Development and Application of Enantioselective H-bond Donor Organocatalysts



A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (D.Phil.)

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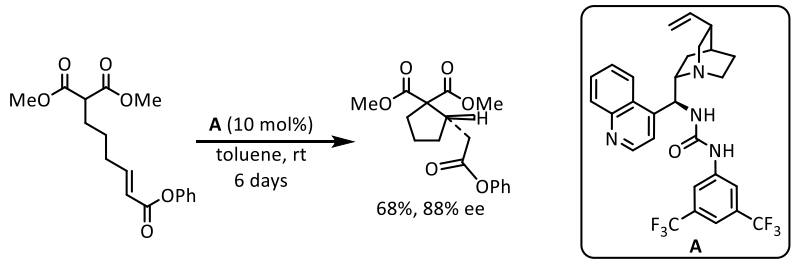
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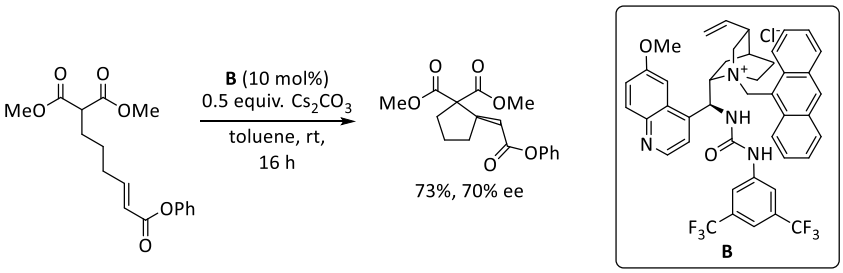
Abstract

Development and Application of Enantioselective H-Bond Donor Organocatalysts

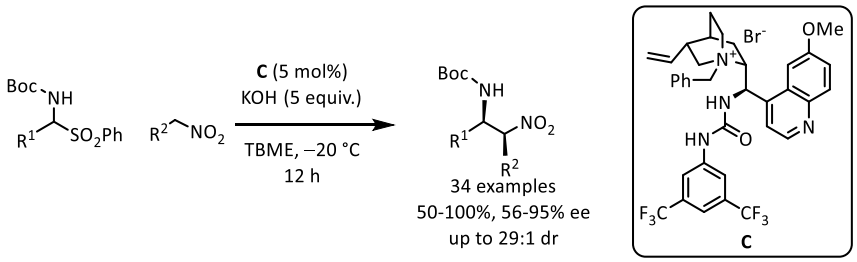
This thesis presents the application and development of H-bond donor organocatalysts. Chapter 2 presents an intramolecular Michael addition of β-dicarbonyls onto α,β-unsaturated esters catalyzed by tertiary amine/H-bond donor bifunctional catalysts, achieving up to 88% ee.



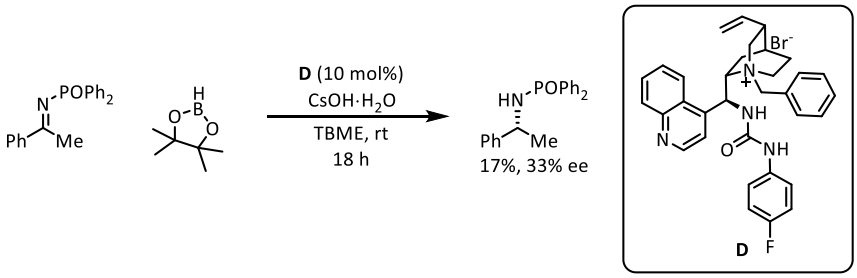
Chapter 3 outlines the design and synthesis of a new family of cinchona-derived H-bond donor/ammonium salt phase-transfer catalysts. The ability of these asymmetric phase-transfer catalysts to activate less reactive substrates than their tertiary amine analogues and to induce higher levels of enantiocontrol than commercially available phase-transfer catalysts was demonstrated in an intramolecular Michael addition.



Chapter 4 details the highly successful application of these new H-bond donor/ammonium salt phase-transfer catalysts to the enantio- and diastereoselective nitro-Mannich reaction of α-amido sulfones with nitroalkanes.



Preliminary investigations into a novel phase-transfer catalyzed asymmetric ketimine reduction demonstrate the ability of these catalysts to provide access to new methods.



Declaration and Contributions

This dissertation is written by me, and any work carried out as part of a collaboration is specified in the text. Catalysts which are not presented and characterized in Chapter 6 were prepared by past or current group members. The work presented in Chapters 2 and 3 is wholly my own, except where specified. In Chapter 4, I carried out the optimization of the nitro-Mannich reaction myself. To assess the scope of this reaction, I coordinated a collaboration with my colleagues David Barber, Marta Garcia, Anna Goldys and Matt Rattley. Only those compounds that I prepared myself are characterized in Chapter 6. Initial optimization of the ketimine reduction in Chapter 4 was carried out by Matt Rattley as an M.Chem. student under my supervision. Only my own work on this project is presented. All compounds included in Chapter 6 were prepared and characterized by me.

Acknowledgements

Thank you first to Darren for allowing me to work in your group and for your infectious enthusiasm towards chemistry. Thank you to Filippo for guiding me in my early days in the lab, and to Pavol for being such a wonderful example of proper scientific conduct. Thank you to Barbara, Tim and Maria for all of your help with NMR spectroscopy. To my proof-readers Daniel, Adam, Matt, Allegra, Pete, Anna, and Iacovos: thank you for your time and invaluable suggestions. Thank you to Yusuke and Bal for your positive leadership in G5 and sharing your wealth of knowledge. Thank you Matt for being such a pleasure to work with and for always knowing when someone might need a muffin. Thank you to Albex for the entertainment, Anna for keeping my plant alive when I wasn't up to the task, and Pete for your unwavering friendship. Thank you to the corridor for letting me play football, even though I'm a girl. And thank you for forgiving me for forgetting to call it football sometimes.

Western Rd, thank you for the family to come home to. Michael, thank you for being on the front line for the first two years. Your friendship was my rock. Thank you Mom, Dad and Alia for your constant support and for your company by the yellow backdrop. And finally, thank you to Simon for keeping me so full through the DPhil process: of food, of joy, and of love.

Abbreviations

A	Lewis base
Ac	acetyl
AcOH	acetic acid
Alk	alkyl group
$[\alpha]_D^T$	specific rotation
app	apparent
aq.	aqueous
Ar	aryl substituent
ATR	attenuated total reflectance
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
°C	degrees Celsius
c	concentration
cat.	catalyst or catalytic
CBz	carboxybenzyl
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclized product
D	sodium D-line (589 nm)
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	N,N'-dicyclohexylcarbodiimide
deg	degrees
δ	chemical shift
DEPT	distortionless enhancement by polarization transfer spectroscopy
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide

dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
En	enolate
eq	equivalents
equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FT	Forier transform
g	gram
h	hours
H-bond	hydrogen bond
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMQC	heteronuclear multiple-quantum correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum coherence spectroscopy
Hz	Hertz
*i*Pr	*iso*-propyl
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
K	Kelvin
K_a	acid dissociation constant
L	litres
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital

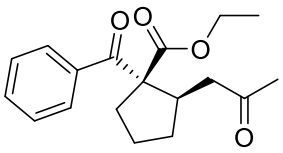
M	molar
M	metal
m	multiplet
m	medium
m	meta
m/z	mass per charge ratio
mbar	millibar
Me	methyl
MeOH	methanol
Ms	mesyl
mg	milligram
MHz	mega Hertz
min.	minutes
mL	millilitres
mmol	millimole
mol	mole
MP	melting point
MTBE	methyl *tert*-butyl ether
MW	molecular weight
NADH	nicotinamide adenine dinucleotide
nd	no data or not determined
nm	nanometers
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	ortho
org	organic phase
p	para
PE	petroleum ether
PG	protecting group
Ph	phenyl
pK_a	-log(pK_a)

ppm	parts per million
Q	generic phase-transfer catalyst
q	quartet
R	generic substituent
rt	room temperature
s	solid phase
s	singlet
s	strong
sat.	saturated
T	temperature
t	triplet
t	retention time
t/*tert*	tertiary
TBAB	tetrabutylammonium bromide
t-Bu	*tert*-butyl
temp.	temperature
Tf	triflate
TFAA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	time of flight
tol	toluene
µg	microgram
UV	ultraviolet
ν_{max}	infrared absorbance
w	weak
X	an electronegative atom
X^-	generic counterion

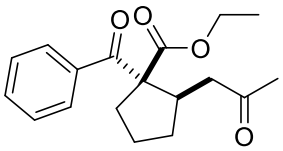
A Note on Stereochemistry

Throughout this thesis, the graphic presentations of absolute and relative stereochemical configurations are in accord with the conventions put forward by Maehr.[1] (1) Solid and broken wedges are used to indicate absolute stereochemical configuration. (2) Solid and broken bold lines portray the relative stereochemical configuration of racemic samples. Molecules presented using such lines represent equally the configuration shown and its mirror image. (3) Wedge outlines and broken lines are used to present relative stereochemical configuration of enantioenriched samples with unknown absolute stereochemical configuration. Molecules presented using such lines represent either the configuration shown or its mirror image. (4) Continuous bonds with normal thickness are used when no stereochemical information is known.

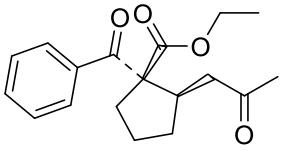
(1) An enantioenriched compound with known absolute stereochemical configuration



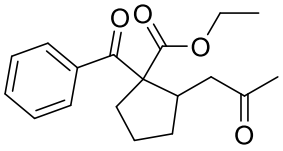
(2) A racemic compound with known relative stereochemical configuration



(3) An enantioenriched compound with known relative stereochemical configuration but unknown absolute stereochemical configuration



(4) A compound with unknown stereochemical configuration



Compound Numbering

Each compound in this thesis has been assigned a three digit identifier. For all compounds other than catalysts, the first digit of this identifier indicates the chapter number in which its synthesis is presented (or the chapter in which it first appears if its synthesis is not described). The second two digits represent the order in which the compound appears within the chapter. For catalysts, the first digit is a "C" and the second two digits represent the order in which the catalyst first appeared in this thesis. In chapter 6, experimental procedures are grouped according to these identifiers: the preparation of compounds beginning with **2** are described in section 6.2, those beginning with a **3** are described in section 6.3, those beginning with a **4** are described in section 6.4, and those beginning with a **C** (i.e. catalysts) are described in section 6.5.

Chapter 1: Introduction

1.1 Introduction to Organocatalysis

The pheromone (*R*)-olean attracts male olive fruit flies while (*S*)-olean attracts female fruit flies (figure 1.01).[2] (*R*)-Carvone smells of spearmint while (*S*)-carvone smells of caraway seeds.[3] (*S,S*)-Ethambutol is an antibiotic, while (*R,R*)-ethambutol shows no antibiotic activity.[4] With such dichotomous properties of enantiomers, it is clear that controlling the stereochemical outcome of chiral syntheses is essential. Nature regularly achieves enormously efficient and enantioselective transformations using enzymes. Organic chemists have exploited nature's catalysts by applying enzymes in synthetic applications, known as biocatalysis.[5–7] While highly efficient and selective, such enzymes are often also highly specific, working only for a narrow range of substrates and providing access to only one enantiomer.[8] Over the 20th century chemists achieved more general asymmetric transformations by pairing transition metals with chiral organic ligands.[9] Indeed, the contributions to this field from Knowles, Noyori and Sharpless were recognized with the Nobel Prize in Chemistry in 2001. However, metals for these transformations are often expensive and toxic, and catalysts can suffer from product inhibition. With around half of all enzymes operating without metals,[10] efficient and selective metal-free transformations are evidently possible.

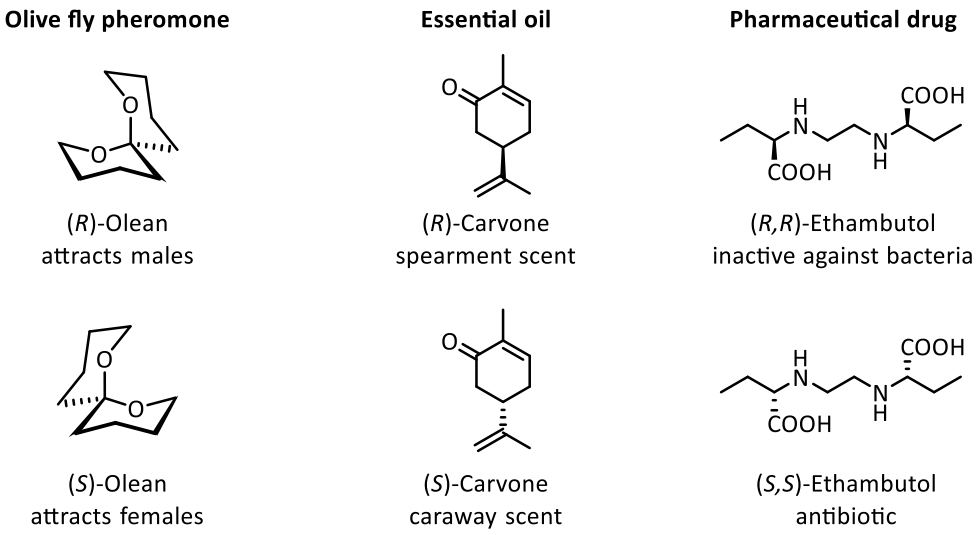
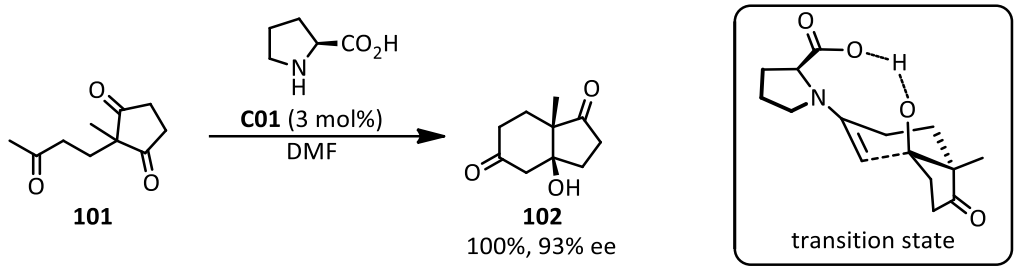


Figure 1.01: *The properties of various chiral molecules and their enantiomers*

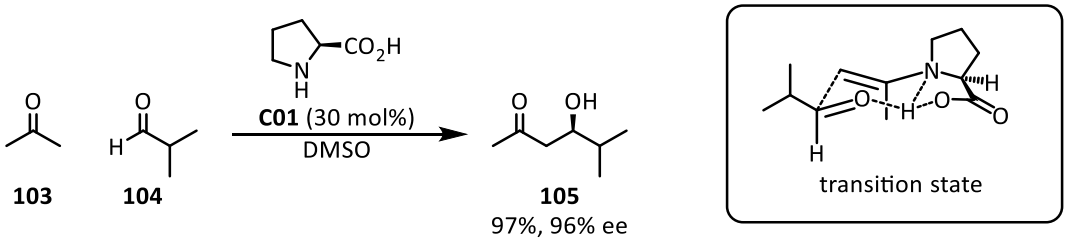
Over the past fifteen years the surge of reports using small organic molecules in metal-free conditions to achieve highly enantioselective transformations has added a third mainstay of asymmetric catalysis to complement bio- and metal-catalysis: organocatalysis.[11] Asymmetric organocatalysis is the acceleration of reactions using small (MW<1000 g/mol), enantiopure organic molecules.[12] Reactions using such catalysts tend to be operationally simple, generally not requiring strict exclusion of air and moisture, and the catalysts tend to be environmentally benign and affordable relative to their Lewis acidic metal counterparts. The idea of using small organic molecules to catalyze chemical transformations is not a new one. One of the earliest, synthetically useful examples of enantioselective catalysis by an organic molecule was the (*S*)-proline catalyzed intramolecular aldol reaction reported by Hajos and Parrish[13] and by Eder, Sauer, and Wiechert[14] in 1971 (scheme 1.01). While these reports were appreciated by the community at the time, the wider applicability and advantages of what would later be coined organocatalysis[15] was not realized until the turn of the 21st century.[16]



Scheme 1.01: *An early example of asymmetric organocatalysis*[17] *(transition state based on Houk's 2004 report*[18]*)*

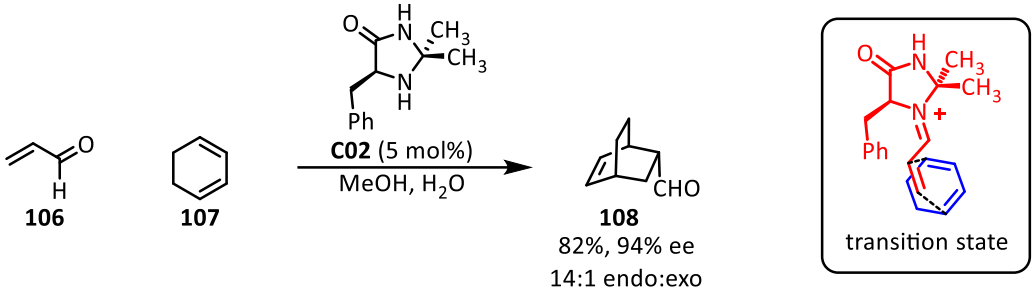
1.1.1 Modes of activation

Two publications that helped lead the recent surge in organocatalysis research are List's[19] (scheme 1.02) and MacMillan's[15] (scheme 1.03) landmark reports in 2000. These methods represent two major general modes of activation that have emerged in organocatalysis: enamine catalysis and iminium catalysis. List and coworkers employed (*S*)-proline to promote aldol reactions between acetone and various aldehydes with excellent enantioselectivities (up to 96% ee, scheme 1.02). They proposed that the (*S*)-proline catalyst condenses with acetone to form an enamine, effectively raising the energy of the highest occupied molecular orbital (HOMO). The enamine then adds to the aldehyde from the *re*-face, which is directed by H-bonding to the proline carboxylic acid. Proline and other chiral secondary amines have since been used to activate carbonyl *α*-carbons in various other reactions including Mannich, Michael, *α*-oxygenation, *α*-amination, *α*-halogenation, *α*-sulphenylation, *α*-alkylation and cycloaddition reactions.[20–23]



Scheme 1.02: *List's enamine catalyzed aldol reaction*

MacMillan and coworkers also used (*S*)-proline derivatives and other chiral secondary amines to promote their Diels-Alder cycloadditions in excellent enantioselectivities (up to 96% ee, scheme 1.03).[15] In this case, chiral secondary amines condensed with *α,β*-unsaturated aldehydes to form *α,β*-unsaturated iminium ions, lowering the energy of the lowest occupied molecular orbital (LUMO) and thus significantly increasing the reactivity of the dieneophile.[24] Enantioselective iminium catalysis has since been applied to various cycloaddition, cyclopropanation, epoxidation, conjugate hydride reduction, amination, oxygenation and conjugate addition reactions.[23]



Scheme 1.03: *MacMillan's iminium catalyzed Diels-Alder reaction*

Both enamine and iminium catalysis use Lewis basic organocatalysts to transfer chiral information through the formation of covalent bonds. A third general mode of activation uses ion pairing between a substrate and a chiral phase-transfer catalyst to promote reactivity and transfer chiral information. In phase-transfer catalysis, the reagents are separated in at least two phases. The phase-transfer catalyst is able to transport a reagent from one phase into the reaction phase to facilitate reactivity. For example, in the nucleophilic substitution of an alkyl halide (RX) with potassium cyanide, the phase transfer catalyst, Q^+, transports CN^- from the aqueous phase to the organic phase to react with the alkyl halide (figure 1.02). In the asymmetric variant of this reaction, the phase-transfer catalyst is typically a lipophilic chiral ammonium (or phosphonium) salt that acts as a Lewis acid,[10] transferring an anionic reagent from an aqueous or solid phase into the organic phase.

For example, in their asymmetric Strecker reaction, Ooi, Uematsu and Maruoka use chiral quaternary ammonium salt **C03** to transport a cyanide ion from the aqueous phase to the organic phase, where it adds to aldimine **109** to give **110** (scheme 1.04).[25] Such chiral cation catalysis is well studied.[26–28]

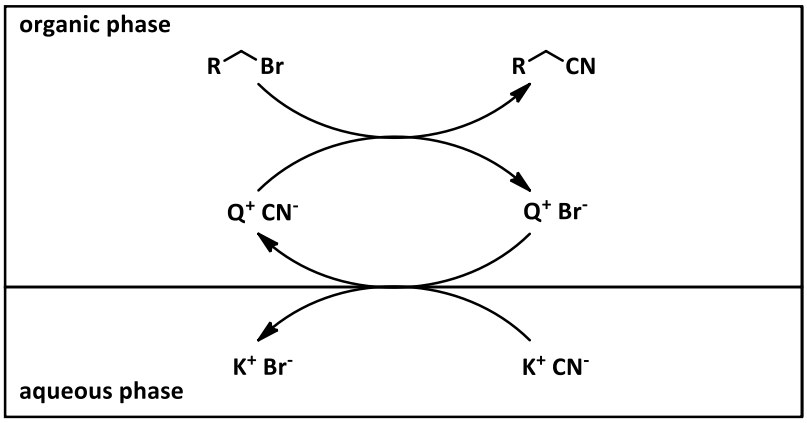
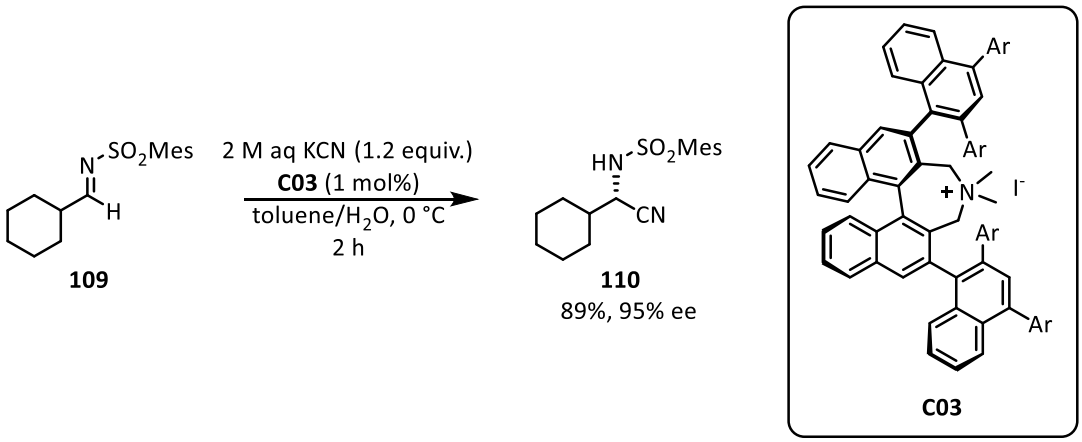


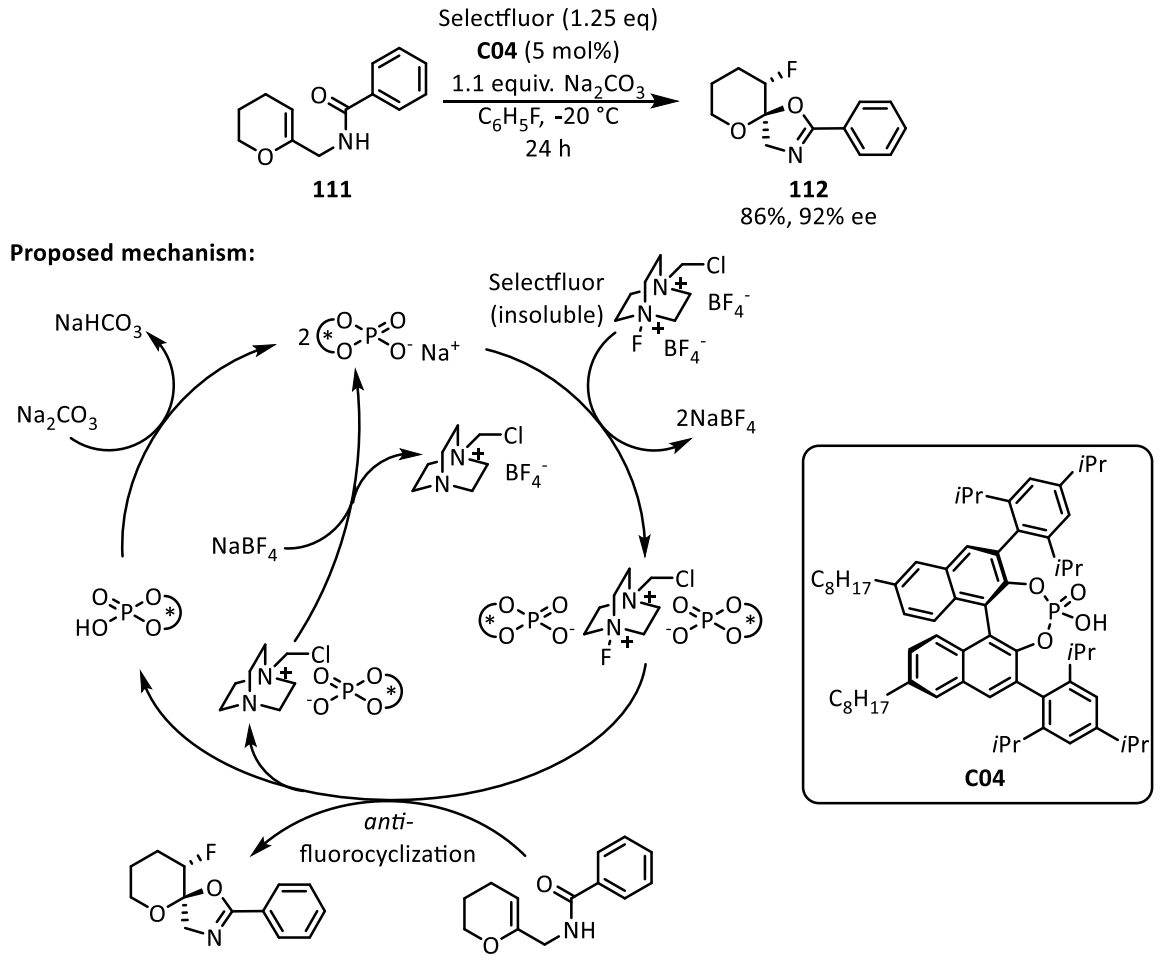
Figure 1.02: *Example phase-transfer mechanism of a nucleophilic substitution; Q^+ = phase-transfer catalyst*



Scheme 1.04: *Maruoka's phase-transfer Strecker reaction*

More recently, Toste and coworkers demonstrated the utility of the largely unexplored anionic chiral phase-transfer catalysis in asymmetric electrophilic fluorination reactions (up to 97% ee, scheme 1.05).[29] Deprotonated **C04** transports the insoluble cation

of Selectfluor™ into the organic phase, where the substrate undergoes electrophilic fluorination and cyclization.



Scheme 1.05: *Toste's chiral anionic phase-transfer catalyzed electrophilic fluorination*

Since many phase-transfer methods involve the use of inorganic bases to form metal enolates, some organocatalysis purists may argue that phase-transfer catalysis cannot strictly be classified as organocatalysis.[11] However, since such metal enolates are generally formed in a preliminary step and the metal is replaced by the chiral cation of the phase-transfer catalysts before the key step in the reaction mechanism, we have included this reaction class in our discussion of organocatalysis. Furthermore, phase-transfer catalysis generally utilizes alkali, not transition metals. Phase-transfer catalysis is introduced in more detail in Chapter

4. This introduction will focus on a fourth key mode of activation in organocatalysis: the hydrogen bond (abbreviated as H-bond).[i]

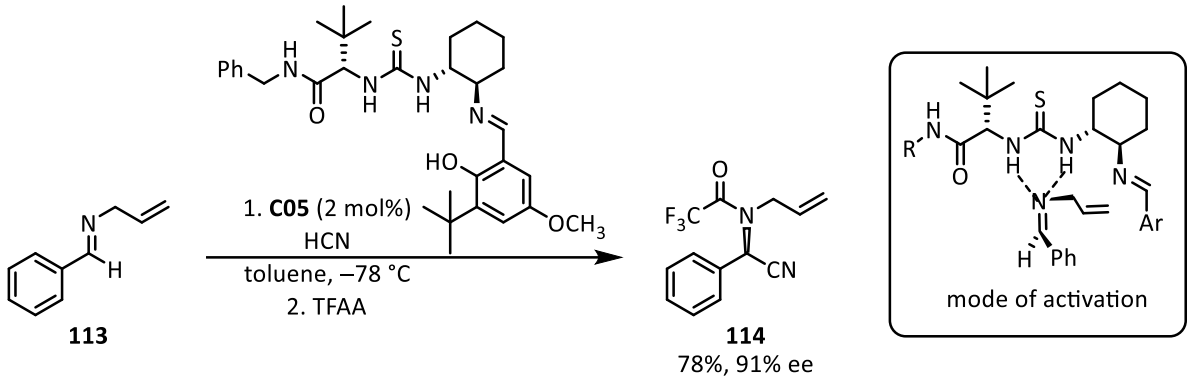
1.1.2 H-bond donor organocatalysis

H-bonds have long been known to play a key role in enzyme catalysis *via* substrate activation, organization, and proton transfer in the transition state (general acid catalysis).[30] However, they were historically considered to be too weak to utilize in small organic catalysts, which lack the macrostructure and rigidity of enzymes thought necessary to transfer chirality. More recently, H-bond donor organocatalysts, especially those bearing strong dual H-bond donors such as diols, ureas and thioureas, have been shown to instil almost as much control as organocatalysts that activate substrates through the formation of covalent bonds.[31] In 1990, Etter and coworkers demonstrated the cocrystallization of diaryl ureas with Lewis bases such as ethers, ketones, nitroaromatics and sulfoxides,[32,33] providing evidence of dual H-bonding between these species.

Because H-bond donors are not as acidic as their Lewis acidic metal counterparts, an organocatalyst incorporating H-bonds alone is often not as activating as an organometallic catalyst.[34] A potential solution to this problem is to use a catalyst with multiple recognition sites that is capable of simultaneously activating both the electrophile and the nucleophile. While synthesizing new chiral (thio)urea-containing Schiff base ligands intended for use with Lewis acidic metals in 1998, Sigman and Jacobsen discovered that their ligands induced higher enantiocontrol in the Strecker reaction on their own (up to 91% ee) than in the presence of Lewis acidic metals (scheme 1.06).[35] Mechanistic studies using NMR, kinetics, and theoretical calculations indicated that imine **113** forms a strong dual H-bond with the (thio)urea of catalyst **C05** (8.5 kcal/mol catalyst-substrate interaction for the urea, 10.0

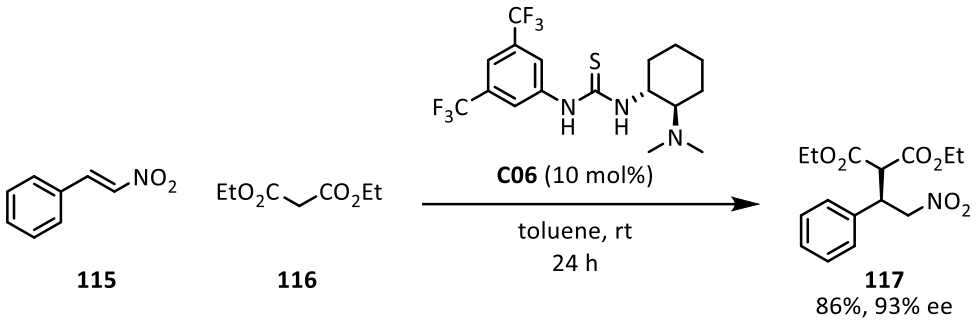
[i] An H-bond is a local bond whereby X—H, where X is an electronegative atom, acts as a proton donor to a Lewis base. Such bonds vary in strength from 0.4 to 40 kcal/mol depending on the species involved.[30]

kcal/mol for the thiourea).[36] This interaction decreases the electron density of imine **113**, thus activating it towards nucleophilic attack.[30] Similar calculations revealed that the catalyst and product **114** interact through only a single H-bond. This decreased interaction with the product importantly allows for catalyst turnover.[36]



Scheme 1.06: *Jacobsen's thiourea-catalyzed Strecker reaction*

Following Jacobsen's demonstration of H-bond donors as highly efficient and selective organocatalysts, Takemoto and coworkers were the first to explicitly developed a bifunctional organocatalyst (**C06**) which incorporated both a thiourea, to activate the electrophile, and a basic tertiary amine, to activate the nucleophile.[37] They demonstrated their bifunctional organocatalyst in the Michael addition of malonates to nitroolefins with great success, achieving up to 93% ee (scheme 1.07).



Scheme 1.07: *Takemoto's bifunctional thiourea in a Michael reaction*

Building on this idea, Ye, Dixon and Hynes from our group developed a bifunctional thiourea/tertiary amine organocatalyst using the privileged[8] cinchona chiral scaffold.[38] The four cinchona alkaloids (figure 1.03) are natural products found in the bark of *Cinchona officinalis*.[39] Quinidine (**C08**) is closely related to cinchonine (**C07**), and quinine (**C10**) is closely related to cinchonidine (**C09**), differing only by the presence or absence of a 6' methoxy group on the quinoline ring. Quinine and cinchonidine are strictly diastereomers of quinidine and cinchonine, respectively. However, because they have opposite stereochemistry at C(8) and C(9) (but the same stereochemistry at the terminal olefin), quinine and cinchonidine are often referred to as 'pseudo-enantiomers' of quinidine and cinchonine, respectively. With both pseudo-enantiomers naturally occurring, accessible and affordable, cinchona alkaloids have been exploited as chiral scaffolds in a vast array of organocatalytic reactions.[40,41]

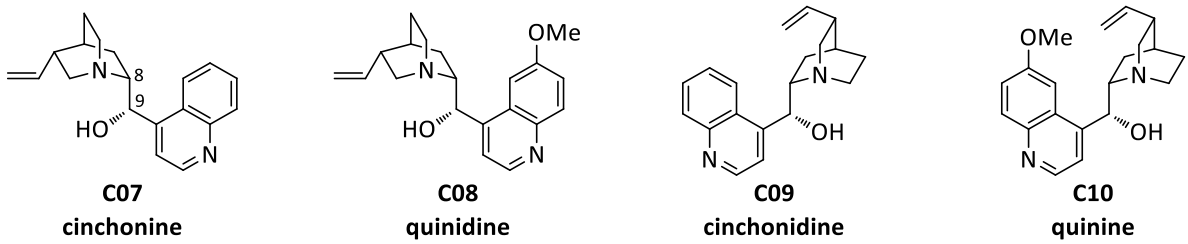
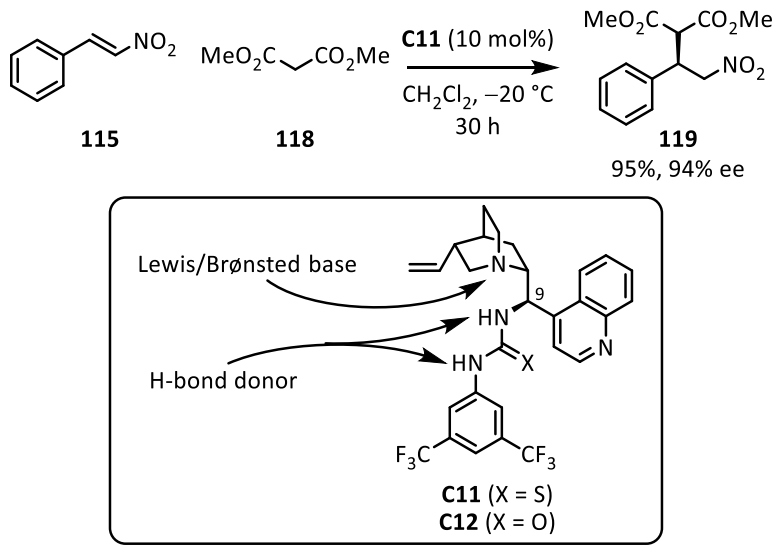


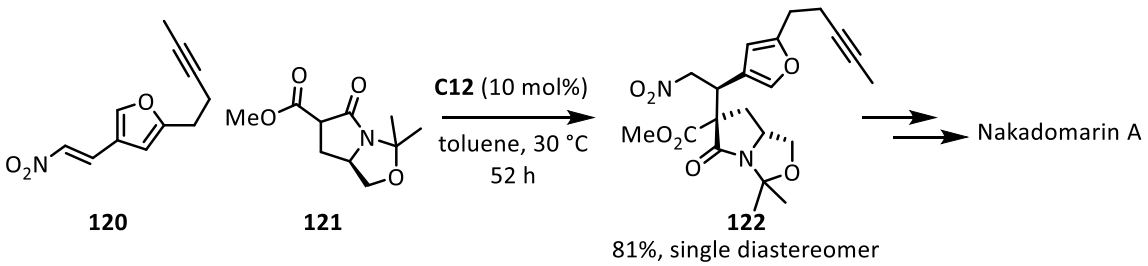
Figure 1.03: *The cinchona alkaloids*

In Dixon *et al.*'s cinchona-derived bifunctional organocatalysts, they replaced the alcohol on the naturally occurring alkaloid with an aryl thiourea (*via* the amine), epimerizing the alkaloid at C(9) in the process (scheme 1.08). The groups of Chen,[42] Soós[43] and Connon[44] independently developed similar catalysts. Our group first demonstrated these catalysts in the Michael addition of malonate esters to nitro olefins, achieving up to 99% yield and 97% ee (scheme 1.08).[38] Connon demonstrated that the absolute stereochemical configuration of **C11** at C(9) is crucial; using an analogue of **C11** with natural alkaloid stereochemistry at C(9) greatly reduced the enantioselectivity.[44] In these reactions the quinuclidine nitrogen acts as a base, deprotonating the malonate. The resulting enolate and the nitroolefin are organized and activated *via* H-bonding with the ammonium and thiourea of the catalyst.



Scheme 1.08: *Dixon's cinchona-derived bifunctional thiourea in a Michael reaction*

Our group later demonstrated the synthetic applicability of urea analogues of these catalysts (**C12**) in the Michael addition step of our total synthesis of Nakadomarin A (scheme 1.09).[45–47] Ours and other groups have also demonstrated related catalysts in numerous conjugate addition, 1,2-addition, and cycloaddition methodologies.[48,49]



Scheme 1.09: *Application of* **C12** *in the total synthesis of Nakadomarin A*

1.1.3 Mechanism of bifunctional (thio)urea organocatalysis

Takemoto and Pápai have proposed two opposing models for nucleophile and electrophile activation using bifunctional (thio)ureas. Takemoto originally proposed that the thiourea H-bonds to and activates the electrophile, while the nucleophile is activated by the protonated tertiary nitrogen (figure 1.04).[37,50] Conversely, using density functional theory (DFT) calculations Pápai propsed that, after deprotonating the nucleophile, the protonated tertiary amine coordinates the electrophile while the thiourea H-bonds to the nucleophile.[51]

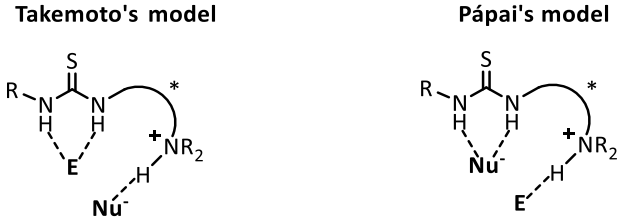
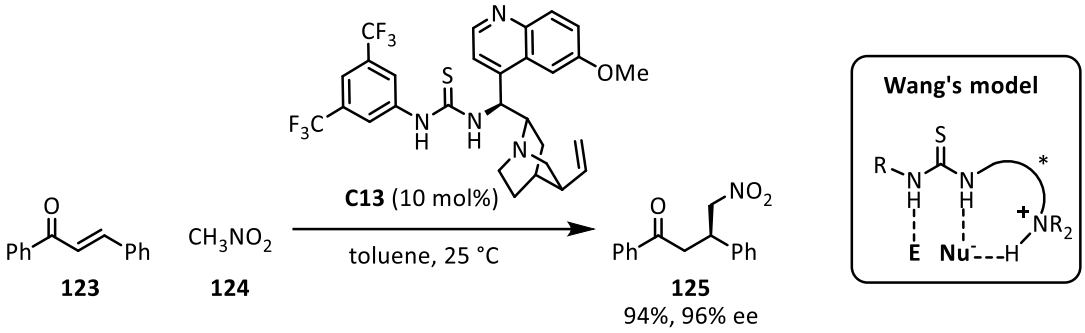


Figure 1.04: *Dual electrophile (E) and nucleophile (Nu^-) activation models*

In 2012 Wang and coworkers refined these previously proposed dual activation models for bifunctional (thio)urea organocatalysts. In their article, they focus on the Michael additions of *α,β*-unsaturated γ-butyrolactam and nitromethane to chalcone catalyzed by cinchona-derived thiourea **C13** (scheme 1.10).[52] Using the model originally proposed by Takemoto, we would expect the tertiary amine to deprotonate and coordinate to the γ-butyrolactam or nitromethane, and the thiourea of **C13** to form a dual H-bond with

the carbonyl of chalcone. Using Pápai's alternative model we would expect the urea to H-bond with the deprotonated nucleophile and the protonated tertiary amine to H-bond with the chalcone. However, using NMR studies and DFT calculations, Wang and coworkers instead concluded that thiourea **C13** forms only a single H-bond with chalcone. Both the second thiourea hydrogen and the ammonium proton H-bond to the nucleophile.



Scheme 1.10: *Wang's dual activation model*

In 2014, Takemoto and coworkers published a detailed mechanistic study of the Mannich reaction using Takemoto-like catalysts. Using snap-shot structural analysis and DFT calculations, they revised their proposed model of activation, concluding that the Pápai-like model of activation is most accurate for this reaction (figure 1.05).[53] The coordination of a (thio)urea with an anionic nucleophile is further supported by multiple studies that demonstrate the strong anion recognition of these H-bond donors.[54] From these studies, it is clear that our mechanistic understanding of organocatalyzed reactions is still evolving.

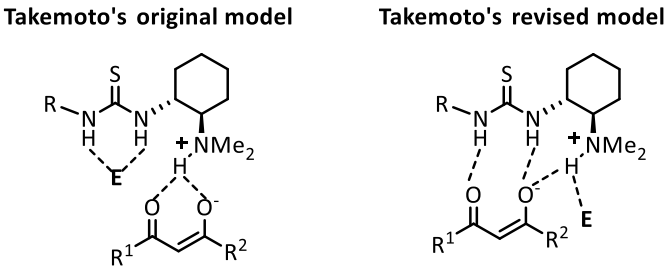


Figure 1.05: *Takemoto's revised dual activation model (E = electrophile)*

1.1.4 Designing new organocatalysts

Interest in organocatalysis continues to grow (figure 1.06). Recent publications report both new applications of known catalysts and the design of new organocatalysts. We continue to strive to mimic enzymes with small enantiopure organic molecules by employing multiple H-bond donors to create a structured and stabilizing transition state to promote highly efficient and selective reactions. As we gain more insight into the mechanisms of organocatalyzed reactions, we will be able to use this information to inform the design of improved and innovative organocatalysts.

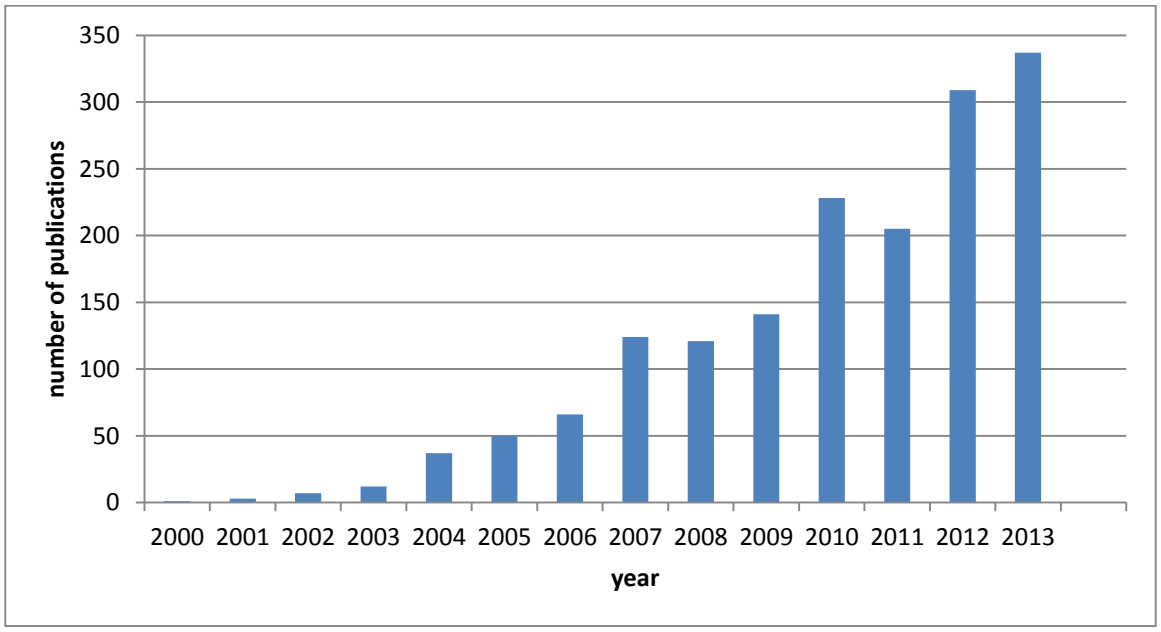


Figure 1.06: *Publications per year found in a SciFinder keyword search for "organocatalysis"*

1.2 Aims

This thesis aims to demonstrate known organocatalysts in new enantioselective methodologies, design new asymmetric organocatalysts to improve known reactions, and to use new organocatalysts to access previously inaccessible reactions. Chapter 2 presents the application of known organocatalysts, such as **C12** introduced by our group and others, in an unreported enantioselective intramolecular Michael reaction.

To expand our intramolecular Michael reaction, we developed a new bifunctional H-bond donor phase-transfer catalyst capable of activating less reactive substrates. The conceptual design and synthesis of this new family of catalysts and their application to our intramolecular Michael reaction are presented in Chapter 3.

Chapter 4 details further applications of our H-bond donor/ammonium salt phase-transfer catalysts. This chapter expands our 2012 report[55] of a phase-transfer catalyzed enantioselective nitro-Mannich reaction. We then present our preliminary studies of a novel phase-transfer ketimine reduction. Finally, Chapter 5 summarizes the contributions of this thesis.

Chapter 2: All-Carbon Quaternary Stereogenic Centres

2.1 Chapter Overview

Organocatalysis has emerged as an incredibly powerful and efficient method for constructing asymmetric carbon-carbon bonds. However, as the complexity of a stereogenic centre increases, so too does the challenge of its construction. Some of the most complex, and thus difficult, motifs to synthesize are all-carbon quaternary stereogenic centres, which are comprised of a carbon atom attached to four different carbon substituents.[56] Such fully substituted centres are ubiquitous in natural products with intriguing biological properties (figure 2.01): Physostigmine is used to treat Alzheimer's disease, guanacastepene A is used as an antibiotic, and hamigeran B is an antiviral agent.[57] Natural products such as these are key sources of drug lead candidates, and thus continued development of highly efficient and selective methods to construct all-carbon stereogenic centres is of great interest and importance.

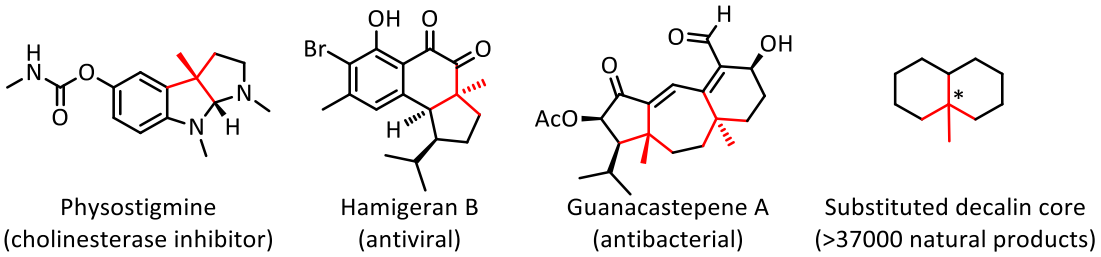


Figure 2.01: *Selected natural products with interesting biological properties that contain all-carbon quaternary stereogenic centres (highlighted in red)*[57]

Constructing any quaternary centre, whether chiral or achiral, can present a challenge due to the high levels of steric interaction between the carbon substituents.[58] Synthesizing quaternary stereocentres enantioselectively naturally adds a further complication, particularly in acyclic systems where there are more degrees of freedom.[59] Despite these

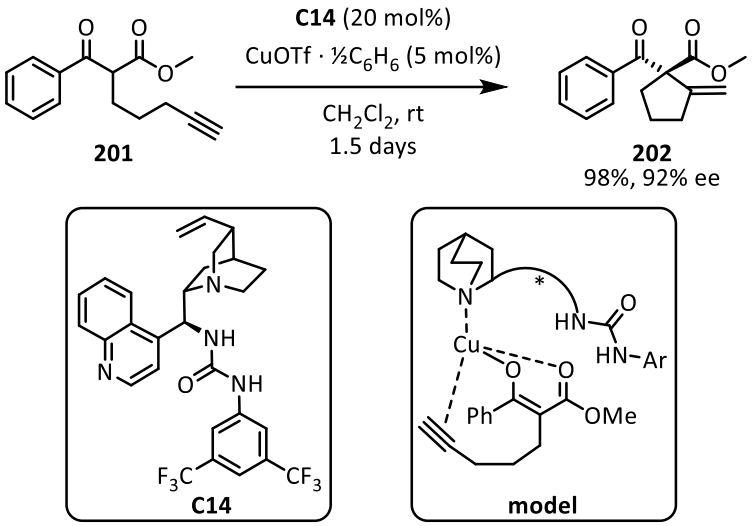
challenges, a wide range of organocatalysts have been successfully applied to the enantioselective construction of all-carbon quaternary stereogenic centres using relatively mild conditions.[59,60] Several reviews have summarized the most important advancements in the construction of all-carbon stereogenic centres in the past two decades.[56,58–69]

This chapter outlines investigations into the generation of all-carbon quaternary stereocentres using H-bonding organocatalysts introduced in Chapter 1. Section 2.2 summarizes how we took inspiration from our successful Conia-ene methodology reported in 2009[70] to develop a new intramolecular Michael addition reaction. Section 2.3 reports initial investigations in pursuit of an enantioselective α-alkylation, and the resulting serendipitous discovery of a new catalyst family.

2.2 Conjugate Additions

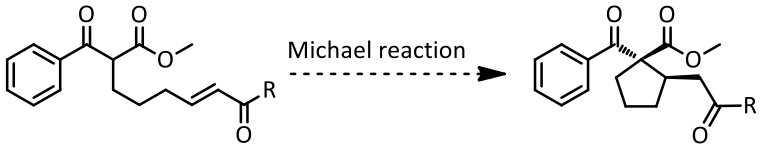
2.2.1 Conia-ene precedence

Our group has demonstrated the effective application of in-house developed organocatalysts in the enantioselective construction of several all-carbon stereogenic centres. For example, a 2009 report described an enantioselective Conia-ene reaction using Brønsted base/Lewis acid cooperative catalysis (scheme 2.01).[71] In this Conia-ene reaction, the tertiary amine in catalyst **C14** acts as a Brønsted base to form an enolate of the β-ketoester. Mechanistic studies and density functional theory (DFT) calculations of transition state structures for the Conia-ene reaction suggest that the bridgehead nitrogen ligates the copper of the copper enolate, and the urea preferentially forms a strong dual H-bond with the more electron-rich carbonyl oxygen of the ketone, which gives rise to the enantioselectivity.[72]



Scheme 2.01: *Proposed mode of activation via cooperative catalysis in Dixon's Conia-ene reaction*[71]

Building on the Conia-ene reaction, we envisaged that by replacing the alkyne moiety of **201** with a Michael acceptor, we could adapt this methodology to an enantioselective intramolecular Michael reaction to access the profuse cyclopentane structural motif with pendant functionality amenable to further derivatization (scheme 2.02). Unlike the Conia-ene reaction, an intramolecular Michael reaction can also form two adjacent stereocentres concurrently.

