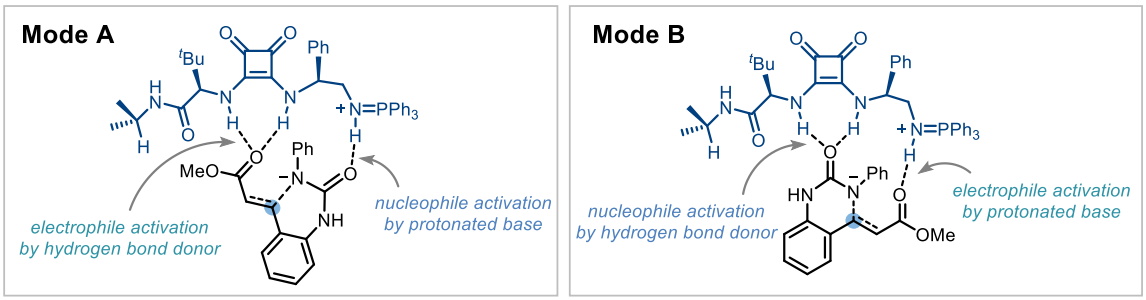
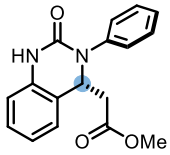


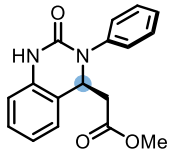
Figure 17. Activation modes of the BIMP catalyst.

Due to the conformational freedom and the existence of two potential activation modes of the BIMP catalyst, we computed and compared all the possible TSs for the stereoenantiochemistry-determining Michael reaction step involving substrate **297**. (**Figure 18**).



(R)-product

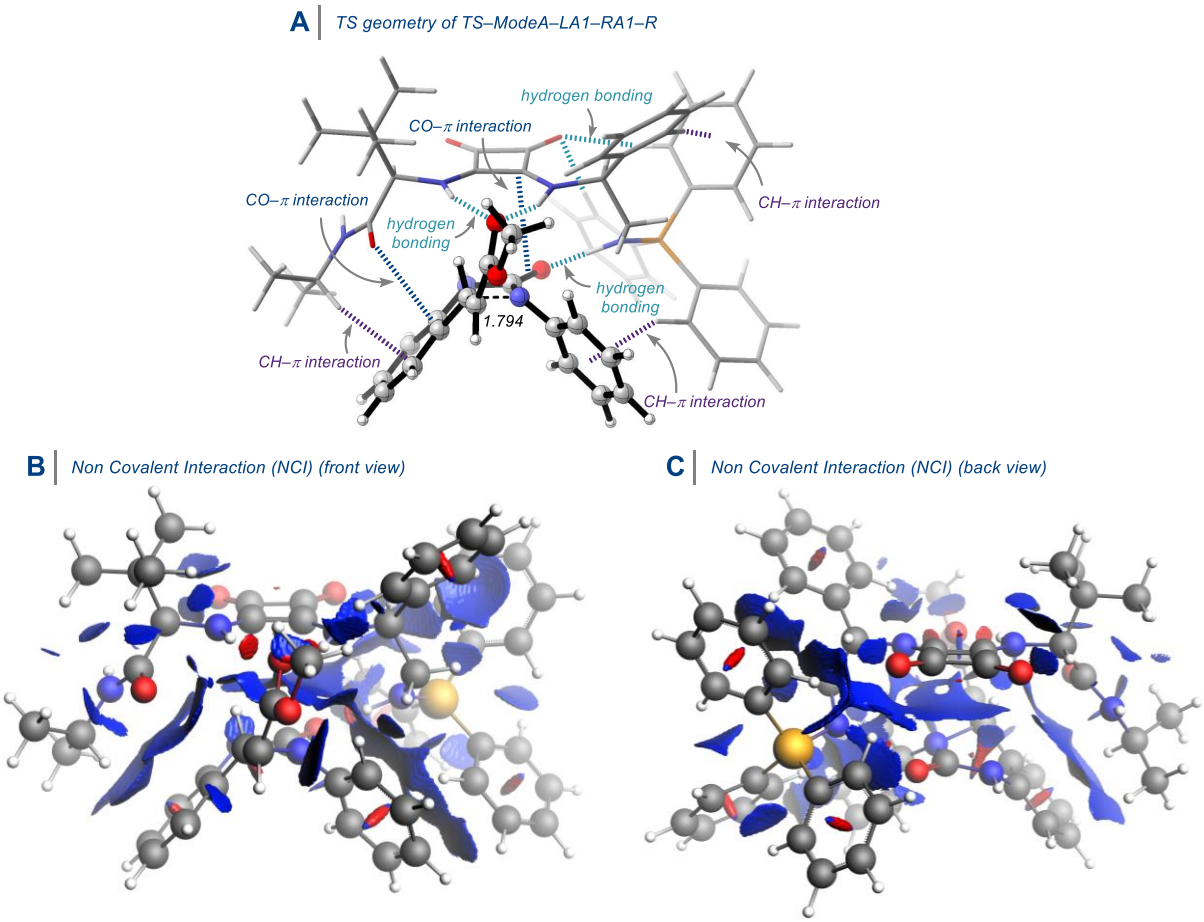
TSs for (R)-product	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$
TS–ModeA–LA1–RA1–*R*	15.1	–7.7
TS–ModeA–LA1–RA2–*R*	18.0	–4.2
TS–ModeA–LA2–RA1–*R*	16.6	–6.7
TS–ModeA–LA2–RA2–*R*	29.3	4.8
TS–ModeB–LA1–RA1–*R*	15.4	–6.5
TS–ModeB–LA1–RA2–*R*	24.0	–2.2
TS–ModeB–LA2–RA1–*R*	16.7	–6.2
TS–ModeB–LA2–RA2–*R*	27.2	2.1



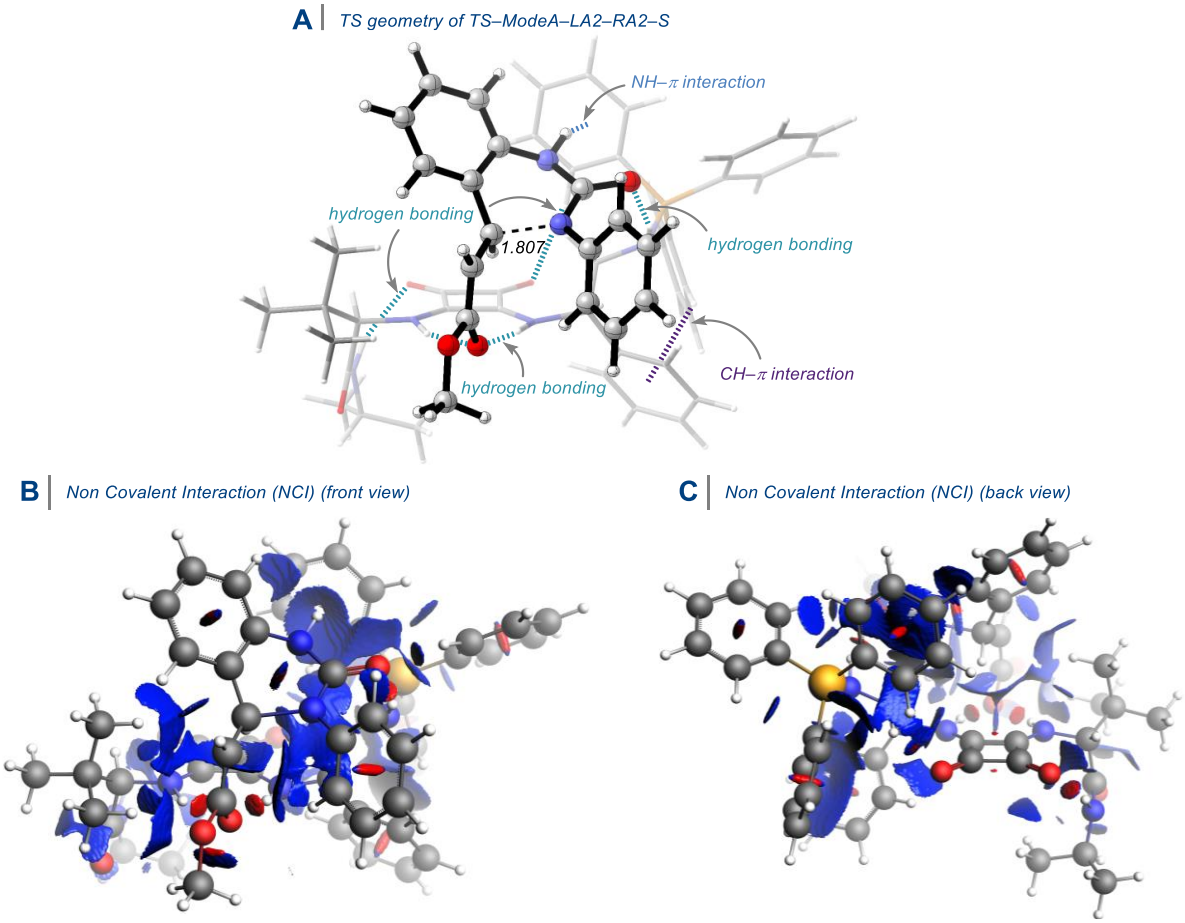
(S)-product

TSs for (S)-product	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$
TS–ModeA–LA1–RA1–*S*	27.7	3.3
TS–ModeA–LA1–RA2–*S*	17.6	–6.5
TS–ModeA–LA2–RA1–*S*	25.0	–0.8
TS–ModeA–LA2–RA2–*S*	16.3	–7.3
TS–ModeB–LA1–RA1–*S*	18.2	–6.3
TS–ModeB–LA1–RA2–*S*	19.7	–1.0
TS–ModeB–LA2–RA1–*S*	20.7	–3.3
TS–ModeB–LA2–RA2–*S*	21.3	–1.7

Figure 18. Relative stability of the possible intramolecular aza-Michael reaction transition structures computed at COSMO(toluene)-ZORA-M06-2X/TZ2P//COSMO(toluene)-ZORA-BLYP-D3(BJ)/DZP. Energies (kcal mol^{-1}) are provided in the insert.



Scheme 83. (A) Transition structure geometry of **TS–ModeA–LA1–RA1–R**, (B) ADFview2020 plot of non-covalent interaction (NCI) regions materialised by reduced density gradient isosurfaces (all default settings were used) colored according to the sign of the signed density $\lambda 2\rho$ (red and blue colors are associated with negatively and positively signed terms) for the transition structure geometry of **TS–ModeA–LA1–RA1–R** from the from view and (C) ADFview2020 plot of noncovalent interaction (NCI) for the transition structure geometry of **TS–ModeA–LA1–RA1–R** from the back view computed at COSMO(toluene)-ZORA-M06-2X/TZ2P//COSMO(toluene)-ZORA-BLYP-D3(BJ)/DZP. A forming bond length (Å) of TS geometry is provided in the insert.

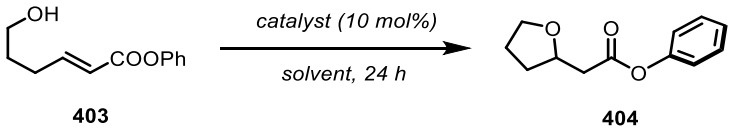


Scheme 84. (A) Transition structure geometry of **TS–ModeA–LA2–RA2–S**, (B) ADFview2020 plot of non-covalent interaction (NCI) regions materialised by reduced density gradient isosurfaces (all default settings were used) colored according to the sign of the signed density $\lambda 2\rho$ (red and blue colors are associated with negatively and positively signed terms) for the transition structure geometry of **TS–ModeA–LA2–RA2–S** from the from view and (C) ADFview2020 plot of noncovalent interaction (NCI) for the transition structure geometry of **TS–ModeA–LA2–RA2–S** from the back view computed at COSMO(toluene)-ZORA-M06-2X/TZ2P//COSMO(toluene)-ZORA-BLYP-D3(BJ)/DZP. A forming bond length (Å) of TS geometry is provided in the insert.

4.3 Experimental Details for Chapter 3

4.3.1 Optimisation Results

General procedure for optimisation of the intramolecular oxy-Michael reaction of alcohol 403:



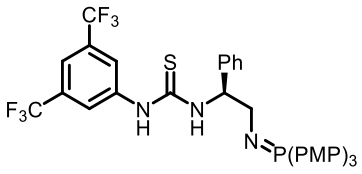
403 **404**

Alcohol **403** (10.3 mg, 0.05 mmol, 1.0 eq) was added to a solution of catalyst (0.005 mmol, 0.1 eq) in the appropriate solvent under N_2 at room temperature. The reaction mixture was stirred at the specified temperature for 24 hours unless otherwise indicated. The reaction was quenched by the addition of 1M AcOH in CH_2Cl_2 (1 mL). Conversion was determined by crude ^1H NMR. Volatiles were removed by a stream of N_2 gas, followed by filtration through silica gel with 30% Et_2O in pentane. The crude product was analysed by chiral HPLC (Chiralcel IB, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 210 nm, t_R (major) = 15.5 min, t_R (minor) = 11.0 min)

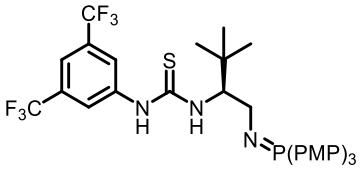
Table 5: Catalyst screen[a]

entry	cat. X	Conv. (%)[b]	er[c]	entry	cat. X	Conv. (%)[b]	er[c]
1	**233**	>95	86.5 : 13.5	18	**E28**	>95	90.5 : 9.5
2	**118**	>95	84.4 : 15.6	19	**E30**	>95	74.5 : 25.5
3	**235**	93%	80 : 20	20	**E31**	95	71.5 : 28.5
4	**243**	>95	79 : 21	21	**E32**	95	87 : 13
5	**244**	95	81.5 : 18.5	22	**E33**	>95	90.5 : 9.5
6	**E25**	93	83 : 17	23	**140**	53	76.5 : 23.5
7	**E29**	91	84 : 16	24	**E34**	>95	84.5 : 15.5
8	**E8**	88	80 : 20	25	**533**	>95	90.5 : 9.5
9	**554**	>95	91 : 9	26	**247**	>95	79 : 21
10	**246**	95	90 : 10	27	**E35**	61	51 : 49
11	**245**	>95	90 : 10	28	**E36**	94	64.5 : 35.5
12	**406**	**>95**	**92 : 8**				
13	**407**	>95	88 : 12				
14	**E26**	>95	85.5 : 14.5				
15	**E27**	>95	83.5 : 16.5				
16	**408**	>95	84 : 16				
17	**409**	>95	82.5 : 17.5				

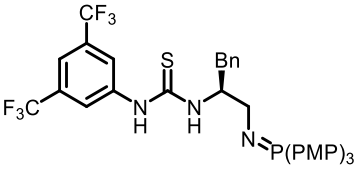
Table 5. Detailed catalyst screen results for the intramolecular oxy-Michael reaction of alcohol **403**. [a] reaction was carried out at room temperature in 0.1 M CPME. [b] determined by ^{1}H NMR analysis of crude reaction mixture. [c] determined by HPLC analysis on chiral stationary phase. CPME = cyclopentyl methyl ether.



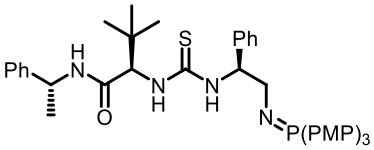
233



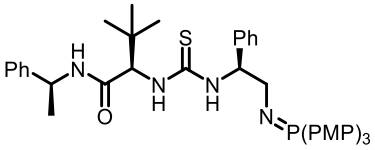
118



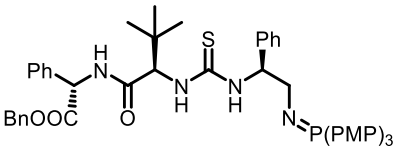
235



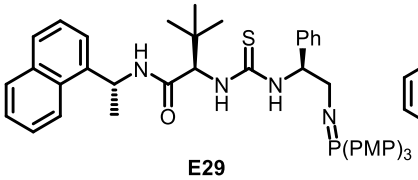
243



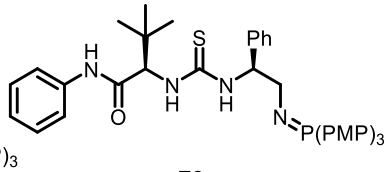
244



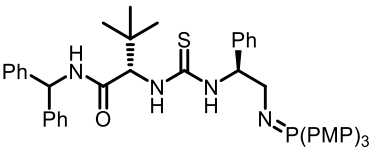
E25



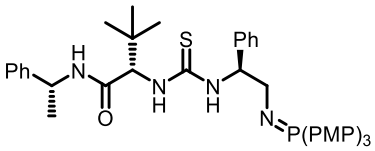
E29



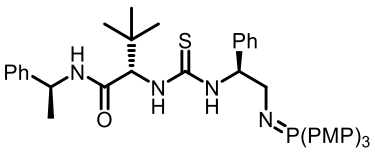
E8



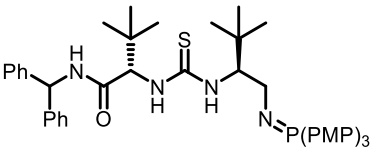
554



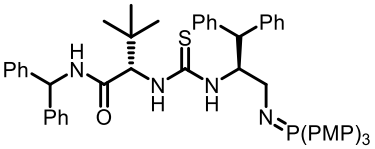
246



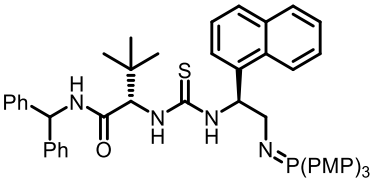
245



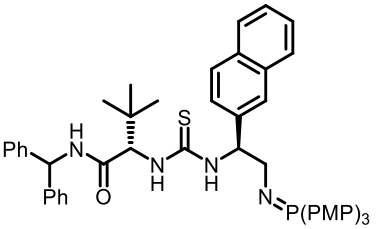
406



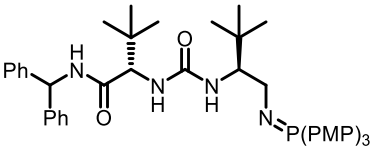
407



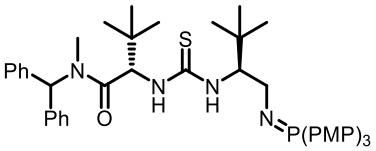
E26



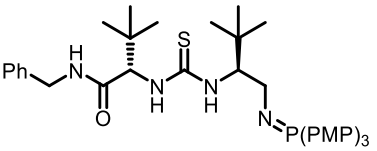
E27



408



409



E28

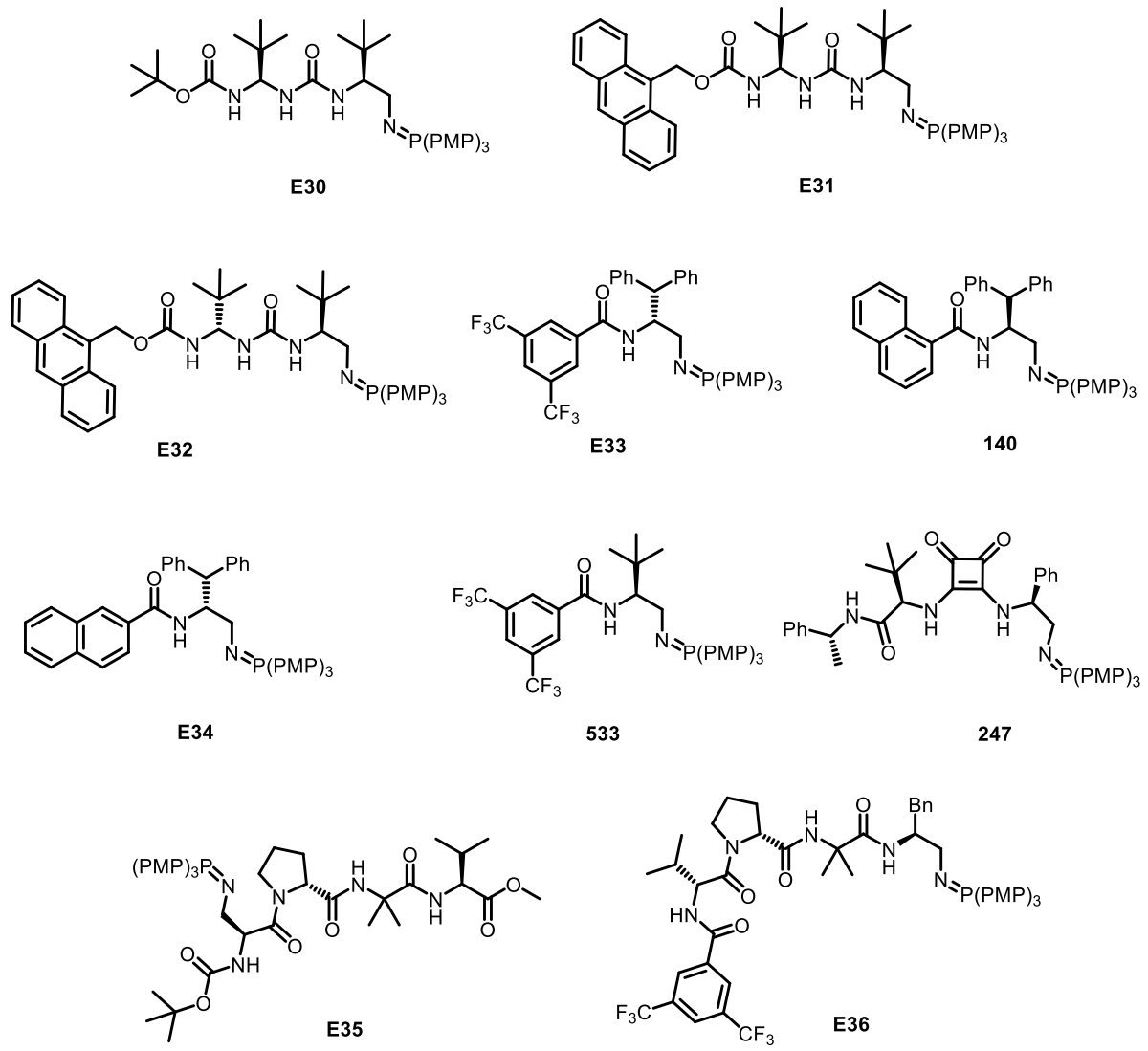


Figure 19. Selected catalysts studied in the optimisation of the intramolecular oxy-Michael reaction of alcohol **403**.

Table 6: Solvent and conditions optimisation

entry	cat. X	Conc.	temp/°C	solvent	Conv. (%)[a]	er[b]
1	**406**	0.1M	rt	CPME	>95	92 : 8
2	**406**	0.1M	rt	Et_2O	>95	92 : 8
3	**406**	0.1M	rt	THF	>95	93 : 7
4	**406**	0.1M	rt	TBME	>95	92.5 : 7.5
5	**406**	**0.1M**	**rt**	**2-methyl THF**	**>95**	**93.4 : 6.6**
6	**406**	0.1M	rt	dioxane	>95	89.5 : 10.5
7	**406**	0.1M	rt	CH_2Cl_2	>95	87.5 : 12.5
8	**406**	0.1M	rt	MeCN	>95	89 : 11
9	**406**	0.1M	rt	EtOAc	>95	92 : 8
10	**406**	0.1M	rt	PhMe	>95	85 : 15
11	**406**	0.1M	3	CPME	>95	91.5 : 8.5
12	**406**	0.1M	-22	CPME	>95	91 : 9
13[c]	**406**	0.1M	40	CPME	>95	91 : 9
14	**406**	0.1M	40	CPME	>95	89.5 : 10.5
15	**406**	**0.025M**	**rt**	**CPME**	**>95**	**94.5 : 5.5**
16	**406**	0.4M	rt	CPME	>95	85 : 15

Table 6. Detailed solvent and conditions optimisation results for the intramolecular oxy-Michael reaction of alcohol **403**. [a] determined by ^{1}H NMR analysis of crude reaction mixture. [b] determined by HPLC analysis on chiral stationary phase. [c] reaction was carried out for 8 hours. rt = room temperature. CPME = cyclopentyl methyl ether. TBME = *tert*-butyl methyl ether.

Table 7: Phosphine screen[a]

entry	cat. X	Conc.	PR_3	solvent	Conv. (%)[b]	er[c]
1	**406**	0.1M	$P(PMP)_3$	CPME	>95	92 : 8
4	**406**	0.1M	$P(^nBu)_3$	CPME	>95	88.5 : 11.5
5	**406**	0.1M	253	CPME	>95	91.2 : 8.8
6	**406**	0.1M	255	CPME	>95	90 : 10
7	**406**	0.1M	E37	CPME	>95	87 : 13
8	**406**	0.025M	E38	2-methyl THF	40	85 : 15
9	**406**	0.025M	P(*p*-Cl-Ph)$_3$	2-methyl THF	6	80 : 20
10	**406**	0.025M	P(*p*-tolyl-Ph)$_3$	2-methyl THF	59	95.5 : 4.5
11	**406**	0.025M	PPh_3	2-methyl THF	87	96 : 4
12	**406**	**0.025M**	**$P(PMP)_3$**	**2-methyl THF**	**>95 (91)[d]**	**95 : 5**
13	**533**	0.025M	PPh_3	2-methyl THF	18	87 : 13
14	**533**	0.025M	P(*p*-tolyl-Ph)$_3$	2-methyl THF	52	92.7 : 7.3
15	**533**	0.025M	253	2-methyl THF	95	89.6 : 10.4
16	**533**	0.025M	P(*m*-tolyl-Ph)$_3$	2-methyl THF	58	90.8 : 9.2

Table 7. Detailed phosphine screen results for the IOMR of alcohol **403**. [a] reaction was carried out at room temperature for 24 hours unless otherwise indicated. [b] determined by ^{1}H NMR analysis of crude reaction mixture. [c] determined by HPLC analysis on chiral stationary phase. [d] yield of isolated product. PMP = *para*-methoxy phenyl.

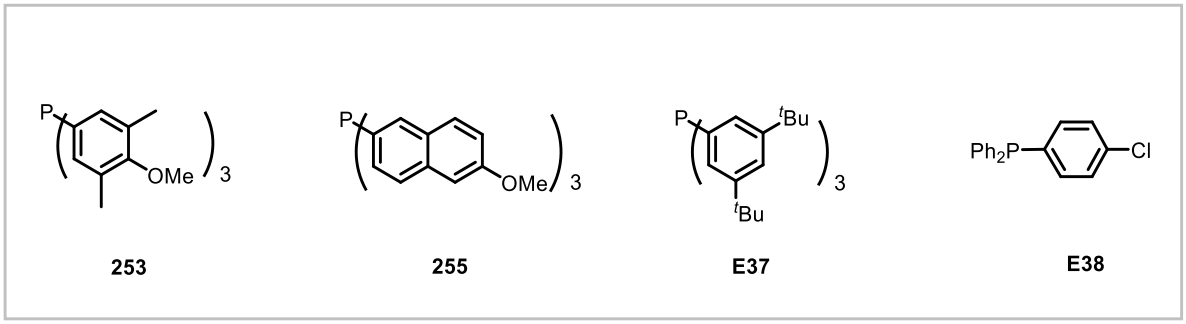
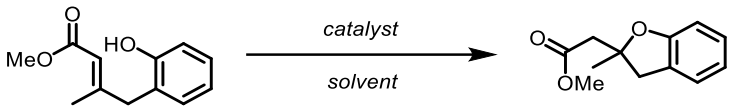


Figure 20. Selected phosphines studied in the optimisation of the intramolecular oxy-Michael reaction of alcohol **403**.

General procedure for optimisation of the intramolecular oxy-Michael reaction of alcohol 509:



509 **510**

Alcohol **509** (20.6 mg, 0.1 mmol, 1.0 eq) was added to a solution of catalyst (0.01 mmol, 0.1 eq (unless otherwise indicated)) in the appropriate solvent under N_2 at room temperature. The reaction mixture was stirred at the specified temperature for specified time. The reaction was quenched by the addition of 1M AcOH in CH_2Cl_2 (1 mL). Conversion was determined by crude ^1H NMR. Volatiles were removed by a stream of N_2 gas, followed by filtration through silica gel with 30% Et_2O in pentane. The crude product was analysed by chiral HPLC (Chiralcel OD, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 220 nm, t_R (major) = 6.8 min, t_R (minor) = 11.0 min)

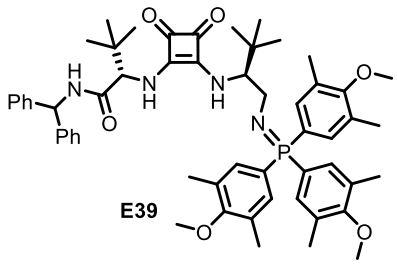
Table 8: Optimisation result

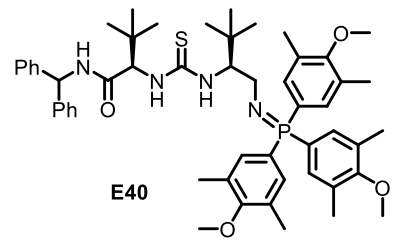
entry	cat. X	Conc.	temp/°C	time/h	solvent	Conv. (%)[a]	er[b]
1	**406**	0.025M	rt	56	2-methyl THF	56	77.5 : 22.5
2	**406**[c]	0.025M	rt	46	2-methyl THF	51	85 : 15
3	**406**	0.025M	60	46	2-methyl THF	97	66 : 34
4	**406**	0.1M	rt	46	2-methyl THF	98	66.5 : 33.5
5	**406**[d]	0.025M	**rt**	46	2-methyl THF	81	76:24
6	**406**[c]	0.05M	rt	24	2-methyl THF	79	79.5 : 20.5
7	**406**[e]	0.025M	rt	24	2-methyl THF	31	N.D.
8	**E39**[e]	0.025M	rt	24	2-methyl THF	18	N.D.
9	**533**[e]	0.025M	rt	24	2-methyl THF	59	83.5 : 16.5
10	**406**[f]	0.025M	rt	24	2-methyl THF	N.R.	N.D.
11	**406**[g]	0.025M	rt	24	2-methyl THF	N.R.	N.D.
12	**406**[c]	0.025M	rt	24	Et2O	95	81 : 19
13	**406**[c]	0.025M	rt	24	CPME	91	82 : 18
14	**406**[c]	0.025M	rt	24	dioxane	<5	67 : 33
15	**406**[c]	0.025M	rt	24	toluene	>95	62 : 38
16	**406**[c]	0.025M	rt	24	EtOAc	89	77 : 23
17	**406**[c]	0.025M	rt	24	DCM	>95	60 : 40

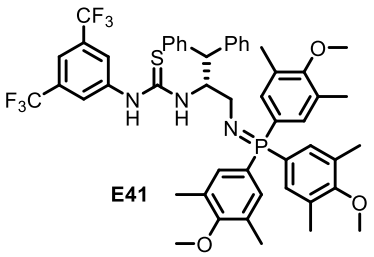
entry	cat. X	Conc.	temp/°C	time/h	solvent	Conv. (%)[a]	er[b]
18	**407**[c]	0.025M	rt	24	CPME	15	52 : 48
19	**E26**[c]	0.025M	rt	24	CPME	77	58 : 42
20	**E27**[c]	0.025M	rt	24	CPME	83	66 : 34
21	**554**[c]	0.025M	rt	24	CPME	44	55 : 45
22	**E40**[c]	0.025M	rt	24	CPME	91	77 : 23
23	**406**[h]	0.025M	rt	24	CPME	85	67 : 33
24	**406**[i]	0.025M	rt	24	CPME	11	77 : 23
25	**118**[c]	0.025M	rt	24	CPME	79	62 : 38
26	**E41**	0.025M	rt	24	CPME	45	68 : 32
27	**235**[c]	0.025M	rt	24	CPME	95	66 : 34
28	**233**[c]	0.025M	rt	24	CPME	46	66 : 34
29	**E42**	0.025M	rt	24	CPME	82	56 : 44
30	**E33**[c]	0.025M	rt	24	CPME	55	63 : 37
31	**140**[c]	0.025M	rt	24	CPME	N.R.	N.D.
32	**E34**[c]	0.025M	rt	24	CPME	23	63 : 37
33	**533**[c]	0.025M	rt	24	CPME	>95	64 : 36
34	**E43**	0.025M	rt	24	CPME	>95	63 : 37
35	**E39**	0.025M	rt	24	CPME	62	82.5 : 17.5
36	**E44**	0.025M	rt	24	CPME	>95	81 : 19
37	**E44**[h]	0.025M	rt	24	CPME	>95	81.5 : 18.5
38	**E45**	0.025M	rt	24	CPME	>95	79 : 21
39	**E46**	0.025M	rt	24	CPME	>95	77 : 23
40	**E46**[h]	0.025M	rt	24	CPME	>95	83 : 17
41	**E44**[h]	0.025M	rt	24	THF	50	81.5 : 18.5
42	**E44**[h]	0.025M	rt	24	2-methyl THF	83	81 : 19
43	**E44**[h]	0.025M	rt	24	Et_2O	>95	82.5 : 17.5
44	**E44**[h]	0.025M	rt	24	TBME	>95	83.5 : 16.5
45	**E44**[h]	0.025M	rt	24	EtOAc	>95	80 : 20
46	**E39**[h]	0.025M	rt	24	TBME	>95	89 : 11
47	**E39**[j]	0.025M	rt	24	TBME	>95	93 : 7
48	**E39**[j]	0.025M	rt	24	2-methyl THF	>95	91.5 : 8.5
49	**E39**[n]	0.025M	rt	24	2-methyl THF	72	75 : 25
50	**E39**[j]	**0.025M**	**0**	**24**	**TBME**	**>95 (90)**[m]	**95 : 5**
51	**E39**[j]	0.025M	-20	24	TBME	25	96 : 4
52	**E39**[j][k]	0.025M	rt	24	TBME	>95	93 : 7
53	**E39**[j][l]	0.025M	rt	24	TBME	>95	94 : 6

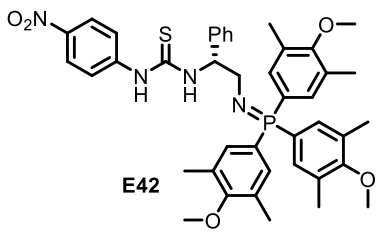
entry	cat. X	Conc.	temp/°C	time/h	solvent	Conv. (%)[a]	er[b]
54	**E39**[i][k]	0.025M	0	24	TBME	52	95.5 : 4.5

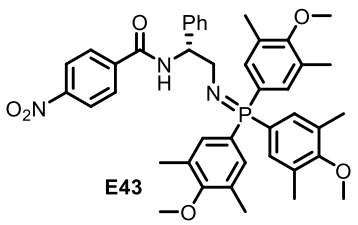
Table 8. Detailed optimisation results for the intramolecular oxy-Michael reaction of alcohol **509**. [a] ^{1}H NMR analysis of crude reaction mixture. [b] HPLC analysis on a chiral stationary phase. [c] phosphine **253** was used when making active catalyst. [d] 20% cat. used. [e] phosphine **254** was used when making active catalyst. [f] phosphine **E47** was used when making active catalyst. [g] phosphine **E48** was used when making active catalyst. [h] phosphine **E37** was used when making active catalyst. [i] triphenylphosphine was used when making active catalyst. [j] phosphine **E49** was used when making active catalyst. [k] 5% cat. used. [l] 2% cat. used. CPME = cyclopentyl methyl ether. [m] yield of isolated product. [n] tri-*para*-methoxyphenylphosphine was used when making active catalyst. TBME = *tert*-butyl methyl ether. N.R. = No Reaction. N.D. = Not Determined.

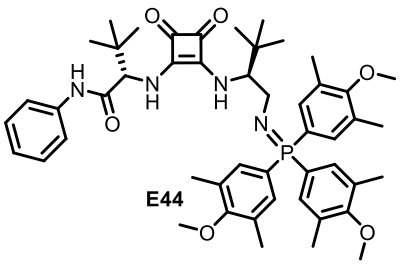


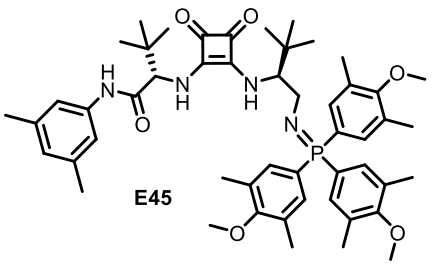












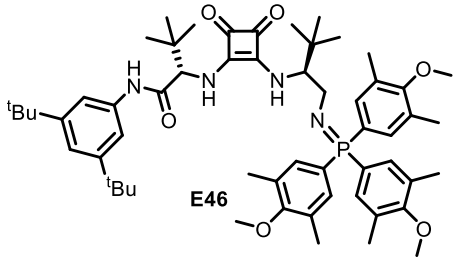
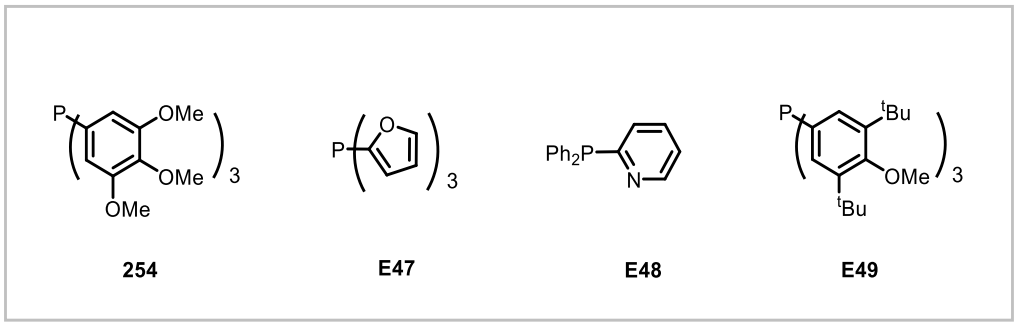


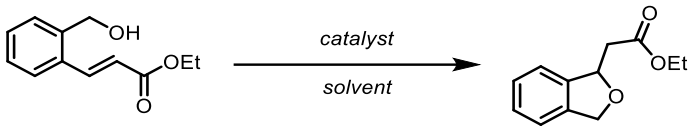
Figure 21. Selected catalysts studied in the optimisation of the intramolecular oxy-Michael reaction of alcohol **509**.



254 **E47** **E48** **E49**

Figure 22. Selected phosphines studied in the optimisation of the intramolecular oxy-Michael reaction of alcohol **509**.

General Procedure for Optimisation of the intramolecular oxy-Michael reaction of alcohol 531:



531 **532**

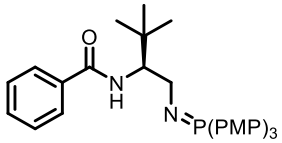
Alcohol **531** (20.6 mg, 0.1 mmol, 1.0 eq) was added to a solution of catalyst (0.005 mmol, 0.05 eq (unless otherwise indicated)) in the appropriate solvent under N_2 at room temperature. The reaction mixture was stirred at the specified temperature for specified time. The reaction was quenched by the addition of 1M AcOH in CH_2Cl_2 (1 mL). Conversion was determined by crude ^{1}H NMR. Volatiles were removed by a stream of N_2 gas, followed by filtration through silica gel with 30% Et_2O in pentane. The crude product was analysed by chiral HPLC (Chiralcel IA, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 210 nm, t_R (major) = 9.5 min, t_R (minor) = 10.7 min)

Table 9: Optimisation result

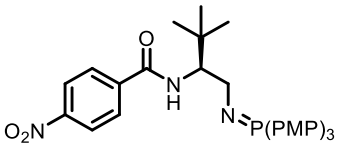
entry	cat. X	Conc.	temp/°C	time/h	solvent	Conv. (%)[a]	er[b]
1	**406**	0.5M	50	7.5	2-methyl THF	>95	73.5:26.5
2	**406**	0.1M	50	7.5	2-methyl THF	94	81.5:18.5
3	**406**	0.5M	rt	7.5	2-methyl THF	92	82:18
4	**E39**[c]	0.5M	50	7.5	TBME	>95	54 : 46
5	**406**	0.025M	rt	16	2-methyl THF	21	85 : 15
6	**406**	0.025M	50	16	2-methyl THF	80	82.5 : 17.5
7	**406**	0.5M	-22	16	2-methyl THF	34	86 : 14
8	**E40**[d]	0.5M	rt	7.5	2-methyl THF	80	75 : 25
9	**406**	0.5M	rt	7.5	toluene	>95	77 : 23
10	**406**	0.5M	rt	7.5	$CF_3C_6H_5$	>95	73.5 : 26.5
11	**406**	0.5M	rt	7.5	DCM	>95	76.5 :23.5
12	**406**	0.5M	rt	7.5	EtOAc	>95	78.5 : 21.5
13	**533**	0.5M	rt	7.5	2-methyl THF	85	91 : 9
14	**533**	0.5M	rt	7.5	THF	74%	91 : 9
15	**533**	0.5M	rt	7.5	TBME	>95	88.5 : 11.5
16	**533**	0.5M	rt	7.5	CPME	>95	89 : 11
17	**533**	0.5M	rt	7.5	Et2O	>95	88.8 : 11.2
18	**533**	0.5M	rt	7.5	dioxane	43%	90 : 10
19	**E33**	0.5M	rt	7.5	2-methyl THF	75	86.5 : 13.5
20	**140**	0.5M	rt	7.5	2-methyl THF	N.R.	N.D.
21	**E50**	0.5M	rt	7.5	2-methyl THF	48	77 : 23

entry	cat. X	Conc.	temp/°C	time/h	solvent	Conv. (%)[a]	er[b]
22	**E51**	0.5M	rt	7.5	2-methyl THF	67	80.5 : 19.5
23	**E52**	0.5M	rt	7.5	2-methyl THF	>95	84.5 : 15.5
24	**E53**	0.5M	rt	7.5	2-methyl THF	36	64 : 36
25	**533**[e]	0.5M	rt	7.5	2-methyl THF	>95	93.5 : 6.5
26	**533**[f]	0.5M	rt	7.5	2-methyl THF	>95	93 : 7
27	**533**[c]	0.5M	rt	7.5	2-methyl THF	75	91.5 : 8.5
28	**533**[e]	0.5M	0	24	2-methyl THF	59	96 : 4
29	**533**[e]	1M	0	7.5	2-methyl THF	26	95.5 : 4.5
30	**533**[e]	0.1M	rt	24	2-methyl THF	87	95.8 : 4.2
31	**533**[e]	0.1M	50	7.5	2-methyl THF	88	94 : 6
32	**533**[e]	0.025M	50	24	2-methyl THF	79	94.5 : 5.5
33	**533**[e]	**0.1M**	**rt**	**24**	**2-methyl THF**	**82**[g]	**95 : 5**

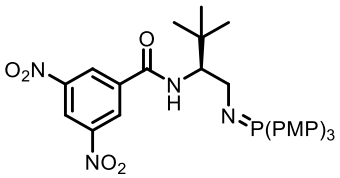
Table 9. Detailed optimisation results for IOMR of alcohol **531**. [a] determined by ^{1}H NMR analysis of crude reaction mixture. [b] determined by HPLC analysis on chiral stationary phase. [c] phosphine **E49** was used when making active catalyst. [d] $P(PMP)_3$ was used when making active catalyst. PMP = *para*-methoxy phenyl. [e] phosphine **E37** was used when making active catalyst. [f] phosphine **253** was used when making active catalyst. [g] yield of isolated product.



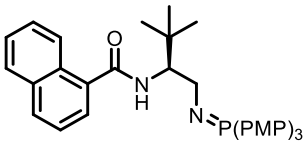
E50



E51



E52



E53

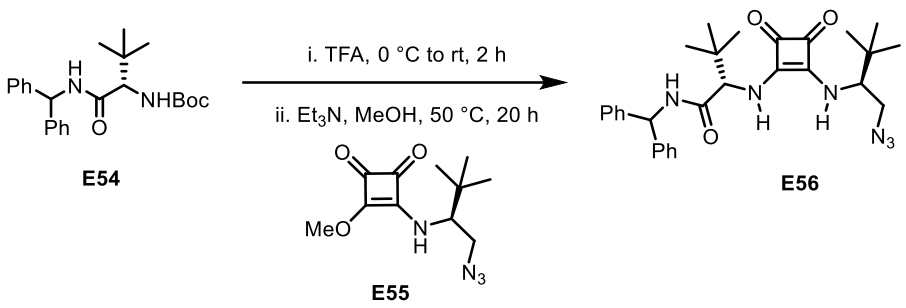
Figure 23. Selected catalysts studied in the optimisation of the intramolecular oxy-Michael reaction of alcohol **531**.

4.3.2 Preparation of Azide Catalyst Precursor, Phosphines and Catalyst

Synthesis of azide catalyst precursor

Catalysts **406** [21] and **534** [22] were prepared according to literature procedures.

Catalyst **512** was prepared according to the following procedure:



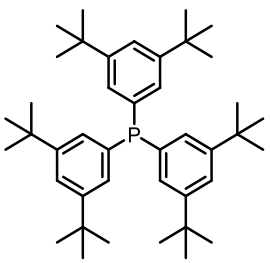
Catalyst Precursor (*S*)-2-((2-(((*S*)-1-azido-3,3-dimethylbutan-2-yl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-*N*-benzhydryl-3,3-dimethylbutanamide (E56) was prepared according to the following procedure. According to the modified literature procedure reported by D. M. Rotstein *et. al.,* [23] trifluoroacetic acid (6.0 mL) was added to the *tert*-butyl (*S*)-(1-(benzhydrylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate **(E54)** [21] (2.03 g, 5.12 mmol, 1.0 eq) under N_2 at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C, before warming to room temperature. Volatiles were removed under a stream of nitrogen gas behind a blast shield to afford TFA salt of (*S*)-2-amino-*N*-benzhydryl-3,3-dimethylbutanamide which was used as crude for next step without any purification.

A solution of the TFA salt of (*S*)-2-amino-*N*-benzhydryl-3,3-dimethylbutanamide in anhydrous MeOH (17.0 mL) was added to a solution of (*S*)-3-((1-azido-3,3-dimethylbutan-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione [24] **(E55)** (1.29 g, 5.12 mmol, 1.0 eq) and triethylamine (3.62 g, 35.84 mmol, 7.0 eq) in anhydrous MeOH (3.2 mL) under N_2 at room temperature. The reaction mixture was heated to 50 °C and stirred for 20 hours. The reaction mixture was cooled to room temperature and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/MeCN = 4/1) afforded the title compound as a white solid (2.12 g, 81%).

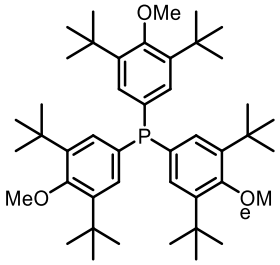
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.42 (d, *J* = 8.8 Hz, 1H, NHCO), 7.84 (d, *J* = 10.1 Hz, 1H, NHC), 7.77 (d, *J* = 10.3 Hz, 1H, NHC), 7.42 – 7.20 (m, 10H, Ar-H), 6.21 (d, *J* = 8.8 Hz, 1H, CHNHCO), 4.68 (d, *J* = 10.1 Hz, 1H, CHNHC), 4.01 (td, *J* = 10.1, 3.1 Hz, 1H, CHNHC), 3.50 (dd, *J* = 13.1, 3.2 Hz, 1H, CH_2), 3.38 (dd, *J* = 13.1, 10.1 Hz, 1H, CH_2), 0.91 (s, 9H, $CHC(CH_3)_3$), 0.89 (s, 9H, $CHC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 182.2 (squaramide CO), 182.1 (squaramide CO), 168.6 (amide CO), 167.9 (squaramide CNH), 167.3 (squaramide CNH), 142.2 (ArC), 142.1 (ArC), 128.4 (ArCH), 128.3 (ArCH), 127.4 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 63.4 (CHNHC), 62.6 (CHNHC), 56.0 (CHNHCO), 51.3 (CH_2), 35.8 ($CHC(CH_3)_3$), 34.0 ($CHC(CH_3)_3$), 26.0 (2 x $CHC(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{29}H_{37}N_6O_3$ ($[M+H]^+$) 517.2922, found 517.2917; **FT-IR (thin film)** ν_{max} 3710, 3628, 3291, 2963, 2359, 2099, 1802, 1651, 1584, 1496, 1459, 1402, 1308, 1274, 1103, 1086, 1002, 943, 908, 890, 823, 746, 703, 694, 686, 677 cm^{-1}; **m.p.**: >230 °C; **$[\alpha]_D^{25}$** = +29.7 (c=0.46, $(CH_3)_2SO$).