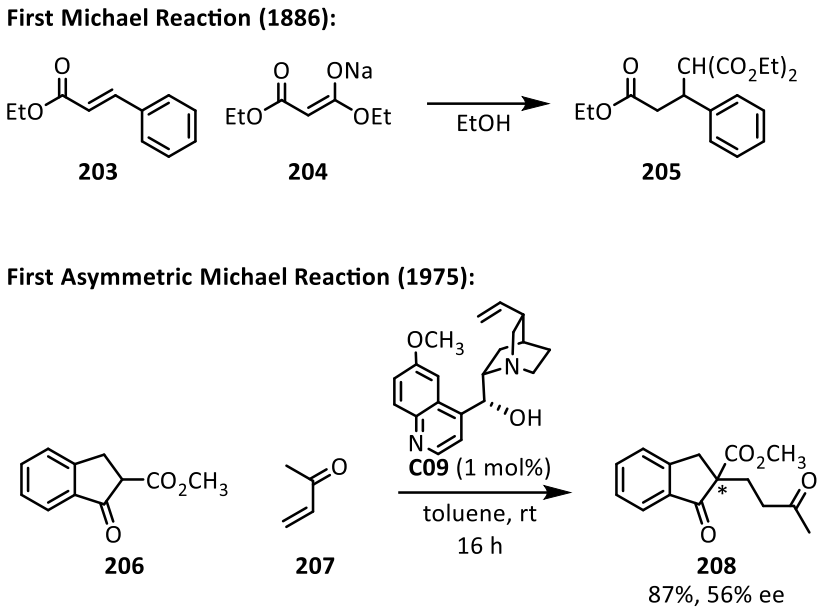


Scheme 2.02: *Proposed intramolecular Michael reaction*

2.2.2 Michael reactions

A reaction between a stabilized carbanion and an electrophilic alkene attached to an electron withdrawing group, like that proposed in scheme 2.02, is called a 1,4-conjugate addition, or Michael reaction.[73] Michael first reported the conjugate addition of the sodium

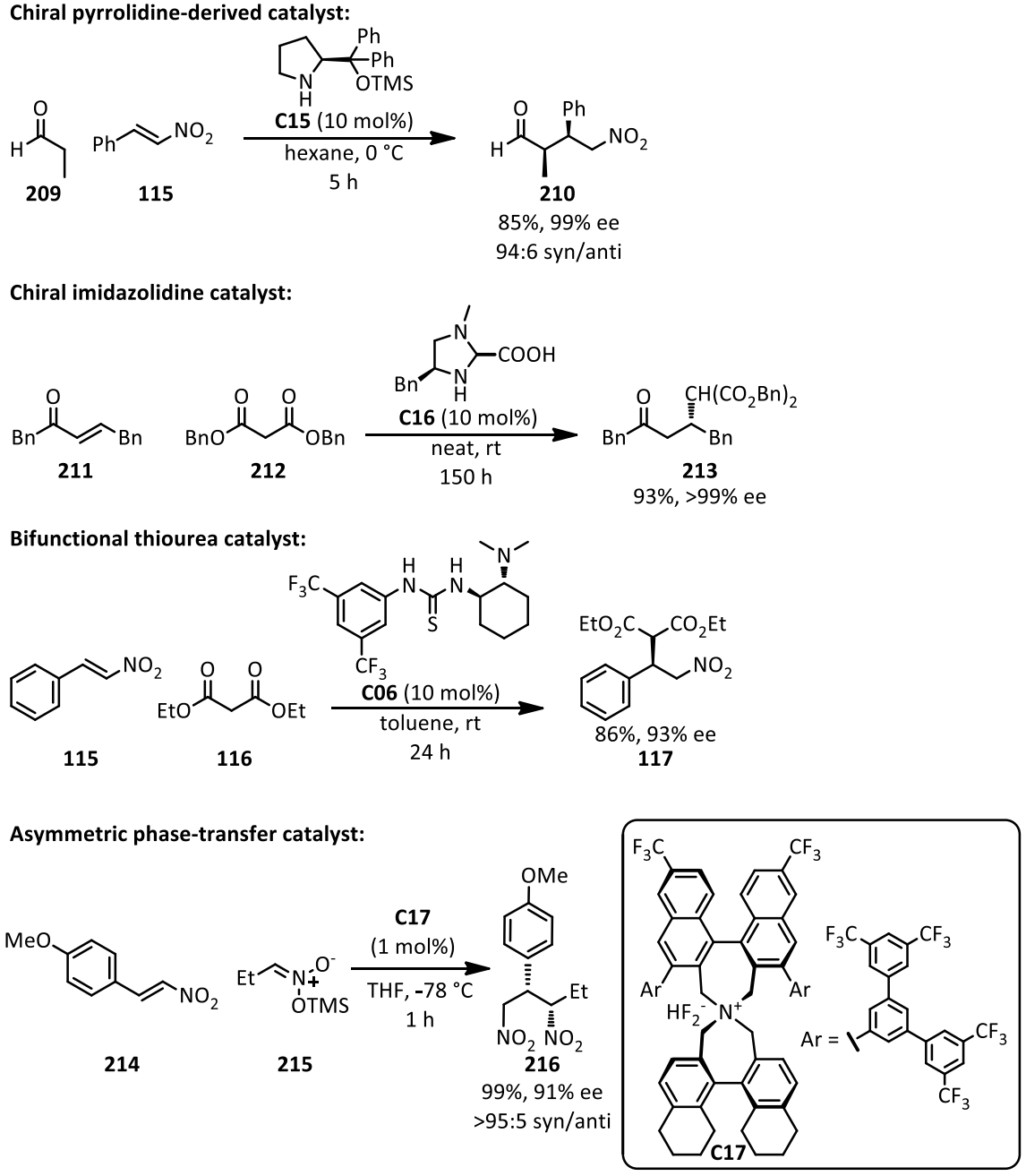
enolate of diethyl malonate onto an *α,β*-unsaturated ester in 1886,[74] and in 1975 Wynberg reported the first asymmetric version of a related Michael reaction using cinchona alkaloid catalyst **C09** (scheme 2.03).[75]



Scheme 2.03: *Seminal reports of a Michael reaction*[74] *and asymmetric Michael reaction*[75]

1,4-Conjugate additions have grown over the past 130 years to become one of the most important and fundamental methods of *β*-alkylation in organic synthesis. Metal-based methods initially dominated asymmetric investigations, with copper and rhodium-BINAP based catalysts achieving particularly high selectivities.[76] In the last few decades, organocatalyst development has helped achieve highly enantio- and diastereoselective metal-free conjugate additions.[77] Enamine catalysis using chiral pyrrolidine[78] and imidazolidine[79] derivatives, bifunctional catalysis using thiourea H-bond donors,[50] and asymmetric phase-transfer catalysis using N-spiro chiral quaternary ammonium bromide[80] are just some of the many successful organocatalytic systems that have emerged (see scheme 2.04 for selected examples).[77] Our own group has reported organocatalytic, enantioselective

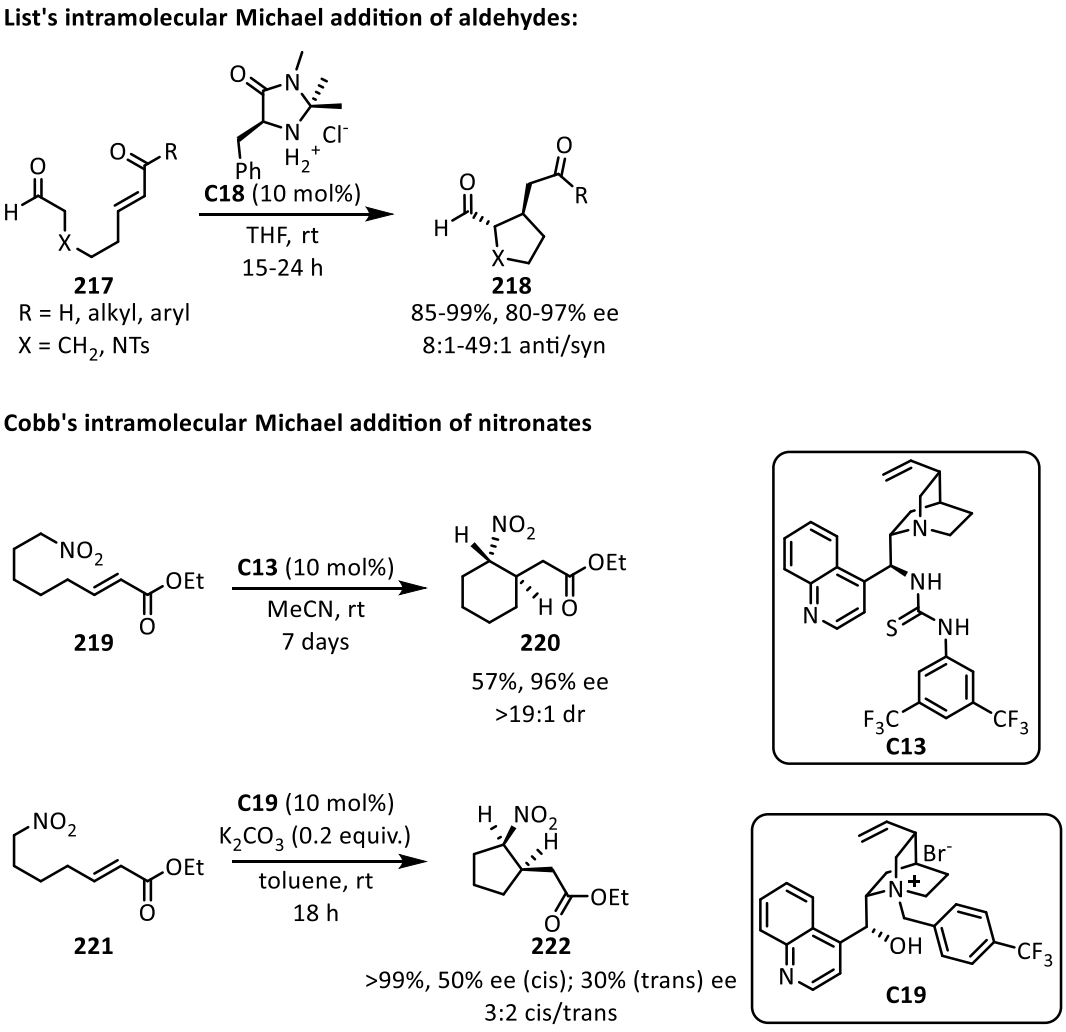
variations of the Michael reaction such as the additions of malonate esters,[81] 5-aryl-1,3-dioxolan-4-one heterocycles,[82] and a 2-oxopyrrolidine-3-carboxylate[83] to nitro olefins.



Scheme 2.04: *Selected examples of enantioselective organocatalytic conjugate additions*[50,78–80]

While many elegant organocatalytic intermolecular Michael reactions achieving excellent enantioselectivities have been communicated, reports of intramolecular variations

are more limited. However, we have demonstrated the power of intramolecular Michael reactions to efficiently and selectively build complexity in natural products in the total syntheses of calyciphylline A-style *Daphniphyllum* alkaloids,[84,85] a strategy also employed by other groups.[86–88] Early reports using stoichiometric proline[89] or chiral amines[90] hinted at the potential of organocatalysis in this reaction class, but List *et al.*'s 2004 paper describing the intramolecular cyclization of aldehydes to *α,β*-unsaturated ketones (**217**) using proline-derived catalyst **C18** was the first excellent example of an enantioselective organocatalytic intramolecular Michael reaction[91] (scheme 2.05). Shortly after, Hayashi and coworkers used a cysteine-derived organocatalyst,[92] Nishiyama and coworkers used a proline-derived anilide,[93] and Gaunt and coworkers used a proline-derived organocatalyst[94] to achieve excellent enantioselectivities in intramolecular conjugate additions of aldehydes to *α,β*-unsaturated ketones. In 2009 Cobb *et al.* achieved a superb intramolecular cyclization of nitronates onto unsaturated esters (**219**) using cinchona-derived bifunctional thiourea organocatalyst **C13** to form 6-membered carbocycles[95] (scheme 2.05). In 2013, Quintavalla *et al.*[96] and Zhao *et al.*[97] both independently built on Cobb's methodology by using a similar bifunctional thiourea organocatalyst to perform a Henry reaction and Michael reaction in tandem. Interestingly, Cobb *et al.* found that changing to a 5-membered carbocycle (**222**) instead of a 6-membered carbocycle (**220**) caused their enantioselectivities to plummet from 90% ee to 30% ee.[98] The enantioselectivity of the 5-membered carbocycle was raised to 50% ee using cinchona-derived phase-transfer catalyst **C19**, but could not be raised further[98] (scheme 2.05). Smith's group has also used chiral isothioureas as organocatalysts to perform intramolecular Michael addition-lactonizations of carboxylic acids onto unsaturated ketones.[99]



Scheme 2.05: *Intramolecular conjugate additions*[91,95,98]

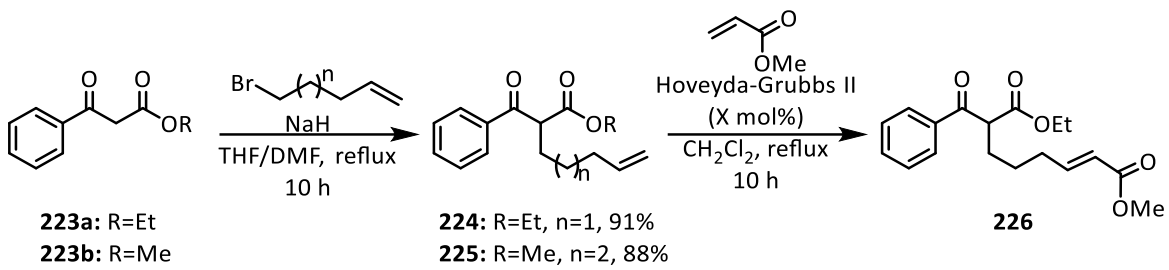
While these selected intramolecular Michael reactions have used organocatalysts to achieve excellent enantioselectivities, methods to access more diverse substrates, and ideally very general methods, are still needed. For example, the literature is dominated by aldehyde or nitronate Michael donors, and, while Cobb's examples are a prominent exception, surprisingly few methods using *α,β*-unsaturated ester Michael acceptors exist given their synthetic value, low cost and abundance. Cobb's reports also highlight how small changes, such as ring size, can drastically affect selectivities. To the best of our knowledge, no intramolecular enantioselective organocatalytic Michael additions of *β*-dicarbonyls to *α,β*-unsaturated esters or ketones to form cyclopentane derivatives have been reported. We set

out to develop such a method based on our previous success with the enantioselective Conia-ene reaction.

2.2.3 Intramolecular conjugate addition of *β*-ketoesters to *α,β*-unsaturated esters

We began our investigations by synthesizing a number of substrates similar to those that were successful in the Conia-ene reaction, as introduced in scheme 2.02. We chose a *β*-ketoester as the Michael donor, since in the Conia-ene reaction the selective H-bonding between the organocatalyst and the more electron rich phenyl ketone was a key contributor to the enantioinduction. For the Michael acceptor, we first chose an *α,β*-unsaturated ester because (a) it provides a good synthetic handle in the cyclopentane product and (b) at the time of these investigations, to the best of our knowledge, no enantioselective cyclopentane-forming intramolecular Michael reactions to unsaturated esters had been reported. While Cobb *et al.* published such an intramolecular conjugate addition to an *α,β*-unsaturated ester during the course of our investigations,[95,98] their method used a different organocatalyst and nitronates rather than *β*-dicarbonyls as the Michael donor (scheme 2.05).

Treatment of *β*-ketoester **223a** with sodium hydride and bromoalkene gave the singly alkylated **224** in excellent yield (91%, scheme 2.06). A cross metathesis catalyzed by Grubbs catalyst was used to install the *α,β*-unsaturated ester Michael acceptor. Grubbs I, Grubbs II and Hoveyda-Grubbs II catalysts all catalyzed the desired cross metathesis to give **226**, but Hoveyda-Grubbs II catalyst gave the cleanest conversion, so was used in further optimization tests (scheme 2.06). Dropping the catalyst loading from 10 mol% to 2.5 mol% only decreased the yield by 3%, thus 2.5 mol% of Hoveyda-Grubbs II was used to catalyze all subsequent metathesis reactions (table 2.01). The catalyst loading was not dropped further to keep the mass of catalyst high enough to allow for accurate weighing on the reaction scale.

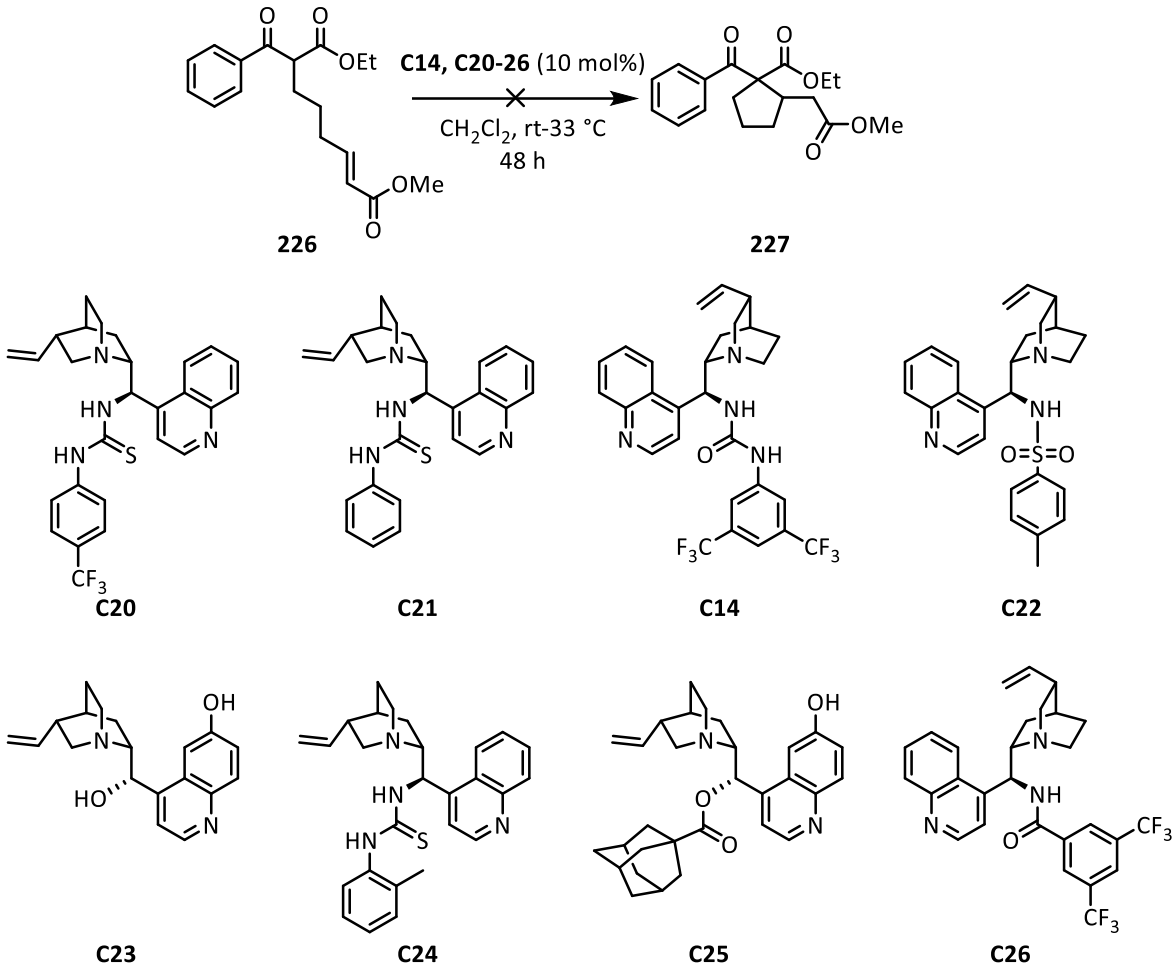


Scheme 2.06: *Synthesis of intramolecular Michael addition substrate* ***226***

X (mol%)	Yield 226 (%)
10	79
5	78
2.5	76

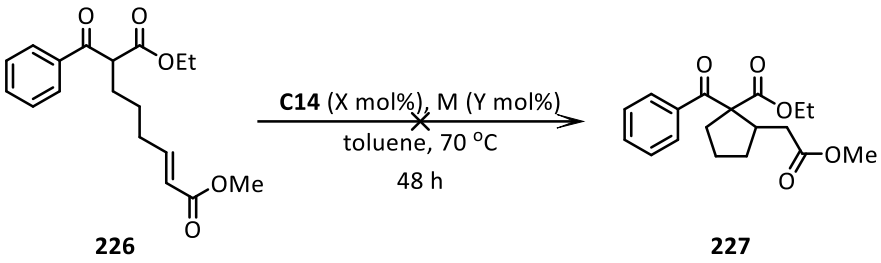
Table 2.01: *Optimization of metathesis catalyst loading*

With substrate **226** in hand, we attempted an intramolecular Michael reaction using a series of bifunctional catalysts (scheme 2.07). No cyclization was observed at room temperature nor at 33 °C when **226** was treated with thioureas **C20**, **C21** or **C24**, urea **C14**, sulphonamide **C22**, alcohol **C23**, ester **C25** or amide **C26**. This result is consistent with observations in the Conia-ene reaction where we similarly saw no reactivity with organocatalyst alone: both organocatalyst and a metal co-catalyst were essential for reactivity.



Scheme 2.07: *Catalysts screened for an intramolecular Michael reaction of* ***226***

In an effort to invoke reactivity, we added a variety of metal co-catalysts. In the Conia-ene reaction, the ratio of bifunctional organocatalyst to metal was important. We hypothesized that the tertiary amine of the bifunctional catalyst bound tightly to the copper co-catalyst. Consequently, it was necessary to have an excess of the bifunctional organocatalyst relative to the copper so that sufficient unbound amine was available to act as the base to form the enolate. Thus, in our intramolecular Michael reaction we tried catalyst **C14** with a variety of metal salt co-catalysts in different ratios (scheme 2.08, table 2.02).



226 **227**

Scheme 2.08: *Attempted intramolecular Michael reaction with a metal co-catalyst*

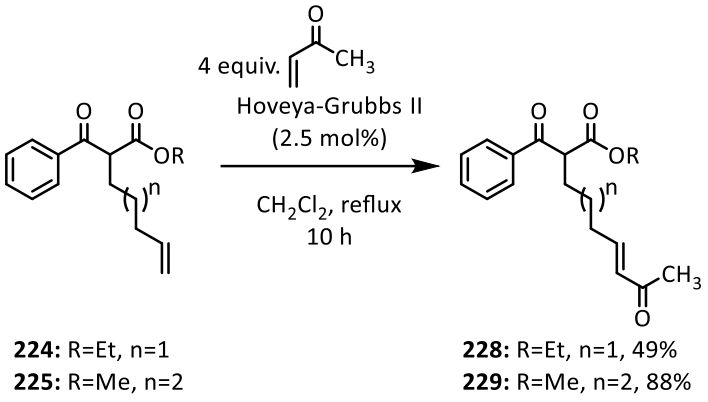
X (mol% C14)	M	Y (mol% M)	Results
20	Cu(OTf)	20	No reaction
20	Cu(OTf)	10	No reaction
10	$Cu(OTf)_2$	10	No reaction
10	$Cu(OTf)_2$	2.5	No reaction
10	$Pd(OAc)_2$	10	No reaction
10	$Pd(OAc)_2$	5	No reaction
10	$FeCl_3$	10	No reaction
10	$FeCl_3$	5	No reaction
10	$NiCl_2{\cdot}(H_2O)_6$	10	No reaction
10	$NiCl_2{\cdot}(H_2O)_6$	5	No reaction
10	$Zn(OAc)_2$	10	No reaction
10	$Zn(OAc)_2$	5	No reaction
10	$CeCl_3{\cdot}(H_2O)_7$	10	No reaction
10	$CeCl_3{\cdot}(H_2O)_7$	5	No reaction

Table 2.02: *Attempted intramolecular Michael reaction with a metal co-catalyst*

Cyclization onto the *α,β*-unsaturated ester, however, proved challenging: no reactivity was observed in any of the reaction conditions screened at room temperature nor elevated temperature (70 °C). In an effort to gain reactivity, we decided to replace the *α,β*-unsaturated ester Michael acceptor with an *α,β*-unsaturated ketone Michael acceptor. Since ketones are more electron withdrawing than esters and form stronger H-bonds with (thio)ureas,[32,33] we hoped that a ketone would increase the electrophilicity of the alkene sufficiently to invoke reactivity.

2.2.4 Intramolecular conjugate addition of a *β*-ketoester to an *α,β*-unsaturated ketone

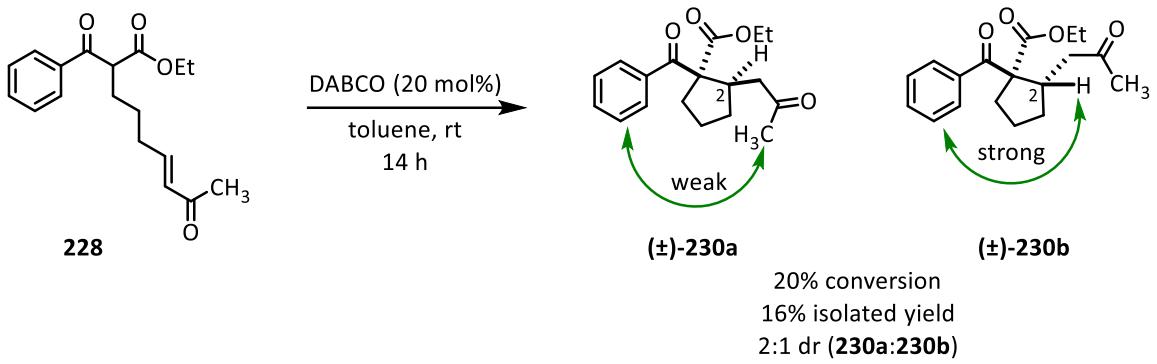
Substrates **228** and **229**, bearing *α,β*-unsaturated ketone Michael acceptors, were synthesized using the same method described above (scheme 2.09). Terminal alkenes **224** and **225** were transformed into *α,β*-unsaturated ketone Michael acceptors *via* a cross metathesis catalyzed by Hoveyda-Grubbs II catalyst (scheme 2.09). In test reactions, we observed no evidence of cyclization of the 6-membered carbocycle precursor **229** in the presence of bifunctional urea catalyst **C14**.



Scheme 2.09: *Synthesis of intramolecular Michael reaction substrates with ketone Michael acceptors*

Treatment of substrate **228** with catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO) gave racemic cyclopentanes **(±)-230a** and **(±)-230b** as a 2:1 (**230a**:**230b**) mixture of diastereomers in 16% combined isolated yield (20% conversion, estimated by analysis of the crude ^{1}H NMR spectrum) after 14 h (scheme 2.10). We assigned the two diastereomers using nuclear Overhauser effect (NOE) NMR experiments. The minor diastereomer, **(±)-230b**, showed a clear NOE between the hydrogen on C(2) and the phenyl ring in both a 1D NOE experiment and a 2D NOESY experiment, and was thus assigned with the structure shown in scheme 2.10. For the major diastereomer, **(±)-230a**, a 1D NOE experiment

irradiating the C(2) hydrogen showed no such NOE to the phenyl ring, nor any other proton signals. A 2D NOESY experiment showed no strong diagnostic NOE signals, but a weak signal between the phenyl ring and the ketone methyl group supports the tentative relative stereochemical configuration assigned in scheme 2.10.



Scheme 2.10: *Cyclization and diastereomer assignment of cyclopentane racemates*

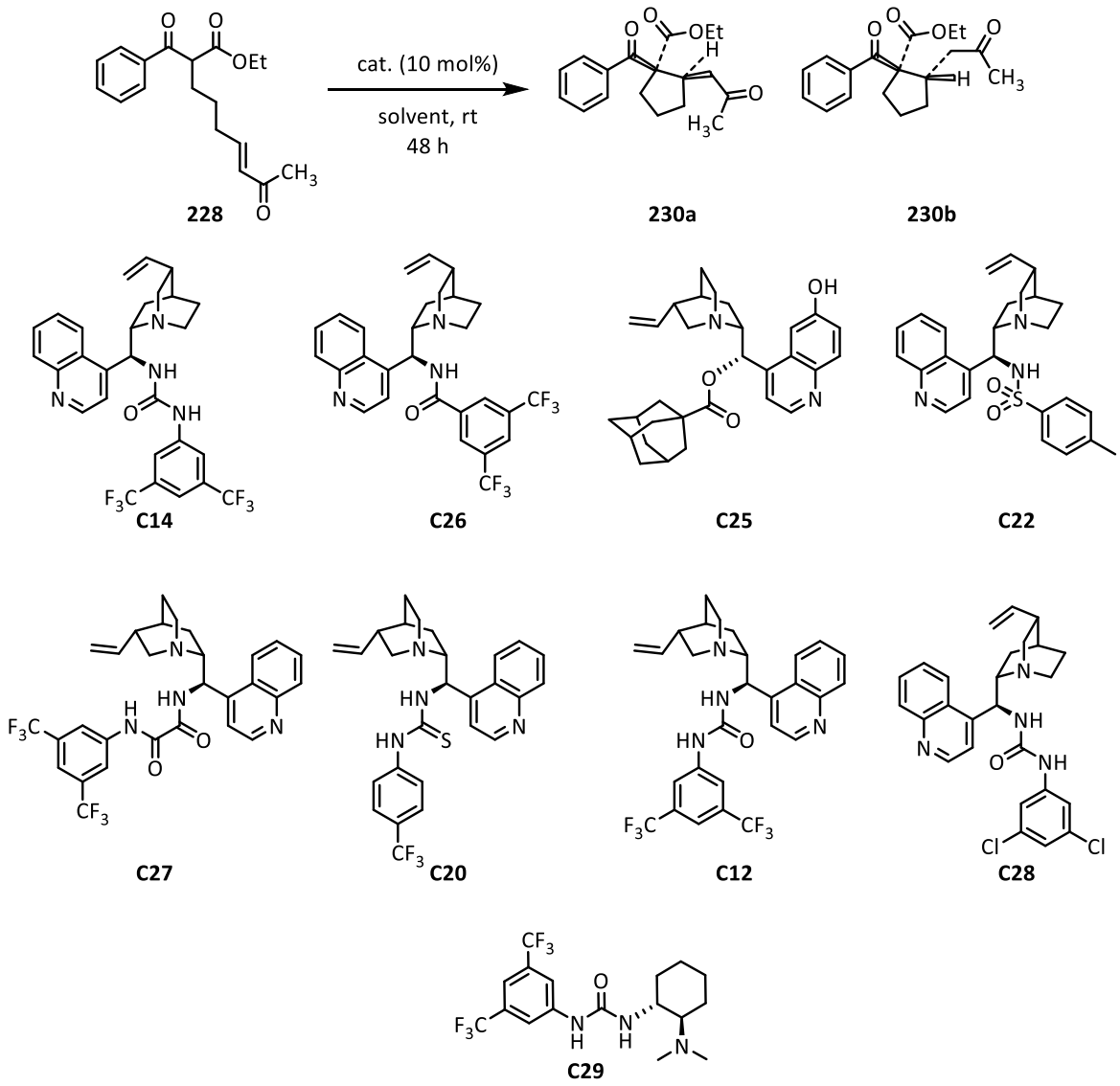
Pleasingly, in the presence of organocatalyst **C14**, **228** cyclized via an intramolecular Michael reaction to give cyclopentanes **230a** and **230b** in a 44:56 (**230a**:**230b**) ratio and with 18% ee and 52% ee, respectively (87% conversion, scheme 2.11, table 2.03, entry 1). We cyclized substrate **228** in the presence of numerous organocatalysts (scheme 2.11) in a variety of solvents in an attempt to improve the enantioselectivity and diastereoselectivity of the intramolecular Michael reaction (table 2.03). The conversion of each reaction was estimated using the relative integrations of the starting material and product peaks in the crude ^{1}H NMR spectrum. To allow for rapid optimization, a sample of each reaction was purified by preparative thin layer chromatography (TLC) for analysis by high performance liquid chromatography (HPLC) with a chiral, non-racemic stationary phase.

With reactivity and enantioselectivity established, we tested organocatalysts bearing different types of H-bond donors (table 2.03). A preliminary solvent screen of toluene, CH_2Cl_2 and methyl *tert*-butyl ether (MTBE) with catalyst **C14** (entries 1-3) revealed that toluene led to the highest enantioselectivities, thus this solvent was used when assessing

various H-bond donors. Organocatalyst **C26**, bearing an amide with a single H-bond donor, catalyzed the reaction, but with low reactivity (18% conversion in 2 days), poor dr (45:55, **230a**:**230b**) and little enantiocontrol (2% ee **230a**, 12% ee **230b**, entry 4). Ester-based organocatalyst **C25**, bearing a free hydroxyl group on the quinoline available for H-bonding, and sulfonamide organocatalyst **C22** gave similarly poor conversions, diastereoselectivities, and enantioselectivities (entries 4-5). These results suggest that a single H-bond donor is not sufficient to invoke significant enantiocontrol, and that the strong dual H-bond donor in urea **C14** plays a key role in the enantioinduction. Dual H-bond donor **C27**, with an extra carbon between the H-bond donors compared to **C14**, gave the products **230a** and **230b** in low conversion (19%) and with little diastereo- (43:57, **230a**:**230b**) or enantiocontrol (7% ee **230a**, 3% ee **230b**, entry 7). This suggests that the geometry of the two H-bond donors in urea **C14** is also important.

Next, we tested thioureas. Thioureas have the same number and geometry of H-bond donors as ureas, but have a higher acidity, with the pK_a of **C20** approximately 12.3 in DMSO versus urea **C14**, which has a pK_a of approximately 17.6 in DMSO.[100] Since H-bond donating tendency correlates to acidity for similar functional groups,[101,102] we might expect thioureas to have greater H-bond donating potential than ureas. However, in our system, thiourea **C20** exhibited limited reactivity and stereocontrol in toluene, outperforming the single H-bond donor organocatalysts, but not approaching the reactivity and selectivity of urea **C14** (entry 8). This is perhaps because the strongest H-bonds form between species with similar pK_a's.[102] Substituted β-keto ester **228** has a pK_a of approximately 16 in DMSO,[103] so is more closely matched to urea catalyst **C14** than thiourea catalyst **C20**. Changing the solvent to MTBE, thiourea **C20** gave the minor diastereomer, **230a**, in the highest enantioselectivity of all catalysts tested (39% ee, entry 10). However, the reactivity was still poor (48% conversion) compared to urea **C14** and the major diastereomer, **230b**,

was obtained in 13% lower ee than with urea **C14**. Thus, dual H-bond donating ureas were established as the best H-bond donors for this reaction.



Scheme 2.11: *Catalyst and solvent screen*

Entry	Catalyst	Solvent	Conversion (%)	dr (230a:230b)	230a ee (%)	230b ee (%)
1	**C14**	Toluene	87	44:56	18	52
2	**C14**	CH_2Cl_2	79	47:53	12	39
3	**C14**	MTBE	80	45:55	30	49
4	**C26**	Toluene	18	45:55	2[a]	12[a]
5	**C25**	Toluene	17	39:61	1[a]	0[a]
6	**C22**	Toluene	17	39:61	10[a,b]	3[a]
7	**C27**	Toluene	19	43:57	7[a,b]	3[a]
8	**C20**	Toluene	27	40:60	25[a,b]	18[a,b]
9	**C20**	CH_2Cl_2	23	40:60	18[a,b]	11[a,b]
10	**C20**	MTBE	47	41:59	39[a,b]	39[a,b]
11	**C12**	Toluene	65	47:53	16[b]	31[b]
12	**C12**	CH_2Cl_2	71	48:52	10[b]	11[b]
13	**C12**	MTBE	36	40:60	18[a,b]	23[a,b]
14	**C28**	Toluene	72	40:60	21	56
15	**C28**	CH_2Cl_2	70	43:57	1	50
16	**C28**	MTBE	64	41:59	23	53
17	**C28**	EtOAc	34	40:60	10	32
18	**C28**	MeOH	88	48:52	0	0
19	**C28**	Acetone	99	45:55	2	46
20	**C29**	Toluene	65	40:60	26	56[b]
21	**C29**	CH_2Cl_2	82	44:66	32	57[b]
22	**C29**	MTBE	66	39:61	21	62[b]
23	**C29**	EtOAc	38	42:58	19	34[b]
24	**C29**	MeOH	90	51:49	2	1[b]
25	**C29**	Acetone	100	47:53	29	54[b]
26	**C29**	DMF	100	46:54	21	45[b]

Table 2.03: *Catalyst and solvent screen for the intramolecular Michael reaction;* [a]*enantioselectivities may be slightly higher than reported due to low conversion (vida infra);* [b]*opposite enantiomer observed*

Using organocatalyst **C12**, the pseudo-enantiomer of **C14**, we were able to obtain the opposite enantiomers of **230a** and **230b**, but unfortunately the enantioselectivity of the major diastereomer was lower (31% ee, entry 11) than with **C14** (52% ee). **C28** was synthesized from the same cinchona alkaloid as **C14** (cinchonidine) but bears a 3,5-dichlorophenyl substituted urea instead of a 3,5-bis(trifluoromethyl)phenyl substituted urea.

This tuning of the electron density of the urea resulted in a slight increase in enantioselectivity of the major diastereomer (56% ee **230b**, entry 14). We achieved the same enantioselectivity for the opposite enantiomer (56% ee, entry 20) using Takemoto-like urea organocatalyst **C29**. Changing to more polar solvents such as EtOAc, acetone, and DMF (entries 17/23, 19/25 and 26) with these catalysts generally resulted in a decrease in enantioselectivity for the major diastereomer, athough a change to dichloromethane had no effect on the enantioselectivity and gave the best conversion for **C29** (82%, entry 23). We hypothesized that straight-chain cyclization precursor **228** and the organocatalyst are less closely associated in more polar solvents, thus resulting in a less tight transition state and an ensuing decrease in enantioselectivity. Using a polar protic solvent such as methanol resulted in almost complete loss of enantiocontrol (entries 19 and 26). Methanol likely competes with the catalyst to form H-bonds with the substrate, thus decreasing catalyst-substrate interaction. A change to the non-polar methyl MTBE with catalyst **C29** gave the highest enantioselectivity for **230b**: 62% ee at 66% conversion after 2 days.

With this partially optimized system, 10 mol% **C29** in MTBE, we attempted to enhance the enantioselectivity using metal cocatalysts. However, the addition of 5 mol% $NiCl_2$(dppe), $In(OTf)_3$, $FeCl_3$, $Zn(OAc)_2$ or $CeCl_3 \cdot 7H_2O$ all resulted in significantly lower enantioselectivities than with organocatalyst **C29** alone (entry 22, table 2.03), with Fe(III) rendering the reaction almost racemic.

While the change from an ester to a ketone Michael acceptor was necessary to gain reactivity, the *α,β*-unsaturated ketone Michael acceptor presented a new problem: the precursor cyclized during purification by flash column chromatography on silica gel, basified silica gel, chilled silica gel, or deactivated alumina to give racemic **(±)-230a** and **(±)-230b**, a problem we also encountered when testing alternative Michael acceptors. This gives rise to both a purification issue, since some **228** is lost upon purification by column

chromatography, and falsely low enantioselectivities at low conversion, since unreacted **228** cyclizes to give racemic **(±)-230a** and **(±)-230b** upon purification for chiral HPLC measurements. To demonstrate the effect of conversion on the measured enantioselectivities, we took aliquots of the reaction illustrated in figure 2.02 at multiple time points, isolated the products by preparative TLC, and analyzed the enantioselectivity of the major diastereomer, **230b**, using HPLC with a chiral, non-racemic stationary phase. Figure 2.02 plots the enantiomeric excess over time. Over the course of 10 days, the measured enantioselectivity increased from 9% ee to 72% ee. The measured enantioselectivity stabilized after 10 days and remained at 72% ee after 21 days.

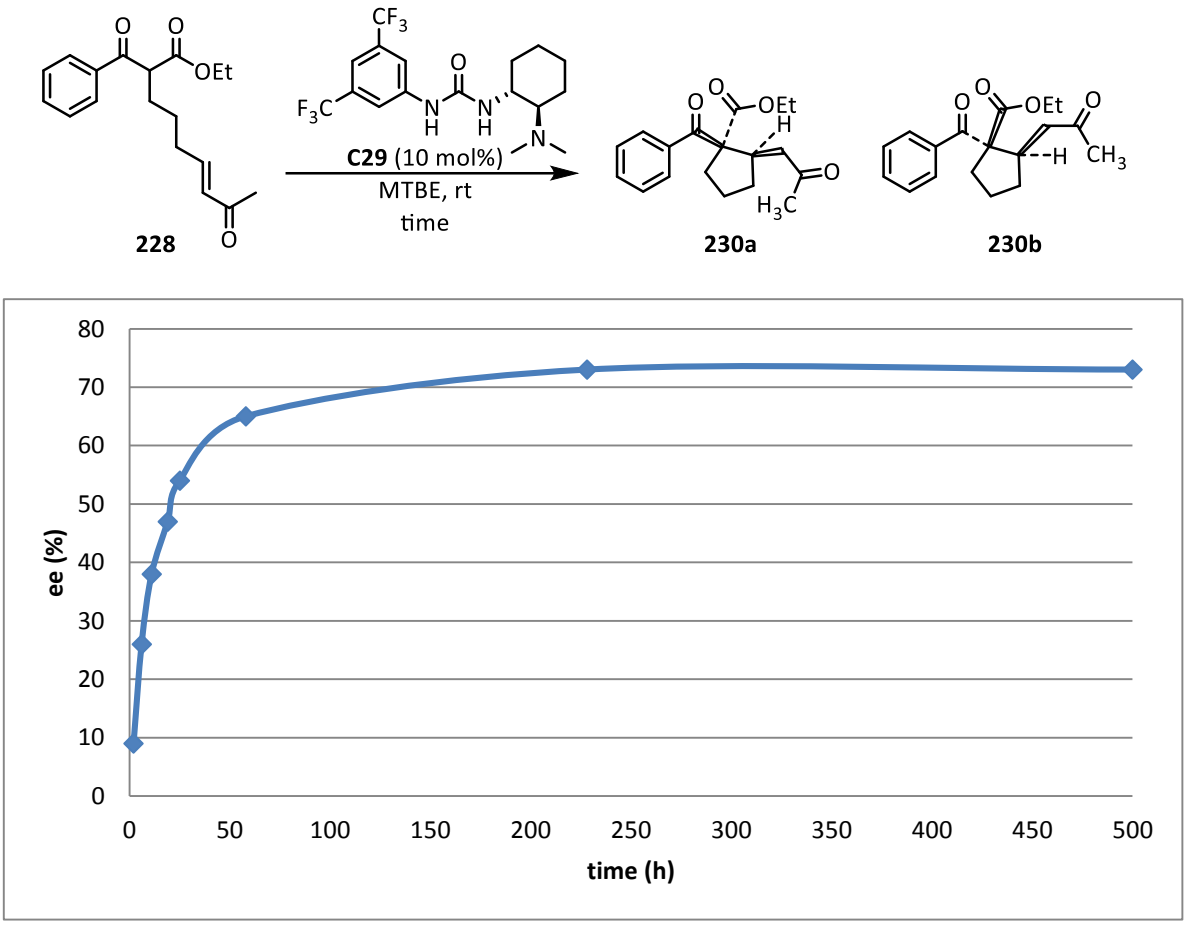


Figure 2.02: *Demonstration of ee erosion at low conversion for* ***230b***

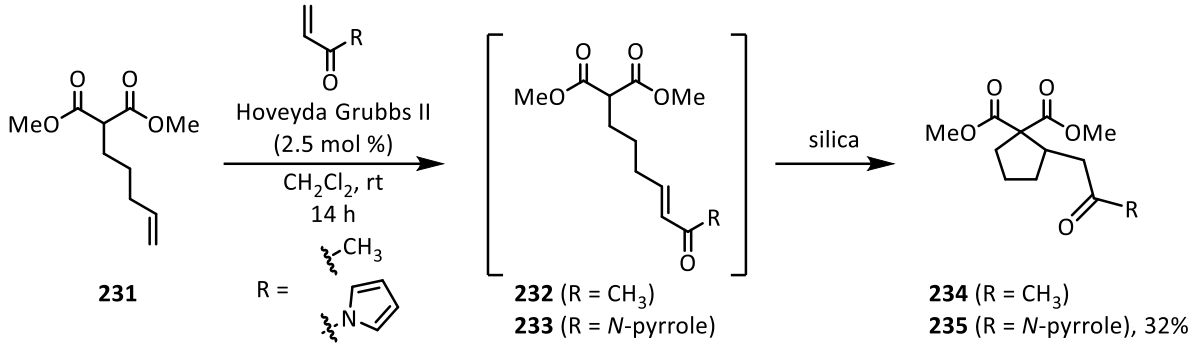
To overcome the purification issue we explored one-pot metathesis/cyclization reactions. Cross metathesis failed in the presence of **C29** with Grubbs 1st and 2nd generation catalysts, but sequential (67% ee, major diastereomer **230b**) and all-at-once (66% ee, major diastereomer **230b**) addition of Hoveyda-Grubbs II catalyst and **C29** in dichloromethane at reflux successfully gave the cyclized product without significant loss of enantioinduction. We could solve the issue of racemic cyclization of unreacted starting material by simply allowing the reactions to reach completion; however, some of the cyclizations are slow and, even after 2 weeks, starting material remains. Finally, while the cyclization of a *β*-ketoester onto an *α,β*-unsaturated ketone proceeds with good reactivity, it suffers from poor diastereoselectivity, thus limiting the synthetic utility of this method.

To address these problems we explored a new substrate class, featuring *β*-diester Michael donors. By replacing the *β*-ketoester with the less acidic *β*-diester, we hoped to decrease the reactivity sufficiently to eliminate cyclization during flash column chromatography, whilst at the same time maintaining sufficient reactivity to promote cyclization with our organocatalysts. Moreover, using symmetric diesters eliminates the issue of low diastereoselectivity.

2.2.5 Intramolecular conjugate addition of a *β*-diester to an *α,β*-unsaturated carbonyl

We first set out to synthesize substrates similar to those investigated above, keeping the unsaturated ketone Michael acceptor, but replacing the *β*-ketoester with a malonate-like *β*-diester. We attempted a cross metathesis of **231** (prepared by alkylation of dimethyl malonate with 5-bromo-1-pentene) with methyl vinyl ketone catalyzed by Hoveyda-Grubbs II catalyst (scheme 2.12). While the crude ^{1}H NMR showed the desired straight chain product **232**, upon purification over silica, only cyclized **234** was isolated (figure 2.03). Likewise, when we tried other activating Michael acceptors such as an *α,β*-

unsaturated pyrrole amide, we also isolated only cyclized product **235** upon purification on silica (scheme 2.12).



Scheme 2.12: *Cyclization during flash column chromatography*

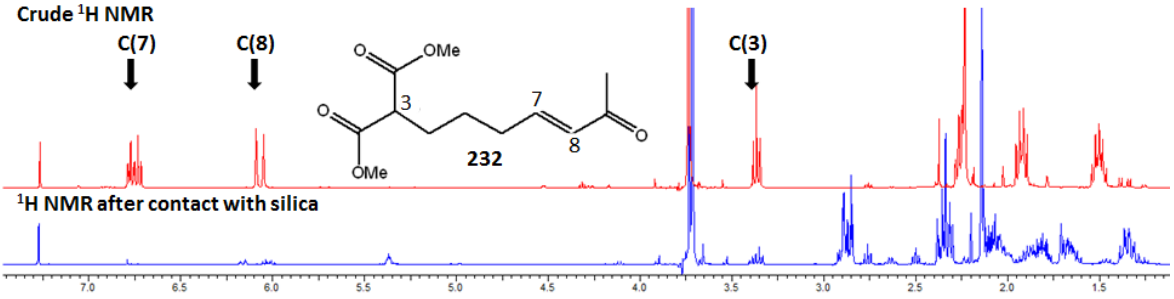
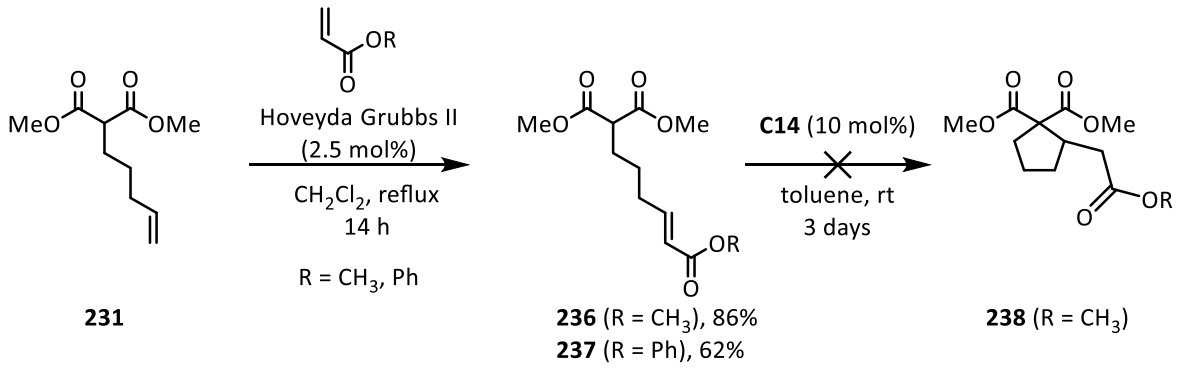


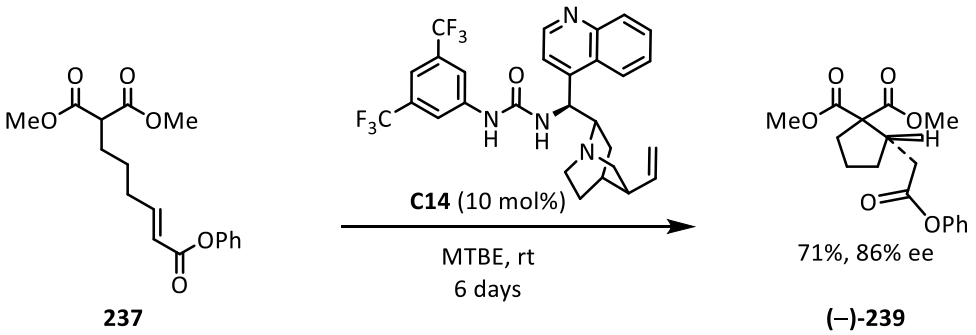
Figure 2.03: *^{1}H NMR evidence of the cyclization of **232** during purification over silica gel*



Scheme 2.13: *β-Diester Michael donor with α,β-unsaturated ester Michael acceptor*

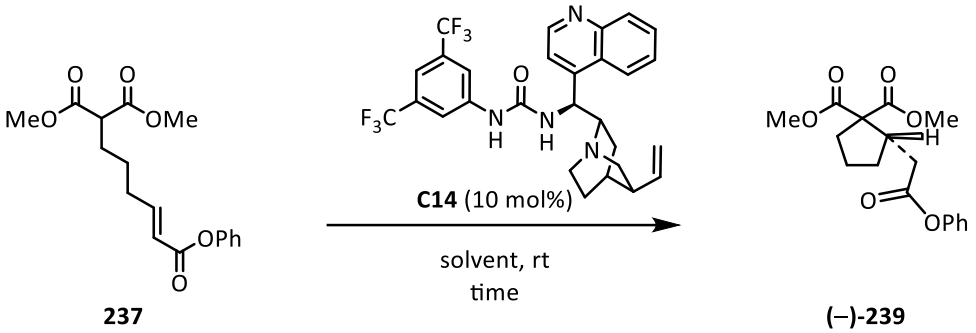
Moving back to the less reactive unsaturated methyl ester Michael acceptor first investigated, we were not able to promote cyclization with urea-based organocatalysts such

as **C14** (scheme 2.13). In an attempt to fine-tune the reactivity of our system so that cyclization occurs in the presence of our organocatalysts but not upon purification over silica, we installed the more electrophilic unsaturated phenyl ester. Pleasingly, **237** showed no signs of cyclization during flash column chromatography, but readily cyclized in the presence of 10 mol% **C14** in MTBE to give the desired product in 71% yield and 86% ee after 6 days (scheme 2.14).



Scheme 2.14: *Successful cyclization with an activated α,β-unsaturated phenyl ester*

This enantioselectivity was fairly consistent in a variety of both polar and nonpolar aprotic solvents, as well as in brine (scheme 2.15, table 2.04). The highest enantioselectivities were in the least polar solvents, with toluene invoking the highest enantioselectivity (88% ee, 68% yield, entry 9). The cyclization proceeded slowly in all solvents, but was accelerated slightly in cyclohexane (68% yield after 4 days, 87% ee, entry 5). Toluene was selected as the best solvent for further optimization because it gave the highest enantioselectivity, but cyclohexane (entry 5), MTBE (entry 1), and benzene (entry 3) gave almost identical results and are also good solvent choices for this cyclization.