Synthesis of phosphine

Phosphines **E37** [24] and **E49** [25] were prepared according to literature procedures.

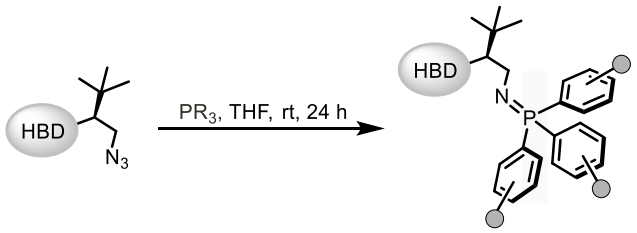


E37



E49

Synthesis of catalyst

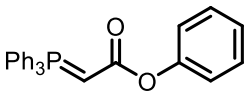


Staudinger reaction for *in-situ* generation of the active BIMP catalysts: THF (0.025 M) was added to the BIMP catalysts precursors (1.0 eq) and the appropriate phosphine (1.0 eq) in a mass spectrometry vial under N_2 at room temperature. The reaction mixture was stirred for 24 hours before evaporating to dryness under a stream of nitrogen gas. The iminophosphorane product was confirmed by LCMS and TLC. The resulting mixture was dried under vacuum then used as crude for enantioselective reactions without any purification.

4.3.3 Preparation of Starting Materials

Preparation of Wittig reagents E57, E58 and E59

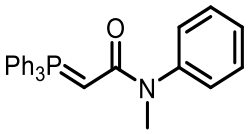
Methyl-, Ethyl-, *iso*-Propyl-, *tert*-Butyl- and Benzyl-(triphenylphosphaneylidene) acetate are commercially available and were used as purchased. Wittig reagents **E57, E58** and **E59** were prepared as followed.



Phenyl-(triphenylphosphaneylidene) acetate (E57) was prepared according to the following procedure. According to the modified literature procedure reported by B. J. Cowen, *et. al.,* [26] a solution of phenyl bromoacetate (10.0 g, 46.5 mmol) in anhydrous $CHCl_3$ (23.3 mL) was slowly added to a solution of triphenylphosphine (12.2 g, 46.5 mmol, 1.0 eq) in anhydrous $CHCl_3$ (23.3 mL) under N_2 at room temperature (exothermic reaction!). The reaction mixture was stirred for 2 hours at room temperature before evaporating to dryness under reduced pressure. The resulting gum-like mixture was triturated with Et_2O (200 mL) and stood for 15 min. The resulting precipitated salt was filtered, washed with Et_2O (3 x 100 mL) and dried under vacuum.

2M NaOH (aq) (270 mL) was added to a solution of the salt in CH_2Cl_2 (250 mL) under air at room temperature. The reaction mixture was stirred for 10 mins at room temperature. The organic layer was then separated, dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure, affording the title compound as a white foam which was used as crude for next step without any further purification (17.5 g, 95% yield) (1:0.5 (**A**:**B**) mixture of rotamers). Data is consistent with the published literature.

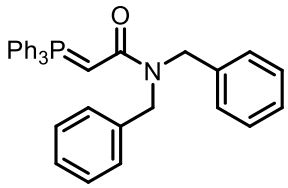
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.66 (m, 10H, Ar-H (**A**)), 7.58 (tq, J = 6.6, 1.6 Hz, 5H, Ar-H (**A**)), 7.53 – 7.44 (m, 7.5H, Ar-H (**B**)), 7.33 – 7.25 (m, 2H, Ar-H (**A**)), 7.19 – 7.12 (m, 3H, Ar-H (**A**) and Ar-H (**B**)), 7.10 – 7.04 (m, 1H, Ar-H (**B**)), 7.02 – 6.96 (m, 0.5H Ar-H (**B**)), 6.70 – 6.57 (m, 1H, Ar-H (**A**)), 3.24 – 3.15 (m, 1H, CH (**A**)), 3.03 – 2.90 (m, 0.5H CH (**B**)) ppm; **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.7 (**A**), 16.9 (**B**) ppm.



***N*-Methyl-*N*-phenyl-2-(triphenylphosphaneylidene)acetamide (E58)** was prepared according to the following procedure. According to the modified literature procedure reported by D. Lee, *et. al.,* [27] 2-chloroacetyl chloride (3.4 g, 30.0 mmol) was slowly added to a solution of *N*-methylaniline (3.6 g, 33.0 mmol, 1.1 eq) and triethylamine (3.7 g, 36.6 mmol, 1.22 eq) in anhydrous $CHCl_3$ (52 mL) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 22 hours before quenching with a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure, affording 2-chloro-*N*-methyl-*N*-phenylacetamide as a light-yellow liquid which was used as crude for next step without any purification (5.6 g, 99% yield).

According to the modified literature procedure reported by K. Diehl, *et. al.,* [28] triphenylphosphine (7.6 g, 29.0 mmol, 1.0 eq) was added to a solution of 2-chloro-*N*-methyl-*N*-phenylacetamide (5.3 g, 29.0 mmol) in toluene (29 mL) under N_2 at room temperature. The reaction mixture was heated to reflux and stirred for 24 hours before cooling to room temperature. The resulting precipitated salt was filtered, washed with toluene (2 x 50 mL) and dried under vacuum. Triethylamine (4.4 g, 43.5 mmol, 1.5 eq) was added to a solution of the salt in $CHCl_3$ (150 mL) under N_2 at room temperature. The reaction mixture was stirred for 3 hours at room temperature before quenching with a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure, affording the title compound as a brown liquid which was used as crude for next step without any purification (10.6 g, 89% yield). Data is consistent with the published literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 5H, Ar-H), 7.52 – 7.38 (m, 10H, Ar-H), 7.32 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.21 – 7.15 (m, 2H, Ar-H), 7.14 – 7.08 (m, 1H, Ar-H), 3.29 (s, 3H, CH_3), 2.81 – 2.69 (m, 1H, CH) ppm; **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 17.1 ppm.



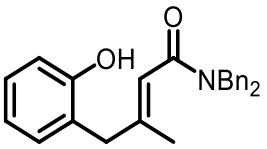
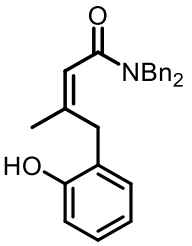
***N, N*-Dibenzyl-2-(triphenylphosphaneylidene)acetamide (E59)** was prepared according to the following procedure. Triphenylphosphine (3.3 g, 12.5 mmol, 1.0 eq) was added to a solution of *N*, *N*-dibenzyl-2-chloroacetamide (3.4 g, 12.5 mmol) in toluene (21 mL) under N_2 at room temperature. The reaction mixture was heated to 80 °C and stirred for 22 hours before cooling to room temperature. The resulting precipitated salt was filtered, washed with toluene (2 x 50 mL) and dried under vacuum.

1M NaOH (aq) (16 mL) was added to a solution of the salt in CH_2Cl_2 (16 mL) under air at room temperature. The reaction mixture was stirred for 1 hour at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure, affording the title compound as a pale-yellow solid which was used as crude for next step without any further purification (3.6 g, 58% yield)

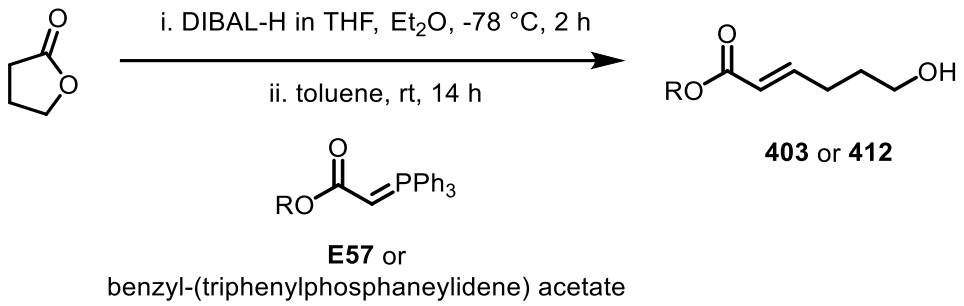
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.67 (m, 5H, Ar-H), 7.59 – 7.51 (m, 3H, Ar-H), 7.50 – 7.44 (m, 7H, Ar-H), 7.34 (d, *J* = 4.4 Hz, 8H, Ar-H), 7.29 – 7.23 (m, 2H, Ar-H), 4.58 (s, 4H, CH_2), 3.24 – 2.76 (m, 1H, CH) ppm; **^{31}P-NMR (162 MHz, $CDCl_3$)** δ 18.1 ppm; **HRMS** (ESI) m/z calcd. for $C_{35}H_{30}NOP$ ($[M+H]^+$) 500.2126, found 500.2138; **m.p.**: 124-126 °C.

General information of starting materials for the intramolecular oxy-Michael reaction

Starting materials for the intramolecular oxy-Michael reaction typically contain <10% inseparable *Z*-isomer while *Z*-isomer was found to show a much slower reaction rate compared to *E*-isomer.

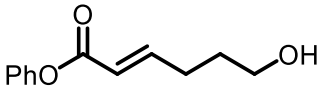
Starting materials	 (*E*)- (**517**)	 (*Z*)- (**517**)
Reaction condition	10% cat. **512**, TBME (0.025M), 40 °C, 96 h	
Intramolecular oxy-Michael reaction outcome	67% yield, 98.5:1.5 er	No reaction

General procedure D for preparation of starting materials 403 and 412



According to the modified literature procedure reported by Y. Kobayashi *et. al.,* [29] DIBAL (4.31 g, 75 mmol, 1.0 M solution in toluene) was slowly added to a solution of dihydrofuran-2-one (3.62 mL, 50 mmol) in Et_2O (50 mL) under N_2 at −78 ºC. The reaction mixture was stirred at the same temperature for 2 hours before quenching with MeOH (50 mL) at −78 ºC. The resulting mixture was gradually warmed up to room temperature and filtered through a pad of Celite. The filter cake was washed with MeOH (3 x 20 mL) and the combined filtrate was carefully evaporated to dryness under reduced pressure, affording crude tetrahydrofuran-2-ol which was used as crude for next step without any purification. Notably, the yield of this reduction reaction depended on the quality of the reagents used.

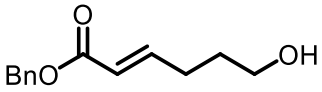
Tetrahydrofuran-2-ol (1.0 eq) in toluene (5 mL) was added to a solution of (triphenylphosphoranylidene)acetate **E57** or benzyl-(triphenylphosphaneylidene) acetate (2.5 eq) in toluene (0.12M) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 14 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography afforded starting materials **403** or **412**.



Phenyl (*E*)-6-hydroxyhex-2-enoate (403) was prepared following **General Procedure D**, using tetrahydrofuran-2-ol (0.93 g, mmol, 10.5 mmol, 1.0 eq), phenyl-(triphenylphosphoranylidene)acetate **E57** (10.4 g, 26.2 mmol, 2.5 eq) and toluene (87 mL) to afford the title compound as an colorless oil (2.8

g, 52%). Silica gel chromatography condition: pentane/EtOAc = 3:2. Data is consistent with the published literature.[29]

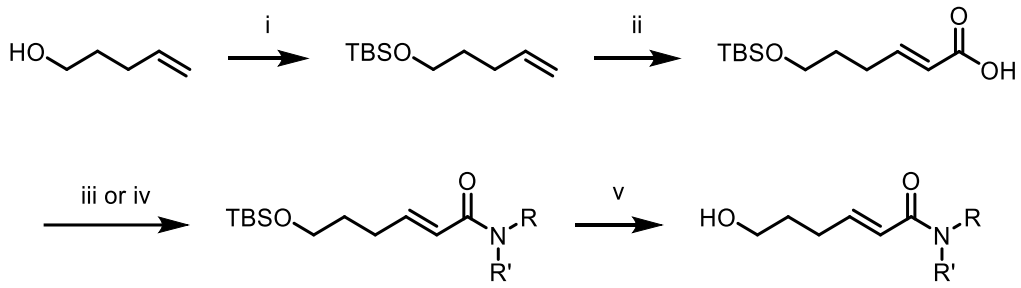
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.25 – 7.15 (m, 2H, Ar-H), 7.13 – 7.09 (m, 2H, Ar-H and CH), 6.06 (dt, *J* = 15.6, 1.6 Hz, 1H, CH), 3.72 (t, *J* = 6.3 Hz, 2H, CH_2), 2.40 (dtd, *J* = 8.3, 7.0, 1.6 Hz, 2H, CH_2), 1.79 (ddt, *J* = 8.4, 7.4, 6.4 Hz, 2H, CH_2), 1.48 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (CO), 150.95 (CH), 150.89 (ArC), 129.5 (ArCH), 125.8 (ArCH), 121.8 (ArCH), 121.2 (CH), 62.1 (CH_2), 31.0 (CH_2), 28.9 (CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{14}O_3Na$ ($[M+Na]^+$) 229.0837, found 229.0835.



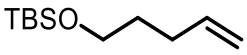
Benzyl (*E*)-6-hydroxyhex-2-enoate (412) was prepared following **General Procedure D**, using tetrahydrofuran-2-ol (0.45 g, 5 mmol, 2.5 eq), benzyl-(triphenylphosphoranylidene)acetate (0.82 g, 2.0 mmol, 1.0 eq) and toluene (6.7 mL) to afford the title compound as an colorless oil (286.4 mg, 65%). Silica gel chromatography condition: pentane/Et_2O = 3:7.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H, Ar-H), 7.03 (dt, *J* = 15.6, 6.9 Hz, 1H, CH), 5.90 (dt, *J* = 15.6, 1.6 Hz, 1H, CH), 5.17 (s, 2H, COOCH_2), 3.64 (t, *J* = 6.4 Hz, 2H, CH_2), 2.30 (dtd, *J* = 8.3, 7.0, 1.6 Hz, 2H, CH_2), 1.99 (s, 1H, OH), 1.77 – 1.65 (m, 2H, CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.5 (CO), 149.4 (CH), 136.2 (ArC), 128.6 (2 x ArCH), 128.3 (ArCH), 121.5 (CH), 66.2 (COOCH_2), 61.9 (CH_2), 30.9 (CH_2), 28.6 (CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{16}O_3Na$ ($[M+Na]^+$) 243.0993, found 243.0992; **FT-IR (thin film)** ν_{max} 3392, 2939, 2360, 2341, 1717, 1653, 1498, 1378, 1319, 1267, 1191, 1097, 1027, 980, 917, 840, 797, 789, 697, 677, 668 cm^{-1}.

Preparation of starting materials 413 and 414

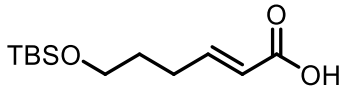


Scheme 85. Synthesis of starting materials **413** and **414**. i. TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 1 h; ii. Hoveyda-Grubbs 2nd generation catalyst, acrylic acid, CH_2Cl_2, 45 °C, 16 h; iii. ethyl chloroformate, *N*,*O*-dimethylhydroxylamine hydrochloride, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; iv. HATU, morpholine, DIPEA, DMF, 0 °C to rt, 16 h; iv. CSA, CH_2Cl_2, MeOH, 4 h.



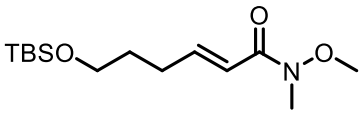
***tert*-Butyldimethyl(pent-4-en-1-yloxy)silane (E60)** was prepared according to the following procedure. According to the modified literature procedure reported by E. M. Stang *et. al.,* [30] *tert*-butyldimethylsilyl chloride (37.3 g, 247.5 mmol, 1.1 eq), imidazole (23.0 g, 337.5 mmol, 1.5 eq) and DMAP (1.4 g, 11.25 mmol, 0.05 eq) were added to a solution of pent-4-en-1-ol (19.4 g, 225 mmol, 1.0 eq) in CH_2Cl_2 (225 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 1 hour before filtering through a silica plug and eluting with 1% EtOAc/hexanes, affording the title compound as a colorless oil (44.7 g, 99%). Data is consistent with the published literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, C<u>H</u>=CH_2), 5.07 – 4.91 (m, 2H, CH=C<u>H</u>$_2$), 3.62 (t, *J* = 6.5 Hz, 2H, C<u>H</u>$_2$$CH_2CH_2CH=CH_2$), 2.11 (dtt, *J* = 8.0, 6.6, 1.5 Hz, 2H, CH_2CH_2C<u>H</u>$_2$$CH=CH_2$), 1.61 (ddt, *J* = 8.5, 7.4, 6.5 Hz, 2H, CH_2C<u>H</u>$_2$$CH_2CH=CH_2$), 0.90 (s, 9H, C(C<u>H</u>$_3$)$_3$), 0.05 (s, 6H, Si(C<u>H</u>$_3$)$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 138.7 (<u>C</u>H=CH_2), 114.6 (CH=<u>C</u>H$_2$), 62.7 (<u>C</u>$H_2CH_2CH_2CH=CH_2$), 32.2 (CH_2<u>C</u>$H_2CH_2CH=CH_2$), 30.2 (CH_2CH_2<u>C</u>$H_2CH=CH_2$), 26.1 (C(<u>C</u>H$_3$)$_3$), 18.5 (<u>C</u>(CH$_3$)$_3$), -5.1 (Si(<u>C</u>H$_3$)$_2$) ppm.



(*E*)-6-((*tert*-Butyldimethylsilyl)oxy)hex-2-enoic acid (E61) was prepared according to the following procedure. A solution of Hoveyda-Grubbs 2nd generation catalyst (31.4 mg, 0.05 mmol, 0.005 eq) in degassed CH_2Cl_2 (5 mL) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of ***tert*-butyldimethyl(pent-4-en-1-yloxy)silane (E60)** (2.0 g, 10 mmol, 1.0 eq) and acrylic acid (2.2 g, 30 mmol, 3.0 eq) under N_2 at 45 °C. The reaction mixture was stirred at 45 °C for 16 hours before filtering through a filter paper. The filter cake was washed with CH_2Cl_2 (2 x 10 mL). The combined filtrate was evaporated to dryness under reduced pressure. Purification by silica gel chromatography (20% Et_2O in pentane and 1% AcOH) afforded the title compound as a white solid (1.9 g, 79%).

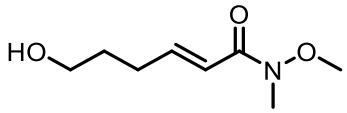
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dt, *J* = 15.6, 7.0 Hz, 1H, $CH_2CH_2CH_2C\underline{H}$=CH), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1H, $CH_2CH_2CH_2CH$=C<u>H</u>), 3.64 (t, *J* = 6.2 Hz, 2H, C<u>H</u>$_2CH_2CH_2CH$=CH), 2.38 – 2.26 (m, 2H, $CH_2CH_2C\underline{H}_2CH$=CH), 1.69 (tt, *J* = 7.3, 6.2 Hz, 2H, $CH_2C\underline{H}_2CH_2CH$=CH), 0.89 (s, 9H, C(C<u>H</u>$_3)_3$), 0.05 (s, 6H, Si(C<u>H</u>$_3)_2$) ppm. (COO<u>H</u> could not be observed); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.0 (<u>C</u>(O)O), 152.1 ($CH_2CH_2CH_2\underline{C}H$=CH), 120.9 ($CH_2CH_2CH_2CH$=<u>C</u>H), 62.3 (<u>C</u>$H_2CH_2CH_2CH$=CH), 31.1 ($CH_2\underline{C}H_2CH_2CH$=CH), 29.0 ($CH_2CH_2\underline{C}H_2CH$=CH), 26.1 (C(<u>C</u>$H_3)_3$), 18.4 (<u>C</u>$(CH_3)_3$), -5.2 (Si(<u>C</u>$H_3)_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{25}O_3Si$ ($[M+H]^+$) 245.1567, found 245.1568; **FT-IR (thin film)** ν_{max} 3026, 2928, 2856, 1692, 1645, 1470, 1424, 1321, 1289, 1256, 1097, 985, 962, 835, 774, 739, 611 cm^{-1}; **m.p.**: 53-54 °C.



(*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylhex-2-enamide (E62) was prepared according to the following procedure. According to the modified literature procedure reported by K. R. Prasad *et. al.,* [31] Et_3N (333.3 mg, 3.3 mmol, 1.3 eq) and ethyl chloroformate (325.6 mg, 3.0 mmol, 1.2 eq) were added to a solution of **(*E*)-6-((*tert*-butyldimethylsilyl)oxy)hex-2-enoic acid (E61)** (611.1 mg,

2.5 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) under N_2 at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before adding *N*,*O*-dimethylhydroxylamine hydrochloride (273.2 mg, 2.8 mmol, 1.1 eq) in one lot, followed by dropwise addition of Et_3N (506.0 mg, 5.0 mmol, 2.0 eq). The mixture was warmed to room temperature and stirred for 1 h before diluting with EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1M HCl (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 3/2) afforded the title compound as a colorless oil (426.0 mg, 60%). Data is consistent with the published literature.[32]

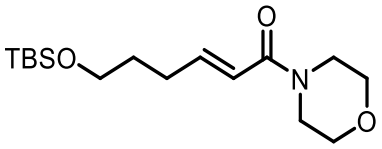
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dt, *J* = 15.5, 7.0 Hz, 1H, $CH_2CH_2CH_2C\underline{H}$=CH), 6.41 (dt, *J* = 15.4, 1.6 Hz, 1H, $CH_2CH_2CH_2CH$=C$\underline{H}$), 3.69 (s, 3H, C$\underline{H}_3$), 3.63 (t, *J* = 6.2 Hz, 2H, C$\underline{H}_2CH_2CH_2CH$=CH), 3.23 (s, 3H, C$\underline{H}_3$), 2.31 (dtd, *J* = 8.3, 7.0, 1.6 Hz, 2H, $CH_2CH_2C\underline{H}_2CH$=CH), 1.68 (ddt, *J* = 8.5, 7.4, 6.3 Hz, 2H, $CH_2C\underline{H}_2CH_2CH$=CH), 0.89 (s, 9H, C(C$\underline{H}_3)_3$), 0.05 (s, 6H, Si(C$\underline{H}_3)_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.2 (C(O)N), 147.5 ($CH_2CH_2CH_2\underline{C}H$=CH), 119.1 ($CH_2CH_2CH_2CH$=$\underline{C}$H), 62.4 ($\underline{C}H_2CH_2CH_2CH$=CH), 61.8 ($\underline{C}H_3$), 32.5 ($\underline{C}H_3$), 31.5 ($CH_2\underline{C}H_2CH_2CH$=CH), 29.0 ($CH_2CH_2\underline{C}H_2CH$=CH), 26.1 (C($\underline{C}H_3)_3$), 18.5 ($\underline{C}(CH_3)_3$), -5.2 (Si($\underline{C}H_3)_2$) ppm.



(*E*)-6-Hydroxy-*N*-methoxy-*N*-methylhex-2-enamide (413) was prepared according to the following procedure. Camphorsulfonic acid (295.0 mg, 1.27 mmol, 1.0 eq) was added to a solution of **(*E*)-6-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylhex-2-enamide (E62)** (363.9 mg, 1.27 mmol, 1.0 eq) in CH_2Cl_2 (6 mL) and CH_3OH (6 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 4 hours before quenching with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL),dried over Na_2SO_4, filtered and evaporated to dryness under reduced

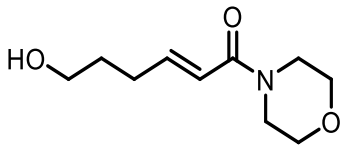
pressure. Purification by silica gel chromatography (CH_2Cl_2/CH_3OH = 95/5) afforded the title compound as a pale-yellow oil (196.2 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dt, *J* = 15.4, 7.0 Hz, 1H, $CH_2CH_2CH_2CH$=CH), 6.43 (dt, *J* = 15.4, 1.6 Hz, 1H, $CH_2CH_2CH_2CH$=C<u>H</u>), 3.74 – 3.63 (m, 5H, C<u>H</u>$_2CH_2CH_2CH$=CH and C<u>H</u>$_3$), 3.23 (s, 3H, C<u>H</u>$_3$), 2.34 (dtd, *J* = 8.3, 7.1, 1.6 Hz, 2H, CH_2CH_2C<u>H</u>$_2CH$=CH), 1.79 – 1.70 (m, 3H, CH_2C<u>H</u>$_2CH_2CH$=CH and O<u>H</u>) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.1 (<u>C</u>(O)N), 147.1 ($CH_2CH_2CH_2$<u>C</u>H=CH), 119.3 ($CH_2CH_2CH_2CH$=<u>C</u>H), 62.2 (<u>C</u>H$_2CH_2CH_2CH$=CH), 61.8 (<u>C</u>H$_3$), 32.5 (<u>C</u>H$_3$), 31.4 (CH_2<u>C</u>H$_2CH_2CH$=CH), 28.9 (CH_2CH_2<u>C</u>H$_2CH$=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_8H_{16}NO_3$ ($[M+H]^+$) 174.1125, found 174.1126; **FT-IR (thin film)** ν_{max} 3409, 2938, 2359, 2341, 1659, 1616, 1427, 1386, 1181, 1113, 1060, 993, 918, 874, 797, 788, 711, 702, 694, 686, 677, 668 cm^{-1}.



(*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-morpholinohex-2-en-1-one (E63) was prepared according to the following procedure. According to the modified literature procedure reported by R. Venkateshwarlu *et. al.,* [33] HATU (24.7 g, 64.9 mmol, 1.1 eq) and DIPEA (11.5 g, 88.5 mmol, 1.5 eq) was added to a solution of **(*E*)-6-((*tert*-butyldimethylsilyl)oxy)hex-2-enoic acid (E61)** (14.4 g, 59.0 mmol, 1.0 eq) in DMF (295 mL) under N_2 at 0 °C. The resulting mixture was stirred at 0 °C for 5 min before warming to room temperature. Morpholine (5.7 g, 64.9 mmol, 1.1 eq) was added. The mixture was stirred at room temperature for 16 hours before quenching with a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine (200 mL),dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O= 1/1) afforded the title compound as a pale-orange oil (14.7 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 15.0, 7.0 Hz, 1H, $CH_2CH_2CH_2C\underline{H}$=CH), 6.20 (dt, *J* = 15.1, 1.6 Hz, 1H, $CH_2CH_2CH_2CH$=C$\underline{H}$), 3.80 – 3.37 (m, 10H, C$\underline{H}_2CH_2CH_2CH$=CH and NC$\underline{H}_2C\underline{H}_2$O), 2.26 (dtd, *J* = 8.3, 6.9, 1.6 Hz, 2H, $CH_2CH_2C\underline{H}_2CH$=CH), 1.71 – 1.58 (m, 2H, $CH_2C\underline{H}_2CH_2CH$=CH), 0.87 (s, 9H, C(C$\underline{H}_3)_3$), 0.03 (s, 6H, Si(C$\underline{H}_3)_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.8 ($\underline{C}$(O)N), 146.8 ($CH_2CH_2CH_2\underline{C}H$=CH), 119.8 ($CH_2CH_2CH_2CH$=$\underline{C}H$), 66.9 (2C, NC$H_2\underline{C}H_2$O), 62.3 ($\underline{C}H_2CH_2CH_2CH$=CH), 46.2 (N$\underline{C}H_2CH_2$O), 42.4 (N$\underline{C}H_2CH_2$O), 31.5 ($CH_2\underline{C}H_2CH_2CH$=CH), 29.0 ($CH_2CH_2\underline{C}H_2CH$=CH), 26.0 (C($\underline{C}H_3)_3$), 18.4 ($\underline{C}(CH_3)_3$), -5.2 (Si($\underline{C}H_3)_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{32}NO_3Si$ ($[M+H]^+$) 314.2146, found 314.2146; **FT-IR (thin film)** ν_{max} 2928, 2856,1660, 1621, 1431, 1361, 1255, 1114, 1025, 977, 836, 776, 715 cm^{-1}.

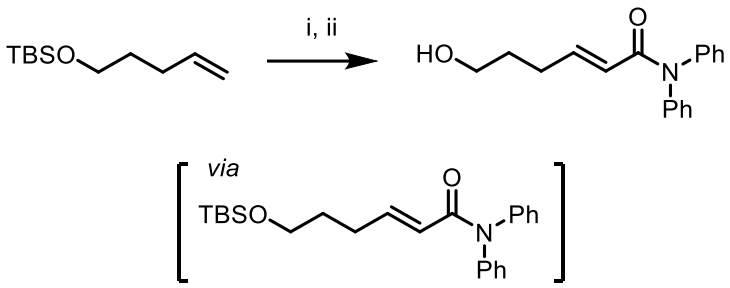


(*E*)-6-Hydroxy-1-morpholinohex-2-en-1-one (414) was prepared following **the procedure for the synthesis of (*E*)-6-hydroxy-*N*-methoxy-*N*-methylhex-2-enamide (413)**, using **(*E*)-6-((*tert*-butyldimethylsilyl)oxy)-1-morpholinohex-2-en-1-one (E63)** (1.3 g, 4.2 mmol, 1.0 eq), Camphorsulfonic acid (2.0 g, 8.4 mmol, 2.0 eq), CH_2Cl_2 (19 mL) and CH_3OH (19 mL) to afford the title compound as an pale-yellow oil (537.0 mg, 64%). Silica gel chromatography condition: CH_2Cl_2/ CH_3OH = 95:5.

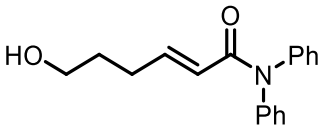
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 14.5, 7.0 Hz, 1H, $CH_2CH_2CH_2C\underline{H}$=CH), 6.23 (dt, *J* = 15.0, 1.6 Hz, 1H, $CH_2CH_2CH_2CH$=C$\underline{H}$), 3.90 – 3.36 (m, 10H, C$\underline{H}_2CH_2CH_2CH$=CH and NC$\underline{H}_2C\underline{H}_2$O), 2.30 (qd, *J* = 7.1, 1.6 Hz, 2H, $CH_2CH_2C\underline{H}_2CH$=CH), 1.88 (s, 1H, O$\underline{H}$), 1.77 – 1.66 (m, 2H, $CH_2C\underline{H}_2CH_2CH$=CH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.8 ($\underline{C}$(O)N), 146.5 ($CH_2CH_2CH_2\underline{C}H$=CH), 120.0 ($CH_2CH_2CH_2CH$=$\underline{C}H$), 66.9 (2C, NC$H_2\underline{C}H_2$O), 62.0 ($\underline{C}H_2CH_2CH_2CH$=CH), 46.2 (N$\underline{C}H_2CH_2$O), 42.4 (N$\underline{C}H_2CH_2$O), 31.4 ($CH_2\underline{C}H_2CH_2CH$=CH), 29.0 ($CH_2CH_2\underline{C}H_2CH$=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{10}H_{18}O_3N$ ($[M+H]^+$) 200.1281, found

200.1280; **FT-IR (thin film)** ν_{max} 3394, 2922, 2855, 1656, 1601, 1437, 1301, 1269, 1238, 1114, 1049, 1020, 979, 854, 701 cm^{-1}.

Preparation of starting materials 415



Scheme 86. Synthesis of starting materials **415**. i. Hoveyda-Grubbs 2nd generation catalyst, acryloyl chloride, CH_2Cl_2, 45 °C, 24 h then diphenylamine, K_3PO_4, 16 h; ii. CSA, CH_2Cl_2, MeOH, 4 h.



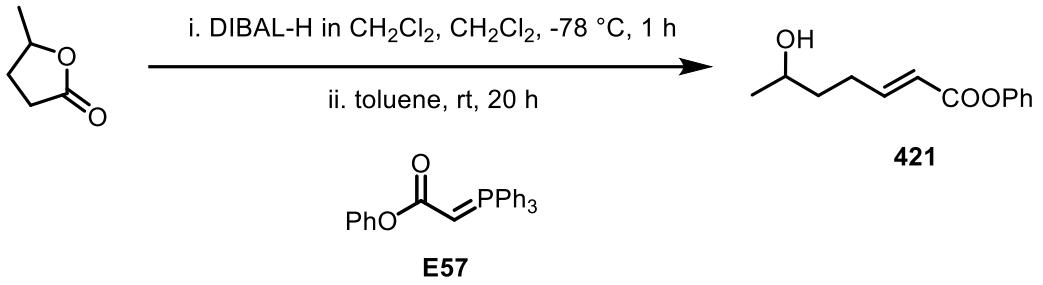
(*E*)-6-Hydroxy-*N*,*N*-diphenylhex-2-enamide (415) was prepared according to the following procedure. A solution of Hoveyda-Grubbs 2nd generation catalyst (3.2 mg, 0.005 mmol, 0.0025 eq) in degassed CH_2Cl_2 (0.5 mL) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of ***tert*-butyldimethyl(pent-4-en-1-yloxy)silane (E60)** (400.4 mg, 2.0 mmol, 1.0 eq) and acryloyl chloride (290.0 mg, 3.2 mmol, 1.6 eq) under N_2 at 45 °C. The resulting mixture was stirred at 45 °C for 1 hour. Another 0.5 mL solution of Hoveyda-Grubbs 2nd generation catalyst (3.2 mg, 0.005 mmol, 0.0025 eq) in degassed CH_2Cl_2 was added dropwise (0.5 mL/h) by using a syringe pump to the mixture. The reaction was further stirred for 21 hours at 45 °C before cooling down to room temperature and quenching with diphenylamine (541.5 mg, 3.2 mmol, 1.6 eq) and K_3PO_4 (1.62 g, 7.6 mmol, 3.8 eq). The resulting slurry was stirred at room temperature for 16 hours before directly loading onto the silica gel. Purification by silica gel chromatography (pentane/EtOAc = 4:1) afforded the TBS-protected acrylamide as a pale-yellow oil (192.2 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.17 (m, 10H, Ar-H), 7.04 (dt, *J* = 15.1, 7.0 Hz, 1H, $CH_2CH_2CH_2CH$=CH), 5.88 (dt, *J* = 15.1, 1.5 Hz, 1H, $CH_2CH_2CH_2CH$=CH), 3.58 (t, *J* = 6.2 Hz, 2H, $CH_2CH_2CH_2CH$=CH), 2.30 – 2.13 (m, 2H, $CH_2CH_2CH_2CH$=CH), 1.71 – 1.52 (m, 2H, $CH_2CH_2CH_2CH$=CH), 0.88 (s, 9H, $C(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$) ppm; **HRMS** (MSSapci) m/z calcd. for $C_{24}H_{34}O_2NSi$ ($[M+H]^+$) 396.2353, found 396.2353

TBS removal followed **the procedure for the synthesis of (*E*)-6-Hydroxy-*N*-methoxy-*N*-methylhex-2-enamide (1120)**, using TBS-protected acrylamide (173.1 mg, 0.44 mmol, 1.0 eq), Camphorsulfonic acid (102.2 mg, 0.44 mmol, 1.0 eq), CH_2Cl_2 (2 mL) and CH_3OH (2 mL) to afford the title compound as a white solid (110.7 mg, 91%). Silica gel chromatography condition: pentane/ acetone = 7:3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.6 Hz, 4H, Ar-H), 7.29 – 7.19 (m, 6H, Ar-H), 7.01 (dt, *J* = 14.6, 7.1 Hz, 1H, $CH_2CH_2CH_2CH$=CH), 5.88 (dt, *J* = 15.1, 1.6 Hz, 1H, $CH_2CH_2CH_2CH$=CH), 3.58 (t, *J* = 6.4 Hz, 2H, $CH_2CH_2CH_2CH$=CH), 2.19 (ddd, *J* = 15.4, 7.4, 1.7 Hz, 2H, $CH_2CH_2CH_2CH$=CH), 1.64 (dt, *J* = 8.2, 6.6 Hz, 3H, $CH_2CH_2CH_2CH$=CH and OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 (C(O)N), 146.4 ($CH_2CH_2CH_2CH$=CH), 142.9 (ArC), 129.3 (ArCH), 127.6 (ArCH), 126.9 (ArCH), 123.0 ($CH_2CH_2CH_2CH$=CH), 62.1 ($CH_2CH_2CH_2CH$=CH), 31.2 ($CH_2CH_2CH_2CH$=CH), 28.8 ($CH_2CH_2CH_2CH$=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{20}O_2N$ ($[M+H]^+$) 282.1489, found 282.1489; **FT-IR (thin film)** ν_{max} 3659, 2981, 2888, 1664, 1630, 1592, 1491, 1381, 1252, 1154, 1073, 955, 830, 757, 700, 668, 625 cm^{-1}; **m.p.**: 72-73 °C.

Preparation of Starting Materials 421



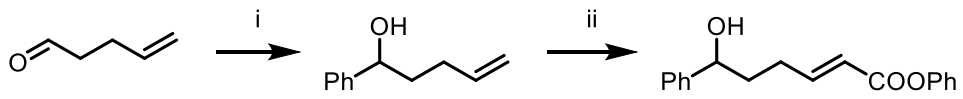
Phenyl (*E*)-6-hydroxyhept-2-enoate (421) was prepared according to the following procedure. DIBAL (1M solution in CH_2Cl_2) (50 mL, 50 mmol, 2.0 eq) was added dropwise to a solution of 5-methyldihydrofuran-2(3H)-one (2.5 g, 25 mmol, 1.0 eq) in CH_2Cl_2 (67mL) under N_2 at −78 ºC. The reaction mixture was stirred at the same temperature for 1 hour before warming up to room temperature and slowly adding H_2O (2 mL), NaOH (15% aqueous solution, 2 mL) and H_2O (5 mL). The resulting mixture was stirred for 15 mins before drying over $MgSO_4$, filtering and carefully evaporating to dryness under reduced pressure to afford the hemiacetal as a colorless oil which was used as crude for next step without any further purification.

hemiacetal (408.5 mg, 4 mmol, 1.0 eq) was added to a solution of phenyl-(triphenylphosphoranylidene)acetate **E57** (4.76 g, 12 mmol, 3 eq) in toluene (40.3 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 20 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/EtOAc = 9/1) afforded the title compound as a colorless oil (162.3 mg, 19%).

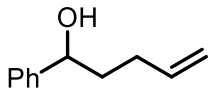
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.25 – 7.15 (m, 2H, CH_2CH=CH and Ar-H), 7.14 – 7.09 (m, 2H, Ar-H), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 3.87 (qd, *J* = 6.3, 4.6 Hz, 1H, OHCH), 2.52 – 2.28 (m, 2H, CH_2CH=CH), 1.66 (td, *J* = 7.7, 5.9 Hz, 2H, OHCHCH_2), 1.39 (d, *J* = 4.4 Hz, 1H, OH), 1.25 (d, *J* = 6.2 Hz, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1 (C(O)O), 151.3 (CH_2CH=CH), 150.9 (ArC), 129.5 (ArCH), 125.8 (ArCH), 121.8 (ArCH), 121.0 (CH_2CH=CH), 67.4 (OHCH), 37.3 (OHCHCH_2), 28.9 (CH_2CH=CH), 23.9 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for

$C_{13}H_{16}O_3Na$ ($[M+Na]^+$) 243.0992, found 243.0993; **FT-IR (thin film)** ν_{max} 2981, 2359, 2341, 1735, 1651, 1494, 1376, 1257, 1197, 1153, 959, 900, 849, 840, 832, 823, 814, 806, 797, 754, 694, 669 cm^{-1}.

Preparation of Starting Materials 422

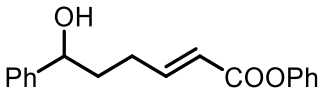


Scheme 87. Synthesis of starting materials **422**. i. PhMgBr (3M in Et_2O), Et_2O, −78 °C, 1 h; ii. Hoveyda-Grubbs 2nd generation catalyst, phenyl acrylate, CH_2Cl_2, 45 °C, 2 h.



1-Phenylpent-4-en-1-ol (**E64**) was prepared according to the following procedure. PhMgBr (3M in Et_2O, 1.1 mL, 3.3 mmol, 1.1 eq) was added dropwise to a solution of pent-4-enal (252.4 mg, 3.0 mmol, 1.0 eq) in Et_2O (3 mL) under N_2 at −78 °C. The reaction mixture was stirred at −78 °C for 1 hour before warming to room temperature and stirring for 24 hours. The mixture was then quenched with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and carefully evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 17:3) afforded the title compound as a yellow oil (201.8 mg, 42%). Data is consistent with the published literature.[34]

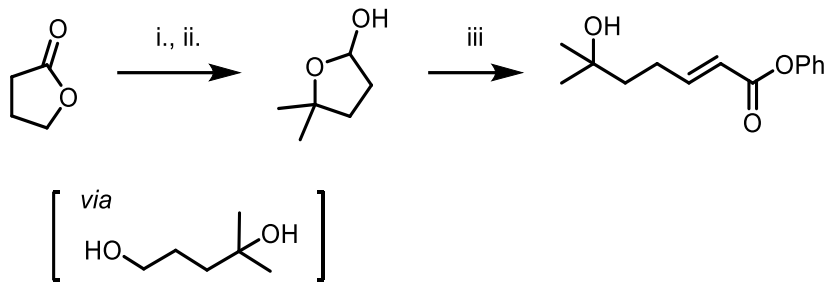
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H, Ar-H), 5.85 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, CH=CH_2), 5.05 (dq, *J* = 17.1, 1.7 Hz, 1H, CH=CH_2), 4.99 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H, CH=CH_2), 4.70 (dd, *J* = 7.7, 5.6 Hz, 1H, OHCH), 2.25 – 2.04 (m, 2H, CH_2CH=CH_2), 2.03 – 1.73 (m, 3H, OHCHCH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 144.8 (ArC), 138.3 (CH=CH_2), 128.6 (ArCH), 127.7 (ArCH), 126.0 (ArCH), 115.1 (CH=CH_2), 74.2 (OHCH), 38.2 (OHCHCH_2), 30.2 (CH_2CH=CH_2) ppm.



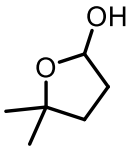
Phenyl (*E*)-6-hydroxy-6-phenylhex-2-enoate (**422**) was prepared according to the following procedure. A solution of Hoveyda-Grubbs 2nd generation catalyst (3.1 mg, 0.005 mmol, 0.005 eq) in degassed CH_2Cl_2 (0.5 mL) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of **1-phenylpent-4-en-1-ol** (**E64**) (162.1 g, 1.0 mmol, 1.0 eq) and phenyl acrylate (444.2 mg, 3 mmol, 3.0 eq) under N_2 at 45 °C. The reaction mixture was stirred at 45 °C for 2 hours before directly loading onto the silica gel. Purification by silica gel chromatography (pentane/EtOAc = 4:1) afforded the title compound as an off-white solid (231.4 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 6H, Ar-H), 7.33 – 7.28 (m, 1H, Ar-H), 7.25 – 7.14 (m, 2H, Ar-H and CH_2CH=CH), 7.13 – 7.07 (m, 2H, Ar-H), 6.04 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 4.74 (dd, *J* = 7.8, 5.4 Hz, 1H, OHCH), 2.53 – 2.27 (m, 2H, CH_2CH=CH), 2.09 – 1.87 (m, 2H, OHCHCH_2), 1.85 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (C(O)O), 150.94 (CH_2CH=CH), 150.89 (ArC), 144.3 (ArC), 129.5 (ArCH), 128.8 (ArCH), 128.0 (ArCH), 126.0 (ArCH), 125.8 (ArCH), 121.8 (ArCH), 121.1 (CH_2CH=CH), 73.9 (OHCH), 37.1 (OHCHCH_2), 28.8 (CH_2CH=CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{18}O_3Na$ ($[M+Na]^+$) 305.1148, found 305.1149; **FT-IR (thin film)** ν_{max} 3654, 2981, 2888, 1737, 1650, 1461, 1383, 1252, 1196, 1148, 1072, 955, 701, 659 cm^{-1}; **m.p.**: 43-44 °C.

Preparation of Starting Materials 423



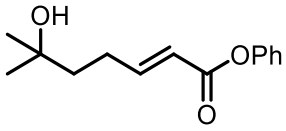
Scheme 88. Synthesis of starting materials **423**. i. MeMgBr (1M in THF), THF, 0 °C, 2 h; ii. IBX, DMSO, acetone, rt, 2 h; iii. Phenyl-(triphenylphosphoranylidene)acetate **E57**, toluene, rt, 20 h.



5,5-Dimethyltetrahydrofuran-2-ol (E65) was prepared according to the following procedure. MeMgBr (1M in THF, 50 mL, 50 mmol, 2.5 eq) was added dropwise to a solution of dihydrofuran-2(3H)-one (1.73 g, 20 mmol, 1.0 eq) in THF (30 mL) under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours before quenching with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3/1) (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and carefully evaporated to dryness under reduced pressure. Purification by silica gel chromatography (acetone) afforded the diol (1.10 g, 47%)

IBX (2.86 g, 10.2 mmol, 1.2 eq) was added to a mixture of DMSO (7.2 mL) and acetone (27 mL) under N_2 at room temperature. The reaction mixture was stirred for 1 hour before adding the diol. The resulting mixture was stirred for 1 hour before quenching with H_2O (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3/1) (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and carefully evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc = 3/1) afforded the title compound as a yellow oil (397.0 mg, 40%). Data is consistent with the published literature.[35]

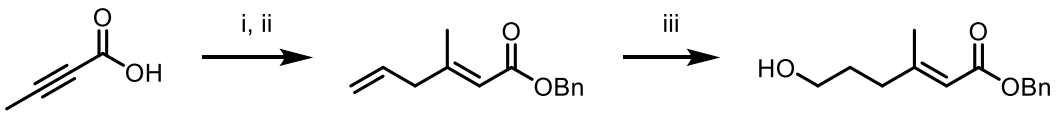
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (ddd, *J* = 4.3, 2.7, 1.3 Hz, 1H, C<u>H</u>), 3.40 (dd, *J* = 2.9, 1.3 Hz, 1H, O<u>H</u>), 2.10 – 1.89 (m, 3H, CHC<u>H</u>$_2$C<u>H</u>$_2$), 1.78 – 1.65 (m, 1H, CHCH$_2$C<u>H</u>$_2$), 1.40 (s, 3H, C<u>H</u>$_3$), 1.19 (s, 3H, C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 98.8 (C<u>H</u>), 82.8(O<u>C</u>), 36.3 (CHCH$_2$<u>C</u>H$_2$), 33.8 (CH<u>C</u>H$_2$CH$_2$), 30.4 (<u>C</u>H$_3$), 28.7 (<u>C</u>H$_3$) ppm.



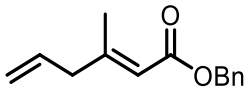
Phenyl (*E*)-6-hydroxy-6-methylhept-2-enoate (423) was prepared according to the following procedure. **5,5-dimethyltetrahydrofuran-2-ol (E65)** (376.4 mg, 3.24 mmol, 1.0 eq) was added to a solution of **phenyl-(triphenylphosphoranylidene)acetate (E57)** (1.29 g, 3.24 mmol, 1.0 eq) in toluene (10.8 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 20 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/EtOAc= 9/1) afforded the title compound as a colorless oil (463.0 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-<u>H</u>), 7.26 – 7.17 (m, 2H, Ar-<u>H</u> and CH$_2$C<u>H</u>=CH), 7.15 – 7.07 (m, 2H, Ar-<u>H</u>), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH$_2$CH=C<u>H</u>), 2.45 – 2.35 (m, 2H, C<u>H</u>$_2$CH=CH), 1.72 – 1.64 (m, 2H, C<u>H</u>$_2$CH$_2$CH=CH), 1.27 (s, 7H, C<u>H</u>$_3$ and O<u>H</u>) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1 (<u>C</u>(O)O), 151.8 (CH$_2$<u>C</u>H=CH), 150.9 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 121.8 (Ar<u>C</u>H), 120.7 (CH$_2$CH=<u>C</u>H), 70.7 (OH<u>C</u>), 41.8 (<u>C</u>H$_2$CH$_2$CH=CH), 29.5 (C<u>H</u>$_3$), 27.6 (<u>C</u>H$_2$CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{18}O_3Na$ ([M+Na]$^+$) 257.1148, found 257.1148; **FT-IR (thin film)** ν_{max} 3392, 2980, 2360, 1735, 1651, 1593, 1493, 1378, 1323, 1250, 1196, 1163, 1128, 1071, 968, 927, 815, 754, 721, 688, 668 cm^{-1}.