Scheme 2.15: *Solvent optimization*

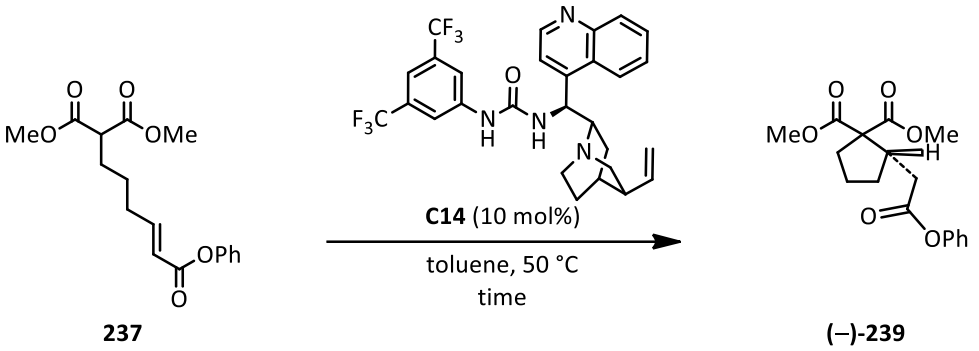
Entry	Solvent	Time (days)	Yield (%)	ee (%)
1	MTBE	6	71	86
2	CH_2Cl_2	9	86	84
3	Benzene	9	82	86
4	THF	6	77	82
5	Cyclohexane	4	68	87
6	Brine	4[a]	48	80
7	Acetonitrile	21	70	79
8	Dioxane	21	86	82
9	**Toluene**	**6**	**68**	**88**

Table 2.04: *Solvent optimization [a]reaction stalled at 50% conversion after 4 days*

Because of the long reaction time, we carried out catalyst loading and concentration tests with elevated temperature (50 °C). Using identical conditions to entry 9 in table 2.04, except heating the reaction at 50 °C, gave the cyclized product **(–)-239** in 71% yield and 85% ee after 22 h (table 2.05, entry 3). Dropping the catalyst loading to 5 mol% gave the desired product with identical enantioselectivity but slightly higher yield (86%), however the reaction took 3 days to reach completion at 50 °C, so we continued to use 10 mol% catalyst loading for subsequent optimization in order to minimize reaction times.

The enantioselectivity was very consistent with respect to concentration (scheme 2.16, table 2.05). Doubling the concentration to 0.26 M had no effect on the enantioselectivity, while decreasing the concentration by a factor of five only enhanced the enantioselectivity very slightly (85.7% ee) and took five times longer to reach completion.

Thus, we proceeded to screen a selection of related urea-based organocatalysts with the solvent (toluene), concentration (0.13 M) and catalyst loading (10 mol%) optimized.

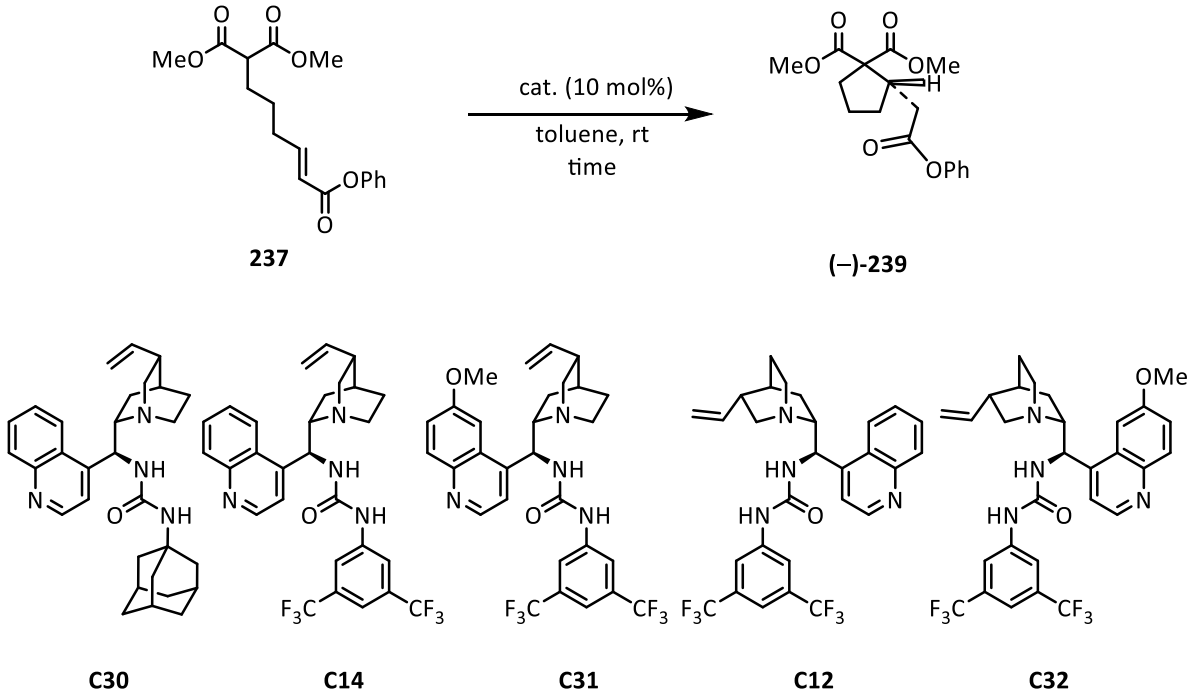


Scheme 2.16: *Catalyst loading and concentration optimization*

Entry	Concentration [M]	X (mol%)	Time	Yield (%)	ee (%)
1	0.26	10	21 h	89	85
2	0.026	10	5 days	88	86
3	0.13	10	22 h	71	85
4	0.13	5	3 days	86	85

Table 2.05: *Catalyst loading and concentration optimization*

Exchanging the aromatic substituent on the urea moiety of the catalyst with the bulky hydrocarbon adamantane significantly reduced both the yield (16%) and enantioselectivity (56% ee) of the cyclization (scheme 2.17, table 2.06, entry 1). Like cinchonidine-derived **C14**, urea-based organocatalysts derived from other cinchona alkaloid scaffolds smoothly catalysed the desired intramolecular Michael reaction. The reaction catalzyed by quinidine derivative **C32** proceeded slowly (16 days, 88% yield), but gave the opposite enantiomer in 75% ee (entry 5). Cinchonine-derived **C12** also gave the opposite enantiomer in higher yield (93%) and enantioselectivity (79% ee), and in less time (6 days). Quinine-derived catalyst **C31** behaved very similarly to cinchonidine, giving the desired product in 91% yield and 87% ee after 6 days (entry 4).



***Scheme 2.17**: Catalyst optimization*

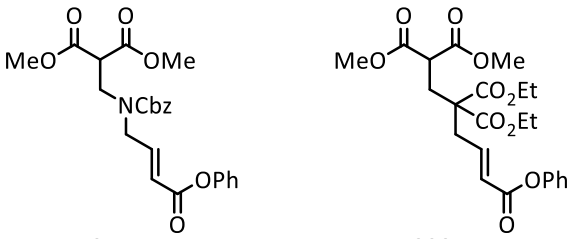
Entry	Catalyst	Time	Yield (%)	ee (%)
1	C30	6 days	16	56
2	**C14**	**6 days**	**68**	**88**
3	C12	6 days	93	79[b]
4	C31	6 days	91	87
5	C32	16 days	88	75[b]

***Table 2.06:** Catalyst optimization; [b]opposite enantiomer [**(+)-239**] obtained*

2.2.6 Limited scope

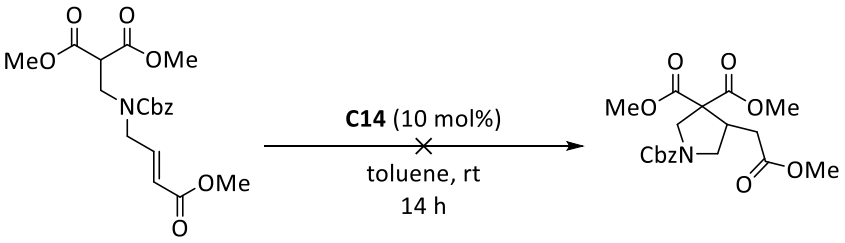
Having successfully demonstrated a new intramolecular Michael reaction of **237** catalyzed by cinchona-derived urea-based bifunctional organocatalysts, we next set out to assess the scope of our methodology. We attempted to prepare heterocycle precursors such as **371** and substituted substrates such as **339** (scheme 2.18). However, attempted syntheses of **371** and **339** and similar compounds were unsuccessful (see Chapter 3 for details). These substrates were more reactive than **237** and cyclized during flash column chromatography on silica gel. We were able to isolate the less reactive α,β-unsaturaed methyl ester analogue of **371**, **361** (see Chapter 3 for synthesis), however **C14** did not promote cyclization of this

substrate (scheme 2.19). The balance between the need for sufficiently high reactivity, so that our organocatalysts are able to promote cyclization, and stability, so that our substrates do not cyclize prematurely, limits the scope of this reaction. Encouraged by our good enantioselectivities for the *β*-diester system presented in section 2.2.5, we hypothesized that a more basic/reactive catalyst could help increase the reactivity, and thus the scope, of this intramolecular Michael reaction (see Chapter 3).



371 **339**

Scheme 2.18: *Inaccessible cyclization precursors for substrate scope*



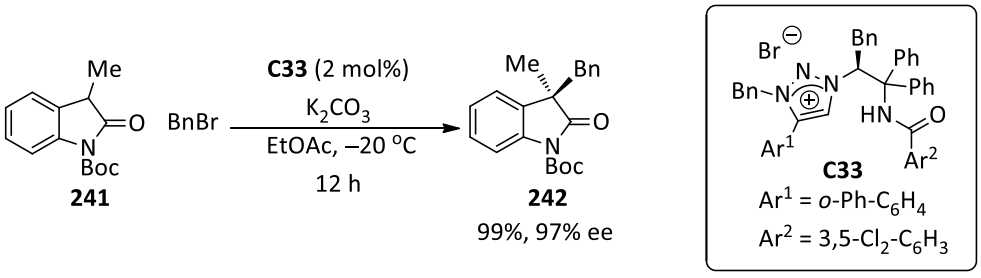
361 **240**

Scheme 2.19: *Attempted cyclization of heterocycle precursor* ***361***

2.3 Enantioselective *α*-Alkylation

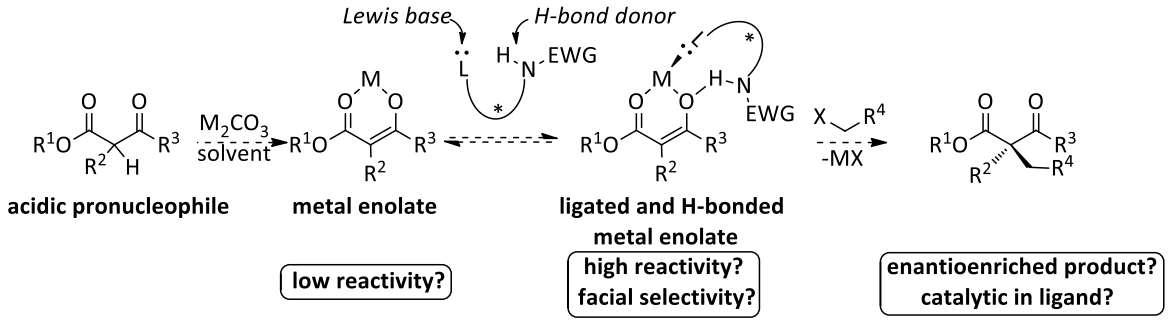
Quaternary stereocentres of *β*-ketoesters can also be accessed through α-alkylation reactions of tertiary carbons. *α*-Alkylations are fundamental transformations in organic synthesis, and enantioselective *α*-alkylations are routinely achieved using stoichiometric chiral auxiliary reagents.[14] Rendering such enantioselective α-alkylations catalytic, however, is not a generally solved problem. The most successful attempts use asymmetric phase transfer catalysis (APTC), and a handful of other approaches are successful but strictly

limited in scope. For example, an asymmetric Tsuji-Trost allylation can give good reactivity and enantioselectivity with acidic methine pro-nucleophiles, but is intrinsically limited to allylations.[15] In a recent state-of-the-art example, Ooi reported the benzylation of *N*-Boc protected oxindole potassium enolates of **241** (scheme 2.20) with 99% yield and 97% ee using phase-transfer catalyst **C33**.[16] Ooi demonstrated that H-bonding to the amide and triazolium moiety of **C33** were both essential to achieve high enantioselectivity. However, these results were highly dependent on the protecting group, with enantioselectivities falling to around 50% ee when the *N*-Boc protecting group was exchanged for methyloxycarbonyl. Clearly, despite the fundamental importance of α-alkylations, catalytic enantioselective options for this transformation are limited and lack generality and predictability.



Scheme 2.20: *Ooi's enantioselective phase-transfer alkylation of oxindole* ***241***[104]

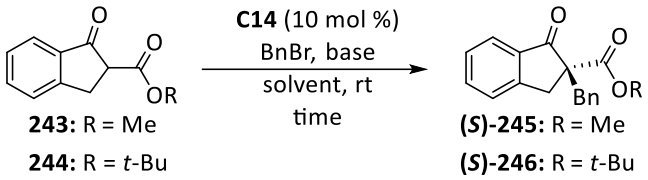
By combining the phase-transfer enolization method of Ooi's recent paper with the Conia-ene reaction previously developed in our group (scheme 2.01), we envisaged that we could enantioselectively alkylate alkali metal enolates in the presence of catalyst **C14** (scheme 2.21). We hypothesized that the bridgehead nitrogen of **C14** could coordinate to the alkali metal enolate, as it coordinates to copper (I) in the Conia-ene reaction, and the urea could form H-bonds preferentially with one of the carbonyl oxygens to afford facial selectivity in the alkylation.



Scheme 2.21: *Enantioselective α-alkylation concept*

2.3.1 Preliminary studies

We carried out proof of concept studies using a variety of solvents and bases (scheme 2.22, table 2.07). The use of potassium carbonate gave low, but significant, enantioselectivity (8% ee, entry 1), which was low because of the competitive background reaction. An even more competitive background reaction, and correspondingly diminished enantioselectivity, was observed with the use of cesium carbonate (entry 2). With lithium carbonate we were able to control the background reaction (entry 3), and had significant acceleration (approximately 60 times faster) in the presence of catalyst **C14**. This suggests that the lithium enolate has low reactivity until catalyst **C14** is ligated. Using the lithium enolate in dichloromethane (entry 6) gave the benzylated product in 10% ee. Increasing the steric bulk by using a *tert*-butyl ester (entries 7-8) had little effect on the enantioselectivity, achieving 11% ee in toluene (entry 7) and 10% ee in dichloromethane (entry 8) for the lithium enolate. These preliminary enantioselectivities are promising even though they are low. However, we were mindful that it is possible that catalyst **C14** is alkylated in-situ, and it is the quaternary ammonium salt that catalyzes the reaction through a phase transfer process.



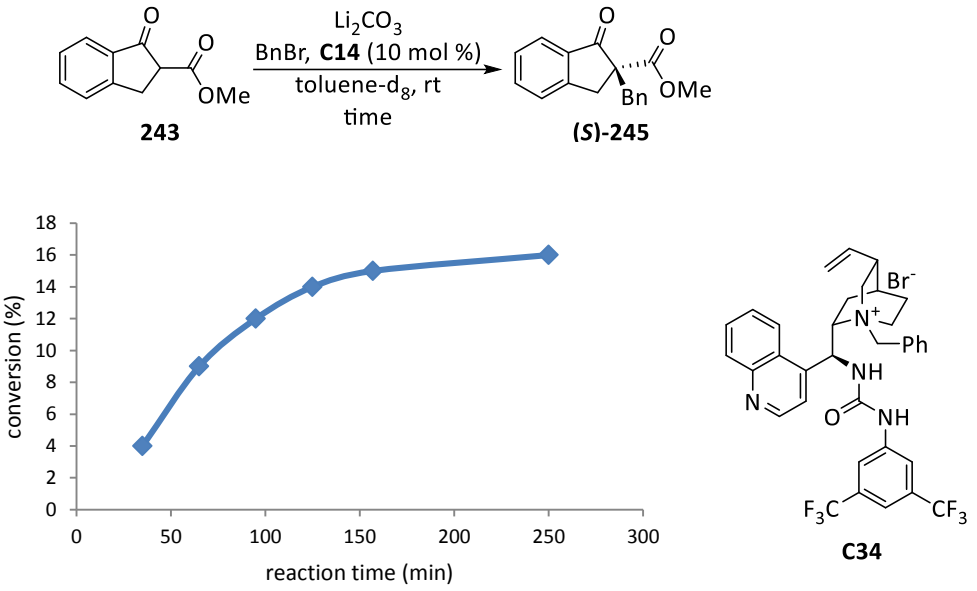
Scheme 2.22: *Preliminary α-alkylation substrate, base and solvent optimization*

	substrate	base	solvent	time (h)	conv.[a] (%)	ee[b] (%)	background conv.[c] (%)
1	**243**	K_2CO_3	Toluene	24	85	8	15
2	**243**	Cs_2CO_3	Toluene	5	93	2[d]	84
3	**243**	Li_2CO_3	Toluene	5	60	6	2
4	**243**	Li_2CO_3	EtOAC	5.5	44	5	3
5	**243**	Li_2CO_3	MTBE	5.5	56	6	1
6	**243**	Li_2CO_3	CH_2Cl_2	5.5	59	10	1
7	**244**	Li_2CO_3	Toluene	5	31	11	2
8	**244**	Li_2CO_3	CH_2Cl_2	5	33	10	7

Table 2.07: *Preliminary optimization of α-alkylation substrate, base, and solvent* [a]*conversion measured by integration against mesitylene internal standard in* [1]*H NMR analysis of crude reaction mixture;* [b]*ee determined by chiral HPLC;* [c]*conversion without addition of* ***C14****;* [d]*(R)-enantiomer observed*

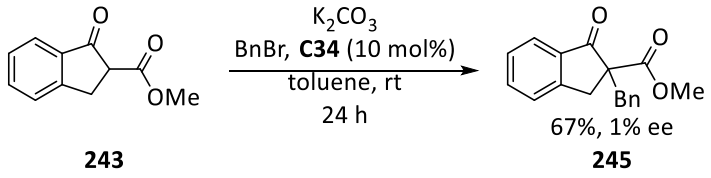
To gain insight into the nature of the catalyst in these reactions, we monitored the formation of the alkylated product **(*S*)-245** over time (scheme 2.23). The rate of product formation was greatest at the beginning of the reaction, suggesting that the true catalyst is **C14**. If the catalyst was formed *in situ* (alkylated catalyst **C34**), we would have expected to observe a low rate of product formation at the beginning of the reaction, representing the lag time associated with the formation of **C34**. Furthermore, by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, catalyst **C14** seems to remain intact on the time scale tested. However, after longer reaction times, at higher concentrations, or at elevated temperatures, we observed some evidence for the alkylation of catalyst **C14** by ^{1}H NMR analysis of the

crude reaction mixture. Thus, we set out to further explore the possibility of a phase transfer catalyst, **C34**, based on catalyst **C14**.



Scheme 2.23: *Conversion to α-alkylation product over time to determine the nature of the catalyst*

We synthesized catalyst **C34** (see Chapter 3 for details) and tested it in our alkylation reaction. Paired with potassium carbonate, phase-transfer catalyst **C34** promoted the alkylation of **243** to give **245** with only 1% ee. This different enantiomeric excess using **C34** compared to using **C14** further supports that the catalyst in scheme 2.22 is **C14**, not **C34**. While **C34** did not promote the asymmetric alkylation of **243**, we hypothesized that this new catalyst may have success in other reactions. In particular, we envisaged that by pairing **C34** with an external inorganic base, we may be able to use less reactive substrates in our intramolecular Michael reaction. These investigations are presented in Chapter 3. With low conversions and enantioselectivities, asymmetric alkylation reactions were not investigated further.

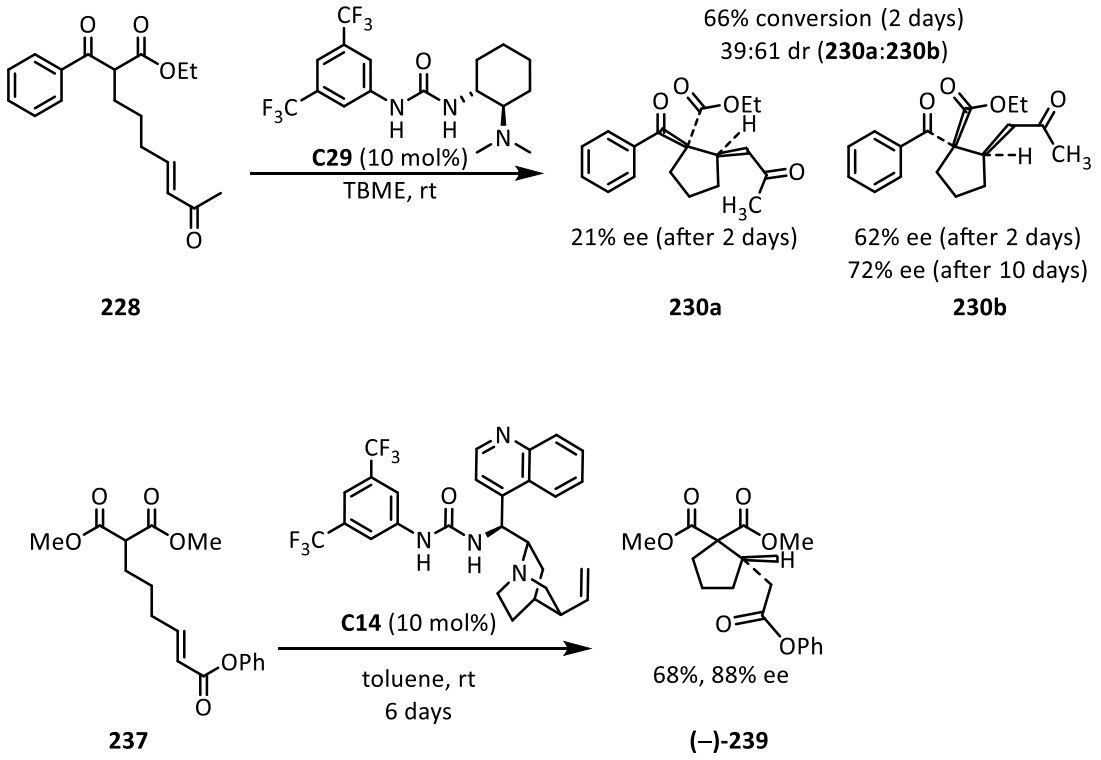


243 **245**

Scheme 2.24: *Phase-transfer catalyzed alkylation of* ***243***

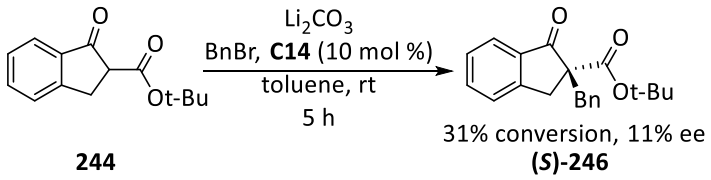
2.4 Chapter Summary

This chapter detailed our investigations into a bifunctional urea/amine organocatalyzed intramolecular Michael reaction. Using Takemoto-like organocatalyst **C29**, we successfully cyclized *β*-ketoesters onto *α,β*-unsaturated ketones to access cyclopentanes in up to 72% ee (major diastereomer, **230b**, figure 2.02). However, premature cyclization of our substrates upon silica purification and poor diastereoselectivities (up to 39:61, **230a**:**230b**) led us to investigate alternate Michael donors and acceptors. Changing our Michael donor to a symmetric *β*-diester and our Michael acceptor to an *α,β*-unsaturated phenyl ester, we eliminated both the issue of poor diastereoselectivity and premature cyclization. Using cinchona-derived urea **C14**, we formed cyclopentane **(–)-239** in up to 88% ee (scheme 2.25). However, like many organocatalyzed reactions, our methodology suffered from long reaction times and limited scope.



Scheme 2.25: *Intramolecular Michael reactions*

Our preliminary investigations into an α-alkylation catalyzed by **C14** achieved low, but significant enantioselectivities (up to 11% ee, scheme 2.26). During the course of our investigations, we observed evidence that catalyst **C14** was benzylated *in situ* under some reaction conditions. We envisaged that such a bifunctional phase-transfer catalyst, when paired with a strong external inorganic base, could help overcome the reactivity issues we encountered in our intramolecular Michael reaction while maintaining high enantioselectivities. We set out to develop such a family of H-bond donor/phase-transfer catalysts and apply them in our intramolecular Michael reaction. These studies are detailed in Chapter 3.



Scheme 2.26: C14*-catalyzed α-alkylation*

Chapter 3: Development of a New Family of Phase-Transfer Catalysts

3.1 Chapter Overview

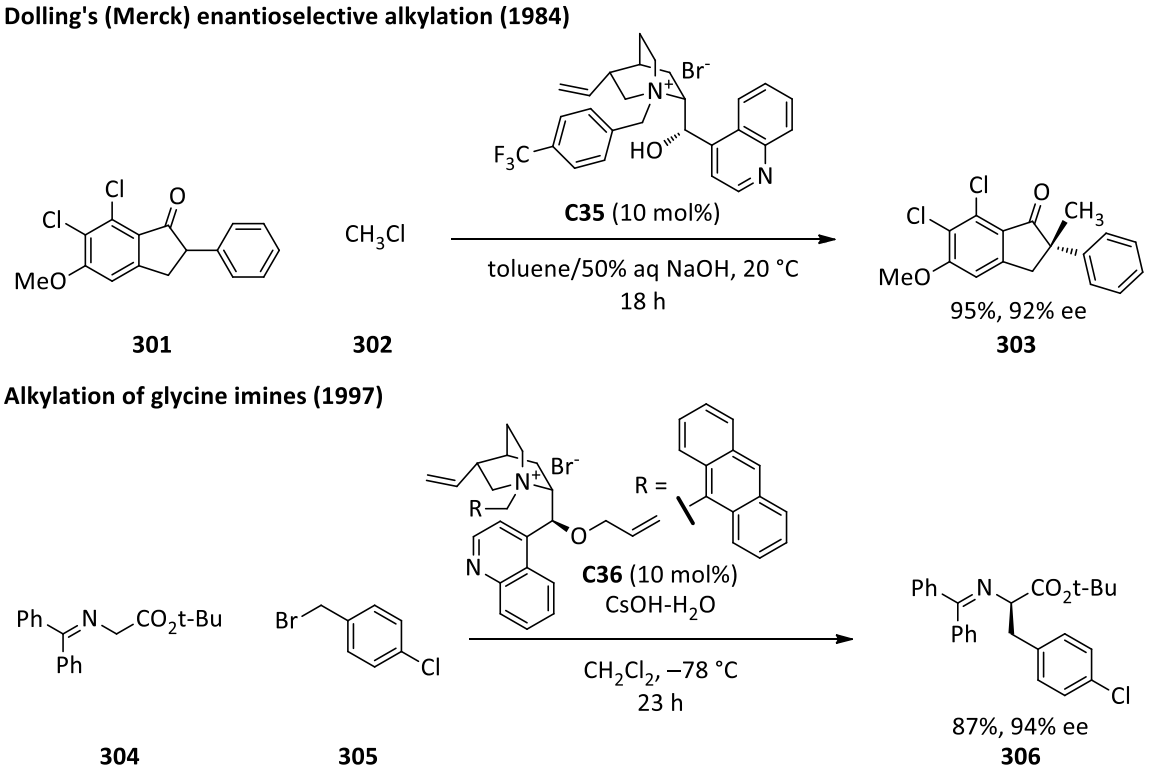
Chapter 2 outlined the development of a new intramolecular enantioselective Michael addition reaction to form 5-membered carbocycles. While we achieved good enantioselectivities (up to 88% ee), our methodology using urea/tertiary amine bifunctional organocatalysts was limited in scope because our catalysts required relatively activated *α,β*-unsaturated carbonyl Michael acceptors and acidic Michael donors to obtain practical levels of reactivity. However, many such activated systems resulted in premature cyclization upon attempted purification by flash column chromatography on silica gel. Inspired by the evidence of catalyst alkylation during the course of our investigations into enantioselective *α*-alkylation reactions, we envisioned that by pairing phase-transfer analogues of the catalysts used in Chapter 2 with strong inorganic bases, we would be able to catalyze intramolecular Michael reactions with less activated substrates while still maintaining enough rigidity in the transition state through H-bonds to invoke high enantioselectivities. This chapter outlines the conceptual design of these new cinchona-derived H-bond donor phase-transfer organocatalysts, their synthesis, and their application to the intramolecular Michael reaction introduced in Chapter 2.

3.2 Asymmetric Phase-Transfer Catalysis

3.2.1 Pioneering work and background

Phase-transfer catalysis, a term introduced by Starks in 1971,[105] involves the use of a catalyst that transfers reagents between two or more phases to facilitate and accelerate heterogeneous reactions. Wynberg's pioneering work in the late 1970's had moderate success using quaternarized ammonium cinchona salts to catalyze enantioselective

epoxidations.[106,107] However, it wasn't until Merck scientists reported highly enantioselective alkylations in 1984[108] and then applied their catalysts to the synthesis of amino acids in 1989[109] that the potential of asymmetric phase-transfer catalysis was more widely realized (scheme 3.01). In 1997, Corey[110] and Lygo[111] independently achieved excellent enantioselectivities in the asymmetric alkylation of glycine imines to produce *α*-amino acids by replacing the *N*-benzyl group in O'Donnell's (Merck) cinchona-derived catalyst with a 9-anthracenylmethyl group (scheme 3.01). Since then, a variety of asymmetric phase-transfer catalysts have been developed; quaternary ammonium salts still dominate, but chiral crown ethers, phosphonium salts, and *N*-spiroammonium salts, based on Maruoka's 1999 C_2-symmetric catalyst, are all common motifs. A representative selection of asymmetric phase-transfer catalysts are presented in figure 3.01.[112]



Scheme 3.01: *Early reports on the successful application of asymmetric phase-transfer catalysis*

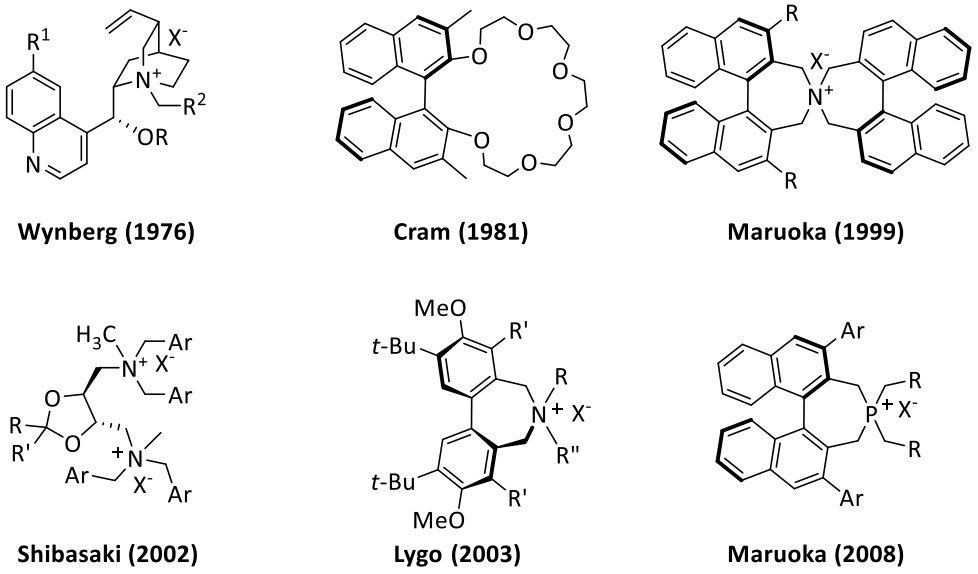


Figure 3.01: *Representative phase-transfer catalysts*[106,113–118]

Asymmetric phase-transfer catalysis is a versatile method that offers several advantages: operational simplicity, mild reaction conditions, easy scalability for industrial applications, reagent affordability, and the use of environmentally benign reagents and solvents.[119] Furthermore, controlling the introduction of a reagent into the phase containing the substrate using a phase-transfer catalyst minimizes undesired side reactions.[120] For any water soluble byproducts that are formed, separation is simplified by the biphasic nature of phase-transfer systems.[120] Phase-transfer catalysts also have the potential to allow the use of less acidic pro-nucleophiles than their tertiary amine organocatalyst analogues. While tertiary amine catalysts are generally limited to pro-nucleophiles with pK_a's less than 11 (in H_2O), phase-transfer catalysts, when paired with an external inorganic base, can access pro-nucleophiles with pK_a's up to 21.[60]

Asymmetric phase-transfer catalysis is not, however, without limitations. First, to induce enantioselectivity, the ion pair between, for example, the cationic chiral catalyst and anionic nucleophile must be tightly bound. That is, if the selectivity of a reaction is controlled largely by ionic interactions, non-polar solvents with low dielectric constants are

generally required to avoid solvent-shared or solvent-separated ion pairs, which would distance the nucleophile from the source of chirality and potentially negatively affect the selectivity (figure 3.02).

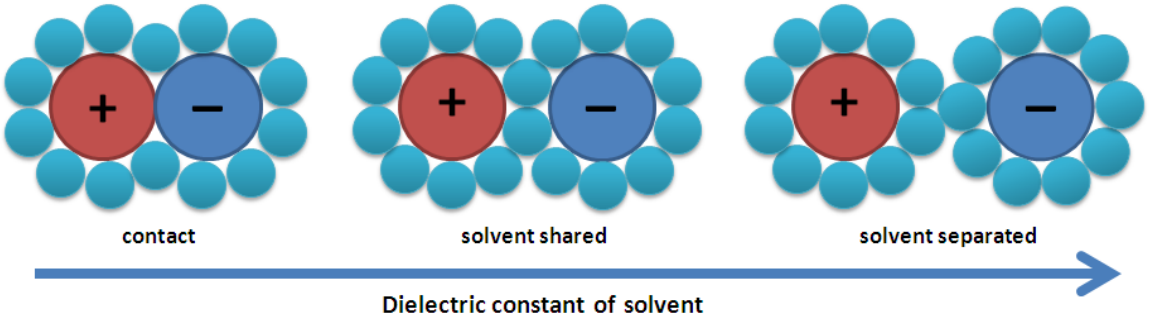


Figure 3.02: *Types of ion pairs*[121]

Furthermore, because the strength of ion-ion interactions is dependent on only the distance between two ions, ion pairs exhibit the lowest inherent *directionality* of common catalyst-substrate interactions[121] (figure 3.03). Conversely, the covalent interactions in an iminium ion, for example, are restricted to approximately 120° to maintain orbital overlap. H-bond donors exhibit intermediate directionality: while the strongest H-bonds have an X—H···A[ii] bond angle of 180°, weaker H-bonds can deviate from this angle significantly.[30] This means that minor substrate changes can sometimes have drastic effects on enantioinduction when using asymmetric phase-transfer catalysts. Historically, enantiocontrol using phase-transfer catalysts has often been governed primarily by sterics. For example, using their highly sterically crowded 9-anthracenylmethylated cinchona alkaloids, as in scheme 3.01, Corey[110] and Lygo[111] found that they could effectively block three of the four faces around the bridgehead nitrogen to achieve high enantioselectivities.

[ii] Where X is an electronegative atom and A is a Lewis base (see Chapter 1).

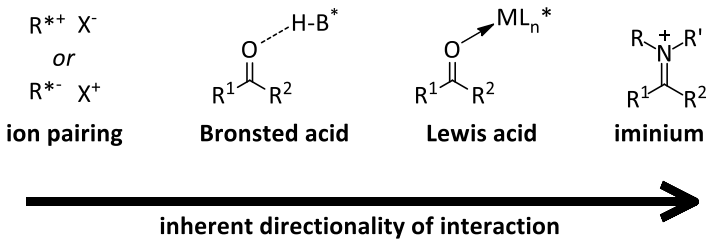


Figure 3.03: *Inherent directionality of common substrate-catalyst interactions*[121]

We hypothesized that by adding secondary recognition sites to phase-transfer catalysts, such as H-bond donors, we could achieve higher enantioselectivities through increased catalyst-substrate interaction directionality and transition state rigidity. Adding such sites could have one of two potential benefits: (1) H-bond donors could act as additional recognition sites for the nucleophile, thus enhancing directionality and organization in the transition state; or (2) the catalyst could activate both the nucleophile and the electrophile, thus lowering the energy of the transition state.

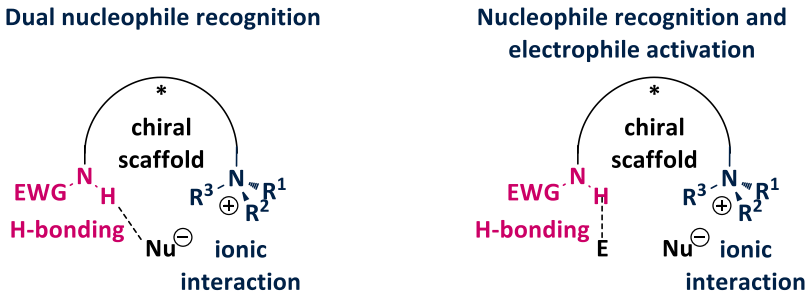
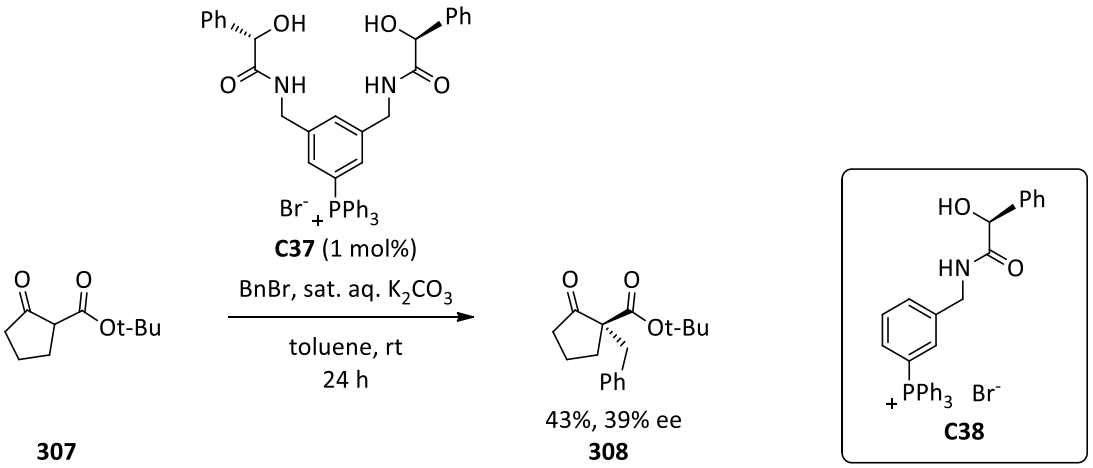


Figure 3.04: *Possible modes of activation of bifunctional phase-transfer catalysts*[122]

3.2.2 Bifunctional phase-transfer catalysis precedent

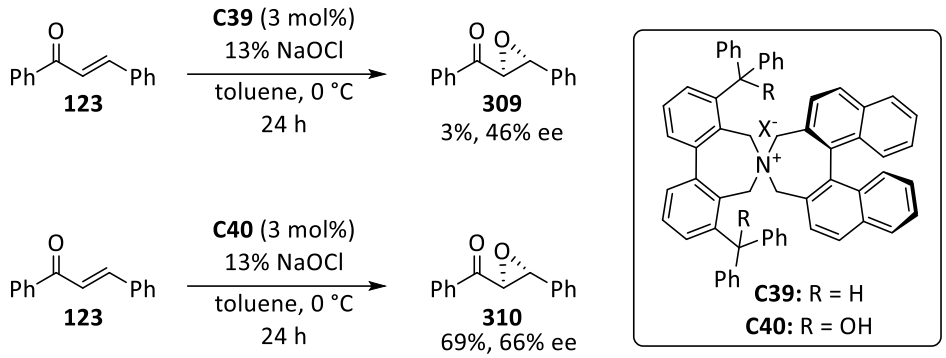
While some examples of asymmetric phase-transfer catalysts (even as early as Wynberg's 1976 effort) included hydroxyl groups, it wasn't until much later that H-bond donors were systematically incorporated and investigated in phase-transfer catalysts. Indeed, subsequent studies have shown that even when catalysts bearing hydroxyl groups are used, under alkylating conditions the active catalyst bears an alkylated ether group, not

a hydroxyl.[123] Even still, only a handful of examples of bifunctional phase-transfer catalysts have been reported to date, as recently reviewed by Novacek and Waser.[122] In 1998, Manabe reported chiral phosphonium salts with amide and hydroxyl H-bond donors, and showed that increasing the number of H-bond donor sites from two (**C38**) to four (**C37**) increased their alkylation enantioselectivities from 1% to 39% ee.[124]



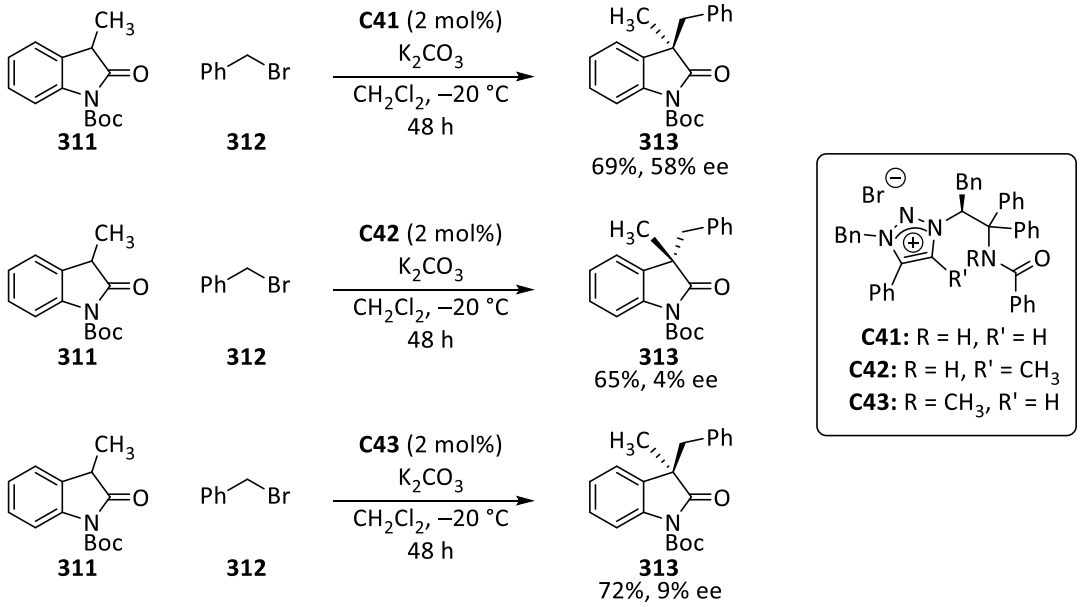
Scheme 3.02: *Manabe's early example of bifunctional phase-transfer catalysts*[124]

In 2004, Maruoka demonstrated the influence of incorporating H-bond donor hydroxyl groups in his *N*-spiroammonium catalysts (scheme 3.03).[125] In his enantioselective epoxidation reaction, he found that adding two hydroxyl groups (**C40**) was essential for reactivity, with his yield increasing from 3% to 69% in 24 h when using hydroxyl-bearing catalyst **C40** instead of **C39**. Maruoka's enantioselectivity likewise increased significantly from 46% ee to 66% ee upon incorporating hydroxyl groups. Further adjustments to **C40** eventually increased their yield to 99% and enantioselectivity to 96% ee.



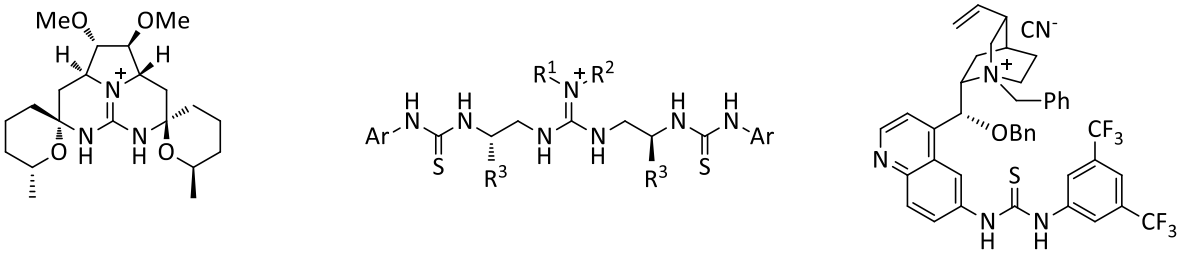
Scheme 3.03: *Maruoka's epoxidation via bifunctional phase-transfer catalysis*[125]

Ooi observed a similarly drastic effect on enantioselectivities when incorporating H-bond donors into his triazolium phase-transfer catalysts (**C41-C43**, scheme 3.04).[104] In his alkylation reaction, he found that two H-bond donors together, one on the amide and one on the triazolium ring (**C41**), were necessary to induce good enantiocontrol. Blocking either of the H-bond donors (**C42**, **C43**) maintained good reactivity, but afforded the product in very low enantioselectivity.



Scheme 3.04: *Ooi's dual H-bond phase-transfer catalyst*[104]

In the past decade, numerous other reports of phase-transfer catalysts, particularly cinchona-derived and Maruoka-type catalysts, have shown that for some reactions a free hydroxyl group on the phase-transfer catalyst is essential for high enantioselectivities.[126–130] At the time of our investigations, there were very few reported phase-transfer catalysts that incorporated strong dual H-bond donors, which have the potential to add more rigidity to transition states than a single hydroxyl group. We were aware of a single example pairing a chiral quaternary ammonium salt with a thiourea[131] and Nagasawa's family of guanidine-derived phase-transfer catalysts,[132] some bearing thioureas[133,134] (figure 3.05). To the best of our knowledge, there were no examples of chiral quaternary ammonium salts paired with ureas, amides, or sulfonamides as H-bond donors. We set out to design and synthesize such catalysts (see Chapter 4 for amide and sulfonamide phase-transfer catalysts).



Nagasawa (2002) **Nagasawa (2005)** **Lassaletta (2010)**

Figure 3.05: *Phase-transfer catalysts incorporating dual H-bond donors (up to 2012)*

3.3 Concept and Design of a New Phase-Transfer Catalyst Family

3.3.1 Conceptual design

Bifunctional Brønsted base/H-bond donor organocatalysts, like those used in Chapter 2, have been widely applied to achieve efficient, enantioselective unions of enolizable pro-nucleophiles to reactive electrophiles such as imines and Michael acceptors.[30,31,40,48,135–139] While high levels of enantiocontrol can be achieved using such

catalysts with a range of pro-nucleophiles and electrophiles, poor reactivity can often be witnessed,[136,140] as we experienced with our intramolecular Michael reactions to *α,β*-unsaturated alkyl esters in Chapter 2. Such challenges are particularly apparent for high pK_a pro-nucleophiles where long reaction times, high reaction temperatures, and/or high catalyst loadings are commonly required.

Using non-racemic chiral phase-transfer catalysts, like those introduced above, offer the opportunity to access less acidic pro-nucleophiles by pairing the catalyst with a strong inorganic base. However, phase-transfer catalysts, too, have drawbacks (*vide supra*); notably, minor substrate changes can drastically affect enantioselectivities due to a lack of directionality in catalyst-substrate interactions.[26]

One design concept that could simultaneously address these issues is to link a (variable) H-bond donor to a quaternary ammonium salt *via* a chiral spacer (figure 3.06). Such a catalyst could potentially combine access to less acidic pro-nucleophiles (when paired with a strong inorganic base) with substrate control, preorganization, and activation, thus leading to desirable levels of reactivity and stereoselectivity in a broad range of reactions. We selected cinchona alkaloids as our chiral scaffold both because we had already demonstrated the success of bifunctional cinchona-derived organocatalysts in inducing good enantioselectivities in our intramolecular Michael reaction (see Chapter 2) and because both pseudo-enantiomers are widely available and affordable to allow easy access to both enantiomers of our cyclization products.

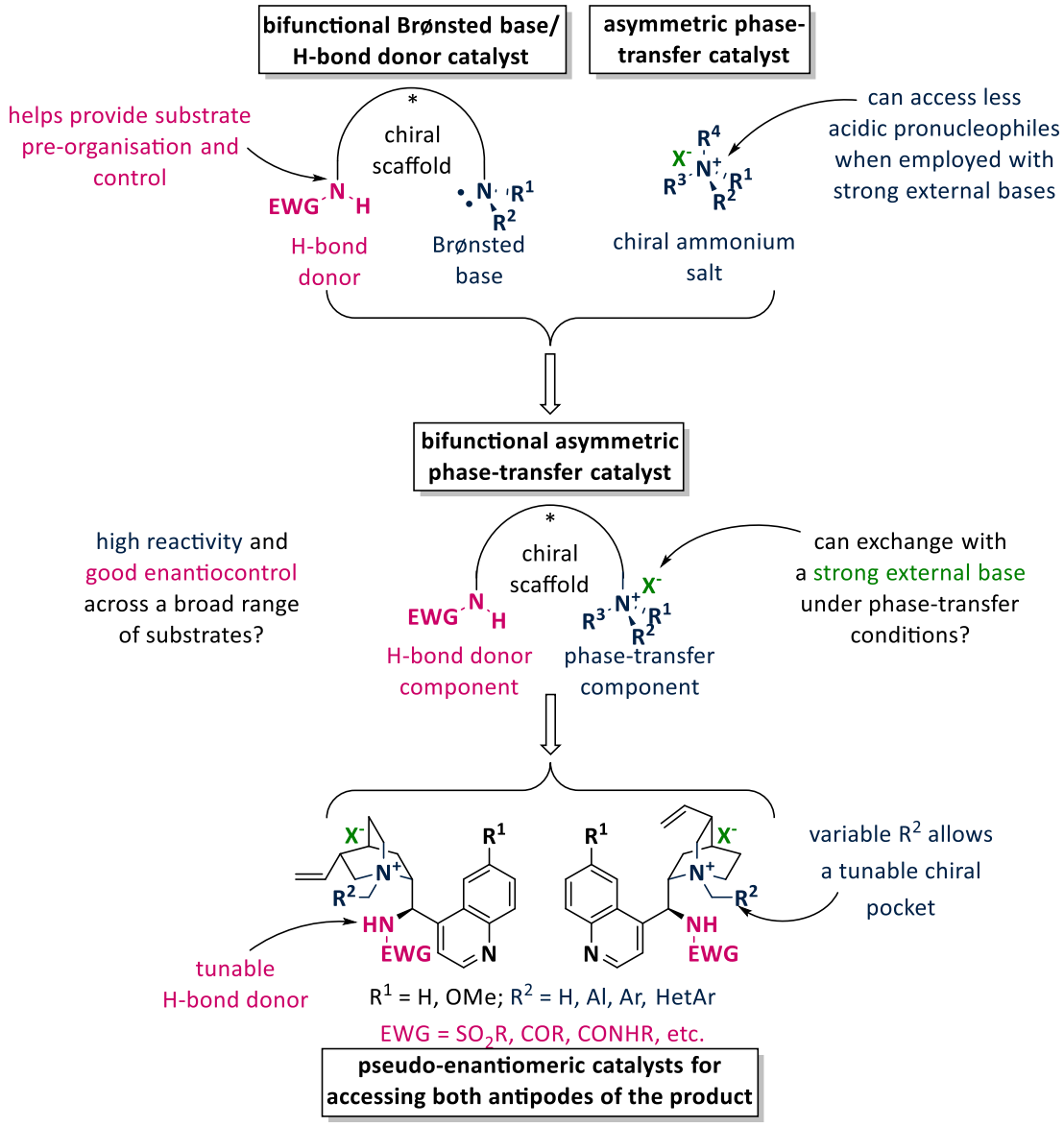


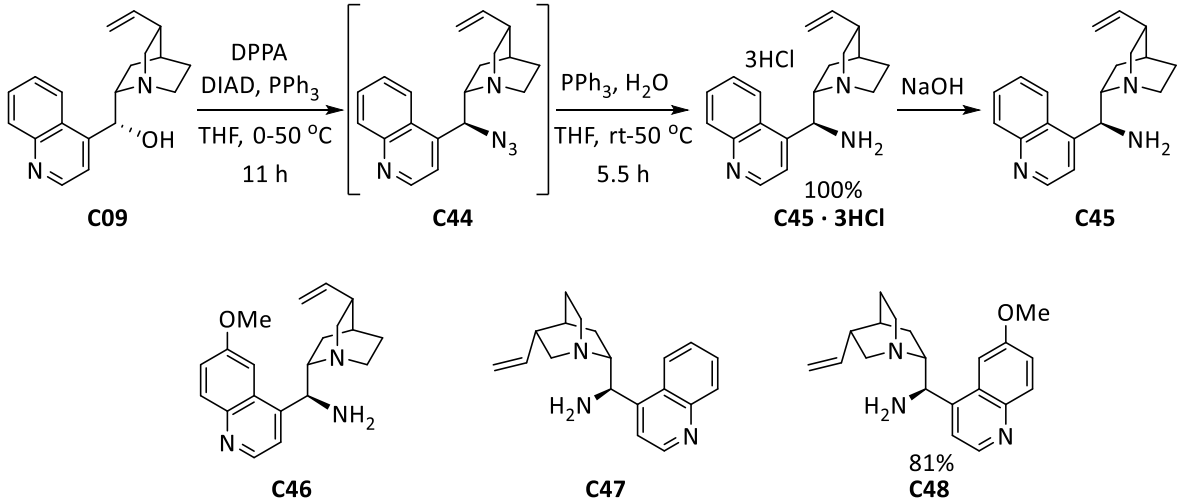
Figure 3.06: *Bifunctional phase-transfer catalyst conceptual design*

3.3.2 Synthesis and isolation

Tactically, we envisaged that we could access these catalysts through a late-stage alkylation of the tertiary bridgehead nitrogen of cinchona-derived Brønsted base/H-bond donor organocatalysts like those used in Chapter 2. We could access such bifunctional organocatalysts in one step from 9-amino(9-deoxy) epicinchona alkaloids. Such an approach allows easy access to focused libraries of catalysts with varied H-bond donors and alkyl groups on the quaternary ammonium salt, thus facilitating rapid optimization in any

reaction of interest. Herein we describe our synthesis of a new family of bifunctional H-bond donor/quaternary ammonium salt phase-transfer catalysts derived from cinchona alkaloids, and their application to the intramolecular Michael reaction introduced in Chapter 2.

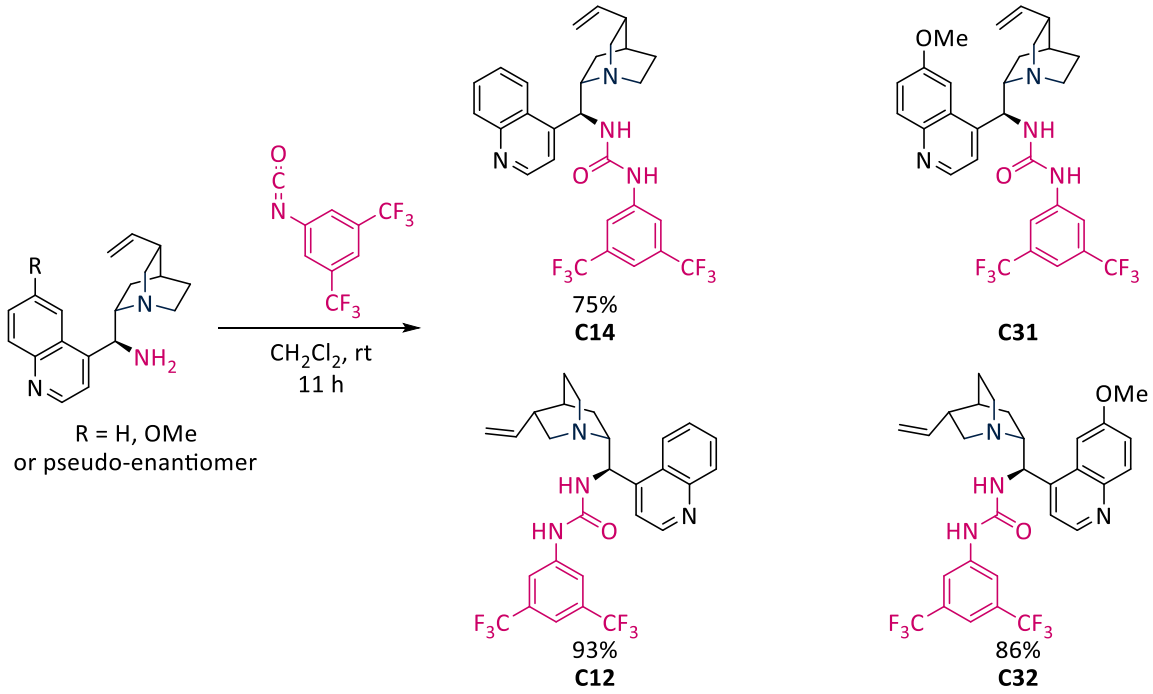
The triple hydrochloride salts of 9-amino(9-deoxy) epicinchonidine, **C45·3HCl** was prepared via a one-pot procedure whereby the hydroxyl group on C(9) was replaced with an azide using a Mitsunobu reaction, and the resulting 9-azido(9-deoxy) epicinchonidine **C44** was reduced to epi-9-amino(9-deoxy) cinchonidine **C45** via a Staudinger reaction and isolated as the triple hydrochloride salt in good yield (scheme 3.05). The hydrochloride salt was dissolved in 4 M aqueous NaOH and extracted with dichloromethane to obtain the free base 9-amino(9-deoxy) epicinchonidine **C45**. Cinchonine (**C47**), quinine (**C46**), and quinidine-derived (**C48**) 9-amino(9-deoxy) epicinchona alkaloids were prepared using an analogous procedure.



Scheme 3.05: *Synthesis of epi-9-amino-9-deoxy cinchona alkaloids*

With **C45-C48** in hand, we synthesized a variety of Brønsted base/H-bond donor catalysts with urea H-bond donor groups (scheme 3.06). Treating **C45** with 3,5-

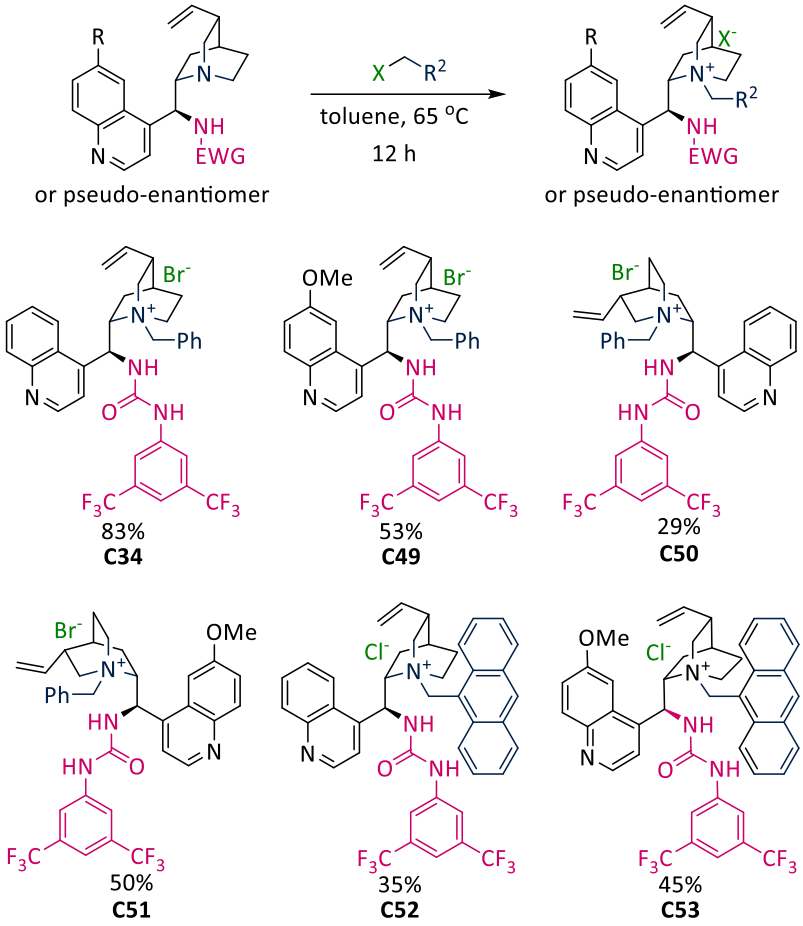
bis(trifluoromethyl) isocyanate gave urea **C14**. Analogues of urea **C14** were also prepared in parallel fashion using amines **C47**, **C46**[iii] and **C48**, respectively (scheme 3.06).



Scheme 3.06: *Synthesis of Brønsted base/ H-bond donor catalysts*

Alkylation of **C14** with benzyl bromide in toluene or THF at 65 °C proceeded smoothly (scheme 3.07), but purification proved challenging. In all eluents tested with flash column chromatography, the desired product eluted with starting material **C14** and/or unknown impurities (presumably byproducts alkylated on undesired nucleophilic sites or byproducts with multiple alkylation sites). Trituration, recrystallization, size-exclusion chromatography, and ion-exchange resin also proved unsuccessful. We effectively obtained pure **C34** using two consecutive chromatography columns with different eluents. First, **C34** and byproducts were separated from starting material **C14** using flash column chromatography with Et_2O/MeOH as the mobile phase. **C34** was then isolated from the undesired byproducts using CH_2Cl_2/MeOH.

[iii] **C46**, **C47**, **C31**, **C49** and **C53** were prepared by my colleague Filippo Sladojevich



Scheme 3.07: *Synthesis of bifunctional H-bond donor phase-transfer catalysts*

Based on literature precedent, we predicted that the dominant alkylation product would have the benzyl group on the quinuclidine nitrogen. However, since **C14** has three potentially nucleophilic sites (the quinuclidine nitrogen, the quinoline nitrogen, and the urea oxygen) it was necessary to confirm the site of alkylation. First, we collected a ^{1}H NMR spectrum in $CHCl_3$, and then added a drop of D_2O and collected the ^{1}H NMR spectrum again (figure 3.07). In the second spectrum we saw the two signals corresponding to the exchangeable protons on the two urea nitrogens decrease significantly, thus confirming that the site of alkylation was not on the urea oxygen.

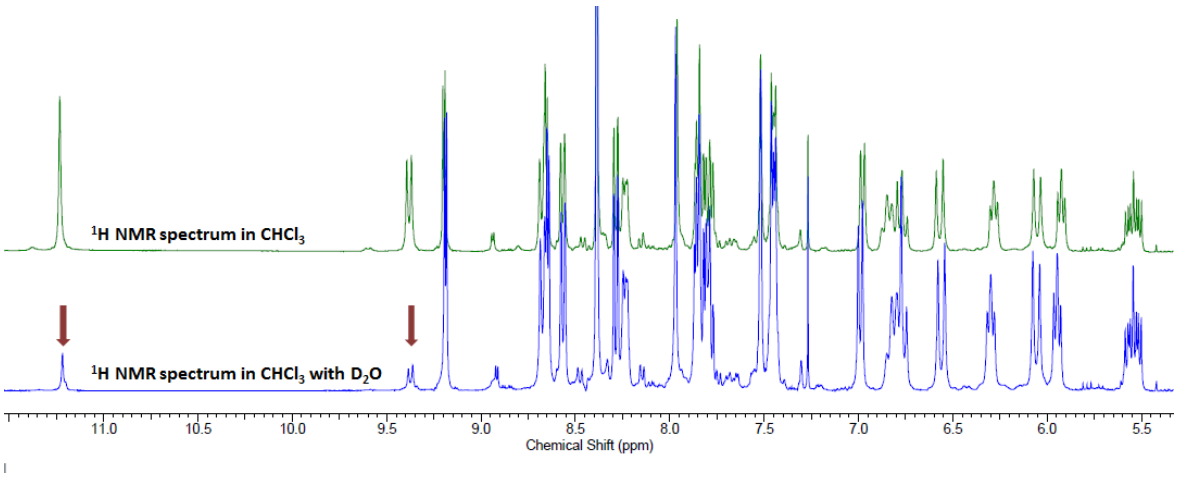


Figure 3.07: *^{1}H NMR D_2O experiment to confirm urea is not alkylated*

We observed only minor changes in the chemical shift of the protons on the quinoline ring compared to the non-alkylated catalyst, suggesting alkylation did not occur on the quinoline nitrogen. Using NOE experiments we were further able to support that the benzyl group was not on the urea oxygen nor the quinoline nitrogen, as we saw no NOE from the benzylic hydrogens to the C(9) hydrogen nor any quinoline hydrogens. We did, however, observe NOEs from the benzylic hydrogens to both the C(2) and C(6) hydrogens supporting the location of the benzyl group on the quinuclidine nitrogen, as drawn in figure 3.08.

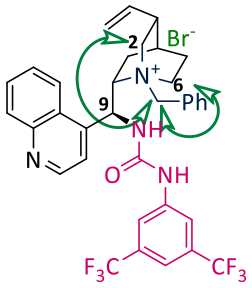


Figure 3.08: *Structure of bifunctional phase-transfer catalyst based on NOE studies*

Upon confirming the structure of **C34**, we synthesized and isolated catalysts **C49–C53** using an analogous method (scheme 3.07). Catalysts **C52** and **C53** were synthesized using 9-anthracenylmethyl chloride. We reported these catalysts in Organic Letters in

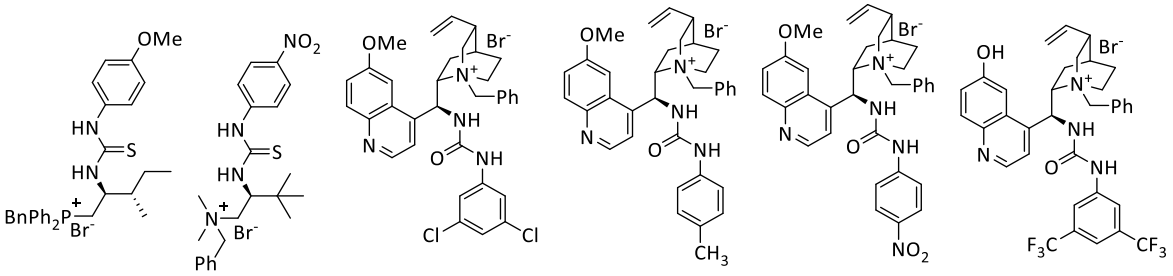
2012.[55,iv] With our phase-transfer catalysts in hand, we set out to test their efficacy in our intramolecular Michael reaction.

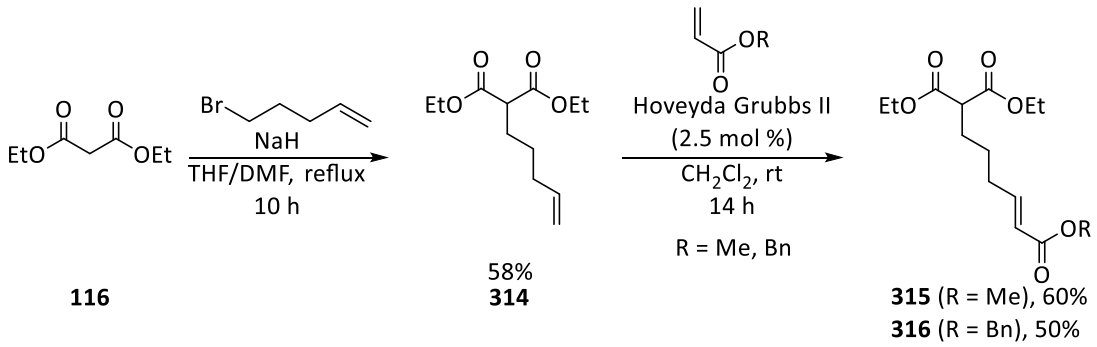
3.4 Application to an Intramolecular Michael Reaction

3.4.1 Establishing reactivity

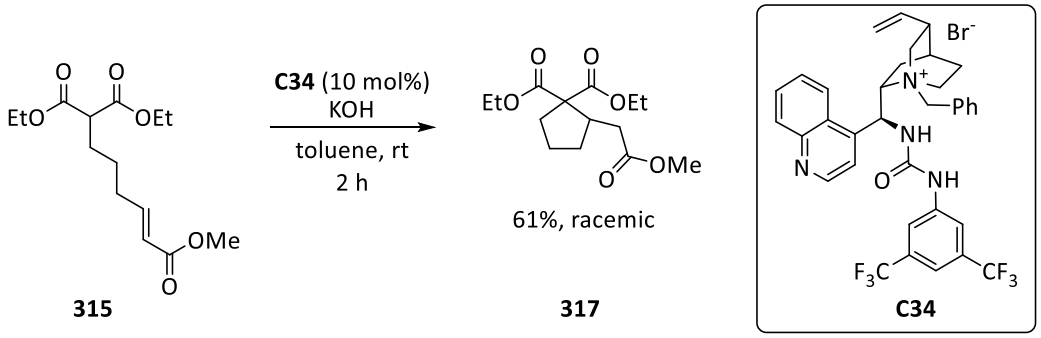
First, we synthesized cyclization precursors **315** and **316** using a procedure analogous to that used in Chapter 2: diethyl malonate was alkylated with 5-bromo-1-pentene to give **314**, then a cross metathesis with methyl or benzyl acrylate catalyzed by Hoveyda-Grubbs II catalyst gave **315** and **316**, respectively (scheme 3.08). To probe catalyst-induced reactivity, **315** was treated with cinchonidine-derived bifunctional phase-transfer catalyst **C34** paired with freshly ground anhydrous potassium hydroxide in toluene. Pleasingly, cyclization was complete after 2 hours; however, analysis *via* HPLC using a chiral, non-racemic stationary phase revealed that product **317** was racemic (scheme 3.09). A subsequent treatment of substrate **315** with only potassium hydroxide revealed a high rate of background cyclization, thus accounting for the racemic result.

[iv] Since then, other groups have reported successful syntheses and applications of bifunctional phase-transfer catalysts with strong dual H-bond donors.[122,207–209]



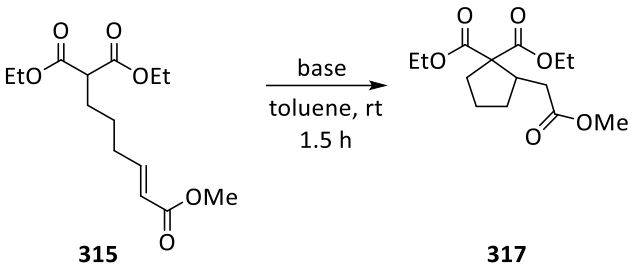


Scheme 3.08: *Synthesis of cyclization precursors* ***315*** *and* ***316***



Scheme 3.09: *Cyclization with potassium hydroxide*

To avoid such background reactivity, we screened five different types of bases: a hydroxide, carbonate, fluoride, hydride, and alkoxide. Under catalyst-free conditions, we found that **315** underwent quantitative cyclization to **317** in 1.5 hours in the presence of potassium hydroxide, sodium hydride, or sodium ethoxide. However, we observed no conversion in this time frame in the presence of potassium carbonate or potassium fluoride (scheme 3.10, table 3.01). This is possibly due to no enolate being formed with these weaker bases in the absence of a phase-transfer catalyst.

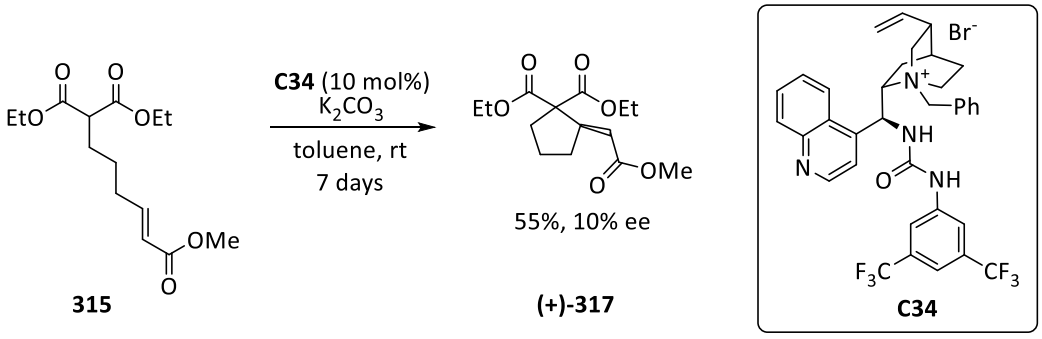


Scheme 3.10: *Background conversion*

Base	Conversion (%)
K_2CO_3	0
KF	0
NaH	100
NaOEt	100

Table 3.01: *Background conversion with various bases*

Adding tetrabutylammonium bromide (TBAB) to a suspension of **315** and potassium fluoride did not promote cyclization after 2 days. However, the addition of TBAB to a suspension of **315** and potassium carbonate resulted in quantitative conversion to cyclized product **317** after 2 days. With these promising results, we tried replacing TBAB with our catalyst **C34**. Pleasingly, cyclized product **(+)-317** was isolated in 55% yield after 7 days with 10% ee (scheme 3.11). The ability of **C34** to catalyze the cyclization of **315**, when catalyst **C14** could not, demonstrates its ability to activate less reactive substrates.



Scheme 3.11: *Cyclization of **315** – establishment of reactivity*

3.4.2 Reaction mechanism

Our enantioselective intramolecular Michael reaction *via* phase-transfer catalysis likely takes place *via* Makosza's interfacial mechanism.[141] In an interfacial mechanism, the enolate forms directly *via* reaction with the solid base *at the phase interface* (as opposed to the base being extracted into the organic phase). The anion of the phase-transfer catalyst then exchanges with the enolate, and the catalyst-enolate ion pair is transported into the organic phase where cyclization takes place (figure 3.09). Makosza found no evidence of carbonate extraction into benzene with potassium or sodium carbonates in solid-liquid phase-transfer catalysis with quaternary ammonium salts.[141] Mechanistic studies of solid-liquid phase-transfer catalyzed alkylations in toluene also lack support for an extractive mechanism,[142] thus supporting the hypothesis that our Michael reaction takes place *via* an interfacial (rather than an extractive) mechanism (figure 3.09).

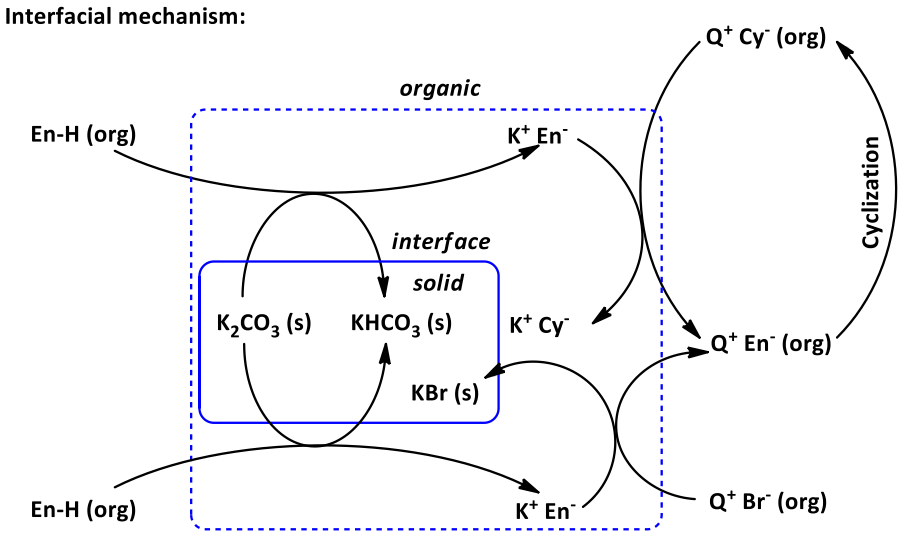


Figure 3.09: *Proposed extractive and interfacial mechanisms(En = enolate, Cy = cyclized product, org = organic phase, s = solid phase)*

Achieving good enantiocontrol with an interfacial mechanism requires that the enolate does not cyclize until it is associated with the phase-transfer catalyst.[143] That is, the

anion exchange must be fast compared to the cyclization, so that cyclization does not occur until the enolate is paired with the phase-transfer catalyst. The enolate must also be more prone to cyclization when associated with the phase-transfer catalyst. The charge separation of the catalyst-enolate ion pair is greater than that in the K^+-enolate ion pair, which would help to contribute to increased reactivity of the catalyst-enolate ion pair. A number of studies have suggested that trace water, termed the *omega phase*, may play an important role in the interfacial mechanism by helping to make the base more accessible.[144]

Enantioinduction requires that the substrate and the catalyst, the source of chirality, are closely associated. The negative charge of the enolate likely forms an ion pair with the quaternary ammonium (figure 3.10). The urea H-bond donor may also associate with the enolate (**318**), or may bond with the *α,β*-unsaturated ester Michael acceptor (**319**), thus increasing its electrophilicity and promoting cyclization. Alternately, it is possible that the enolate forms a dual H-bond with the urea while the ester is activated by the quaternary ammonium (**320**).

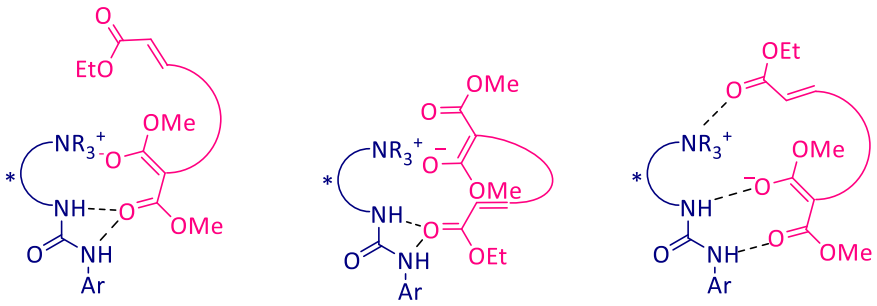


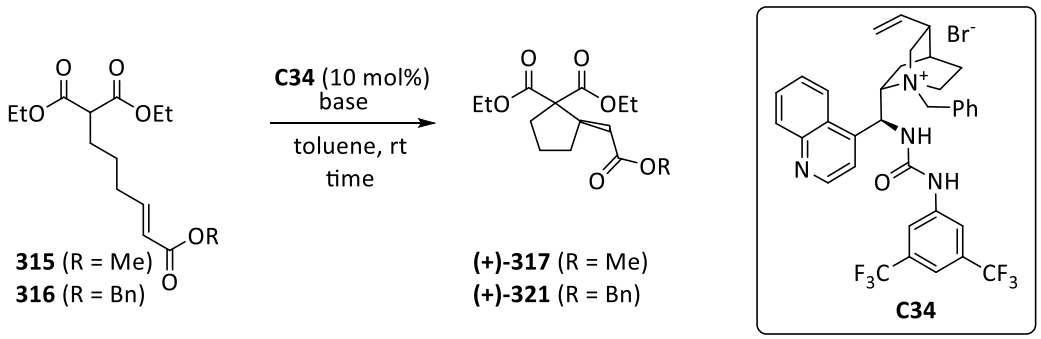
Figure 3.10: *Possible catalyst-substrate interactions*

3.4.3 Optimization

With reactivity established, we began optimization of our reaction conditions. Changing the base to the strong organic base BEMP decreased the reaction time from 7 to 2 days, but the enantioselectivity also dropped (from 10% ee to 6% ee, scheme 3.12, table

3.02, entry 1). Based on the success of potassium carbonate, we tried other carbonate bases. Neither sodium nor lithium carbonates promoted cyclization, but cesium carbonate did promote cyclization and improved the reaction rate significantly, achieving 69% yield and 11% ee after just 16 hours. This rate acceleration is likely due to the higher basicity of Cs_2CO_3.

The enantioselectivity was fairly consistent with respect to both base loading and concentration. Decreasing the equivalents of base to 0.2 (entry 6) or increasing the equivalents of base to 1.0 (entry 7) had minor deleterious effects on the enantioselectivity so 0.5 equivalents of base was used for subsequent reactions. Increasing the concentration to 0.33 M (entry 8) or decreasing the concentration to 0.05 M (entry 9) both resulted in small decreases in enantioselectivity; a concentration of 0.13 M gave the highest enantioselectivity. Changing the Michael acceptor from an *α,β*-unsaturated methyl ester (**315**) to an *α,β*-unsaturated benzyl ester (**316**) to include an opportunity for *π*-stacking had no effect on the enantioselectivity, so the *α,β*-unsaturated methyl ester Michael acceptor was used for subsequent catalyst optimization.



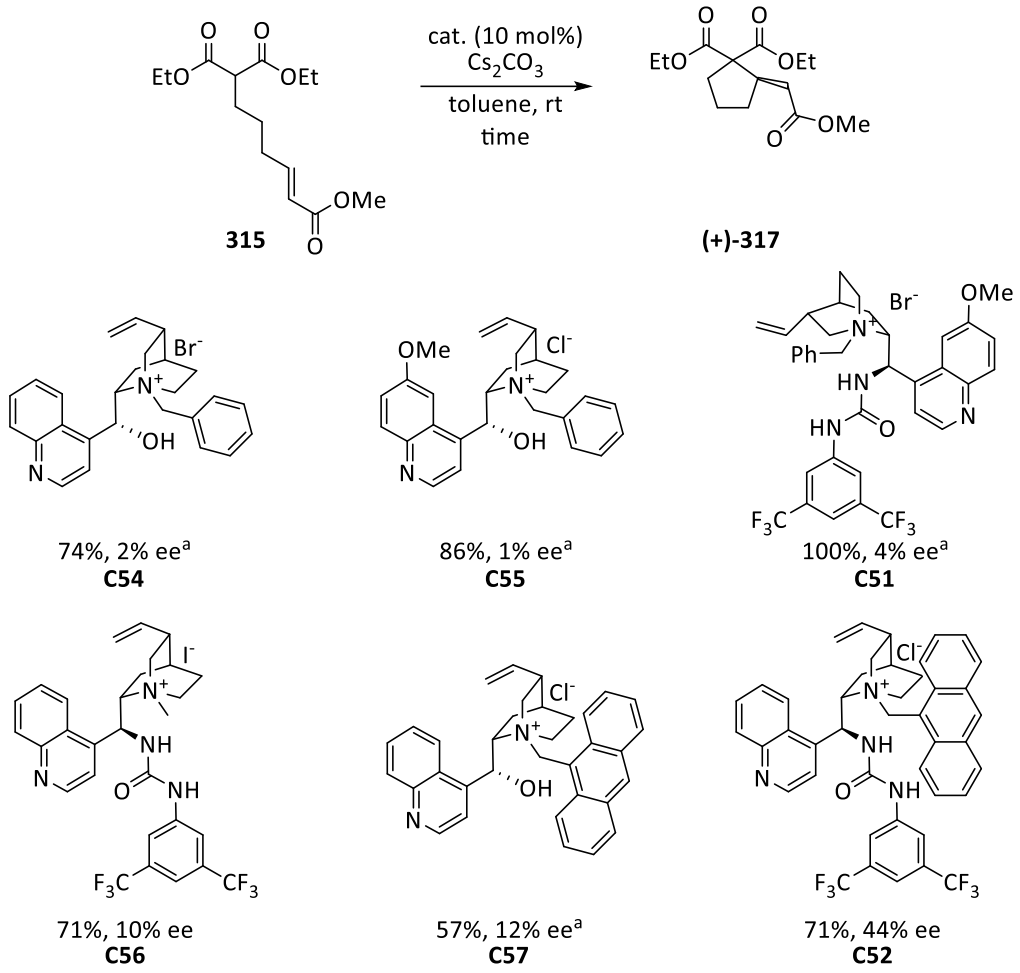
Scheme 3.12: *Intramolecular Michael reaction optimization*

Entry	R	Base	Base loading (equiv.)	Concentration [M]	Time	Yield (%)	e.e. (%)
1	Me	BEMP	0.5	0.13	2 days	75	6
2	Me	Li_2CO_3	0.5	0.13	7 days	-	-
3	Me	Na_2CO_3	0.5	0.13	7 days	-	-
4	Me	K_2CO_3	0.5	0.13	7 days	55	10
5	Me	**Cs_2CO_3**	**0.5**	**0.13**	**16 h**	**69**	**11**
6	Me	Cs_2CO_3	0.2	0.13	16 h	54	9
7	Me	Cs_2CO_3	1.0	0.13	16 h	63	8
8	Me	Cs_2CO_3	0.5	0.33	16 h	77	7
9	Me	Cs_2CO_3	0.5	0.05	16 h	78	8
10	Bn	Cs_2CO_3	0.5	0.13	43 h	75	11

Table 3.02: *Phase-transfer catalyst intramolecular Michael reaction optimization (- indicates no observed conversion to product)*

Having optimized the base, base loading, and concentration, we tested a number of commercial and in-house synthesized catalysts (scheme 3.13). Our phase-transfer catalyst **C34** has a benzyl group on the quaternary nitrogen and is derived from cinchonidine, so as a first point of comparison we tested the commercially available **C54**, which is the bromide salt of benzylated cinchonidine. Although **C54** promoted cyclization, giving the product in 74% yield, enantiocontrol was minimal (2% ee, **(–)-317**). While we would need to flip the stereochemistry of **C54** at C(9) to make a rigorous comparison, this result suggests that the H-bonds, not just ionic interactions, play a key role in enantioinduction and our dual H-bond donor helps promote higher enantioselectivities. When changing the cinchona chiral scaffold, we found that commercially available quinine-derived catalyst **C55** gave **(–)-317** in good yield (86%) but poor enantioselectivity (1% ee) and quinidine-derived urea **C51** gave **(–)-317** in quantitative yield, but only 4% ee. Next, we tested different alkylating groups on the quaternary nitrogen. Changing the alkyl group of the cinchonidine-derived urea catalyst to a methyl group (**C56**) gave a similar enantioselectivity as **C34** (10% ee, **(+)-317**). Using commercially available **C57**, bearing an anthracenylmethyl group, increased the enantioselectivity to 12% ee [**(–)-317**]. Inspired by this result, we tested our cinchonidine

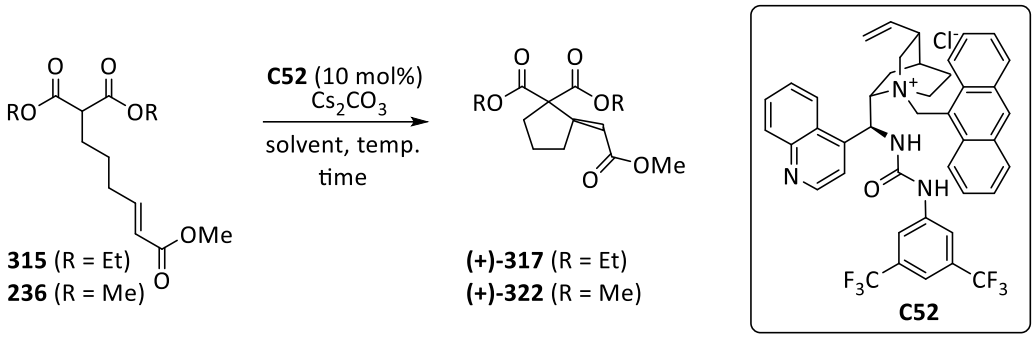
urea catalyst with a 9-anthracenylmethyl alkyl group (**C52**). Pleasingly, **C52** promoted the cyclization in good yield (71%) with significantly improved enantioselectivity (44% ee, **(+)-317**).



Scheme 3.13: *Catalyst optimization; [a]opposite enantiomer observed*

Next, we proceeded with a solvent screen and experiments to establish the role of temperature on the enantioselectivity (scheme 3.14, table 3.03). Enantioselectivities decreased significantly in more polar solvents such as ethyl acetate, tetrahydrofuran and acetonitrile. This is likely because these solvents can interfere with hydrogen bonding and tight ion pairing. Interestingly, acetonitrile resulted in a 10% enantiomeric excess for the opposite enantiomer compared to toluene. Dichloromethane gave **(+)-317** in both poor yield (38%) and enantiomeric excess (6% ee). Toluene (44% ee) was the best performing solvent

followed by MTBE (32% ee). The cyclization still proceeded quickly at –20 °C, achieving 73% isolated yield after 22 hours, but lowering the reaction temperature from 20 °C to 0 °C or –20 °C did not result in a significant change in enantioselectivity (table 3.03, entries 6-8). Changing from a diethyl to a dimethyl malonate had no effect on the enantioselectivity (entry 9).



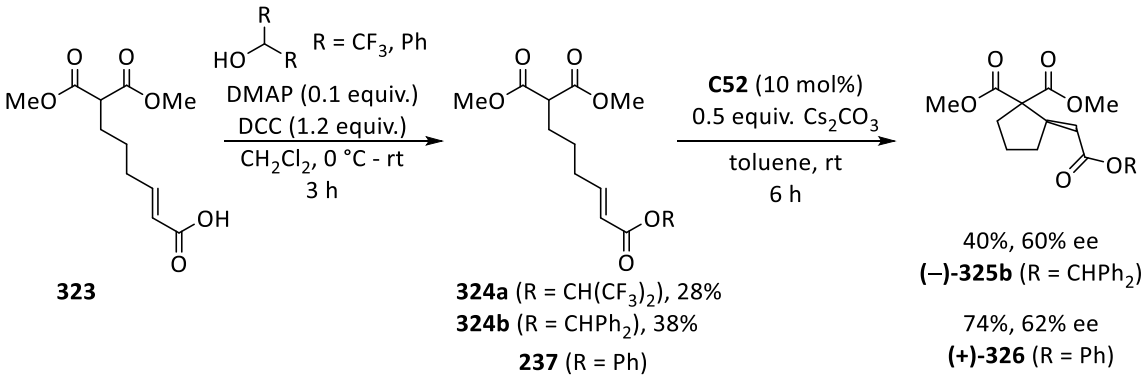
Scheme 3.14: *Solvent and temperature optimization with* ***C52***

	R	Solvent	Temperature (°C)	Time (h)	Yield (%)	e.e. (%)
1	Et	CH_2Cl_2	20	16	38	6
2	Et	MTBE	20	16	84	32
3	Et	MeCN	20	16	100	10[a]
4	Et	EtOAc	20	16	62	11
5	Et	THF	20	16	74	8
6	Et	Toluene	20	16	64	44
7	Et	Toluene	0	22	47	42
8	Et	**Toluene**	**–20**	**22**	**73**	**50**
9	Me	Toluene	20	16	83	44

Table 3.03: *Solvent and temperature optimization with* ***C52****; [a]opposite enantiomer observed*

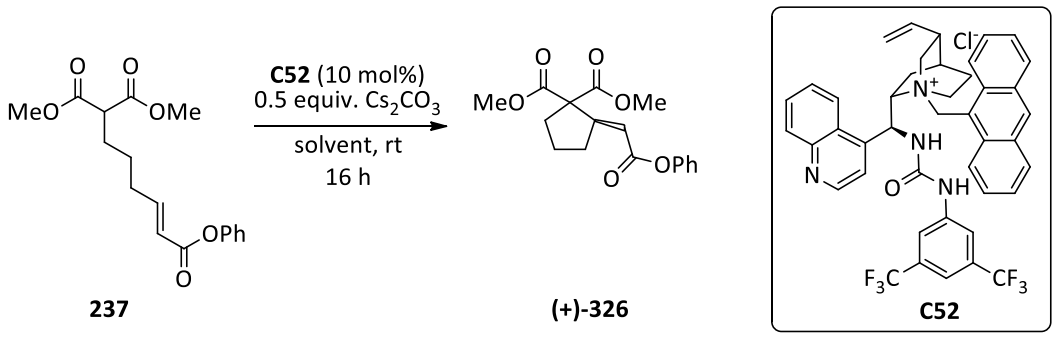
In an attempt to further increase the enantioselectivity, we synthesized substrates with different esters at the Michael acceptor and subjected them to our optimized cyclization conditions (scheme 3.15). Bis-(CF_3) **324a** gave only a trace of the cyclized product, but, pleasingly, benzhydryl **324b** cyclized smoothly to **(–)-325b** in 68% yield after 6 hours with 60% ee. The phenyl ester **237** gave an even greater boost in enantioselectivity, achieving

74% yield and 62% ee. On this system, **C52** also out-performed the commercially available anthracenylmethyl cinchonidinium chloride phase-transfer catalyst **C57**, which in 22 hours gave the cyclized product **(–)-326** in 76% yield and only 37% ee.



Scheme 3.15: *Preparation of substrates with more electrophilic Michael acceptors*

A small solvent screen using substrate **237** and catalyst **C52** again showed toluene or benzene to be the best solvents (scheme 3.16, table 3.04). Cyclohexane gave the cyclized product **(+)-326** in excellent yield (95%), but the enantioselectivity decreased slightly to 56% ee.

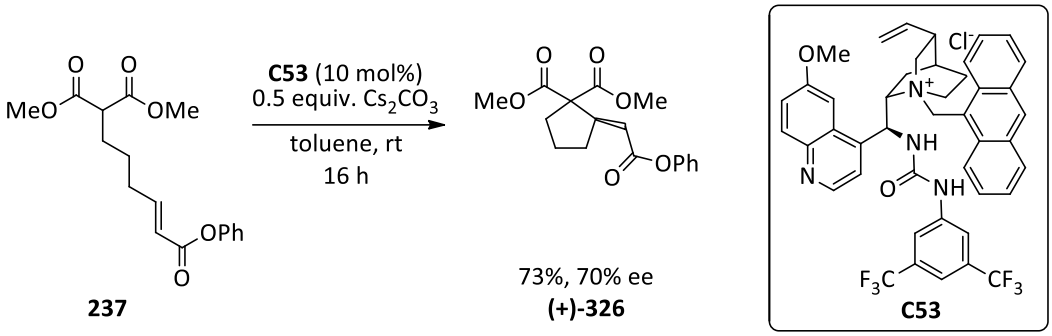


Scheme 3.16: *Solvent optimization with phenyl ester **237***

Entry	Solvent	Yield (%)	e.e. (%)
1	Toluene	74	62
2	Cyclohexane	95	56
3	Benzene	78	63

Table 3.04: *Solvent optimization with phenyl ester **237***

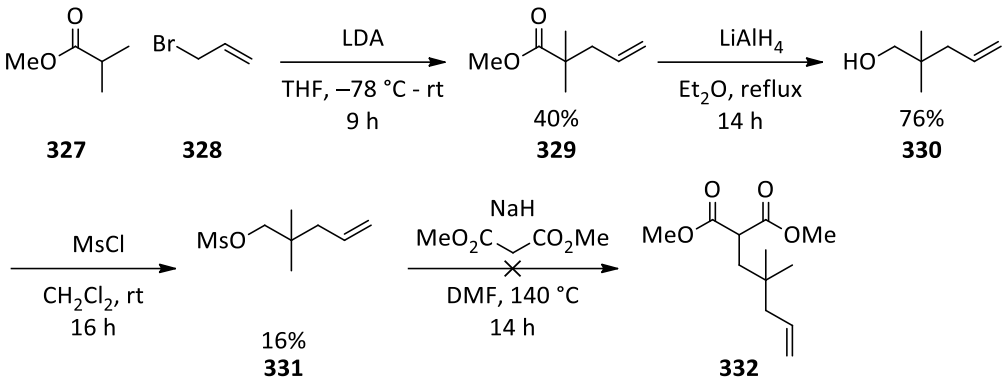
Finally, changing the chiral scaffold of **C52** from cinchonidine to quinine (**C53**) resulted in another boost in enantioselectivity to 70% ee (scheme 3.17). With these optimized conditions, we set out to expand this methodology to other pre-cyclization substrates in an attempt to access both substituted carbocycles and heterocycles.



Scheme 3.17: *Intramolecular Michael reaction with quinine-derived **C53***

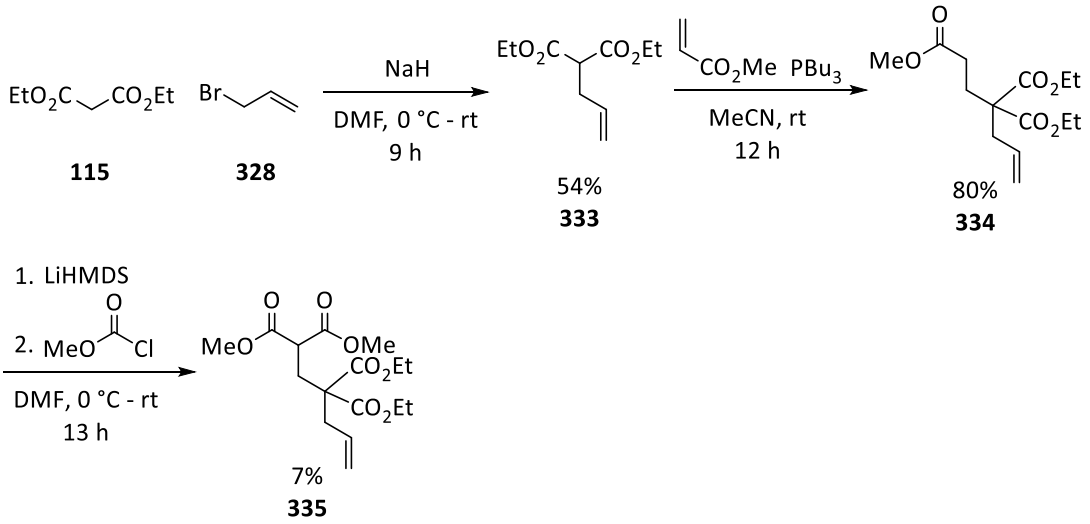
3.4.4 Substrate scope

To expand the substrate scope of our methodology, we first attempted to synthesize substrates with substituents on the cyclopentane ring. To synthesize a substrate with a dimethyl substituent, we started by allylating methyl isobutyrate (**327**) to give **329** in 38% yield (scheme 3.18). We reduced the resulting ester **329** with lithium aluminium hydride in refluxing diethyl ether. Treatment of alcohol **330** with mesyl chloride gave **331**. Unfortunately, attempts to substitute mesylate **331** with a deprotonated malonate were all unsuccessful (scheme 3.18).



Scheme 3.18: *Attempted synthesis of dimethyl substituted substrate*

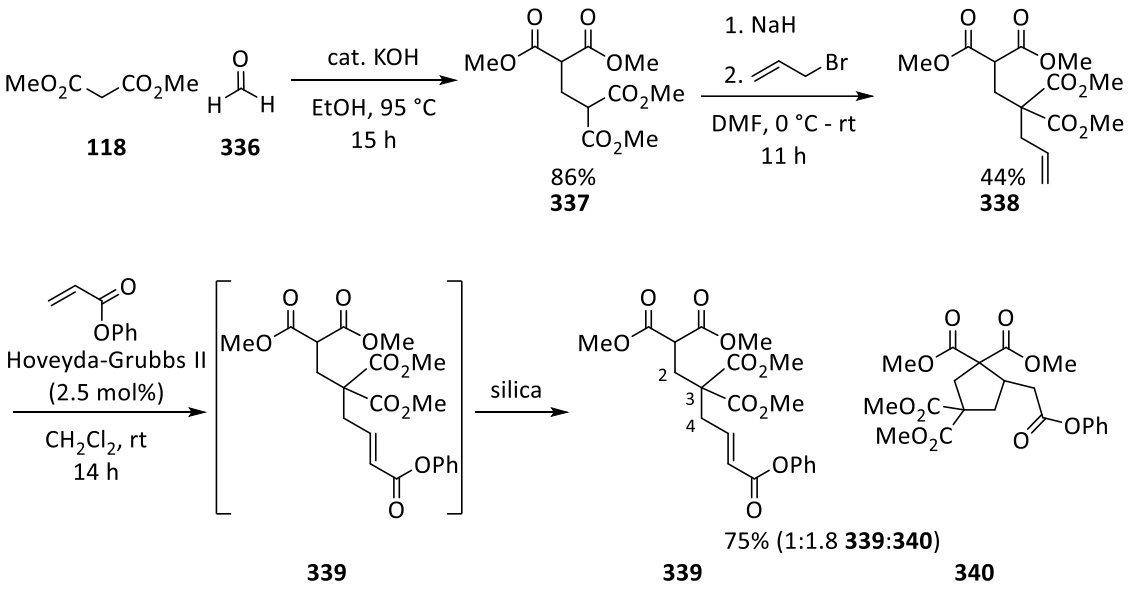
Next, we attempted to synthesize a cyclopentane with an additional diester substituent (scheme 3.19). First, we allylated ethyl malonate to give **333**, then synthesized triester **334** via a phase-transfer catalyzed Michael addition to methyl methacrylate. Under the basic conditions used to form the second diester, we isolated the desired product **335** in only 7% yield. The remaining mass was recovered as **333**, resulting from the retro Michael reaction of **334**.



Scheme 3.19: *Synthesis of a bis(diester) substrate*

Thus, we adopted an alternate route whereby we first formed diester **337** via a condensation reaction between dimethyl malonate and formaldehyde (scheme 3.20).

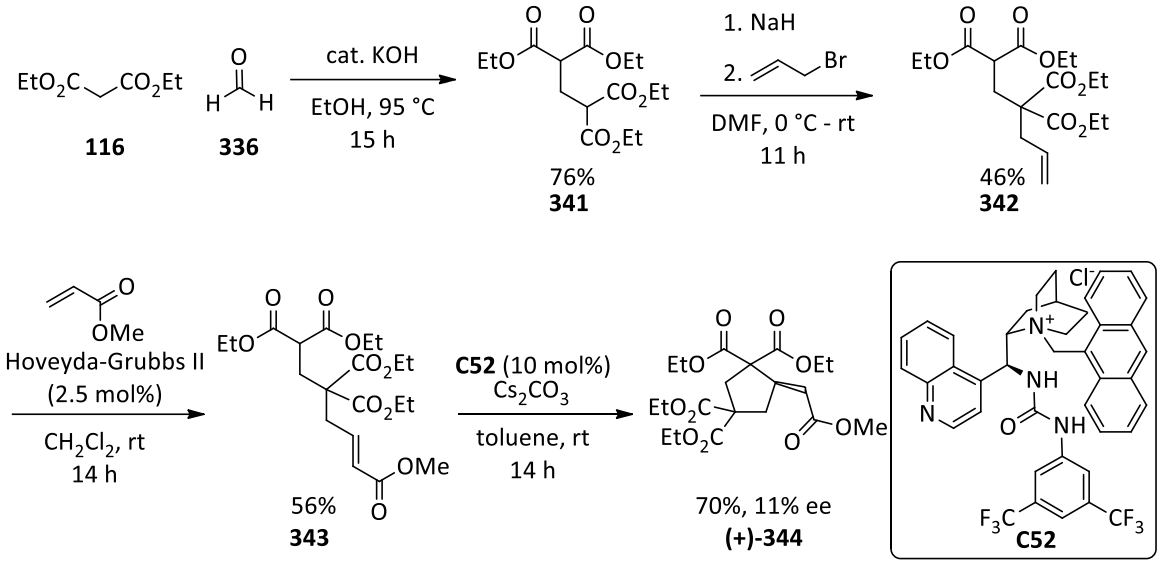
Allylation of **337** gave **338** in only 44% yield due to the competing double allylation (23% yield). While analysis of the crude ^{1}H NMR spectrum indicated that our subsequent metathesis with phenyl acrylate was successful, unfortunately the desired straight-chain substrate **339** was isolated as an inseparable mixture with the cyclized product **340** (1:1.8, **339**:**340**), formed during flash column chromatography. Such substitution on C(3) (numbering arbitrary) forces the **339** C(2)-C(3)-C(4) bond angle to be smaller than if C(3) was bonded to two hydrogens and forces the two reactive ends of the molecule into closer proximity (Thorpe-Ingold effect). This may account for the higher reactivity and resulting purification issues witnessed with this substrate.