Preparation of Starting Materials 430



Scheme 89. Synthesis of starting materials **430**. i. BnBr, K_2CO_3, DMF, rt, 20 h; ii. $Cu(OAc)_2$, allylboronic acid pinacol ester, MeOH, −78 °C for 20 mins then rt 3 h. iii. 9-BBN, −78 °C to rt, 3h then H_2O and $NaBO_3 \cdot 4H_2O$, rt, 20 h.

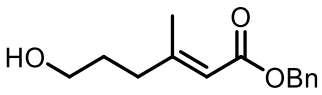


Benzyl (*E*)-3-methylhexa-2,5-dienoate (E66) was prepared according to the following procedure. According to the modified literature procedure reported by Y. Yamamoto *et. al.,* [36] a solution of but-2-ynoic acid (3.00 g, 35.73 mmol, 1.1 eq) in DMF (21 mL) and BnBr (5.51 g, 32.20 mmol, 1.0 eq) were added to a suspension of K_2CO_3 (5.78 g, 41.90 mmol, 1.3 eq) in DMF (32 mL) under N_2 at room temperature. The resulting mixture was stirred at room temperature for 20 hours before diluting with EtOAc (100 mL) and H_2O (300 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 95/5) afforded the benzyl but-2-ynoate as a colorless oil (5.26 g, 94%).

A solution of benzyl but-2-ynoate (1.43 g, 8.22 mmol, 1.0 eq), $Cu(OAc)_2$ (45.4 mg, 0.25 mmol, 0.03 eq) and Allylboronic acid pinacol ester (2.07 g, 12.33 mmol, 1.5 eq) in anhydrous MeOH (16.5 mL) was degassed at −78 °C for 20 mins. The resulting mixture was warmed to room temperature and stirred for 3 hours under N_2 before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a colorless oil (1.72 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H, Ar-H), 5.85 – 5.71 (m, 2H, CHCH$_2$C and CHC(O)), 5.18 – 5.06 (m, 4H, OCH$_2$ and CH=CH$_2$), 2.88 (dq, *J* = 6.9, 1.3 Hz, 2H, CHCH$_2$C), 2.18 (d, *J* = 1.3 Hz,

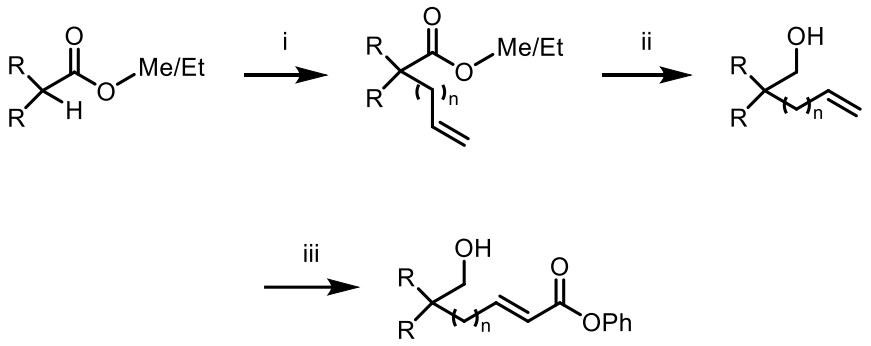
3H, C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 166.6 (<u>C</u>(O)O), 158.8 (<u>C</u>CH$_3$), 136.5 (Ar<u>C</u>), 134.3 (<u>C</u>HCH$_2$C or <u>C</u>HC(O)), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 118.1 (CH=<u>C</u>H$_2$), 116.2 (<u>C</u>HCH$_2$C or <u>C</u>HC(O)), 65.6 (O<u>C</u>H$_2$), 45.1 (CH<u>C</u>H$_2$C), 19.1 (C<u>C</u>H$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{17}O_2$ ([M+H]$^+$) 217.1223, found 217.1224; **FT-IR (thin film)** ν_{max} 2981, 1715, 1650, 1455, 1389, 1353, 1215, 1140, 1027, 920, 834, 746, 697 cm^{-1}.



Benzyl (*E*)-6-hydroxy-3-methylhex-2-enoate (430) was prepared according to the following procedure. According to the modified literature procedure reported by Y. Yamamoto *et. al.,* 9-BBN (0.5M in THF) (15.2 mL, 7.6 mmol, 1.0 eq) was added to **benzyl (*E*)-3-methylhexa-2,5-dienoate (E66)** (1.64 g, 7.6 mmol, 1.0 eq) under argon at −78 °C. The mixture was degassed for 5 mins and back filled with argon before warming to room temperature and stirred for 3 hours. H_2O (44.7 mL) and $NaBO_3{\cdot}4H_2O$ (6.00 g, 38.8 mmol, 5.1 eq) was added under argon at room temperature. The reaction mixture was stirred for 20 hours before extracting with E_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 3/7) afforded the title compound as a colorless oil (1.03 g, 58%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.27 (m, 5H, Ar-<u>H</u>), 5.76 (h, *J* = 1.3 Hz, 1H, CC<u>H</u>), 5.14 (s, 2H, OC<u>H</u>$_2$), 3.65 (t, *J* = 6.4 Hz, 2H, OHC<u>H</u>$_2$CH$_2$CH$_2$), 2.28 – 2.21 (m, 2H, OHCH$_2$CH$_2$C<u>H</u>$_2$), 2.21 – 2.17 (m, 3H, C<u>H</u>$_3$), 1.80 – 1.68 (m, 2H, OHCH$_2$C<u>H</u>$_2$CH$_2$), 1.53 (s, 1H, O<u>H</u>) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 166.6 (<u>C</u>(O)O), 160.3 (<u>C</u>CH$_3$), 136.5 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 115.7 (C<u>C</u>H), 65.6 (O<u>C</u>H$_2$), 62.2 (OH<u>C</u>H$_2$CH$_2$CH$_2$), 37.3 (OHCH$_2$CH$_2$<u>C</u>H$_2$), 30.4 (OHCH$_2$<u>C</u>H$_2$CH$_2$), 19.0 (C<u>C</u>H$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{18}O_3Na$ ([M+Na]$^+$) 257.1148, found 257.1148; **FT-IR (thin film)** ν_{max} 2981, 1713, 1645, 1455, 1391, 1219, 1142, 1067, 1015, 745, 697 cm^{-1}.

General procedure E for preparation of starting materials 420 and 433-438



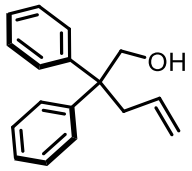
Scheme 90. General Procedure **E** for preparation of starting materials **420** and **433-438**. i. $iPrNH_2$, n-BuLi, THF, alkylating agent, −78 °C to rt, 16 h; ii. $LiAlH_4$ in THF, Et_2O, 0 °C to rt, 1 h; iii. Hoveyda-Grubbs 2nd generation catalyst, phenyl acrylate, CH_2Cl_2, 45 °C, 3 h.

i. According to the modified literature procedure reported by J. Escudero *et. al.,* [37] *n*BuLi (2.5M in hexanes, 1.08 eq) was added dropwise to a solution of *i*PrNH$_2$ (1.1 eq) in THF (0.4M) under N_2 at −78 °C. The mixture was stirred at −78 °C for 15 mins before adding corresponding ester (1 eq) slowly. The mixture was then stirred at −78 °C for 10 mins before adding corresponding alkylating reagent (1.2 eq) slowly. The resulting mixture was then warmed to room temperature and stirred for 16 hours before quenching with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and carefully evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O) afforded the alkyl esters.

ii. A solution of the alkyl esters (1.0 eq) in Et_2O (1M) was added slowly to a solution of $LiAlH_4$ (1.5 eq) in THF (1M) under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour before quenching with H_2O (5 mL) carefully at 0 °C. The mixture was then warmed to room temperature and more H_2O was added until it became white. The resulting suspension was filtered through a pad of Celite® and carefully evaporated to dryness under reduced pressure to afford the alcohols which were used as crude for next step without any purification.

iii. A solution of Hoveyda-Grubbs 2nd generation catalyst (0.005 eq) in degassed CH_2Cl_2 (0.01M) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of the alcohols (1.0 eq) and phenyl

acrylate (3.0 eq) under N_2 at 45 °C. The reaction mixture was stirred at 45 °C for 3 hours before loading directly onto silica gel. Purification by silica gel chromatography (pentane/EtOAc) afforded starting materials **420** and **433-438**.



2,2-Diphenylpent-4-en-1-ol (E67) was prepared following General Procedure **E**. Data is consistent with the published literature.[38]

Step i.

Starting Materials: ethyl 2,2-diphenylacetate (2.40 g, 10.0 mmol, 1.0 eq) and 3-bromoprop-1-ene (1.45 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 95/5.

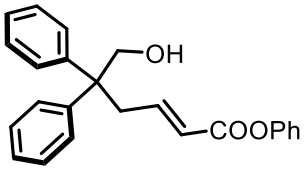
Product: ethyl 2,2-diphenylpent-4-enoate: colorless oil (2.68 g, 96%).

Step ii.

Starting Materials: ethyl 2,2-diphenylpent-4-enoate (2.36 g, 8.4 mmol, 1.0 eq)

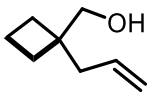
Product: **2,2-diphenylpent-4-en-1-ol (E67)**: colorless oil (1.97 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 10H, Ar-H), 5.45 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H, CH=CH_2), 5.15 – 5.05 (m, 1H, CH=CH_2), 5.00 (ddt, *J* = 10.1, 2.3, 1.1 Hz, 1H, CH=CH_2), 4.16 (d, *J* = 6.8 Hz, 2H, CH_2OH), 2.98 (dt, *J* = 7.1, 1.2 Hz, 2H, CH_2CH), 1.21 (t, *J* = 6.9, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 145.4 (ArC), 134.7 (CH=CH_2), 128.4 (ArCH), 128.3 (ArCH), 126.5 (ArCH), 118.2 (CH=CH_2), 68.1 (CH_2OH), 51.7 (C), 41.1 (CH_2CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{17}O$ ([M-H]$^-$) 237.1279, found 237.0794.



Phenyl (*E*)-6-hydroxy-5,5-diphenylhex-2-enoate (420) was prepared following **General Procedure E step iii**, using **2,2-diphenylpent-4-en-1-ol (E67)** (480.8 mg, 2.02 mmol, 1.0 eq) to afford the title compound as a white solid (514.3 mg, 71%). Silica gel chromatography condition: pentane/Et_2O = 7/3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 6H, Ar-H), 7.29 – 7.18 (m, 7H, Ar-H), 7.11 – 7.03 (m, 2H, Ar-H), 6.85 (dt, *J* = 15.3, 7.5 Hz, 1H, CH_2CH=CH), 6.06 (dt, *J* = 15.6, 1.4 Hz, 1H, CH_2CH=CH), 4.19 (d, *J* = 6.6 Hz, 2H, CH_2OH), 3.21 (dd, *J* = 7.5, 1.5 Hz, 2H, CH_2CH=CH), 1.27 (t, *J* = 6.6 Hz, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.5 (C(O)O), 150.8 (ArC), 147.6 (CH_2CH=CH), 144.5 (2C, ArC), 129.4 (2C, ArCH), 128.6 (4C, ArCH), 128.1 (4C, ArCH), 127.0 (2C, ArCH), 125.8 (ArCH), 123.7 (CH_2CH=CH), 121.7 (2C, ArCH), 68.1 (CH_2OH), 52.0 (C), 39.5 (CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{23}O_3$ ($[M+H]^+$) 359.1642, found 359.1640; **FT-IR (thin film)** ν_{max} 3418, 2980, 2360, 1731, 1650, 1594, 1493, 1445, 1334, 1253, 1195, 1163, 1144, 1068, 1024, 980, 855, 756, 729, 700, 669 cm^{-1}; **m.p.**: 93-94 °C.



(1-Allylcyclobutyl)methanol (E68) was prepared following General Procedure **E**. Data is consistent with the published literature.[39]

Step i.

Starting Materials: ethyl cyclobutanecarboxylate (1.28 g, 10.0 mmol, 1.0 eq) and 3-bromoprop-1-ene (1.45 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 95/5.

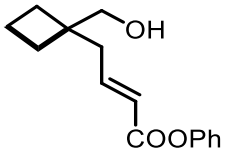
Product: ethyl 1-allylcyclobutane-1-carboxylate: pale-yellow oil (1.49 g, 89%).

Step ii.

Starting Materials: ethyl 1-allylcyclobutane-1-carboxylate (1.32 g, 7.9 mmol, 1.0 eq)

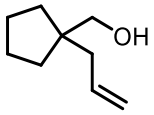
Product: **(1-allylcyclobutyl)methanol (E68)**: pale-orange oil (547.6 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.4, 10.1, 7.3 Hz, 1H, C<u>H</u>=CH_2), 5.19 – 4.99 (m, 2H, CH=C<u>H</u>$_2$), 3.54 (d, *J* = 5.1 Hz, 2H, C<u>H</u>$_2$OH), 2.26 (dt, *J* = 7.3, 1.3 Hz, 2H, C<u>H</u>$_2$CH), 1.95 – 1.72 (m, 6H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.41 (t, *J* = 5.4 Hz, 1H, O<u>H</u>) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.3 (<u>C</u>H=CH_2), 117.1 (CH=<u>C</u>H$_2$), 68.8 (<u>C</u>H$_2$OH), 42.9 (<u>C</u>), 41.6 (<u>C</u>H$_2$CH), 27.9 (2C, <u>C</u>H$_2$CH$_2$<u>C</u>H$_2$), 15.2 (CH$_2$<u>C</u>H$_2$CH$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_8H_{14}ONa$ ([M+Na]$^+$) 149.0937, found 149.0122.



Phenyl (*E*)-4-(1-(hydroxymethyl)cyclobutyl)but-2-enoate (433) was prepared following **General Procedure E step iii**, using **(1-allylcyclobutyl)methanol (E68)** (252.2 mg, 2.0 mmol, 1.0 eq) to afford the title compound as a pale-brown oil (348.7 mg, 71%). Silica gel chromatography condition: pentane/EtOAc = 4/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-<u>H</u>), 7.25 – 7.20 (m, 1H, Ar-<u>H</u>), 7.20 – 7.09 (m, 3H, Ar-<u>H</u> and CH_2C<u>H</u>=CH), 6.10 (dt, *J* = 15.6, 1.5 Hz, 1H, CH_2CH=C<u>H</u>), 3.59 (d, *J* = 4.9 Hz, 2H, C<u>H</u>$_2$OH), 2.50 (dd, *J* = 7.7, 1.4 Hz, 2H, C<u>H</u>$_2$CH), 1.99 – 1.80 (m, 6H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 1.51 – 1.40 (m, 1H, O<u>H</u>) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.9 (<u>C</u>(O)O), 150.9 (Ar<u>C</u>), 148.3 (CH_2<u>C</u>H=CH), 129.5 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 122.9 (CH_2CH=<u>C</u>H), 121.8 (Ar<u>C</u>H), 68.4 (<u>C</u>H$_2$OH), 43.1 (<u>C</u>), 39.8 (<u>C</u>H$_2$CH), 28.1 (2C, <u>C</u>H$_2$CH$_2$<u>C</u>H$_2$), 15.3 (CH$_2$<u>C</u>H$_2$CH$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{15}H_{19}O_3$ ([M+H]$^+$) 247.1329, found 247.1330; **FT-IR (thin film)** ν_{max} 3418, 2980, 2360, 2341, 1733, 1650, 1592, 1493, 1384, 1336, 1251, 1196, 1163, 1025, 984, 814, 779, 754, 720, 703, 687, 677, 668 cm^{-1}.



(1-Allylcyclopentyl)methanol (E69) was prepared following General Procedure **E**. Data is consistent with the published literature.[37]

Step i.

Starting Materials: methyl cyclopentanecarboxylate (1.28 g, 10.0 mmol, 1.0 eq) and 3-bromoprop-1-ene (1.45 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 98/2.

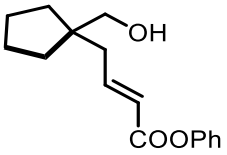
Product: methyl 1-allylcyclopentane-1-carboxylate: pale-yellow oil (1.46 g, 95%).

Step ii.

Starting Materials: methyl 1-allylcyclopentane-1-carboxylate (1.24 g, 8.0 mmol, 1.0 eq)

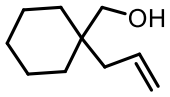
Product: **(1-allylcyclopentyl)methanol (E69)**: colorless oil (0.88 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H, C<u>H</u>=CH_2), 5.13 – 5.01 (m, 2H, CH=C<u>H</u>$_2$), 3.42 – 3.37 (m, 2H, C<u>H</u>$_2$OH), 2.16 (dt, *J* = 7.4, 1.3 Hz, 2H, C<u>H</u>$_2$CH), 1.68 – 1.51 (m, 4H, C<u>H</u>$_2$ (cyclopentane)), 1.51 – 1.34 (m, 5H, O<u>H</u> and C<u>H</u>$_2$ (cyclopentane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.4 (<u>C</u>H=CH_2), 117.1 (CH=<u>C</u>H$_2$), 69.2 (<u>C</u>H$_2$OH), 47.4 (<u>C</u>), 42.2 (<u>C</u>H$_2$CH), 34.3 (2C, <u>C</u>H$_2$ (cyclopentane)), 25.3 (2C, <u>C</u>H$_2$ (cyclopentane)) ppm.



Phenyl (*E*)-4-(1-(hydroxymethyl)cyclopentyl)but-2-enoate (434) was prepared following **General Procedure E step iii**, using **(1-allylcyclopentyl)methanol (E69)** (160.2 mg, 1.2 mmol, 1.0 eq) to afford the title compound as a pale-yellow oil (183.4 mg, 62%). Silica gel chromatography condition: pentane/EtOAc = 17/3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.25 – 7.14 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.09 (m, 2H, Ar-H), 6.08 (dt, *J* = 15.5, 1.4 Hz, 1H, CH_2CH=CH), 3.44 (s, 2H, CH_2OH), 2.40 (dd, *J* = 7.8, 1.4 Hz, 2H, CH_2CH), 1.72 – 1.58 (m, 4H, CH_2 (cyclopentane)), 1.57 – 1.41 (m, 5H, OH and CH_2 (cyclopentane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.9 (C(O)O), 150.9 (ArC), 149.3 (CH_2CH=CH), 129.5 (ArCH), 125.8 (ArCH), 122.8 (CH_2CH=CH), 121.8 (ArCH), 68.8 (CH_2OH), 47.8 (C), 40.2 (CH_2CH), 34.4 (2C, CH_2 (cyclopentane)), 25.3 (2C, CH_2 (cyclopentane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}O_3$ ($[M+H]^+$) 261.1485, found 261.1485; **FT-IR (thin film)** ν_{max} 3434, 2950, 2868, 1732, 1650, 1592, 1492, 1316, 1249, 1195, 1163, 1149, 1118, 1038, 981, 815, 778, 750, 688 cm^{-1}.



(1-Allylcyclohexyl)methanol (E70) was prepared following General Procedure **E**. Data is consistent with the published literature.[37]

Step i.

Starting Materials: methyl cyclohexanecarboxylate (1.43 g, 10.0 mmol, 1.0 eq) and 3-bromoprop-1-ene (1.45 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 95/5.

Product: methyl 1-allylcyclohexane-1-carboxylate: colorless oil (1.67 g, 92%).

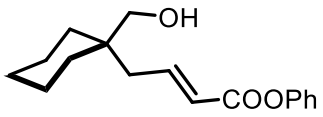
Step ii.

Starting Materials: methyl 1-allylcyclohexane-1-carboxylate (1.45 g, 8.0 mmol, 1.0 eq)

Product: **(1-allylcyclohexyl)methanol (E70)**: colorless oil (1.05 g, 85%).

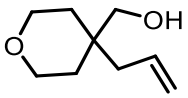
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 – 5.80 (m, 1H, $CH=CH_2$), 5.11 – 5.02 (m, 2H, $CH=CH_2$), 3.42 (d, *J* = 5.9 Hz, 2H, CH_2OH), 2.12 (dt, *J* = 7.6, 1.2 Hz, 2H, CH_2CH), 1.52 – 1.40 (m, 5H, CH_2 (cyclohexane)), 1.39 – 1.28 (m, 6H, OH and CH_2 (cyclohexane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.5 ($CH=CH_2$), 117.2 ($CH=CH_2$), 69.0 (CH_2OH), 40.2 (CH_2CH), 37.9 (C), 32.5 (2C, CH_2 (cyclohexane)), 26.5 (CH_2

(cyclohexane)), 21.6 (2C, CH_2 (cyclohexane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{10}H_{19}O$ ($[M+H]^+$) 155.1430, found 155.1432.



Phenyl (*E*)-4-(1-(hydroxymethyl)cyclohexyl)but-2-enoate (435) was prepared following **General Procedure E step iii**, using **(1-allylcyclohexyl)methanol (E70)** (308.3 mg, 2.0 mmol, 1.0 eq) to afford the title compound as a white solid (413.4 mg, 76%). Silica gel chromatography condition: pentane/EtOAc = 17/3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 2H, Ar-H), 7.26 – 7.16 (m, 2H, Ar-H and CH_2CH=CH), 7.16 – 7.09 (m, 2H, Ar-H), 6.07 (dt, *J* = 15.5, 1.4 Hz, 1H, CH_2CH=CH), 3.47 (s, 2H, CH_2OH), 2.37 (dd, *J* = 8.0, 1.4 Hz, 2H, CH_2CH), 1.49 (tt, *J* = 6.3, 4.2 Hz, 5H, CH_2 (cyclohexane)), 1.44 – 1.32 (m, 6H, OH and CH_2 (cyclohexane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.8 (C(O)O), 150.9 (ArC), 148.8 (CH_2CH=CH), 129.5 (ArCH), 125.8 (ArCH), 122.9 (CH_2CH=CH), 121.8 (ArCH), 68.4 (CH_2OH), 38.8 (C), 38.2 (CH_2CH), 32.5 (2C, CH_2 (cyclohexane)), 26.3 (CH_2 (cyclohexane)), 21.6 (2C, CH_2 (cyclohexane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{23}O_3$ ($[M+H]^+$) 275.1642, found 275.1642; **FT-IR (thin film)** ν_{max} 3411, 2927, 2858, 1731, 1649, 1592, 1492, 1454, 1313, 1250, 1196, 1163, 1134, 1117, 1027, 985, 927, 815, 777, 737, 688, 628 cm^{-1}; **m.p.**: 48-49 °C.



(4-Allyltetrahydro-2H-pyran-4-yl)methanol (E71) was prepared following General Procedure **E**. Data is consistent with the published literature.[40]

Step i.

Starting Materials: methyl tetrahydro-2H-pyran-4-carboxylate (1.45 g, 10.0 mmol, 1.0 eq) and 3-bromoprop-1-ene (1.45 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 4/1.

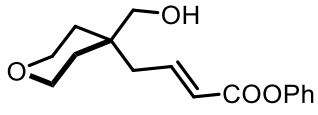
Product: methyl 4-allyltetrahydro-2H-pyran-4-carboxylate: yellow oil (1.67 g, 98%).

Step ii.

Starting Materials: methyl 4-allyltetrahydro-2H-pyran-4-carboxylate (1.37 g, 8.1 mmol, 1.0 eq)

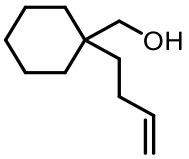
Product: **(4-allyltetrahydro-2H-pyran-4-yl)methanol (E71)**: pale-yellow oil (1.17 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 16.8, 10.3, 7.5 Hz, 1H, C<u>H</u>=CH_2), 5.36 – 4.89 (m, 2H, CH=C<u>H</u>$_2$), 3.67 (t, *J* = 5.5 Hz, 4H, OC<u>H</u>$_2$$CH_2$), 3.50 (s, 2H, C<u>H</u>$_2$OH), 2.22 (dt, *J* = 7.5, 1.2 Hz, 2H, C<u>H</u>$_2$CH), 1.60 (s, 1H, O<u>H</u>), 1.56 – 1.40 (m, 4H, OCH_2C<u>H</u>$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 134.4 (<u>C</u>H=CH_2), 118.0 (CH=<u>C</u>H$_2$), 67.8 (<u>C</u>H_2OH), 63.7 (O<u>C</u>$H_2$$CH_2$), 39.7 (<u>C</u>$H_2$CH), 35.8 (<u>C</u>), 32.4 (OCH_2<u>C</u>H_2) ppm; **HRMS** (MSSesi) m/z calcd. for $C_9H_{17}O_2$ ([M+H]$^+$) 157.1223, found 157.1224.



Phenyl (*E*)-4-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)but-2-enoate (438) was prepared following **General Procedure E step iii**, using **(4-allyltetrahydro-2H-pyran-4-yl)methanol (E71)** (320.8 mg, 2.05 mmol, 1.0 eq) to afford the title compound as an off-white solid (214.6 mg, 38%). Silica gel chromatography condition: pentane/EtOAc = 3/7.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.26 – 7.14 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.09 (m, 2H, Ar-H), 6.10 (dt, *J* = 15.5, 1.4 Hz, 1H, CH_2CH=CH), 3.71 (t, *J* = 5.5 Hz, 4H, OCH_2CH_2), 3.57 (d, *J* = 4.1 Hz, 2H, CH_2OH), 2.47 (dd, *J* = 7.9, 1.4 Hz, 2H, CH_2CH), 1.61 (t, *J* = 2.9 Hz, 1H, OH), 1.59 – 1.47 (m, 4H, OCH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.6 (C(O)O), 150.8 (ArC), 147.4 (CH_2CH=CH), 129.5 (ArCH), 125.9 (ArCH), 123.6 (CH_2CH=CH), 121.7 (ArCH), 67.3 (CH_2OH), 63.6 (OCH_2CH_2), 38.0 (CH_2CH)), 36.6 (C), 32.5 (OCH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{20}O_4Na$ ($[M+Na]^+$) 299.1254, found 299.1253; **FT-IR (thin film)** ν_{max} 3434, 2980, 1732, 1650, 1592, 1492, 1391, 1315, 1240, 1196, 1163, 1135, 1106, 1043, 1025, 994, 897, 837, 779, 749, 689, 648, 628 cm^{-1}; **m.p.**: 57-58 °C.



(1-(But-3-en-1-yl)cyclohexyl)methanol (E72) was prepared following General Procedure **E**. Data is consistent with the published literature.[41]

Step i.

Starting Materials: methyl cyclohexanecarboxylate (1.43 g, 10.0 mmol, 1.0 eq) and 4-bromobut-1-ene (1.61 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 96/4.

Product: methyl 1-(but-3-en-1-yl)cyclohexane-1-carboxylate: colorless oil (1.90 g, 97%).

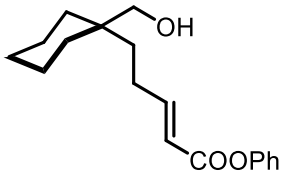
Step ii.

Starting Materials: methyl 1-(but-3-en-1-yl)cyclohexane-1-carboxylate (1.54 g, 7.8 mmol, 1.0 eq)

Product: **(1-(but-3-en-1-yl)cyclohexyl)methanol (E72):** colorless oil (1.24 g, 94%).

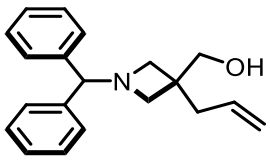
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, $CH=CH_2$), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H, $CH=CH_2$), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H, $CH=CH_2$), 3.43 (d, *J* = 5.8 Hz, 2H, CH_2OH),

1.99 (dddd, J = 12.9, 6.4, 2.9, 1.4 Hz, 2H, $CH_2C\underline{H}_2CH$), 1.52 – 1.23 (m, 13H, O$\underline{H}$, $C\underline{H}_2CH_2CH$ and $C\underline{H}_2$ (cyclohexane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 139.8 ($\underline{C}H=CH_2$), 114.1 ($CH=\underline{C}H_2$), 68.5 ($\underline{C}H_2OH$), 37.1 ($\underline{C}$), 34.1 ($\underline{C}H_2CH_2CH$), 32.6 (2C, $\underline{C}H_2$ (cyclohexane)), 27.7 ($CH_2\underline{C}H_2CH$), 26.5 ($\underline{C}H_2$ (cyclohexane)), 21.6 (2C, $\underline{C}H_2$ (cyclohexane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{11}H_{21}O$ ($[M+H]^+$) 169.1587, found 169.1588.



Phenyl (*E*)-5-(1-(hydroxymethyl)cyclohexyl)pent-2-enoate (436) was prepared following **General Procedure E step iii**, using **(1-(but-3-en-1-yl)cyclohexyl)methanol (E72)** (335.5 mg, 2.0 mmol, 1.0 eq) to afford the title compound as a colorless oil (492.2 mg, 86%). Silica gel chromatography condition: pentane/EtOAc = 4/1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-$\underline{H}$), 7.25 – 7.17 (m, 2H, Ar-$\underline{H}$ and $CH_2C\underline{H}$=CH), 7.14 – 7.06 (m, 2H, Ar-$\underline{H}$), 6.04 (dt, J = 15.7, 1.6 Hz, 1H, $CH_2CH=C\underline{H}$), 3.46 (s, 2H, $C\underline{H}_2OH$), 2.30 – 2.19 (m, 2H, $CH_2C\underline{H}_2CH$), 1.63 – 1.52 (m, 2H, $C\underline{H}_2CH_2CH$), 1.52 – 1.28 (m, 10H, $C\underline{H}_2$ (cyclohexane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.2 ($\underline{C}$(O)O), 152.5 ($CH_2\underline{C}H=CH$), 150.9 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$H), 125.8 (Ar$\underline{C}$H), 121.8 (Ar$\underline{C}$H), 120.4 ($CH_2CH=\underline{C}H$), 68.3 ($\underline{C}H_2OH$), 37.2 (2C, $\underline{C}H_2$ (cyclohexane)), 33.2 ($\underline{C}H_2CH_2CH$), 32.6, 26.6 ($CH_2\underline{C}H_2CH$), 26.5 ($\underline{C}H_2$ (cyclohexane)), 21.6 (2C, $\underline{C}H_2$ (cyclohexane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{25}O_3$ ($[M+H]^+$) 289.1836, found 289.1834; **FT-IR (thin film)** ν_{max} 3399, 2926, 2853, 1734, 1650, 1593, 1492, 1454, 1247, 1197, 1163, 1148, 1024, 976, 928, 846, 751, 722, 688, 650, 627 cm^{-1}.



(3-Allyl-1-benzhydrylazetidin-3-yl)methanol (E73) was prepared following General Procedure **E**.

Step i.

Starting Materials: methyl 1-benzhydrylazetidine-3-carboxylate (2.82 g, 10.0 mmol, 1.0 eq) and 3-bromoprop-1-ene (1.45 g, 12.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 90/10.

Product: methyl 3-allyl-1-benzhydrylazetidine-3-carboxylate: colorless oil (2.14 g, 67%).

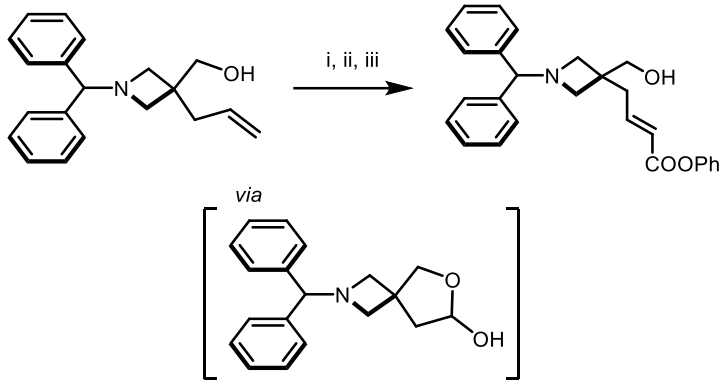
Step ii.

Starting Materials: methyl 3-allyl-1-benzhydrylazetidine-3-carboxylate (2.03 g, 6.3 mmol, 1.0 eq)

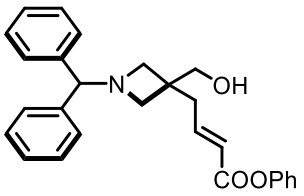
Product: **(3-allyl-1-benzhydrylazetidin-3-yl)methanol (E73)**: white solid (1.77 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H, Ar-H), 7.31 – 7.22 (m, 4H, Ar-H), 7.20 – 7.14 (m, 2H, Ar-H), 5.77 – 5.62 (m, 1H, CH=CH_2), 5.09 – 4.99 (m, 2H, CH=CH_2), 4.34 (s, 1H, NCH), 3.70 (s, 2H, CH_2OH), 3.60 – 3.36 (m, 1H, OH), 3.21 – 3.14 (m, 2H, NCH_2), 2.94 – 2.87 (m, 2H, NCH_2), 2.24 (dt, *J* = 7.3, 1.2 Hz, 2H, CH_2CH=CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 142.0 (ArC), 134.0 (CH=CH_2), 128.6 (4C, ArCH), 127.5 (4C, ArCH), 127.3 (2C, ArCH), 117.7 (CH=CH_2), 77.6 (NCH), 67.8 (CH_2OH), 60.4 (2C, NCH_2), 40.1 (CH_2CH=CH_2), 39.2 (C); **HRMS** (ESI) m/z calcd. for $C_{20}H_{24}NO$ ($[M+H]^+$) 294.1850, found 294.1850; **FT-IR (thin film)** ν_{max} 3345, 3027, 2930, 2838, 1639, 1599, 1492, 1452, 1346, 1253, 1208, 1029, 996, 917, 800, 744, 703, 643, 623, 612 cm^{-1}; **m.p.:** 57-58 °C.

Preparation of starting materials 437



Scheme 91. Synthesis of starting materials **437**. i. *N*-Methylmorpholine *N*-oxide (50% (w/w) in H_2O), OsO_4 (4% aqueous solution), ^{t}BuOH, THF, rt, 24 h; ii. $NaIO_4$, THF, H_2O, rt, 2 h. iii. Phenyl-(triphenylphosphoranylidene)acetate **E57**, toluene, rt, 48 h.



Phenyl (*E*)-4-(1-benzhydryl-3-(hydroxymethyl)azetidin-3-yl)but-2-enoate (437) was prepared according to the following procedure.

i. *N*-Methylmorpholine *N*-oxide (50% (w/w) in H_2O, 5.6 mL, 1.2 eq) and OsO_4 (4% aqueous solution, 0.53 mL, 0.002 eq) were added to a solution of **(3-allyl-1-benzhydrylazetidin-3-yl)methanol (E73)** (1.22 g, 4.15 mmol, 1.0 eq) in ^{t}BuOH (28 mL) and THF (11 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours before cooling to 0 °C and quenching with an aqueous solution of $NaHSO_3$ (12 mL, 3M). The resulting mixture was warmed to room temperature and stirred for 45 mins. The aqueous layer was extracted with $CHCl_3$/IPA (3/1) (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to afford the diol which was used as crude for next step without any purification.

ii. $NaIO_4$ (2.31 g, 10.80 mmol, 2.6 eq) was added to a solution of the diol in THF (55 mL) and H_2O (28 mL) under N_2 at room temperature. The reaction mixture was stirred for 2 hours before extracting with

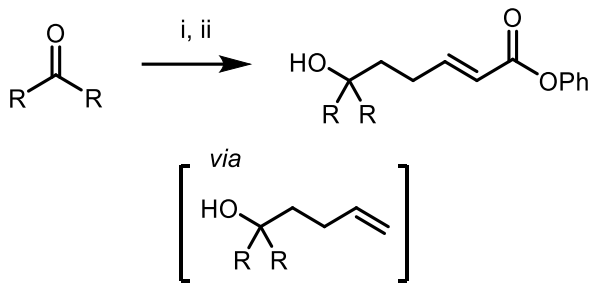
$CHCl_3$/IPA (3/1) (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc= 1/1) afforded the hemiacetal as a pale-yellow sticky oil (427.0 mg, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 4H, Ar-H), 7.30 – 7.22 (m, 4H, Ar-H), 7.22 – 7.13 (m, 2H, Ar-H), 5.48 (dd, *J* = 4.0, 2.6 Hz, 1H, OCH), 4.31 (s, 1H, NCH), 4.20 (d, *J* = 8.7 Hz, 1H, OCH_2), 3.98 (d, *J* = 8.7 Hz, 1H, OCH_2), 3.35 – 3.06 (m, 4H, CH_2NCH_2), 2.54 (s, 1H, OH), 2.18 – 2.12 (m, 2H, CH_2CH) ppm; **HRMS** (MSSesi) m/z calcd. for $C_{19}H_{22}NO_2$ ($[M+H]^+$) 296.1645, found 296.1643.

iii. hemiacetal (378.0 mg, 1.28 mmol, 1.0 eq) was added to a solution of **phenyl-(triphenylphosphoranylidene)acetate E57** (760.6 mg, 1.92 mmol, 1.5 eq) in toluene (6.4 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 48 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc= 3/2) afforded the title compound as a sticky white foam (1:0.2 = ***E*** isomer : ***Z*** isomer) (344.5 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (ddt, *J* = 8.4, 7.2, 2.0 Hz, 7H, Ar-H (***E*** and ***Z***)), 7.31 – 7.21 (m, 6H, Ar-H (***E*** and ***Z***)), 7.21 – 7.14 (m, 3H, Ar-H (***E*** and ***Z***)), 7.14 – 7.06 (m, 3H, CH_2CH=CH (***E***) and Ar-H (***E*** and ***Z***)), 6.37 (dt, *J* = 11.5, 8.2 Hz, 0.2H, CH_2CH=CH (***Z***)), 6.13 (dt, *J* = 11.5, 1.5 Hz, 0.2H, CH_2CH=CH (***Z***)), 6.06 (dt, *J* = 15.5, 1.5 Hz, 1H, CH_2CH=CH (***E***)), 4.44 – 4.25 (m, 1.2H, NCH, (***E*** and ***Z***)), 3.78 – 3.62 (m, *J* = 4.1 Hz, 2.4H, OCH_2 (***E*** and ***Z***)), 3.17 (d, *J* = 7.3 Hz, 2.6H, CH_2NCH_2 (***E*** and ***Z***) and OH (***Z***)), 2.98 (t, *J* = 8.5 Hz, 3.4H, CH_2NCH_2 (***E*** and ***Z***) and OH (***E***)), 2.56 – 2.49 (m, 2.4H, CH_2CH (***E*** and ***Z***)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.6 (C(O)O), 150.8 (ArC), 146.9 (CH_2CH=CH), 141.9 (ArC), 129.57 (ArCH), 129.55 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 127.52 (ArCH), 127.46 (ArCH and ArC), 127.4 (ArCH), 125.9 (ArCH), 123.1 (CH_2CH=CH), 121.7 (ArCH), 77.5 (NCH), 67.5 (OCH_2), 60.0 (CH_2NCH_2), 39.2 ($OHCH_2C$), 38.2 (CH_2CH) ppm. Only ^{13}C NMR for ***E*** isomer was observed; **HRMS** (ESI) m/z calcd. for $C_{27}H_{28}NO_3$ ($[M+H]^+$) 414.2064, found 414.2054; **FT-IR (thin film)** ν_{max} 3659, 2981, 2888, 1729, 1462, 1383, 1252, 1152, 1073, 955, 819, 704 cm^{-1}.

General procedure F for preparation of starting materials 424, 445-449, 452-453, 463, 465



Scheme 92. Synthesis of starting materials **424**, **445-449**, **452-453**, **463**, **465**. i. but-3-en-1-ylmagnesium bromide or but-3-en-1-ylcerium(III) chloride, THF, 0 °C to rt, 16 h; ii. Hoveyda-Grubbs 2nd generation catalyst, phenyl acrylate, CH_2Cl_2, 45 °C, 3 h.

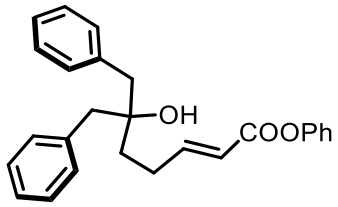
But-3-en-1-ylmagnesium bromide was prepared according to literature procedure and titrated before use.[42]

But-3-en-1-ylcerium(III) chloride was prepared according to the following procedure. $CeCl_3$ (1.0 eq) (anhydrous grade, stored and weighed in a glove box) was stirred at 90 °C for 30 mins and 135 °C for 2 hours under reduced pressure before cooling down to 0 °C. Anhydrous THF (0.5M) was added to the reaction vessel under N_2 at 0 °C. The resulting slurry was warmed to room temperature and stirred for 24 hours under N_2 before cooling down to −78 °C. But-3-en-1-ylmagnesium bromide (1.0 eq) was added dropwise under N_2 at −78 °C. The resulting mixture was stirred at −78 °C for 1 h, affording a THF solution of but-3-en-1-ylcerium(III) chloride which was used as crude for the addition without any purification.

i. Starting materials **424**, **445-449**, **452-453**, **463**, **465** was prepared according to the following procedure. A solution of ketone (1.0 eq) in THF (0.1M) was added to but-3-en-1-ylmagnesium bromide or But-3-en-1-ylcerium(III) chloride (THF solution, 1.2 eq) under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour before warming to room temperature and stirring for 15 hours. The mixture was then quenched with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4,

filtered and carefully evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc) afforded the terminal alkene.

ii. A solution of Hoveyda-Grubbs 2nd generation catalyst (0.005 eq) in degassed CH_2Cl_2 (0.01M to the catalyst) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of the terminal alkene (1.0 eq) and phenyl acrylate (3.0 eq) under N_2 at 45 °C. The reaction mixture was stirred at 45 °C for 3 hours before directly loading onto the silica gel. Purification by silica gel chromatography (pentane/EtOAc) afforded starting materials **424**, **445-449**, **452-453**, **463**, **465**.



Phenyl (*E*)-6-benzyl-6-hydroxy-7-phenylhept-2-enoate (424) was prepared following General Procedure **F**.

Step i.

Starting Materials: 1,3-diphenylpropan-2-one (3.06 g, 14.55 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (17.46 mmol, 1.5 eq).

Silica gel chromatography condition: pentane/CH_2Cl_2 = 3/2.

Product: **2-benzyl-1-phenylhex-5-en-2-ol**: colorless oil (1.28 g, 33%).

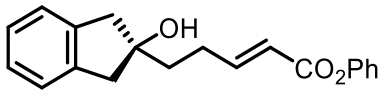
Step ii.

Starting Materials: **2-benzyl-1-phenylhex-5-en-2-ol** (567.0 mg, 2.13 mmol, 1.0 eq)

Silica gel chromatography condition: pentane/EtOAc = 9/1.

Product: **phenyl (*E*)-6-benzyl-6-hydroxy-7-phenylhept-2-enoate (424)**: off-white solid (342.7 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 13H, Ar-H), 7.16 – 7.05 (m, 3H, Ar-H and CH_2CH=CH), 5.98 (dt, *J* = 15.7, 1.6 Hz, 1H, CH_2CH=CH), 2.83 (s, 4H, $ArCH_2$), 2.51 – 2.40 (m, 2H, CH_2CH_2CH=CH), 1.60 – 1.51 (m, 2H, CH_2CH_2CH=CH), 1.44 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (C(O)O), 151.3 (CH_2CH=CH), 150.9 (ArC), 136.9 (ArC), 130.8 (ArCH), 129.5 (ArCH), 128.6 (ArCH), 126.9 (ArCH), 125.8 (ArCH), 121.7 (ArCH), 120.8 (CH_2CH=CH), 73.9 (OHC), 45.8 ($ArCH_2$), 36.5 (CH_2CH_2CH=CH), 27.1 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{26}H_{26}ONa$ ($[M+Na]^+$) 409.1774, found 409.1774; **FT-IR (thin film)** ν_{max} 2981, 1731, 1650, 1593, 1493, 1454, 1323, 1250, 1196, 1163, 1146, 1110, 1031, 969, 753, 729, 702, 689 cm^{-1}; **m.p.**: 51-53 °C.



Phenyl (*E*)-5-(2-hydroxy-2,3-dihydro-1H-inden-2-yl)pent-2-enoate (445) was prepared following General Procedure **F**.

Step i.

Starting Materials: 1,3-dihydro-2H-inden-2-one (330.4 mg, 2.5 mmol, 1.0 eq) and but-3-en-1-ylcerium(III) chloride (3.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 4/1.

Product: **2-(but-3-en-1-yl)-2,3-dihydro-1H-inden-2-ol**: orange oil (222.1 mg, 48%).

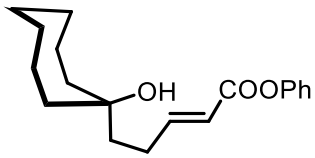
Step ii.

Starting Materials: **2-(but-3-en-1-yl)-2,3-dihydro-1H-inden-2-ol** (188.5 mg, 1.0 mmol, 1.0 eq).

Silica gel chromatography condition: pentane/Et_2O = 3/2.

Product: **phenyl (*E*)-5-(2-hydroxy-2,3-dihydro-1H-inden-2-yl)pent-2-enoate (445)**: off-white solid (239.5 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.05 (m, 10H, Ar-H and CH_2CH=CH), 6.09 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=C**H**), 3.19 – 2.90 (m, 4H, ArCH_2), 2.66 – 2.44 (m, 2H, CH_2CH_2CH=CH), 2.07 – 1.90 (m, 2H, CH_2CH_2CH=CH), 1.75 (s, 1H, O**H**) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1 (**C**(O)O), 151.5 (CH_2**C**H=CH), 150.9 (Ar**C**), 141.0 (Ar**C**), 129.5 (Ar**C**H), 127.0 (Ar**C**H), 125.8 (Ar**C**H), 125.4 (Ar**C**H), 121.8 (Ar**C**H), 120.9 (CH_2CH=**C**H), 82.2 (O**C**), 47.2 (Ar**C**H_2), 38.8 (**C**H_2CH_2CH=CH), 28.0 (CH_2**C**H_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{20}O_3Na$ ($[M+Na]^+$) 331.1305, found 331.1304; **FT-IR (thin film)** ν_{max} 3430, 2921, 1734, 1650, 1593, 1491, 1240, 1196, 1163, 1142, 1024, 984, 896, 741, 689, 625 cm^{-1}; **m.p.**: 58-60 °C.



Phenyl (*E*)-5-(1-hydroxycyclooctyl)pent-2-enoate (446) was prepared following General Procedure **F**.

Step i.

Starting Materials: cyclooctanone (406.8 mg, 3.23 mmol, 1.0 eq) and but-3-en-1-ylcerium(III) chloride (3.88 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 4/1.

Product: **1-(but-3-en-1-yl)cyclooctan-1-ol:** yellow oil (398.3 mg, 68%).

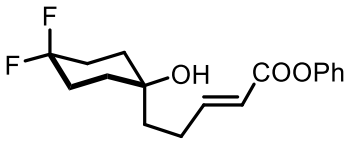
Step ii.

Starting Materials: **1-(but-3-en-1-yl)cyclooctan-1-ol** (273.3 mg, 1.5 mmol, 1.0 eq).

Silica gel chromatography condition: pentane/Et_2O = 13/7.