Scheme 3.20: *Synthesis of bis(diester) substrate*

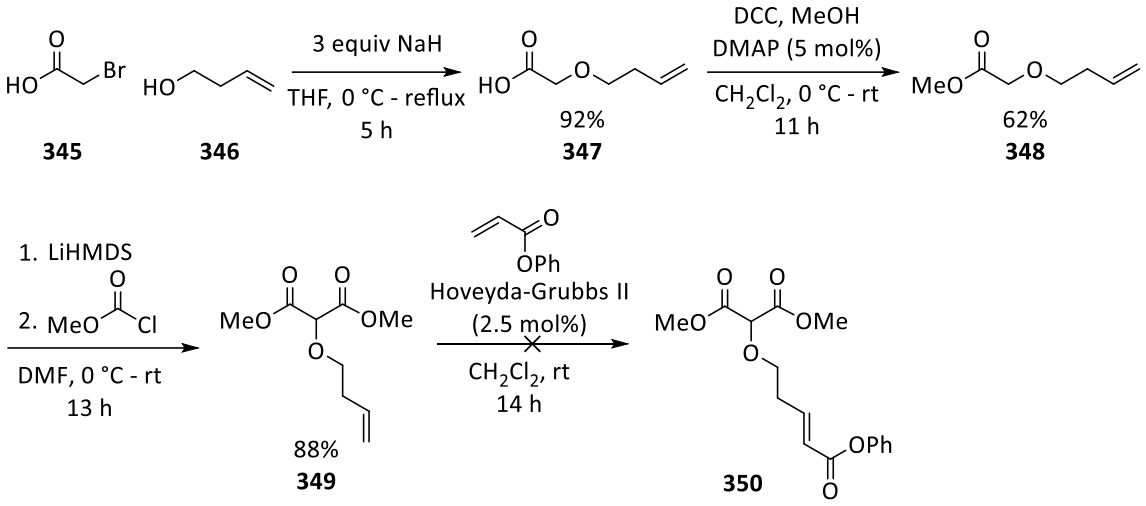
Using an analogous method to scheme 3.20 but starting with diethyl malonate, we were able to successfully isolate *α,β*-unsaturated methyl ester **343** (scheme 3.21). Catalyst **C52** promoted an intramolecular Michael reaction of **343** to give **(+)-344**; however, **(+)-344** was isolated in only 11% ee. We used the cinchonidine-derived catalyst **C52** rather than the quinine-derived catalyst **C53** for this initial test because of its easier and higher-yielding synthesis. With cyclopentane precursors cyclizing prematurely when using *α,β*-unsaturated

phenyl esters and with low enantioselectivities when using *α,β*-unsaturated methyl esters, we instead turned our focus to forming heterocyclic analogues of our cyclopentane products.



Scheme 3.21: *Synthesis of bis(diester) substrate*

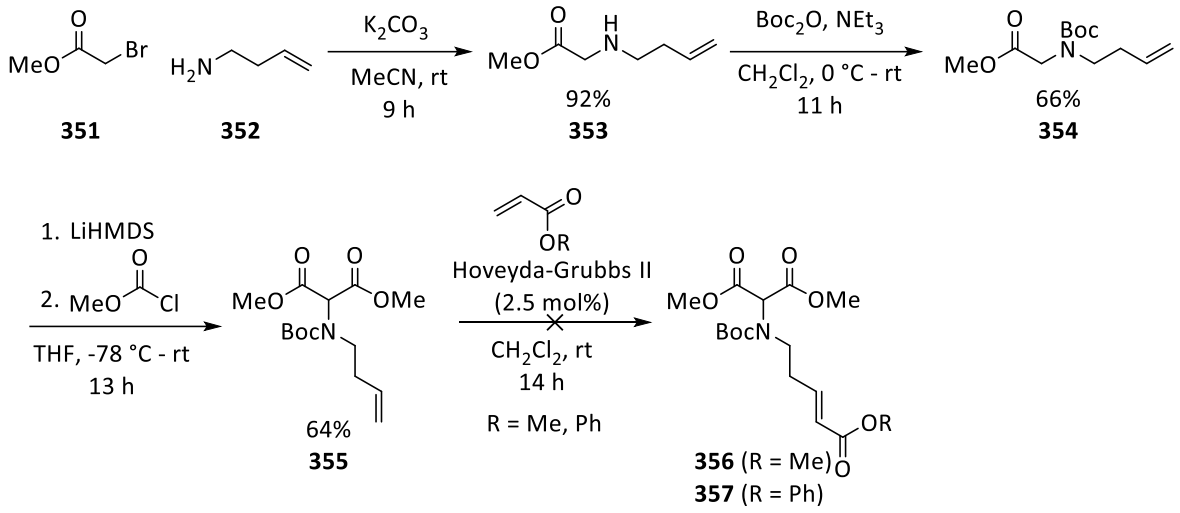
We first set out to synthesize tetrahydrofuran analogues. A nucleophilic substitution reaction between homoallyl alcohol **346** and 2-bromoacetic acid **345** and subsequent DCC coupling with methanol gave ester **348** (scheme 3.22). A direct substitution reaction between homoallyl alcohol and methyl 2-bromoacetate was not possible because of the competing transesterification reaction. Deprotonation and reaction with methyl chloroformate gave substituted malonate **349**. Unfortunately, multiple attempts to transform the terminal alkene into an *α,β*-unsaturated methyl or phenyl ester *via* a cross metathesis reaction were unsuccessful.



345 **346** **347** **348** **349** **350**

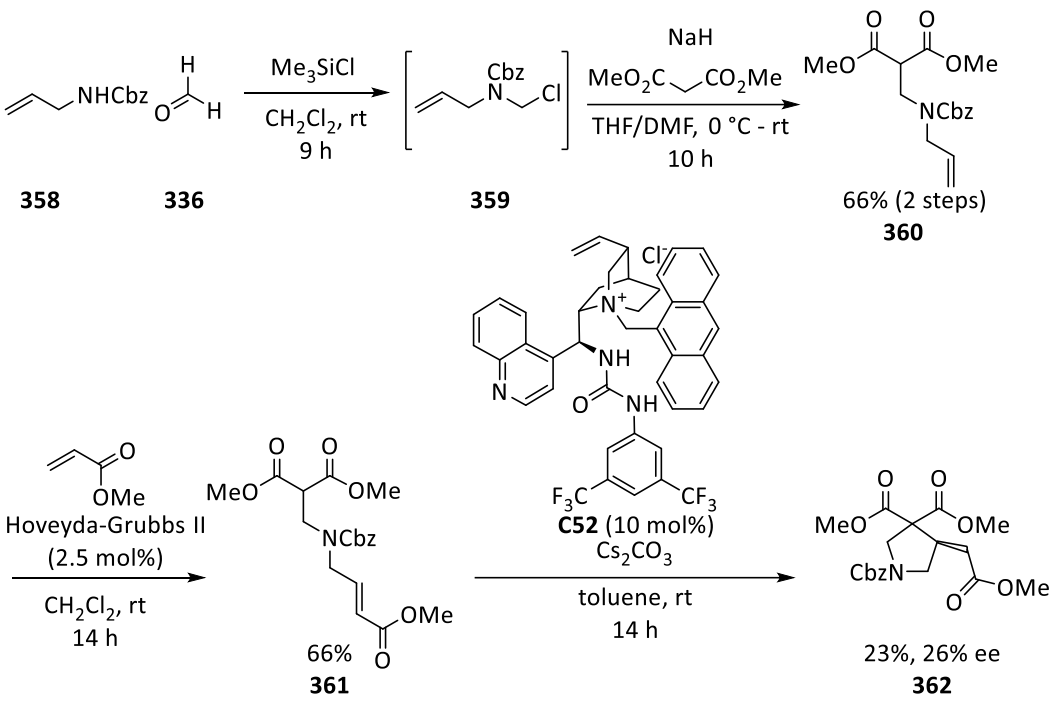
Scheme 3.22: *Attempted synthesis of furan substrate precursor*

Instead, we attempted to synthesize a pyrrolidine analogue. *N*-Alkylation of *N*-Boc protected dimethyl 2-aminomalonate failed, and the substitution of dimethyl 2-bromomalonate with homoallyl amine gave the non-protected analogue of **355** in only 9% yield. Thus, we took a longer but more reliable route (scheme 3.23). Nucleophilic substitution of methyl 2-bromoacetate **351** with homoallyl amine **352** gave secondary amine **353** in excellent yield (92%). Sequential *N*-Boc protection and nucleophilic addition to methyl chloroformate gave **355**. However, like with oxygen analogue **349**, cross metathesis with methyl or phenyl acrylate was unsuccessful.



Scheme 3.23: *Attempted synthesis of pyrrolidine substrate precursor*

Recognizing a pattern of failed cross metathesis reactions with a heteroatom next to the methine carbon, we pursued a pyrrolidine analogue with a carbon separating the methine carbon and the heteroatom in the straight-chain substrate (scheme 3.24). We formed *N*-chloromethyl *N*-Cbz protected allyl amine **359** *in situ*, then added it to the sodium enolate of dimethyl malonate to give **360** in 66% yield over two steps. Metathesis with phenyl acrylate resulted in cyclization on silica gel, cold silica gel, and neutral alumina, even when excess Hoveyda-Grubbs II catalyst was first removed using Quadrasil-MP®. However, metathesis with methyl acrylate successfully gave **361**. Our catalyst **C52** promoted cyclization of **361** to give pyrrolidine **362**, albeit in modest yield (23%) and enantioselectivity (26% ee).



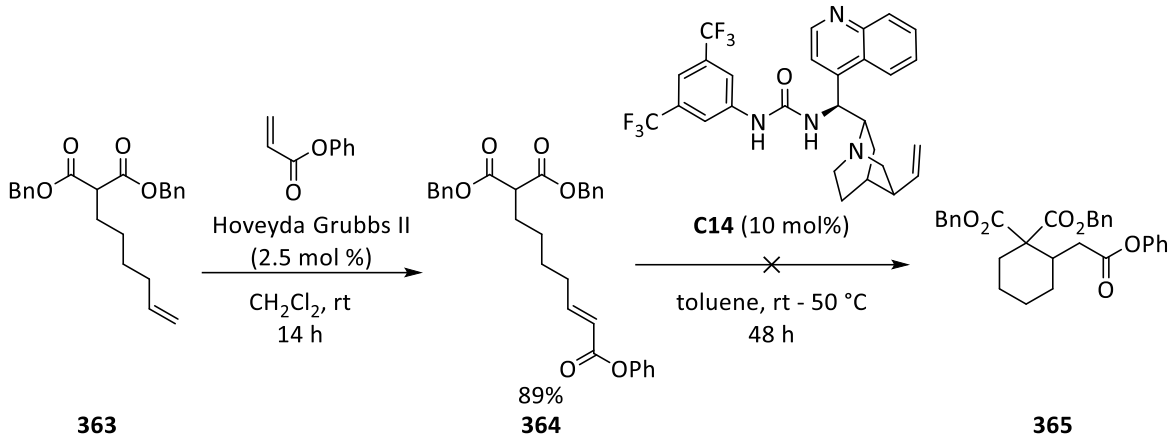
Scheme 3.24: *Synthesis of substituted pyrrolidine*

Unfortunately, the difficulty in synthesizing varied substrates limits the applicability of our methodology. While we were able to successfully cyclize nitrogen-containing and diester-substituted five membered rings with our catalyst, we were not able to do so with *α,β*-unsaturated phenyl esters, which we'd shown as important in obtaining high enantioselectivities. Ultimately, while we achieved promising enantioselectivities with cyclopentanes, our methodology has a narrow scope. We thus set out to test our methodology in forming cyclohexanes and lactams *via* alternate substrates amenable to intramolecular Michael additions.

3.4.5 Cyclohexanes

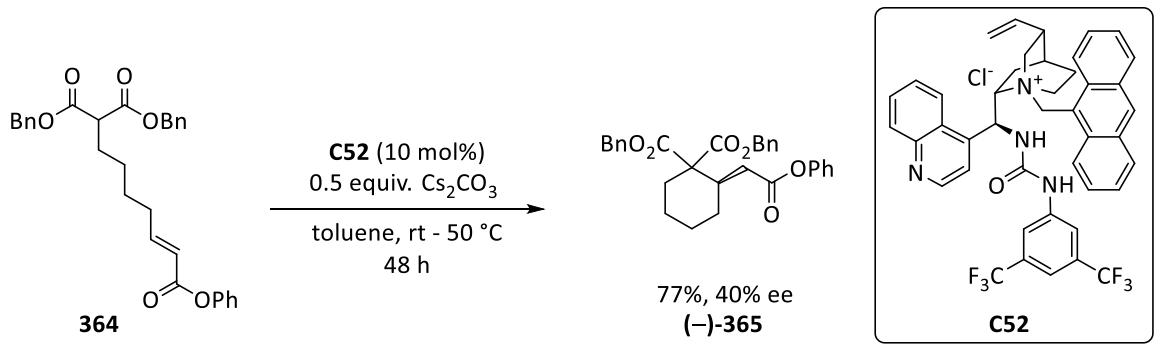
To investigate the applicability of our method to access cyclohexanes, we synthesized cyclization precursor **364** (scheme 3.25). We obtained starting material **363** by alkylating dibenzyl malonate with 6-bromohex-1-ene. Cross metathesis with phenyl acrylate proceeded smoothly to give **364**. We first attempted to cyclize **364** using non-

phase-transfer organocatalysts from Chapter 2. We observed no evidence of cyclization in the presence of **C14**, even at elevated temperature (50 °C) for 48 h.



Scheme 3.25: *Synthesis of cyclohexane precursor*

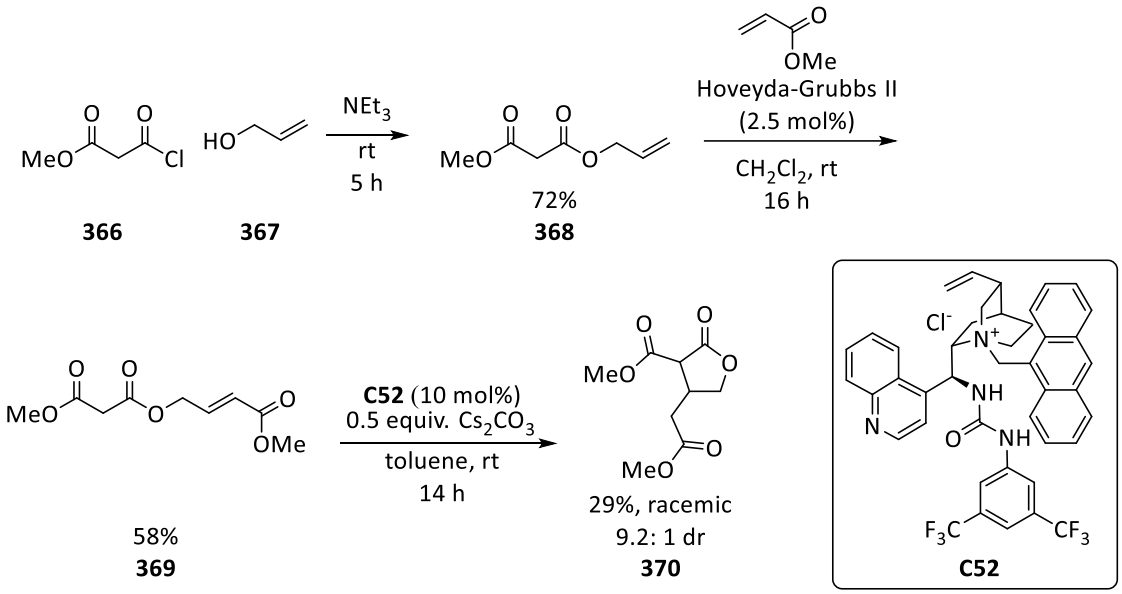
Using our optimized conditions from our cyclopentane cyclizations (but with the cinchonidine-derived **C52** rather than quinine-derived **C53**), we successfully obtained cyclohexane **(–)-365** in 77% yield (scheme 3.26). The enantioselectivity, however, was unfortunately lower (40% ee) than with cyclopentanes (62% ee under identical conditions). Despite this modest enantiocontrol, this is a further demonstration of the ability of our phase-transfer analogues of **C14** to catalyze reactions that are inaccessible to **C14** itself.



Scheme 3.26: *Enantioselective phase-transfer cyclohexane cyclization*

3.4.6 Lactams

We envisaged that by appending our Michael acceptor to one of the malonate oxygens, rather than between the two malonate esters, we could potentially access cyclic lactams via an intramolecular Michael reaction. To access such substrates, we first performed a nucleophilic addition of allyl alcohol to acid chloride **366** to give **368** in 71% yield (scheme 3.27). Cross metathesis with methyl acrylate successfully afforded our cyclization precursor **369**. An enolate of **369** has one smaller side, the methyl ester, and one larger side, containing the Michael acceptor. We hoped that our phase-transfer catalysts would be able to invoke stereocontrol by exploiting this size discrepancy. However, while catalyst **C52** did promote cyclization, the resulting lactam **370** was racemic (9:1 dr, relative stereochemistry not determined).



Scheme 3.27: *Lactam synthesis*

3.5 Conclusions and Further Applications

This chapter detailed our successful design and synthesis of a new family of bifunctional H-bond donor/ammonium salt phase-transfer catalysts. The application of these new catalysts to the intramolecular Michael reaction introduced in Chapter 2 was then

presented. Pleasingly, our phase-transfer catalysts successfully promoted cyclization onto *α,β*-unsaturated alkyl esters, which were inaccessible to the bifunctional H-bond donor/amine catalysts used in Chapter 2. This demonstrates the advantage of our new bifunctional ammonium phase-transfer catalysts to access less reactive substrates compared to their tertiary amine analogues.

For substrates that both the tertiary amine/H-bond donor and quaternary ammonium/H-bond donor catalysts cyclized, another advantage of the phase-transfer catalysts over their tertiary amine analogues is that we were able to access the cyclized products in hours rather than days or weeks. Our phase-transfer catalysts also induced significantly higher enantioselectivities than commercially available phase-transfer catalysts. They did not, however, reach the same level of enantiocontrol as the catalysts in Chapter 2 (up to 70% ee versus up to 88% ee).

While an *α,β*-unsaturated phenyl ester was not necessary to invoke reactivity under phase-transfer conditions, as it was with tertiary amine catalysts in Chapter 2, we did find that incorporating a phenyl ester greatly improved our enantioselectivities. Unfortunately this meant that we were met with the same challenges we faced in Chapter 2: because *α,β*-unsaturated phenyl esters are relatively activated Michael acceptors, some cyclization precursors cyclized prematurely during purification, thus limiting the scope of our reaction.

Even still, our H-bond donor/ammonium salt phase-transfer catalysts showed great promise. As predicted, they promoted significantly higher reactivity than their tertiary amine analogues and invoked significantly higher enantioselectivities than traditional cinchona-derived phase-transfer catalysts. The limited substrate scope of our intramolecular Michael reaction and good, but not excellent, enantioselectivities with this particular methodology meant that we weren't able to demonstrate the full potential of our catalysts.

Thus, we set out to find methods better suited to our bifunctional phase-transfer catalysts. These highly successful demonstrations of our new catalysts are presented in Chapter 4.

Chapter 4: Applications of H-bonding Phase-Transfer Catalysts

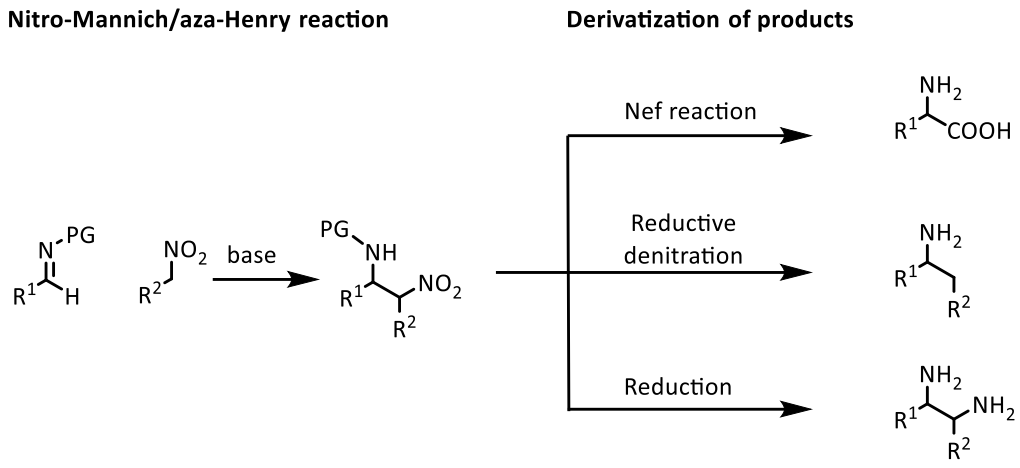
4.1 Chapter Overview

Chapter 3 presented the design and synthesis of a new family of bifunctional H-bond donor phase-transfer catalysts. The ability of these catalysts to induce good enantioinduction and activate less reactive substrates was successfully demonstrated in an intramolecular Michael reaction. However, difficulties synthesizing varied substrates for this methodology meant we were not able to demonstrate the full potential and utility of our new catalyst family. This chapter presents the highly successful application of our H-bond donor phase-transfer catalysts to the nitro-Mannich reaction of α-amido sulfones, followed by preliminary studies applying these catalysts to a new enantioselective ketimine reduction.

4.2 Nitro-Mannich Reaction

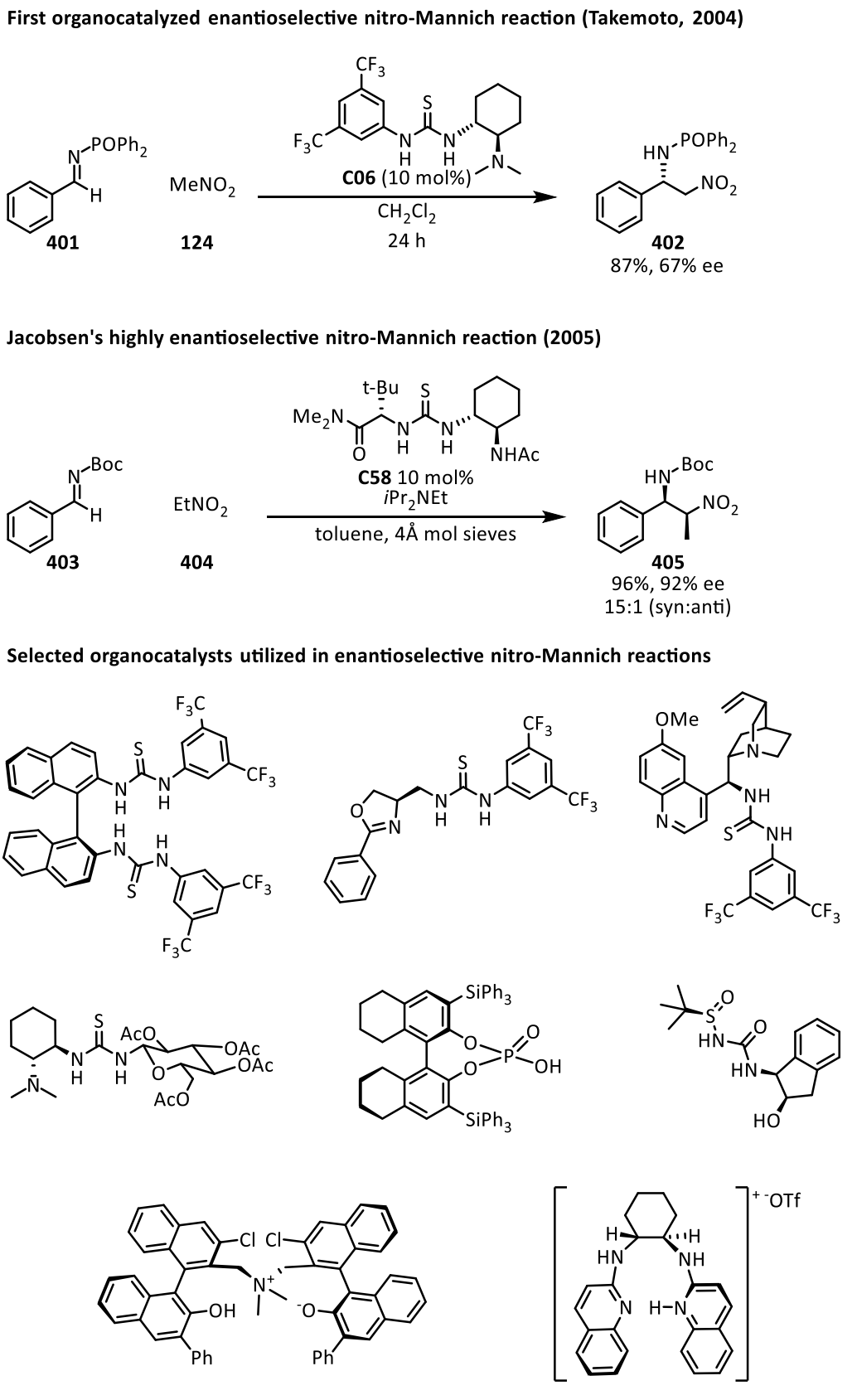
4.2.1 Pioneering work and background

The aza-Henry or nitro-Mannich reaction, which involves the nucleophilic addition of nitroalkanes to imines, has emerged as a fundamental carbon-carbon bond forming reaction. This methodology has been successfully applied to the syntheses of complex natural products, as our group has demonstrated in syntheses of (–)-nakadomarin A[45–47] and paroxetine.[83,145] The resulting β-nitroamine products are also highly versatile. For example, the β-nitroamine's vicinal nitrogen atoms are present in different oxidation states, which allows facile selective manipulation of either nitrogen.[128,146] β-Nitroamines can also be transformed into: α-amino acids via the Nef reaction for use as enzyme-inhibitors or robust analogues of natural amino acids;[147] monoamines via reductive denitration;[148] or 1,2-diamines via reduction[148] for use as building blocks, ligands, or organocatalysts (scheme 4.01).



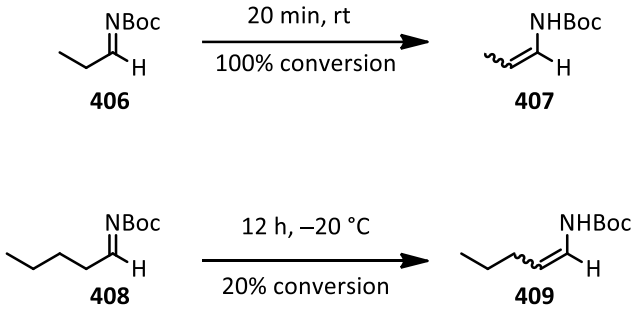
Scheme 4.01: *Nitro-Mannich/aza-Henry reaction and derivatization of products*

Henry reported the first such nucleophilic addition of nitroalkanes to imines in 1896, but it was over a century later in 1999 that Shibasaki achieved the first catalytic asymmetric variant using a Yb/K heterobimetallic BINOL catalyst (up to 83% ee).[149] Five years later, Takemoto and coworkers reported the first metal-free enantioselective nitro-Mannich reaction of *N*-phosphinoyl imines and nitromethane using bifunctional cinchona-derived organocatalyst **C06** bearing a thiourea and *N*,*N*-dimethylamino group.[150] Takemoto's enantioselectivities were moderate (63-76% ee, scheme 4.02), but shortly afterwards Yoon and Jacobsen reported a new thiourea catalyst **C58** that promoted the nucleophilic addition of nitromethane and nitroethane to *N*-Boc protected imines with excellent enantioselectivities (92-97% ee, scheme 4.02).[151] Since then, several reports have demonstrated the successful application of numerous organocatalysts to promote enantioselective nitro-Mannich reactions, including other (thio)urea catalysts,[148,152–157] bisamidine triflate salts,[147,158] ammonium betaines,[159] and Brønsted acids[160] (see scheme 4.02).



Scheme 4.02: *Takemoto's*[150] *and Jacobsen's*[151] *nitro-Mannich reactions and selected organocatalysts used to catalyze enantioselective nitro-Mannich reactions*[150–154,156–161]

All of these reports were limited to the use of aromatic[147,148,150–159] or other non-enolizable[160] imines only, except for Ellman's later (limited) aliphatic examples.[161] This apparent limitation is due to difficulty isolating alkyl imines and the inherent instability of enolizable imines, which are prone to undergo *α*-deprotonation rather than addition.[128] Deng *et al.* reported that *N*-Boc protected propyl imine **406** tautomerized to the corresponding enamine **407** within minutes at room temperature, and tautomerism continued to occur at a significant rate even when the temperature was lowered to –20 °C (scheme 4.03).[162]

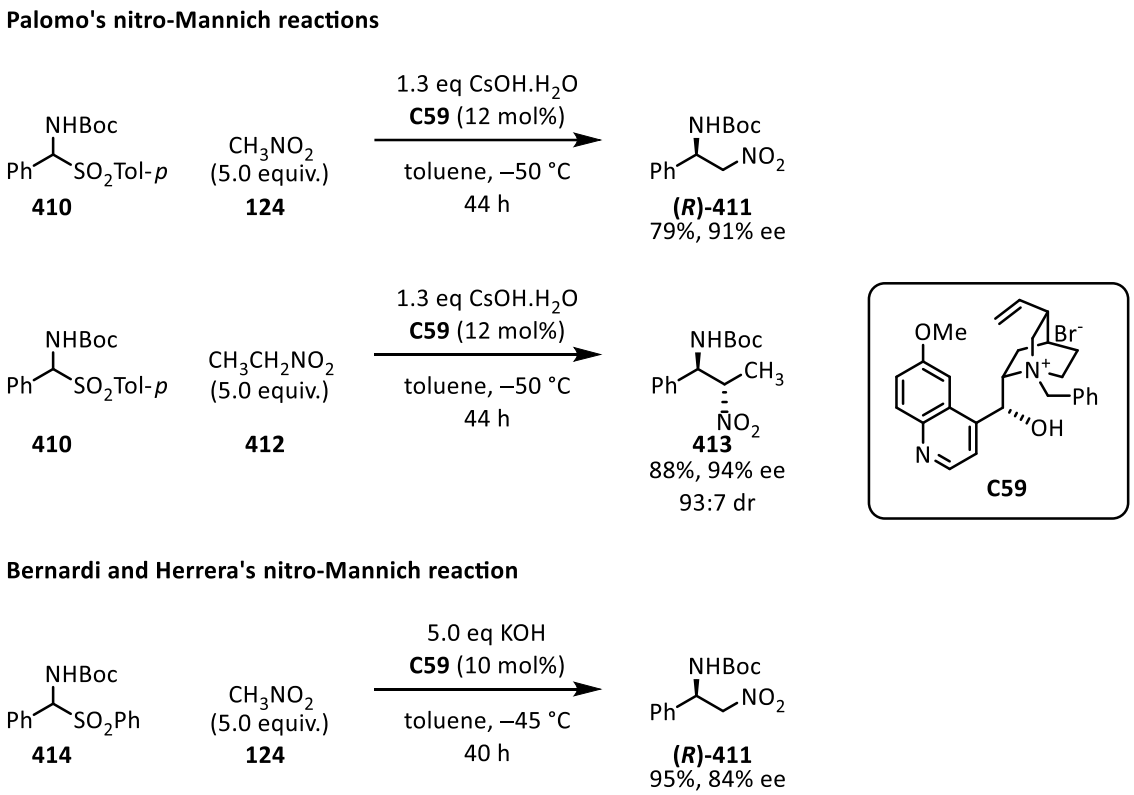


Scheme 4.03: *Tautomerism of alkyl imines*

4.2.2 Phase-transfer catalyzed nitro-Mannich reaction

One possible solution to this imine tautomerism problem is to form the imines *in situ*. Palomo's[126] and Bernardi and Herrera's[127] groups independently developed this approach by forming imines *in situ* from their corresponding *α*-amido sulfones. Both reports employed an *N*-benzyl quininium chloride phase-transfer catalyst (**C59**) paired with an external base to promote the nucleophilic addition of nitroalkanes to imines produced *in situ* from *α*-amido sulfones (scheme 4.04). Bernardi and Herrera *et al.* used potassium hydroxide as an inorganic base, while Palomo *et al.* found cesium hydroxide monohydrate to marginally outperform potassium hydroxide under slightly different conditions. Both groups were able to show reactivity with multiple aliphatic imines in good yields and enantioselectivities. While Bernardi and Herrera limited their study to the addition of

nitromethane, Palomo's report included addition to nitroethane, yielding **413** with good diastereoselectivity (scheme 4.04).



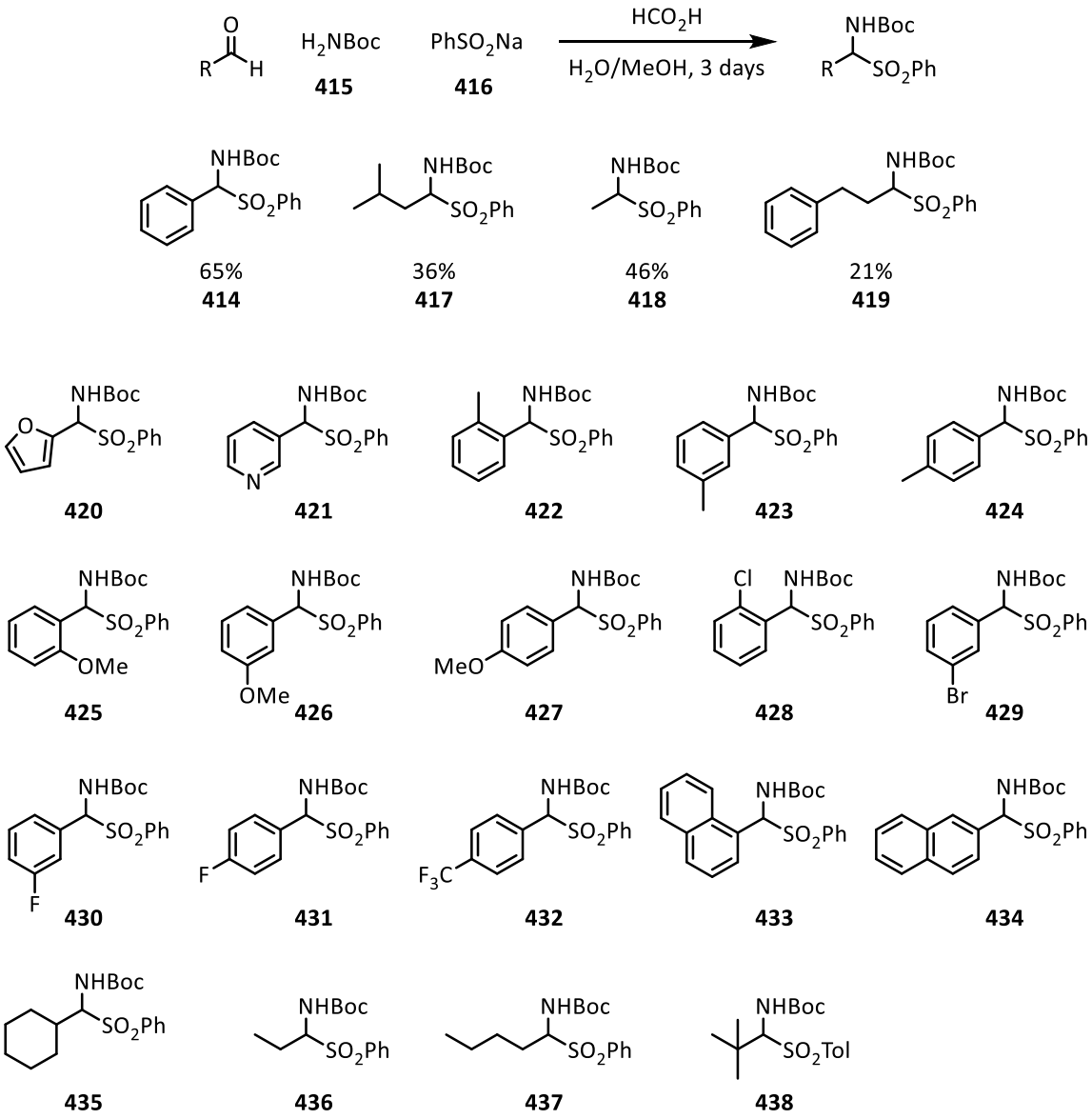
Scheme 4.04: *Palomo's and Bernardi and Herrera's phase-transfer nitro-Mannich reactions*[126,127]

While both groups reported very successful methodologies, we envisaged that our H-bond donor phase-transfer catalysts could offer enhanced, reliable stereocontrol and expand the existing methodology. For example, while Herrera and Bernardi report good enantioselectivity for the (*R*)-enantiomer above (scheme 4.04), in their supporting information they reveal that at 25 °C using a fluoride base, catalyst **C59** gave the (*R*)-enantiomer (from the imine) in 68% ee while the pseudo-enantiomeric catalyst derived from quinidine gave the (*S*)-enantiomer (from *α*-amido sulfone **414**) in only 12% ee.[127] In a recently reported similar method, which replaces the catalyst's benzyl group with a benzotriazole, He *et al.* reported a similar loss of enantiocontrol upon using the pseudo-

enantiomer of **C59**.[163] This reflects a common problem when using pseudo-enantiomeric cinchona-type phase-transfer catalysts: as the catalysts are diastereomers, one enantiomer of the desired product can sometimes be accessible with much higher enantioselectivity than the other. We hypothesized that the strong H-bond donor in our catalysts might help to enhance the organization and directionality of the substrate-catalyst interaction and thus provide consistently high enantioselectivities for both enantiomers. Herrera and Bernardi's supporting information also detailed how protecting the hydroxyl group of **C59** with a benzyl group reduced the enantioselectivity almost by half, suggesting that the H-bond donor is essential to the enantioinduction. In a follow-up report, Palomo *et al.* also presented drastic loss of reactivity (conversions <10%) when using the benzyl ether protected analogue of phase-transfer catalyst **C59**.[128] These reports both support the importance of the H-bond donor in these organocatalysts, and motivate the exploration of phase-transfer catalysts with varied H-bond donors.

4.2.3 Establishing reactivity and optimization

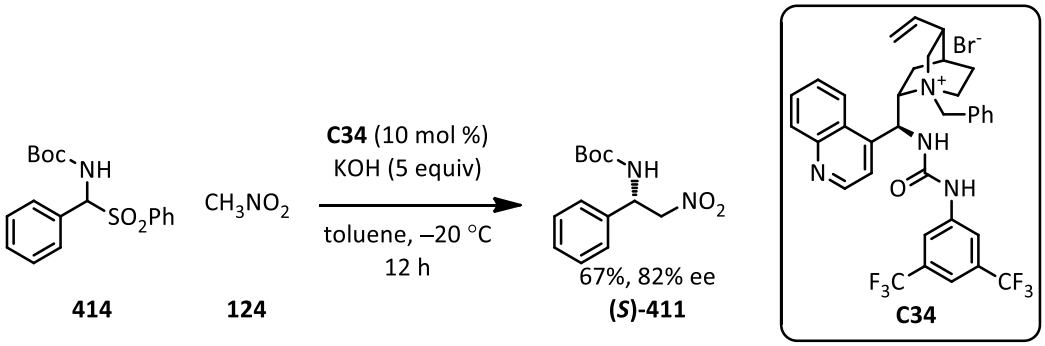
Amido sulfone **414** was prepared via three-component coupling using the literature procedure.[164] Vigorously stirring benzaldehyde with *tert*-butyl carbamate (**415**) and sodium benzenesulfinate (**416**) in formic acid, water and methanol for three days gave the corresponding α-amido sulfone **414** as a white powder in 82% yield (scheme 4.05). α-Amido sulfones **417-419** were prepared in an analogous fashion, using the appropriate aldehydes, while the remaining amido sulfones for subsequent studies were prepared by my colleagues David Barber (**420-437**) and Anna Goldys (**438**).



Scheme 4.05: *Preparation of α-amido sulfones*

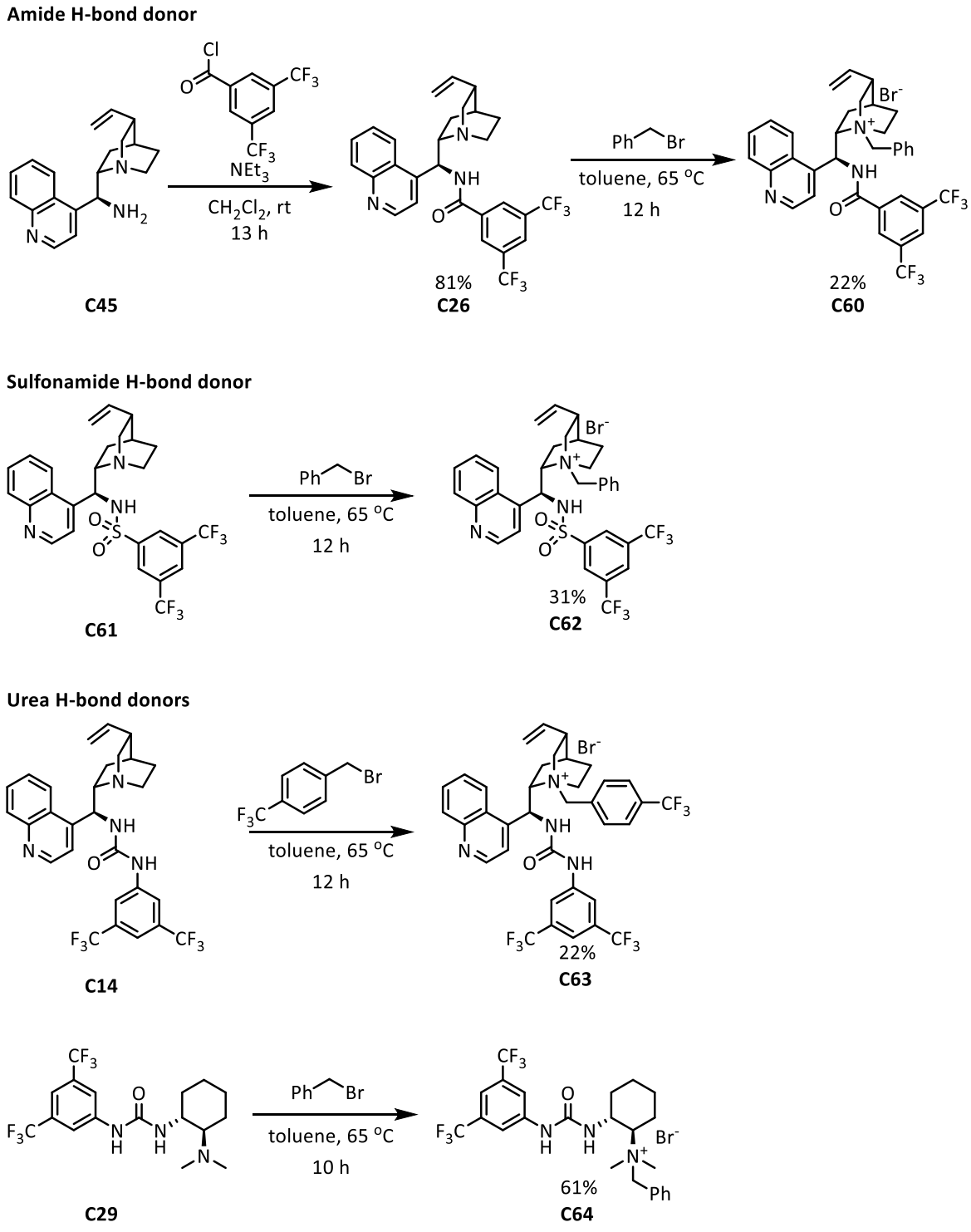
With phenyl amido sulfone **414** in hand, we set out to test our catalyst in the enantioselective phase-transfer nitro-Mannich reaction using four different bases: KOH, CsOH, K_2CO_3, and Cs_2CO_3. Pleasingly, in the presence of freshly ground anhydrous KOH, catalyst **C34** promoted the nucleophilic addition of nitromethane to the benzyl imine generated *in situ* to give the desired *β*-nitroamine **(*S*)-411** in 67% yield and 82% ee after 12 hours at –20 °C (scheme 4.06). That is, under non-optimized conditions, **C34** promoted the

nitro-Mannich reaction at almost four times the rate that Bernardi and Herrera observed with **C59** and with only a 2% ee loss at a temperature elevated by 25 °C. Interestingly, none of the other three bases tested promoted the nitro-Mannich reaction. Thus, we used freshly ground anhydrous KOH for all subsequent optimization.



Scheme 4.06: *Establishing reactivity*

With good reactivity and selectivity established, we tested a range of H-bond donor phase-transfer catalysts. In addition to the cinchona-derived bifunctional phase-transfer catalysts described in detail in Chapter 3 (figure 4.01), we synthesized four new phase-transfer catalysts: **C60**, **C62**, **C63** and **C64** (scheme 4.07). Catalysts **C60**, **C62** and **C63** were prepared using the same design and synthetic approach as the catalysts in Chapter 3. Cinchonidine-derived **C63** incorporates an electron withdrawing *para*-CF_3 substituent on the benzyl group to probe electronic effects on the quaternary nitrogen. We synthesized phase-transfer catalysts **C60** and **C62**, which feature an amide and a sulfonamide, respectively, to test the effects of different H-bond donor groups. The final catalyst, **C64**, is based on the urea analogue of Takemoto's catalyst in scheme 4.02. Both Takemoto's catalyst and cinchona-derived chiral scaffolds have been successfully demonstrated in the nitro-Mannich reaction, and we therefore envisaged that they would serve as successful chiral backbones for our H-bond donor phase-transfer catalysts.



Scheme 4.07: *Synthesis of new H-bond donor phase-transfer catalyst*

First, we maintained the cinchonidine chiral scaffold and varied the H-bond donor group. Sulfonamide **C62** was incompetent as a phase-transfer catalyst in this reaction and did not promote nucleophilic addition (scheme 4.08, table 4.01, entry 6). This is possibly

due to the higher acidity NH group being deprotonated under the reaction conditions, thus forming an inner salt and thereby rendering the catalyst inactive. Amide **C60** successfully promoted addition, albeit with diminished enantioselectivity (58% ee, entry 5). This suggests that the strong dual-H bond donor of the urea in catalyst **C34** plays an important role in the enantioinduction, and offers more control than a single H-bond donor such as amide **C60**.

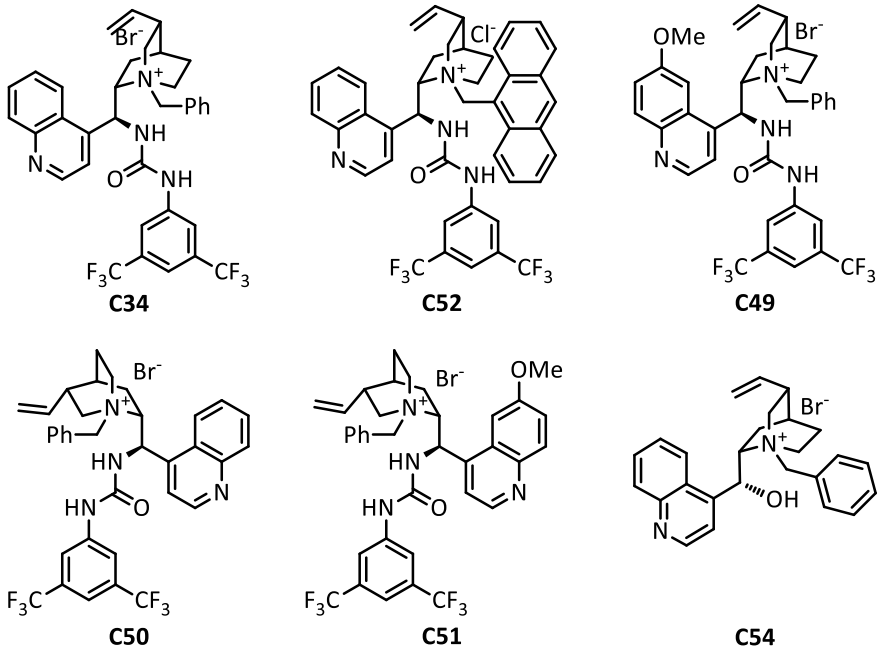
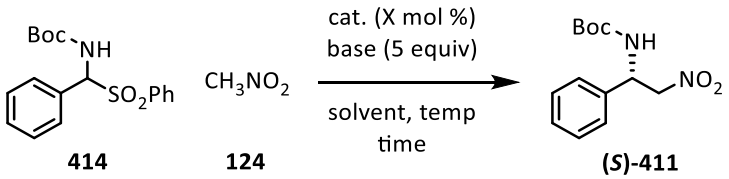


Figure 4.01: *Additional catalysts screened in the nitro-Mannich reaction*

Comparing the performance of a series of cinchonidine-derived ureas with varying quaternary ammonium alkylating groups, *p*-CF_3 benzylated catalyst **C63** performed almost identically to benzylated catalyst **C34** (81% ee). Increasing steric bulk at the quaternary nitrogen, by replacing the benzyl group with a 9-anthracenylmethyl group (**C52**), resulted in a decrease in both yield (51%) and enantioselectivity (71% ee). Thus, we selected a urea as our H-bond donor group and benzyl bromide as our alkylating group on the quaternary nitrogen. Importantly, a simple cross-check using commercial *N*-benzyl-cinchonidinium bromide **C54** as the catalyst, under identical reaction conditions, afforded **(*R*)-411** in

substantially reduced yield (29%) with poor stereocontrol (34% ee). This result confirmed that the urea functionality plays a key role in controlling the stereochemical course of the reaction.



Scheme 4.08: *Nitro-Mannich optimization conditions (see table 4.01 for results)*

	cat.	X	Base	Solvent	C ([M])	Temp. (°C)	Time (h)	Yield (%)	ee (%)
1	**C34**	10	KOH	toluene	0.1	–20	12	67	82
2	**C34**	10	K_2CO_3	toluene	0.1	–20	34	n.d.	–
3	**C34**	10	Cs_2CO_3	toluene	0.1	–20	34	n.d.	–
4	**C34**	10	CsOH	toluene	0.1	–20	13	n.d.	–
5	**C60**	10	KOH	toluene	0.1	–20	12	78	58
6	**C62**	10	KOH	toluene	0.1	–20	12	nd	–
7	**C63**	10	KOH	toluene	0.1	–20	12	70	81
8	**C52**	10	KOH	toluene	0.1	–20	12	53	71
9	**C50**	10	KOH	toluene	0.1	–20	12	78	85[a]
10	**C49**	10	KOH	toluene	0.1	–20	12	59	80
11	**C51**	10	KOH	toluene	0.1	–20	12	91	85[a]
12	**C51**	10	KOH	toluene	0.1	–40	40	71	84[a]
13	**C51**	10	KOH	toluene	0.05	–20	12	79	85[a]
14	**C51**	10	KOH	toluene	0.2	–20	12	77	85[a]
15	**C51**	5	KOH	toluene	0.1	–20	12	72	85[a]
16	**C51**	5	KOH	EtOAc	0.1	–20	12	78	80[a]
17	**C51**	5	KOH	CH_2Cl_2	0.1	–20	12	73	84[a]
18	**C51**	5	KOH	tol/$CHCl_3$	0.1	–20	12	35	86[a]
19	**C51**	**5**	**KOH**	**MTBE**	**0.1**	**–20**	**12**	**79**	**89**[a]
20	**C49**	5	KOH	MTBE	0.1	–20	24	66	84
21	**C64**	5	KOH	MTBE	0.1	–20	x	x	46

Table 4.01: *Nitro-Mannich optimization; [a]**(R)-426** was obtained*

Next, we tested different cinchona alkaloids as chiral scaffolds. Pleasingly, switching from cinchonidine-derived **C34** to the pseudo-enantiomeric cinchonine-derived **C50** gave *β*-nitroamine **(*R*)-411** as the opposite enantiomer with similarly high enantioselectivity (85% ee, entry 9). This demonstrates a great advantage of our dual H-bond donor catalysts over commercially available catalysts: we can access both enantiomers of the product with reliable and good enantioselectivities. Quinine-derived catalyst **C49** gave **(*S*)-411** with similar enantioselectivity (81% ee) to **C34**, and quinidine-derived catalyst **C51** gave the same enantiomer [**(*R*)-411**] and enantioselectivity (85% ee) as cinchonine-derived **C50**. We chose quinidine-derived catalyst **C51** over cinchonine-derived catalyst **C50** for subsequent optimization because it provided *β*-nitroamine **(*R*)-411** in higher yield (91%, entry 11).

Having established the best cinchona-derived catalyst to promote the nitro-Mannich reaction, we tested the effects of temperature, concentration, and catalyst loading. Temperature had little effect on the enantioselectivity of the nucleophilic addition: lowering the temperature to –40 °C greatly increased the reaction time (40 h, entry 12) and lowered the yield (71%) without increasing the enantioselectivity (84% ee), therefore subsequent reactions were maintained at –20 °C. Doubling or halving the concentration afforded the *β*-nitroamine in the same amount of time and with the same 85% ee, but slightly reduced yield (entries 13-14). We then reduced the catalyst loading from 10 mol% to 5 mol% and found good conversion after 12 h and no loss of enantioselectivity (entry 15). We did not attempt to lower the catalyst loading further in order to keep the mass of catalyst high enough to allow for accurate weighing on the reaction scale.

Using catalyst **C51**, –20 °C, 5 mol% catalyst loading and 0.1 M concentration, we then screened a variety of solvents. The enantioselectivity was fairly consistent over all solvents tested including more polar solvents such as ethyl acetate, dichloromethane, and a

mixture of toluene and chloroform; this contrasts with the strong solvent-dependency observed by Palomo.[128] Pleasingly, we observed a small boost in enantioselectivity to 89% ee in MTBE. Under these same, optimized conditions, we tested our new Takemoto-like catalyst **C64**. This alternate chiral scaffold gave *β*-nitroamine **(*S*)-411** in only 46% ee. Thus, we retained the cinchona alkaloids as our chiral scaffold.

Overall, we found that our methodology was very tolerant of different reaction conditions, with our catalyst inducing similarly good conversions and enantioselectivities at varying temperatures, concentrations, and catalyst loadings and in various solvents. Through testing each of these factors we established our optimized conditions as 5 mol% cinchona-derived phase-transfer catalyst **C51** at –20 °C and 0.1 M in MTBE. Under these same conditions, **C49** gave access to the opposite enantiomer with good enantioselectivity (84% ee, entry 20).

4.2.4 Reaction mechanism and model

The mechanism of this reaction is probably very similar to the experimentally and computationally grounded mechanism proposed by Palomo in 2008.[128] Palomo found little difference in yield and enantioselectivity when replacing the *α*-amido sulfone used in scheme 4.03 with the corresponding pre-formed imine. This suggests that, when using an *α*-amido sulfone, the imine is formed independently prior to the nitro-Mannich reaction and that the resulting sulfinate salts do not affect the reaction. Monitoring the reaction by ^{1}H NMR spectroscopy, Palomo did not observe intermediate imine peaks, suggesting that imine consumption via nitronate addition is much faster than imine formation. Furthermore, Palomo found that both nitroalkane and phase-transfer catalyst were required to promote reactivity in the presence of their *α*-amido sulfones and cesium hydroxide. This suggests that, as was the case in the Michael reaction in Chapter 3, the phase-transfer catalyst does not extract the base into the organic layer. Instead, the nitronate anion is likely formed at

the phase interface, transported into the organic phase by the phase-transfer catalyst, and then acts as the base to promote imine formation from the α-amido sulfone or adds to an already formed imine. Taking these observations, along with Palomo's kinetic and computational data, we proposed the mechanism shown in figure 4.02.

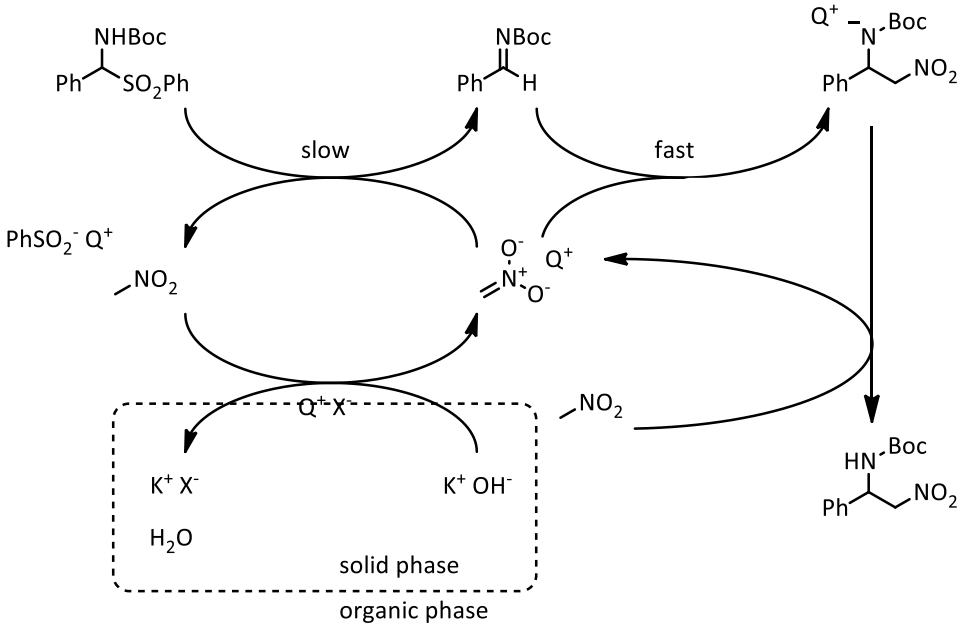


Figure 4.02: *Proposed mechanism based on Palomo's mechanistic investigations*[128]

Without extensive experimental results and/or theoretical calculations, we cannot be sure how our catalyst and substrates interact to invoke high enantioselectivities. However, we can propose a simplified representation based on models reported for related reactions and catalysts. It is possible that our dual H-bond donor urea coordinates with the nitronate, the imine, or both species. With their free hydroxyl benzylated catalyst **C59**, Palomo *et al.*'s calculations suggest that hydrogen bonding between the hydroxyl group and the nitronate and interaction between the ammonium and the imine led to more stable catalyst-substrate interactions than if the location of the imine and nitronate were switched.[128] Furthermore, the authors found that the interaction between the ammonium and imine involved hydrogen bonding from the α-carbon hydrogens to the nitrogen of the imine. Thus, we assum that our

dual H-bond donor urea interacts most strongly with the nitronate species, and the nitrogen of our imine H-bonds with the alkyl groups around the quaternary nitrogen. Based on these assumptions, we propose the transition state model in figure 4.03 for our phase-transfer nitro-Mannich reaction with **C34**.

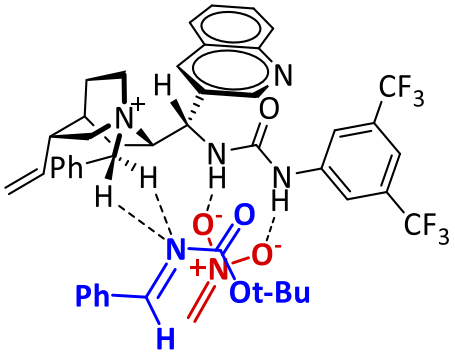


Figure 4.03: *Proposed phase-transfer catalysed nitro-Mannich transition state*

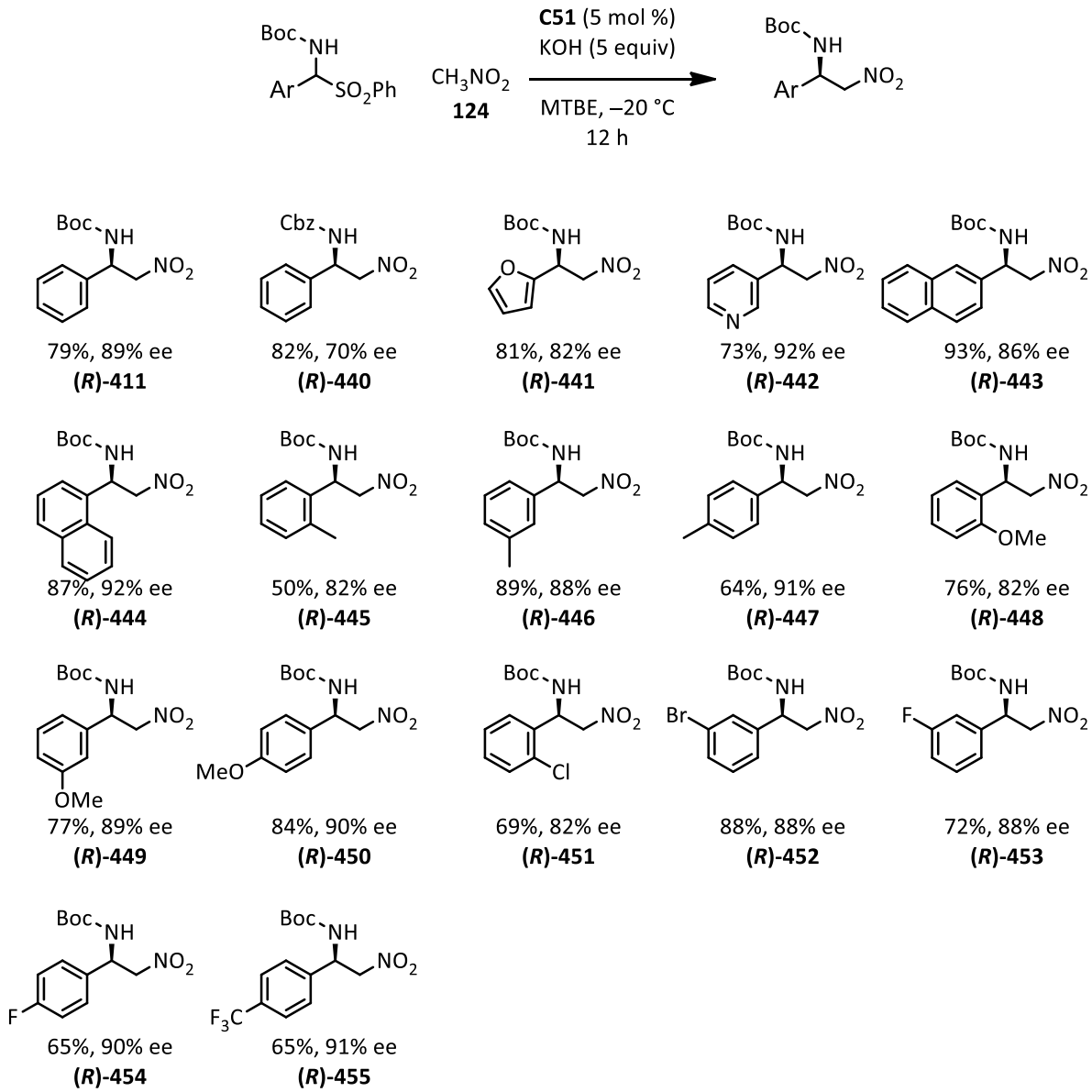
In our model, one or both oxygens of the nitronate (shown in red) form a strong dual H-bond with the urea moiety of the catalyst. The imine (shown in blue) approaches from the *si*-face, opposite the aryl group, while the nitrogen interacts with the benzyl hydrogens *α* to the quaternary ammonium. The carbonyl oxygen of the *tert*-butyl carbamate protecting group orients towards the urea, rather than adopting the s-*cis* conformation typical of ester derivatives, to allow for potential additional H-bonding interactions. Addition to the *si*-face gives the observed **(*S*)-411** *β*-nitroamine. After the reaction is complete, the nitro group of the *β*-nitroamine becomes neutral and so is no longer as tightly bound to the urea H-bond donor. Thus, *β*-nitroamine **411** is released, and the catalyst is available for further reactions.

4.2.5 Nitro-Mannich scope[v]

With our optimized conditions established, we tested the nucleophilic addition of nitromethane to aryl imines produced *in situ* from a variety of *α*-amido sulfones (see scheme 4.05). First, we tried replacing the *N*-Boc protecting group with an *N*-Cbz group [**(*R*)-440**, scheme 4.09]. However, the enantioselectivity fell to 70% ee, suggesting that the *tert*-butyl group is important for enantiocontrol. Next, we tested heteroaromatic amido sulfones. 2-Substitued furan **(*R*)-441** and 3-substitued pyridine **(*R*)-442** were both produced in good yield and enantioselectivity, up to 92% ee for **(*R*)-442**. Polycyclic aromatic compounds were also well-tolerated and we obtained 1-naphthyl [**(*R*)-443**] and 2-naphthyl [**(*R*)-444**] *β*-nitroamines in 92% ee and 86% ee, respectively.

Next, we tested the effects of substitution on the phenyl ring. *Ortho*-methyl substitution resulted in diminished enantioselectivity [**(*R*)-445**, 82% ee], while *meta* [**(*R*)-446**, 88% ee] and *para* [**(*R*)-447**, 91% ee] substitution gave higher enantioselectivities. These substitution effects held consistent for both electron donating and withdrawing substituents, with methyl, methoxy, and halogen substituents giving almost identical enantioselectivities at the same substitution site. *Para*-substitution was universally well-tolerated, with methyl [**(*R*)-447**], methoxy [**(*R*)-450**], fluoro [**(*R*)-454**], and trifluoromethyl [**(*R*)-455**] *para* substituents all giving 90+% ee. These results suggest that steric effects are more important than electronic consideration in controlling enantioinduction among these substrates.

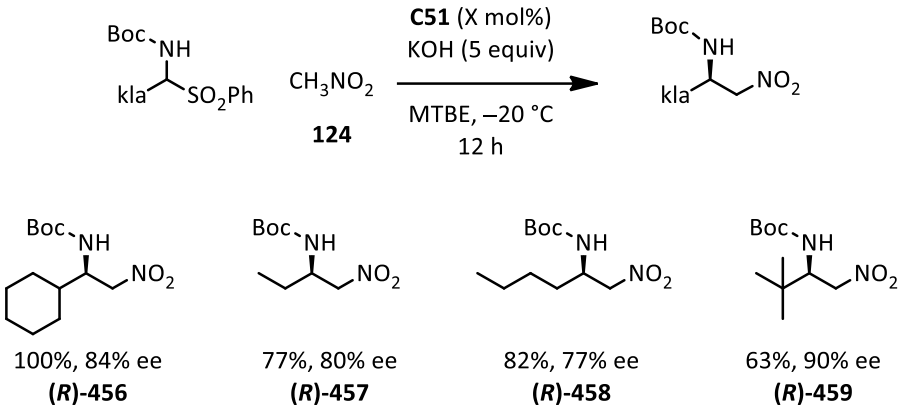
[v] Some substrates in this section were prepared by my colleagues David Barber, Marta Garcia, Anna Goldys and Matt Rattley under my supervision. Only the *β*-nitroamines that I prepared myself are presented and characterized in Chapter 6.



Scheme 4.09: *Aryl α-amido sulfone substrate scope with nitromethane*

Next, we tested alkyl *α*-amido sulfones (scheme 4.10). Catalyst **C51** successfully promoted the *in situ* generation of alkyl imines and subsequent nucleophilic addition, albeit in lower enantioselectivities than with aryl *α*-amido sulfones. We observed an increase in enantioselectivity as we increased the steric bulk of the alkyl group close to the imine from an ethyl [**(*R*)-457**] to cyclohexyl [**(*R*)-456**] to *tert*-butyl [**(*R*)-459**] group. Notably, *tert*-butyl

β-nitroamine **(*R*)-459**, which was previously unknown, was obtained in 90% ee (scheme 4.10).

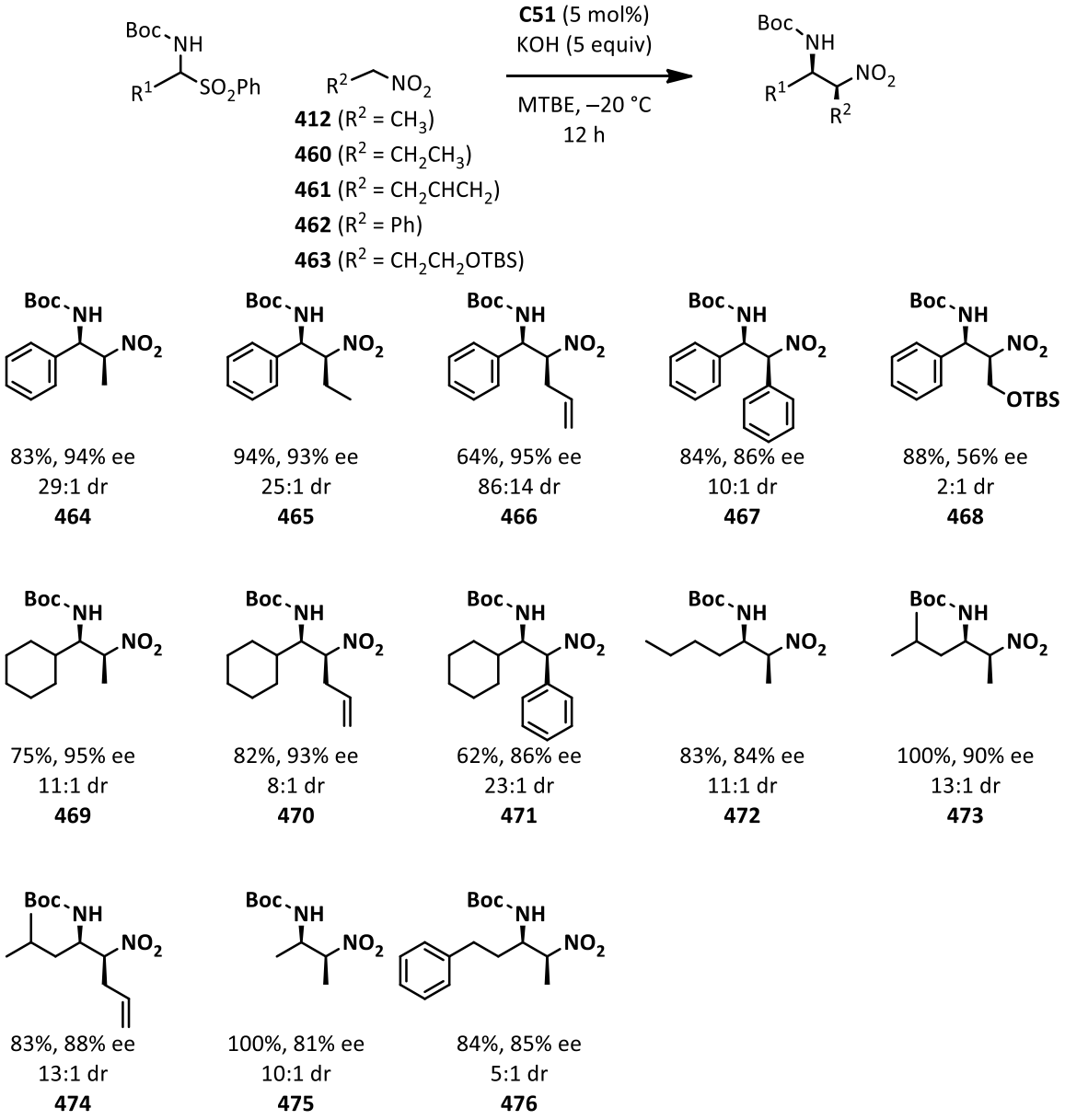


Scheme 4.10: *Nitro-Mannich reaction of alkyl α-amido sulfones with nitromethane*

Next, we investigated the nucleophilic addition of larger nitroalkanes to simultaneously form two adjacent stereocenters (scheme 4.11). Pleasingly, adding nitroethane to phenyl amido sulfone enhanced the enantioselectivity to 94% ee (compared to 89% ee with nitromethane) and gave the *anti*[vi] *β*-nitroamine **464** with excellent diastereoselectivity (29:1 *anti*:*syn*[vii]). The relative stereochemistry was determined by comparison of ^{1}H NMR spectra with known compounds (see experimental section for details). The addition of nitropropane (**465**) and nitrobut-1-ene (**466**) gave similarly high enantio- and diastereoselectivities. The addition of nitrobenzene (**467**) led to a small decrease in both the enantio- and diastereoselectivities, and TBS-protected nitroethanol (**468**) drastically reduced the enantioselectivity to 56% ee, achieving only 2:1 (*anti*:*syn*) diastereoselectivity. Alkyl amido sulfones experienced a similar enantioselectivity boost using larger nitroalkanes, with cyclohexyl *β*-nitroamine increasing from 84% ee with nitromethane to 95% ee with nitroethane (**469**) and 93% ee with nitrobut-1-ene (**470**). Alkyl

[vi] *anti* and *syn* are defined by the relative configurations of the NBoc amine and nitro group, as established by Anderson *et al*. in the first diastereoselective nitro-Mannich reaction[210]
[vii] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

amido sulfones with higher steric bulk gave higher enantioselectivities while enantioselectivities and diastereoselectivites were diminished with amido sulfones bearing small alkyl groups such as methyl (**475**). We published a summary of this work in Organic Letters in early 2012.[55]



Scheme 4.11: *Enantio- and diasteroselective nitro-Mannich reaction*

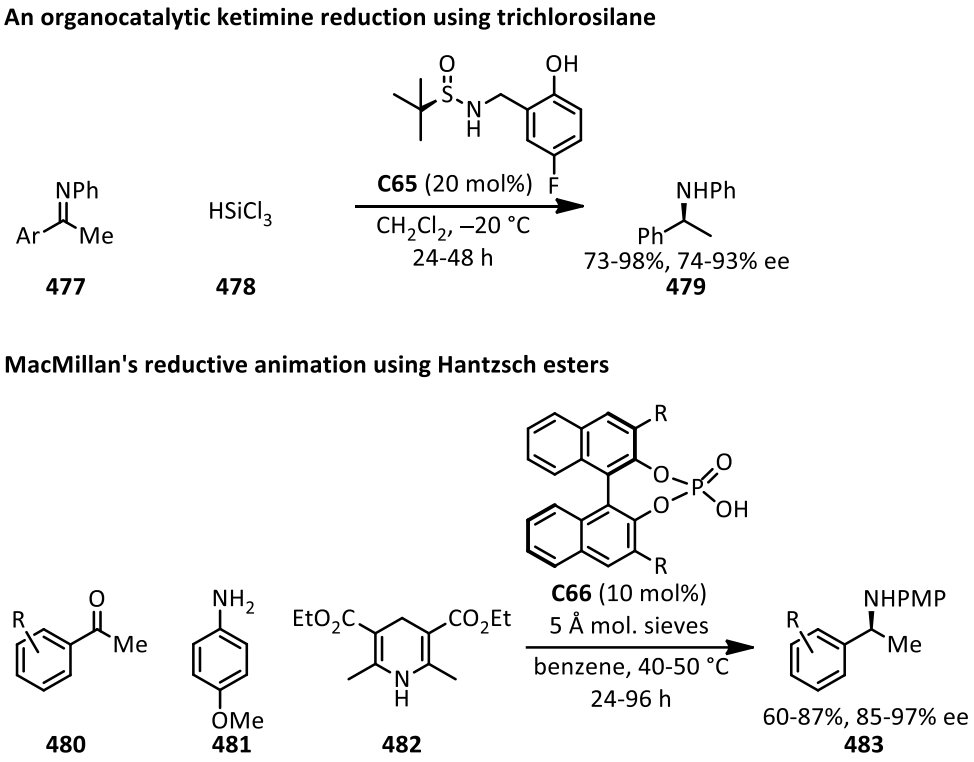
4.2.6 Nitro-Mannich summary

We successfully demonstrated the application of our new family of H-bond donor phase-transfer catalysts in the nitro-Mannich reaction of nitroalkanes with *α*-amido sulfones. We achieved good to excellent enantioselectivities (up to 95% ee) and excellent diastereoselectivities (up to 29:1 *anti*:*syn*) with a wide range of aryl and alkyl amido sulfones and nitroalkanes (34 examples). Our catalysts are able to achieve similarly high enantioselectivities to those previously reported for phase-transfer catalysis[126,127,163] at a much higher temperature (–20 °C vs –50 °C) and thus at a much faster rate (at least 4x faster). Furthermore, unlike many previously reported cinchona-derived phase-transfer catalysts, we are able to reliably obtain either *β*-nitroamine enantiomer using pseudo-enantiomeric cinchona alkaloid scaffolds without loss of enantioselectivity. These advantages demonstrate how the strong dual H-bond donor incorporated in our phase-transfer catalyst helps to provide a more ordered transition state, which translates to excellent and reliable enantioselectivities.

4.3 Ketimine Reductions

4.3.1 Introduction and background

Chiral amines are ubiquitous in natural products, pharmaceuticals, agrochemicals, and as ligands in transition metal mediated asymmetric transformations.[165] Highly successful enantioselective ketimine reductions and reductive aminations routinely employ transition metal catalysts such as ruthenium,[166] rhenium,[167] and iridium[168] to access chiral amines. However, on large scale, such methods are expensive and involve dangers of metal contamination and high pressures of hydrogen. Over the past several years, various metal-free enantioselective organocatalytic methods have also emerged, often featuring catalysts bearing an amide moiety (scheme 4.12).

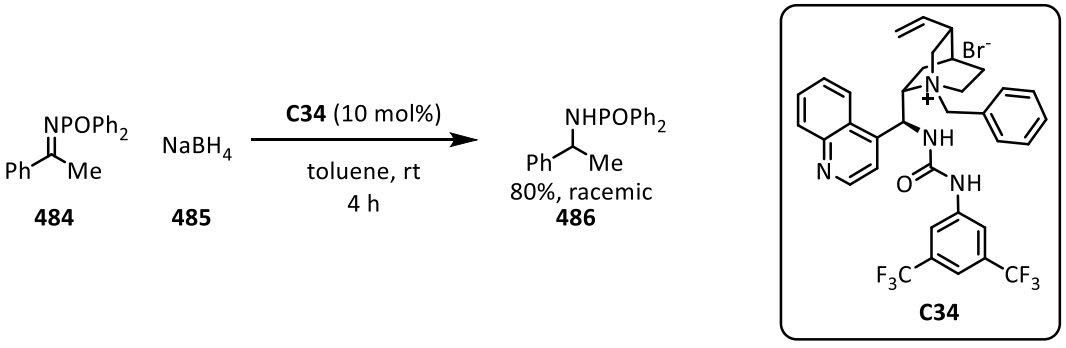


Scheme 4.12: *Sample enantioselective organocatalyzed ketimine reductions*

Building on Kobayashi's 1996 report that trichlorosilane in the presence of dimethylformamide (DMF) can reduce ketones and imines,[169] many such organocatalytic methods employ trichlorosilane as a reducing agent[170–177] with amide-bearing catalysts as chiral DMF analogues. Some organocatalytic reductions also feature a biomimetic Hantzsch ester reductant (an NADH analogue),[178] as first introduced by MacMillan in 2006.[179] As is common with organocatalysis, many of these methods require long reaction times, high catalyst loadings, and elevated temperatures. We hypothesized that our H-bond donor phase-transfer catalyst could help overcome these drawbacks. To the best of our knowledge, enantioselective phase-transfer catalyzed ketimine reductions are currently unprecedented in the literature. Thus, we set out to test the efficacy of our bifunctional phase-transfer catalysts in such a reduction.

4.3.2 Initial findings[viii]

In both our solid/liquid phase-transfer catalyzed Michael reaction and nitro-Mannich reaction, the solid phase reactant was a base. We were interested in developing a reaction where our phase-transfer catalyst transports a fundamental insoluble reagent (other than a base) into the organic reaction phase. Sodium borohydride in alcohol is commonly used to reduce both ketones and imines. However, since sodium borohydride is insoluble in non-alcoholic organic solvents, we envisaged that our phase-transfer catalyst could help to transport the borohydride anion into a non-alcoholic organic phase containing an imine where it could catalyze its enantioselective reduction. We set up such a test reaction using phosphoketimine **484**, $NaBH_4$, and phase-transfer catalyst **C34** in toluene (scheme 4.13). Although the reduction was complete after four hours, the resulting protected amine **486** was racemic. Replacing the reductant with the less reactive sodium cyanoborohydride or sodium triacetoxyborohydride resulted in no reaction. Thus, we decided to take a different approach in our reduction.

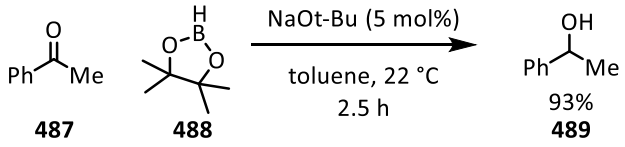


Scheme 4.13: *Phase-transfer ketimine reduction with sodium borohydride*

We were inspired by Clark's 2011 alkoxide catalyzed reduction of ketones with pinacolborane (scheme 4.14).[180] Clark proposed that butoxide acts as a Lewis base and adds

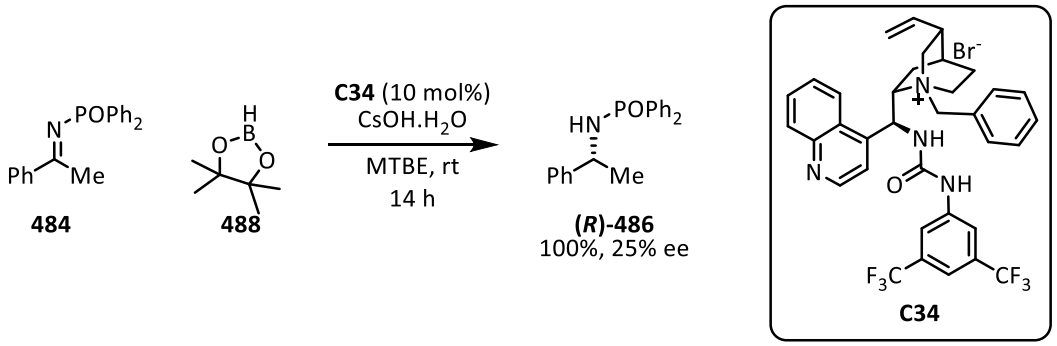
[viii] Matt Rattley carried out early optimization reactions for this ketimine reduction as an M.Chem. student under my supervision. All work presented here is my own.

to the pinacolborane, thereby activating it to transfer a hydride to the ketone. Clark noted, however, that the borohydride species formed *in situ* was largely insoluble in benzene. We envisaged that by replacing sodium butoxide with an insoluble inorganic base, our phase-transfer catalyst could transfer the resulting borohydride into the organic phase and catalyze an enantioselective ketimine reduction.



Scheme 4:14: *Clark's alkoxide catalyzed ketone reduction*[180]

Pleasingly, phosphoketimine **484**, pinacolborane **488**, and cesium hydroxide monohydrate in MTBE in the presence of phase-transfer catalyst **C34** gave imine **(*R*)-486** in 100% yield and 25% ee after 14 hours (scheme 4.15). The reaction was not moisture sensitive, with the addition of 4 Å molecular sieves having no effect on the reaction. However, the reaction proved to be very sensitive to air, with the enantioselectivity dropping to only 2% ee when the reaction was performed in air instead of under a nitrogen atmosphere.



Scheme 4.15: *Initial enantioselective ketimine reduction test*

4.3.3 Proposed mechanism

We propose that the hydroxide acts as a Lewis base and adds to the boron at the phase interface (figure 4.04). The phase-transfer catalyst then transports the borohydride to the organic phase, where a hydride adds to the phophoketimine, and the resultant amide anion is protonated by the boric acid. The newly formed boronate ion pairs with the cationic catalyst, which acts as the phase-transfer catalyst for subsequent reaction cycles.

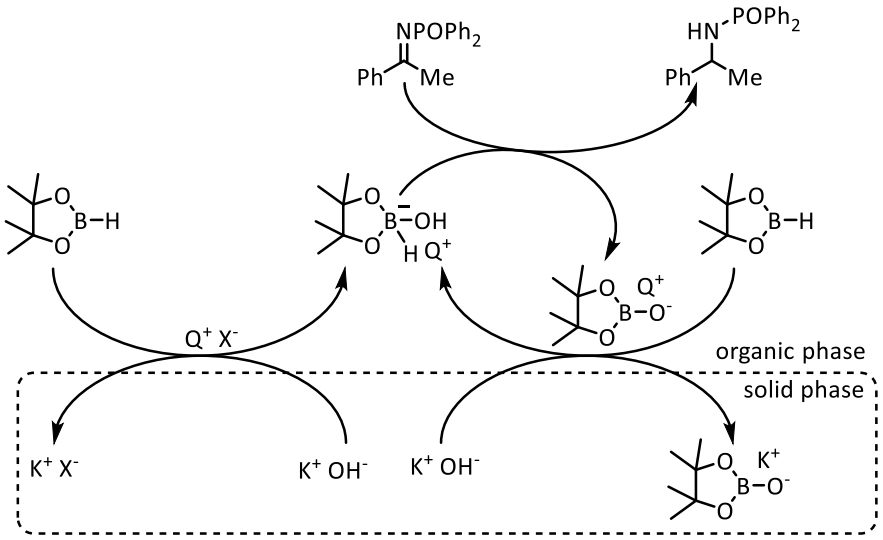
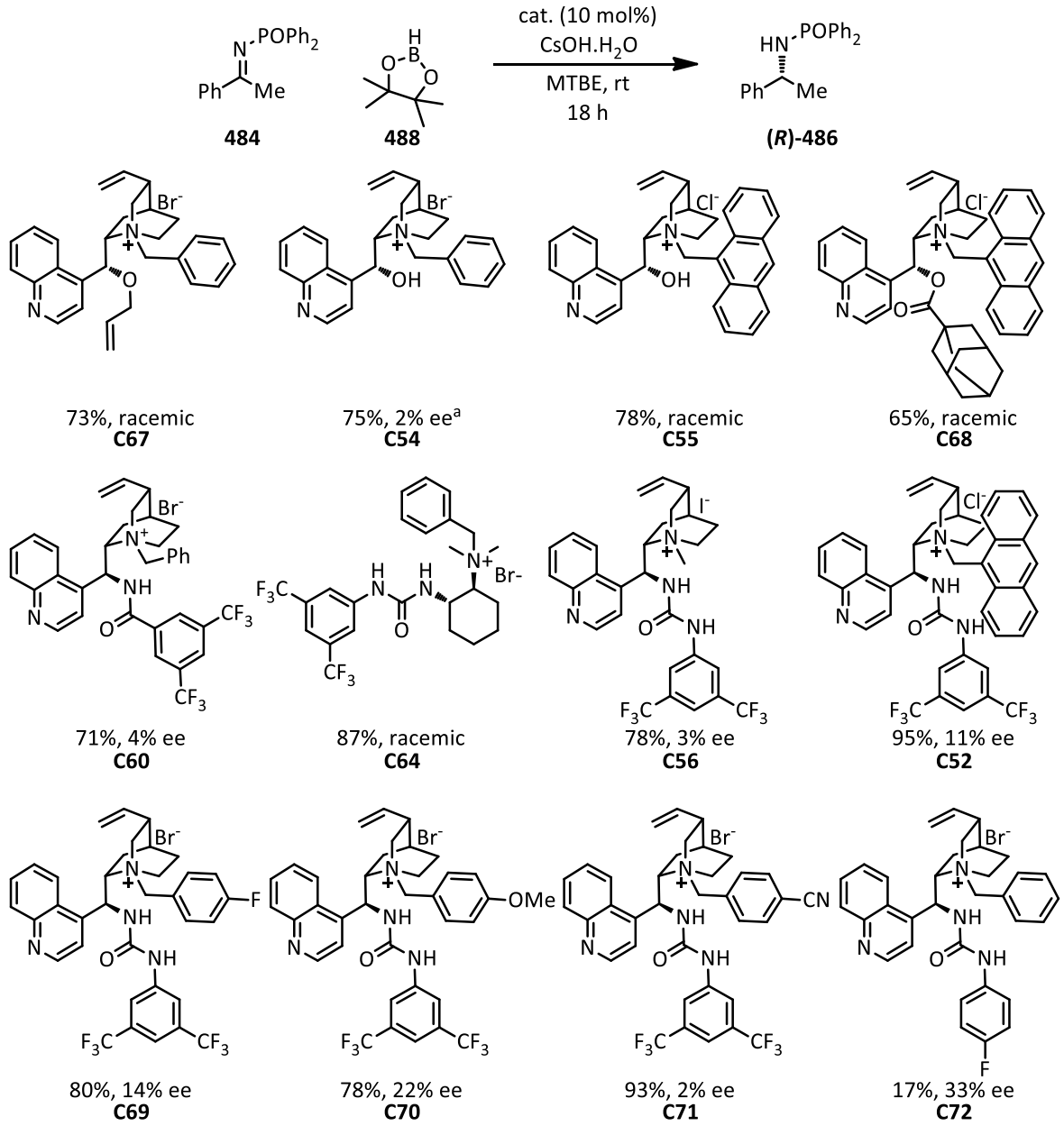


Figure 4.04: *Proposed ketimine reduction mechanism*

4.3.4 Preliminary optimization

With reactivity established, we screened a number of different catalysts (scheme 4.16). First, we tried commercially available cinchonidine-derived phase-transfer catalysts **C67**, **C54**, and **C55**, all of which gave amine **486** as a racemic, or almost racemic, mixture. Next, we tried varying the H-bond donor. Neither ester **C68** nor amide **C60** gave **486** with significant enantiocontrol. Changing the chiral scaffold to the Takemoto-like catalyst **C64** also rendered the reduction non-enantioselective.



*Scheme **4.16:** Preliminary catalyst scan; [a]**(S)-486** was obtained*

Maintaining our standard cinchona scaffold attached to a urea H-bond donor, we next tried varying the steric environment of the quaternary nitrogen alkylating group. Both significantly decreasing steric bulk at the quaternary nitrogen by using a methyl group (**C56**) or significantly increasing the steric bulk by using an anthracenylmethyl group (**C52**) led to considerably reduced enantioselectivity. Adding a *para*-fluoro (**C69**) or *para*-cyano (**C71**) substituent to the *N*-benzyl group also resulted in diminished enantioselectivities. However,

the use of an electron donating *para*-methoxybenzyl group (**C70**) had little effect on the enantioselectivity compared to the *N*-benzyl group alone. Finally, adjusting the electronics on the aryl group attached to the urea by replacing the 3,5-bis(trifluoromethyl) groups with a *para*-fluoro group (**C72**) increased the enantioselectivity to 33% ee.

4.3.5 Future directions

While the enantioselectivity of our ketimine reduction is modest, it is promising that our H-bond donor phase-transfer catalysts were able to achieve significant enantioselectivities in contrast with commercially available phase-transfer catalysts, which provided no enantiocontrol whatsoever. We hope that through continued adjustment of our catalyst and through extensive optimization of the base, solvent, substrate, and hydride source, we will be able to achieve high enantioselectivities and thereby report this first example of a phase-transfer catalyzed ketimine reduction in due course.

4.4 Summary

This chapter demonstrated the ability of our H-bond donor phase-transfer catalysts to catalyze the nucleophilic addition of nitroalkanes to *N*-Boc protected imines formed *in situ* from α-amido sulfones with excellent enantio- and diastereoselectivities. Unlike previously reported phase-transfer catalysts used in enantioselective nitro-Mannich reactions, we were able to easily access either enantiomer of the β-nitroamine products without loss of enantioselectivity by simply using the pseudo-enantiomer of our cinchona alkaloid chiral scaffold.

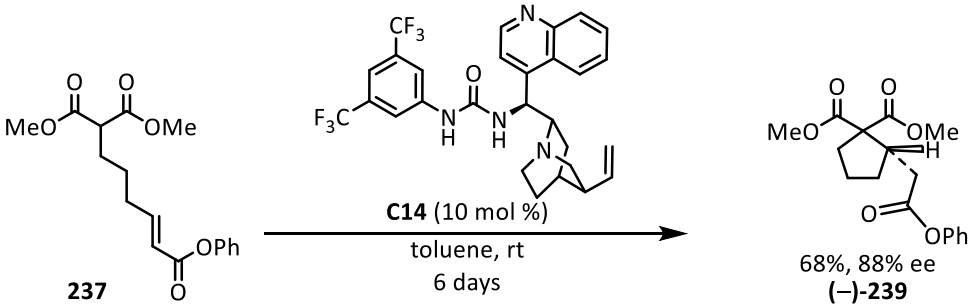
Through the preliminary results of our ketimine reductions, we also demonstrated the ability of our new catalysts to facilitate transformations not previously accessible by phase-transfer catalysts. While this methodology requires further optimization to achieve

useful levels of enantiocontrol, it represents the only known report of an enantioselective phase-transfer ketimine reduction.

Chapter 5: Conclusions

5.1 Conclusions

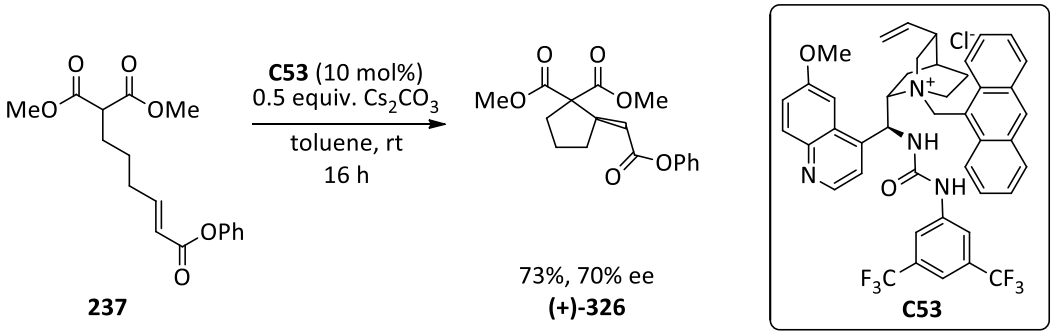
The work presented in this thesis has demonstrated the ability of previously reported bifunctional H-bond donor organocatalysts to continue to provide access to new enantioselective methods. A new intramolecular Michael addition reaction of a *β*-diester onto an *α,β*-unsaturated phenyl ester catalyzed by cinchona-derived **C14** was reported, achieving good enantioselectivities (up to 88% ee, scheme 5.01). This work highlighted the high enantiocontrol attainable using H-bond donor organocatalysts, but also brought to light some of the limitations of this catalyst class. Namely, tertiary amine/H-bond donor bifunctional organocatalysts can suffer from long reaction times and limited reactivity, as observed in the limited substrate scope of this intramolecular Michael reaction.



Scheme 5.01: *Intramolecular Michael reaction catalyzed by a tertiary amine/urea organocatalyst*

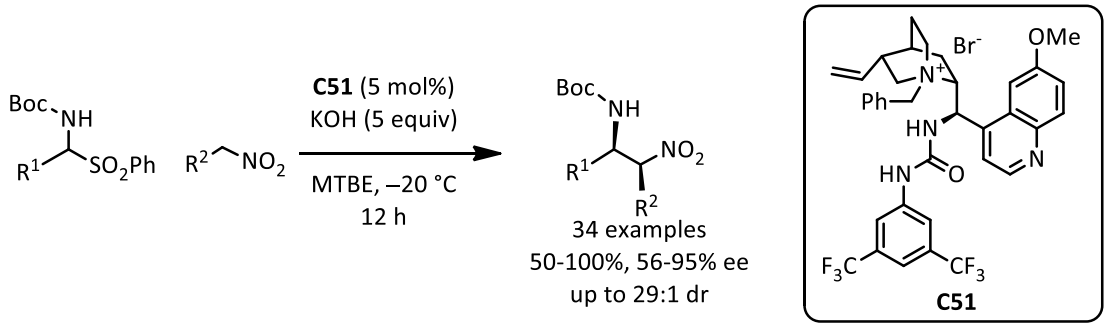
A new H-bond donor phase-transfer catalyst discovered during preliminary investigations into an enantioselective *α*-alkylation reaction offered a solution to this limited reactivity: when paired with an external inorganic base, this new family of H-bond donor/ammonium salt phase-transfer catalysts promoted the intramolecular Michael reaction of substrates that were unreactive with tertiary amine/H-bond donor

organocatalysts. The inclusion of a dual H-bond donor urea on these phase-transfer catalysts proved essential to obtaining good enantioselectivities. These new catalysts were both more reactive than traditional tertiary amine/H-bond donor organocatalysts and more enantioselective than commercially available cinchona-derived phase-transfer catalysts (scheme 5.02).

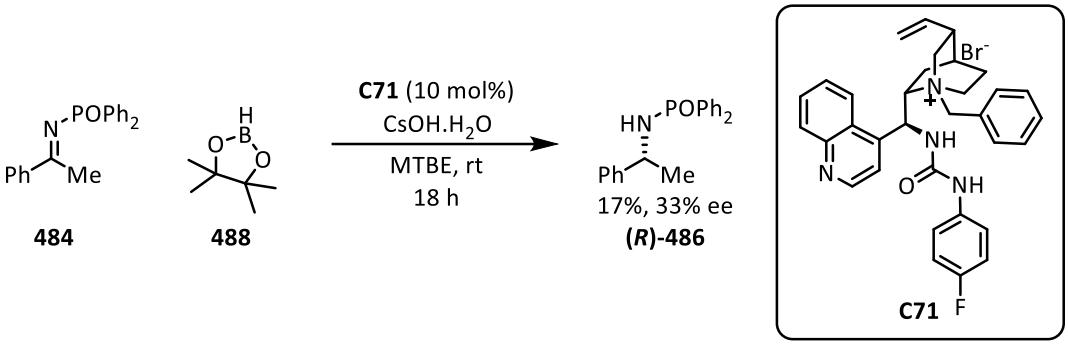


Scheme 5.02: *Intramolecular Michael reaction catalyzed by an H-bond donor/ammonium salt phase-transfer catalyst*

Chapter 4 presented the highly enantio- and distereoselective nitro-Mannich reaction of α-amido sulfones and nitroalkanes catalyzed by these H-bond donor phase-transfer catalysts (scheme 5.03). Preliminary results from a novel ketimine reduction also demonstrated the power of this new catalyst family to catalyze enantioselective reactions that are not possible with commercial phase-transfer catalysts (scheme 5.04). With their high reactivity and enantioselectivity, these phase-transfer catalysts have the potential to find applications well beyond those presented here.



Scheme 5.03: *H-bond donor phase-transfer catalyzed nitro-Mannich reaction*



Scheme 5.04: *Preliminary studies of a phase-transfer catalyzed ketimine reduction*

Chapter 6: Experimental

6.1 General Experimental

6.1.1 General techniques

All reactions were carried out at ambient temperature (20-25 °C) under a nitrogen atmosphere, unless otherwise stated. All glassware was oven-dried and allowed to cool under a nitrogen atmosphere before use. Temperatures of 0 °C and –78 °C were obtained using an ice/water bath and a dry ice/acetone bath, respectively. Reflux conditions were achieved using an oil bath or DrySyn© heating block equipped with a contact thermometer. For heated reactions, the quoted temperature refers to the temperature of the oil bath.

6.1.2 Compound naming

All compounds were named systematically according to standard IUPAC convention, as generated by ACD/I-Lab.

6.1.3 Solvents and Reagents

All reaction solvents are anhydrous, unless otherwise specified. Anhydrous methanol, acetonitrile, tetrahydrofuran, dichloromethane, toluene and benzene were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58Å, basic, Sigma-Aldrich) columns. Anhydrous MTBE and DMF were used directly as received from Sigma-Aldrich. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide pellets. Petroleum ether (PE) refers to the fractions boiling in the range 30-40 °C. Bulk solutions were concentrated *in vacuo* using a Büchi Rotovapor R-114 or R-124 rotary evaporator (water bath temperature = 40 °C). Brine refers to a saturated aqueous solution of sodium chloride. Na_2SO_4 and $MgSO_4$ refer to anhydrous sodium sulphate and

anhydrous magnesium sulphate, respectively. All commercial reagents and work-up solvents were used as supplied without further purification unless otherwise stated.

6.1.4 Chromatography

Flash column chromatography was carried out using Merck Geduran Si 60 silica gel (40-63 μm) in the solvent system stated. Analytical and preparative thin layer chromatography (TLC) were performed using Merck DC Kieselgel 60 F_{254} (230-400 mesh) aluminium-backed plates pre-coated with fluorescent-treated silica. TLC visualization was carried out under ultraviolet light (254 nm), followed by staining with aqueous $KMnO_4$ or ethanolic vanillin solutions. High performance liquid chromatography (HPLC) was performed on an Agilent Technologies 1200 series machine fitted with the specified commercially available column with a chiral, non-racemic stationary phase and using the stated solvent system. Retention times are quoted in minutes from the time of sample injection.

6.1.5 Melting points

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

6.1.6 Polarimetry

Optical rotations were recorded using a Perkin Elmer 341 Optical Activity polarimeter. Specific rotations ($[\alpha]_D^T$) are reported in 10^{-1} deg·cm^{-2}·g^{-1}. Concentrations (*c*) are quoted in g/100 mL of solution. D refers to the D-line of sodium (589 nm). Temperatures (T) are given in degrees Celsius (°C).

6.1.7 Infra-red spectroscopy

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer fitted with an Attenuated Total Reflectance (ATR) sampling accessory as neat films or compressed

solids. Only selected (dominant and/or diagnostic) absorbances (ν_{max}) are reported [in wavenumbers (cm^{-1})]. The relative strength of the absorbances are indicated using s (strong), m (medium) and w (weak).

6.1.8 NMR spectroscopy

All ^{1}H, ^{13}C, COSY, DEPT, HSQC, HMQC and HMBC NMR spectra were recorded on either a Bruker DPX400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker AVII400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker AVIII400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker DRX500 (500 MHz ^{1}H, 125 MHz ^{13}C), Bruker AVII500 with cryoprobe (500 MHz ^{1}H, 125 MHz ^{13}C), or a Bruker DRX300 (300 MHz ^{1}H, 75 MHz ^{13}C) at 300 K (unless otherwise stated) in the deuterated solvent specified. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm ± 0.01 ppm) downfield of trimethylsilane, relative to the residual protiosolvent against an internal deuterium lock. Coupling constants (*J*) are given in Hertz (Hz ± 0.1 Hz). ^{1}H NMR spectra are reported as follows: δ / ppm (multiplicity, coupling constant (if applicable), number of protons, assignment). The abbreviations s, d, t, q, and m (and any combination thereof) denote singlet, doublet, triplet, quartet and multiplet, respectively. "App" before a multiplicity is used to denote an observed coupling pattern when this is clearly not the expected coupling pattern. Assignments were determined either on the basis of unambiguous chemical shifts or coupling patterns and using COSY, DEPT, HSQC, HMQC and HMBC experiments. Where an assignment could not be made unambiguously, none is given. Carbon numbering for the purposes of NMR assignment is arbitrary and does not follow IUPAC convention. Where possible, atom numbers are consistent across related compounds.

6.1.9 Mass spectrometry

Low resolution mass spectra (LRMS, *m/z*) were acquired by electrospray ionization (ESI) on a Waters LCT premier spectrometer. High resolution mass spectra (HRMS) were acquired by ESI using a Bruker μTOF spectrometer.

6.1.10 Literature references

Known compounds are indicated by a reference to a previous literature report following their IUPAC name. If a literature procedure was followed, this is stated explicitly in the text.

6.2 Chapter 2 Experimental

6.2.1 General procedure 2A

General procedure for Table 2.03: H-bond donor catalyst (0.1 eq) was added to a solution of cyclization precursor (1.0 eq) in the reaction solvent (0.15 M). The mixture was stirred at ambient temperature for 48 h. The solvent was removed under a stream of nitrogen, and the crude reaction mixture was analyzed by NMR. An aliquot of the crude mixture was purified on silica for analysis by HPLC using a chiral, non-racemic stationary phase.

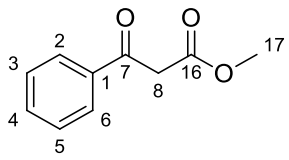
6.2.2 General procedure 2B

General procedure for the Michael addition of *β*-diesters onto *α,β*-unsaturated esters: H-bond donor catalyst (0.1 eq) was added to a solution of cyclization precursor (1.0 eq) in the reaction solvent (0.13 M). The mixture was stirred at ambient temperature until complete by TLC. Water and EtOAc were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and then purified by flash column chromatography.

6.2.3 General procedure 2C

General procedure for enantioselective *α*-alkylations: Benzyl bromide (1.0 eq) was added to a suspension of M_2CO_3 (1.0 eq), *β*-ketoester (1.0 eq), and **243** or **244** (0.1 eq) in the reaction solvent (0.15 M). The resulting mixture was stirred at ambient temperature for 5-24 h, then the solvent was removed under a stream of nitrogen. Mesitylene (1.0 eq) was added to the dried crude reaction mixture as an internal standard, then the mixture was diluted with H_2O, and extracted with Et_2O (3 x). The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* (at ambient temperature), and the conversions were calculated by ^1H NMR integration against the internal standard. Background reactions were set up in parallel without the catalyst. An aliquot of the crude mixture was purified on silica (by preparative TLC) for HPLC analysis. The ee was determined by HPLC analysis: **(*S*)-245** [Chiralpak AD, hexane/*iso*-propanol 90:10, λ 220 nm, 0.5 mL/min] t (minor) = 7.1 min., t (major) = 8.1 min.; **(*S*)-246** [Chiralpak AD-H, hexane/*iso*-propanol 99:1, λ 220 nm, 0.5 mL/min] t (minor) = 29.8 min., t (major) = 32.4 min.. The absolute stereochemical configuration of **(*S*)-245** was assigned according to its described order of elution in HPLC using a non-racemic chiral column,[181] and the absolute stereochemical configuration of **(*S*)-246** was assigned by analogy.