Product: **phenyl (*E*)-5-(1-hydroxycyclooctyl)pent-2-enoate (446)**: pale-yellow oil (336.8 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-H), 7.28 – 7.16 (m, 2H, Ar-H and CH_2CH=CH), 7.15 – 7.07 (m, 2H, Ar-H), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 2.47 – 2.34 (m, 2H, CH_2CH_2CH=CH), 1.87 – 1.75 (m, 2H, CH_2 (cyclooctane)), 1.74 – 1.48 (m, 11H, CH_2CH_2CH=CH and CH_2 (cyclooctane)), 1.47 – 1.37 (m, 3H, CH_2 (cyclooctane)), 1.27 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1 (C(O)O), 152.3 (CH_2CH=CH), 150.9 (ArC), 129.5 (ArCH), 125.8 (ArCH) , 121.8 (ArCH), 120.5 (CH_2CH=CH), 74.7 (OHC), 39.5 (CH_2CH_2CH=CH), 36.5 (CH_2 (cyclooctane)), 28.3 (CH_2 (cyclooctane)), 26.6 (CH_2CH_2CH=CH), 25.2 (CH_2 (cyclooctane)), 22.5 (CH_2 (cyclooctane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{26}O_3Na$ ([M+Na]$^+$) 325.1774, found 325.1775; **FT-IR (thin film)** ν_{max} 3439, 2921, 2853, 1735, 1650, 1593, 1492, 1448, 1321, 1248, 1196, 1162, 1146, 1023, 978, 900, 847, 751, 721, 688, 645, 619 cm^{-1}.



Phenyl (*E*)-5-(4,4-difluoro-1-hydroxycyclohexyl)pent-2-enoate (447) was prepared following General Procedure **F**.

Step i.

Starting Materials: 4,4-difluorocyclohexan-1-one (335.3 mg, 2.5 mmol, 1.0 eq) and but-3-en-1-ylcerium(III) chloride (3.0 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 17/3.

Product: **1-(but-3-en-1-yl)-4,4-difluorocyclohexan-1-ol**: colorless oil (303.6 mg, 64%).

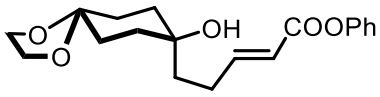
Step ii.

Starting Materials: **1-(but-3-en-1-yl)-4,4-difluorocyclohexan-1-ol** (247.2 mg, 1.3 mmol, 1.0 eq).

Silica gel chromatography condition: pentane/Et_2O = 3/2.

Product: **phenyl (*E*)-5-(4,4-difluoro-1-hydroxycyclohexyl)pent-2-enoate (447)**: off-white solid (354.8 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 2H, Ar-H), 7.26 – 7.14 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.07 (m, 2H, Ar-H), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 2.45 – 2.35 (m, 2H, CH_2CH_2CH=CH), 2.22 – 2.01 (m, 2H, $CH_2CH_2CF_2CH_2CH_2$), 1.94 (ddddd, *J* = 13.2, 10.8, 7.4, 5.3, 2.9 Hz, 2H, $CH_2CH_2CF_2CH_2CH_2$), 1.79 – 1.60 (m, 6H, CH_2CH_2CH=CH and $CH_2CH_2CF_2CH_2CH_2$), 1.28 – 1.20 (m, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (C(O)O), 151.2 (CH_2CH=CH), 150.8 (ArC), 129.5 (ArCH), 125.9 (ArCH), 125.8 – 121.2 (m, CF_2), 121.7 (ArCH), 121.0 (CH_2CH=CH), 69.9 (d, *J* = 1.6 Hz, OHC), 40.9 (CH_2CH_2CH=CH), 33.6 (d, *J* = 9.1 Hz, $CH_2CH_2CF_2CH_2CH_2$), 30.3 – 29.2 (m, $CH_2CH_2CF_2CH_2CH_2$), 26.5 (CH_2CH_2CH=CH) ppm; **^{19}F NMR (376 MHz, $CDCl_3$)** δ −92.86 (d, *J* = 235.6 Hz), −104.16 (dt, *J* = 237.2, 33.6 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{20}O_3F_2Na$ ($[M+Na]^+$) 333.1273, found 333.1274; **FT-IR (thin film)** ν_{max} 3371, 2943, 1734, 1718, 1655, 1593, 1494, 1361, 1326, 1287, 1250, 1197, 1168, 1148, 1115, 1023, 969, 853, 820, 767, 688, 645 cm^{-1}; **m.p.**: 112-114 °C.



Phenyl (*E*)-5-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pent-2-enoate (448) was prepared following General Procedure **F**.

Step i.

Starting Materials: 1,4-dioxaspiro[4.5]decan-8-one (468.6 mg, 3.0 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (3.6 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/EtOAc = 7/3.

Product: **8-(but-3-en-1-yl)-1,4-dioxaspiro[4.5]decan-8-ol**: colorless oil (177.2 mg, 28%).

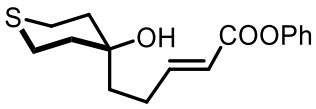
Step ii.

Starting Materials: **8-(but-3-en-1-yl)-1,4-dioxaspiro[4.5]decan-8-ol** (160.6 mg, 0.76 mmol, 1.0 eq).

Silica gel chromatography condition: pentane/EtOAc = 1/1.

Product: **phenyl (*E*)-5-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pent-2-enoate (448)**: off-white solid (197.1 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-H), 7.25 – 7.15 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.07 (m, 2H, Ar-H), 6.04 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 4.02 – 3.87 (m, 4H, OCH_2CH_2O), 2.46 – 2.36 (m, 2H, CH_2CH_2CH=CH), 1.89 (ddd, *J* = 12.7, 9.4, 7.0 Hz, 2H, $CCH_2CH_2CCH_2CH_2$), 1.73 – 1.57 (m, 8H, CH_2CH_2CH=CH and $CCH_2CH_2CCH_2CH_2$), 1.36 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1 (C(O)O), 151.8 (CH_2CH=CH), 150.9 (ArC), 129.5 (ArCH), 125.8 (ArCH), 121.8 (ArCH), 120.7 (CH_2CH=CH), 108.7 (OCO), 70.4 (OHC), 64.5 (OCH_2CH_2O), 64.4 (OCH_2CH_2O), 40.7 (CH_2CH_2CH=CH), 34.8 ($CCH_2CH_2CCH_2CH_2$), 30.6 ($CCH_2CH_2CCH_2CH_2$), 26.7 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{24}O_5Na$ ($[M+Na]^+$) 355.1516, found 355.1514; **FT-IR (thin film)** ν_{max} 3746, 3474, 2940, 2439, 1738, 1650, 1594, 1493, 1439, 1254, 1197, 1165, 1145, 1110, 1036, 931, 825, 745, 718, 690, 676 cm^{-1}; **m.p.**: 36-37 °C.



Phenyl (*E*)-5-(4-hydroxytetrahydro-2H-thiopyran-4-yl)pent-2-enoate (449) was prepared following General Procedure **F**.

Step i.

Starting Materials: tetrahydro-4H-thiopyran-4-one (1.49 g, 12.8 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (15.4 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/EtOAc = 4/1.

Product: **4-(but-3-en-1-yl)tetrahydro-2H-thiopyran-4-ol**: orange oil (383.7 mg, 18%).

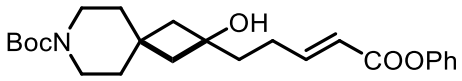
Step ii.

Starting Materials: **4-(but-3-en-1-yl)tetrahydro-2H-thiopyran-4-ol** (138.4 mg, 0.8 mmol, 1.0 eq).

Silica gel chromatography condition: pentane/EtOAc = 4/1.

Product: **phenyl (*E*)-5-(4-hydroxytetrahydro-2H-thiopyran-4-yl)pent-2-enoate (449)**: off-white solid (220 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 2H, Ar-H), 7.25 – 7.14 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.07 (m, 2H, Ar-H), 6.05 (dt, *J* = 15.7, 1.7 Hz, 1H, CH_2CH=CH), 2.96 (brs, 2H, CH_2), 2.51 – 2.34 (m, 4H, CH_2), 1.89 (dt, *J* = 14.0, 3.9 Hz, 2H, CH_2), 1.78 (ddd, *J* = 14.0, 11.3, 3.6 Hz, 2H, CH_2), 1.69 – 1.60 (m, 2H, CH_2), 1.50 – 1.13 (m, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (C(O)O), 151.4 (CH_2CH=CH), 150.8 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 120.9 (CH_2CH=CH), 69.8 (OC), 41.6 (CH_2), 38.3 (CH_2), 25.9 (CH_2), 24.3 (CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{20}O_3NaS$ ($[M+Na]^+$) 315.1025, found 315.1023; **FT-IR (thin film)** ν_{max} 3474, 2931, 2360, 2341, 1728, 1650, 1593, 1492, 1426, 1320, 1246, 1196, 1163, 1145, 1024, 977, 921, 817, 730, 689, 659, 615 cm^{-1}; **m.p.**: 88-89 °C



***tert*-Butyl (*E*)-2-hydroxy-2-(5-oxo-5-phenoxypent-3-en-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate (452)** was prepared following General Procedure **F**.

Step i.

Starting Materials: *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (486.0 mg, 2.03 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (2.44 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 1/4.

Product: ***tert*-butyl 2-(but-3-en-1-yl)-2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate**: orange oil (577.2 mg, 97%).

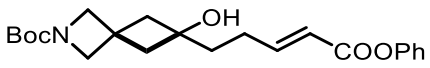
Step ii.

Starting Materials: ***tert*-butyl 2-(but-3-en-1-yl)-2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate** (320.4 mg, 1.09 mmol, 1.0 eq). 6% Hoveyda-Grubbs 2nd generation catalyst was used.

Silica gel chromatography condition: pentane/EtOAc = 3/2.

Product: ***tert*-butyl (*E*)-2-hydroxy-2-(5-oxo-5-phenoxypent-3-en-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate (452)**: off-white solid (240.6 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H, Ar-H), 7.25 – 7.17 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.07 (m, 2H, Ar-H), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 3.37 – 3.24 (m, 4H, CH_2NCH_2), 2.38 (dddd, *J* = 10.1, 8.4, 6.5, 1.6 Hz, 2H, CH_2CH_2CH=CH), 2.01 – 1.93 (m, 2H, CCH_2CCH_2), 1.91 – 1.84 (m, 2H, CCH_2CCH_2), 1.84 – 1.74 (m, 2H, CH_2CH_2CH=CH), 1.70 – 1.63 (m, 2H, $CH_2CH_2NCH_2CH_2$), 1.60 (brs, 1H, OH), 1.52 – 1.46 (m, 2H, $CH_2CH_2NCH_2CH_2$), 1.45 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (C(O)O), 155.1 (C(O)N), 151.4 (CH_2CH=CH), 150.9 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 120.9 (CH_2CH=CH), 79.5 ($C(CH_3)_3$), 71.1 (OHC), 45.7 (CCH_2CCH_2), 41.8 (CH_2CH_2CH=CH), 40.9 (CH_2NCH_2), 40.7 (CH_2NCH_2), 38.9 ($CH_2CH_2NCH_2CH_2$), 38.0 ($CH_2CH_2NCH_2CH_2$), 29.5 (NCH_2C), 28.6 ($C(CH_3)_3$), 26.7 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{33}O_5NNa$ ($[M+Na]^+$) 438.2251, found 438.2249; **FT-IR (thin film)** ν_{max} 3438, 2919, 2845, 1737, 1691, 1667, 1594, 1493, 1426, 1366, 1270, 1245, 1197, 1148, 970, 924, 863, 772, 732, 689, 661, 625 cm^{-1}; **m.p.**: 69-70 °C.



***tert*-Butyl (*E*)-6-hydroxy-6-(5-oxo-5-phenoxypent-3-en-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (453)** was prepared following General Procedure **F**.

Step i.

Starting Materials: *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (508.0 mg, 2.4 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (2.9 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 1/4.

Product: ***tert*-butyl 6-(but-3-en-1-yl)-6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate**: orange oil (154.0 mg, 24%).

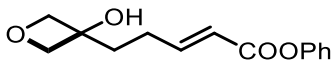
Step ii.

Starting Materials: ***tert*-butyl 6-(but-3-en-1-yl)-6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate** (286.6 mg, 1.07 mmol, 1.0 eq). 3% Hoveyda-Grubbs 2nd generation catalyst was used.

Silica gel chromatography condition: pentane/Et_2O = 1/4.

Product: ***tert*-butyl (*E*)-6-hydroxy-6-(5-oxo-5-phenoxypent-3-en-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (453)**: off-white solid (255.8 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-H), 7.25 – 7.15 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.07 (m, 2H, Ar-H), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 3.91 (d, *J* = 13.7 Hz, 4H, CH_2NCH_2), 2.46 – 2.29 (m, 4H, CCH_2CCH_2 and CH_2CH_2CH=CH), 2.27 – 2.17 (m, 2H, CCH_2CCH_2), 1.76 (brs, 1H, OH), 1.73 – 1.66 (m, 2H, CH_2CH_2CH=CH), 1.43 (s, 9H, $C(CH_3)_3$) pp; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 (C(O)O), 156.2 (C(O)N), 151.1 (CH_2CH=CH), 150.9 (ArC), 129.5 (ArCH) , 125.9 (ArCH), 121.7 (ArCH), 121.0 (CH_2CH=CH), 79.6 ($C(CH_3)_3$), 71.0 (OHC), 61.9 (CH_2NCH_2), 61.2 (CH_2NCH_2), 47.0 (CCH_2CCH_2), 39.0 (CH_2CH_2CH=CH), 29.5 (NCH_2C), 28.5 ($C(CH_3)_3$), 26.9 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{29}O_5NNa$ ($[M+Na]^+$) 410.1938, found 410.1941; **FT-IR (thin film)** ν_{max} 3390, 2923, 2359, 1737, 1700, 1676, 1594, 1493, 1417, 1366, 1317, 1247, 1197, 1164, 1026, 985, 926, 856, 772, 689, 626, 610 cm^{-1}; **m.p.**: 120-121 °C



Phenyl (*E*)-5-(3-hydroxyoxetan-3-yl)pent-2-enoate (463) was prepared following General Procedure **F**.

Step i.

Starting Materials: cyclobutanone (216.2 mg, 3.0 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (3.6 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/EtOAc = 3/2.

Product: **3-(but-3-en-1-yl)oxetan-3-ol**: colorless oil (309.7 mg, 81%).

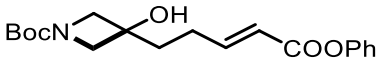
Step ii.

Starting Materials: **3-(but-3-en-1-yl)oxetan-3-ol** (250.6 mg, 1.96 mmol, 1.0 eq)

Silica gel chromatography condition: pentane/EtOAc = 3/2.

Product: **phenyl (*E*)-5-(3-hydroxyoxetan-3-yl)pent-2-enoate (463)**: off-white solid (306.2 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 2H, Ar-H), 7.29 – 7.16 (m, 2H, Ar-H and CH_2CH=CH), 7.15 – 7.07 (m, 2H, Ar-H), 6.08 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 4.63 – 4.52 (m, 4H, CH_2OCH_2), 2.50 – 2.34 (m, 3H, CH_2CH_2CH=CH and OH), 2.12 – 2.02 (m, 2H, CH_2CH_2CH=CH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.9 (C(O)O), 150.8 (ArC), 150.5 (CH_2CH=CH), 129.6 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 121.4 (CH_2CH=CH), 84.0 (CH_2OCH_2), 74.5 (OHC), 36.0 (CH_2CH_2CH=CH), 26.6 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{16}O_4Na$ ($[M+Na]^+$) 271.0941, found 271.0940; **FT-IR (thin film)** ν_{max} 3660, 2981, 2888, 1735, 1462, 1382, 1252, 1152, 1073, 956, 818, 652 cm^{-1}; **m.p.**: 36-37 °C



***tert*-Butyl (*E*)-3-hydroxy-3-(5-oxo-5-phenoxypent-3-en-1-yl)azetidine-1-carboxylate (465)** was prepared following General Procedure **F**.

Step i.

Starting Materials: *tert*-butyl 3-oxoazetidine-1-carboxylate (1.16 g, 6.75 mmol, 1.0 eq) and but-3-en-1-ylmagnesium bromide (8.10 mmol, 1.2 eq).

Silica gel chromatography condition: pentane/Et_2O = 2/3.

Product: ***tert*-butyl 3-(but-3-en-1-yl)-3-hydroxyazetidine-1-carboxylate**: white solid (878.2 mg, 57%).

Step ii.

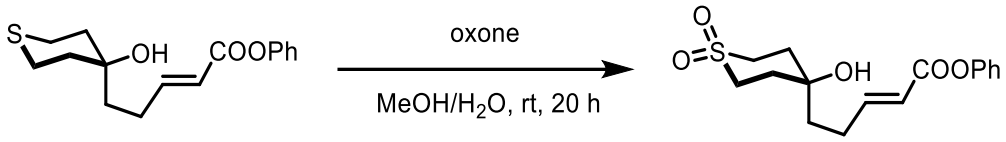
Starting Materials: ***tert*-butyl 3-(but-3-en-1-yl)-3-hydroxyazetidine-1-carboxylate** (454.3 mg, 2.0 mmol, 1.0 eq). 5% Hoveyda-Grubbs 2nd generation catalyst was used.

Silica gel chromatography condition: pentane/Et_2O = 3/7.

Product: ***tert*-butyl (*E*)-3-hydroxy-3-(5-oxo-5-phenoxypent-3-en-1-yl)azetidine-1-carboxylate (465)**: off-white solid (663.9 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.25 – 7.15 (m, 2H, Ar-H and CH_2CH=CH), 7.14 – 7.08 (m, 2H, Ar-H,), 6.06 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 3.92 – 3.75 (m, 4H, CH_2NCH_2), 2.73 – 2.30 (m, 3H, CH_2CH_2CH=CH and OH), 2.00 – 1.90 (m, 2H, CH_2CH_2CH=CH), 1.45 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.9 (C(O)O), 156.6 (C(O)N), 150.8 (ArC), 150.5 (CH_2CH=CH), 129.5 (ArCH), 125.9 (ArCH) , 121.7 (ArCH), 121.3 (CH_2CH=CH), 80.1 ($C(CH_3)_3$), 70.3 (OHC), 62.3 (CH_2NCH_2), 37.1 (CH_2CH_2CH=CH), 28.5 ($C(CH_3)_3$), 26.7 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{25}O_5Na$ ($[M+Na]^+$) 370.1625, found 370.1627; **FT-IR (thin film)** ν_{max} 3385, 1737, 1676, 1593, 1493, 1426, 1367, 1316, 1247, 1197, 1163, 1104, 984, 929, 855, 773, 689, 643, 610 cm^{-1}; **m.p.**: 88-89 °C.

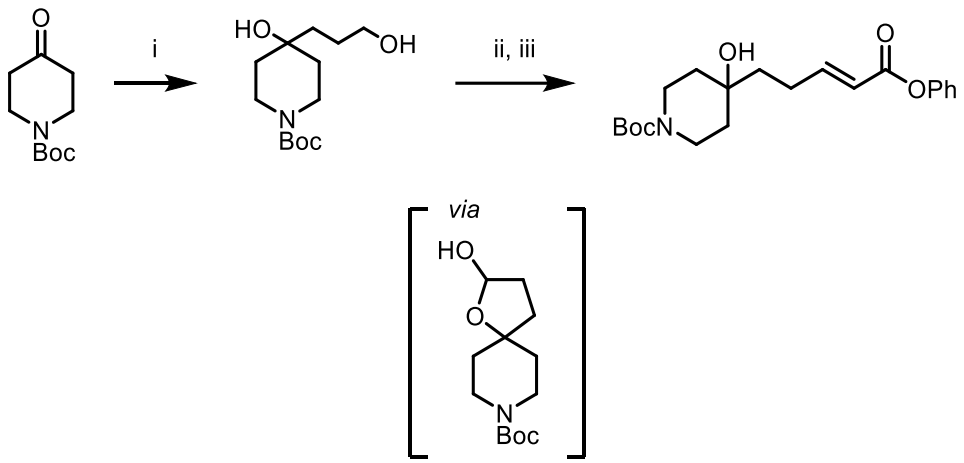
Preparation of starting materials 450



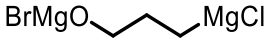
Phenyl (*E*)-5-(4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pent-2-enoate (450) was prepared according to the following procedure. Oxone (264.4 mg, 0.86 mmol, 2.0 eq) was added to a solution of **phenyl (*E*)-5-(4-hydroxytetrahydro-2H-thiopyran-4-yl)pent-2-enoate (449)** (125.4 mg, 0.43 mmol, 1.0 eq) in MeOH (1.1 mL) and H_2O (1.1 mL) at room temperature. The resulting mixture was stirred at room temperature for 20 hours before quenching with a solution of Na_2SO_3 (108.4 mg, 0.86 mmol, 2.0 eq) in H_2O (5 mL). The mixture was stirred at room temperature for 30 mins. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc = 1/1) afforded the title compound as a white solid (97.3 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 2H, Ar-H), 7.26 – 7.21 (m, 1H, Ar-H), 7.16 (dd, *J* = 15.6, 6.8 Hz, 1H, CH_2CH=CH), 7.13 – 7.06 (m, 2H, Ar-H), 6.07 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 3.40 (td, *J* = 13.8, 3.7 Hz, 2H, $CH_2CH_2SCH_2CH_2$), 2.92 – 2.81 (m, 2H, $CH_2CH_2SCH_2CH_2$), 2.46 – 2.35 (m, 2H, CH_2CH_2CH=CH), 2.21 (td, *J* = 14.2, 3.7 Hz, 2H, $CH_2CH_2SCH_2CH_2$), 2.07 – 1.96 (m, 2H, $CH_2CH_2SCH_2CH_2$), 1.79 – 1.70 (m, 2H, CH_2CH_2CH=CH), 1.54 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.9 (C(O)O), 150.7 (ArC), 150.1 (CH_2CH=CH), 129.6 (ArCH), 126.0 (ArCH), 121.7 (ArCH), 121.5 (CH_2CH=CH), 68.5 (OHC), 46.9 ($CH_2CH_2SCH_2CH_2$), 41.0 (CH_2CH_2CH=CH), 35.0 ($CH_2CH_2SCH_2CH_2$), 26.4 (CH_2CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{20}O_5SNa$ ($[M+Na]^+$) 347.0924, found 347.0922; **FT-IR (thin film)** ν_{max} 3659, 2981, 2888, 1462, 1383, 1252, 1151, 1073, 955, 818 cm^{-1}; **m.p.**: 140-141 °C.

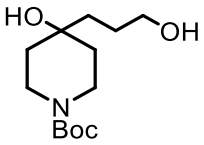
Preparation of starting materials 451



Scheme 93. Synthesis of starting materials **451**. i. Grignard reagent **E74**, THF, 0 °C to rt, 24 h; ii. DMP, CH_2Cl_2, 0 °C to rt, 4 h; iii. Phenyl-(triphenylphosphoranylidene)acetate **E57**, toluene, rt, 48 h.



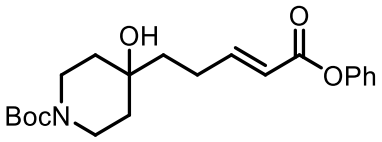
Grignard reagent **E74** was prepared according to literature procedure.[43]



***tert*-Butyl 4-hydroxy-4-(3-hydroxypropyl)piperidine-1-carboxylate (E75)** was prepared according to the following procedure. Grignard reagent **E74** (0.285M in THF) (21 mL, 6.0 mmol, 1.2 eq) was added dropwise to a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (995.6 mg, 5.0 mmol, 1.0 eq) in THF (5 mL) under N_2 at 0 °C. The resulting mixture was warmed to room temperature and stirred for 24 hours before quenching with a saturated aqueous solution of NH_4Cl (20 mL) and diluting with H_2O (20 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3/1) (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced

pressure. Purification by silica gel chromatography (CH_2Cl_2/MeOH = 95/5) afforded the title compound as a pale-yellow oil (746.9 mg, 58%). Data is consistent with the published literature.[44]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 – 3.71 (m, 2H, C$\underline{H}_2$), 3.66 (dt, *J* = 17.4, 6.1 Hz, 2H, C$\underline{H}_2$), 3.22 – 3.11 (m, 2H, C$\underline{H}_2$), 2.39 (brs, 2H, O$\underline{H}$), 1.77 – 1.64 (m, 2H, C$\underline{H}_2$), 1.63 – 1.48 (m, 6H, C$\underline{H}_2$), 1.45 (s, 9H, C(C$\underline{H}_3$)$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.0 (C(O)N), 79.5 ($\underline{C}(CH_3)_3$), 69.2 (OH$\underline{C}$), 63.4 ($\underline{C}H_2$), 63.0 ($\underline{C}H_2$), 40.2 ($\underline{C}H_2$), 37.0 ($\underline{C}H_2$), 32.8 ($\underline{C}H_2$), 28.6 (C($\underline{C}H_3$)$_3$), 26.0 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{25}O_4NNa$ ([M+Na]$^+$) 282.1676, found 282.1674.



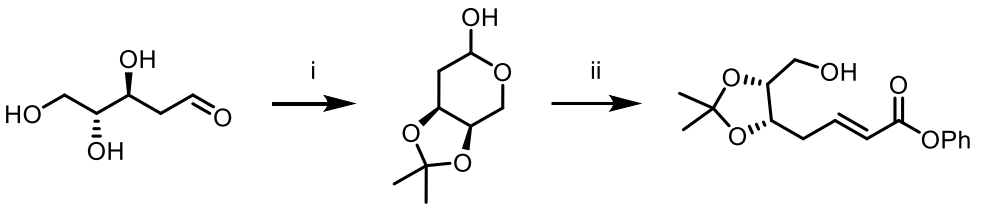
***tert*-Butyl (*E*)-4-hydroxy-4-(5-oxo-5-phenoxypent-3-en-1-yl)piperidine-1-carboxylate (451)** was prepared according to the following procedure. DMP (1.37 g, 3.22 mmol,1.1 eq) was added to a solution of ***tert*-butyl 4-hydroxy-4-(3-hydroxypropyl)piperidine-1-carboxylate (E75)** (756.5 mg, 2.92 mmol, 1.0 eq) in CH_2Cl_2 (42 mL) under N_2 at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours then room temperature for 2 hours before quenching with an aqueous solution of NaOH (1M, 20 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/MeOH = 95/5) afforded the hemiacetal as a pale-yellow oil (449.4 mg, 60%).

A solution of hemiacetal (407.2 mg, 1.59 mmol, 1.0 eq) in toluene (2 mL) was added to a solution of **phenyl-(triphenylphosphoranylidene)acetate E57** (757.2 mg, 1.91 mmol, 1.2 eq) in toluene (6.4 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 48 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 3/7) afforded the title compound as a white solid (132.1 mg, 22%).

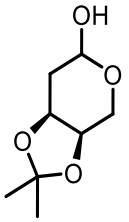
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-$\underline{H}$), 7.25 – 7.14 (m, 2H, Ar-$\underline{H}$ and $CH_2C\underline{H}$=CH), 7.14 – 7.06 (m, 2H, Ar-$\underline{H}$), 6.05 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=C$\underline{H}$), 3.83 (dt, *J* = 13.4, 4.0 Hz, 2H,

$CH_2C\underline{H}_2NCH_2CH_2$), 3.23 – 3.08 (m, 2H, $CH_2CH_2NC\underline{H}_2CH_2$), 2.46 – 2.35 (m, 2H, $CH_2C\underline{H}_2CH{=}CH$), 1.71 – 1.59 (m, 2H, $C\underline{H}_2CH_2CH{=}CH$), 1.55 (dd, *J* = 8.7, 4.0 Hz, 4H, $C\underline{H}_2CH_2NCH_2C\underline{H}_2$), 1.46 (s, 9H, $C(C\underline{H}_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0 ($\underline{C}(O)O$), 154.9 ($\underline{C}(O)N$), 151.4 ($CH_2\underline{C}H{=}CH$), 150.8 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$H), 125.9 (Ar$\underline{C}$H), 121.7 (Ar$\underline{C}$H), 120.9 ($CH_2CH{=}\underline{C}H$), 79.7 ($\underline{C}(CH_3)_3$), 69.7 (OH$\underline{C}$), 41.2 ($\underline{C}H_2CH_2CH{=}CH$), 39.8 ($CH_2\underline{C}H_2N\underline{C}H_2CH_2$), 36.8 ($\underline{C}H_2CH_2NCH_2\underline{C}H_2$), 28.6 ($C(\underline{C}H_3)_3$), 26.1 ($CH_2\underline{C}H_2CH{=}CH$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{29}O_5NNa$ ($[M+Na]^+$) 398.1938, found 398.1935; **FT-IR (thin film)** ν_{max} 3659, 2981, 2888, 1665, 1383, 1250, 1152, 1073, 955, 819 cm^{-1}; **m.p.**: 94-96 °C.

Preparation of starting materials 468



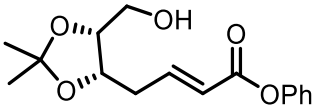
Scheme 94. Synthesis of starting materials **468**. i. *p*-TSA, acetone, 0 °C, 3 h. The reaction mixture was stirred at 0 °C for 3 h; ii. Phenyl-(triphenylphosphoranylidene)acetate **E57**, toluene, rt, 24 h.



(3a*R*,7a*S*)-2,2-Dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-6-ol (E76) was prepared according to the literature procedure reported by R. W. Davis, *et. al.* [45] *p*-TSA (262.5 mg, 1.38 mmol, 0.1 eq) was added to a solution of *D*-2-deoxyribose (1.85 g, 13.8 mmol, 1.0 eq) in acetone (27.6 mL) at under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 3 h before quenching with a saturated aqueous solution of $NaHCO_3$ (20 mL). The slurry was filtered and washed with EtOAc (100 mL). The combined filtrate was evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc = 1/1) afforded the title compound as a pale-yellow oil (1:0.5 (**A**:**B**) mixture of anomers) (284.3 mg, 12%). Data is consistent with the published literature.[46]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (dd, *J* = 7.1, 4.3 Hz, 1H, C<u>H</u>(**A**)), 5.07 (t, *J* = 3.7 Hz, 0.5H, C<u>H</u>(**B**)), 4.47 (dt, *J* = 6.6, 4.3 Hz, 1H, C<u>H</u>(**A**)), 4.41 (dt, *J* = 5.8, 4.5 Hz, 0.5H, C<u>H</u>(**B**)), 4.22 – 4.13 (m, 1.5H, C<u>H</u>(**A** and **B**)), 3.97 – 3.95 (m, 0.5H, C<u>H$_2$</u>(**B**)), 3.95 – 3.90 (m, 1H, C<u>H$_2$</u>(**A**)), 3.74 – 3.69 (m, 1H, C<u>H$_2$</u>(**A**)), 3.69 – 3.66 (m, 0.5H, C<u>H$_2$</u>(**B**)), 3.16 – 2.56 (brs, 1.5H, O<u>H</u>(**A** and **B**)), 2.24 (dt, *J* = 14.8, 4.3 Hz, 1H, C<u>H$_2$</u>(**A**)), 2.09 (dd, *J* = 4.6, 3.7 Hz, 1H, C<u>H$_2$</u>(**B**)), 1.77 (ddd, *J* = 14.8, 7.1, 4.2 Hz, 1H, C<u>H$_2$</u>(**A**)), 1.56 (d, *J* = 0.7 Hz, 1.5H, C<u>H$_3$</u>(**B**)), 1.49 (d, *J* = 0.7 Hz, 3H, C<u>H$_3$</u>(**A**)), 1.36 (d, *J* = 0.8 Hz, 1.5H, C<u>H$_3$</u>(**B**)), 1.34 (d,

J = 0.7 Hz, 3H, C<u>H</u>$_3$(**A**)); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 109.5 (O<u>C</u>O(**B**)), 108.9 (O<u>C</u>O(**A**)), 91.5 (<u>C</u>H(**B**)), 91.1 (<u>C</u>H(**A**)), 71.8 (<u>C</u>H(**A**)), 71.3 (<u>C</u>H(**B**)), 70.8 (<u>C</u>H(**B**)), 70.5 (<u>C</u>H(**A**)), 62.2 (<u>C</u>H$_2$(**A**)), 60.8 (<u>C</u>H$_2$(**B**)), 32.4 (<u>C</u>H$_2$(**B**)), 32.3 (<u>C</u>H$_2$(**A**)), 28.1 (<u>C</u>H$_3$(**B**)), 27.4 (<u>C</u>H$_3$(**A**)), 25.7 (<u>C</u>H$_3$(**B**)), 25.5 (<u>C</u>H$_3$(**A**)) ppm.

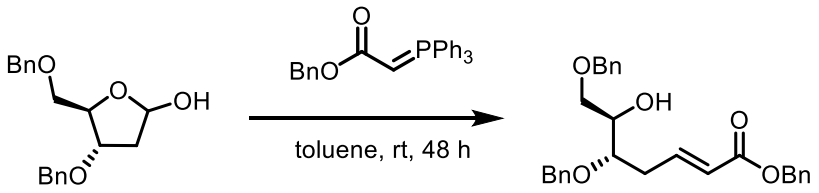


Phenyl (*E*)-4-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (468) was prepared according to the following procedure. A solution of **(3a*R*,7a*S*)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-6-ol (E76)** (271.2 mg, 1.56 mmol, 1.0 eq) in toluene (2 mL) was added to a solution of **phenyl-(triphenylphosphoranylidene)acetate E57** (927.0 mg, 2.34 mmol, 1.5 eq) in toluene (7.8 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 1/1) afforded the title compound as a white solid (210.0 mg, 46%).

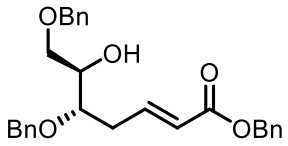
The title compound decomposed in $CDCl_3$ within a couple of hours, indicated by the better cleanness of ^{1}H NMR spectrum compared to ^{13}C NMR spectrum.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.34 (m, 2H, Ar-<u>H</u>), 7.25 – 7.14 (m, 2H, Ar-<u>H</u> and CH$_2$C<u>H</u>=CH), 7.14 – 7.08 (m, 2H, Ar-<u>H</u>), 6.14 (dt, *J* = 15.7, 1.6 Hz, 1H, CH$_2$CH=C<u>H</u>), 4.36 (ddd, *J* = 9.0, 6.3, 4.5 Hz, 1H, OC<u>H</u>), 4.25 (td, *J* = 6.1, 4.9 Hz, 1H, OC<u>H</u>), 3.76 – 3.64 (m, 2H, OCHC<u>H$_2$</u>), 2.69 – 2.47 (m, 2H, OCHC<u>H$_2$</u>), 1.86 (s, 1H, O<u>H</u>), 1.50 (d, *J* = 0.8 Hz, 3H, C<u>H$_3$</u>), 1.39 (d, *J* = 0.8 Hz, 3H, C<u>H$_3$</u>) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 164.7 (<u>C</u>(O)O), 150.8 (Ar<u>C</u>), 147.0 (CH$_2$<u>C</u>H=CH), 129.5 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 123.0 (CH$_2$CH=<u>C</u>H), 121.7 (Ar<u>C</u>H), 108.8 (O<u>C</u>O), 77.6 (<u>C</u>H), 75.4 (<u>C</u>H), 61.6 (<u>C</u>H$_2$), 32.8 (<u>C</u>H$_2$), 28.1 (<u>C</u>H$_3$), 25.4 (<u>C</u>H$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{20}O_5Na$ ([M+Na]$^+$) 315.1203, found 315.1203; **FT-IR (thin film)** ν_{max} 3449, 2935, 1732, 1654, 1592, 1492, 1456, 1371, 1320, 1250, 1196, 1163, 1149, 1112, 1070, 1044, 987, 904, 846, 755, 688, 652, 626, 611 cm^{-1}; **m.p.**: 39-40 °C; **$[\alpha]_D^{25}$** = −30.2 (c=0.95, $CHCl_3$).

Preparation of starting materials 470



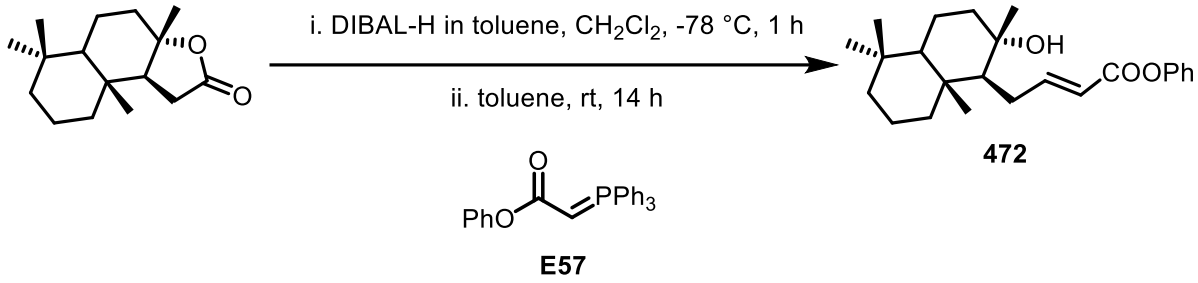
(4*S*,5*R*)-4-(Benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol was prepared according to literature procedure.[47]



Benzyl (5*S*,6*R*,*E*)-5,7-bis(benzyloxy)-6-hydroxyhept-2-enoate (470) was prepared according to the following procedure. A solution of (4*S*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (512.8 mg, 1.64 mmol, 1.0 eq) in toluene (2 mL) was added to a solution of benzyl-(triphenylphosphoranylidene)acetate (1.69 g, 4.12 mmol, 2.5 eq) in toluene (5.5 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 48 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 3/2) afforded the title compound as a colorless oil (403.4 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 15H, Ar-H), 7.09 (dt, *J* = 15.7, 7.4 Hz, 1H, CH_2CH=CH), 5.97 (dt, *J* = 15.6, 1.4 Hz, 1H, CH_2CH=CH), 5.18 (s, 2H, $ArCH_2O$), 4.62 – 4.44 (m, 4H, $ArCH_2O$), 3.83 (tdd, *J* = 6.2, 4.9, 3.7 Hz, 1H, $BnOCH_2CH$), 3.66 – 3.53 (m, 3H, $CHCH_2CH$=CH and $BnOCH_2$), 2.63 – 2.48 (m, 2H, CH_2CH=CH), 2.42 (d, *J* = 5.0 Hz, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 (C(O)O), 146.0 (CH_2CH=CH), 137.97 (ArC), 137.89 (ArC), 136.3 (ArC), 128.7 (ArCH), 128.63 (ArCH), 128.57 (ArCH), 128.31 (ArCH), 128.28 (ArCH), 128.1 (ArCH), 128.03 (ArCH), 128.00 (ArCH), 127.97 (ArCH), 123.6 (CH_2CH=CH), 78.4 ($CHCH_2CH$=CH), 73.6 ($ArCH_2O$), 72.5 ($ArCH_2O$), 71.5 ($BnOCH_2CH$), 70.9 ($BnOCH_2$), 66.2 ($ArCH_2O$), 33.4 (CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{28}H_{30}O_5Na$ ($[M+Na]^+$) 469.1985, found 469.1982; **FT-IR (thin film)** ν_{max} 3483, 3031, 2866, 1716, 1654, 1496, 1454, 1315, 1265, 1214, 1165, 1073, 1027, 910, 750, 697, 608 cm^{-1}; **$[\alpha]_D^{25}$** = +16.5 (c=0.66, $CHCl_3$).

Preparation of starting materials 472



472

E57

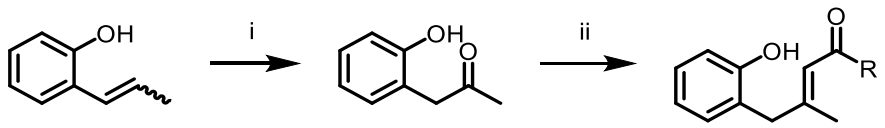
Phenyl (*E*)-4-((1*R*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)but-2-enoate (472) was prepared according to the following procedure. According to the modified literature procedure reported by J. L. Wang *et. al.,* [48] DIBAL (25% wt solution in toluene) (4.72 mL, 7.1 mmol, 1.2 eq) was added dropwise (0.4 mL/min) to a solution of sclareolide (1.48 g, 5.9 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) under N_2 at −78 ºC. The reaction mixture was stirred at the same temperature for 1 hour before quenching with 2M HCl (61.5 mL) at −78 ºC. The resulting mixture was gradually warmed up to room temperature and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure to afford the hemiacetal (1.34 g, 90%) as a white solid which was used as crude for next step without any further purification.

hemiacetal (504.8 mg, 2 mmol, 1.0 eq) was added to a solution of phenyl-(triphenylphosphoranylidene)acetate **E57** (1.19 g, 3 mmol, 1.5 eq) in toluene (10 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 14 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/EtOAc = 9/1) afforded the title compound as a white solid (279.1 mg, 38%).

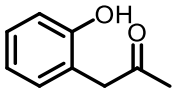
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H, Ar-H), 7.34 – 7.24 (m, 1H, CH_2CH=CH), 7.24 – 7.18 (m, 1H, Ar-H), 7.15 – 7.07 (m, 2H, Ar-H), 6.00 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH=CH), 2.52 (dddd, *J* = 15.4, 7.0, 5.0, 1.7 Hz, 1H, CH_2CH=CH), 2.32 (dddd, *J* = 15.4, 7.4, 5.3, 1.5 Hz, 1H, CH_2CH=CH), 1.91 (dt, *J* = 12.3, 3.1 Hz, 1H, CH_2), 1.73 – 1.53 (m, 3H, CH_2), 1.51 – 1.23 (m, 6H, CH, CH_2 and OH),

1.22 – 1.09 (m, 4H, C<u>H</u>$_2$ and C<u>H</u>$_3$), 1.01 – 0.91 (m, 2H, C<u>H</u> and C<u>H</u>$_2$), 0.88 (s, 3H, C<u>H</u>$_3$), 0.86 (d, *J* = 0.9 Hz, 3H, C<u>H</u>$_3$), 0.81 (s, 3H, C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.3 (<u>C</u>O), 155.4 (CH_2<u>C</u>H=CH), 151.0 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 121.8 (Ar<u>C</u>H), 119.6 (CH_2CH=<u>C</u>H), 74.0 (<u>C</u>), 61.7 (<u>C</u>H), 56.3 (<u>C</u>H), 44.8 (<u>C</u>H_2), 41.9 (<u>C</u>H_2), 40.3 (<u>C</u>H_2), 39.3 (<u>C</u>), 33.6 (<u>C</u>), 33.4 (<u>C</u>H_2), 28.6 (<u>C</u>H_2CH=CH), 24.1 (<u>C</u>H_3), 21.6 (<u>C</u>H_2), 20.6 (<u>C</u>H_3), 18.6 (<u>C</u>H_2), 15.5 (<u>C</u>H_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{34}O_3Na$ ($[M+Na]^+$) 393.2400, found 393.2397; **FT-IR (thin film)** ν_{max} 3501, 3010, 2926, 1723, 1645, 1592, 1492, 1457, 1388, 1312, 1254, 1196, 1162, 1140, 1083, 1025, 972, 937, 909, 754, 688, 666, 642 cm^{-1}; **$[\alpha]D^{25}$** = −3.1 (c=0.50, ($CHCl_3$); **m.p.**: 64-66 °C

General procedure G for preparation of starting materials 509, 513-517



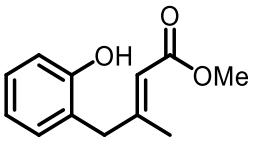
Scheme 95. Synthesis of starting materials **509**, **513-517**. i. $VO(acac)_2$, CH_2Cl_2, 5 mins at rt then *tert*-Butyl hydroperoxide, 40 °C 16 h; ii. Wittig reagents, toluene, rt, 24 h.



1-(2-Hydroxyphenyl)propan-2-one (E77) was prepared according to the following procedure. According to the modified literature procedure reported by A. Lattanzi, *et. al.,* [49] $VO(acac)_2$ (26.6 mg, 0.1 mmol, 0.02 eq) was added to a solution of 2-(prop-1-en-1-yl)phenol (6.68 g, 49.8 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (200 mL) under N_2 at room temperature. The mixture was stirred for 5 mins before adding *tert*-Butyl hydroperoxide (5.5M in nonane) (10.9 mL, 59.8 mmol, 1.2 eq). The reaction mixture was heated to 40 °C and stirred for 16 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a pale-yellow oil (3.97 g, 53%). Data is consistent with the published literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 1H, Ar-H), 7.08 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 7.05 – 6.95 (m, 1H, OH), 6.94 – 6.84 (m, 2H, Ar-H), 3.75 (s, 2H, CH_2), 2.29 (d, *J* = 1.5 Hz, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 210.4 (C(O)), 155.2 (COH), 131.1 (ArCH), 129.2 (ArCH), 121.1 (ArCH), 117.52 (ArCH or ArC), 117.48 (ArCH or ArC), 46.6 (CH_2), 30.3 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_9H_9O_2$ ($[M-H]^-$) 149.0608, found 149.0599.

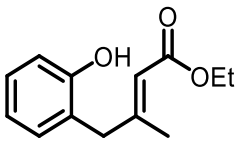
ii. 1-(2-Hydroxyphenyl)propan-2-one (E77) (1.0 eq) in toluene (5 mL) was added to a solution of Wittig reagents (1.5 eq) in toluene (0.1M) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography afforded starting materials **509**, **513-517**.



Methyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (509) was prepared following **General Procedure G step ii**, using methyl 2-(triphenyl-l5-phosphaneylidene)acetate (5.12 g, 15.3 mmol, 1.5 eq) to afford the title compound as a colorless oil (946.7 mg, 45%). Silica gel chromatography condition: CH_2Cl_2/EtOAc = 97.5/2.5. Data is consistent with the published literature.[29]

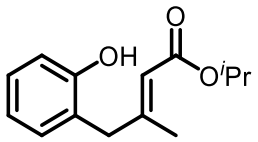
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 1H, Ar-H), 7.10 – 7.04 (m, 1H, Ar-H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 6.78 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 5.64 (h, *J* = 1.4 Hz, 1H, CH), 5.01 (brs, 1H, OH), 3.67 (s, 3H, OCH_3), 3.50 – 3.45 (m, 2H, CH_2), 2.19 (d, *J* = 1.3 Hz, 3H, CCH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (C(O)O), 158.7 (COH or C=CH), 154.0 (COH or C=CH), 131.4 (ArCH), 128.4 (ArCH), 124.1 (ArC), 121.1 (ArCH), 116.3 (CH), 115.8 (ArCH), 51.1 (OCH_3), 41.1 (CH_2), 19.1 (CCH_3) ppm.



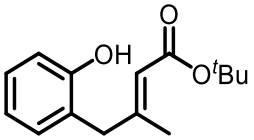
Ethyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (513) was prepared following **General Procedure G step ii**, using ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (1.29 g, 3.7 mmol, 1.5 eq) to afford the title compound as a colorless oil (391.5 mg, 73%). Silica gel chromatography condition: CH_2Cl_2/EtOAc = 98/2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (td, *J* = 7.7, 1.7 Hz, 1H, Ar-H), 7.08 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-H), 5.64 (h, *J* = 1.3 Hz, 1H, CH), 5.07 (s, 1H, OH), 4.14 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 3.49 – 3.44 (m, 2H, CCH_2), 2.19 (d, *J* = 1.3 Hz, 3H, CCH_3), 1.26 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.1 (C(O)O), 158.3 (COH or C=CH), 154.1 (COH or C=CH), 131.4 (ArCH), 128.4 (ArCH), 124.1 (ArC), 121.1 (ArCH), 116.8 (CH), 115.8 (ArCH), 59.9 (CH_2CH_3), 41.1 (CCH_2), 19.1 (CCH_3), 14.4 (CH_2CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{15}O_3$ ($[M-H]^-$) 219.1027, found 219.1021; **FT-IR (thin film)** ν_{max} 3391, 2981, 2360, 1687, 1648, 1595, 1505, 1456, 1352, 1224, 1148, 916, 848, 754, 694, 686, 668 cm^{-1}.