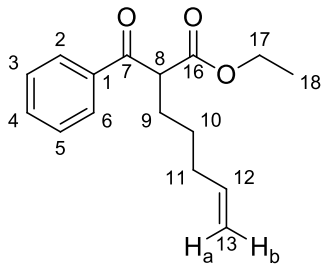
6.2.4 Preparation of 223b



Methyl 3-oxo-3-phenylpropanoate:[182] Acetophenone (2.00 mL, 17.1 mmol, 1.00 eq) was added dropwise to a stirring solution of hexanes-washed (1 × 10 mL) NaH (60% suspension in mineral oil, 1.37 g, 34.3 mmol, 2.00 eq) in 19 mL THF. After 30 min, dimethylcarbonate (8.20 mL, 97.3 mmol, 5.70 eq) was added dropwise and the resulting solution was heated to

reflux. After 6 h, the reaction mixture was allowed to cool to ambient temperature, acidified with 38 mL 3 M acetic acid, and extracted with Et_2O (3 × 30 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (1 × 30 mL) and brine (1 × 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the title compound as a 4.5:1 keto:enol mixture and as an amber oil (3.05 g, 17.1 mmol, 100%). δ_H (400 MHz, $CDCl_3$) *keto form:* 7.92-7.99 (m, 2 H, C(6)*H* and C(2)*H*), 7.61 (tt, *J* = 7.3, 1.3 Hz, 1 H, C(4)*H*), 7.47-7.53 (m, 2 H, C(5)*H* and C(3)*H*), 4.02 (s, 2 H, C(8)H_2), 3.77 (s, 3H, C(17)H_3); *enol form*: 12.51 (s, 1 H, O*H*) , 7.76-7.82 (m, 2 H, C(6)*H* and C(2)*H*) , 7.40-7.47 (m, 3 H, C(5)*H*, C(3)*H* and C(4)*H*), 5.69 (s, 1 H, C(8)*H*), 3.82 (s, 3 H, C(17)H_3) ppm; δ_C (100 MHz, $CDCl_3$) *keto form:* 192.3 (*C*(7)), 167.9 (*C*(16)), 135.9 (*C*(1)), 133.8 (*C*(4)), 128.8 (*C*(3) and *C*(5)), 128.5 (*C*(2) and *C*(6)), 52.5 (*C*(17)H_3), 45.7 (*C*(8)); *enol form (visible peaks)*: 131.3 (*C*(4)), 128.5 (*C*(3) and *C*(5)), 126.1 (*C*(2) and *C*(6)), 87.0 (*C*(8)), 51.4 (*C*(17)H_3) ppm; ν_{max} 3062 (w, Ar-H), 2923 (w, Alk-H), 1741 (m, ester C=O), 1685 (m, ketone C=O), 1450 (m, Ph ring stretch), 1269 (m, C–O–C stretch), 809 (m), 688 (m) cm^{-1}.

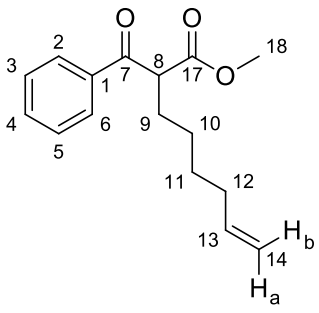
6.2.5 Preparation of 224



Ethyl 2-benzoylhept-6-enoate:[183] Ethyl benzoylacetate (5.76 g, 27.0 mmol, 1.00 eq) was added to a suspension of NaH (1.24 g, 31.0 mmol, 1.15 eq) in 25 mL anhydrous THF at 0 °C. The resulting mixture was allowed to warm to ambient temperature, then 5-bromo-1-pentene (3.40 mL, 28.3 mmol, 1.05 eq) and 25 mL DMF were added sequentially. The solution was stirred at ambient temperature for 12 h, then heated to reflux for 6 h. A second

portion of 5-bromo-1-pentene (0.65 mL, 5.4 mmol, 0.2 eq) was added and the reaction mixture was maintained at reflux. After 12 h, the solution was allowed to cool to ambient temperature, then quenched with 30 mL 1 M HCl and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with H_2O (2 x 20 mL) and brine (1 x 20 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (20:1 PE/EtOAc) to afford **224** as a clear, colourless oil (6.40 g, 91%). δ_H (400 MHz, $CDCl_3$) 7.92-8.04 (m, 2 H, C(2)*H* and C(6)*H*), 7.54-7.64 (m, 1 H, C(4)*H*), 7.49 (t, *J* = 7.8 Hz, 2 H, C(3)*H* and C(5)*H*), 5.79 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1 H, C(12)*H*), 5.02 (dq, *J* = 17.2, 1.5 Hz, 1 H, C(13)H_a), 4.95-4.99 (m, 1 H, C(13)H_b), 4.30 (t, *J* = 7.1 Hz, 1 H, C(8)*H*), 4.15 (q, *J* = 7.2 Hz, 2 H, C(17)H_2), 2.11 (td, *J* = 7.3, 6.7 Hz, 2 H, C(11)H_2), 1.94-2.07 (m, 2 H, C(9)H_2), 1.39-1.54 (m, 2 H, C(10)H_2), 1.18 (t, *J* = 7.2 Hz, 3 H, C(18)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 195.1 (*C*(7)), 170.0 (*C*(16)), 138.0 (*C*(12)), 136.3 (C(1)), 133.4 (C(4)), 128.7 (C(3) and *C*(5)), 128.5 (C(2) and *C*(6)), 115.0 (*C*(13)), 61.3 (*C*(17)), 54.2 (*C*(8)), 33.5 (*C*(11)), 28.4 (*C*(9)), 26.8 (*C*(10)), 14.0 (*C*(18)) ppm; ν_{max} 2934 (w), 1735 (s, C=O ester), 1686 (s, C=O ketone), 1640 (w, C=C), 1448 (Ph ring stretch), 1221 (m, C–O–C antisymmetric stretch), 773 (m), 690 (m) cm^{-1}.

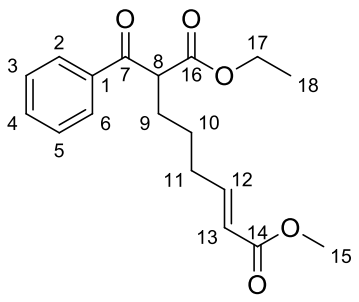
6.2.6 Preparation of 225



Methyl 2-benzoyloct-7-enoate: A solution of methyl benzoylacetate (0.50 g, 2.8 mmol, 1.0 eq) in 1 mL THF was added to a suspension of NaH (60% dispersion in mineral oil, 0.16 g, 3.4 mmol, 1.2 eq) in 2 mL THF at 0 °C. The mixture was allowed to warm to ambient

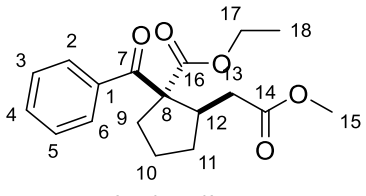
temperature, then 6-bromo-1-hexene (0.43 mL, 3.2 mmol, 1.15 eq) and 3 mL DMF were added sequentially and the reaction mixture was heated to reflux. After 16 h, the solution was allowed to cool to ambient temperature, then acidified with 5 mL 1 M HCl. The reaction mixture was extracted with Et_2O (3 × 10 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20:1 PE/EtOAc) to yield the title compound as a clear, colourless oil (0.61 g, 2.5 mmol, 88%). δ_H (400 MHz, $CDCl_3$) 7.91-8.07 (m, 2 H, C(2)*H* and C(6)*H*), 7.60 (tt, *J* = 7.3, 1.3 Hz, 1 H, C(4)*H*), 7.41-7.54 (m, 2 H, C(3)*H* and C(5)*H*), 5.78 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1 H, C(13)*H*), 4.99 (ddt, *J* = 17.1, 2.0, 1.8 Hz, 1 H, C(14)H_b), 4.94 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1 H, C(14)H_a), 4.32 (t, *J* = 7.2 Hz, 1 H, C(8)*H*), 3.69 (s, 3 H, C(18)H_3), 1.93-2.18 (m, 4 H, C(9)H_2 and C(12)H_2), 1.27-1.52 (m, 4 H, C(10)H_2 and C(11)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 195.1 (*C*(7)), 170.5 (*C*(17)), 138.5 (*C*(13)), 136.2 (C(1)), 133.5 (C(4)), 128.8 (C(3) and *C*(5)), 128.6 (C(2) and *C*(6)), 114.6 (*C*(14)), 54.0 (*C*(8)), 52.4 (*C*(18)), 33.4 (*C*(12)), 28.9 (*C*(9)), 28.6 (*C*(11)), 27.1 (*C*(10)) ppm; LRMS *m/z* (ESI^+) 543 (100%, $[2M+Na]^+$), 283 (65%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 283.1309, $C_{16}H_{20}NaO_3^+$ requires 283.1305; ν_{max} 3072 (w), 2928 (m), 2857 (w), 1739 (s, ester C=O), 1684 (m, ketone C=O), 1448 (Ph ring stretch), 1229 (ester C–O–C anti-symmetric stretch), 690 (m) cm^{-1}.

6.2.7 Preparation of 226

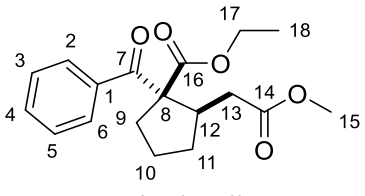


8-ethyl 1-methyl (2*E*)-7-benzoyloct-2-enedioate: Hoveyda-Grubbs II catalyst (60.0 mg, 0.0960 mmol, 2.50 mol%) was added to a solution of ethyl 2-benzoylhept-6-enoate (0.970 mL, 3.84 mmol, 1.00 eq) and methyl acrylate (1.38 mL, 15.36 mmol, 4.00 eq) in 38 mL CH_2Cl_2 and the mixture was heated to reflux. After 18 h, the solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (9:1 to 2:1 PE/Et_2O) to yield the title compound as a green oil (1.00 g, 3.14 mmol, 82%). δ_H (400 MHz, $CDCl_3$) 7.93-8.03 (m, 2 H, C(2)*H* and C(6)*H*), 7.60 (tt, *J* = 7.3, 1.1 Hz, 1 H, C(4)*H*), 7.44-7.55 (m, 2 H, C(3)*H* and C(5)*H*), 6.93 (dt, *J* = 15.7, 7.1 Hz, 1 H, C(12)*H*), 5.83 (dt, *J* = 15.7, 1.5 Hz, 1 H, C(13)*H*), 4.29 (t, *J* = 7.2 Hz, 1 H, C(8)*H*), 4.15 (q, *J* = 7.2 Hz, 2 H, C(17)H_2), 3.72 (s, 3 H, C(15)H_3), 2.26 (q, *J* = 7.1 Hz, 2 H, C(11)H_2), 1.96-2.11 (m, 2 H, C(9)H_2), 1.47-1.61 (m, 2 H, C(10)H_2), 1.17 (t, *J* = 7.2 Hz, 3 H, C(18)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 194.8 (*C*(7)), 169.7 (*C*(16)), 166.9 (*C*(14)), 148.3 (*C*(12)), 136.1 (*C*(1)), 133.5 (*C*(4)), 128.7 (*C*(3) and *C*(5)), 128.5 (*C*(2) and *C*(6)), 121.4 (*C*(13)), 61.4 (*C*(17)), 54.0 (*C*(8)), 51.4 (*C*(15)), 31.9 (*C*(11)), 28.3 (*C*(9)), 26.0 (*C*(10)), 13.9 (*C*(18)) ppm; LRMS *m/z* (ESI^+) 341 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 341.1356, $C_{18}H_{22}NaO_5^+$ requires 341.1359; ν_{max} 2951 (w), 1721 (s, ketone C=O), 1685 (s, ester C=O), 1657 (m, ester C=O), 1448 (m, Ph ring stretch), 1270 (s, C–O–C anti-symmetric stretch), 1179 (s, C–O–C anti-symmetric stretch), 691 (m) cm^{-1}.

6.2.8 Preparation of (±)-227



(1*S,2*R**)**



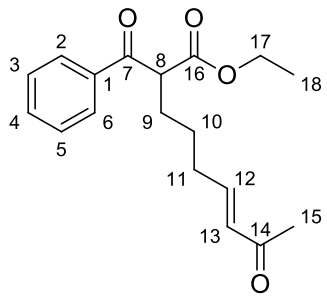
(1*R,2*R**)**

Ethyl (1*S,2*R**)-1-benzoyl-2-(2-methoxy-2-oxoethyl)cyclopentanecarboxylate and ethyl (1*R**,2*R**)-1-benzoyl-2-(2-methoxy-2-oxoethyl)cyclopentanecarboxylate:**

Pyrrolidine (10.3 μL, 0.125 mmol, 1.01 eq) was added to a solution of 8-ethyl 1-methyl (2*E*)-7-benzoyloct-2-enedioate (39.5 mg, 0.124 mmol, 1.00 eq) in 0.85 mL benzene (0.15 M) and the resulting mixture was heated to reflux. After 12 h, the solution was allowed to cool to ambient temperature, quenched with 1 mL 1 M HCl, and extracted with EtOAc (3 × 5 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (9:1 PE/EtOAc) to give a mixture of diastereomers (3.0:1.0, (1*S**,2*R**):(1*R**,2*R**)) of the title compound as a clear, colourless film (15 mg, 0.047 mmol, 57% based on 13.3 mg recovered starting material). δ_H (400 MHz, $CDCl_3$) *(1S*,2R*)*: 7.79-7.30 (m, 2 H, C(2)*H* and C(6)*H*), 7.50-7.55 (m, 1 H, C(4)*H*), 7.39-7.45 (m, 2 H, C(3)*H* and C(5)*H*), 4.01-4.11 (m, 2 H, C(17)H_2), 3.71 (s, 3 H, C(15)H_3), 3.28-3.37 (m, 1 H, C(12)*H*), 2.76-2.85 (m, 1 H, C(11)*H'*H"), 2.73 (dd, *J* = 15.4, 3.5 Hz, 1 H, C(13)*H'*H"), 1.90-2.11 (m, 3 H, C(9)*H'*H", C(10)*H'*H" and C(13)H'*H"*), 1.60-1.80 (m, 2 H, C(9)H'*H"* and C(10)H'*H"*), 1.41-1.52 (m, 1 H, C(11)H'*H"*), 1.00 (t, *J* = 7.1 Hz, 3 H, C(18)H_3) ppm; *(1R*,2R*)*: 7.83-7.87 (m, 2 H, C(2)*H* and C(6)*H*), 7.50-7.55 (m, 1 H, C(4)*H*), 7.39-7.45 (m, 2 H, C(3)*H* and C(5)*H*), 4.03-4.16 (m, 2 H, C(17)H_2), 3.62 (s, 3 H, C(15)H_3), 3.13-3.21 (m, 1 H, C(12)*H*), 2.43-2.56 (m, 2 H, C(13)H_2), 2.32-2.41 (m, 1 H, C(9)*H'*H"), 2.20-2.28 (m, 1 H, C(11)*H'*H"), 1.92-2.11 (m, 3 H, C(9)H'*H"* and C(10)H_2), 1.64-1.80 (m, 1 H, C(11)H'*H"*), 0.94 (t, *J* = 7.1 Hz, 3 H, C(18)H_3) ppm; δ_C (100 MHz, $CDCl_3$) *reported as visible peaks for the mixture of diastereomers*: 195.7 (O=*C*(7) x 2), 173.3 (O=*C*), 172.9 (O=*C*), 172.3 (O=*C*), 172.1 (O=*C*), 133.0 (*C*(Ar)), 132.8 (*C*(Ar)), 132.7 (*C*(Ar)), 128.7 (*C*(Ar)), 128.6 (*C*(Ar)), 128.4 (*C*(Ar)), 128.1 (*C*(Ar)), 65.7, 61.3 (*C*(17)), 51.6, 42.2 (*C*(12)), 36.2, 35.7, 34.8 (*C*(13)), 34.6, 34.1, 32.0, 30.6, 23.5, 22.3, 17.7, 14.1, 13.7 (*C*(18)) ppm; LRMS *m/z* (ESI^+) 659 (100%, $[2M+Na]^+$), 341 (85%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found

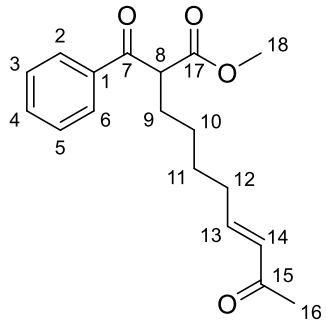
$[M+Na]^+$ 341.1353, $C_{18}H_{22}NaO_5^+$ requires 341.1359; ν_{max} 2954 (w), 1743 (s, C=O), 1682 (s, C=O), 1448 (m, phenyl ring stretch), 1259 (m) cm^{-1}.

6.2.9 Preparation of 228



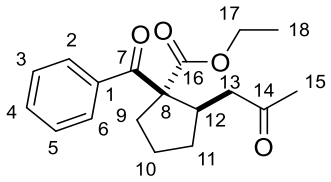
Ethyl (6*E*)-2-benzoyl-8-oxonon-6-enoate: Hoveyda-Grubbs II catalyst (30.0 mg, 0.0480 mmol, 2.50 mol%) was added to a solution of ethyl 2-benzoylhept-6-enoate (0.490 mL, 1.92 mmol, 1.00 eq) and methyl vinyl ketone (90% purity, 0.700 mL, 7.69 mmol, 4.00 eq) in 19 mL CH_2Cl_2. The resulting mixture was heated to reflux. After 8 h, the solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (4:1 toluene/Et_2O) to yield the title compound as a green oil (0.29 g, 49%). δ_H (400 MHz, $CDCl_3$) 7.93-8.03 (m, 2 H, C(2)*H* and C(6)*H*), 7.56-7.64 (m, 1 H, C(4)*H*), 7.45-7.55 (m, 2 H, C(3)*H* and C(5)*H*), 6.77 (dt, *J* = 15.9, 6.8 Hz, 1 H, C(12)*H*), 6.08 (dt, *J* = 15.9, 1.4 Hz, 1 H, C(13)*H*), 4.30 (t, *J* = 7.1 Hz, 1 H, C(8)*H*), 4.15 (q, *J* = 7.0 Hz, 2 H, C(17)H_2), 2.28 (td, *J* = 7.4, 6.8 Hz, 2 H, C(11)H_2), 2.24 (s, 3 H, C(15)H_3), 1.97-2.10 (m, 2 H, C(9)H_2), 1.50-1.60 (m, 2 H, C(10)H_2), 1.17 (t, *J* = 7.0 Hz, 3 H, C(18)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 198.5 (*C*(14)), 194.8 (*C*(7)), 169.7 (*C*(16)), 147.1 (*C*(12)), 136.1 (*C*(1)), 133.6 (*C*(4)), 131.7 (*C*(13)), 128.8 (*C*(3) and *C*(5)), 128.5 (*C*(2) and *C*(6)), 61.5 (*C*(17)), 54.0 (*C*(8)), 32.2 (*C*(11)), 28.4 (*C*(9)), 26.9 (*C*(15)), 26.0 (*C*(10)), 14.0 (*C*(18)) ppm; LRMS *m/z* (ESI^+) 325 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 325.1408, $C_{18}H_{22}NaO_4$ requires 325.1410; ν_{max} (film)/cm^{-1} 3062 (w), 2936 (w), 1732 (m, ester C=O), 1675 (s, C=O), 1626 (m, C=O), 1448 (m, Ph ring stretch), 1254 (m), 979 (m), 691 (m) cm^{-1}.

6.2.10 Preparation of 229

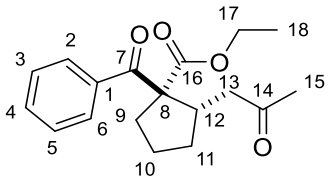


Methyl (7*E*)-2-benzoyl-9-oxodec-7-enoate: Methyl vinyl ketone (0.28 mL, 3.1 mmol, 3.0 eq) and Hoveyda-Grubbs II (16 mg, 0.026 mmol, 0.025 eq) were added sequentially to a solution of methyl 2-benzoyloct-7-enoate (270 mg, 1.0 mmol, 1.0 eq) in 10 mL CH_2Cl_2 (0.1 M). The reaction mixture was heated to reflux. After 16 h, the solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography (9:1 toluene/EtOAc) to give a pale brown oil (276 mg, 88 %). δ_H (500 MHz, $CDCl_3$) 7.99 (d, *J* = 8.3 Hz, 2 H, C(2)*H* and C(6)*H*), 7.61 (s, 1 H, C(4)*H*), 7.46-7.55 (m, 2 H, C(3)*H* and C(5)*H*), 6.77 (dt, *J* = 15.9, 6.9 Hz, 1 H, C(13)*H*), 6.06 (d, *J* = 15.9 Hz, 1 H, C(14)*H*), 4.32 (t, *J* = 7.1 Hz, 1 H, C(8)*H*), 3.69 (s, 3 H, C(18)H_3), 2.14-2.32 (m, 5 H, C(12)H_2 and C(16)H_3), 1.93-2.11 (m, 2 H, C(9)H_2), 1.49-1.56 (m, 2 H, C(11)H_2), 1.39 (tt, *J* = 8.3, 7.6 Hz, 2 H, C(10)H_2) ppm; δ_C (125 MHz, $CDCl_3$) 198.6 (*C*(15)), 194.9 (*C*(7)), 170.3 (*C*(17)), 147.7 (*C*(13)), 136.0 (*C*(1)), 133.6 (*C*(4)), 131.4 (*C*(14)), 128.8 (*C*(3) and *C*(5)), 128.5 (*C*(2) and *C*(6)), 53.8 (*C*(8)), 52.5 (*C*(18)), 32.0 (*C*(12)), 28.7 (*C*(9)), 27.8 (*C*(11)), 27.1 (*C*(10)), 26.8 (*C*(16)) ppm; LRMS *m/z* (ESI^+) 325 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 325.1424, $C_{18}H_{22}NaO_4^+$ requires 325.1410; ν_{max} (film)/cm^{-1} 2949 (w), 1739 (s, ester C=O), 1674 (s, C=O), 1626 (w), 1448 (m, Ph ring stretch), 1216 (m), 980 (w), 691 (w) cm^{-1}.

6.2.11 Preparation of (±)-230a and (±)-230b



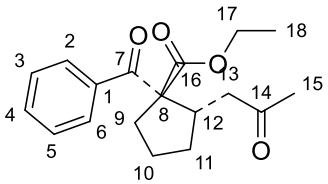
(1*S,2*R**)**
(±)-230a



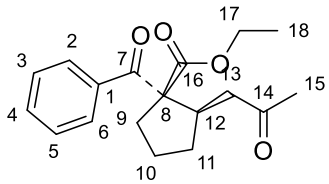
(1*S,2*S**)**
(±)-230b

Ethyl (1*S,2*S**)-1-benzoyl-2-(2-oxopropyl)cyclopentanecarboxylate and ethyl (1*S**,2*S**)-1-benzoyl-2-(2-oxopropyl)cyclopentanecarboxylate:** DABCO (2.1 mg, 0.020 mmol, 0.20 eq) was added to a solution of **228** (30.0 mg, 0.100 mmol, 1.0 eq) in 6.6 mL toluene and the resulting mixture was stirred at ambient temperature for 2.5 days, then heated to 75 °C. After 10 h, the solution was allowed to cool to ambient temperature, acidified with 1 mL 1 M HCl, and extracted with Et_2O (3 × 5 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue (20% conversion to product by NMR spectroscopic analysis of crude reaction mixture) was purified by flash column chromatography (3:1 PE/EtOAc) to give the title compound as a clear, colourless film (4.8 mg, 0.016 mmol, 16%) and as a mixture of diastereomers (2:1 **230a**:**230b**). Spectroscopic data are identical to those reported for the enantioenriched sample, below **230a** and **230b**.

6.2.12 Preparation of 230a and 230b



230a

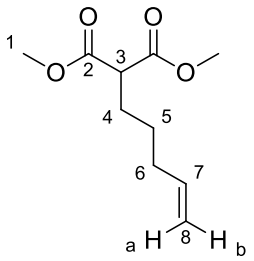


230b

Enantioenriched ethyl 1-benzoyl-2-(2-oxopropyl)cyclopentanecarboxylate: C12 (6.8 mg, 0.013 mmol, 0.10 eq) was added to a solution of **228** (37.7 mg, 0.125 mmol) in 0.83 mL toluene. After 48 h, the mixture was concentrated under a stream of nitrogen. The title compound was isolated by flash column chromatography (6:1 PE/EtOAc) as a clear, colourless oil (25 mg, 65%) and as a mixture of diastereomers [47:53, (**230a**):(**230b**)]. The ee was determined by HPLC analysis [Chiralpak OJ, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min] ***major (230b)***: t (major) = 18.1 min., t (minor) = 40.1 min. (31% ee), ***minor (230a)***: t (minor) = 12.8 min., t (major) = 22.0 min. (−16% ee). $[\alpha]_D^{20}$ = +10.4 (*c* 0.10, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) ***(230b)***: 7.80-7.87 (m, 2 H, C(2)*H* and C(6)*H*), 7.49-7.57 (m, 1 H, C(4)*H*), 7.38-7.47 (m, 2 H, C(3)*H* and C(5)*H*), 4.02 (q, *J* = 7.2 Hz, 2 H, C(17)H_2), 3.08-3.19 (m, 1 H, C(12)*H*), 2.73 (dd, *J* = 17.8, 10.2 Hz, 1 H, C(13)*H'*H"), 2.58 (dd, *J* = 17.8, 3.5 Hz, 1 H, C(13)*H'*H"), 2.40-2.48 (m, 2 H, C(9)H_2), 2.16-2.27 (m, 1 H, C(11)*H'*H"), 2.07 (s, 3 H, C(15)H_3), 1.67-1.78 (m, 2 H, C(10)H_2), 1.50-1.58 (m, 1 H, C(11)H'*H"*), 0.94 (t, *J* = 7.2 Hz, 3 H, C(18)H_3) ppm; ***(230a)***: 7.76-7.89 (m, 2 H, C(2)*H* and C(6)*H*), 7.48-7.58 (m, 1 H, C(4)*H*), 7.42 (t, *J* = 7.7 Hz, 2 H, C(3)*H* and C(5)*H*), 4.05-4.18 (m, 2 H, C(17)H_2), 3.30 (tdd, *J* = 11.1, 6.5, 3.2 Hz, 1 H, C(12)*H*), 2.80-2.87 (m, 1 H, C(13)*H'*H"), 2.69-2.79 (m, 1 H, C(9)*H'*H"), 2.20 (s, 3 H, C(15)H_3), 2.09-2.15 (m, 1 H, C(13)H'*H"*), 1.99-2.05 (m, 1 H, C(11)*H'*H"), 1.87-1.99 (m, 2 H, C(9)H'*H"* and C(10)*H'*H"), 1.60-1.70 (m, 1 H, C(10)H'*H"*), 1.30-1.44 (m, 1 H, C(11)H'*H"*), 1.03 (t, *J* = 7.2 Hz, 3 H, C(18)H_3) ppm; δ_C (100 MHz, $CDCl_3$) ***(230b)***: 207.5 (*C*(14)), 196.7 (*C*(7)), 173.7 (*C*(16)), 136.3 (*C*(1)), 132.8

(*C*(4)), 128.6 (*C*(5) and *C*(3)), 128.1 (*C*(2) and *C*(6)), 66.4 (*C*(8)), 61.3 (*C*(17)), 44.9 (*C*(13)), 42.3 (*C*(12)), 34.7 (*C*(9)), 32.2 (*C*(11)), 30.4 (*C*(15)), 22.5 (*C*(10)), 13.6 (*C*(18)) ppm; ***(230a)***: 207.6 (*C*(14)), 196.0 (*C*(7)), 173.0 (*C*(16)), 135.5 (*C*(1)), 132.7 (*C*(4)), 128.7 (*C*(5) and *C*(3)), 128.4 (*C*(2) and *C*(6)), 65.7 (*C*(8)), 61.2 (*C*(17)), 45.8 (*C*(13)), 41.5 (*C*(12)), 34.7 (*C*(9)), 30.5 (*C*(11)), 29.9 (*C*(15)), 23.6 (*C*(10)), 13.8 (*C*(18)); LRMS *m/z* (ESI^+) 325 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na^-]^+$ 325.1408, $C_{18}H_{22}O_4Na^+$ requires 325.1408; ν_{max} 2936 (w), 1733 (s, ester C=O), 1675 (s, C=O), 1626 (m), 1448 (Ph ring stretch), 1254 (s, C–O–C anti-symmetric stretch), 978 (m), 691 (m) cm^{-1}.

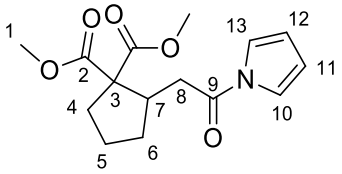
6.2.13 Preparation of 231



Dimethyl pent-4-en-1-ylpropanedioate: Dimethylmalonate (3.09 mL, 27.0 mmol, 1.00 eq) was added to a suspension of NaH (60%, 1240 mg, 31.1 mmol, 1.15 eq) in 25 mL anhydrous THF at 0 °C. The resulting mixture was allowed to warm to ambient temperature, then 5-bromo-1-pentene (3.62 mL, 30.6 mmol, 1.13 eq) and 25 mL anhydrous DMF were added sequentially. The solution was heated to reflux for 12 h, then allowed to cool to ambient temperature. 1 M HCl (30 mL) and Et_2O (30 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with H_2O (2 x 30 mL) and brine (1 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (25:1 PE/EtOAc) to give **231** as a clear, colourless oil (2.90 g, 54%). δ_H (300 MHz, $CDCl_3$) 5.58-5.73 (m, 1 H, C(7)*H*), 4.80-4.96 (m, 2 H, C(8)H_2), 3.18-3.33 (m, 6 H, C(1)H_3 x 2), 3.18-3.33 (m, 1 H, C(3)*H*), 1.89-2.06 (m, 2 H, C(6)H_2), 1.64-1.89 (m, 2 H, C(4)H_2), 1.23-

1.38 (m, 2 H, C(5)H_2) ppm; δ_C (75 MHz, $CDCl_3$) 169.6 (*C*(2) x 2), 137.7 (*C*(7)), 114.9 (*C*(8)), 52.2 (*C*(1) x 2), 51.3 (*C*(3)), 33.1 (*C*(6)), 28.1 (*C*(4)), 26.4 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 423 (100%, $[2M+Na]^+$, 10% $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 201.11195, $C_{10}H_{17}O_4^+$ requires 201.11214; ν_{max} 2954 (w), 1733 (s, ester C=O), 1641 (w, C=C), 1435 (m), 1152 (m), 913 (m) cm^{-1}.

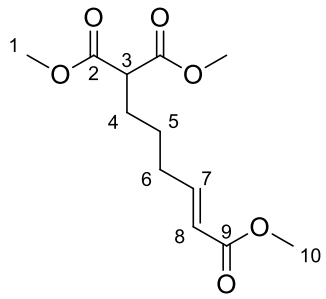
6.2.14 Preparation of 235



Dimethyl 2-[2-oxo-2-(1*H*-pyrrol-1-yl)ethyl]cyclopentane-1,1-dicarboxylate: Hoveyda-Grubbs II catalyst (8.1 mg, 0.013 mmol, 0.022 eq) was added to a solution of dimethyl 2-(pent-4-en-1-yl)malonate **231** (120 mg, 0.60 mmol, 1.0 eq) and 1*H*-pyrrole acrylate (130 mg, 1.07 mmol, 1.8 eq) in 6 mL CH_2Cl_2 and the resulting solution was stirred at ambient temperature. After 13 h, the solvent was removed *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture supported successful cross metathesis to give the straight chain cyclization precursor; however, the straight-chain substrate cyclized upon purification by flash column chromatography (6:1 PE/EtOAc) to yield the title compound as a clear, colourless oil (57 mg, 32%). δ_H (300 MHz, $CDCl_3$) 7.35-7.40 (m, 2 H, C(10)*H* and C(13)*H*), 6.27-6.30 (m, 2 H, C(11)*H* and C(12)*H*), 3.74 (s, 6 H, C(1)H_3 x 2), 3.38 (dd, *J* = 15.5, 3.2 Hz, 1 H, C(8)*H'*H"), 2.97 (app. tdd, *J* = 10.7, 7.3, 3.2 Hz, 1 H, C(7)*H*), 2.66 (dd, *J* = 15.5, 10.7 Hz, 1 H, C(8)H'*H"*), 2.33-2.47 (m, 1H, C(4)*H'*H"), 2.05-2.20 (m, 2 H, C(4)H'*H"* and C(6)*H'*H"), 1.80-1.96 (m, 1 H, C(5)*H'*H"), 1.64-1.77 (m, 1 H, C(5)H'*H"*), 1.46-1.63 (m, 1 H, C(6)H'*H"*) ppm; δ_C (75 MHz, $CDCl_3$) 172.3 (*C*(2)'), 171.6 (*C*(2)"), 169.7 (*C*(9)), 119.3 (*C*(10) and *C*(13)), 113.2 (*C*(11) and *C*(12)), 62.8 (*C*(3)), 52.8 (*C*(1)'), 52.5 (*C*(1)"), 43.1 (*C*(7)), 36.8 (*C*(8)), 34.3 (*C*(4)), 30.8 (*C*(6)), 22.6 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 316 (100%,

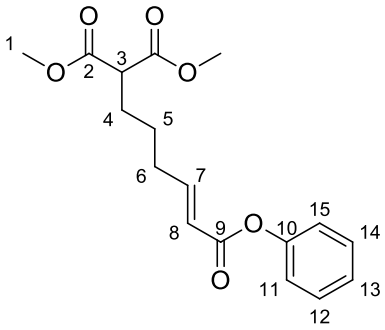
$[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 316.11465, $C_{15}H_{19}O_5NNa^+$ requires 316.11554; ν_{max} 2954 (w, C-H stretch), 1723 (s, ester C=O), 1469 (m), 1435 (m), 1341 (m), 1265 (m), 1206 (m), 922(m), 743 (m) cm^{-1}.

6.2.15 Preparation of 236



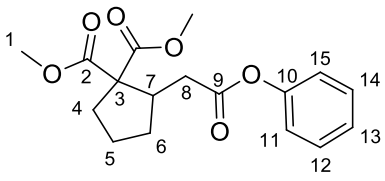
Trimethyl (5*E*)-hex-5-ene-1,1,6-tricarboxylate: Hoveyda-Grubbs II catalyst (33 mg, 0.053 mmol, 0.025 eq) was added to a solution of terminal alkene **231** (420 mg, 2.10 mmol, 1.0 eq) and methyl acrylate (754 µL, 8.37 mmol, 4.0 eq) in 21 mL CH_2Cl_2. The mixture was stirred at ambient temperature for 10 h, then concentrated *in vacuo* and purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a clear, colourless oil (380 mg, 86%). δ_H (400 MHz, $CDCl_3$) 6.93 (dt, *J* = 15.6, 6.9 Hz, 1 H, C(7)*H*), 5.84 (d, *J* = 15.6 Hz, 1 H, C(8)*H*), 3.75 (s, 6 H, C(1)H_3 x 2), 3.73 (s, 3 H, C(10)H_3), 3.37 (t, *J* = 7.5 Hz, 1 H, C(3)*H*), 2.20-2.29 (m, 2 H, C(6)H_2), 1.89-1.97 (m, 2 H, C(4)H_2), 1.45-1.55 (m, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 169.6 (*C*(2) x 2), 166.9 (*C*(9)), 148.2 (*C*(8)), 121.6 (*C*(7)), 52.5 (*C*(1) x 2), 51.4 (*C*(3)), 51.4 (*C*(10)), 31.7 (*C*(6)), 28.3 (*C*(4)), 25.7 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 259 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 281.09906, $C_{12}H_{18}O_6Na^+$ requires 281.09956; ν_{max} 2954 (w), 1726 (s, ester C=O), 1655 (w, C=C), 1437 (m), 1274 (m), 1203 (m), 1151 (m) cm^{-1}.

6.2.16 Preparation of 237



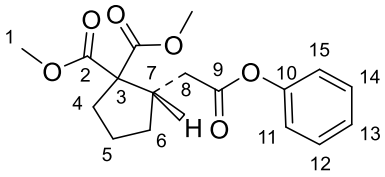
1,1-Dimethyl 6-phenyl (5*E*)-hex-5-ene-1,1,6-tricarboxylate: Hoveyda-Grubbs II catalyst (56 mg, 0.090 mmol, 0.023 eq) was added to a solution of dimethyl 2-(pent-4-en-1-yl)malonate (801 mg, 4.00 mmol, 1.0 eq) and phenyl acrylate (2.2 mL, 14 mmol, 3.5 eq) in 40 mL CH_2Cl_2 (0.1 M) and the resulting solution was stirred at ambient temperature. After 23 h, the solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (6:1 PE/EtOAc) to yield the title compound as a clear, colourless oil (1.17 g, 62%). δ_H (400 MHz, $CDCl_3$) 7.32-7.44 (m, 2 H, C(12)*H* and C(14)*H*), 7.17-7.26 (m, 1 H, C(13)*H*), 7.11-7.17 (m, 1 H, C(7)*H*), 7.07-7.11 (m, 2 H, C(11)*H* and C(15)*H*), 5.98-6.08 (m, 1 H, C(8)*H*), 3.68-3.78 (app. m, 6 H, C(1)H_3 x 2), 3.33-3.47 (m, 1 H, C(3)*H*), 2.25-2.35 (m, 2 H, C(6)H_2), 1.90-2.02 (m, 2 H, C(4)H_2), 1.48-1.59 (m, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 169.4 (*C*(2) x 2), 164.6 (*C*(9)), 150.5 (*C*(10)), 150.2 (*C*(7)), 129.2 (*C*(12) and *C*(14)), 125.5 (*C*(13)), 121.4 (*C*(11) and *C*(15)), 121.0 (*C*(8)), 52.4 (*C*(1) x 2), 51.2 (*C*(3)), 31.7 (*C*(6)), 28.1 (*C*(4)), 25.4 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 343 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 343.11470, $C_{17}H_{20}O_6Na^+$ requires 343.11521; ν_{max} 2954 (w), 1731 (s, ester C=O), 1651 (m, C=C), 1435 (m), 1194 (s), 1139 (s), 689 (m) cm^{-1}.

6.2.17 Preparation of (±)-239



Dimethyl 2-(2-oxo-2-phenoxyethyl) cyclopentane-1,1-dicarboxylate: Tetrabutylammonium bromide (4.3 mg, 0.013 mmol, 0.10 eq) and anhydrous Cs_2CO_3 (21 mg, 0.064 mmol, 0.50 eq) were sequentially added to a solution of **237** (42 mg, 0.13 mmol, 1.0 eq) in toluene (1.0 mL). The resulting mixture was stirred at ambient temperature for 10 h, then 0.1 M acetic acid (0.64 mL) and brine (2 mL) were added. The aqueous layer was extracted with EtOAc (3 x 2 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a clear, colourless oil (28 mg, 68%). Spectroscopic data are identical to those reported below for the enantioenriched sample **(−)-239**.

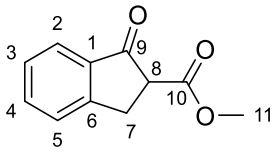
6.2.18 Preparation of (−)-239



(−)-Dimethyl 2-(2-oxo-2-phenoxyethyl)cyclopentane-1,1-dicarboxylate: The title compound was prepared according to general procedure 2B using **237** (42 mg, 0.13 mmol) and **C14** (7.0 mg, 0.013 mmol) in 1.0 mL toluene for 6 days. The title product was isolated by flash column chromatography (8:1 PE/EtOAc) as a clear, colourless oil (29 mg, 68%). The ee was determined by HPLC analysis [Chiralpak OD, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min] t (major) = 8.4 min., t (minor) = 9.6 min. (88% ee). $[\alpha]_D^{20} = -56.3$ (*c* 0.13, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.33-7.44 (m, 2 H, C(12)*H* and C(14)*H*), 7.17-7.26 (m, 1 H, C(13)*H*), 7.06-7.12 (m, 2 H, C(11)*H* and C(15)*H*), 3.76 (s, 6 H, C(1)H_3 x 2), 2.97-3.10 (m, 2 H, C(7)*H* and C(8)*H'*H"), 2.37-2.54 (m, 2 H, C(4)*H'*H" and C(8)H'*H"*), 2.09-2.25 (m, 2 H, C(4)H'*H"* and C(6)*H'*H"), 1.80-1.99 (m, 1 H, C(5)*H'*H"), 1.63-1.80 (m, 1 H, C(5)H'*H"*), 1.47-1.61 (m, 1 H, C(6)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 172.2 (O=*C*), 171.5 (O=*C*), 170.9

(O=*C*), 150.6 (*C*(10)), 129.4 (*C*(12) and *C*(14)), 125.8 (*C*(13)), 121.5 (*C*(11) and *C*(15)), 62.6 (*C*(3)), 52.8 (*C*(1)'), 52.3 (*C*(1)"), 42.7 (*C*(7)), 36.2 (*C*(8)), 34.3 (*C*(4)), 30.9 (*C*(6)), 22.6 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 343 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 343.11451, $C_{17}H_{20}O_6Na^+$ requires 343.11521; ν_{max} (film)/cm^{-1} 2956 (w), 2930 (w), 1765 (m, ester C=O), 1727 (s, ester C=O), 1593 (w), 1334 (m), 1199 (m) cm^{-1}.

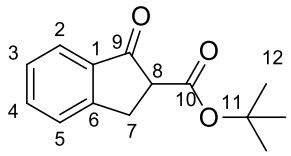
6.2.19 Preparation of 243



Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate:[184] Dimethyl carbonate (14.4 mL, 172 mmol, 6.00 eq) was added to a solution of hexanes-washed (3 × 20 mL) NaH (60% dispersion in mineral oil, 2.86 g, 71.5 mmol, 2.50 eq) in 40 mL toluene. The mixture was warmed to 60 °C, then a solution of 1-indanone (3.78 g, 28.6 mmol, 1.00 eq) in 40 mL toluene was added dropwise over 1 h. The mixture was maintained at this temperature for a further 1 h, then allowed to cool to ambient temperature, acidified with acetic acid (5 mL) and 2 M HCl (60 mL), and extracted with toluene (2 × 50 mL). The organic layer was washed with H_2O (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by distillation (131-140 °C, 3.2 Torr) to afford the product (6:1 keto/enol) as a colourless oil (2.40 g, 12.63 mmol, 44%). δ_H (400 MHz, $CDCl_3$) *keto form*: 7.77 (d, *J* = 7.6 Hz, 1 H, C(2)*H*), 7.58-7.66 (m, 1 H, C(4)*H*), 7.50 (dd, *J* = 7.6, 0.8 Hz, 1 H, C(5)*H*), 7.34-7.43 (m, 1 H, C(3)*H*), 3.79 (s, 3 H, C(11)H_3), 3.74 (dd, *J* = 8.2, 4.0 Hz, 1 H, C(8)*H*), 3.56 (dd, *J* = 17.3, 4.0 Hz, 1 H, C(7)*H'*H"), 3.37 (dd, *J* = 17.3, 8.2 Hz, 1 H, C(7)H'*H"*); *enol form*: 9.85-10.72 (m, 1 H, O*H*), 7.58-7.66 (m, 1 H, C(Ar)*H*), 7.43-7.48 (m, 1 H, C(Ar)*H*), 7.34-7.43 (m, 2 H, C(Ar)*H* × 2), 3.85 (s, 3 H, C(11)H_3), 3.51 (s, 2 H, C(7)H_2) ppm; δ_C (100 MHz, $CDCl_3$) *keto form*: 199.4 (*C*(9)), 169.5 (*C*(10)), 153.5 (*C*(6)), 135.4

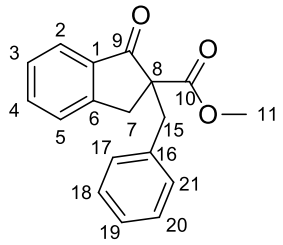
(*C*(4)), 135.1 (*C*(1)), 127.8 (*C*(3)), 126.5 (*C*(5)), 124.6 (*C*(2)), 53.1 (*C*(8)), 52.7 (*C*(11)H_3), 30.2 (*C*(7)); *enol form (visible peaks)*: 143.1 (*C*(3)), 129.3 (*C*(Ar)), 126.8 (*C*(Ar)), 124.7 (*C*(Ar)), 120.7 (*C*(Ar)), 102.1 (*C*(8)), 51.2 (*C*(11)H_3), 32.4 (*C*(7)) ppm; ν_{max} 3035 (w), 1740 (s, C=O), 1709 (vs, C=O), 1653 (m), 1434 (m), 1258 (m), 1208 (s), 1152 (s), 962 (m), 761 (s), 679 (m) cm^{-1}.

6.2.20 Preparation of 244



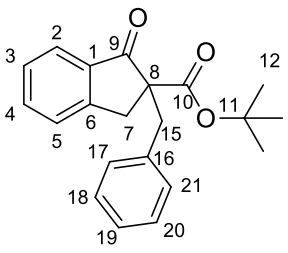
***tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate:**[185] Indanone (3.50 g, 26.5 mmol, 1.00 eq) in 27 mL THF was added to a suspension of NaH (60% suspension in mineral oil, 2.11 g, 53.0 mmol, 2.00 eq) in 106 mL THF. The solution was heated to reflux and *N*-boc pyrrole (8.86 g, 53.0 mmol, 2.00 eq) in 13 mL THF was added dropwise. After 6 h, the mixture was cooled to 0 °C, acidified with 1 M HCl, and extracted with EtOAc (3 x 30 mL). The organic layer was washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography (9:1 PE/Et_2O) to yield the title compound as a pale purple waxy solid (6:1 keto-enol, 5.22 g, 22.5 mmol, 85%). δ_H (400 MHz, $CDCl_3$) 7.77 (d, *J* = 7.6 Hz, 1 H, C(2)*H*), 7.57-7.68 (m, 1 H, C(4)*H*), 7.50 (dt, *J* = 7.7, 0.8 Hz, 1 H, C(5)*H*), 7.34-7.43 (m, 1 H, C(3)*H*), 3.63 (dd, *J* = 8.1, 4.0 Hz, 1 H, C(8)*H*), 3.52 (dt, *J* = 17.2, 4.0 Hz, 1 H, C(7)*H'*H"), 3.34 (dd, *J* = 17.2, 8.1 Hz, 1 H, C(7)H'*H"*), 1.50 (s, 9 H, C(12)H_3 x 3) ppm; δ_C (100 MHz, $CDCl_3$) 200.0 (*C*(9)), 168.3 (*C*(10), 153.7 (*C*(1)), 135.5 (*C*(6)), 135.2 (*C*(4)), 127.7 (*C*(3)), 126.5 (*C*(5)), 124.6 (*C*(2)), 82.0 (*C*(11)), 54.4 (*C*(8)), 30.3 (*C*(7)), 28.0 (*C*(12) x 3) ppm; ν_{max} 2979 (w), 1709 (s, C=O), 1147 (s), 760 (s) cm^{-1}.

6.2.21 Preparation of (±)-245



Methyl 2-benzyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate:[185] *tert*-Butyl 1-oxoindane-2-carboxylate (20.0 mg, 0.105 mmol, 1.00 eq) and Cs_2CO_3 (34.2 mg, 0.105 mmol, 1.00 eq) were diluted in 0.7 mL toluene. Benzyl bromide (12.5 μL, 0.105 mmol, 1.0 eq) was added and the resulting solution was stirred at ambient temperature for 24 h, then diluted with 5 mL H_2O and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title product as a film (28 mg, 95%). δ_H (400 MHz, $CDCl_3$) 7.75 (d, *J* = 7.8 Hz, 1 H, C(2)*H*), 7.50-7.60 (m, 1 H, C(4)*H*), 7.32-7.39 (m, 2 H, C(3)*H* and C(5)*H*), 7.09-7.24 (m, 5 H, C(17)*H*, C(18)*H*, C(19)*H*, C(20)*H* and C(21)*H*), 3.73 (s, 3 H, C(11)H_3), 3.64 (d, *J* = 17.2 Hz, 1 H, C(7)*H'*H"), 3.50 (d, *J* = 13.9 Hz, 1 H, C(15)*H'*H"), 3.30 (d, *J* = 13.9 Hz, 1 H, C(15)H'*H"*), 3.18 (d, *J* = 17.2 Hz, 1 H, C(7)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 202.1 (*C*(9)), 171.2 (*C*(10)), 153.1 (*C*(1)), 136.3 (*C*(16)), 135.3 (*C*(6)), 135.1 (*C*(4)), 129.9 (*C*(19)), 128.3 (*C*(18) and *C*(20)), 127.6 (*C*(3)), 126.8 (*C*(17) and *C*(21)), 126.2 (*C*(5)), 124.7 (*C*(2)), 61.7 (*C*(8)), 52.9 (*C*(11)), 39.8 (*C*(15)), 35.4 (*C*(7)) ppm.

6.2.22 Preparation of (±)-246



***tert*-Butyl 2-benzyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate:**[185] Benzyl bromide (22.0 μL, 0.180 mmol, 1.05 eq) was added to a mixture of *tert*-butyl 1-oxoindane-2-carboxylate (40 mg, 0.17 mmol, 1.0 eq), finely ground K_2CO_3 (29 mg, 0.20 mmol, 1.2 eq) and *tert*-butylammonium bromide (11 mg, 0.034 mmol, 0.20 eq) in 1.1 mL CH_2Cl_2. The resulting suspension was stirred vigorously at ambient temperature for 12 h, then diluted with 5 mL H_2O and extracted with Et_2O (3 × 5 mL). The organic layer was washed with brine (5 mL), dried over Mg_2SO_4, filtered, and concentrated *in vacuo* to give **(±)-246** as a clear film (54 mg, 100%). δ_H (400 MHz, $CDCl_3$) 7.73 (d, *J* = 7.6 Hz, 1 H, C(2)*H*), 7.48-7.57 (m, 1 H, C(4)*H*), 7.28-7.41 (m, 2 H, C(3)*H* and C(5)*H*), 7.03-7.23 (m, 5 H, C(17)*H*, C(18)*H*, C(19)*H*, C(20)*H*, and C(21)*H*), 3.57 (d, *J* = 17.2 Hz, 1 H, C(7)*H'*H"), 3.44 (d, *J* = 14.1 Hz, 1 H, C(15)*H'*H"), 3.27 (d, *J* = 14.1 Hz, 1 H, C(15)H'*H"*), 3.13 (d, *J* = 17.2 Hz, 1 H, C(7)H'*H"*), 1.39 (s, 9 H, C(12)H_3 x 3) ppm; δ_C (100 MHz, $CDCl_3$) 202.6 (*C*(9)), 169.7 (*C*(10)), 153.3 (*C*(1)), 136.8 (*C*(16)), 135.4 (*C*(6)), 135.0 (*C*(4)), 129.9 (*C*(19)), 128.2 (*C*(18) and *C*(20)), 127.4 (*C*(3)), 126.6 (*C*(17) and *C*(21)), 126.1 (*C*(5)), 124.5 (*C*(2)), 82.0 (*C*(11)), 62.4 (*C*(8)), 39.4 (*C*(15)), 35.6 (*C*(7)), 27.7 (*C*(12) x 3) ppm.

6.3 Chapter 3 Experimental

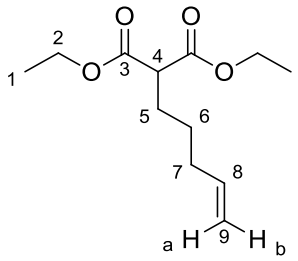
6.3.1 General procedure 3A

General procedure for the preparation of racemic intramolecular Michael addition products: Cyclization precursor (1.0 eq) was dissolved in toluene (0.13 M). Tetrabutylammonium bromide (0.1 eq) and base (0.5 eq) were added sequentially, and the mixture was stirred at ambient temperature. After 14 h, the solution was neutralized with 0.1 M aqueous acetic acid (1.0 eq), extracted with EtOAc (3 x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (PE/EtOAc).

6.3.2 General procedure 3B

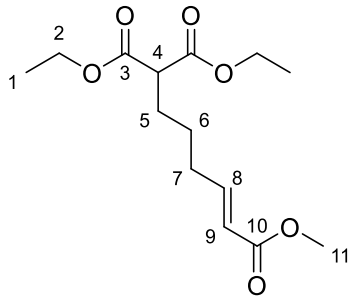
General procedure for enantioselective phase-transfer catalyzed intramolecular Michael reactions: Cyclization precursor (1.0 eq) was dissolved in solvent (0.13 M). Catalyst (0.1 eq) and anhydrous Cs_2CO_3 (0.5 eq) were added sequentially, and the mixture was stirred at ambient temperature. After 8-23 h, 0.1 M acetic acid (0.5 eq) and brine were added, and the resulting mixture was extracted with EtOAc (3 x). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash column chromatography (PE/EtOAc).