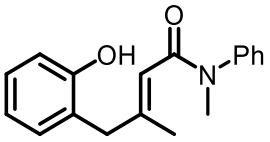
***iso*-Propyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (514)** was prepared following **General Procedure G step ii**, using *iso*-propyl 2-(triphenyl-l5-phosphaneylidene)acetate (1.11 g, 3.06 mmol, 1.5 eq) to afford the title compound as a colorless oil (356.9 mg, 75%). Silica gel chromatography condition: CH_2Cl_2/EtOAc = 98/2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.7, 1.7 Hz, 1H, Ar-H), 7.09 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-H), 6.79 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar-H), 5.62 (h, *J* = 1.3 Hz, 1H, C=CH), 5.09 – 4.95 (m, 2H, OH and $CH(CH_3)_2$), 3.49 – 3.44 (m, 2H, CCH_2), 2.18 (d, *J* = 1.3 Hz, 3H, CCH_3), 1.24 (s, 3H, $CH(CH_3)_2$), 1.23 (s, 3H, $CH(CH_3)_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.6 (C(O)O), 157.7 (COH or C=CH), 154.1 (COH or C=CH), 131.4 (ArCH), 128.4 (ArCH), 124.1 (ArC), 121.1 (ArCH), 117.4 (C=CH), 115.8 (ArCH), 67.1 ($CH(CH_3)_2$), 41.1 (CCH_2), 22.1 ($CH(CH_3)_2$), 19.1 (CCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}O_3$ ($[M+H]^+$) 235.1329, found 235.1329; **FT-IR (thin film)** ν_{max} 3392, 2981, 2360, 1684, 1645, 1595, 1505, 1456, 1373, 1298, 1229, 1149, 1105, 1043, 916, 841, 754, 729, 694, 686 cm^{-1}.



***tert*-Butyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (515)** was prepared following **General Procedure G step ii**, using *tert*-butyl 2-(triphenyl-l5-phosphaneylidene)acetate (702.7 mg, 1.87 mmol, 1.5 eq) to afford the title compound as an off-white powder (206.3 mg, 67%). Silica gel chromatography condition: CH_2Cl_2/EtOAc = 97.5/2.5.

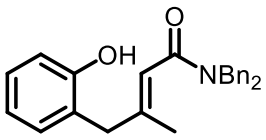
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.10 (m, 1H, Ar-H), 7.08 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 6.79 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-H), 5.59 (h, *J* = 1.3 Hz, 1H, CH), 5.13 (s, 1H, OH), 3.46 – 3.41 (m, 2H, CCH_2), 2.14 (d, *J* = 1.3 Hz, 3H, CCH_3), 1.47 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.6 (C(O)O), 156.4 (COH or C=CH), 154.2 (COH or C=CH), 131.4 (ArCH), 128.3 (ArCH), 124.2 (ArC), 121.0 (ArCH), 118.7 (CH), 115.9 (ArCH), 80.1 ($C(CH_3)_3$), 41.1 (CCH_2), 28.4 ($C(CH_3)_3$), 18.9 (CCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{15}H_{20}O_3Na$ ($[M+Na]^+$) 271.1305, found 271.1305; **FT-IR (thin film)** ν_{max} 3404, 2980, 2360, 1682, 1646, 1595, 1456, 1391, 1366, 1318, 1239, 1141, 1098, 1044, 916, 848, 754, 686, 677 cm^{-1}; **m.p.**: 70-71 °C.

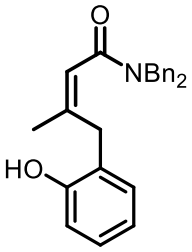


(*E*)-4-(2-Hydroxyphenyl)-*N*,3-dimethyl-*N*-phenylbut-2-enamide (516) was prepared following **General Procedure G step ii**, using *N*-methyl-*N*-phenyl-2-(triphenyl-l5-phosphaneylidene)acetamide (**E58**) (1.44 g, 3.52 mmol, 1.5 eq) to afford the title compound as an white powder (108.8 mg, 17%). Silica gel chromatography condition: pentane/Et_2O = 2/3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.16 (m, 3H, Ar-H), 7.14 – 7.07 (m, 2H, Ar-H), 7.06 – 6.96 (m, 1H, Ar-H), 6.74 (dq, *J* = 15.3, 7.0, 6.3 Hz, 3H, Ar-H), 6.29 (s, 1H, OH), 5.45 (s, 1H, CH), 3.30 (s, 3H,

NC$\underline{H}_3$), 3.27 (d, *J* = 10.7 Hz, 2H, CC$\underline{H}_2$), 2.07 (d, *J* = 1.3 Hz, 3H, CC$\underline{H}_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.0 ($\underline{C}$(O)N), 154.5 ($\underline{C}$OH or $\underline{C}$=CH), 151.4 ($\underline{C}$OH or $\underline{C}$=CH), 144.1 (Ar$\underline{C}$), 130.8 (Ar$\underline{C}$H), 129.9 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 127.8 (Ar$\underline{C}$H), 127.2 (Ar$\underline{C}$H), 127.15 (Ar$\underline{C}$H), 127.06 (Ar$\underline{C}$H), 124.6 (Ar$\underline{C}$), 120.3 (Ar$\underline{C}$H), 119.1 ($\underline{C}$H), 115.8 (Ar$\underline{C}$H), 40.4 (C$\underline{C}$H$_2$), 37.0 (N$\underline{C}$H$_3$), 18.8 (C$\underline{C}$H$_3$); **HRMS** (ESI) m/z calcd. for $C_{18}H_{20}O_2N$ ([M+H]$^+$) 282.1489, found 282.1489; **FT-IR (thin film)** ν_{max} 3649, 2981, 2889, 2360, 2341, 1590, 1496, 1457, 1392, 1265, 1153, 1071, 952, 849, 806, 771, 694, 686 cm^{-1}; **m.p.**: 71-72 °C.





(*E*)-*N*,*N*-Dibenzyl-4-(2-hydroxyphenyl)-3-methylbut-2-enamide (*E*-517) and **(*Z*)-*N*,*N*-dibenzyl-4-(2-hydroxyphenyl)-3-methylbut-2-enamide (*Z*-517)** were prepared following **General Procedure G step ii**, using *N*,*N*-dibenzyl-2-(triphenyl-l5-phosphaneylidene)acetamide (**E59**) (2.21 g, 4.43 mmol, 1.5 eq) to afford the title compounds as white powder.

E-isomer (***E*-517**): 384.1 mg, 35%; Silica gel chromatography condition: pentane/Et_2O = 2/3.

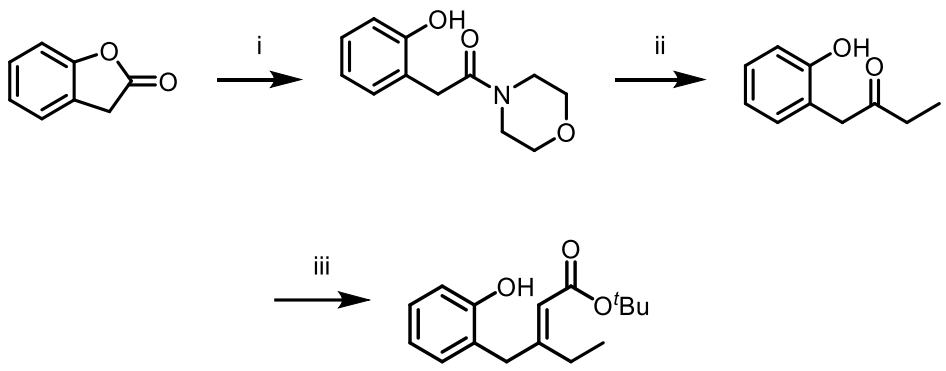
Z-isomer (***Z*-517**): 396.0 mg, 36%; Silica gel chromatography condition: pentane/Et_2O = 7/3.

E-isomer (***E*-517**): **^{1}H NMR (400 MHz, $(CD_3)_2SO$)** δ 9.30 (s, 1H, O$\underline{H}$), 7.40 – 7.17 (m, 8H, Ar-$\underline{H}$), 7.15 – 7.07 (m, 2H, Ar-$\underline{H}$), 7.00 (td, *J* = 7.7, 1.7 Hz, 1H, Ar-$\underline{H}$), 6.90 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-$\underline{H}$), 6.77 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-$\underline{H}$), 6.66 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-$\underline{H}$), 5.94 (q, *J* = 1.3 Hz, 1H, C$\underline{H}$), 4.45 (d, *J* = 22.2 Hz, 4H, NC$\underline{H}_2$), 3.30 (s, 2H, CC$\underline{H}_2$), 1.87 (d, *J* = 1.2 Hz, 3H, C$\underline{H}_3$) ppm ; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 167.7 ($\underline{C}$(O)N), 155.3 ($\underline{C}$OH or $\underline{C}$=CH), 149.0 ($\underline{C}$OH or $\underline{C}$=CH), 137.8 (Ar$\underline{C}$), 137.3 (Ar$\underline{C}$), 130.4 (Ar$\underline{C}$H), 128.6 (Ar$\underline{C}$H), 128.4 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$H), 127.2 (Ar$\underline{C}$H), 127.0 (Ar$\underline{C}$H), 126.9 (Ar$\underline{C}$H), 124.4 (Ar$\underline{C}$), 118.9 (Ar$\underline{C}$H), 118.3 ($\underline{C}$H), 115.0 (Ar$\underline{C}$H), 50.2 (N$\underline{C}$H$_2$), 47.2 (N$\underline{C}$H$_2$), 39.0 (C$\underline{C}$H$_2$), 18.4 ($\underline{C}$H$_3$) ppm ; **HRMS** (ESI) m/z calcd. for $C_{25}H_{26}O_2N$ ([M+H]$^+$) 372.1958,

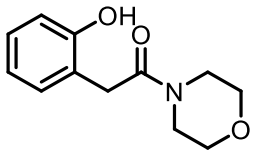
found 372.1955 ; **FT-IR (thin film)** ν_{max} 3660, 2981, 2889, 1593, 1495, 1454, 1382, 1237, 1155, 1082, 955, 822, 753, 700 cm^{-1} ; **m.p.**: 119-120 °C

Z-isomer (***Z*-517**): **^{1}H NMR (400 MHz, $(CD_3)_2SO$)** δ 9.86 (s, 1H, OH), 7.43 – 7.19 (m, 10H, Ar-H), 7.10 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 7.07 – 7.00 (m, 1H, Ar-H), 6.79 – 6.67 (m, 2H, Ar-H), 6.24 (d, *J* = 1.5 Hz, 1H, CH), 4.57 (d, *J* = 15.5 Hz, 4H, NCH_2), 3.68 (s, 2H, CCH_2), 1.66 (d, *J* = 1.3 Hz, 3H, CH_3) ppm ; **^{13}C NMR (101 MHz, $(CD_3)_2SO$)** δ 168.4 (C(O)N), 155.6 (COH or C=CH), 150.3 (COH or C=CH), 137.3 (ArC), 136.9 (ArC), 130.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 123.8 (ArC), 118.8 (ArCH), 118.2 (CH), 115.4 (ArCH), 50.5 (NCH_2), 47.7 (NCH_2), 33.7 (CCH_2), 23.1 (CH_3) ppm ; **HRMS** (ESI) m/z calcd. for $C_{25}H_{26}O_2N$ ($[M+H]^+$) 372.1958, found 372.1960 ; **FT-IR (thin film)** ν_{max} 3659, 2981, 2889, 1603, 1473, 1382, 1250, 1152, 1073, 955, 819, 700 cm^{-1} ; **m.p.**: 49-50 °C

Preparation of starting materials 518

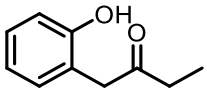


Scheme 96. Synthesis of starting materials **518**. i. morpholine, toluene, 110 °C, 20 h; ii. ethylcerium(III) chloride, THF, −78 °C, 2 h; iii. *tert*-butyl 2-(triphenyl-l5-phosphaneylidene)acetate, toluene, rt, 20 h.



2-(2-Hydroxyphenyl)-1-morpholinoethan-1-one (E78) was prepared according to the following procedure. Morpholine (1.31 g, 15.0 mmol, 1.5 eq) was added to a solution of benzofuran-2(3H)-one (1.34 g, 10.0 mmol, 1.0 eq) in toluene (100 mL) under N_2 at room temperature. The reaction mixture was heated to 110 °C and stirred for 20 hours before evaporating to dryness under reduced pressure, affording the title compound as a pale-yellow solid (2.0 g, 90%) which was used as crude for next step without any purification. Data is consistent with the published literature.

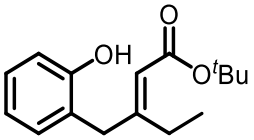
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H, OH), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H, Ar-H), 6.98 (ddd, *J* = 16.5, 7.8, 1.5 Hz, 2H, Ar-H), 6.83 (td, *J* = 7.4, 1.3 Hz, 1H, Ar-H), 3.73 (s, 2H, $ArCH_2$), 3.71 – 3.59 (m, 8H, $NCH_2CH_2OCH_2CH_2$) ppml; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.7 (C(O)N), 156.8 (COH), 130.2 (ArCH), 129.2 (ArCH), 120.7 (ArC), 120.3 (ArCH), 118.1 (ArCH), 66.63 ($NCH_2CH_2OCH_2CH_2$), 66.58 ($NCH_2CH_2OCH_2CH_2$), 47.2 ($NCH_2CH_2OCH_2CH_2$), 42.6 ($NCH_2CH_2OCH_2CH_2$), 36.2 ($ArCH_2$) ppm.



1-(2-Hydroxyphenyl)butan-2-one (E79) was prepared according to the following procedure. $CeCl_3$ (1.85 g, 7.5 mmol, 3.0 eq) (anhydrous grade, stored and weighed in a glove box) was stirred at 90 °C for 30 mins and 135 °C for 2 hours under reduced pressure before cooling down to 0 °C. Anhydrous THF (15 mL) was added to the reaction vessel under N_2 at 0 °C. The resulting slurry was warmed to room temperature and stirred for 24 hours under N_2 before cooling down to −78 °C. Ethylmagnesium bromide (1M in THF) (7.25 mL, 7.25 mmol, 2.9 eq) was added dropwise under N_2 at −78 °C. The resulting mixture was stirred at −78 °C for 1 hour, affording a solution of ethylcerium(III) chloride which was used as crude for the addition without any purification.

A solution of **2-(2-hydroxyphenyl)-1-morpholinoethan-1-one (E78)** (552.8 mg, 2.5 mmol, 1.0 eq) in anhydrous THF (2.5 mL) was added dropwise to the ethylcerium(III) chloride under N_2 at −78 °C. The resulting mixture was stirred at −78 °C for 2 hours before quenching with a saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a yellow solid (245.9 mg, 60%). Data is consistent with the published literature.[51]

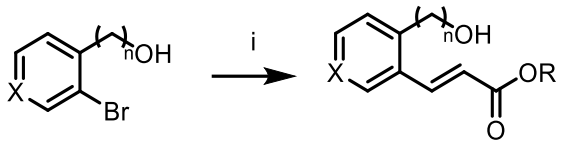
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H, O<u>H</u>), 7.17 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H, Ar-<u>H</u>), 7.07 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-<u>H</u>), 6.93 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar-<u>H</u>), 6.87 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-<u>H</u>), 3.73 (s, 2H, ArC<u>H</u>$_2$), 2.65 (q, *J* = 7.2 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.07 (t, *J* = 7.2 Hz, 3H, CH$_2$C<u>H</u>$_3$) ppm ; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 213.5 (<u>C</u>(O)), 155.5 (<u>C</u>OH), 131.0 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 121.3 (Ar<u>C</u>), 120.9 (Ar<u>C</u>H), 117.7 (Ar<u>C</u>H), 45.7 (Ar<u>C</u>H$_2$), 36.5 (<u>C</u>H$_2$CH$_3$), 7.6 (CH$_2$<u>C</u>H$_3$) ppm ; **HRMS** (ESI) m/z calcd. for $C_{10}H_{12}O_2Na$ ([M+Na]$^+$) 187.0730, found 187.0730.



***tert*-Butyl (*E*)-3-(2-hydroxybenzyl)pent-2-enoate (518)** was prepared according to the following procedure. **1-(2-Hydroxyphenyl)butan-2-one (E79)** (213.2 mg, 1.30 mmol, 1.0 eq) was added to a solution of *tert*-butyl 2-(triphenyl-l5-phosphaneylidene)acetate (733.6 mg, 1.95 mmol, 1.5 eq) in toluene (6.5 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 20 hours before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as an off-white solid (229.3 mg, 68%).

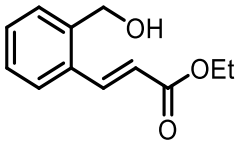
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (td, *J* = 7.7, 1.7 Hz, 1H, Ar-H), 7.09 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar-H), 6.90 (td, *J* = 7.4, 1.2 Hz, 1H, Ar-H), 6.79 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar-H), 5.50 – 5.45 (m, 1H, CH), 4.82 (s, 1H, OH), 3.46 (d, *J* = 1.5 Hz, 2H, $ArCH_2$), 2.59 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 1.10 (t, *J* = 7.5 Hz, 3H, CH_2CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.1 (C(O)O), 161.7 (COH or C=CH), 154.1 (COH or C=CH), 131.5 (ArCH), 128.3 (ArCH), 124.3 (ArC), 121.2 (ArCH), 118.2 (CH), 115.9 (ArCH), 80.0 ($C(CH_3)_3$), 38.5 ($ArCH_2$), 28.4 ($C(CH_3)_3$), 25.4 (CH_2CH_3), 13.3 (CH_2CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{22}O_3Na$ ($[M+Na]^+$) 285.1461, found 285.1461; **FT-IR (thin film)** ν_{max} 3416, 2935, 2357, 1683, 1642, 1595, 1507, 1456, 1367, 1313, 1229, 1173, 1141, 1100, 989, 847, 753, 663, 641, 620, 611 cm^{-1}; **m.p.**: 101-102 °C.

General procedure H for preparation of starting materials 531, 535-536



Scheme 97. Synthesis of starting materials **531**, **535-536**. i. $Pd(OAc)_2$, acrylate, tris(*o*-tolyl)phosphine, triethylamine, 95 °C, 8-18 h.

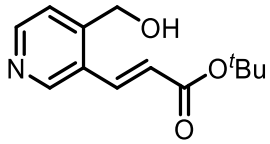
acrylate (1.5 eq) was added to a solution of aryl-bromide (1.0 eq), $Pd(OAc)_2$ (0.05 eq) and tris(*o*-tolyl)phosphine (0.1 eq) in triethylamine (1.44M) in a sealed tube under N_2 at room temperature. The sealed tube was flushed twice with argon gas before sealed with a screw cap. The reaction mixture was heated to 95 °C and stirred for designated time. After cooled back to room temperature, the resulting mixture was diluted with H_2O (50 mL) and extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography afforded starting materials **531**, **535-536.**



Ethyl (*E*)-3-(2-(hydroxymethyl)phenyl)acrylate (531) was prepared following **General Procedure H**, using (2-bromophenyl)methanol (2.18 g, 11.63 mmol, 1.0 eq) and ethyl acrylate (1.75 g, 17.45 mmol, 1.5 eq) to afford the title compound as a pale-yellow oil (846.5 mg, 36%). Reaction time: 11 hours. Silica gel chromatography condition: pentane/EtOAc = 7/3. (Longer reaction time led to a greater amount of oxy-Michael cyclisation product) Data is consistent with the published literature.[52]

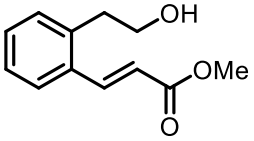
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 15.9 Hz, 1H, C<u>H</u>=CH), 7.58 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar-<u>H</u>), 7.47 – 7.41 (m, 1H, Ar-<u>H</u>), 7.37 (td, *J* = 7.4, 1.5 Hz, 1H, Ar-<u>H</u>), 7.31 (td, *J* = 7.5, 1.6 Hz, 1H, Ar-<u>H</u>), 6.38 (d, *J* = 15.9 Hz, 1H, CH=C<u>H</u>), 4.81 (s, 2H, C<u>H</u>$_2$OH), 4.25 (q, *J* = 7.1 Hz, 2H, C<u>H</u>$_2$CH$_3$), 2.34 (s, 1H, O<u>H</u>), 1.33 (t, *J* = 7.1 Hz, 3H, CH$_2$C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.1 (<u>C</u>(O)O), 141.5

(CH=CH), 139.7 (ArC), 133.2 (ArC), 130.2 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 126.9 (ArCH), 120.4 (CH=CH), 63.0 (CH_2OH), 60.7 (CH_2CH_3), 14.4 (CH_2CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1016, found 207.1017.



***tert*-Butyl (*E*)-3-(4-(hydroxymethyl)pyridin-3-yl)acrylate (535)** was prepared following **General Procedure H**, using (3-bromopyridin-4-yl)methanol (1.0 g, 5.33 mmol, 1.0 eq) and *tert*-butyl acrylate (1.03 g, 8.00 mmol, 1.5 eq) to afford the title compound as a white solid (337.8 mg, 27%). Reaction time: 8 hours. Silica gel chromatography condition: CH_2Cl_2/EtOAc = 1/1. (Longer reaction time led to a greater amount of oxy-Michael cyclisation product).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H, Ar-H), 8.56 (d, *J* = 5.1 Hz, 1H, Ar-H), 7.71 (dd, *J* = 15.9, 0.6 Hz, 1H, CH=CH), 7.53 (dq, *J* = 5.2, 0.9 Hz, 1H, Ar-H), 6.36 (d, *J* = 16.0 Hz, 1H, CH=CH), 4.87 (d, *J* = 0.9 Hz, 2H, CH_2OH), 2.95 (brs, 1H, OH), 1.53 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.7 (C(O)O), 150.3 (ArCH), 148.5 (ArC), 147.5 (ArCH), 136.9 (ArCH), 128.6 (ArC), 124.3 (CH=CH), 121.5 (CH=CH), 81.4 ($C(CH_3)_3$), 61.4 (CH_2OH), 28.3 ($C(CH_3)_3$)ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{18}O_3N$ ($[M+H]^+$) 236.1281, found 236.1280; **FT-IR (thin film)** ν_{max} 3660, 2981, 2888, 1710, 1462, 1382, 1323, 1252, 1154, 1073, 955, 831 cm^{-1}; **m.p.**: 84-85 °C.

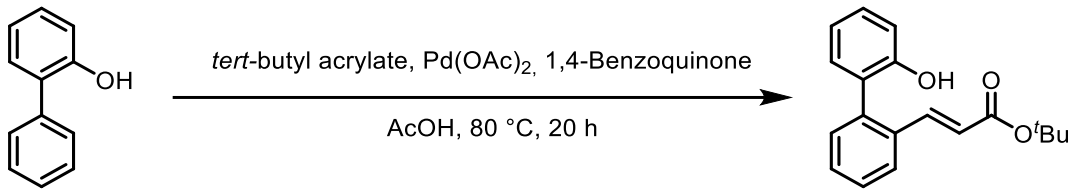


Methyl (*E*)-3-(2-(2-hydroxyethyl)phenyl)acrylate (536) was prepared following **General Procedure H**, using 2-(2-bromophenyl)ethan-1-ol (1.0 g, 5.0mmol, 1.0 eq) and methyl acrylate (645.7 mg, 7.5 mmol,

1.5 eq) to afford the title compound as a pale-yellow oil (543.0 mg, 53%). Reaction time: 18 hours. Silica gel chromatography condition: pentane/Et_2O = 2/3. Data is consistent with the published literature.[53]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 15.8 Hz, 1H, C<u>H</u>=CH), 7.62 – 7.55 (m, 1H, Ar-<u>H</u>), 7.36 – 7.30 (m, 1H, Ar-<u>H</u>), 7.29 – 7.23 (m, 2H, Ar-<u>H</u>), 6.37 (d, *J* = 15.8 Hz, 1H, CH=C<u>H</u>), 3.81 (d, *J* = 5.6 Hz, 5H, C<u>H</u>$_2$CH$_2$ and C<u>H</u>$_3$), 3.03 (t, *J* = 6.8 Hz, 2H, CH$_2$C<u>H</u>$_2$), 1.83 (s, 1H, O<u>H</u>) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.5 (<u>C</u>(O)O), 142.3 (<u>C</u>H=CH), 138.2 (Ar<u>C</u>), 133.7 (Ar<u>C</u>), 131.0 (Ar<u>C</u>H), 130.3 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 119.6 (CH=<u>C</u>H), 63.5 (<u>C</u>H$_2$CH$_2$), 51.9 (<u>C</u>H$_3$), 36.6 (CH$_2$<u>C</u>H$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1016, found 207.1017

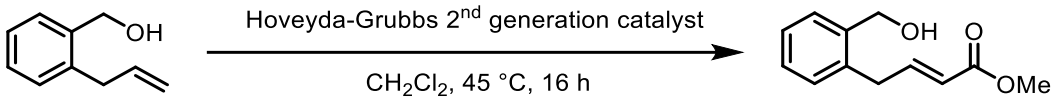
Preparation of starting materials 537



***tert*-Butyl (*E*)-3-(2'-hydroxy-[1,1'-biphenyl]-2-yl)acrylate (537)** was prepared according to the literature procedure reported by C. Zhang *et. al.* To an oven-dried screw-cap vial equipped with a magnetic stirrer bar was added [1,1'-biphenyl]-2-ol (851.1 mg, 5.0 mmol, 1.0 eq), *tert*-butyl acrylate (1.28 g, 10.0 mmol, 2.0 eq), $Pd(OAc)_2$ (112.3 mg, 0.5 mmol, 0.1 eq), 1,4-Benzoquinone (540.5 mg, 5.0 mmol, 1.0 eq) and AcOH (10 mL). The vial was closed under air atmosphere and heated to 80 °C for 20 hours. After cooled to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 17:3) afforded the title compound as an off-white solid (795.7 mg, 54%). Data is consistent with the published literature.[54]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 1H, Ar-H), 7.52 – 7.39 (m, 3H, CH=CH and Ar-H), 7.38 – 7.33 (m, 1H, Ar-H), 7.29 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H, Ar-H), 7.10 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-H), 7.03 – 6.93 (m, 2H, Ar-H), 6.34 (d, *J* = 16.0 Hz, 1H, CH=CH), 4.89 (s, 1H, OH), 1.46 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2 (C(O)O), 152.8 (ArC), 141.4 (CH=CH), 137.6 (ArC), 134.1 (ArC), 131.3 (ArCH), 131.1 (ArCH), 130.3 (ArCH), 129.9 (ArCH), 128.7 (ArCH), 126.9 (ArCH), 126.1 (ArC), 121.6 (CH=CH), 120.8 (ArCH), 116.0 (ArCH), 80.6 ($C(CH_3)_3$), 28.3 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{20}O_3Na$ ($[M+Na]^+$) 319.1305, found 319.1305; **m.p.**: 102-103 °C.

Preparation of starting materials 541

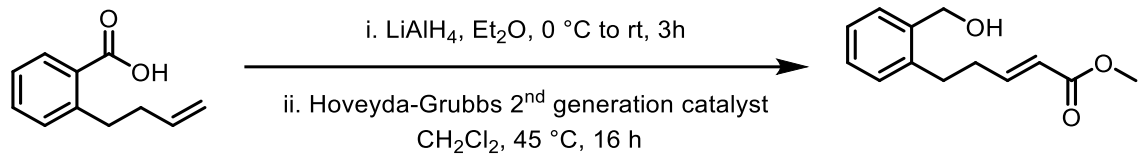


(2-allylphenyl)methanol was prepared according to literature procedure.[55]

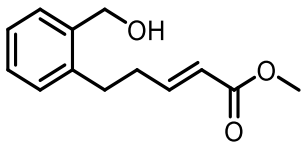
Methyl (*E*)-4-(2-(hydroxymethyl)phenyl)but-2-enoate (541) was prepared according to the following procedure. A solution of Hoveyda-Grubbs 2nd generation catalyst (12.6 mg, 0.02 mmol, 0.01 eq) in degassed CH_2Cl_2 (1 mL) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of (2-allylphenyl)methanol (296.2 mg, 2.0 mmol, 1.0 eq) and methyl acrylate (516.6 mg, 6.0 mmol, 3.0 eq) under N_2 at 45 °C. The reaction mixture was stirred at 45 °C for 16 hours before directly loading onto the silica gel. Purification by silica gel chromatography (pentane/EtOAc = 3:1) afforded the title compound as a pale-yellow oil (117.7 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 1H, Ar-H), 7.40 – 7.32 (m, 2H, Ar-H), 7.28 – 7.16 (m, 2H, CH_2CH=CH and Ar-H), 5.82 (dt, *J* = 15.6, 1.8 Hz, 1H, CH_2CH=CH), 4.76 (d, *J* = 5.2 Hz, 2H, CH_2OH), 3.79 (s, 3H, CH_3), 3.71 (dd, *J* = 6.4, 1.8 Hz, 2H, CH_2CH=CH), 1.78 (t, *J* = 5.6 Hz, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.0 (C(O)O), 147.7 (CH_2CH=CH), 138.7 (ArC), 136.1(ArC), 130.3 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 127.4 (ArCH), 122.1 (CH_2CH=CH), 63.4 (CH_2OH), 51.6 (CH_3), 35.2 (CH_2CH=CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{14}O_3Na$ ($[M+Na]^+$) 229.0835, found 229.0835; **FT-IR (thin film)** ν_{max} 3428, 1719, 1653, 1492, 1436, 1338, 1275, 1205, 1167, 1106, 1039, 1013, 987, 948, 927, 841, 755, 611 cm^{-1}.

Preparation of starting materials 542



2-(but-3-en-1-yl)benzoic acid was prepared according to literature procedure.[56]



Methyl (*E*)-5-(2-(hydroxymethyl)phenyl)pent-2-enoate (542) was prepared according to the following procedure. 2-(but-3-en-1-yl)benzoic acid (768.4 mg, 4.37 mmol, 1.0 eq) was added slowly to a suspension of $LiAlH_4$ (182.6 mg, 4.81 mmol, 1.1 eq) in Et_2O (14.6 mL) under N_2 at 0 °C. The resulting mixture was warmed to room temperature and stirred for 3 hours before quenching with 10% HCl aqueous solution (10 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and carefully evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O= 7/3) afforded the alcohol as a pale-yellow oil (403.1 mg, 57%).

A solution of Hoveyda-Grubbs 2nd generation catalyst (5.4 mg, 0.0086 mmol, 0.005 eq) in degassed CH_2Cl_2 (1 mL) was added dropwise (0.5 mL/h) by using a syringe pump to a mixture of the alcohol (278.0 mg, 1.72 mmol, 1.0 eq) and methyl acrylate (444.3 mg, 5.16 mmol, 3.0 eq) under N_2 at 45 °C. The reaction mixture was stirred at 45 °C for 16 hours before directly loading onto the silica gel. Purification by silica gel chromatography (pentane/Et_2O = 3:2) afforded the title compound as a white solid (251.7 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.4, 1.6 Hz, 1H, Ar-H), 7.31 – 7.16 (m, 3H, Ar-H), 7.02 (dt, *J* = 15.7, 6.9 Hz, 1H, CH_2CH_2CH=CH), 5.86 (dt, *J* = 15.6, 1.6 Hz, 1H, CH_2CH_2CH=CH), 4.71 (s, 2H, CH_2OH), 3.72 (s, 3H, CH_3), 2.90 – 2.81 (m, 2H, CH_2CH_2CH=CH), 2.58 – 2.48 (m, 2H, CH_2CH_2CH=CH), 1.77 (s, 1H, OH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.2, (C(O)O), 148.5

($CH_2CH_2\underline{C}H=CH$), 139.2 (Ar$\underline{C}$), 138.4 (Ar$\underline{C}$), 129.4 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 126.8 (Ar$\underline{C}$H), 121.6 ($CH_2CH_2CH=\underline{C}H$), 63.4 ($\underline{C}H_2OH$), 51.6 ($\underline{C}H_3$), 33.7 ($CH_2\underline{C}H_2CH=CH$), 30.9 ($\underline{C}H_2CH_2CH=CH$) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{16}O_3Na$ ($[M+Na]^+$) 243.0992, found 243.0992; **FT-IR (thin film)** ν_{max} 3392, 2921, 2364, 1721, 1656, 1437, 12821204, 1110, 1017, 852, 758, 646, 633, 610 cm^{-1}; **m.p.**: 54-55 °C.

4.3.4 Preparation of Racemic Compounds

DBU (0.2 eq) or BEMP (0.2 eq) was added to a solution of starting materials (0.20 mmol, 1.0 eq) in THF (0.1M) under N_2 at room temperature. The reaction was stirred at room temperature for 16 hours before loading directly onto silica gel. Purification by silica gel chromatography (pentane/Et_2O) afforded the pure samples of racemic compounds for HPLC analysis.

4.3.5 Preparation of Enantioenriched Products

General procedure I for the intramolecular oxy-Michael reaction

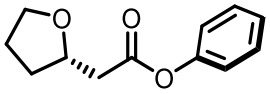
Corresponding alcohol (0.2 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst **406** (0.02 mmol, 0.1 eq) in 2-Me-THF (0.025M, 8 mL) unless otherwise indicated under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours unless otherwise indicated before quenching with 1M AcOH in CH_2Cl_2 (4 mL). The resulting mixture was then evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O) afforded the pure intramolecular oxy-Michael reaction products, which were taken the isolated yield and analysed by chiral HPLC.

General procedure J for the intramolecular oxy-Michael reaction

Corresponding alcohol (0.2 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst **512** (0.02 mmol, 0.1 eq) in TBME (0.025M, 8 mL) unless otherwise indicated under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 24 hours unless otherwise indicated before quenching with 1M AcOH in CH_2Cl_2 (4 mL). The resulting mixture was then evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O) afforded the pure intramolecular oxy-Michael reaction products, which were taken the isolated yield and analysed by chiral HPLC.

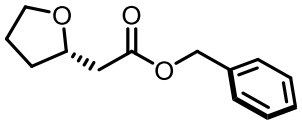
General procedure K for the intramolecular oxy-Michael reaction

Corresponding alcohol (0.2 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst **534** (0.01 mmol, 0.05 eq) in 2-Me-THF (0.1M, 2.0 mL) unless otherwise indicated under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours unless otherwise indicated before quenching with 1M AcOH in CH_2Cl_2 (0.5 mL). The resulting mixture was then evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O) afforded the pure intramolecular oxy-Michael reaction products, which were taken the isolated yield and analysed by chiral HPLC.



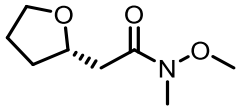
Phenyl (*S*)2-(tetrahydrofuran-2-yl)acetate (404) was prepared following **General Procedure I**, using **phenyl (*E*)-6-hydroxyhex-2-enoate (403)** (41.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (37.6 mg, 91%, 95:5 er). Data is consistent with the published literature.[29]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, Ar-H), 7.25 – 7.18 (m, 1H, Ar-H), 7.13 – 7.07 (m, 2H, Ar-H), 4.38 (p, *J* = 6.8 Hz, 1H, CH), 3.94 (dt, *J* = 8.3, 6.7 Hz, 1H, CH_2O), 3.80 (td, *J* = 8.0, 6.4 Hz, 1H, CH_2O), 2.85 (dd, *J* = 15.2, 7.1 Hz, 1H, $CH_2C(O)O$), 2.72 (dd, *J* = 15.2, 6.1 Hz, 1H, $CH_2C(O)O$), 2.17 (dddd, *J* = 12.0, 8.2, 6.6, 5.3 Hz, 1H, $CHCH_2CH_2$), 2.01 – 1.89 (m, 2H, $CHCH_2CH_2$), 1.67 (ddt, *J* = 12.2, 8.7, 7.3 Hz, 1H, $CHCH_2CH_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9 (C(O)O), 150.8 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 75.3 (CH), 68.2 (CH_2O), 40.8 ($CH_2C(O)O$), 31.4 ($CHCH_2CH_2$), 25.7 ($CHCH_2CH_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1016, found 207.1017; $[\alpha]_D^{25}$ = 6.64 (c=0.12, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 210 nm, t_R (major) = 15.5 min, t_R (minor) = 11.0 min.



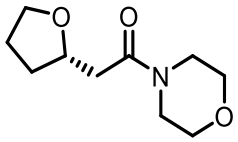
Benzyl (*S*)-2-(tetrahydrofuran-2-yl)acetate (416) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF) using **benzyl (*E*)-6-hydroxyhex-2-enoate (412)** (44.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a pale-yellow oil (41.5 mg, 94%, 94:6 er). Data is consistent with the published literature.[57]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, Ar-H), 5.15 (s, 2H, CH_2Ar), 4.33 – 4.23 (m, 1H, CH), 3.87 (dt, *J* = 8.4, 6.8 Hz, 1H, CH_2O), 3.75 (ddd, *J* = 8.4, 7.5, 6.4 Hz, 1H, CH_2O), 2.66 (dd, *J* = 15.2, 7.3 Hz, 1H, $CH_2C(O)O$), 2.52 (dd, *J* = 15.2, 6.0 Hz, 1H, $CH_2C(O)O$), 2.08 (dddd, *J* = 12.2, 8.2, 6.6, 5.4 Hz, 1H, $CHCH_2CH_2$), 1.89 (ddddd, *J* = 12.2, 11.1, 9.2, 5.8, 3.8 Hz, 2H, $CHCH_2CH_2$), 1.55 (ddt, *J* = 12.1, 8.6, 7.4 Hz, 1H, $CHCH_2CH_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.2 (C(O)O), 136.0 (ArC), 128.6 (2C, ArCH), 128.3 (3C, ArCH), 75.3 (CH), 68.1 (CH_2O), 66.4 (CH_2Ar), 40.8 ($CH_2C(O)O$), 31.3 ($CHCH_2CH_2$), 25.7 ($CHCH_2CH_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O_3$ ($[M+H]^+$) 221.1172, found 221.1172; **$[\alpha]_D^{25}$** = 6.4 (c=0.40, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 254 nm, t_R (major) = 11.4 min, t_R (minor) = 9.5 min.



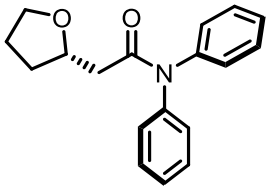
(*S*)-*N*-methoxy-*N*-methyl-2-(tetrahydrofuran-2-yl)acetamide (417) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.1M CPME for 2 days) using **(*E*)-6-hydroxy-*N*-methoxy-*N*-methylhex-2-enamide (413)** (34.8 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/acetone = 17/3) afforded the title compound as a colorless oil (30.0 mg, 87%, 97.5:2.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (dq, *J* = 7.6, 6.5 Hz, 1H, C<u>H</u>), 3.85 (ddd, *J* = 8.5, 7.2, 6.3 Hz, 1H, C<u>H</u>$_2$O), 3.72 (ddd, *J* = 8.4, 7.4, 6.5 Hz, 1H, C<u>H</u>$_2$O), 3.68 (s, 3H, OC<u>H</u>$_3$), 3.16 (s, 3H, NC<u>H</u>$_3$), 2.82 (dd, *J* = 15.3, 6.8 Hz, 1H, C<u>H</u>$_2$C(O)N), 2.49 (dd, *J* = 15.4, 6.3 Hz, 1H, C<u>H</u>$_2$C(O)N), 2.10 (dddd, *J* = 12.1, 8.0, 6.4, 5.4 Hz, 1H, CHC<u>H</u>$_2$CH$_2$), 1.88 (dddd, *J* = 15.2, 7.6, 6.5, 3.0 Hz, 2H, CHCH$_2$C<u>H</u>$_2$), 1.54 (ddt, *J* = 12.2, 8.7, 7.5 Hz, 1H, CHC<u>H</u>$_2$CH$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.2 (<u>C</u>(O)N), 75.6 (<u>C</u>H), 67.9 (<u>C</u>H$_2$O), 61.3 (O<u>C</u>H$_3$), 38.1(<u>C</u>H$_2$C(O)N), 32.1 (N<u>C</u>H$_3$), 31.6 (CH<u>C</u>H$_2$CH$_2$), 25.7 (CHCH$_2$<u>C</u>H$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_8H_{16}NO_3$ ([M+H]$^+$) 174.1125, found 174.1124; **FT-IR (thin film)** ν_{max} 3734, 3648, 2980, 2360, 2341, 1655, 1461, 1388, 1250, 1178, 1060, 1000, 966, 753, 667, 613 cm^{-1}; **$[\alpha]_D^{25}$** = −1.7 (c=0.49, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 200 nm, t_R (major) = 15.0 min, t_R (minor) = 13.1 min.



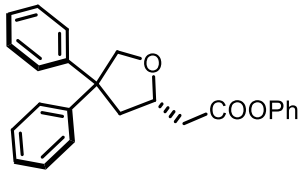
(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethan-1-one (418) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out with 15% cat. **406** in 0.1M CPME for 2 days), using **(*E*)-6-hydroxy-1-morpholinohex-2-en-1-one (414)** (27.7 mg, 0.14 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/acetone = 3/2) afforded the title compound as a white solid (25.5 mg, 92%, 99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (dq, *J* = 7.7, 6.4 Hz, 1H, C<u>H</u>), 3.82 (dt, *J* = 8.4, 6.7 Hz, 1H, C<u>H</u>$_2$O), 3.70 (dt, *J* = 8.3, 7.0 Hz, 1H, C<u>H</u>$_2$O), 3.66 – 3.41 (m, 8H, NC<u>H</u>$_2$C<u>H</u>$_2$OC<u>H</u>$_2$C<u>H</u>$_2$), 2.66 (dd, *J* = 14.8, 6.5 Hz, 1H, C<u>H</u>$_2$C(O)N), 2.43 (dd, *J* = 14.8, 5.9 Hz, 1H, C<u>H</u>$_2$C(O)N), 2.18 – 2.05 (m, 1H, CHC<u>H</u>$_2$CH$_2$), 1.95 – 1.81 (m, 2H, CHCH$_2$C<u>H</u>$_2$), 1.61 – 1.48 (m, 1H, CHC<u>H</u>$_2$CH$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (<u>C</u>(O)O), 76.2 (<u>C</u>H), 68.0 (<u>C</u>H$_2$O), 66.9 (NCH$_2$<u>C</u>H$_2$O<u>C</u>H$_2$CH$_2$), 66.8 (NCH$_2$<u>C</u>H$_2$O<u>C</u>H$_2$CH$_2$), 46.4 (N<u>C</u>H$_2$CH$_2$OCH$_2$<u>C</u>H$_2$), 42.0 (N<u>C</u>H$_2$CH$_2$OCH$_2$<u>C</u>H$_2$), 39.2 (<u>C</u>H$_2$C(O)N), 31.6 (CH<u>C</u>H$_2$CH$_2$), 25.7 (CHCH$_2$<u>C</u>H$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{10}H_{18}NO_3$ ($[M+H]^+$) 200.1281, found 200.1280; **FT-IR (thin film)** ν_{max} 3853, 3837, 3734, 3648, 3503, 2980, 2885, 2360, 2341, 1716, 1635, 1558, 1541, 1507, 1458, 1437, 1381, 1233, 1151, 1114, 1067, 1034, 965, 850, 754, 669, 659 cm^{-1}; **m.p.**: 70-71 °C; **$[\alpha]_D^{25}$** = −3.6 (c=0.53, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 220 nm, t_R (major) = 24.2 min, t_R (minor) = 29.6 min.



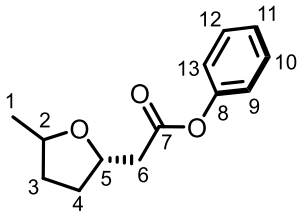
(*S*)-*N*,*N*-diphenyl-2-(tetrahydrofuran-2-yl)acetamide (419) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out with 15% cat. **406** in 0.1M CPME for 2 days), using **(*E*)-6-hydroxy-*N*,*N*-diphenylhex-2-enamide (415)** (58.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/acetone = 4/1) afforded the title compound as a white solid (57.6 mg, 99%, 96:4 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.02 (m, 10H, Ar-H), 4.34 (p, *J* = 6.7 Hz, 1H, CH), 3.74 (dtd, *J* = 26.6, 8.3, 6.5 Hz, 2H, CH_2O), 2.66 (dd, *J* = 15.4, 6.4 Hz, 1H, $CH_2C(O)N$), 2.39 (dd, *J* = 15.4, 6.7 Hz, 1H, $CH_2C(O)N$), 2.20 – 2.10 (m, 1H, $CHCH_2CH_2$), 1.92 – 1.76 (m, 2H, $CHCH_2CH_2$), 1.51 (dq, *J* = 12.3, 7.9 Hz, 1H, $CHCH_2CH_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.9 (C(O)N), 142.8 (ArC), 131.3 – 125.3 (ArCH), 76.3 (CH), 67.8 (CH_2O), 41.3 ($CH_2C(O)O$), 31.5 ($CHCH_2CH_2$), 25.7 ($CHCH_2CH_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{20}NO_2$ ($[M+H]^+$) 282.1489, found 282.1488; **FT-IR (thin film)** ν_{max} 3009, 2362, 1668, 1594, 1491, 1452, 1347, 1254, 1216, 1160, 1061, 754, 701, 666 cm^{-1}; **m.p.**: 101-102 °C; **$[\alpha]_D^{25}$** = +7.1 (c=1.04, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 254 nm, t_R (major) = 14.6 min, t_R (minor) = 18.9 min.



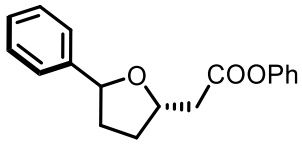
Phenyl (*S*)-2-(4,4-diphenyltetrahydrofuran-2-yl)acetate (425) was prepared following **General Procedure I**, using **phenyl (*E*)-6-hydroxy-5,5-diphenylhex-2-enoate (420)** (71.6 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (65.2 mg, 91%, 90:10 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 8H, Ar-H), 7.23 – 7.13 (m, 5H, Ar-H), 7.10 – 7.02 (m, 2H, Ar-H), 4.60 (dd, *J* = 8.7, 1.1 Hz, 1H, OCH_2), 4.54 (dq, *J* = 9.1, 6.2 Hz, 1H, CH), 4.22 (d, *J* = 8.8 Hz, 1H, OCH_2), 2.89 (dd, *J* = 15.5, 6.9 Hz, 1H, CH_2CHCH_2), 2.85 – 2.71 (m, 2H, CH_2CHCH_2), 2.49 (dd, *J* = 12.3, 9.2 Hz, 1H, CH_2CHCH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.7 (C(O)O), 150.7 (ArC), 145.9 (ArC), 145.6 (ArC), 129.5 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 127.23 (ArCH), 127.17 (ArCH), 126.7 (ArCH), 126.5 (ArCH), 126.0 (ArCH), 121.7 (ArCH), 77.1 (OCH_2), 75.0 (CH), 56.2 (OCH_2C), 44.5 (CH_2CHCH_2), 40.9 (CH_2CHCH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{23}O_3$ ($[M+H]^+$) 359.1642, found 359.1643; **FT-IR (thin film)** ν_{max} 3734, 3648, 2980, 2886, 2360, 2341, 1757, 1593, 1492, 1457, 1382, 1250, 1193, 1130, 1068, 954, 812, 756, 700, 669, 658, 623, 611 cm^{-1}; **$[\alpha]_D^{25}$** = −52.7 (c=0.33, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 80/20, 1.0 ml/min, λ = 210 nm, t_R (major) = 20.2 min, t_R (minor) = 7.8 min.



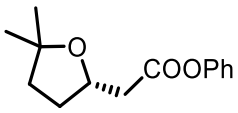
Phenyl 2-((2*S*)-5-methyltetrahydrofuran-2-yl)acetate (426) was prepared following **General Procedure I**, using **phenyl (*E*)-6-hydroxyhept-2-enoate (421)** (43.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 17/3) afforded the title compound as a colorless oil (1:1 (**A**:**B**) mixture of diastereomers) (43.0 mg, 98%, 95.5:4.5 er, 98.5:1.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 4H, 9-13 (**A** and **B**)), 7.25 – 7.18 (m, 2H, 9-13 (**A** and **B**)), 7.10 (dq, *J* = 6.8, 1.1 Hz, 4H, 9-13 (**A** and **B**)), 4.53 (p, *J* = 6.7 Hz, 1H, 5 (**A** or **B**)), 4.35 (p, *J* = 6.8 Hz, 1H, 5 (**A** or **B**)), 4.19 (dp, *J* = 8.0, 6.0 Hz, 1H, 2 (**B**)), 4.03 (dp, *J* = 7.7, 6.2 Hz, 1H, 2 (**A**)), 2.86 (ddd, *J* = 15.0, 12.0, 6.7 Hz, 2H, 6 (**A** and **B**)), 2.71 (ddd, *J* = 15.1, 14.4, 6.5 Hz, 2H, 6 (**A** and **B**)), 2.30 – 1.98 (m, 4H, 3-4 (**A** and **B**)), 1.81 – 1.66 (m, 2H, 4 (**A** and **B**)), 1.61 – 1.47 (m, 2H, 3 (**A** and **B**)), 1.28 (d, *J* = 6.1 Hz, 3H, 1 (**A**)), 1.25 (d, *J* = 6.1 Hz, 3H, 1 (**B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9 (7 (**A** or **B**)), 169.8 (7 (**A** or **B**)), 150.8 (8 (**A** and **B**)), 129.5 (9-13 (**A** and **B**)), 125.9 (9-13 (**A** and **B**)), 121.7 (9-13 (**A** and **B**)), 75.9 (2 (**A**)), 75.4 (5 (**A** or **B**)), 75.2 (2 (**B**)), 74.8 (5 (**A** or **B**)), 41.4 (6 (**A** or **B**)), 41.2 (6 (**A** or **B**)), 33.7 (3 (**A** or **B**)), 32.8 (3 (**A** or **B**)), 32.2 (4 (**A** or **B**)), 31.3 (4 (**A** or **B**)), 21.5 (1 (**A** or **B**)), 21.3 (1 (**A** or **B**)) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O_3$ ($[M+H]^+$) 221.1172, found 221.1174; **FT-IR (thin film)** ν_{max} 2970, 2360, 2341, 1758, 1593, 1493, 1457, 1377, 1195, 1162, 1146, 1081, 1024, 934, 894, 814, 768, 690, 636, 618 cm^{-1}; **$[\alpha]_D^{25}$** = +7.9 (c=0.75, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 220 nm, diastereomer **A** t_R (major) = 10.4 min, t_R (minor) = 11.3 min; diastereomer **B** t_R (major) = 13.4 min, t_R (minor) = 15.6 min.



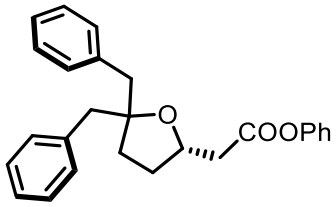
Phenyl 2-((2*S*)-5-phenyltetrahydrofuran-2-yl)acetate (427) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out for 8 hours), using **phenyl (*E*)-6-hydroxy-6-phenylhex-2-enoate (422)** (109.0 mg, 0.39 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 17/3) afforded the title compound as a colorless oil (1:1 (**A**:**B**) mixture of diastereomers) (107.9 mg, 99%, 98:2 er, 94.5:5.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dddd, *J* = 12.8, 6.5, 4.1, 2.0 Hz, 12H, Ar-H (**A** and **B**)), 7.23 – 7.13 (m, 4H, Ar-H (**A** and **B**)), 7.10 – 7.01 (m, 4H, Ar-H (**A** and **B**)), 5.04 (dd, *J* = 7.8, 6.3 Hz, 1H, CCH (**A**)), 4.89 (t, *J* = 7.0 Hz, 1H, CCH (**B**)), 4.73 – 4.62 (m, 1H, CHCH$_2$C(O)O (**A** or **B**)), 4.52 (p, *J* = 6.6 Hz, 1H, CHCH$_2$C(O)O (**A** or **B**)), 2.93 (ddd, *J* = 16.7, 15.2, 6.9 Hz, 2H, CH$_2$C(O)O (**A** or **B**)), 2.77 (td, *J* = 15.6, 6.3 Hz, 2H, CH$_2$C(O)O (**A** or **B**)), 2.37 (dddd, *J* = 14.3, 7.7, 4.7, 2.9 Hz, 1H, CCHCH$_2$ (**A**)), 2.32 – 2.15 (m, 3H, CCHCH$_2$ (**A** and **B**) and CCHCH$_2$CH$_2$ (**A** and **B**)), 1.93 – 1.71 (m, 4H, CCHCH$_2$ (**A** and **B**) and CCHCH$_2$CH$_2$ (**A** and **B**)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.73 (C(O)O (**A** or **B**)), 169.71 (C(O)O (**A** or **B**)), 150.7 (2C, ArC (**A** and **B**)), 143.4 (ArC (**A** or **B**)), 142.9 (ArC (**A** or **B**)), 129.5 (4C, ArCH (**A** and **B**)), 128.40 (2C, ArCH (**A** and **B**)), 128.37 (2C, ArCH (**A** and **B**)), 127.3 (ArCH (**A** or **B**)), 127.2 (ArCH (**A** or **B**)), 125.9 (2C, ArCH (**A** and **B**)), 125.8 (2C, ArCH (**A** and **B**)), 125.5 (2C, ArCH (**A** and **B**)), 121.7 (4C, ArCH (**A** and **B**)), 81.3 (CCH (**B**)), 80.6 (CCH (**A**)), 75.9 (CHCH$_2$C(O)O (**A** or **B**)), 75.8 (CHCH$_2$C(O)O (**A** or **B**)), 41.1 (CHCH$_2$C(O)O (**A** or **B**)), 41.0 (CHCH$_2$C(O)O (**A** or **B**)), 35.2 (CCHCH$_2$ (**A**)), 34.3 (CCHCH$_2$ (**B**)), 32.2 (CCHCH$_2$CH$_2$ (**A** or **B**)), 31.3 (CCHCH$_2$CH$_2$ (**A** or **B**)) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{19}O_3$ ($[M+H]^+$) 283.1329, found 283.1330; **FT-IR (thin film)** ν_{max} 2980, 2365, 1757, 1593, 1493, 1453, 1194, 1163, 1134, 1055, 1026, 931, 753, 699, 690, 652, 628, 620, 607 cm^{-1}; **$[\alpha]_D^{25}$** = +12.9 (c=0.34, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 99/1, 1.0 ml/min, λ = 220 nm, diastereomer **A** t_R (major) = 23.9 min, t_R (minor) = 26.5 min; diastereomer **B** t_R (major) = 41.3 min, t_R (minor) = 33.3 min.



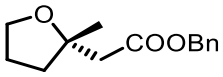
Phenyl (*S*)-2-(5,5-dimethyltetrahydrofuran-2-yl)acetate (428) was prepared following **General Procedure I**, using **phenyl (*E*)-6-hydroxy-6-methylhept-2-enoate (423)** (46.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (43.6 mg, 93%, 98:2 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, Ar-H), 7.25 – 7.18 (m, 1H, Ar-H), 7.13 – 7.05 (m, 2H, Ar-H), 4.52 – 4.41 (m, 1H, CH), 2.88 (dd, *J* = 15.1, 6.2 Hz, 1H, CH_2C(O)O), 2.70 (dd, *J* = 15.1, 7.0 Hz, 1H, CH_2C(O)O), 2.30 – 2.15 (m, 1H, CH_2CH_2), 1.89 – 1.72 (m, 3H, CH_2CH_2), 1.30 (s, 3H, CH_3), 1.26 (s, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9 (C(O)O), 150.8 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 81.4(C), 74.7 (CH), 41.6 (CH_2C(O)O), 38.4 (CH_2CH_2), 31.9 (CH_2CH_2), 29.3 (CH_3), 28.2 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}O_3$ ($[M+H]^+$) 235.1329, found 235.1330; **FT-IR (thin film)** ν_{max} 2970, 2360, 1757, 1594, 1493, 1458, 1366, 1299, 1196, 1163, 1137, 1051, 936, 814, 754, 689 cm^{-1}; **$[\alpha]_D^{25}$** = −2.3 (c=0.77, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 210 nm, t_R (major) = 9.1 min, t_R (minor) = 7.7 min.



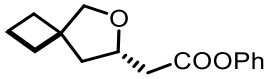
Phenyl (*S*)-2-(5,5-dibenzyltetrahydrofuran-2-yl)acetate (429) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using **phenyl (*E*)-6-benzyl-6-hydroxy-7-phenylhept-2-enoate (424)** (77.1 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a white solid (67.8 mg, 88%, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H, Ar-H), 7.32 – 7.15 (m, 11H, Ar-H), 7.13 – 7.05 (m, 2H, Ar-H), 4.13 (tt, *J* = 8.1, 5.7 Hz, 1H, CH), 2.90 (dd, *J* = 13.6, 11.2 Hz, 2H, CCH_2C), 2.76 (dd, *J* = 28.9, 13.5 Hz, 2H, CCH_2C), 2.60 (dd, *J* = 15.0, 7.7 Hz, 1H, $CH_2C(O)O$), 2.42 (dd, *J* = 15.0, 5.6 Hz, 1H, $CH_2C(O)O$), 1.92 – 1.76 (m, 2H, CH_2CH_2), 1.64 (ddt, *J* = 12.1, 6.9, 5.3 Hz, 1H, CH_2CH_2), 0.90 (dq, *J* = 12.0, 8.8 Hz, 1H, CH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.0 (C(O)O), 150.9 (ArCO), 138.10 (ArC), 138.03 (ArC), 131.1 (ArCH), 131.0 (ArCH), 129.5 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 126.4 (ArCH), 126.3 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 86.0 (C), 75.6 (CH), 46.8 (CCH_2C), 46.6 (CCH_2C), 41.0 ($CH_2C(O)O$), 33.0 (CH_2CH_2), 32.0 (CH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{26}H_{27}O_3$ ($[M+H]^+$) 387.1955, found 387.1955; **FT-IR (thin film)** ν_{max} 3027, 1757, 1594, 1493, 1454, 1278, 1194, 1162, 1143, 1084, 1051, 1029, 922, 754, 702, 668 cm^{-1}; **m.p.**: 38-39 °C; **$[\alpha]_D^{25}$** = +16.2 (c=1.21, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 10.9 min, t_R (minor) = 9.0 min.



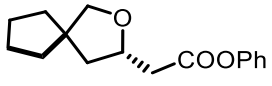
Benzyl (*S*)-2-(2-methyltetrahydrofuran-2-yl)acetate (431) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out with 15% cat. **406** in 0.2M 2-Me-THF at 50 °C for 3 days), using **benzyl (*E*)-6-hydroxy-3-methylhex-2-enoate (430)** (46.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (24 mg, 52%, 94:6 er). Data is consistent with the published literature.[58]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, Ar-H), 5.13 (s, 2H, CH_2Ar), 3.90 – 3.75 (m, 2H, CH_2CH_2O), 2.59 (d, *J* = 2.7 Hz, 2H, $CH_2C(O)O$), 2.03 (ddd, *J* = 11.8, 8.6, 6.3 Hz, 1H, CH_2CH_2), 2.00 – 1.85 (m, 2H, CH_2CH_2), 1.73 (ddd, *J* = 11.8, 8.1, 6.0 Hz, 1H, CH_2CH_2), 1.32 (s, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.0 (C(O)O), 136.1 (ArC), 128.7 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 81.0 (C), 67.5 (CH_2CH_2O), 66.3 (CH_2Ar), 45.6 ($CH_2C(O)O$), 36.9 (CH_2CH_2), 26.5 (CH_2CH_2), 25.9 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}O_3$ ($[M+H]^+$) 235.1329, found 235.1330; **FT-IR (thin film)** ν_{max} 2972, 2360, 1733, 1498, 1455, 1377, 1216, 1096, 1044, 754, 697, 668, 608 cm^{-1}; **$[\alpha]_D^{25}$** = +6.8 (c=0.64, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 210 nm, t_R (major) = 30.0 min, t_R (minor) = 31.6 min.



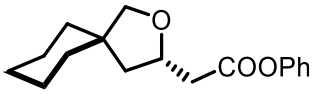
Phenyl (*S*)-2-(6-oxaspiro[3.4]octan-7-yl)acetate (439) was prepared following **General Procedure I**, using **phenyl (*E*)-4-(1-(hydroxymethyl)cyclobutyl)but-2-enoate (433)** (49.4 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/EtOAc = 9/1) afforded the title compound as a colorless oil (46.4 mg, 94%, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, Ar-H), 7.27 – 7.17 (m, 1H, Ar-H), 7.14 – 7.06 (m, 2H, Ar-H), 4.42 (ddt, *J* = 8.2, 7.2, 6.1 Hz, 1H, CH), 3.84 (d, *J* = 8.4 Hz, 1H, CH_2O), 3.77 (d, *J* = 8.4 Hz, 1H, CH_2O), 2.85 (dd, *J* = 15.3, 7.2 Hz, 1H, $CH_2C(O)O$), 2.71 (dd, *J* = 15.3, 6.0 Hz, 1H, $CH_2C(O)O$), 2.26 (dd, *J* = 12.3, 6.4 Hz, 1H, $CHCH_2C$), 2.15 – 2.00 (m, 4H, CH_2 (cyclobutane)), 1.98 – 1.81 (m, 2H, CH_2 (cyclobutane)), 1.74 (dd, *J* = 12.4, 8.2 Hz, 1H, $CHCH_2C$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 79.2 (CH_2O), 74.9 (CH), 46.2 ($CHCH_2C$), 45.1 ($CHCH_2C$), 41.1 ($CH_2C(O)O$), 33.1 (CH_2 (cyclobutane)), 31.4 (CH_2 (cyclobutane)), 16.5 (CH_2 (cyclobutane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{15}H_{19}O_3$ ($[M+H]^+$) 247.1329, found 247.1328; **FT-IR (thin film)** ν_{max} 2929, 2852, 2360, 1758, 1593, 1493, 1386, 1195, 1162, 1135, 1106, 1045, 929, 897, 815, 768, 690, 607 cm^{-1}; **$[\alpha]_D^{25}$** = −2.7 (c=0.82, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 70/30, 1.0 ml/min, λ = 210 nm, t_R (major) = 15.8 min, t_R (minor) = 6.0 min.



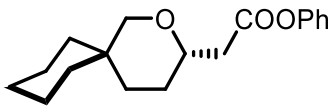
Phenyl (*S*)-2-(2-oxaspiro[4.4]nonan-3-yl)acetate (440) was prepared following **General Procedure I**, using **phenyl (*E*)-4-(1-(hydroxymethyl)cyclopentyl)but-2-enoate (434)** (52.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (51.7 mg, 99%, 93.5:6.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 2H, Ar-H), 7.25 – 7.19 (m, 1H, Ar-H), 7.14 – 7.06 (m, 2H, Ar-H), 4.48 (ddt, *J* = 8.7, 7.2, 6.2 Hz, 1H, CH), 3.70 (d, *J* = 8.1 Hz, 1H, CH_2O), 3.60 (d, *J* = 8.1 Hz, 1H, CH_2O), 2.89 (dd, *J* = 15.3, 7.2 Hz, 1H, $CH_2C(O)O$), 2.74 (dd, *J* = 15.3, 6.0 Hz, 1H, $CH_2C(O)O$), 2.09 (dd, *J* = 12.2, 6.5 Hz, 1H, $CHCH_2C$), 1.75 – 1.53 (m, 9H, $CHCH_2C$ and CH_2 (cyclopentane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 78.8 (CH_2O), 75.4 (OCH), 51.1 ($CHCH_2C$), 45.1 ($CHCH_2C$), 41.3 ($CH_2C(O)O$), 37.6 (CH_2 (cyclopentane)), 36.8 (CH_2 (cyclopentane)), 24.88 (CH_2 (cyclopentane)), 24.86 (CH_2 (cyclopentane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}O_3$ ($[M+H]^+$) 261.1485, found 261.1483; **FT-IR (thin film)** ν_{max} 2952, 2862, 1758, 1593, 1493, 1453, 1194, 1162, 1112, 1055, 929, 897, 754, 690, 667, 643 cm^{-1}; **$[\alpha]_D^{25}$** = −1.1 (c=0.86, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 230 nm, t_R (major) = 36.9 min, t_R (minor) = 11.2 min.



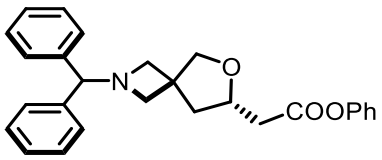
Phenyl (*S*)-2-(2-oxaspiro[4.5]decan-3-yl)acetate (441) was prepared following **General Procedure I**, using **phenyl (*E*)-4-(1-(hydroxymethyl)cyclohexyl)but-2-enoate (435)** (54.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 17/3) afforded the title compound as a colorless oil (54.2 mg, 99%, 94:6 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, Ar-H), 7.25 – 7.17 (m, 1H, Ar-H), 7.14 – 7.06 (m, 2H, Ar-H), 4.45 (dq, *J* = 8.9, 6.6 Hz, 1H, CH), 3.67 (d, *J* = 8.5 Hz, 1H, CH_2O), 3.59 (d, *J* = 8.5 Hz, 1H, CH_2O), 2.88 (dd, *J* = 15.3, 7.2 Hz, 1H, $CH_2C(O)O$), 2.73 (dd, *J* = 15.3, 6.0 Hz, 1H, $CH_2C(O)O$), 2.06 (dd, *J* = 12.4, 6.6 Hz, 1H, $CHCH_2C$), 1.63 – 1.32 (m, 11H, $CHCH_2C$ and CH_2 (cyclohexane)) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 78.6 (CH_2O), 74.9 (OCH), 51.1 ($CHCH_2C$), 44.1 ($CHCH_2C$), 41.3 ($CH_2C(O)O$), 37.0 (CH_2 (cyclohexane)), 35.6 (CH_2 (cyclohexane)), 30.4 (CH_2 (cyclohexane)), 26.1 (CH_2 (cyclohexane)), 24.1 (CH_2 (cyclohexane)), 23.6 (CH_2 (cyclohexane)) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{23}O_3$ ($[M+H]^+$) 275.1642, found 275.1641; **FT-IR (thin film)** ν_{max} 2923, 2851, 2360, 1758, 1593, 1492, 1449, 1389, 1297, 1194, 1163, 1148, 1115, 1056, 1023, 928, 896, 815, 768, 690 cm^{-1}; **$[\alpha]_D^{25}$** = −6.5 (c=0.97, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 240 nm, t_R (major) = 33.1 min, t_R (minor) = 10.7 min.



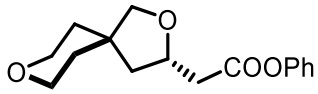
Phenyl (*S*)-2-(2-oxaspiro[5.5]undecan-3-yl)acetate (442) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out with 8% cat. **406** for 3 days), using **phenyl (*E*)-5-(1-(hydroxymethyl)cyclohexyl)pent-2-enoate (436)** (72.0 mg, 0.25 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a colorless oil (43.2 mg, 60%, 91:9 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2H, Ar-H), 7.25 – 7.18 (m, 1H, Ar-H), 7.12 – 7.06 (m, 2H, Ar-H), 3.87 – 3.71 (m, 2H, CH_2O and CH), 3.16 (d, *J* = 11.4 Hz, 1H, CH_2O), 2.79 (dd, *J* = 15.2, 7.7 Hz, 1H, $CH_2C(O)O$), 2.66 (dd, *J* = 15.2, 5.3 Hz, 1H, $CH_2C(O)O$), 1.80 (dq, *J* = 13.4, 3.2 Hz, 1H, CH_2), 1.69 – 1.34 (m, 10H, CH_2), 1.27 (td, *J* = 13.0, 5.3 Hz, 1H, CH_2), 1.20 – 1.12 (m, 2H, CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.0 (C(O)O), 150.8 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 76.9 (CH_2O), 75.0 (CH), 41.5 ($CH_2C(O)O$), 36.6 (CH_2), 34.1 (CH_2), 32.1 (C), 31.3 (CH_2), 27.3 (CH_2), 26.9 (CH_2), 21.7 (CH_2), 21.6 (CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{25}O_3$ ($[M+H]^+$) 289.1798, found 289.1799; **FT-IR (thin film)** ν_{max} 2980, 2926, 2850, 2360, 2341, 1760, 1593, 1492, 1454, 1381, 1241, 1193, 1162, 1149, 1120, 1093, 1023, 938, 891, 817, 762, 688, 652, 622, 609 cm^{-1}; **$[\alpha]_D^{25}$** = −23.8 (c=0.74, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 210 nm, t_R (major) = 10.0 min, t_R (minor) = 8.7 min.



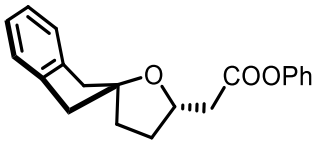
Phenyl (*S*)-2-(2-benzhydryl-6-oxa-2-azaspiro[3.4]octan-7-yl)acetate (443) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out for 2 days), using **phenyl (*E*)-4-(1-benzhydryl-3-(hydroxymethyl)azetidin-3-yl)but-2-enoate (437)** (82.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 1/1) afforded the title compound as a white solid (56.4 mg, 68%, 84:16 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 4H, Ar-H), 7.38 – 7.33 (m, 2H, Ar-H), 7.26 (dd, *J* = 8.4, 6.8 Hz, 4H, Ar-H), 7.23 – 7.13 (m, 3H, Ar-H), 7.12 – 7.04 (m, 2H, Ar-H), 4.40 – 4.32 (m, 1H, OCH), 4.32 (s, 1H, NCH), 4.05 (d, *J* = 8.9 Hz, 1H, CH_2O), 3.90 (d, *J* = 8.9 Hz, 1H, CH_2O), 3.26 – 3.10 (m, 4H, CH_2 (azetidine)), 2.81 (dd, *J* = 15.4, 7.2 Hz, 1H, $CH_2C(O)O$), 2.68 (dd, *J* = 15.4, 6.0 Hz, 1H, $CH_2C(O)O$), 2.40 (dd, *J* = 12.7, 6.5 Hz, 1H, $CHCH_2C$), 1.88 (dd, *J* = 12.8, 7.9 Hz, 1H, $CHCH_2C$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C(O)O), 150.7 (ArCO), 142.3 (ArCCH), 129.5 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 127.2 (ArCH), 126.0 (ArCH), 121.6 (ArCH), 78.1 (NCH), 77.6 (CH_2O), 75.0 (OCH), 64.1 (CH_2 (azetidine)), 63.5 (CH_2 (azetidine)), 43.4 (CH_2O), 41.2 ($CHCH_2C$), 40.8 ($CH_2C(O)O$) ppm; **HRMS** (ESI) m/z calcd. for $C_{27}H_{28}NO_3$ ($[M+H]^+$) 414.2064, found 414.2055; **FT-IR (thin film)** ν_{max} 3025, 2935, 2826, 2361, 1756, 1594, 1492, 1452, 1194, 1162, 1112, 1073, 1050, 1028, 928, 896, 753, 704, 667, 645, 609 cm^{-1}; **m.p.**: 80-81 °C; **$[\alpha]_D^{25}$** = −2.2 (c=1.05, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 93/7, 1.0 ml/min, λ = 220 nm, t_R (major) = 15.9 min, t_R (minor) = 15.0 min.



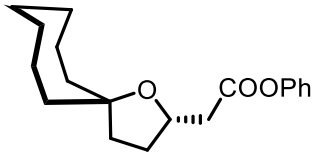
Phenyl (*S*)-2-(2,8-dioxaspiro[4.5]decan-3-yl)acetate (444) was prepared following **General Procedure I**, using **phenyl (*E*)-4-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)but-2-enoate (438)** (56.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 3/7) afforded the title compound as a white solid (56.3 mg, 99%, 92.5:7.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H, Ar-H), 7.28 – 7.17 (m, 1H, Ar-H), 7.13 – 7.05 (m, 2H, Ar-H), 4.46 (dtd, *J* = 8.8, 6.9, 6.0 Hz, 1H, CH), 3.73 (d, *J* = 8.7 Hz, 1H, CCH_2O), 3.70 – 3.61 (m, 5H, CCH_2O and CCH_2CH_2O), 2.89 (dd, *J* = 15.5, 7.1 Hz, 1H, $CH_2C(O)O$), 2.75 (dd, *J* = 15.4, 6.0 Hz, 1H, $CH_2C(O)O$), 2.15 (dd, *J* = 12.5, 6.6 Hz, 1H, $CHCH_2C$), 1.70 – 1.57 (m, 4H, CCH_2CH_2O), 1.53 (dd, *J* = 12.6, 8.9 Hz, 1H, $CHCH_2C$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C(O)O), 150.6 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.6 (ArCH), 78.0 (CCH_2O), 74.8 (OCH), 65.8 (CCH_2CH_2O), 65.4 (CCH_2CH_2O), 43.8 ($CHCH_2C$), 41.8 ($CHCH_2C$), 41.0 ($CH_2C(O)O$), 36.7 (CCH_2CH_2O), 35.6 (CCH_2CH_2O) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}O_4$ ($[M+H]^+$) 277.1434, found 277.1435; **FT-IR (thin film)** ν_{max} 3852, 3734, 3648, 2980, 2849, 2360, 2341, 1758, 1593, 1492, 1457, 1388, 1303, 1232, 1194, 1163, 1107, 1055, 1016, 944, 898, 841, 754, 691, 668, 645, 625 cm^{-1}; **m.p.**: 28-30 °C; **$[\alpha]_D^{25}$** = −6.0 (c=1.05, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 220 nm, t_R (major) = 18.3 min, t_R (minor) = 19.4 min.



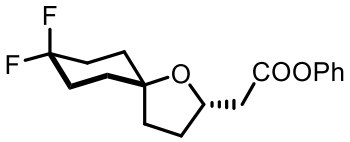
Phenyl (*S*)-2-(1',3',4,5-tetrahydro-3H-spiro[furan-2,2'-inden]-5-yl)acetate (454) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.1M 2-Me-THF for 2 days), using **phenyl (*E*)-5-(2-hydroxy-2,3-dihydro-1H-inden-2-yl)pent-2-enoate (445)** (61.5 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 17/3) afforded the title compound as a white solid (59 mg, 96%, 95:5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.29 – 7.14 (m, 5H, Ar-H), 7.14 – 7.06 (m, 2H, Ar-H), 4.57 (p, *J* = 6.8 Hz, 1H, CH), 3.24 (dd, *J* = 15.9, 4.2 Hz, 2H, CCH_2C), 3.10 – 2.89 (m, 3H, $CH_2C(O)O$ and CCH_2C), 2.77 (dd, *J* = 15.1, 7.1 Hz, 1H, $CH_2C(O)O$), 2.39 – 2.27 (m, 1H, CH_2CH_2), 2.17 – 2.00 (m, 2H, CH_2CH_2), 1.92 (ddt, *J* = 12.3, 8.4, 7.0 Hz, 1H, CH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 150.7 (ArC), 141.5 (ArC), 141.4 (ArC), 129.5 (2C, ArCH), 126.6 (2C, ArCH), 125.9 (ArCH), 124.7 (ArCH), 124.6 (ArCH), 121.7 (2C, ArCH), 91.6 (C), 75.0 (CH), 46.3 (CCH_2C), 45.5 (CCH_2C), 41.5 ($CH_2C(O)O$), 36.9 (CH_2CH_2), 31.6 (CH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{20}H_{21}O_3$ ($[M+H]^+$) 309.1308, found 309.1485; **FT-IR (thin film)** ν_{max} 2942, 1756, 1593, 1492, 1459, 1417, 1302, 1195, 1162, 1073, 1054, 1023, 932, 898, 814, 744, 689, 625 cm^{-1}; **m.p.**: 52-53 °C; **$[\alpha]_D^{25}$** = +15.3 (c=1.14, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 220 nm, t_R (major) = 17.3 min, t_R (minor) = 13.8 min.



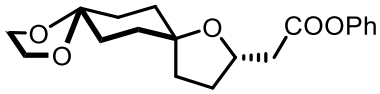
Phenyl (*S*)-2-(1-oxaspiro[4.7]dodecan-2-yl)acetate (455) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using **phenyl (*E*)-5-(1-hydroxycyclooctyl)pent-2-enoate (446)** (60.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a colorless oil (59.1 mg, 98%, 98:2 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, Ar-H), 7.25 – 7.19 (m, 1H, Ar-H), 7.13 – 7.05 (m, 2H, Ar-H), 4.41 (p, *J* = 6.8 Hz, 1H, CH), 2.87 (dd, *J* = 14.8, 6.3 Hz, 1H, CH_2C(O)O), 2.68 (dd, *J* = 14.9, 7.0 Hz, 1H, CH_2C(O)O), 2.23 – 2.09 (m, 1H, CH_2CH_2), 1.91 – 1.40 (m, 17H, CH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.0 (C(O)O), 150.8 (ArC), 129.5 (ArCH), 125.8 (ArCH), 121.7 (ArCH), 86.7 (C), 74.2 (CH), 41.6 (CH_2C(O)O), 37.1 (CH_2CH_2), 37.0 (CH_2CH_2), 35.7 (CH_2CH_2), 31.5 (CH_2CH_2), 28.5 (CH_2CH_2), 28.3 (CH_2CH_2), 24.8 (CH_2CH_2) , 23.0 (CH_2CH_2), 22.7 (CH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{27}O_3$ ($[M+H]^+$) 303.1955, found 303.1956; **FT-IR (thin film)** ν_{max} 2920, 1758, 1594, 1492, 1446, 1298, 1194, 1162, 1144, 1116, 1072, 1051, 935, 898, 814, 753, 689 cm^{-1}; **$[\alpha]_D^{25}$** = +9.6 (c=1.07, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 220 nm, t_R (major) = 6.8 min, t_R (minor) = 7.9 min.



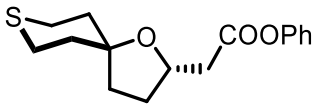
Phenyl (*S*)-2-(8,8-difluoro-1-oxaspiro[4.5]decan-2-yl)acetate (456) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using **phenyl (*E*)-5-(4,4-difluoro-1-hydroxycyclohexyl)pent-2-enoate (447)** (61.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a white solid (58.8 mg, 95%, 95.5:4.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H, Ar-H), 7.29 – 7.20 (m, 1H, Ar-H), 7.13 – 7.05 (m, 2H, Ar-H), 4.57 – 4.36 (m, 1H, CH), 2.83 (dd, *J* = 14.8, 7.0 Hz, 1H, CH_2C(O)O), 2.73 (dd, *J* = 14.9, 6.2 Hz, 1H, CH_2C(O)O), 2.32 – 2.04 (m, 3H, CH_2), 1.94 (dtdd, *J* = 13.6, 7.7, 3.8, 2.0 Hz, 2H, CH_2), 1.88 – 1.72 (m, 6H, CH_2), 1.72 – 1.61 (m, 1H, CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 150.8 (ArC), 129.5 (ArCH), 126.0 (ArCH), 123.7 (dd, *J* = 243.1, 240.1 Hz, CF), 121.6 (ArCH), 80.6 (d, *J* = 1.6 Hz, CH_2C), 74.9 (CH), 41.5 (CH_2C(O)O), 36.5 (d, *J* = 2.3 Hz, CH_2CH_2CH), 34.6 (dd, *J* = 8.5, 1.8 Hz, CH_2CH_2C), 33.1 (dd, *J* = 8.6, 1.7 Hz, CH_2CH_2C), 31.2 (CH_2CH_2CH), 30.9 (ddd, *J* = 25.5, 23.7, 2.3 Hz, 2C, CH_2CH_2C) ppm; **^{19}F NMR (377 MHz, $CDCl_3$)** δ −93.54 (d, *J* = 234.5 Hz), −102.91 (dt, *J* = 235.9, 32.8 Hz) ppm; **HRMS** (ESI) m/z calcd. for $C_{17}H_{20}O_3F_2Na$ ($[M+Na]^+$) 333.1273, found 333.1270; **FT-IR (thin film)** ν_{max} 3728, 3608, 2943, 2361, 2342, 1758, 1594, 1493, 1441, 1377, 1358, 1261, 1195, 1162, 1139, 1111, 1052, 982, 935, 895, 815, 770, 753, 720, 690, 660, 626 cm^{-1}; **m.p.**: 39-40 °C; **$[\alpha]_D^{25}$** = +17.2 (c=0.29, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 99/1, 1.0 ml/min, λ = 210 nm, t_R (major) = 13.5 min, t_R (minor) = 15.0 min.



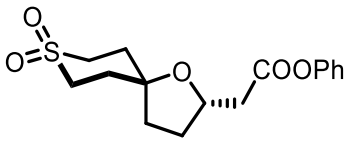
Phenyl (*S*)-2-(1,4,9-trioxadispiro[4.2.48.25]tetradecan-10-yl)acetate (457) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using **phenyl (*E*)-5-(8-hydroxy-1,4-dioxaspiro[4.5]decan-8-yl)pent-2-enoate (448)** (66.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 11/9) afforded the title compound as a colorless oil (58.2 mg, 88%, 97:3 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H, Ar-H), 7.25 – 7.16 (m, 1H, Ar-H), 7.11 – 7.03 (m, 2H, Ar-H), 4.50 – 4.39 (m, 1H, CH), 3.99 – 3.87 (m, 4H, CH_2CH_2O), 2.83 (dd, *J* = 14.8, 6.8 Hz, 1H, $CH_2C(O)O$), 2.69 (dd, *J* = 14.8, 6.5 Hz, 1H, $CH_2C(O)O$), 2.26 – 2.11 (m, 1H, CH_2CH), 1.96 – 1.82 (m, 2H, CCH_2CH_2C), 1.82 – 1.72 (m, 5H, CH_2CH, CH_2CH_2CH, CCH_2CH_2C), 1.72 – 1.54 (m, 4H, CCH_2CH_2C) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.9 (C(O)O), 150.8 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 108.8 (OCO), 81.6 (OC), 74.6 (CH), 64.35 (CH_2CH_2O), 64.26 (CH_2CH_2O), 41.7 ($CH_2C(O)O$), 36.4 (CCH_2CH_2C), 35.7 (CCH_2CH_2C), 34.3 (CH_2CH_2CH), 31.9 (CCH_2CH_2C), 31.8 (CCH_2CH_2C), 31.3 (CH_2CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{25}O_5$ ($[M+H]^+$) 333.1697, found 333.1695; **FT-IR (thin film)** ν_{max} 2935, 2878, 2360, 1756, 1593, 1493, 1445, 1373, 1195, 1163, 1143, 1100, 1049, 964, 931, 815, 769, 690, 659, 645, 628 cm^{-1}; **$[\alpha]_D^{25}$** = +15.0 (c=0.88, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 220 nm, t_R (major) = 18.9 min, t_R (minor) = 29.8 min.



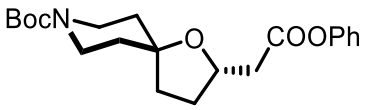
Phenyl (*S*)-2-(1-oxa-8-thiaspiro[4.5]decan-2-yl)acetate (458) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using **phenyl (*E*)-5-(4-hydroxytetrahydro-2H-thiopyran-4-yl)pent-2-enoate (449)** (58.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (49.4 mg, 85%, 98:2 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H, Ar-H), 7.25 – 7.19 (m, 1H, Ar-H), 7.12 – 7.04 (m, 2H, Ar-H), 4.45 (qd, *J* = 7.0, 5.9 Hz, 1H, CH), 3.15 – 2.87 (m, 2H, SCH_2CH_2), 2.81 (dd, *J* = 14.9, 7.0 Hz, 1H, $CH_2C(O)O$), 2.70 (dd, *J* = 14.9, 6.3 Hz, 1H, $CH_2C(O)O$), 2.46 (p, *J* = 7.0, 6.2 Hz, 2H, SCH_2CH_2), 2.24 – 2.10 (m, 1H, CH_2CH_2CH), 1.92 (dq, *J* = 13.7, 5.3, 4.5 Hz, 2H, SCH_2CH_2), 1.86 – 1.68 (m, 5H, CH_2CH_2CH, CH_2CH_2CH and SCH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.6 (ArCH), 81.0 (C), 74.7 (CH), 41.6 ($CH_2C(O)O$), 39.7 (SCH_2CH_2), 38.1 (SCH_2CH_2), 37.7 (CH_2CH_2CH), 31.1 (CH_2CH_2CH), 25.8 (SCH_2CH_2), 25.7 (SCH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}O_3S$ ($[M+H]^+$) 293.1206, found 293.1208; **FT-IR (thin film)** ν_{max} 2931, 1756, 1593, 1493, 1426, 1242, 1194, 1163, 1146, 1064, 937, 814, 753, 689, 654, 628 cm^{-1}; **$[\alpha]_D^{25}$** = +18.8 (c=0.90, $CHCl_3$); **Chiral HPLC:** Chiralcel AS, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 230 nm, t_R (major) = 28.1 min, t_R (minor) = 15.4 min.



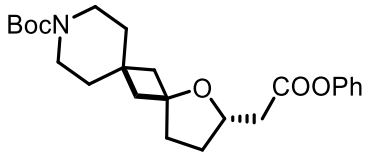
Phenyl (*S*)-2-(8,8-dioxido-1-oxa-8-thiaspiro[4.5]decan-2-yl)acetate (459) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using **phenyl (*E*)-5-(4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pent-2-enoate (450)** (64.8 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (Et_2O) afforded the title compound as a white solid (61.5 mg, 95%, 90:10 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-H), 7.25 – 7.20 (m, 1H, Ar-H), 7.11 – 7.03 (m, 2H, Ar-H), 4.48 (tt, *J* = 7.3, 6.1 Hz, 1H, CH), 3.44 – 3.30 (m, 2H, SCH_2CH_2), 2.87 (dp, *J* = 14.7, 3.9 Hz, 2H, $CH_2C(O)O$), 2.82 – 2.70 (m, 2H, SCH_2CH_2), 2.35 – 2.14 (m, 3H, CH_2CH_2CH and SCH_2CH_2), 2.10 – 1.96 (m, 2H, SCH_2CH_2), 1.95 – 1.74 (m, 3H, CH_2CH_2CH and CH_2CH_2CH) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3 (C(O)O), 150.5 (ArC), 129.6 (ArCH), 126.0 (ArCH), 121.5 (ArCH), 78.7 (C), 75.4 (CH), 48.2 (SCH_2CH_2), 48.1 (SCH_2CH_2), 41.1 ($CH_2C(O)O$), 37.0 (CH_2CH_2CH or CH_2CH_2CH), 36.1 (SCH_2CH_2), 34.5 (SCH_2CH_2), 31.0 (CH_2CH_2CH or CH_2CH_2CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}O_5S$ ($[M+H]^+$) 325.1104, found 325.1100; **FT-IR (thin film)** ν_{max} 3022, 2362, 1754, 1593, 1493, 1324, 1291, 1194, 1163, 1132, 1066, 927, 847, 752, 690, 667 cm^{-1}; **m.p.**: 89-90 °C; **$[\alpha]_D^{25}$** = +16.7 (c=1.11, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 85/15, 1.0 ml/min, λ = 254 nm, t_R (major) = 23.1 min, t_R (minor) = 27.2 min.



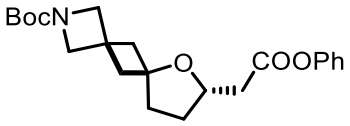
***tert*-Butyl (*S*)-2-(2-oxo-2-phenoxyethyl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (460)** was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF for 2 days), using ***tert*-butyl (*E*)-4-hydroxy-4-(5-oxo-5-phenoxypent-3-en-1-yl)piperidine-1-carboxylate (451)** (74.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 1/1) afforded the title compound as a colorless oil (67.2 mg, 90%, 98.5:1.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H, Ar-H), 7.24 – 7.18 (m, 1H, Ar-H), 7.11 – 7.03 (m, 2H, Ar-H), 4.52 – 4.36 (m, 1H, CH), 3.61 (d, *J* = 13.5 Hz, 2H, SCH_2CH_2), 3.33 (ddt, *J* = 13.4, 9.9, 3.8 Hz, 2H, SCH_2CH_2), 2.81 (dd, *J* = 14.8, 7.0 Hz, 1H, $CH_2C(O)O$), 2.70 (dd, *J* = 14.8, 6.3 Hz, 1H, $CH_2C(O)O$), 2.28 – 2.13 (m, 1H, CH_2CH_2CH), 1.89 – 1.69 (m, 3H, CH_2CH_2CH and CH_2CH_2CH), 1.68 – 1.48 (m, 4H, SCH_2CH_2), 1.45 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 154.9 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.6 (ArCH), 80.7 (C), 79.4 (C), 74.7 (CH), 41.6 ($CH_2C(O)O$), 41.3 (brs, 2C, SCH_2CH_2), 37.8 (SCH_2CH_2), 36.6 (CH_2CH_2CH), 36.4 (SCH_2CH_2), 31.1 (CH_2CH_2CH), 28.5 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{21}H_{29}O_5NNa$ ($[M+Na]^+$) 398.1938, found 398.1934; **FT-IR (thin film)** ν_{max} 2937, 2872, 2360, 2341, 1758, 1692, 1594, 1422, 1365, 1278, 1194, 1150, 1070, 895, 822, 690, 658, 630 cm^{-1}; **$[\alpha]_D^{25}$** = 18.5 (c=0.40, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 210 nm, t_R (major) = 19.0 min, t_R (minor) = 44.9 min.



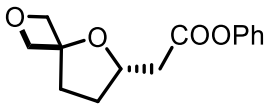
***tert*-Butyl (*S*)-2-(2-oxo-2-phenoxyethyl)-1-oxa-10-azadispiro[4.1.57.15]tridecane-10-carboxylate (461)** was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.05M 2-Me-THF for 2 days), using ***tert*-butyl (*E*)-2-hydroxy-2-(5-oxo-5-phenoxypent-3-en-1-yl)-7-azaspiro[3.5]nonane-7-carboxylate (452)** (82.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel (pentane/Et_2O = 1/1) afforded the title compound as a white solid (78.8 mg, 95%, 98:2 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H, Ar-H), 7.21 (ddt, *J* = 7.9, 6.9, 1.1 Hz, 1H, Ar-H), 7.11 – 7.04 (m, 2H, Ar-H), 4.40 (p, *J* = 6.8 Hz, 1H, CH), 3.35 – 3.24 (m, 4H, NCH_2CH_2), 2.82 (dd, *J* = 15.1, 6.7 Hz, 1H, $CH_2C(O)O$), 2.67 (dd, *J* = 15.1, 6.7 Hz, 1H, $CH_2C(O)O$), 2.15 (dddd, *J* = 12.2, 7.8, 6.7, 5.5 Hz, 1H, CH_2CH), 2.10 – 2.03 (m, 2H, CCH_2C), 2.02 – 1.87 (m, 4H, CH_2CH_2CH and CCH_2C), 1.70 (ddt, *J* = 12.3, 8.2, 7.3 Hz, 1H, CH_2CH), 1.61 – 1.54 (m, 2H, NCH_2CH_2), 1.53 – 1.47 (m, 2H, NCH_2CH_2), 1.44 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.7 (C(O)O), 155.1 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.6 (ArCH), 79.6 (C), 79.5 (C), 74.4 (CH), 45.7 (CCH_2C), 45.4 (CCH_2C), 41.5 ($CH_2C(O)O$), 41.1 (NCH_2CH_2), 40.9 (NCH_2CH_2), 39.2 (CH_2CH_2CH), 38.7 (NCH_2CH_2), 36.8 (NCH_2CH_2), 31.0 (CH_2CH), 29.5 (C), 28.5 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{33}O_5NNa$ ($[M+Na]^+$) 438.2251, found 438.2249; **FT-IR (thin film)** ν_{max} 3015, 2916, 2843, 1759, 1691, 1594, 1493, 1422, 1365, 1271, 1243, 1194, 1163, 1147, 1063, 1026,896, 864, 754, 689, 671, 661, 625 cm^{-1}; **m.p.**: 71-72 °C; **$[\alpha]_D^{25}$** = +13.7 (c=0.23, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 210 nm, t_R (major) = 13.7 min, t_R (minor) = 12.0 min.



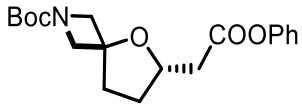
***tert*-Butyl (*S*)-8-(2-oxo-2-phenoxyethyl)-7-oxa-2-azadispiro[3.1.46.14]undecane-2-carboxylate (462)** was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.05M 2-Me-THF), using ***tert*-butyl (*E*)-6-hydroxy-6-(5-oxo-5-phenoxypent-3-en-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate (453)** (77.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 1/1) afforded the title compound as a colorless oil (74.0 mg, 95%, 94.5:5.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, Ar-H), 7.24 – 7.17 (m, 1H, Ar-H), 7.11 – 7.03 (m, 2H, Ar-H), 4.41 (p, *J* = 6.8 Hz, 1H, CH), 3.89 (d, *J* = 11.9 Hz, 4H, NCH_2 or CCH_2C), 2.78 (dd, *J* = 15.2, 6.9 Hz, 1H, $CH_2C(O)O$), 2.66 (dd, *J* = 15.2, 6.3 -Hz, 1H, $CH_2C(O)O$), 2.46 – 2.36 (m, 2H, NCH_2 or CCH_2C), 2.27 – 2.19 (m, 2H, NCH_2 or CCH_2C), 2.19 – 2.11 (m, 1H, CH_2CH), 1.96 – 1.81 (m, 2H, CH_2CH_2CH), 1.78 – 1.65 (m, 1H, CH_2CH), 1.42 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C(O)O), 156.2 (C(O)O), 150.7 (ArC), 129.5 (ArCH), 125.9 (ArCH), 121.6 (ArCH), 79.4 (C), 79.1 (C), 74.9 (CH), 61.8 (NCH_2 or CCH_2C), 60.4 (NCH_2 or CCH_2C), 47.0 (NCH_2 or CCH_2C), 46.4 (NCH_2 or CCH_2C), 41.5 ($CH_2C(O)O$), 36.8 (CH_2CH_2CH), 30.9 (CH_2CH), 29.5 (C), 28.5 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{30}O_5N$ ($[M+H]^+$) 388.2118, found 388.2114; **FT-IR (thin film)** ν_{max} 2925, 2360, 1758, 1698, 1594, 1493, 1403, 1366, 1318, 1244, 1216, 1194, 1162, 1063, 931, 753, 690, 667 cm^{-1}; **$[\alpha]_D^{25}$** = +12.3 (c=1.34, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 220 nm, t_R (major) = 11.7 min, t_R (minor) = 13.3 min.



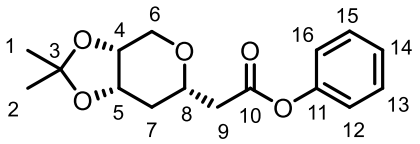
Phenyl (*S*)-2-(2,5-dioxaspiro[3.4]octan-6-yl)acetate (464) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out in 0.2M 2-Me-THF at –22 °C for 10 hours), using **phenyl (*E*)-5-(3-hydroxyoxetan-3-yl)pent-2-enoate (463)** (49.4 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 3/7) afforded the title compound as a colorless oil (38.0 mg, 77%, 91:9 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 2H, Ar-H), 7.27 – 7.19 (m, 1H, Ar-H), 7.13 – 7.05 (m, 2H, Ar-H), 4.86 – 4.76 (m, 2H, OCH_2), 4.58 – 4.51 (m, 2H, OCH_2), 4.51 – 4.41 (m, 1H, CH), 2.80 (dd, *J* = 15.4, 6.9 Hz, 1H, $CH_2C(O)O$), 2.70 (dd, *J* = 15.4, 6.2 Hz, 1H, $CH_2C(O)O$), 2.40 – 2.29 (m, 1H, CH_2CH_2), 2.29 – 2.11 (m, 2H, CH_2CH_2), 1.80 – 1.65 (m, 1H, CH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 (C(O)O), 150.6 (ArC), 129.5 (ArCH), 126.0 (ArCH), 121.6 (ArCH), 84.4 (OCH_2), 83.9 (OCH_2), 82.6 (C), 75.9 (CH), 41.0 ($CH_2C(O)O$), 35.2 (CH_2CH_2), 30.9 (CH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{17}O_4$ ($[M+H]^+$) 249.1121, found 249.1122; **FT-IR (thin film)** ν_{max} 2947, 2872, 1756, 1593, 1493, 1350, 1216, 1194, 1163, 1145, 1128, 1025, 971, 753, 689, 667 cm^{-1}; **$[\alpha]_D^{25}$** = +13.4 (c=0.69, $CHCl_3$); **Chiral HPLC:** Chiralcel AD, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 210 nm, t_R (major) = 22.8 min, t_R (minor) = 24.8 min.

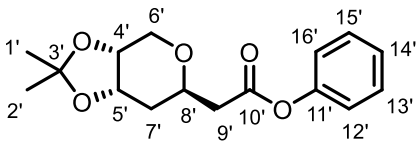


***tert*-butyl (*S*)-6-(2-oxo-2-phenoxyethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (466)** was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out at –22 °C), using ***tert*-butyl (*E*)-3-hydroxy-3-(5-oxo-5-phenoxypent-3-en-1-yl)azetidine-1-carboxylate (465)** (69.6 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 1/1) afforded the title compound as a off-white solid (61.9 mg, 89%, 92.5:7.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 2H, Ar-H), 7.22 (ddt, J = 7.9, 6.9, 1.2 Hz, 1H, Ar-H), 7.12 – 7.04 (m, 2H, Ar-H), 4.47 (tt, *J* = 7.0, 6.0 Hz, 1H, CH), 4.04 (ddd, *J* = 8.9, 5.6, 1.1 Hz, 2H, NCH_2), 3.86 (td, *J* = 9.0, 1.1 Hz, 2H, NCH_2), 2.81 (dd, *J* = 15.4, 7.0 Hz, 1H, $CH_2C(O)O$), 2.71 (dd, *J* = 15.4, 6.2 Hz, 1H, $CH_2C(O)O$), 2.25 – 2.07 (m, 3H, CH_2CH_2), 1.80 – 1.69 (m, 1H, CH_2CH_2), 1.43 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 (C(O)O), 156.5 (C(O)O), 150.6 (ArC), 129.5 (ArCH), 126.0 (ArCH), 121.6 (ArCH), 79.6 (C), 78.4 (C), 75.9 (CH), 62.3 (NCH_2), 41.0 ($CH_2C(O)O$), 35.9 2 (CH_2CH_2), 30.8 2 (CH_2CH_2), 28.5 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{26}O_5N$ ($[M+H]^+$) 348.1805, found 348.1799; **FT-IR (thin film)** ν_{max} 2976, 2877, 2359, 1759, 1699, 1594, 1493, 1403, 1367, 1194, 1163, 1085, 1024, 933, 902, 813, 753, 690, 667, 620 cm^{-1}; **m.p.**: 42-43 °C; **$[\alpha]_D^{25}$** = +13.5 (c=1.20, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 220 nm, t_R (major) = 24.3 min, t_R (minor) = 21.8 min.



A



B

Phenyl 2-((3a*R*,6*S*,7a*S*)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-6-yl)acetate (A) (467) was prepared following **General Procedure I**, using **phenyl (*E*)-4-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (468)** (61.2 mg, 0.21 mmol, 1.0 eq). After 24 hours, the rest reaction mixture was filtered through a short silica pad to quench catalyst and analysed by NMR (Crude: 93%, **A**:**B** = 94:6 dr), which was then purified by silica gel chromatography (pentane/Et_2O = 13/7) affording the compound as a colorless oil (52 mg, 85%, **A**:**B** = >99.5:0.5 dr) and 8% of mixed diastereomers product (**A**:**B** = 35:65 dr).

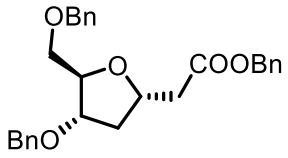
Phenyl 2-((3a*R*,6*R*,7a*S*)-2,2-dimethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-6-yl)acetate (B) (E80) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out with 10% cat. **473**) using **phenyl (*E*)-4-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (468)** (61.2 mg, 0.21 mmol, 1.0 eq). After 24 hours, the rest reaction mixture was filtered through a short silica pad to quench catalyst and analysed by NMR (Crude: 99%, **A**:**B** = 30:70 dr), which was then purified by silica gel chromatography (pentane/Et_2O = 13/7) affording the compound as a colorless oil (45.9 mg, 75%, **A**:**B** = >0.5:99.5 dr) and 16% of mixed diastereomers product (**A**:**B** = 97:3 dr).

Reaction carried out with 10% BEMP under identical conditions afforded the compound (54% yield, **A**:**B** = 44:56 dr);

A (467): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H, 12-16), 7.25 – 7.18 (m, 1H, 12-16), 7.11 – 7.03 (m, 2H, 12-16), 4.36 – 4.23 (m, 2H, 5 and 6), 4.03 (ddd, *J* = 5.3, 2.6, 1.2 Hz, 1H, 4), 3.85 – 3.74 (m, 2H, 6 and 8), 2.86 (dd, *J* = 15.7, 8.0 Hz, 1H, 9), 2.66 (dd, *J* = 15.7, 5.1 Hz, 1H, 9), 2.03 (ddd, *J* = 13.1, 6.9, 2.1 Hz, 1H, 7), 1.63 (ddd, *J* = 13.2, 11.3, 9.6 Hz, 1H, 7), 1.55 (s, 3H, 1 or 2), 1.36 (s, 3H, 1 or 2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (10), 150.7 (11), 129.5 (12-16), 126.0 (12-16), 121.6 (12-16), 109.2 (3), 71.52 (4), 71.48 (5), 71.1 (8), 66.7 (6), 41.0 (9), 35.3 (7), 28.5 (1 or 2), 26.5 (1 or 2) ppm; **HRMS** (ESI)

m/z calcd. for $C_{16}H_{21}O_5$ ([M+H]$^+$) 293.1384, found 293.1384; **FT-IR (thin film)** ν_{max} 3409, 3016, 2923, 1756, 1593, 1492, 1397, 1320, 1243, 1194, 1162, 1139, 1089, 1066, 1007, 983, 937, 882, 816, 754, 714, 689, 661, 620 cm^{-1}; $[\alpha]_D^{25}$ = −34.9 (c=0.87, $CHCl_3$).

B (E80): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.9 Hz, 2H, 12'-16'), 7.22 (t, *J* = 7.4 Hz, 1H, 12'-16'), 7.12 – 7.06 (m, 2H, 12'-16'), 4.44 – 4.36 (m, 1H, 5'), 4.15 (ddt, *J* = 11.5, 8.4, 3.9 Hz, 2H, 4' and 8'), 3.94 (dd, *J* = 11.6, 6.5 Hz, 1H, 6'), 3.42 (dd, *J* = 11.6, 9.4 Hz, 1H, 6'), 2.78 – 2.62 (m, 2H, 9'), 2.21 (dt, *J* = 14.9, 2.5 Hz, 1H, 7'), 1.85 (ddd, *J* = 15.2, 11.7, 3.9 Hz, 1H, 7'), 1.52 (s, 3H, 1' or 2'), 1.37 (s, 3H, 1' or 2') ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.4 (10'), 150.7 (11'), 129.5 (12'-16'), 126.0 (12'-16'), 121.7 (12'-16'), 109.2 (3'), 71.5 (5'), 70.0 (4' or 8'), 69.2 (4' or 8'), 67.9 (6'), 41.0 (9'), 32.5 (7'), 28.3 (1' or 2'), 26.3 (1' or 2') ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{21}O_5$ ([M+H]$^+$) 293.1384, found 293.1384; **FT-IR (thin film)** ν_{max} 2988, 2937, 2360, 1758, 1593, 1493, 1457, 1427, 1380, 1217, 1195, 1164, 1143, 1061, 1022, 928, 896, 859, 820, 754, 716, 688, 668, 608 cm^{-1}; $[\alpha]_D^{25}$ = +45.8 (c=0.92, $CHCl_3$).

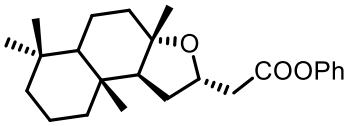


Benzyl 2-((2*S*,4*S*,5*R*)-4-(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)acetate (469) was prepared following **General Procedure I**, (variation from standard conditions: reaction carried out with 10% cat. **473** in 0.1M 2-Me-THF), using **benzyl (5*S*,6*R*,*E*)-5,7-bis(benzyloxy)-6-hydroxyhept-2-enoate (470)** (87.9 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a colorless oil (82.6 mg, 94%, 97.5:2.5 dr).

Reaction carried out with 10% cat. **406** under identical conditions afforded the compound in 98% conversion, 64:36 dr.

Reaction carried out with 10% DBU under identical conditions afforded the compound in 99% conversion, 53.5:46.5 dr.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 15H, Ar-H), 5.18 (s, 2H, OCH_2Ar), 4.67 – 4.47 (m, 5H, CHCH_2C(O)O and OCH_2Ar), 4.19 (td, *J* = 4.9, 2.6 Hz, 1H, BnOCHCH), 4.12 – 4.05 (m, 1H, BnOCH), 3.57 (dd, *J* = 10.2, 4.6 Hz, 1H, CH_2OBn), 3.47 (dd, *J* = 10.2, 5.4 Hz, 1H, CH_2OBn), 2.78 (dd, *J* = 15.4, 6.8 Hz, 1H, CH_2C(O)O), 2.60 (dd, *J* = 15.4, 6.2 Hz, 1H, CH_2C(O)O), 2.23 (ddd, *J* = 13.1, 5.3, 1.6 Hz, 1H, CH_2CHCH_2C(O)O), 1.81 – 1.69 (m, 1H, CH_2CHCH_2C(O)O) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.8 (C(O)O), 138.3 (ArC), 138.2 (ArC), 136.0 (ArC), 128.6 (2C, ArCH), 128.45 (2C, ArCH), 128.42 (2C, ArCH), 128.3 (3C, ArCH), 127.69 (3C, ArCH), 127.65 (3C, ArCH), 83.7 (BnOCHCH), 81.2 (BnOCH), 75.0 (CHCH_2C(O)O), 73.5 (OCH_2Ar), 71.1 (OCH_2Ar), 71.0 (CH_2OBn), 66.4 (OCH_2Ar), 40.4 (CH_2C(O)O), 38.0 (CH_2CHCH_2C(O)O) ppm; **HRMS** (ESI) m/z calcd. for $C_{28}H_{31}O_5$ ($[M+H]^+$) 447.2166, found 447.2167; **FT-IR (thin film)** ν_{max} 3031, 2917, 1736, 1497, 1454, 1363, 1215, 1157, 1094, 1028, 995, 750, 697, 612 cm^{-1}; **$[\alpha]_D^{25}$** = +20.2 (c=1.57, $CHCl_3$).



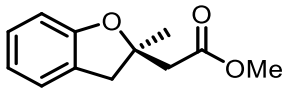
Phenyl 2-((2*S*,3a*S*,9a*R*,9b*S*)-3a,6,6,9a-tetramethyldodecahydronaphtho[2,1-b]furan-2-yl)acetate (471) was prepared following **General Procedure I**, using **phenyl (*E*)-4-((1*S*,2*S*,8a*R*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)but-2-enoate (472)** (73.6 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 1/1) afforded the title compound as a white solid (67.7 mg, 92%, 99:1 dr).

Reaction carried out with 10% cat. **473** under identical conditions afforded the compound in 61% conversion, 60:40 dr.

Reaction carried out with 10% BEMP under identical conditions afforded the compound in 60% conversion, 1:1 dr.

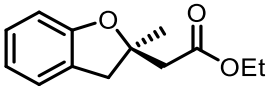
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 2H, Ar-H), 7.25 – 7.17 (m, 1H, Ar-H), 7.14 – 7.06 (m, 2H, Ar-H), 4.59 – 4.36 (m, 1H, CHCH$_2$C(O)O), 2.96 (dd, *J* = 15.2, 7.1 Hz, 1H, CH$_2$C(O)O), 2.74 (dd, *J* = 15.2, 7.1 Hz, 1H, CH$_2$C(O)O), 2.10 – 2.01 (m, 1H, OCHCH$_2$CH), 1.96 (dt, *J* = 11.6, 3.2 Hz, 1H, CH$_2$CH$_2$CHC(CH$_3$)$_2$), 1.87 – 1.71 (m, 1H, CH$_2$CH$_2$CHC(CH$_3$)$_2$), 1.70 – 1.56 (m, 3H, OCHCH$_2$CH, CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$ and OCHCH$_2$CH), 1.52 – 1.39 (m, 4H, 1H for CH$_2$CH$_2$CHC(CH$_3$)$_2$ and 3H for CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 1.37 – 1.26 (m, 1H, CH$_2$CH$_2$CHC(CH$_3$)$_2$), 1.19 (d, *J* = 0.9 Hz, 4H, CH$_3$ and CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 1.11 – 1.03 (m, 1H, CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 0.98 (dd, *J* = 12.4, 2.7 Hz, 1H, CHC(CH$_3$)$_2$), 0.88 (s, 3H, CH$_3$), 0.87 (s, 3H, CH$_3$), 0.84 (s, 3H, CH$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 150.8 (ArC), 129.4 (ArCH), 125.8 (ArCH), 121.7 (ArCH), 81.2 (CO), 74.4 (CHCH$_2$C(O)O), 61.0 (OCHCH$_2$CH), 57.2 (CHC(CH$_3$)$_2$), 43.3 (CH$_2$C(O)O), 42.5 (CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 40.3 (CH$_2$CH$_2$CHC(CH$_3$)$_2$), 40.1 (CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 36.4 (C), 33.6 (CH$_3$), 33.2 (C), 29.5 (OCHCH$_2$CH), 24.8 (CH$_3$), 21.2 (CH$_3$), 20.9 (CH$_2$CH$_2$CHC(CH$_3$)$_2$), 18.5 (CH$_2$CH$_2$CH$_2$C(CH$_3$)$_2$), 15.6 (CH$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{24}H_{35}O_3$ ([M+H]$^+$) 371.2581, found 371.2581; **FT-IR (thin film)** ν_{max} 2999, 2924, 2867, 2360, 2342, 1759, 1594, 1493, 1458, 1379,

1334, 1299, 1274, 1220, 1195, 1163, 1119, 1080, 1068, 1042, 1026, 1003, 985, 962, 937, 900, 814, 752, 711, 689, 668, 628 cm^{-1}; **m.p.**: 55-56 °C; **$[\alpha]_D^{25}$** = −7.5 (c=1.24, $CHCl_3$).



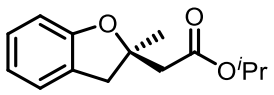
Methyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (510) was prepared following **General Procedure J**, using **methyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (509)** (38.1 mg, 0.19 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 95/5) afforded the title compound as a colorless oil (34.3 mg, 90%, 95:5 er). Data is consistent with the published literature.[29]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.06 (m, 2H, Ar-H), 6.84 (td, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 6.75 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.66 (s, 3H, OCH_3), 3.37 (d, *J* = 15.8 Hz, 1H, $CH_2C(O)O$), 3.05 (dd, *J* = 15.9, 1.2 Hz, 1H, $CH_2C(O)O$), 2.78 (d, *J* = 2.5 Hz, 2H, $ArCH_2$), 1.58 (s, 3H, CCH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.8 (C(O)O), 158.4 (ArCO), 128.2 (ArCH), 126.7 (ArCC), 125.3 (ArCH), 120.5 (ArCH), 109.7 (ArCH), 86.1(CH_2C), 51.8 (OCH_3), 45.0 ($ArCH_2$), 41.4 ($CH_2C(O)O$), 26.5 (CCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1016, found 207.1017; **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 220 nm, t_R (major) = 6.8 min, t_R (minor) = 11.0 min.



Ethyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (519) was prepared following **General Procedure J**, (variation from standard conditions: reaction carried out for 17h), using **ethyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (513)** (44.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a colorless oil (43.9 mg, 99.5%, 97.5:2.5 er).

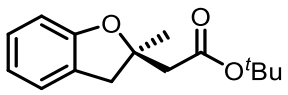
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.06 (m, 2H, Ar-H), 6.83 (td, *J* = 7.4, 0.9 Hz, 1H, Ar-H), 6.75 (d, *J* = 8.0 Hz, 1H, Ar-H), 4.17 – 4.05 (m, 2H, OCH_2CH_3), 3.39 (d, *J* = 15.8 Hz, 1H, $CH_2C(O)O$), 3.04 (d, *J* = 15.8 Hz, 1H, $CH_2C(O)O$), 2.83 – 2.70 (m, 2H, $ArCH_2$), 1.58 (s, 3H, CCH_3), 1.21 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.3 ($C(O)O$), 158.5 ($ArCO$), 128.2 ($ArCH$), 126.7 ($ArCC$), 125.2 ($ArCH$), 120.5 ($ArCH$), 109.7 ($ArCH$), 86.2(CH_2C), 60.6 (OCH_2CH_3), 45.4 ($ArCH_2$), 41.3 ($CH_2C(O)O$), 26.7 (CCH_3), 14.2 ((OCH_2CH_3)) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O_3$ ($[M+H]^+$) 221.1172, found 221.1174; **FT-IR (thin film)** ν_{max} 2980, 2360, 1732, 1598, 1480, 1460, 1372, 1242, 1065, 1031, 888, 752, 668 cm^{-1}; **$[\alpha]_D^{25}$** = +4.6 (c=0.68, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 230 nm, t_R (major) = 6.9 min, t_R (minor) = 10.2 min.



***iso*-Propyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (520)** was prepared following **General Procedure J**, (variation from standard conditions: reaction carried out for 17h), using ***iso*-propyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (514)** (46.7 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a colorless oil (43.9 mg, 94%, 98:2 er).

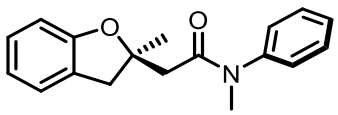
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.06 (m, 2H, Ar-H), 6.83 (td, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 6.74 (d, *J* = 8.0 Hz, 1H, Ar-H), 4.99 (hept, *J* = 6.3 Hz, 1H, OCH), 3.41 (d, *J* = 15.8 Hz, 1H, $CH_2C(O)O$), 3.03 (d, *J* = 15.8 Hz, 1H, $CH_2C(O)O$), 2.81 – 2.66 (m, 2H, $ArCH_2$), 1.57 (s, 3H, CCH_3), 1.19 (dd, *J* = 8.4, 6.3 Hz, 6H, $OCH(CH_3)_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 ($C(O)O$), 158.6 ($ArCO$), 128.1 ($ArCH$), 126.8 ($ArCC$), 125.2 ($ArCH$), 120.4 ($ArCH$), 109.7 ($ArCH$), 86.2 (CH_2C), 68.1 (OCH), 45.8 ($ArCH_2$), 41.3 ($CH_2C(O)O$), 26.9 (CCH_3), 21.83 ($OCH(CH_3)_2$), 21.81 ($OCH(CH_3)_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}O_3$ ($[M+H]^+$) 235.1329, found 235.1330; **FT-IR (thin film)** ν_{max} 3648, 2980, 2360, 2341, 1728, 1598, 1481, 1460, 1375, 1327, 1243, 1146, 1106, 1065, 1016, 966, 885, 752, 668 cm^{-1}; **$[\alpha]_D^{25}$**

= +3.0 (c=0.80, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 99.5/0.5, 1.0 ml/min, λ = 220 nm, t_R (major) = 6.4 min, t_R (minor) = 5.8 min.



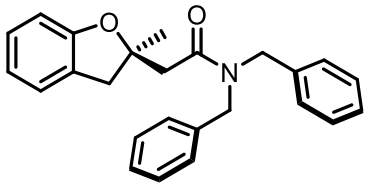
***tert*-Butyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (521)** was prepared following **General Procedure J**, (variation from standard conditions: reaction carried out for 17h), using ***tert*-butyl (*E*)-4-(2-hydroxyphenyl)-3-methylbut-2-enoate (515)** (49.4 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 95/5) afforded the title compound as a colorless oil (45.9 mg, 93%, 99.5:0.5 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 2H, Ar-H), 6.83 (td, *J* = 7.5, 1.1 Hz, 1H, Ar-H), 6.74 (d, *J* = 7.9 Hz, 1H, Ar-H), 3.42 (dd, *J* = 15.8, 1.0 Hz, 1H, $CH_2C(O)O$), 3.02 (dd, *J* = 15.8, 1.1 Hz, 1H, $CH_2C(O)O$), 2.72 (d, *J* = 14.3 Hz, 1H, $ArCH_2$), 2.64 (d, *J* = 14.3 Hz, 1H, $ArCH_2$), 1.56 (s, 3H, CCH_3), 1.38 (s, 9H, $OC(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C(O)O), 158.7 (ArCO), 128.1 (ArCH), 126.9 (ArCC), 125.2 (ArCH), 120.4 (ArCH), 109.6 (ArCH), 86.3 (CH_2C), 81.0 ($OC(CH_3)_3$), 46.8 ($ArCH_2$), 41.2 ($CH_2C(O)O$), 28.1 ($OC(CH_3)_3$), 27.0 (CCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{15}H_{20}O_3Na$ ($[M+Na]^+$) 271.1305, found 271.1306; **FT-IR (thin film)** ν_{max} 3649, 2980, 2360, 2341, 1727, 1598, 1481, 1460, 1368, 1244, 1160, 1112, 1065, 1016, 956, 888, 866, 842, 751, 708, 668 cm^{-1}; **$[\alpha]_D^{25}$** = +4.3 (c=0.73, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 99.5/0.5, 1.0 ml/min, λ = 210 nm, t_R (major) = 10.1 min, t_R (minor) = 8.6 min.



(*R*)-*N*-methyl-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)-*N*-phenylacetamide (522) was prepared following **General Procedure J**, (variation from standard conditions: reaction carried out at 40 °C for 4 days), using **(*E*)-4-(2-hydroxyphenyl)-*N*,3-dimethyl-*N*-phenylbut-2-enamide (516)** (56.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a pale-yellow oil (47.3 mg, 84%, 99:1 er).

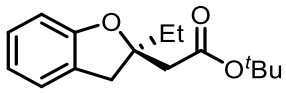
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.3, 6.7 Hz, 2H, Ar-H), 7.32 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.21 – 7.10 (m, 3H, Ar-H), 7.06 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.80 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.65 (d, *J* = 7.9 Hz, 1H, Ar-H), 3.47 (d, *J* = 16.1 Hz, 1H, $CH_2C(O)N$), 3.27 (s, 3H, NCH_3), 3.09 (d, *J* = 16.1 Hz, 1H, $CH_2C(O)N$), 2.68 – 2.53 (m, 2H, $ArCH_2$), 1.53 (s, 3H, CCH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8 (C(O)O), 158.1 (ArCO), 143.9 (ArCN), 130.0 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 127.3 (ArCC), 125.3 (ArCH), 120.3 (ArCH), 109.4 (ArCH), 87.8 (CH_2C), 44.0 ($ArCH_2$), 41.7 ($CH_2C(O)N$), 37.4 (NCH_3), 26.5 (CCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{18}H_{20}O_2N$ ($[M+H]^+$) 282.1489, found 282.1488; **FT-IR (thin film)** ν_{max} 2980, 2360, 1651, 1596, 1496, 1480, 1459, 1387, 1239, 1217, 1113, 1069, 884, 751, 700, 667 cm^{-1}; **$[\alpha]_D^{25}$** = +81.9 (c=0.87, $CHCl_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 93/7, 1.0 ml/min, λ = 230 nm, t_R (major) = 10.4 min, t_R (minor) = 8.6 min.



(*R*)-*N*,*N*-dibenzyl-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetamide (523) was prepared following **General Procedure J**, (variation from standard conditions: reaction carried out at 40 °C for 4 days), using **(*E*)-*N*,*N*-dibenzyl-4-(2-hydroxyphenyl)-3-methylbut-2-enamide (517)** (74.2 mg, 0.2

mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a colorless oil (49.7 mg, 67%, 98.5:1.5 er).

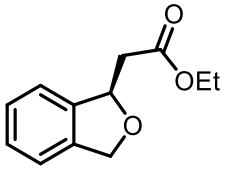
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 6.97 (m, 12H, Ar-H), 6.91 (t, *J* = 7.4 Hz, 1H, Ar-H), 6.72 (d, *J* = 7.9 Hz, 1H, Ar-H), 4.85 (d, *J* = 15.0 Hz, 1H, NCH_2), 4.73 (t, *J* = 16.1 Hz, 1H, NCH_2), 4.42 (dd, *J* = 15.9, 3.7 Hz, 2H, NCH_2), 3.68 (d, *J* = 16.1 Hz, 1H, CH_2C(O)N), 3.22 – 3.13 (m, 1H, CH_2C(O)N), 3.02 (d, *J* = 14.7 Hz, 1H, ArCH_2), 2.93 (d, *J* = 14.7 Hz, 1H, ArCH_2), 1.66 (s, 3H, CCH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.6 (C(O)N), 158.2 (ArCO), 137.1 (ArCCH_2N), 136.6 (ArCCH_2N), 129.1 (ArCH), 128.7 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 127.3 (ArCH), 127.1 (ArCCH_2C), 126.5 (ArCH), 125.5 (ArCH), 120.6 (ArCH), 109.5 (ArCH), 87.7 (CH_2C), 50.4 (NCH_2), 48.2 (NCH_2), 43.7 (ArCH_2), 41.2 (CH_2C(O)N), 27.5 (CCH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{25}H_{26}O_2N$ ($[M+H]^+$) 372.1958, found 372.1953; **FT-IR (thin film)** ν_{max} 3029, 1639, 1480, 1451, 1361, 1328, 1242, 1080, 1029, 958, 884, 751, 699, 655, 619 cm^{-1}; **$[\alpha]_D^{25}$** = +57.1 (c=0.83, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 230 nm, t_R (major) = 20.8 min, t_R (minor) = 17.9 min.



***tert*-Butyl (*R*)-2-(2-ethyl-2,3-dihydrobenzofuran-2-yl)acetate (524)** was prepared following **General Procedure J**, using ***tert*-butyl (*E*)-3-(2-hydroxybenzyl)pent-2-enoate (518)** (52.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 95/5) afforded the title compound as a colorless oil (47.6 mg, 91%, 99.5:0.5 er).

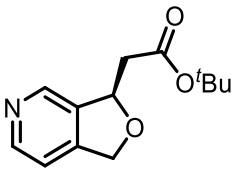
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.04 (m, 2H, Ar-H), 6.81 (td, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 6.77 – 6.70 (m, 1H, Ar-H), 3.38 (dd, *J* = 15.9, 1.1 Hz, 1H, CH_2C(O)O), 3.06 (dt, *J* = 16.1, 1.1 Hz, 1H, CH_2C(O)O), 2.73 – 2.59 (m, 2H, ArCH_2), 1.86 (q, *J* = 7.1 Hz, 2H, CC$H_2$$CH_3$), 1.34 (s, 9H, OC(C$H_3$)$_3$), 0.98 (t, *J* = 7.4 Hz, 3H, CCH_2CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.7 (C(O)O), 159.1 (ArCO), 128.0 (ArCH), 127.0 (ArCC), 125.1 (ArCH), 120.2 (ArCH), 109.4 (ArCH), 88.7 (CH_2C), 80.9 (OC(CH$_3$)$_3$),

44.8 (Ar<u>C</u>H_2), 38.9 (<u>C</u>H_2C(O)O), 32.8 (C<u>C</u>H_2CH_3), 28.0 (OC(<u>C</u>H_3)$_3$), 8.0 (CCH_2<u>C</u>H_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{16}H_{22}O_3Na$ ([M+Na]$^+$) 285.1461, found 285.1461; **FT-IR (thin film)** ν_{max} 3013, 2975, 2930, 1727, 1598, 1482, 1461, 1392, 1368, 1326, 1295, 1246, 1160, 1086, 1016, 1003, 950, 889, 869, 843, 749, 708, 652, 633, 610 cm^{-1}; **[α]D^{25}** = +17.3 (c=0.81, $CHCl_3$); **Chiral HPLC:** Chiralcel AD, hexane/isopropanol = 99.5/0.5, 1.0 ml/min, λ = 230 nm, t_R (major) = 5.3 min, t_R (minor) = 4.7 min.



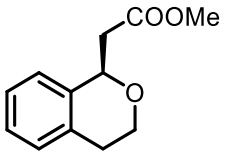
Ethyl (*R*)-2-(1,3-dihydroisobenzofuran-1-yl)acetate (532) was prepared following **General Procedure K**, using **ethyl (*E*)-3-(2-(hydroxymethyl)phenyl)acrylate (531)** (41.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (35.1 mg, 85%, 95:5 er). Data is consistent with the published literature.[52]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.12 (m, 4H, Ar-<u>H</u>), 5.72 – 5.55 (m, 1H, OC<u>H</u>), 5.13 (ddd, J = 12.2, 2.6, 0.8 Hz, 1H, C<u>H</u>$_2$C(O)O), 5.09 – 5.00 (m, 1H, C<u>H</u>$_2$C(O)O), 4.18 (q, *J* = 7.1 Hz, 2H, OC<u>H</u>$_2$CH$_3$), 2.83 – 2.66 (m, 2H, CHOC<u>H</u>$_2$), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.0 (<u>C</u>(O)O), 140.8 (Ar<u>C</u>), 139.3 (Ar<u>C</u>), 128.0 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 121.3 (Ar<u>C</u>H), 121.2 (Ar<u>C</u>H), 80.5 (O<u>C</u>H), 72.8 (<u>C</u>H_2C(O)O), 60.8 (O<u>C</u>H_2CH_3), 41.8 (CHO<u>C</u>H_2), 14.3 (OCH_2<u>C</u>H_3) ppm; **[α]D^{25}** = +32.7 (c=0.24, $CHCl_3$); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 210 nm, t_R (major) = 9.5 min, t_R (minor) = 10.7 min.



***tert*-Butyl (*R*)-2-(1,3-dihydrofuro[3,4-c]pyridin-3-yl)acetate (538)** was prepared following **General Procedure K**, (variation from standard conditions: reaction carried out at 50 °C for 3 days), using ***tert*-butyl (*E*)-3-(4-(hydroxymethyl)pyridin-3-yl)acrylate (535)** (47.3 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (CH_2Cl_2/CH_3OH = 97/3) afforded the title compound as a colorless oil (25.5 mg, 54%, 80:20 er).

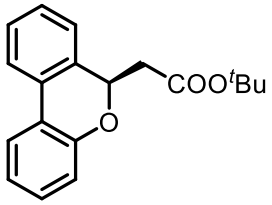
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.45 (m, 2H, Ar-H), 7.16 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar-H), 5.62 (tt, *J* = 6.3, 2.1 Hz, 1H, CH), 5.09 (ddd, *J* = 13.7, 2.6, 1.0 Hz, 1H, CH_2), 5.00 (ddd, *J* = 13.7, 1.6, 0.9 Hz, 1H, CH_2), 2.70 (d, *J* = 6.2 Hz, 2H, CH_2), 1.40 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.5 (C(O)O), 148.9 (ArC), 148.7 (ArCH), 143.4 (ArCH), 137.2 (ArC), 116.5 (ArCH), 81.2 ($C(CH_3)_3$), 79.2 (CH), 72.1 (CH_2), 42.4 (CH_2), 28.1 ($C(CH_3)_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{18}O_3N$ ($[M+H]^+$) 236.1281, found 236.1282; **FT-IR (thin film)** ν_{max} 2966, 2360, 1780, 1727, 1592, 1457, 1422, 1394, 1368, 1307, 1279, 1250, 1219, 1151, 1071, 1029, 1003, 844, 756, 695, 660, 609 cm^{-1}; **$[\alpha]_D^{25}$** = +5.3 (c=0.49, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 210 nm, t_R (major) = 31.4 min, t_R (minor) = 23.2 min.



Methyl (*R*)-2-(isochroman-1-yl)acetate (539) was prepared following **General Procedure K**, (variation from standard conditions: reaction carried out in 2-Me THF (0.5M) with 10% cat. **534** at 50 °C for 3 days), using **methyl (*E*)-3-(2-(2-hydroxyethyl)phenyl)acrylate (536)** (41.2 mg, 0.2 mmol, 1.0

eq). Purification by silica gel chromatography (pentane/Et_2O = 4/1) afforded the title compound as a colorless oil (33.8 mg, 82%, 90:10 er). Data is consistent with the published literature.[57]

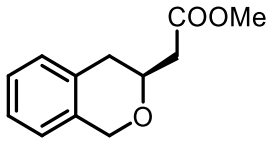
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 2H, Ar-H), 7.15 – 7.09 (m, 1H, Ar-H), 7.08 – 7.01 (m, 1H, Ar-H), 5.25 (dd, *J* = 9.6, 3.5 Hz, 1H, CH), 4.13 (ddd, *J* = 11.5, 5.3, 4.2 Hz, 1H, OCH_2CH_2), 3.82 (ddd, *J* = 11.4, 9.1, 4.0 Hz, 1H, OCH_2CH_2), 3.77 (s, 3H, CH_3), 3.05 – 2.93 (m, 1H, OCH_2CH_2), 2.90 (dd, *J* = 15.2, 3.5 Hz, 1H, $CH_2C(O)O$), 2.82 – 2.68 (m, 2H, $CH_2C(O)O$ and OCH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.8, (C(O)O), 136.8 (ArC), 134.0 (ArC), 129.2 (ArCH), 126.8 (ArCH), 126.4 (ArCH), 124.6 (ArCH), 73.0 (CH), 63.2 (OCH_2CH_2), 52.0 (CH_3), 41.7 ($CH_2C(O)O$), 28.9 (OCH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}O_3$ ($[M+H]^+$) 207.1016, found 207.1018; **$[\alpha]_D^{25}$** = +93.8 (c=0.36, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 210 nm, t_R (major) = 23.0 min, t_R (minor) = 19.4 min.



***tert*-Butyl (*R*)-2-(6H-benzo[c]chromen-6-yl)acetate (540)** was prepared following **General Procedure K**, (variation from standard conditions: reaction carried out with 10% cat. **534** in 0.025M 2-Me-THF at –22 °C), using ***tert*-butyl (*E*)-3-(2'-hydroxy-[1,1'-biphenyl]-2-yl)acrylate (537)** (59.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 9/1) afforded the title compound as a white solid (57.4 mg, 97%, 87.5:12.5 er).

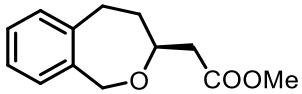
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (ddd, *J* = 8.1, 5.0, 1.3 Hz, 2H, Ar-H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H, Ar-H), 7.29 (td, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.27 – 7.22 (m, 1H, Ar-H), 7.18 (ddt, *J* = 7.6, 1.4, 0.6 Hz, 1H, Ar-H), 7.06 (td, *J* = 7.5, 1.3 Hz, 1H, Ar-H), 6.98 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 5.67 (dd, *J* = 9.0, 5.1 Hz, 1H, CH), 2.85 (dd, *J* = 14.9, 9.0 Hz, 1H, $CH_2C(O)O$), 2.62 (dd, *J* = 14.9, 5.1 Hz, 1H, $CH_2C(O)O$), 1.49 (s, 9H, $C(CH_3)_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.6 (C(O)O), 152.5 (ArC), 133.4 (ArC),

129.8 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 124.9 (Ar<u>C</u>H), 123.1 (Ar<u>C</u>H), 122.4 (Ar<u>C</u>H), 122.24 (Ar<u>C</u>), 122.23 (Ar<u>C</u>H), 118.3 (Ar<u>C</u>H), 81.1 (<u>C</u>(CH_3)$_3$), 74.5 (C<u>H</u>), 41.5 (<u>C</u>H_2C(O)O), 28.2 (C(<u>C</u>H_3)$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{19}H_{20}O_3Na$ ([M+Na]$^+$) 319.1305, found 319.1305; **FT-IR (thin film)** ν_{max} 2977, 1727, 1607, 1593, 1485, 1456, 1440, 1392, 1367, 1301, 1247, 1199, 1150, 1123, 1098, 1041, 1020, 959, 842, 807, 755, 725, 645, 617 cm^{-1}; **m.p.**: 58-60 °C; **[α]D^{25}** = +33.1 (c=1.08, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 240 nm, t_R (major) = 9.9 min, t_R (minor) = 28.6 min.



Methyl (*S*)-2-(isochroman-3-yl)acetate (544) was prepared following **General Procedure K**, (variation from standard conditions: reaction carried out in 2-Me THF (0.5M) with 10% cat. **534** for 3 days), using **methyl (*E*)-4-(2-(hydroxymethyl)phenyl)but-2-enoate (541)** (41.1 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 17/3) afforded the title compound as a pale-yellow oil (38.6 mg, 94%, 92:8 er).

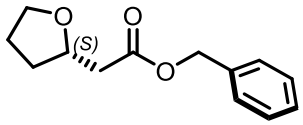
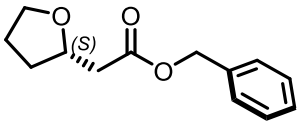
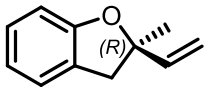
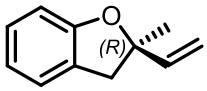
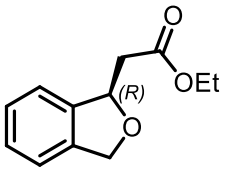
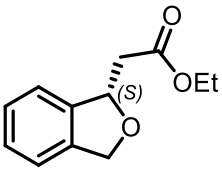
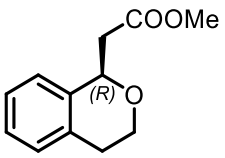
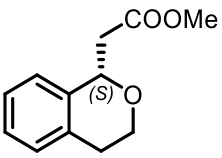
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 2H, Ar-<u>H</u>), 7.10 (dd, *J* = 5.4, 3.6 Hz, 1H, Ar-<u>H</u>), 7.00 (dd, *J* = 5.4, 3.6 Hz, 1H, Ar-<u>H</u>), 4.84 (s, 2H, ArC<u>H</u>$_2$O), 4.17 (tdd, *J* = 7.7, 6.5, 5.2 Hz, 1H, C<u>H</u>), 3.74 (s, 3H, C<u>H</u>$_3$), 2.80 (d, *J* = 7.0 Hz, 2H, ArC<u>H</u>$_2$CH), 2.72 (dd, *J* = 15.4, 7.8 Hz, 1H, C<u>H</u>$_2$C(O)O), 2.60 (dd, *J* = 15.4, 5.1 Hz, 1H, C<u>H</u>$_2$C(O)O) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.6 (<u>C</u>(O)O), 134.4 (Ar<u>C</u>), 132.7 (Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 124.3 (Ar<u>C</u>H), 71.6 (<u>C</u>H), 68.4 (Ar<u>C</u>H_2O), 51.9 (<u>C</u>H_3), 41.0 (<u>C</u>H_2C(O)O), 33.7 (Ar<u>C</u>H_2CH) ppm; **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}O_3$ ([M+H]$^+$) 207.1016, found 207.1017; **FT-IR (thin film)** ν_{max} 3023, 2952, 1738, 1493, 1437, 1374, 1344, 1300, 1246, 1217, 1160, 1098, 1060, 1037, 994, 863, 753, 672, 643, 632, 611 cm^{-1}; **[α]D^{25}** = −92.5 (c=0.71, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 210 nm, t_R (major) = 18.6 min, t_R (minor) = 7.9 min.

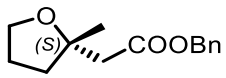
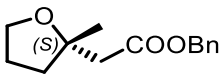
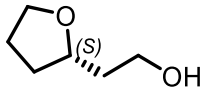
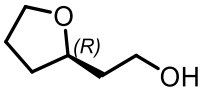
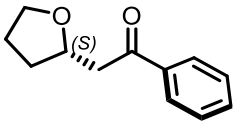
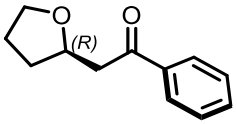


Methyl (*S*)-2-(1,3,4,5-tetrahydrobenzo[c]oxepin-3-yl)acetate (545) was prepared following **General Procedure K**, (variation from standard conditions: reaction carried out in 2-Me THF (0.5M) with 10% cat. **534** at 60 °C for 3 days), using **methyl (*E*)-5-(2-(hydroxymethyl)phenyl)pent-2-enoate (542)** (43.2 mg, 0.2 mmol, 1.0 eq). Purification by silica gel chromatography (pentane/Et_2O = 17/3) afforded the title compound as a colorless oil (12.1 mg, 28%, 91:9 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.10 (m, 4H, Ar-H), 4.69 (d, *J* = 3.5 Hz, 2H, ArCH_2O), 4.23 (tdd, *J* = 10.3, 5.0, 2.0 Hz, 1H, CH), 3.71 (s, 3H, CH_3), 3.12 (ddd, *J* = 14.4, 12.1, 2.0 Hz, 1H, CHCH_2CH_2), 2.88 (ddd, *J* = 15.0, 6.8, 1.9 Hz, 1H, CHCH_2CH_2), 2.60 (dd, *J* = 15.3, 8.1 Hz, 1H, CH_2C(O)O), 2.44 (dd, *J* = 15.3, 5.0 Hz, 1H, CH_2C(O)O), 1.95 (ddt, *J* = 14.0, 6.8, 2.0 Hz, 1H, CHCH_2CH_2), 1.60 (dddd, *J* = 14.1, 12.3, 10.6, 1.9 Hz, 1H, CHCH_2CH_2) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.9 (C(O)O), 142.0 (ArC), 139.9 (ArC), 129.2 (ArCH), 128.6 (ArCH), 128.1 (ArCH), 126.4 (ArCH), 81.7 (CH), 74.0 (ArCH_2O), 51.8 (CH_3), 42.0 (CH_2C(O)O), 34.8 (CHCH_2CH_2), 34.3 (CHCH_2CH_2) ppm; **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O_3$ ([M+H]$^+$) 221.1172, found 221.1174; **FT-IR (thin film)** ν_{max} 2951, 2848, 1738, 1437, 1361, 1282, 1203, 1150, 1121, 1086, 1063, 1028, 755, 671, 625 cm^{-1}; **$[\alpha]_D^{25}$** = +1.6 (c=0.21, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 220 nm, t_R (major) = 14.2 min, t_R (minor) = 9.4 min.

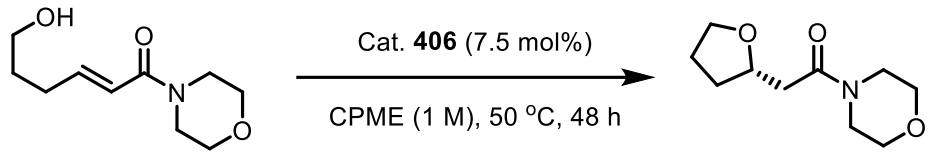
4.3.6 Determination of stereochemical configuration

Compound	This work	Literature
416		
	$[\alpha]_D^{25}$ = +6.4 (c=0.40, $CHCl_3$) er = 94:6	$[\alpha]_D^{25}$ = +3.1 (c = 0.40, $CHCl_3$) er = 97:3 [57]
529		
	$[\alpha]_D^{25}$ = +6.0 (c=0.32, $CHCl_3$) er = 99:1	$[\alpha]_D^{23}$ = +9.4 (c=1.0, $CHCl_3$) er = 90.5:9.5 [59]
532		
	$[\alpha]_D^{25}$ = +32.7 (c=0.24, $CHCl_3$) er = 95:5	$[\alpha]_D^{26}$ = −35.8 (c=0.40, $CHCl_3$) er = 90.5:9.5 [52]
539		
	$[\alpha]_D^{25}$ = +93.8 (c=0.36, $CHCl_3$) er = 90:10	$[\alpha]_D^{25}$ = −51.5 (c = 0.50, $CHCl_3$) er = 67:33 [57]

Compound	This work	Literature
431		
	$[\alpha]_D^{25}$ = +6.8 (c=0.64, $CHCl_3$) er = 94:6	$[\alpha]_D^{25}$ = +4.5 (c = 0.30, $CHCl_3$) er = 95:5 [58]
506		
	$[\alpha]_D^{25}$ = +11.0 (c=0.23, $CHCl_3$) er = 96.5:3.5	$[\alpha]_D^{26}$ = −5.9 (c=2.96, EtOH) er = 97:3 [60]
503		
	$[\alpha]_D^{23}$ = +2.3 (c=4.98, CH_2Cl_2) er = 92.5:7.5	$[\alpha]_D^{23}$ = −3.5 (c=4.98, CH_2Cl_2) er = 97.5:2.5 [60]

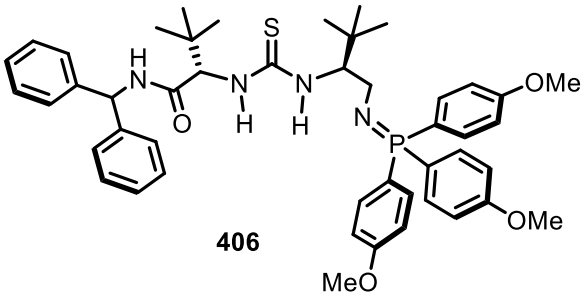
4.3.7 Scale up and Derivatisation

Preparative scale synthesis of 418



414; 41.2 mmol

418
7.6 g, 93%, 95:5 e.r.
after recrystallisation
96.5:3.5 e.r.



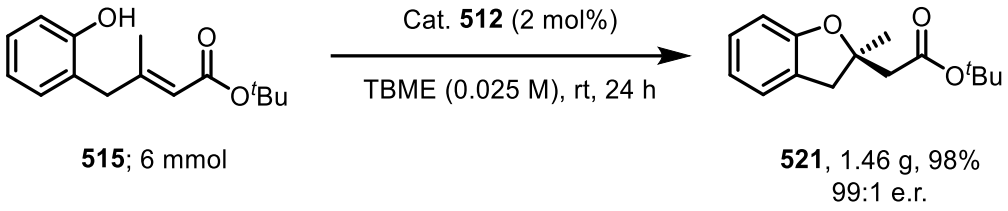
406

CPME (0.025 M, 124 mL) was added to the BIMP catalysts precursor (1.484 g, 3.09 mmol, 0.075 eq) and tris(4-methoxyphenyl)phosphine (1.088 g, 3.09 mmol, 0.075 eq) in a 250 mL RBF under N_2 at room temperature. The reaction mixture was stirred for 24 hours before evaporating to dryness under reduced pressure. The iminophosphorane product was confirmed by HRMS and TLC and used as crude for enantioselective reactions without any purification.

Alcohol **414** (8.21 g, 41.2 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst (3.09 mmol, 0.075 eq) in CPME (1M, 41.2 mL) under N_2 at 50 °C. The reaction mixture was stirred at room temperature for 48 hours before quenching with 1M AcOH in CH_2Cl_2 (20 mL). The resulting mixture was then evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/acetone = 3/2) afforded **418** as an off-white solid (7.60 g, 93%, 95:5 er).

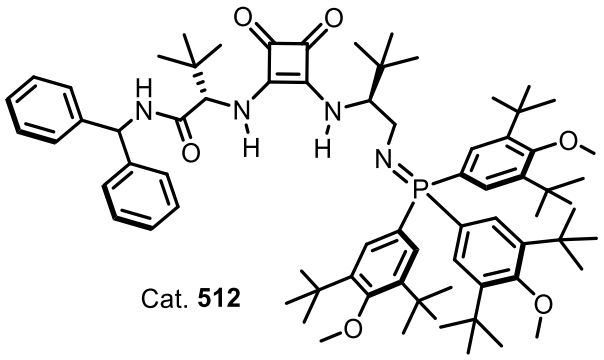
Material was refluxed in the minimum volume of hexane (approximately 100 mL) before carefully cooling down to room temperature. The crushed out solid was filtered, washed with minimum volume of cold hexane (approximately 10 mL) and dried under reduced pressure to afford **418** in 96.5:3.5 er.

Preparative scale synthesis of 521



515; 6 mmol

521, 1.46 g, 98%
99:1 e.r.

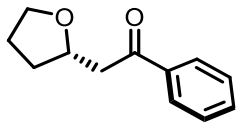


Cat. **512**

THF (0.025 M, 4.8 mL) was added to the BIMP catalysts precursors (62 mg, 0.12 mmol, 0.02 eq) and tris(4-methoxyphenyl)phosphine (82.7 mg, 0.12 mmol, 0.02 eq) in a 10 mL RBF under N_2 at room temperature. The reaction mixture was stirred for 24 hours before evaporating to dryness under reduced pressure. The iminophosphorane product was confirmed by HRMS and TLC and used as crude for enantioselective reactions without any purification.

Alcohol **515** (1.49 g, 6.0 mmol, 1.0 eq) was added to a solution of the *in situ* generated catalyst (0.12 mmol, 0.02 eq) in TBME (0.025M, 240 mL) under N_2 at room temperature. The reaction mixture was stirred at room temperature for 24 hours before quenching with 1M AcOH in CH_2Cl_2 (120 mL). The resulting mixture was then evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 95/5) afforded **521** as a colorless oil (1.46 g, 98%, 99:1 er).

Derivatisation

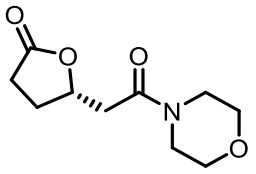


(*S*)-1-phenyl-2-(tetrahydrofuran-2-yl)ethan-1-one (503) was prepared according to the following procedure. $CeCl_3$ (296.0 mg, 1.2 mmol, 3.0 eq) (anhydrous grade, stored and weighed in a glove box) was stirred at 90 °C for 30 mins and 135 °C for 2 hours under reduced pressure before cooling down to 0 °C. Anhydrous THF (2.4 mL) was added to the reaction vessel under N_2 at 0 °C. The resulting slurry was warmed to room temperature and stirred for 24 hours under N_2 before cooling down to −78 °C. Phenylmagnesium bromide (1M in THF) (1.0 mL, 1.0 mmol, 2.5 eq) was added dropwise under N_2 at −78 °C. The resulting mixture was stirred at −78 °C for 1 hour, affording a solution of phenylcerium(III) chloride which was used as crude for the addition without any purification.

A solution of **(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethan-1-one (418)** (79.7 mg, 0.4 mmol, 1.0 eq, 96.5:3.5 er) in anhydrous THF (0.4 mL) was added dropwise to the phenylcerium(III) chloride under N_2 at −78 °C. The resulting mixture was stirred at −78 °C for 2 hours before quenching with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 7/3) afforded the title compound as a colorless oil (57.0 mg, 75%, 92.5:7.5 er). Data is consistent with the published literature.[60]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H, Ar-H), 7.59 – 7.49 (m, 1H, Ar-H), 7.49 – 7.39 (m, 2H, Ar-H), 4.39 (dq, *J* = 7.6, 6.4 Hz, 1H, CH), 3.88 (dt, *J* = 8.3, 6.8 Hz, 1H, $OCH_2CH_2CH_2$), 3.79 – 3.68 (m, 1H, $OCH_2CH_2CH_2$), 3.38 (dd, *J* = 16.3, 6.1 Hz, 1H, $CH_2C(O)$), 3.04 (dd, *J* = 16.2, 6.7 Hz, 1H, $CH_2C(O)$), 2.18 (ddt, *J* = 12.3, 7.9, 6.1 Hz, 1H, $OCH_2CH_2CH_2$), 1.91 (dqd, *J* = 9.5, 7.2, 2.1 Hz, 2H, $OCH_2CH_2CH_2$), 1.55 (ddt, *J* = 12.4, 8.8, 7.7 Hz, 1H, $OCH_2CH_2CH_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 198.5 (C(O)), 137.2 (ArC), 133.2 (ArCH), 128.7 (ArCH), 128.3 (ArCH), 75.5 (CH), 67.9 ($OCH_2CH_2CH_2$), 44.7 ($CH_2C(O)$), 31.7 ($OCH_2CH_2CH_2$), 25.7 ($OCH_2CH_2CH_2$) ppm; **HRMS** (ESI) m/z

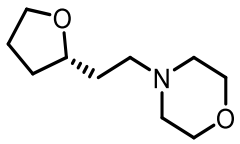
calcd. for $C_{12}H_{15}O_2$ ([M+H]$^+$) 191.1067, found 191.1067; **FT-IR (thin film)** ν_{max} 2871, 1683, 1598, 1580, 1449, 1280, 1214, 1064, 1002, 926, 752, 690, 668 cm^{-1}; **[α]$_D^{23}$** = +2.3 (c=4.98, CH_2Cl_2); **Chiral HPLC:** Chiralcel IA, hexane/isopropanol = 99/1, 1.0 ml/min, λ = 280 nm, t_R (major) = 22.4 min, t_R (minor) = 20.7 min.



(*S*)-5-(2-morpholino-2-oxoethyl)dihydrofuran-2(3H)-one (504) was prepared according to the following procedure. According to the modified literature procedure reported by H. Y. Kwon *et. al.*, [61] $NaIO_4$ (0.69 g, 3.2 mmol, 8 eq) and $RuCl_3 \cdot 3H_2O$ (2.1 mg, 0.008 mmol, 0.02 eq) were added to a solution of **(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethan-1-one (418)** (79.7 mg, 0.4 mmol, 1.0 eq, 96.5:3.5 er) in a mixture of CCl_4 (6.7 mL), MeCN (6.7 mL) and H_2O (10 mL) under air at room temperature. The resulting mixture was stirred for 24 hours at room temperature before extracting with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/acetone = 11:9) afforded the title compound as a white solid (29.0 mg, 34%, >99.5:0.5 er).

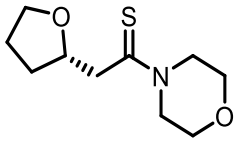
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 – 4.83 (m, 1H, C<u>H</u>), 3.74 – 3.52 (m, 6H, NC<u>H</u>$_2$C<u>H</u>$_2$O), 3.44 (td, *J* = 4.4, 1.3 Hz, 2H, NC<u>H</u>$_2$C<u>H</u>$_2$O), 2.88 (dd, *J* = 15.8, 5.5 Hz, 1H, C<u>H</u>$_2$C(O)N), 2.63 – 2.47 (m, 4H, C<u>H</u>$_2$C(O)N and C<u>H</u>$_2$C<u>H</u>$_2$C(O)O), 2.04 – 1.88 (m, 1H, C<u>H</u>$_2$CH$_2$C(O)O) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.7 (<u>C</u>(O)), 167.6 (<u>C</u>(O)), 77.5 (<u>C</u>H), 66.8 (N<u>C</u>H$_2$<u>C</u>H$_2$O), 66.6 (N<u>C</u>H$_2$<u>C</u>H$_2$O), 46.2 (N<u>C</u>H$_2$<u>C</u>H$_2$O), 42.0 (N<u>C</u>H$_2$<u>C</u>H$_2$O), 38.5 (<u>C</u>H$_2$C(O)N), 28.6 (<u>C</u>H$_2$<u>C</u>H$_2$C(O)O), 28.3 (<u>C</u>H$_2$<u>C</u>H$_2$C(O)O) ppm; **HRMS** (ESI) m/z calcd. for $C_{10}H_{16}O_4N$ ([M+H]$^+$) 214.1074, found 214.1076; **FT-IR (thin film)** ν_{max} 3500, 3018, 2922, 2857, 2349, 1769, 1637, 1444, 1353, 1302, 1274, 1233, 1180, 1146, 1114, 1069, 1036, 963, 920, 851, 752, 665, 652, 632, 613 cm^{-1}; **m.p.**: 78-79 °C; **[α]$_D^{25}$** = +2.9 (c=0.70, $CHCl_3$); **Chiral**

GC: Supelco β-dex™ 325, 30 m, 0.25 mm, 0.25 μm, carrier gas He (flow rate 20 cm/s); column temperature: 30 ℃ for 10 mins, then ramp 20 ℃/min to 230 ℃ for 10 min, then 230 ℃ for 40 mins; t_R (single enantiomer) = 23.84 min.



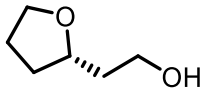
(*S*)-4-(2-(tetrahydrofuran-2-yl)ethyl)morpholine (502) was prepared according to the following procedure. According to the modified literature procedure reported by G. Barbe *et. al.*, [62] Tf_2O (124.2 mg, 0.44 mmol, 1.1 eq) was added to a solution of **(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethan-1-one (418)** (79.7 mg, 0.40 mmol, 1.0 eq, 96.5:3.5 er) in CH_2Cl_2 (1.6 mL) under N_2 at room temperature. The resulting mixture was stirred for 5 mins at room temperature before adding Hantzsch ester (254.0 mg, 1.0 mmol, 2.5 eq). The mixture was stirred for 16 hours before quenching with MeOH (1.6 mL) and 12M NaOH aqueous solution (0.4 mL). The resulting mixture was further stirred for 2 hours. The aqueous layers was extracting with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/MeOH = 1/0 to 97.5/2.5) afforded the title compound as a colorless oil (43.2 mg, 59%, 98:2 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 – 3.77 (m, 2H, C<u>H</u> and C<u>H</u>$_2$), 3.74 – 3.64 (m, 5H, C<u>H</u>$_2$), 2.43 (ttt, *J* = 17.8, 12.2, 5.6 Hz, 6H, C<u>H</u>$_2$), 2.05 – 1.93 (m, 1H, C<u>H</u>$_2$), 1.92 – 1.80 (m, 2H, C<u>H</u>$_2$), 1.80 – 1.60 (m, 2H, C<u>H</u>$_2$), 1.52 – 1.39 (m, 1H, C<u>H</u>$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 77.7 (<u>C</u>H), 67.8 (<u>C</u>H$_2$), 67.0 (<u>C</u>H$_2$), 56.3 (<u>C</u>H$_2$), 53.9 (<u>C</u>H$_2$), 32.8 (<u>C</u>H$_2$), 31.7 (<u>C</u>H$_2$), 25.8 (<u>C</u>H$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{10}H_{20}O_2N$ ($[M+H]^+$) 186.1489, found 186.1488; **FT-IR (thin film)** ν_{max} 3486, 2950, 2853, 1656, 1448, 1360, 1275, 1208, 1142, 1117, 1071, 1007, 916, 865, 753, 610 cm^{-1}; $[\alpha]_D^{25}$ = +9.5 (c=0.89, $CHCl_3$); **Chiral GC:** Supelco β-dex™ 325, 30 m, 0.25 mm, 0.25 μm, carrier gas He (flow rate 20 cm/s); column temperature: 30 ℃ for 10 mins, then ramp 20 ℃/min to 230 ℃ for 10 min, then 230 ℃ for 40 mins; t_R (major) = 33.64 min, t_R (minor) = 32.88 min.



(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethane-1-thione (505) was prepared according to the following procedure. According to the modified literature procedure reported by L. K. Ransborg *et. al.*,[63] Lawesson's reagent (66.8 mg, 0.17 mmol, 0.55 equiv) was added to a solution of **(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethan-1-one (418)** (59.8 mg, 0.3 mmol, 1.0 equiv, 96.5:3.5 er) in anhydrous THF (0.7 mL) under N_2 at room temperature. The reaction mixture was stirred at 60 °C for 3 days before evaporating to dryness under reduced pressure. Purification by silica gel chromatography (CH_2Cl_2/EtOAc = 9:1) afforded the title compound as a colorless oil (29.7 mg, 46%, 97:3 er).

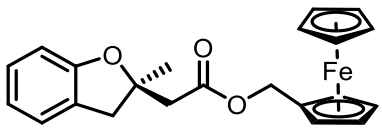
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (ddd, *J* = 13.6, 5.7, 3.3 Hz, 1H), 4.29 (qd, *J* = 7.2, 4.7 Hz, 1H, C<u>H</u>), 4.09 (ddd, *J* = 13.5, 7.6, 3.4 Hz, 1H, NC<u>H$_2$</u>C<u>H$_2$</u>O), 4.01 – 3.89 (m, 1H, NC<u>H$_2$</u>C<u>H$_2$</u>O), 3.85 – 3.62 (m, 7H, OC<u>H$_2$</u>CH$_2$CH$_2$ and NC<u>H$_2$</u>C<u>H$_2$</u>O), 3.17 – 3.01 (m, 2H, C<u>H$_2$</u>C(S)), 2.18 – 2.05 (m, 1H, OCH$_2$CH$_2$C<u>H$_2$</u>), 1.88 (p, *J* = 7.0 Hz, 2H, OCH$_2$C<u>H$_2$</u>CH$_2$), 1.76 – 1.62 (m, 1H, OCH$_2$CH$_2$C<u>H$_2$</u>) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 200.3 (<u>C</u>(S)), 79.0 (<u>C</u>H), 68.1 (NC<u>H$_2$</u>C<u>H$_2$</u>O or OC<u>H$_2$</u>CH$_2$CH$_2$), 66.7 (NC<u>H$_2$</u>C<u>H$_2$</u>O or OC<u>H$_2$</u>CH$_2$CH$_2$), 66.6 (NC<u>H$_2$</u>C<u>H$_2$</u>O or OC<u>H$_2$</u>CH$_2$CH$_2$), 51.1 (NC<u>H$_2$</u>C<u>H$_2$</u>O or OC<u>H$_2$</u>CH$_2$CH$_2$), 50.3 (NC<u>H$_2$</u>C<u>H$_2$</u>O or OC<u>H$_2$</u>CH$_2$CH$_2$), 49.0 (<u>C</u>H$_2$C(S)), 31.5 (OCH$_2$CH$_2$<u>C</u>H$_2$), 25.6 (OCH$_2$<u>C</u>H$_2$CH$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_{10}H_{18}O_2NS$ ([M+H]$^+$) 216.1053, found 206.1053; **FT-IR (thin film)** ν_{max} 3774, 3706, 3487, 2919, 2855, 2349, 2283, 1711, 1691, 1658, 1641, 1548, 1492, 1433, 1281, 1199, 1116, 1090, 1063, 1024, 871, 771, 718, 664, 652, 639, 621, 612 cm^{-1}; **$[\alpha]_D^{25}$** = +18.6 (c=0.58, $CHCl_3$); **Chiral HPLC:** Chiralcel OD, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 280 nm, t_R (major) = 19.7 min, t_R (minor) = 24.0 min.



(*S*)-2-(Tetrahydrofuran-2-yl)ethan-1-ol (506) was prepared according to the following procedure. According to the modified literature procedure reported by M. Szostak *et. al.*, [64] to an oven-dried round bottom flask equipped with a magnetic stirrer bar was added **(*S*)-1-morpholino-2-(tetrahydrofuran-2-yl)ethan-1-one (418)** (79.7 mg, 0.4 mmol, 1.0 eq, 96.5:3.5 er), Samarium(II) iodide (0.1M THF solution) (32 mL, 3.2 mmol, 8.0 eq), degassed Et_3N (4 mL) and degassed H_2O (0.52 mL) under N_2 at room temperature. The resulting mixture was stirred vigorously under N_2 at room temperature. After 18 hours, air was bubbled through the mixture to quench the reaction. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and 1M NaOH (10 mL) before extracting with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 3:7) afforded the title compound as a colorless oil (21.7 mg, 47%, 96.5:3.5 er). Data is consistent with the published literature.[60]

The reaction was repeated in a 0.05 mmol scale and 1.0 mL reaction mixture was taken after air bubbling for GC analysis. GC yield and er was determined with DMSO as an external standard to be 98% yield and 96.5:3.5 er.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (tdd, *J* = 8.0, 6.4, 4.3 Hz, 1H, C<u>H</u>), 3.88 (ddd, *J* = 8.3, 7.3, 6.3 Hz, 1H, C<u>H</u>$_2$), 3.80 – 3.68 (m, 3H, C<u>H</u>$_2$), 2.64 (brs, 1H, O<u>H</u>), 2.07 – 1.95 (m, 1H, C<u>H</u>$_2$), 1.95 – 1.82 (m, 2H, C<u>H</u>$_2$), 1.80 – 1.67 (m, 2H, C<u>H</u>$_2$), 1.52 (ddt, *J* = 11.9, 8.7, 7.7 Hz, 1H, C<u>H</u>$_2$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 79.3 (<u>C</u>H), 68.0 (<u>C</u>H$_2$), 61.7 (<u>C</u>H$_2$), 37.4 (<u>C</u>H$_2$), 31.8 (<u>C</u>H$_2$), 25.6 (<u>C</u>H$_2$) ppm; **HRMS** (ESI) m/z calcd. for $C_6H_{13}O_2$ ($[M+H]^+$) 117.0910, found 117.0912; **FT-IR (thin film)** ν_{max} 3020, 2922, 2851, 1434, 1312, 1216, 1029, 759, 650, 630, 608 cm^{-1}; **$[\alpha]_D^{25}$** = +11.0 (c=0.23, $CHCl_3$); **Chiral GC:** Supelco β-dex™ 325, 30 m, 0.25 mm, 0.25 μm, carrier gas He (flow rate 20 cm/s); column temperature: 30 ℃ for 10 mins, then ramp 20 ℃/min to 230 ℃ for 10 min, then 230 ℃ for 40 mins; t_R (major) = 27.56 min, t_R (minor) = 27.65 min.



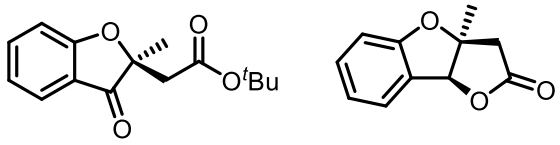
Ferrocene-methyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (525) was prepared according to the following procedure. Trifluoroacetic acid (4.3 mL, 7 mL/mmol) was added dropwise to a solution of the ***tert*-butyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (521)** (150.7 mg, 0.61 mmol, 1.0 eq, 99:1 er) in CH_2Cl_2 (4.3 mL, 7 mL/mmol) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. Volatiles were removed under a stream of nitrogen gas to afford (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetic acid which was used as crude for next step without any purification.

Thionyl chloride (217.7 mg, 1.83 mmol, 3.0 eq) and a few drops of DMF was added dropwise to a solution of the (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetic acid in CH_2Cl_2 (1.6 mL, 0.4M) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. Volatiles were removed under a stream of nitrogen gas to afford (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetyl chloride which was used as crude for next step without any purification.

Ferrocenemethanol (158.2 mg, 0.74 mmol, 1.2 eq) and Et_3N (74.9 mg, 0.74 mmol, 1.2 eq) was added to a solution of the (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetyl chloride in CH_2Cl_2 (2.6 mL) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours before quenching with saturated aqueous solution of NH_4Cl (10 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et2O = 4/1) afforded the title compound as a pale-yellow oil (82.5 mg, 35%, 96:4 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.07 (m, 2H, Ar-H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 6.75 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar-H), 4.90 (s, 2H, OCH_2), 4.29 (s, 1H, Ar-H (ferrocene)), 4.25 (dq, *J* = 2.6, 1.5 Hz, 2H, Ar-H (ferrocene)), 4.20 – 4.15 (m, 5H, Ar-H (ferrocene)), 4.14 (s, 1H, Ar-H (ferrocene)), 3.41 – 3.33 (m, 1H, CH_2C(O)O), 3.06 – 2.97 (m, 1H, CH_2C(O)O), 2.83 – 2.70 (m, 2H, ArCH_2), 1.56 (s, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.1 (C(O)O), 158.4 (ArCO), 128.1 (ArCH), 126.6 (ArCC),

125.2 (Ar<u>C</u>H), 120.5 (Ar<u>C</u>H), 109.7 (Ar<u>C</u>H), 86.1 (Ar<u>C</u> (ferrocene) or O<u>C</u>), 81.1 (Ar<u>C</u> (ferrocene) or O<u>C</u>), 69.6 (Ar<u>C</u>H (ferrocene)), 69.4 (Ar<u>C</u>H (ferrocene)), 68.9 (Ar<u>C</u>H (ferrocene)), 68.6 (Ar<u>C</u>H (ferrocene)), 68.5 (Ar<u>C</u>H (ferrocene)), 68.4 (Ar<u>C</u>H (ferrocene)), 68.0 (Ar<u>C</u>H (ferrocene)), 63.1 (O<u>C</u>H$_2$), 45.2 (Ar<u>C</u>H$_2$), 41.3 (<u>C</u>H$_2$C(O)O), 26.6 ppm; **HRMS** (ESI) m/z calcd. for $C_{22}H_{22}O_3Fe$ ([M+H+Na]$^+$) 414.0364, found 414.0364; **FT-IR (thin film)** ν_{max} 2980, 1731, 1598, 1481, 1461, 1378, 1329, 1242, 1190, 1170, 1106, 1064, 1040, 1000, 924, 885, 820, 751, 710, 625 cm^{-1}; **$[\alpha]_D^{25}$** = +5.4 (c=1.51, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 98/2, 1.0 ml/min, λ = 280nm, t_R (major) = 11.7 min, t_R (minor) = 13.0 min.



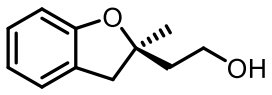
526 **527**

***tert*-Butyl (*S*)-2-(2-methyl-3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (526)** and **(3a*S*,8b*S*)-3a-methyl-3a,8b-dihydrofuro[3,2-b]benzofuran-2(3H)-one (527)** were prepared according to the following procedure. To an oven-dried screw-cap vial equipped with a magnetic stirrer bar was added $K_2S_2O_8$ (316.3 mg, 1.17 mmol, 3.0 equiv), $CuSO_4$ (62.3 mg, 0.39 mmol, 1.0 equiv), ***tert*-butyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (521)** (97.2 mg, 0.39 mmol, 1.0 equiv, 99:1 er), MeCN (14 mL) and H_2O (14 mL). The vial was closed and heated to 80 °C. The resulting mixture was stirred at 80 °C for 1 hour. After cooled to room temperature, the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL). The resulting mixture was dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 95:5) afforded **526** as a white solid (22.8 mg, 23%, 96.5:3.5 er) and (pentane/Et_2O = 1:1) afforded **527** as a white solid (38.5 mg, 52%, 99:1 er).

526: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 1H, Ar-<u>H</u>), 7.60 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H, Ar-<u>H</u>), 7.11 – 7.05 (m, 2H, Ar-<u>H</u>), 3.03 (d, *J* = 15.7 Hz, 1H, C<u>H</u>$_2$), 2.80 (d, *J* = 15.7 Hz, 1H, C<u>H</u>$_2$), 1.43 (s,

3H, C<u>H</u>$_3$), 1.14 (s, 9H, C(C<u>H</u>$_3$)$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 202.7 (<u>C</u>(O)), 171.2 (C(O)O), 167.6 (Ar<u>C</u>O), 137.8 (Ar<u>C</u>H), 124.8 (Ar<u>C</u>H), 121.9 (Ar<u>C</u>H), 121.0 (Ar<u>C</u>C), 113.5 (Ar<u>C</u>H), 86.9 (O<u>C</u>), 81.7 (<u>C</u>(CH$_3$)$_3$), 43.5 (C<u>H</u>$_2$), 27.7 (C(<u>C</u>H$_3$)$_3$), 22.9 (C<u>H</u>$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{15}H_{18}O_4Na$ ([M+Na]$^+$) 285.1097, found 285.1098; **FT-IR (thin film)** ν_{max} 2980, 2358, 1726, 1614, 1478, 1465, 1393, 1369, 1323, 1307, 1271, 1158, 1121, 1074, 963, 873, 845, 757, 688, 628 cm^{-1}; **m.p.**: 51-53 °C; **[α]$_D^{25}$** = +12.3 (c=0.70, CHCl$_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 97/3, 1.0 ml/min, λ = 254 nm, t_R (major) = 7.6 min, t_R (minor) = 9.0 min.

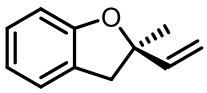
527: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H, Ar-<u>H</u>), 7.33 (ddd, *J* = 8.2, 7.5, 1.4 Hz, 1H, Ar-<u>H</u>), 6.98 (td, *J* = 7.5, 0.9 Hz, 1H, Ar-<u>H</u>), 6.85 (dq, *J* = 8.2, 0.7 Hz, 1H, Ar-<u>H</u>), 5.58 (s, 1H, C<u>H</u>), 3.12 (d, *J* = 18.8 Hz, 1H, C<u>H</u>$_2$), 2.84 (d, *J* = 18.8 Hz, 1H, C<u>H</u>$_2$), 1.62 (s, 3H, C<u>H</u>$_3$) ppm; **^{13}C NMR (101 MHz, CDCl$_3$)** δ 174.4 (<u>C</u>(O)O), 160.2 (Ar<u>C</u>O), 132.2 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 122.9 (Ar<u>C</u>), 121.7 (Ar<u>C</u>H), 111.0 (Ar<u>C</u>H), 89.7 (O<u>C</u>), 88.1 (C<u>H</u>), 41.0 (C<u>H</u>$_2$), 23.0 (C<u>H</u>$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{11}H_9O_3$ ([M-H]$^-$) 189.0546, found 189.0549; **FT-IR (thin film)** ν_{max} 1779, 1614, 1601, 1478, 1468, 1403, 1384, 1329, 1297, 1257, 1192, 1166, 1123, 1075, 996, 940, 896, 877, 840, 822, 753, 702, 624 cm^{-1}; **m.p.**: 79-80 °C; **[α]$_D^{25}$** = −22.5 (c=0.72, CHCl$_3$); **Chiral HPLC:** Chiralcel AD-H, hexane/isopropanol = 90/10, 1.0 ml/min, λ = 280 nm, t_R (major) = 18.6 min, t_R (minor) = 12.9 min.



(*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)ethan-1-ol (528) was prepared according to the following procedure. $LiAlH_4$ (0.54 mL, 2M in THF, 1.5 eq) was added dropwise to a solution of the ***tert*-butyl (*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)acetate (521)** (176.1 mg, 0.71 mmol, 1.0 eq, 99:1 er) in THF (0.71 mL) under N_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 hours before quenching with saturated aqueous solution of NH_4Cl (5 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered and

evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane/Et_2O = 3/2) afforded the title compound as a colorless oil (84.8 mg, 67%, 99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.07 (m, 2H, Ar-H), 6.84 (td, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 6.74 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.90 (ddd, *J* = 12.3, 7.4, 5.5 Hz, 1H, CH_2CH_2), 3.82 (q, *J* = 5.6 Hz, 1H, CH_2CH_2), 3.20 – 3.12 (d, *J* = 15.5 Hz, 1H, $ArCH_2$), 2.99 (d, *J* = 15.5 Hz, 1H, $ArCH_2$), 2.17 – 2.05 (m, 2H, CH_2CH_2 and OH), 1.99 (ddd, *J* = 14.5, 6.2, 5.3 Hz, 1H, CH_2CH_2), 1.48 (s, 3H, CH_3) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.5 (ArCO), 128.3 (ArCH), 126.7 (ArCC), 125.3 (ArCH), 120.6 (ArCH), 109.8 (ArCH), 88.7 (OC), 59.4 (CH_2CH_2), 43.0 (CH_2CH_2), 42.3 ($ArCH_2$), 26.4 (CH_3) ppm; **HRMS** (ESI) m/z calcd. for $C_{11}H_{15}O_2$ ($[M+H]^+$) 179.1067, found 179.1067; **FT-IR (thin film)** ν_{max} 3384, 2929, 1597, 1481, 1461, 1327, 1239, 1123, 1053, 1016, 870, 750, 710, 667 cm^{-1}; **$[\alpha]_D^{25}$** = +6.4 (c=0.56, $CHCl_3$); **Chiral HPLC:** Chiralcel IB, hexane/isopropanol = 95/5, 1.0 ml/min, λ = 230nm, t_R (major) = 10.0 min, t_R (minor) = 11.5 min.



(*R*)-2-Methyl-2-vinyl-2,3-dihydrobenzofuran (529) was prepared according to the following procedure. According to the modified literature procedure reported by L. F. Tietze *et. al.*, [65] 2-nitrophenyl selenocyanate (190.8 mg, 0.84 mmol, 2.0 eq) and $^nBu_3P$ (161.9 mg, 0.80 mmol, 1.91 eq) were added to a solution of **(*R*)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)ethan-1-ol (528)** (74.8 mg, 0.42 mmol, 1.0 eq, 99:1 er) in THF (5.3 mL) under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h before adding additional 2-nitrophenyl selenocyanate (47.7 mg, 0.21 mmol, 0.50 eq) and $^nBu_3P$ (40.5 mg, 0.20 mmol, 0.48 eq). The stirring was continued at 0 °C for 2.5 h before quenching with saturated aqueous solution of $NaHCO_3$ (10 mL) at 0 °C. The aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure affording (*R*)-2-methyl-2-(2-((2-nitrophenyl)selanyl)ethyl)-2,3-dihydrobenzofuran which was used as crude for next step without any purification.

H_2O_2 (30% (w/w) in H_2O, 0.1 mL) was added to a solution of (*R*)-2-methyl-2-(2-((2-nitrophenyl)selanyl)ethyl)-2,3-dihydrobenzofuran in THF (5 mL) under N_2 at 0 °C. additional H_2O_2 (30% (w/w) in H_2O, 0.1 mL) was added every 1 hour to the reaction mixture. After 3 hours, the reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by silica gel chromatography (pentane to pentane/Et_2O = 95/5) afforded the title compound as a pale-yellow oil (42.6 mg, 64%, 99:1 er). Data is consistent with the published literature.[59]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (tq, *J* = 7.7, 0.8 Hz, 2H, Ar-H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 6.81 (dt, *J* = 7.5, 0.9 Hz, 1H, Ar-H), 6.07 (dd, *J* = 17.3, 10.7 Hz, 1H, CHCH$_2$), 5.33 (dd, *J* = 17.3, 1.1 Hz, 1H, CHCH$_2$), 5.11 (dd, *J* = 10.7, 1.1 Hz, 1H, CHCH$_2$), 3.20 (dt, *J* = 15.4, 1.0 Hz, 1H, ArCH$_2$), 3.07 (dt, *J* = 15.4, 1.0 Hz, 1H, ArCH$_2$), 1.57 (s, 3H, CH$_3$) ppm; **^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.0 (ArCO), 141.8 (CHCH$_2$), 128.2 (ArCH), 126.6 (ArCC), 125.2 (ArCH), 120.4 (ArCH), 112.9 (CHCH$_2$), 109.7 (ArCH), 87.6 (OC), 42.2 (ArCH$_2$), 26.2 (CH$_3$) ppm; **HRMS** (ESI) m/z calcd. for $C_{11}H_{13}O$ ($[M+H]^+$) 161.0961, found 161.0961; $[\alpha]_D^{25}$ = 6.0 (c=0.32, $CHCl_3$); **Chiral HPLC:** Chiralcel AS-H hexane/isopropanol = 99.5/0.5, 1.0 ml/min, λ = 280nm, t_R (major) = 3.9 min, t_R (minor) = 4.1 min.

4.4 References for Chapter 4

[1]. Ruppenthal, S.; Brückner, R. Asymmetric Sulfinylations of N-Methylephedrine-Modified Tri- or Tetraalkyl Zincates by Symmetric Diaryl Sulfoxides. *Eur. J. Org. Chem.,* **2018**, 2518-2530.

[2]. Bera, S.; Panda, G. A Rapid Entry to Amino Acid Derived Diverse 3,4-Dihydropyrazines and Dihydro[1,2,3]Triazolo[1,5-A]Pyrazines through 1,3-Dipolar Cycloaddition. *Org. Biomol. Chem.,* **2014,** *12,* 3976-3985.

[3]. Lu, M.; Lu, Q.; Honek, J. F. Squarate-Based Carbocyclic Nucleosides: Syntheses, Computational Analyses and Anticancer/Antiviral Evaluation. *Bioorg. Med. Chem. Lett.,* **2017**, *27*, 282-287.

[4]. Rotstein, D. M.; Gabriel, S. D.; Manser, N.; Filonova, L.; Padilla, F.; Sankuratri, S.; Ji, C.; Rosier, A. de; Dioszegi, M.; Heilek, G.; Jekle, A.; Weller, P.; Berry, P. Synthesis, SAR and Evaluation of [1,4']-Bipiperidinyl-4-Yl-Imidazolidin-2-One Derivatives as Novel CCR5 Antagonists. *Bioorg. Med. Chem. Lett.,* **2010**, *20*, 3219-3222.

[5]. Manna, M. S.; Mukherjee, S. Remarkable Influence of Secondary Catalyst Site on Enantioselective Desymmetrisation of Cyclopentenedione. *Chem. Sci.,* **2014**, *5*, 1627-1633.

[6]. Ahire, M. M.; Pol, M. D.; Kavale, D. S.; Gonnade, R. G.; Mhaske, S. B. Stereoselective Construction of Deoxy-Cruciferane Alkaloids by NHC-Catalysed Intramolecular Annulation of Homoenolate with Quinazolinone. *Org. Biomol. Chem.*, **2019**, *17*, 7135-7139.

[7]. Sakamoto, T.; Kondo, Y.; Yamanaka, H. Condensed Heteroaromatic Ring Systems. IV. Synthesis of Naphthyridine Derivatives by Cyclisation of Aminopyridineacrylic Esters. *Chem. Pharm. Bull.,* **1985***, 11,* 4764-4768.

[8]. Park, S. J.; Park, S. J.; Lee, M. J.; Rhima, H.; Kim, Y.; Lee, J.; Chung, B. Y.; Lee, J. Y. Synthesis and SAR Studies of a Novel Series of T-Type Calcium Channel Blockers. *Bioorg. Med. Chem.,* **2006**, *14*, 3502-3511.

[9]. Humphrey, G. R.; Dalby, S. M.; Andreani, T.; Xiang, B.; Luzung, M. R.; Song, Z. J.; Shevlin, M.; Christensen, M.; Belyk, K. M.; Tschaen, D. M. Asymmetric Synthesis of Letermovir Using a Novel Phase-Transfer-Catalysed Aza-Michael Reaction. *Org. Process Res. Dev.,* **2016**, *20*, 1097-1103.

[10]. Molina, P.; Aller, E.; Lorenzo, A. Tetrabutylammonium Fluoride Promoted Intramolecular Nucleophilic Attack of a Carbodiimide Group on an α,β-Unsaturated Ester Group. *Synthesis,* **1998**, *3*, 283-287.

[11]. Cosier, J.; Glazer, A. M. A Nitrogen-Gas-Stream Cryostat for General X-Ray Diffraction Studies. *J. Appl. Cryst.,* **1986**, *19*, 105-107.

[12]. Palatinus, L.; Lee, A. J. van der. Symmetry Determination Following Structure Solution in P1. *Appl. Crystallogr.* **2008**, *41*, 975–984.

[13]. Palatinus, L.; The Charge-Flipping Algorithm in Crystallography. *Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater.* **2013**, *69*, 1–16.

[14]. Palatinus, L. ; Chapuis, G. J. SUPERFLIP–A Computer Program for the Solution of Crystal Structures by Charge Flipping In Arbitrary Dimensions. *Appl. Crystallogr.* **2007**, *40*, 786–790.

[15]. Parois, P.; Cooper, R. I.; Thompson, A. L. Crystal Structures of Increasingly Large Molecules: Meeting the Challenges with CRYSTALS Software. *Chem. Cent. J.,* **2015**, 9:30.

[16]. Cooper, R. I.; Thompson, A. L.; Watkin, D. J. CRYSTALS Enhancements: Dealing With Hydrogen Atoms in Refinement. *J. Appl. Cryst.* **2010**, *43*, 1100-1107.

[17]. Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalysed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[18]. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. Enantio- and Diastereoselective Michael Reaction of 1,3-Dicarbonyl Compounds to Nitroolefins Catalysed by a Bifunctional Thiourea. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

[19]. Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C−C Bond Formation. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

[20]. Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. On the Mechanism of Bifunctional Squaramide-Catalysed Organocatalytic Michael Addition: A Protonated Catalyst as an Oxyanion Hole. *Chem. Eur. J.* **2014**, *20*, 5631–5639.

[21]. Farley, A. J. M.; Sandford, C.; Dixon, D. J. Bifunctional Iminophosphorane Catalysed Enantioselective Sulfa-Michael Addition to Unactivated α-Substituted Acrylate Esters, *J. Am. Chem. Soc.* **2015**, *137*, 15992-15995.

[22]. Nun˜ez, M. G.; Farley, A. J. M.; Dixon, D. J. Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction, *J. Am. Chem. Soc.* **2013**, *135*, 16348-16351.

[23]. Rotstein, D. M.; Gabriel, S. D.; Manser, N.; Filonova, L.; Padilla, F.; Sankuratri, S.; Ji, C.; Rosier, A. de; Dioszegi, M.; Heilek, G.; Jekle, A.; Weller, P.; Berry, P. Synthesis, SAR and evaluation of [1,4']-bipiperidinyl-4-yl-imidazolidin-2-one derivatives as novel CCR5 antagonists, *Bioorg. Med. Chem. Lett.,* **2010**, *20*, 3219-3222.

[24]. Rozsar, D.; Formica, M.; Yamazaki, K.; Hamlin, T.; Dixon, D. J. Bifunctional Iminophosphorane Catalysed Enantioselective Sulfa-Michael Addition to Unactivated α,β-Unsaturated Amides, 10.26434/chemrxiv.14355422.

[25]. Matsuda, Y.; Tsuji, Y.; Fujihara, T. Cu-Catalysed Three-Component Coupling Reactions Using Nitriles, 1,3-Dienes and Silylboranes, *Chem. Commun.,* **2020**, *56*, 4648-4651.

[26]. Cowen, B. J.; Saunders, L. B.; Miller, S. J. Pyridylalanine (Pal)-Peptide Catalysed Enantioselective Allenoate Additions to *N*-Acyl Imines, *J. Am. Chem. Soc.,* **2009**, *131*, 17, 6105-6107.

[27]. Lee, D.; Kim, D.; Lee, S.; Kim, T.; Kim, J.; Kim, S.; Liu, K. H.; Lee, S.; Bae, J. S.; Song, K. S.; Cho, C. W.; Son, Y. K.; Baek, D. J.; Lee, T. Efficient Syntheses of 1,2,3-Triazoloamide Derivatives Using Solid- and Solution-Phase Synthetic Approaches, *Molecules.* **2015**, *20*, 11, 19984-20013.

[28]. Diehl, K.; Himbert, G.; Henn, L. Intramolekulare Diels-Alder-Reaktionen bei Allencarboxaniliden; Variation der Substituenten in p-Position des Anilinkerns, *Chem. Ber.* **1986**, *119*, 2430-2443.

[29]. Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. A Powerful Hydrogen-Bond-Donating Organocatalyst for the Enantioselective Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Amides and Esters. *Angew. Chem. Int. Ed.,* **2013**, *52*, 11114-11118.

[30]. Stang, E. M.; White, M. C. Molecular Complexity *via* C–H Activation: A Dehydrogenative Diels–Alder Reaction. *J. Am. Chem. Soc.* **2011**, *133*, 38, 14892–14895.

[31]. Prasad, K. R.; Pawar, A. B. Enantioselective Formal Synthesis of Palmerolide A. *Org. Lett.,* **2011**, *13*, 16, 4252–4255.

[32]. Lauberteaux, J.; Crévisy, C.; Baslé, O.; Figueiredo, R. M. de; Mauduit, M.; Campagne, J. M. Copper-Catalysed Asymmetric Conjugate Additions of Bis(pinacolato)diboron and Dimethylzinc to Acyl-N-methylimidazole Michael Acceptors: A Highly Stereoselective Unified Strategy for 1,3,5,...n (OH, Me) Motif Synthesis. *Org. Lett.,* **2019**, *21*, 6, 1872–1876.

[33]. Venkateshwarlu, R.; Chinnababu, B.; Ramulu, U.; Reddy, K. P.; Reddy, M. D.; Sowjanya, P.; Rao, P. V.; Aravind, S. Synthesis and Biological Evaluation of (−)-Kunstleramide and Its Derivatives. *Med. Chem. Commun.,* **2017**, *8*, 394-404.

[34]. Hamaguchi, T.; Takahashi, Y.; Tsuji, H.; Kawatsura, M. Nickel-Catalysed Hydroarylation of *in Situ* Generated 1,3-Dienes with Arylboronic Acids Using a Secondary Homoallyl Carbonate as a Surrogate for the 1,3-Diene and Hydride Source. *Org. Lett.,* **2020**, *22*, 3, 1124–1129.

[35]. Barton, D. H. R.; Gokturk, A. K. Functionalisation of Saturated Hydrocarbons. Part 3. The Oxidation of 3β,5α,6β-Triacetoxycholestane using the Gif System. *J. Chem. Soc., Perkin Trans.* **1985**, *1*, 2109-2117.

[36]. Yamamoto, Y.; Yamada, S.; Nishiyama, H. Copper-Catalysed Regio- and Stereoselective Conjugate Allylation of Electron-Deficient Alkynes with Allylboronates under Mild Conditions. *Chem. Eur. J.* **2012**, *18*, 3153–3156.

[37]. Escudero, J.; Bellosta, V.; Cossy, J. Rhodium-Catalysed Cyclisation of O,ω-Unsaturated Alkoxyamines: Formation of Oxygen-Containing Heterocycles. *Angew. Chem. Int. Ed.,* **2018**, *57*, 574–578.

[38]. Yip, S. Y. Y.; Aïssa, C. Isomerisation of Olefins Triggered by Rhodium-Catalysed C–H Bond Activation: Control of Endocyclic β-Hydrogen Elimination *Angew. Chem. Int. Ed.* **2015**, *54*, 6870–6873.

[39]. Frantz, D. E.; Singleton, D. A. Carbometalations of Simple Alkenes with Allyldibromoborane. *Org. Let.,* **1999**, *1*, 3, 485–486.

[40]. Wang, D.; Lichtenfeld, C. M.; Daniliuc, C. G.; Studer, A. Radical Aryl Migration from Boron to Carbon. *J. Am. Chem. Soc.* **2021**, *143*, 25, 9320–9326.

[41]. Clive, D. L. J.; M. P.; Pham, Subedi, R. Carbocyclisation by Radical Closure onto O-Trityl Oximes: Dramatic Effect of Diphenyl Diselenide. *J. Am. Chem. Soc.* **2007**, *129*, 9, 2713–2717.

[42]. Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. Total Synthesis of Manzamine A and Related Alkaloids. *J. Am. Chem. Soc.* **2012**, *134*, 42, 17482–17485.

[43]. Huy, P. H.; Koskinen, A. M. P. Efficient, Stereodivergent Access to 3-Piperidinols by Traceless $P(OEt)_3$ Cyclodehydration. *Org. Lett.,* **2013**, *15*, 20, 5178–5181.

[44]. Cooper, L. C.; Carlson, E. J.; Castro, J. L.; Chicchi, G. G.; Dinnell, K.; Salvo, J. D.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Ridgill, M. P.; Rycroft, W.; Tsao, K. L.; Swain, C. J. 4,4-Disubstituted cyclohexylamine NK1 receptor antagonists II. *Bioorg. Med. Chem. Lett.,* **2002**, *12*, 13, 1759-1762.

[45]. Davis, R. W.; Allweil, A.; Tian, J.; Brash, A. R.; Sulikowski, G. A. Stereocontrolled Synthesis of Four Isomeric Linoleate Triols of Relevance to Skin Barrier Formation and Function. *Tetrahedron Lett.,* **2018**, *59*, 4571-4573.

[46]. Hurtak, J. A.; McDonald, F. E. Synthesis of the ABC Substructure of Brevenal by Sequential exo-Mode Oxacyclisations of Acyclic Polyene Precursors. *Org. Lett.,* **2017**, *19*, 22, 6036–6039.

[47]. Adamo, M. F. A.; Pergoli, R. Studies on the Generation of Unnatural C-Nucleosides with 1-Alkynyl-2-deoxy-d-riboses. *Org. Lett.,* **2007**, *9*, 22, 4443–4446.

[48]. Wang, J. L.; Li, H. J.; Wang, H. S.; Wu, Y. C. Regioselective 1,2-Diol Rearrangement by Controlling the Loading of $BF_3{\cdot}Et_2O$ and Its Application to the Synthesis of Related Nor-

Sesquiterene- and Sesquiterene-Type Marine Natural Products. *Org. Lett.,* **2017**, *19*, 14, 3811–3814.

[49]. Lattanzi, A.; Senatore, A.; Massa, A.; Scettri, A. Novel Highly Regioselective $VO(acac)_2$/TBHP Mediated Oxidation of o-Alkenyl Phenols to o-Hydroxybenzyl Ketones. *J. Org. Chem.* **2003**, *68*, 9, 3691–3694.

[50]. Nicholson, W. I.; Barreteau, F.; Leitch, J. A.; Payne, R.; Priestley, I.; Godineau, E.; Battilocchio, C.; Browne, D. L. Direct Amidation of Esters by Ball Milling. *Angew. Chem. Int. Ed.,* **2021**, *60*, 21868–21874.

[51]. Ledoussal, B.; Gorgues, A.; Coq, A. L. Reduction Par Les Sels Chromeux De Bromures Benzyliques Ortho-O-Acyles Avec Transposition Du Groupement Acyle: De L' Ester : Acces Aux Ortho-Hydroxybenzyl Cetones Non Masquees Et Une Nouvelle Preparation De Benzo¦B¦Furannes Substitues En Position-2. *Tetrahedron.,* **1987**, *43*, 5841-5852.

[52]. Son, E. C.; Kim, S. Y.; Kim, S. G. Squaramide-Catalysed Asymmetric Intramolecular Oxa-Michael Reaction of α,β-Unsaturated Carbonyls Containing Benzyl Alcohol: Construction of Chiral 1-Substituted Phthalans. *J. Org. Chem.* **2021**, *86*, 9, 6826-6839.

[53] Miyata, K.; Kutsuna, H.; Kawakami, S.; Kitamura, M. A Chiral Bidentate sp2-N Ligand, Naph-diPIM: Application to CpRu-Catalysed Asymmetric Dehydrative C-, N-, and O-Allylation. *Angew. Chem. Int. Ed.* **2011**, *50*, 4649–4653.

[54]. Zhang, C.; Ji, J.; Sun, P. Palladium-Catalysed Alkenylation via sp2 C–H Bond Activation Using Phenolic Hydroxyl as the Directing Group. *J. Org. Chem*. **2014**, *79*, 7, 3200–3205.

[55]. Chen, D.; Berhane, I. A.; Chemler, S. R. Copper-Catalysed Enantioselective Hydroalkoxylation of Alkenols for the Synthesis of Cyclic Ethers. *Org. Lett.* **2020**, *22*, 19, 7409–7414.

[56]. Verma, A.; Jana, S.; Prasad, C. D.; Yadava, A.; Kumar, S. Organoselenium and DMAP co-catalysis: regioselective synthesis of medium-sized halolactones and bromooxepanes from unactivated alkenes. *Chem. Commun.,* **2016**, *52*, 4179-4182.

[57]. Lee, S.; Kaib, P. S. J.; List, B. Asymmetric Catalysis via Cyclic, Aliphatic Oxocarbenium Ions. *J. Am. Chem. Soc.* **2017**, *139*, 6, 2156-2159.

[58]. Lee, S.; Bae, H. Y.; List, B. Can a Ketone Be More Reactive than an Aldehyde? Catalytic Asymmetric Synthesis of Substituted Tetrahydrofurans. *Angew. Chem. Int. Ed.* **2018**, *57*, 12162–12166.

[59]. Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. Palladium-Catalysed Oxidative Wacker Cyclisations in Nonpolar Organic Solvents with Molecular Oxygen: A Stepping Stone to Asymmetric Aerobic Cyclisations. *Angew. Chem. Int. Ed.* **2003**, *42*, 2892-2895.

[60]. Asano, K.; Matsubara, S. Asymmetric Catalytic Cycloetherification Mediated by Bifunctional Organocatalysts. *J. Am. Chem. Soc.,* **2011**, *133*, 42, 16711-16713.

[61]. Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J. H.; Kang, S. H. Asymmetric Iodocyclisation Catalysed by Salen–CrIIICl: Its Synthetic Application to Swainsonine. *Chem. Eng. J.,* **2008**, *14*, 1023-1028.

[62]. Barbe, G.; Charette, A. B. Highly Chemoselective Metal-Free Reduction of Tertiary Amides. *J. Am. Chem. Soc.* **2008**, *130*, 1, 18–19.

[63]. Ransborg, L. K.; Albrecht, Ł.; Weise, C. F.; Bak, J. R.; Jørgensen, K. A. Optically Active Thiophenes *via* an Organocatalytic One-Pot Methodology. *Org. Lett.,* **2012**, *14*, 3, 724-727.

[64]. Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. Highly Chemoselective Reduction of Amides (Primary, Secondary, Tertiary) to Alcohols using SmI_2/Amine/H_2O under Mild Conditions. *J. Am. Chem. Soc.* **2014**, *136*, 6, 2268-2271.

[65]. Tietze, L. F.; Jackenkroll, S.; Hierold, J.; Ma, L.; Waldecker, B. A Domino Approach to the Enantioselective Total Syntheses of Blennolide C and Gonytolide C. *Chem. Eng. J.,* **2014**, *20*, 8628-8635.