6.3.3 Preparation of 314



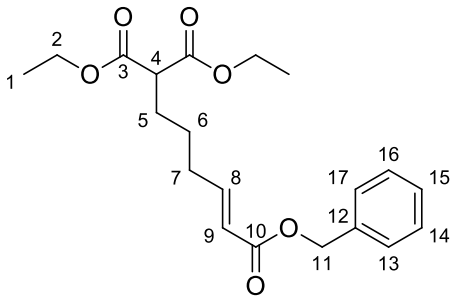
Diethyl pent-4-en-1-ylpropanedioate: Diethylmalonate (1.82 mL, 12.0 mmol, 1.0 eq) was added to a suspension of NaH (60% suspension in mineral oil, 552 mg, 13.8 mmol, 1.15 eq), in 11 mL anhydrous THF at 0 °C. The resulting mixture was allowed to warm to ambient temperature, then 5-bromo-1-pentene (1.61 mL, 13.6 mmol, 1.13 eq) and 11 mL anhydrous DMF were added sequentially. The solution was heated to reflux for 12 h, then allowed to cool to ambient temperature and 1M HCl (15 mL) and Et_2O (15 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20:1 PE/EtOAc) to give the title compound as a clear, colourless oil (1.58 g, 58%). δ_H (300 MHz, $CDCl_3$) 5.79 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1 H, C(8)*H*), 4.89-5.09 (m, 2 H, C(9)H_2), 4.20 (q, *J* = 7.1 Hz, 4 H, C(2)H_2 x 2), 3.32 (t, *J* = 7.6 Hz, 1 H, C(4)*H*), 2.06-2.12 (m, 2 H, C(7)H_2), 1.83-2.02 (m, 2 H, C(5)H_2), 1.36-1.50 (m, 2 H, C(6)H_2), 1.27 (t, *J* = 7.1 Hz, 6 H, C(1)H_3 x 2) ppm; δ_C (75 MHz, $CDCl_3$) 169.5 (*C*(3) x 2), 138.0 (*C*(8)), 115.0 (*C*(9)), 61.3 (*C*(2) x 2), 51.9 (*C*(4)), 33.3 (*C*(7)), 28.2 (*C*(5)), 26.5 (*C*(6)), 14.1 (*C*(1) x 2) ppm; LRMS *m/z* (ESI^+) 229 (33%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 229.14316, $C_{12}H_{21}O_4^+$ requires 229.14344; ν_{max} 2981 (w), 1730 (s, ester C=O), 1150 (m), 995 (m), 861 (m) cm^{-1}.

6.3.4 Preparation of 315



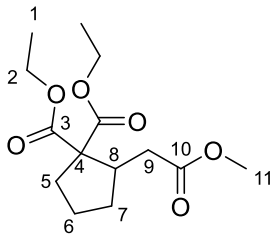
1,1-Diethyl 6-methyl (5*E*)-hex-5-ene-1,1,6-tricarboxylate: Hoveyda-Grubbs II catalyst (24 mg, 0.038 mmol, 0.025 eq) was added to a solution of dibenzyl 2-(pent-4-en-1-yl)malonate **314** (520 mg, 1.48 mmol, 1.00 eq) and methyl acrylate (560 µL, 6.85 mmol, 4.60 eq) in 16 mL anhydrous CH_2Cl_2. The mixture was heated to reflux and, after 15 h, the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography (10:1 PE/EtOAc) to yield the title compound as a clear, colourless oil (397 mg, 60%; *N.B.* remaining mass coeluted with methyl acrylate dimer). δ_H (400 MHz, $CDCl_3$) 6.94 (dt, *J* = 15.6, 6.9 Hz, 1 H, C(8)*H*), 5.78-5.90 (m, 1 H, C(9)*H*), 4.19 (q, *J* = 7.2 Hz, 4 H, C(2)H_2 x 2), 3.71 (s, 3 H, C(11)H_3), 3.31 (t, *J* = 7.5 Hz, 1 H, C(4)*H*), 2.20-2.41 (m, 2 H, C(7)H_2), 1.87-1.98 (m, 2 H, C(5)H_2), 1.46-1.58 (m, 2 H, C(6)H_2), 1.26 (t, *J* = 7.2 Hz, 6 H, C(1)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 169.2 (*C*(3) x 2), 167.0 (*C*(10), 148.3 (*C*(8)), 121.5 (*C*(9)), 61.4 (*C*(2) x 2), 51.8 (*C*(4)), 51.4 (*C*(11)), 31.7 (*C*(7)), 28.1 (*C*(5)), 25.7 (*C*(6)), 14.1 (*C*(1) x 2) ppm; LRMS *m/z* (ESI^+) 287 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 287.14832, $C_{14}H_{23}O_6^+$ requires 287.14891; ν_{max} 2983 (w), 2952 (w), 1723 (s, ester C=O), 1657 (w), 1438 (w), 1270 (m), 1148 (m), 1027 (m) cm^{-1}.

6.3.5 Preparation of 316



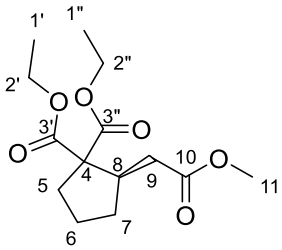
6-Benzyl 1,1-diethyl (5*E*)-hex-5-ene-1,1,6-tricarboxylate: Hoveyda-Grubbs II catalyst (33 mg, 0.053 mmol, 2.5 mol%) was added to a solution of **314** (506 mg, 2.10 mmol, 1.00 eq) and benzyl acrylate (1.26 mL, 8.39 mmol, 4.00 eq) with in 21 mL CH_2Cl_2. After 14 h, the mixture was concentrated *in vacuo.* The title compound was purified by flash column chromatography (8:1 PE/EtOAc) to yield a pale yellow oil (380 mg, 50%). δ_H (500 MHz, $CDCl_3$) 7.28-7.40 (m, 5 H, C(Ar)*H* x 5), 6.97 (dt, *J* = 15.8, 6.9 Hz, 1 H, C(8)*H*), 5.88 (d, *J* = 15.8 Hz, 1 H, C(9)*H*), 5.17 (s, 2 H, C(11)H_2), 4.19 (q, *J* = 7.0 Hz, 4 H, C(2)H_2 x 2), 3.31 (t, *J* = 7.4 Hz, 1 H, C(4)*H*), 2.24 (app. q, *J* = 7.1 Hz, 2 H, C(7)H_2), 1.91 (app. q, *J* = 7.6 Hz, 2 H, C(5)H_2), 1.45-1.55 (m, 2 H, C(6)H_2), 1.26 (t, *J* = 7.0 Hz, 6 H, C(1)H_3 x 2) ppm; δ_C (125 MHz, $CDCl_3$) 169.4 (*C*(3) x 2), 166.5 (*C*(10)), 148.8 (*C*(8)), 136.2 (*C*(12)), 128.7 (*C*(Ar) x 2), 128.4 (*C*(Ar) x 2), 128.3 (*C*(Ar)), 121.7 (*C*(9)), 66.2 (*C*(11)), 61.6 (*C*(2) x 2), 51.9 (*C*(4)), 31.9 (*C*(7)), 28.3 (*C*(5)), 25.8 (*C*(6)), 14.2 (*C*(1) x 2) ppm; LRMS *m/z* (ESI^+) 385 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 385.16127, $C_{20}H_{26}O_6Na^+$ requires 385.16216; ν_{max} 3020 (w), 2982 (w), 1747 (m, ester C=O), 1726 (s, ester C=O), 1654 (w), 1456 (w), 1370 (w), 1264 (m), 1174 (m), 1147 (m), 1026 (m) cm^{-1}.

6.3.6 Preparation of (±)-317



Diethyl 2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate (racemate): Obtained according to general procedure 3A using **315** (37 mg, 0.13 mmol) and ground KOH (85%, 4.3 mg). The product was isolated using flash column chromatography (8:1 PE/EtOAc) as a clear, colourless oil (23 mg, 61%). ^{1}H NMR and ^{13}C NMR data match those reported for the enantioenriched product, **(+)-317**, below.

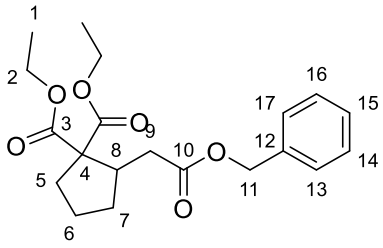
6.3.7 Preparation of (+)-317



(+)-Diethyl 2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3B using **315** (37 mg, 0.13 mmol) and **C52** (10 mg, 0.013 mmol) in toluene (1.0 mL). The title compound was isolated by flash column chromatography (8:1 PE/EtOAc) as a clear, colourless oil (26 mg, 71%). The ee was determined by HPLC [Chiralpak AD, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min] t (minor) = 5.3 min., t (major) = 5.7 min. (44% ee). $[\alpha]_D^{20}$ = +24.1 (*c* 1.00, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 4.10-4.25 (m, 4 H, C(2)*H*$_2$ x 2), 3.67 (s, 3 H, C(11)*H*$_3$), 2.90 (app. tdd, *J* = 10.9, 7.2, 3.6 Hz, 1 H, C(8)*H*), 2.77 (dd, *J* = 15.7, 3.6 Hz, 1 H, C(9)*H*'H"), 2.37 (ddd, *J* = 13.7, 8.7, 6.6 Hz, 1 H, C(5)*H*'H"), 2.21 (dd, *J* = 15.7, 10.9 Hz, 1 H, C(9)H'*H"*), 2.02-2.13

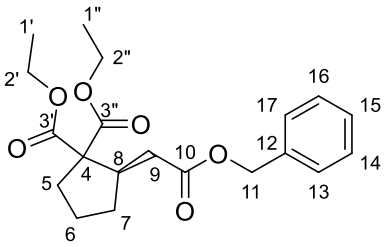
(m, 2 H, C(5)H'*H"* and C(7)*H'*H"), 1.79-1.89 (m, 1 H, C(6)*H'*H"), 1.59-1.70 (m, 1 H, C(6)H'*H"*), 1.39-1.50 (m, 1 H, C(7)H'*H"*), 1.22-1.27 (m, 6 H, C(1)H_3 x 2) ppm; δ_C (125 MHz, $CDCl_3$) 173.2 (O=*C*), 172.0 (O=*C*), 171.2 (O=*C*), 62.8 (*C*(4)), 61.4 (*C*(2)'), 61.3 (*C*(2)"), 51.7 (*C*(11)), 42.7 (*C*(8)), 36.1 (*C*(9)), 34.3 (*C*(5)), 31.1 (*C*(7)), 22.7 (*C*(6)), 14.3 (*C*(1)'), 14.2 (*C*(1)") ppm; LRMS *m/z* (ESI^+) 309 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 309.13005, $C_{14}H_{22}O_6Na^+$ requires 309.13086; ν_{max} 2980 (w), 1726 (s, ester C=O), 1438 (w), 1367 (w), 1259 (m), 1097 (w), 1030 (w) cm^{-1}.

6.3.8 Preparation of (±)-321



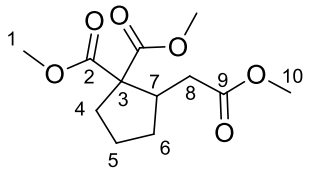
Diethyl 2-[2-(benzyloxy)-2-oxoethyl]cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3A using **316** (47 mg, 0.13 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol) in toluene (1.0 mL). The product was isolated using flash column chromatography (8:1 PE/EtOAc) as a clear, colourless oil (31 mg, 66%). ^1H NMR and ^{13}C NMR data match those reported for the enantioenriched product, **(+)-321**, below.

6.3.9 Preparation of (+)-321



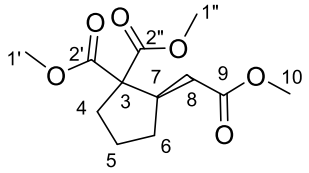
(+)-Diethyl 2-[2-(benzyloxy)-2-oxoethyl]cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3B using **316** (47 mg, 0.13 mmol) and **C34** (9 mg, 0.013 mmol) in toluene (1.0 mL). After 18 h, the product was purified by flash column chromatograph (8:1 PE/EtOAc), yielding a clear, colourless oil (35 mg, 75%). The ee was determined by HPLC [Chiralpak AD, hexane/*iso*-propanol 90:10, λ 210 nm, 1.0 mL/min] t (minor) = 6.4 min., t (major) = 8.6 min. (11% ee). $[\alpha]_D^{20}$ = +5.1 (c 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.28-7.41 (m, 5 H, C(Ar)*H* x 5), 5.12 (s, 2 H, C(11)H_2), 4.07-4.23 (m, 4 H, C(2)H_2 x 2), 2.92 (tdd, *J* = 10.6, 7.3, 3.6 Hz, 1 H, C(8)*H*), 2.82 (dd, *J* = 15.8, 3.6 Hz, 1 H, C(9)*H'*H"), 2.37 (ddd, *J* = 13.9, 8.5, 6.6 Hz, 1 H, C(5)*H'*H"), 2.26 (dd, *J* = 15.8, 10.9 Hz, 1 H, C(9)H'*H"*), 2.01-2.12 (m, 2 H, C(7)*H'*H" and C(5)H'*H"*), 1.78-1.88 (m, 1 H, C(6)*H'*H"), 1.59-1.69 (m, 1 H, C(6)H'*H"*), 1.40-1.50 (m, 1 H, C(7)H'*H"*), 1.24 (t, *J* = 7.1 Hz, 6 H, C(1)H_3 x 2) ppm; δ_C (125 MHz, $CDCl_3$) 172.5 (O=*C*), 171.9 (O=*C*), 171.2 (O=*C*), 136.1 (*C*(12)), 128.7 (*C*(Ar) x 2), 128.3 (*C*(Ar) x 2), 128.3 (*C*(15)), 66.4 (*C*(11)), 62.8 (*C*(4)), 61.4 (*C*(2)'), 61.3 (*C*(2)"), 42.7 (*C*(8)), 36.3 (*C*(9)), 34.3 (*C*(5)), 31.1 (*C*(7)), 22.7 (*C*(6)), 14.2 (*C*(1)'), 14.2 (*C*(1)") ppm; LRMS *m/z* (ESI^+) 385 (80%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 385.16114, $C_{20}H_{26}O_6Na^+$ requires 385.16216; ν_{max} 2980 (w), 1724 (s, ester C=O), 1455 (w), 1367 (w), 1257 (m), 1150 (m), 1028 (m), 750 (m), 698 (m) cm^{-1}.

6.3.10 Preparation of (±)-322



Dimethyl 2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3A using **236** (34 mg, 0.13 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol) in toluene (1.0 mL). The product was isolated using flash column chromatography (6:1 PE/EtOAc) as a clear, colourless oil (27 mg, 80%). ^{1}H NMR and ^{13}C NMR data match those reported for the enantioenriched product, **(+)-322**, below.

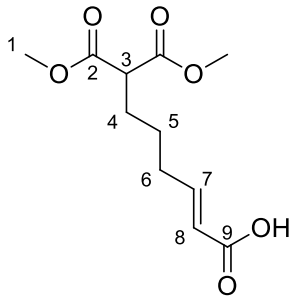
6.3.11 Preparation of (+)-322



(+)-Dimethyl 2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3B using **236** (34 mg, 0.13 mmol) and **C52** (10 mg, 0.013 mmol) in toluene (1 mL). The title compound was isolated by flash column chromatography (6:1 PE/EtOAc) as a clear, colourless oil (28 mg, 83%). The ee was determined by HPLC [Chiralpak OD, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min] t (major) = 6.5 min., t (minor) = 8.8 min. (44% ee). $[\alpha]_D^{20}$ = +15.1 (c 0.530, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.66 (s, 3 H, C(1)'*H*$_3$), 3.64 (s, 3 H, C(1)"*H*$_3$), 3.60 (s, 3 H, C(10)*H*$_3$), 2.79-2.89 (m, 1 H, C(7)*H*), 2.67 (dd, *J* = 15.8, 3.7 Hz, 1 H, C(8)*H'*H"), 2.26-2.36 (m, 1 H, C(4)*H'*H"), 2.13 (dd, *J* = 15.8, 10.9 Hz, 1 H, C(8)H'*H"*), 1.94-2.08 (m, 2 H, C(4)H'*H"* and C(6)*H'*H"), 1.71-1.83 (m, 1 H, C(5)*H'*H"), 1.53-1.65 (m, 1 H, C(5)H'*H"*), 1.32-1.45 (m, 1 H, C(6)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 172.9 (O=*C*), 172.2 (O=*C*), 171.5 (O=*C*), 62.6 (*C*(3)), 52.5 (*C*(1)'), 52.2

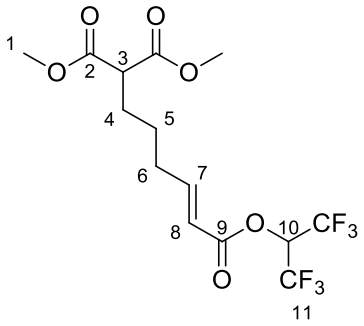
(*C*(1)"), 51.6 (*C*(10)), 42.7 (*C*(7)), 35.9 (*C*(8)), 34.2 (*C*(4)), 30.9 (*C*(6)), 22.5 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 281 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 281.09921, $C_{12}H_{18}O_6Na^+$ requires 281.09921; ν_{max} 2955 (w), 1731 (s), ester C=O), 1436 (m), 1266 (m), 1155 (m) cm^{-1}.

6.3.12 Preparation of 323



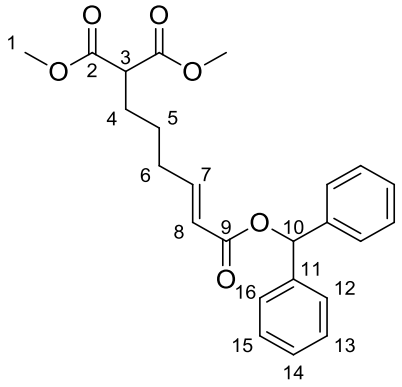
(2*E*)-8-Methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid: Hoveyda-Grubbs II catalyst (56 mg, 0.088 mmol, 0.022 eq) was added to a stirred solution of **231** (800 mg, 4.00 mmol, 1.00 eq) and acrylic acid (1.08 mL, 16.0 mmol, 4.00 eq) in CH_2Cl_2 (8.5 mL). After 13 h, the mixture was concentrated *in vacuo* and purified by flash column chromatography (2:1 PE/EtOAc) to give **323** as a clear, colourless oil (827 mg, 85%). δ_H (400 MHz, $CDCl_3$) 9.37 (br s, 1 H, O*H*), 7.00-7.12 (m, 1 H, C(7)*H*), 5.86 (d, *J* = 15.7 Hz, 1 H, C(8)*H*), 3.74-3.78 (m, 6 H, C(1)H_3 x 2), 3.39 (t, *J* = 7.5 Hz, 1 H, C(3)*H*), 2.25-2.33 (m, 2 H, C(6)H_2), 1.84-2.05 (m, 2 H, C(4)H_2), 1.48-1.58 (m, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 171.8 (*C*(9)), 169.8 (*C*(2) x 2), 151.0 (*C*(7)), 121.4 (*C*(8)), 52.7 (*C*(1) x 2), 51.5 (*C*(3)), 31.9 (*C*(6)), 28.4 (*C*(4)), 25.7 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 267 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 267.08359, $C_{11}H_{16}O_6Na^+$ requires 267.08391; ν_{max} 2956 (w, br, C-H stretch and OH stretch), 1730 (s, ester C=O), 1695 (s, acid C=O), 1651 (m), 1436 (m), 1197 (m), 1151 (m) cm^{-1}.

6.3.13 Preparation of 324a



6-(1,1,1,3,3,3-Hexafluoropropan-2-yl) 1,1-dimethyl (5*E*)-hex-5-ene-1,1,6-tricarboxylate: 1,1,1,3,3,3-Hexafluoropropan-2-ol (69 µL, 1.3 mmol, 3.0 eq) and DMAP (2.0 mg, 0.033 mmol, 0.10 eq) were added to a solution of acid **323** (40.0 mg, 0.327 mmol, 1.00 eq) in CH_2Cl_2 (0.5 mL). The mixture was cooled to 0 °C, then DCC (40.5 mg, 0.392 mmol, 1.20 eq) was added. The resulting mixture was stirred at this temperature for 10 min, then allowed to warm to ambient temperature. After 3 h, the precipitate was removed *via* filtration over silica/Celite®. The filtrate was washed with 3 M HCl (2 mL), sat. aq. $NaHCO_3$ (2 mL) and brine (2 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (8:1 PE/EtOAc) to give **324a** as a clear colourless oil (36.6 mg, 28%). δ_H (400 MHz, $CDCl_3$) 7.19 (dt, *J* = 15.7, 6.8 Hz, 1 H, C(7)*H*), 5.96 (dt, *J* = 15.7, 1.5 Hz, 1 H, C(8)*H*), 5.83 (spt, *J* = 6.2 Hz, 1 H, C(10)*H*), 3.76 (s, 6 H, C(1)H_3 x 2), 3.39 (t, *J* = 7.4 Hz, 1 H, C(3)*H*), 2.29-2.37 (m, 2 H, C(6)H_2), 1.92-1.99 (m, 2 H, C(4)H_2), 1.51-1.58 (m, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 169.5 (*C*(2) x 2), 162.7 (*C*(9)), 153.7 (*C*(7)), 120.5 (q, *J* = 281 Hz, *C*(11) x 2), 118.5 (*C*(8)), 65.9-66.7 (m, *C*(10)), 52.6 (*C*(1) x 2), 51.3 (*C*(3)), 32.1 (*C*(6)), 28.2 (*C*(4)), 25.3 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 395 (20%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 417.07321, $C_{14}H_{16}O_6F_6Na^+$ requires 417.07433; ν_{max} 3022 (w), 2940 (w), 1734 (s, ester C=O), 1441 (w), 1367 (m), 1226 (m), 1204 (m), 1108 (w) cm^{-1}.

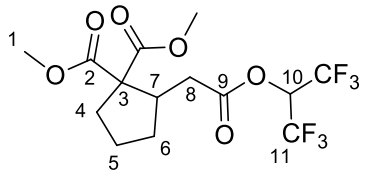
6.3.14 Preparation of 324b



6-(Diphenylmethyl) 1,1-dimethyl (5*E*)-hex-5-ene-1,1,6-tricarboxylate: To a solution of (*E*)-8-methoxy-7-(methoxycarbonyl)-8-oxooct-2-enoic acid **323** (200 mg, 0.820 mmol, 1.00 eq) in CH_2Cl_2 (2.5 mL, 0.33 M) was added diphenylmethanol (600 mg, 3.26 mmol, 4.00 eq) and DMAP (10 mg, 0.082 mmol, 0.10 eq). The solution was cooled to 0 °C in an ice/water bath, then DCC (203 mg, 0.980 mmol, 1.20 eq) was added. After 10 min, the ice bath was removed and the mixture was allowed to warm to ambient temperature. After 3 h, the mixture was filtered over silica/Celite®. The filtrate was then washed with 3 M HCl (5 mL), sat. aq. $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a clear, colourless oil (127 mg, 38%). δ_H (400 MHz, $CDCl_3$) 7.25-7.38 (m, 10 H, C(Ar)*H* x 10), 7.02 (dt, *J* = 15.6, 6.8 Hz, 1 H, C(7)*H*), 6.93 (s, 1 H, C(10)*H*), 5.96 (dt, *J* = 15.6, 1.5 Hz, 1 H, C(8)*H*), 3.74 (s, 6 H, C(1)H_3 x 2), 3.37 (t, *J* = 7.6 Hz, 1 H, C(3)*H*), 2.21-2.30 (m, 2 H, C(6)H_2), 1.88-1.97 (m, 2 H, C(4)H_2), 1.44-1.56 (m, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 169.7 (*C*(2) x 2), 165.6 (*C*(9)), 149.1 (*C*(7)), 140.4 (*C*(11) x 2), 128.6 (*C*(Ar) x 4), 128.0 (*C*(Ar) x 2), 127.3 (*C*(Ar) x 4), 121.8 (*C*(8)), 76.8 (*C*(10)), 52.7 (*C*(1) x 2), 51.5 (*C*(3)), 31.9 (*C*(6)), 28.4 (*C*(4)), 25.8 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 433 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found

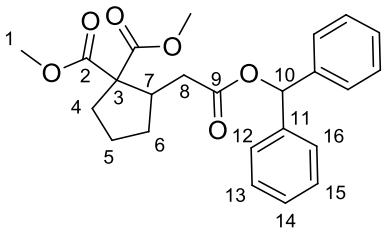
$[M+Na]^+$ 433.16078, $C_{24}H_{26}O_6Na^+$ requires 433.16216; ν_{max} 3032 (w), 2955 (w), 1733 (s, C=O), 1497 (w), 1444 (w), 1267 (m), 1154 (m) cm^{-1}.

6.3.15 Preparation of (±)-325a



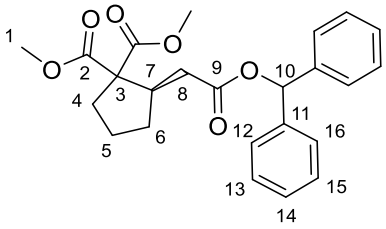
Dimethyl 2-{2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-2-oxoethyl}cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3A using **324a** (36 mg, 0.092 mmol) and Cs_2CO_3 (15 mg, 0.046 mmol). The product was isolated using flash column chromatography (6:1 PE/EtOAc) as a clear, colourless oil (23 mg, 64%). δ_H (400 MHz, $CDCl_3$) 5.72-5.81 (m, 1 H, C(10)*H*), 3.74 (s, 3 H, C(1)'*H*$_3$), 3.73 (s, 3 H, C(1)"*H*$_3$), 2.99 (dd, *J* = 16.2, 3.9 Hz, 1 H, C(8)*H'*H"), 2.84-2.94 (m, 1 H, C(7)*H*), 2.41-2.50 (m, 1 H, C(8)H'*H"*), 2.31-2.41 (m, 1 H, C(4)*H'*H"), 2.14 (ddd, *J* = 13.9, 9.8, 6.1 Hz, 1 H, C(4)H'*H"*), 2.02-2.12 (m, 1 H, C(6)*H'*H"), 1.79-1.96 (m, 1 H, C(5)*H'*H"), 1.60-1.77 (m, 1 H, C(5)H'*H"*), 1.40-1.55 (m, 1 H, C(6)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 172.1 (O=*C*), 171.4 (O=*C*), 169.6 (O=*C*), 120.6 (q, J_{CF} = 282.0 Hz, *C*(11) x 2), 66.6 (sept, J_{CF} = 34.0 Hz, *C*(10)), 62.6 (*C*(3)), 52.8 (*C*(1)'), 52.6 (*C*(1)"), 42.6 (*C*(7)), 35.3 (*C*(8)), 34.4 (*C*(4)), 30.7 (*C*(6)), 22.6 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 417 (80%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 417.07321, $C_{14}H_{16}O_6F_6Na^+$ requires 417.07433; ν_{max} 3016 (w), 2971 (w), 1738 (s, ester C=O), 1436 (m), 1367 (s), 1229 (s), 1108 (m), 906 (w), 691 (w) cm^{-1}.

6.3.16 Preparation of (±)-325b



Dimethyl 2-[2-(diphenylmethoxy)-2-oxoethyl]cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3A using **324b** (76.4 mg, 0.186 mmol, 1.00 eq), tetrabutylammonium bromide (5.7 mg, 0.019 mmol) and Cs_2CO_3 (30 mg, 0.093 mmol) in toluene (1.4 mL) for 8 h. The crude product was purified by flash column chromatography (6:1 PE/EtOAc) to give the title compound as a clear, colourless oil (16.7 mg, 22 5). The ^{1}H and ^{13}C NMR data are identical to those reported for the enantioenriched product, **(–)-325b**, below.

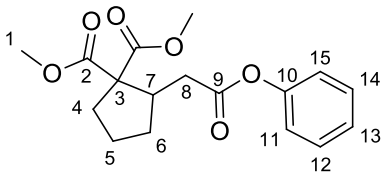
6.3.17 Preparation of (–)-325b



(–)-Dimethyl 2-[2-(diphenylmethoxy)-2-oxoethyl]cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3B using **324b** (53 mg, 0.13 mmol), **C52** (5.2 mg, 0.013 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol) in toluene (1.0 mL) for 6 h. The crude product was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a clear, colourless oil (21.2 mg, 40%). The ee was determined by HPLC [Chiralpak AD-H, hexane/*iso*-propanol 90:10, λ 210 nm, 1.0 mL/min] t (minor) = 12.5 min., t (major) = 15.2 min. (60% ee). $[\alpha]_D^{20}$ = –24.6 (*c* 1.00, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.23-7.37 (m, 10 H, C(Ar)*H* x 10), 6.88 (s, 1 H, C(10)*H*), 3.70 (s, 3 H, C(1)'H_3), 3.68 (s, 3 H,

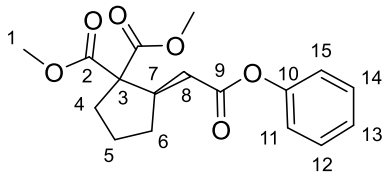
C(1)"*H*$_3$), 2.95 (tdd, *J* = 10.6, 7.1, 3.8 Hz, 1 H, C(7)*H*), 2.86 (dd, *J* = 15.8, 3.8 Hz, 1 H, C(8)*H'*H"), 2.27-2.42 (m, 2 H, C(8)H'*H"* and C(4)*H'*H"), 2.06-2.15 (m, 1 H, C(4)H'*H"*), 1.94-2.03 (m, 1 H, C(6)*H'*H"), 1.76-1.87 (m, 1 H, C(5)*H'*H"), 1.55-1.68 (m, 1 H, C(5)H'*H"*), 1.37-1.48 (m, 1 H, C(6)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 172.4 (O=*C*), 171.7 (O=*C*), 171.6 (O=*C*), 140.3 (*C*(11) x 2), 128.6 (*C*(Ar) x 2), 128.6 (*C*(Ar) x 2), 128.1 (*C*(14)'), 128.0 (*C*(14)"), 127.3 (*C*(Ar) x 2), 127.2 (*C*(Ar) x 2), 77.1 (*C*(10)), 62.8 (*C*(3)), 52.7 (*C*(1)'), 52.5 (*C*(1)"), 42.8 (*C*(7)), 36.5 (*C*(8)), 34.4 (*C*(4)), 31.0 (*C*(6)), 22.7 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 433 (60%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 433.16076, $C_{24}H_{26}O_6Na^+$ requires 433.16216; ν_{max} 3076 (w), 2960 (w), 1750 (s, C=O), 1734 (s, C=O), 1725 (C=O), 1443 (w), 1371 (m), 1223 (m), 1206 (m) cm^{-1}.

6.3.18 Preparation of (±)-326



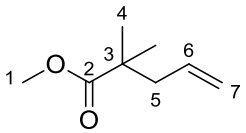
Dimethyl (2*S*)-2-(2-oxo-2-phenoxyethyl)cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3A using **237** (42 mg, 0.13 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol). The product was isolated using flash column chromatography (6:1 PE/EtOAc) as a clear, colourless oil (28 mg, 68%). ^{1}H NMR and ^{13}C NMR data match those reported for the enantioselective cyclization, **(+)-236**, below.

6.3.19 Preparation of (+)-326



(+)-Dimethyl 2-(2-oxo-2-phenoxyethyl)cyclopentane-1,1-dicarboxylate: Obtained according to general procedure 3B using **237** (42 mg, 0.13 mmol), **C52** (10 mg, 0.013 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol). The product was isolated using flash column chromatography (6:1 PE/EtOAc) as a clear, colourless oil (30.7 mg, 74%, 62% ee). Spectroscopic data are identical to those reported for **(−)-239**, except with the opposite enantiomer enriched.

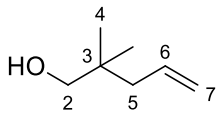
6.3.20 Preparation of 329



Methyl 2,2-dimethylpent-4-enoate:[186] The title compound was prepared following a known literature procedure.[186] *n*-Butyllithium (2.3 M in hexane, 9.08 mL, 20.6 mmol, 1.00 eq) was added dropwise to a solution of di-*iso*-propylamine (3.18 mL, 22.7 mmol, 1.10 eq) in anhydrous THF (6.8 mL) at −78 °C. After 10 min, the solution was allowed to warm to 0 °C and stirred at this temperature for 30 min. The solution was then returned to −78 °C and methyl *iso*-butyrate (2.36 mL, 20.6 mL, 1.00 eq) was added. After 1.5 h, allyl bromide (2.14 mL, 24.8 mmol, 1.20 eq) was added and the mixture was allowed to warm to ambient temperature. After 13 h, the mixture was diluted with pentane and filtered through a pad of silica, then concentrated *in vacuo*. The crude oil was purified by flash column chromatography (20:1 PE/EtOAc) to give **329** as a clear, colourless oil (1.17 g, 40%). δ_H (400 MHz, $CDCl_3$) 5.61-5.75 (m, 1 H, C(6)*H*), 4.96-5.05 (m, 2 H, C(7)H_2), 3.62 (s, 3 H,

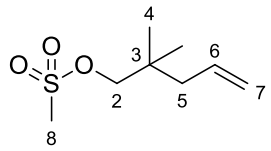
C(1)*H*$_3$), 2.24 (d, *J* = 7.3 Hz, 2 H, C(5)*H*$_2$), 1.14 (s, 6 H, C(4)*H*$_3$ x 2) ppm; δ_C (100 MHz, $CDCl_3$) 178.0 (*C*(2)), 134.3 (*C*(6)), 117.9 (*C*(7)), 51.7 (*C*(1)), 44.8 (*C*(5)), 42.4 (*C*(3)), 24.9 (*C*(4) x 2) ppm.

6.3.21 Preparation of 330



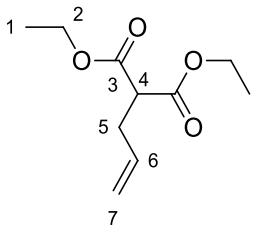
2,2-Dimethylpent-4-en-1-ol:[186] The title compound was prepared according to a known literature procedure.[186] A solution of **329** (644 mg, 4.50 mmol, 1.00 eq) in Et_2O (3.7 mL) was added to a solution of $LiAlH_4$ (223 mg, 5.86 mmol, 1.30 eq) in Et_2O (3.7 mL) at 0 °C. The mixture was allowed to warm to ambient temperature, then heated to reflux. After 5 h, the mixture was allowed to cool to ambient temperature and then 15 mL 1 M HCl and 15 mL Et_2O were added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were subsequently washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **330** as a clear, colourless oil (393 mg, 76%). δ_H (400 MHz, $CDCl_3$) 5.75-5.90 (m, 1 H, C(6)*H*), 4.98-5.08 (m, 2 H, C(7)*H*$_2$), 3.30 (s, 2 H, C(2)*H*$_2$), 2.00 (d, *J* = 7.6 Hz, 2 H, C(5)*H*$_2$), 1.69-1.84 (m, 1 H, O*H*), 0.87 (s, 6 H, C(4)*H*$_3$ x 2) ppm; δ_C (100 MHz, $CDCl_3$) 135.4 (*C*(6)), 117.2 (*C*(7)), 71.8 (*C*(2)), 43.5 (*C*(5)), 35.6 (*C*(3)), 23.9 (*C*(4) x 2) ppm.

6.3.22 Preparation of 331



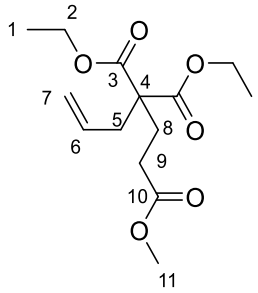
2,2-Dimethylpent-4-en-1-yl methanesulfonate: The following method was modified from a known literature procedure.[187] Methanesulfonyl chloride (32.0 µL, 0.413 mmol, 1.2 eq) was added to a solution of alcohol **330** (39.3 mg, 0.344 mmol, 1.0 eq) and triethylamine (57.5 µL, 0.413 mmol, 1.2 eq) in CH_2Cl_2 (1.7 mL) at 0 °C. After 1 h at this temperature, brine (2 mL) was added and the mixture was allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (6:1 PE/EtOAc) to give mesylate **331** as a clear, colourless oil (10.8 mg, 16%). δ_H (400 MHz, $CDCl_3$) 5.70-5.84 (m, 1 H, C(6)*H*), 5.02-5.13 (m, 2 H, C(7)H_2), 3.89 (s, 2 H, C(2)H_2), 3.00 (s, 3 H, C(8)H_3), 2.06 (d, J = 7.5 Hz, 2 H, C(5)H_2), 0.97 (s, 6 H, C(4)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 133.5 (*C*(6)), 118.4 (*C*(7)), 77.2 (*C*(2)), 42.8 (*C*(5)), 37.0 (*C*(8)), 34.3 (*C*(3)), 23.7 (*C*(4) x 2) ppm; LRMS *m/z* (ESI^+) 215 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 215.07118, $C_8H_{16}O_3Na^+$ requires 215.07124; ν_{max} 2970 (w), 1742 (m), 1357 (s), 1173 (s), 951 (s), 838 (s) cm^{-1}.

6.3.23 Preparation of 333



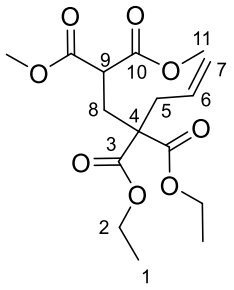
Diethyl prop-2-en-1-ylpropanedioate:[188] Diethylmalonate (3.05 mL, 20.0 mmol, 1.00 eq) was added to a suspension of NaH (60% suspension in mineral oil, 840 mg, 21.0 mmol, 1.05 eq) in anhydrous DMF (15 mL) at 0 °C. After 25 min, allyl bromide (1.72 mL, 20.0 mmol, 1.00 eq) was added and the solution was allowed to warm to ambient temperature. After 14 h, 1 M HCl (15 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatograph (50:1 to 25:1 PE/EtOAc) to give **333** as a clear, colourless oil (2.16 g, 54%). δ_H (400 MHz, $CDCl_3$) 5.65-5.80 (m, 1 H, C(6)*H*), 4.95-5.12 (m, 2 H, C(7)H_2), 4.10-4.19 (m, 4 H, C(2)H_2 x 2), 3.33-3.39 (m, 1 H, C(4)*H*), 2.54-2.62 (m, 2 H, C(5)H_2), 1.15-1.25 (m, 6 H, C(1)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 168.7 (*C*(3) x 2), 133.9 (*C*(6)), 117.3 (*C*(7)), 61.2 (*C*(2) x 2), 51.5 (*C*(4)), 32.7 (*C*(5)), 13.9 (*C*(1) x 2) ppm.

6.3.24 Preparation of 334



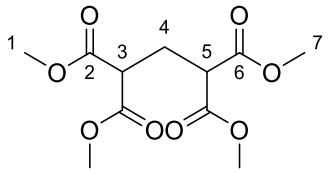
3,3-Diethyl 1-methyl hex-5-ene-1,3,3-tricarboxylate: The following method was modified from a known literature procedure.[189] Tributylphosphine (125 µL, 0.500 mmol, 0.100 eq) was added to a solution of **333** (1.00 g, 4.99 mmol, 1.00 eq) and methyl acrylate (560 µL, 7.49 mmol, 1.50 eq) in MeCN (2.3 mL) and the resulting mixture was stirred at ambient temperature. After 11 h, the mixture was concentrated *in vacuo* and the resulting crude oil was purified by flash column chromatography (15:1 to 9:1 PE/EtOAc) to give **334** as a clear, colourless oil (1.15 g, 80%). δ_H (400 MHz, $CDCl_3$) 5.63 (ddt, *J* = 17.1, 9.8, 7.4 Hz, 1 H, C(6)*H*), 5.05-5.13 (m, 2 H, C(7)H_2), 4.11-4.21 (m, 4 H, C(2)H_2 x 2), 3.64 (s, 3 H, C(11)H_3), 2.61 (d, *J* = 7.4 Hz, 2 H, C(5)H_2), 2.25-2.33 (m, 2 H, C(9)H_2), 2.14-2.21 (m, 2 H, C(8)H_2), 1.23 (t, *J* = 7.1 Hz, 6 H, C(1)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 173.1 (*C*(10)), 170.6 (*C*(3) x 2), 131.9 (*C*(6)), 119.3 (*C*(7)), 61.3 (*C*(2) x 2), 56.5 (*C*(4)), 51.6 (*C*(11)), 37.5 (*C*(5)), 29.1 (*C*(9)), 27.5 (*C*(8)), 14.0 (*C*(1) x 2) ppm; LRMS *m/z* (ESI^+) 309 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 309.13021, $C_{14}H_{22}O_6Na^+$ requires 309.13086; ν_{max} 2981 (w), 1734 (s, ester C=O), 1437 (m), 1201 (m), 1148 (m), 1085 (w), 1020 (m) cm^{-1}.

6.3.25 Preparation of 335



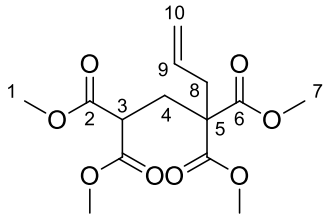
3,3-Diethyl 1,1-dimethyl hex-5-ene-1,1,3,3-tetracarboxylate: To a solution of LiHMDS (1 M in THF, 245 µL, 0.245 mmol, 2.40 eq) in anhydrous THF (0.51 mL) at −78 °C was added a solution of ester **334** (29.2 mg, 0.102 mmol, 1.00 eq) in anhydrous THF (0.51 mL) dropwise. The solution was stirred for 20 min, then methyl chloroformate (15.7 µL, 0.294 mmol, 2.00 eq) was added dropwise. The resultant mixture was allowed to warm to ambient temperature. After 12 h, a 1:1 solution of sat. aq. NH_4Cl and H_2O (1 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 2 mL) and the combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (6:1 PE/EtOAc) to give **335** as a clear, colourless oil (2.5 mg, 7%) and retro-Michael product **333** as a clear, colourless oil (2.3 mg, 0.011 mmol, 11%). δ_H (400 MHz, $CDCl_3$) 5.56-5.71 (m, 1 H, C(6)*H*), 5.04-5.18 (m, 2 H, C(7)H_2), 4.05-4.23 (m, 4 H, C(2)H_2 x 2), 3.71 (s, 6 H, C(11)H_3 x 2), 3.61 (t, *J* = 6.0 Hz, 1 H, C(9)*H*), 2.64 (d, *J* = 7.5 Hz, 2 H, C(5)H_2), 2.52 (d, *J* = 6.0 Hz, 2 H, C(8)H_2), 1.23 (t, *J* = 7.1 Hz, 6 H, C(1)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 170.4 (O=*C* x 2), 169.5 (O=*C*(10)), 131.7 (*C*(6)), 119.7 (*C*(7)), 61.5 (*C*(2) x 2), 56.2 (*C*(4)), 52.7 (*C*(11) x 2), 47.8 (*C*(9)), 38.2 (*C*(5)), 31.4 (*C*(8)), 13.9 (*C*(1) x 2) ppm; LRMS *m/z* (ESI^+) 345 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 345.15361, $C_{16}H_{25}O_6^+$ requires 345.15439; ν_{max} 2962 (w), 1735 (s, ester C=O), 1437 (w), 1365 (w), 1221 (m), 1149 (w) cm^{-1}.

6.3.26 Preparation of 337



Tetramethyl propane-1,1,3,3-tetracarboxylate:[190] The following method was modified from a reported literature procedure.[191] To a mixture of dimethyl malonate (1.65 mL, 14.4 mmol, 4.00 eq) and paraformaldehyde (110 mg, 3.60 mmol, 1.00 eq) was added 2 drops of a 2 M KOH solution in EtOH. The mixture was heated to 70 °C for 8 h, then purified by flash column chromatography (6:1 PE/EtOAc) to give **337** as a clear, colourless oil (854 mg, 86%). δ_H (400 MHz, $CDCl_3$) 3.72 (s, 12 H, C(1)*H*$_3$ x 2 and C(7)*H*$_3$ x 2), 3.48 (t, *J* = 7.5 Hz, 2 H, C(3)*H* and C(5)*H*), 2.46 (t, *J* = 7.5 Hz, 2 H, C(4)*H*$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 168.8 (*C*(2) x 2 and *C*(6) x 2), 52.7 (*C*(1) x 2 and *C*(7) x 2), 48.9 (*C*(3) and *C*(5)), 27.3 (*C*(4)) ppm.

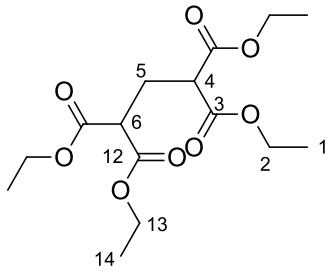
6.3.27 Preparation of 338



Tetramethyl hex-5-ene-1,1,3,3-tetracarboxylate: Tetraester **337** (674 mg, 2.44 mmol, 1.00 eq) was added to a suspension of 60% NaH (98.0 mg, 2.56 mmol, 1.05 eq) in anhydrous DMF (4.9 mL) at 0 °C. After 25 min, allyl bromide (211 µL, 2.44 mmol, 1.00 eq) was added and the solution was allowed to warm to ambient temperature. After 14 h, 1 M HCl (5 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatograph (6:1 PE/EtOAc) to give **338** as a clear, colourless oil (337 mg, 44%). δ_H (400 MHz, $CDCl_3$)

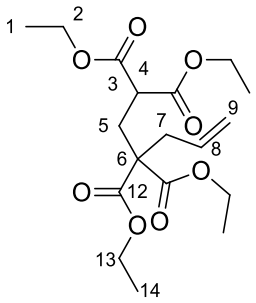
5.67-5.84 (m, 1 H, C(9)*H*), 5.07-5.14 (m, 2 H, C(10)H_2), 3.70 (s, 6 H, C(7)H_3 x 2), 3.67 (s, 6 H, C(1)H_3 x 2), 3.59 (t, *J* = 6.1 Hz, 1 H, C(3)*H*), 2.63 (d, *J* = 7.5 Hz, 2 H, C(8)H_2), 2.50 (d, *J* = 6.1 Hz, 2 H, C(4)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 170.8 (*C*(6) x 2), 169.4 (*C*(2) x 2), 131.5 (*C*(9)), 119.8 (*C*(10)), 56.3 (*C*(5)), 52.7 (*C*(1) x 2), 52.5 (*C*(7) x 2), 47.8 (*C*(3)), 38.3 (*C*(8)), 31.5 (*C*(4)) ppm; LRMS *m/z* (ESI^+) 317 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 317.12229, $C_{14}H_{21}O_8^+$ requires 317.12309; ν_{max} 2956 (w), 1730 (s, ester C=O), 1435 (m), 1201 (m), 1148 (m) cm^{-1}.

6.3.28 Preparation of 341



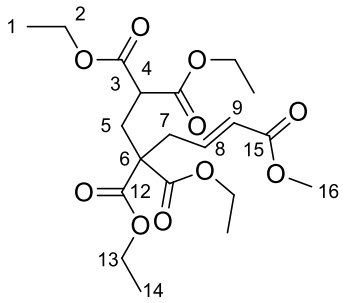
Tetraethyl propane-1,1,3,3-tetracarboxylate:[192] The following method was modified from a reported literature procedure.[191] To a mixture of diethyl malonate (2.19 mL, 14.4 mmol, 4.00 eq) and paraformaldehyde (110 mg, 3.60 mmol, 1.00 eq) was added 2 drops of a 10% KOH solution in EtOH. The mixture was heated to 70 °C for 8 h, then purified by flash column chromatography (8:1 to 6:1 PE/EtOAc) to give **341** as a clear, colourless oil (912 mg, 76%). δ_H (400 MHz, $CDCl_3$) 4.17-4.25 (m, 8 H, C(2)H_2 x 2 and C(13)H_2 x 2), 3.48 (t, *J* = 7.6 Hz, 2 H, C(4)*H* and C(6)*H*), 2.48 (t, *J* = 7.6 Hz, 2 H, C(5)H_2), 1.28 (t, *J* = 7.2 Hz, 12 H, C(1)H_3 x 2 and C(14)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 168.6 (*C*(3) x 2 and *C*(12) x 2), 61.6 (*C*(2) x 2 and *C*(13) x 2), 49.4 (*C*(4) and C(6)), 27.3 (*C*(5)), 14.0 (*C*(1) x 2 and *C*(14) x 2) ppm.

6.3.29 Preparation of 342



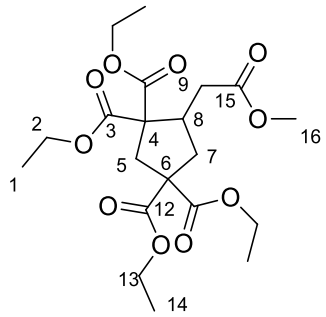
Tetraethyl hex-5-ene-1,1,3,3-tetracarboxylate: Tetraester **341** (500 mg, 1.50 mmol, 1.00 eq) was added to a suspension of 60% NaH (60.0 mg, 1.58 mmol, 1.05 eq) in anhydrous DMF (3.0 mL) at 0 °C. After 25 min, allyl bromide (130 µL, 1.50 mmol, 1.00 eq) was added and the solution was allowed to warm to ambient temperature. After 14 h, 1 M HCl (5 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatograph (10:1 PE/EtOAc) to give **342** as a clear, colourless oil (258 mg, 46%). δ_H (400 MHz, $CDCl_3$) 5.64 (ddt, *J* = 17.1, 10.0, 7.4 Hz, 1 H, C(8)*H*), 5.03-5.17 (m, 2 H, C(9)H_2), 4.05-4.22 (m, 8 H, C(2)H_2 x 2 and C(13)H_2 x 2), 3.53 (t, *J* = 5.9 Hz, 1 H, C(4)*H*), 2.63 (d, *J* = 7.4 Hz, C(7)H_2), 2.52 (d, *J* = 5.9 Hz, 2 H, C(5)H_2), 1.19-1.28 (m, 12 H, C(1)H_3 x 2 and C(14)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 170.6 (O=*C* x 2), 169.3 (O=*C* x 2), 131.9 (*C*(8)), 119.8 (*C*(9)), 61.7 (*C*(2) x 2), 61.6 (*C*(13) x 2), 56.5 (*C*(6)), 48.3 (*C*(4)), 38.2 (*C*(7)), 31.3 (*C*(5)), 14.1 (*C*(1) x 2), 14.1 (*C*(14) x 2) ppm; LRMS *m/z* (ESI^+) 373 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 373.18519, $C_{18}H_{29}O_8^+$ requires 373.18569; ν_{max} 2983 (w), 1730 (s, ester C=O), 1642 (w), 1466 (w), 1278 (m), 1222 (m), 1018 (m) cm^{-1}.

6.3.30 Preparation of 343



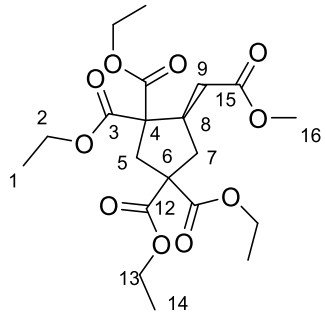
1,1,3,3-Tetraethyl 6-methyl (5*E*)-hex-5-ene-1,1,3,3,6-pentacarboxylate: Hoveyda-Grubbs II catalyst (11.0 mg, 0.0174 mmol, 0.0470 eq) was added to a solution of **342** (138 mg, 0.371 mmol, 1.00 eq) and methyl acrylate (134 µL, 1.64 mmol, 4.40 eq) in 3.7 mL anhydrous CH_2Cl_2 (0.1 M) under N_2. The mixture was stirred at ambient temperature and, after 15 h, the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (6:1 PE/EtOAc) to yield the title compound as a clear, colourless oil (89.3 mg, 56%). δ_H (400 MHz, $CDCl_3$) 5.85 (d, *J* = 15.6 Hz, 1 H, C(9)*H*), 4.04-4.25 (m, 8 H, C(13)H_2 x 2 and C(2)H_2 x 2), 3.69 (s, 3 H, C(16)H_3), 3.50 (t, *J* = 5.9 Hz, 1 H, C(4)*H*), 2.75 (dd, *J* = 7.8, 1.2 Hz, 2 H, C(7)H_2), 2.51 (d, *J* = 5.9 Hz, 2 H, C(5)H_2), 1.16-1.28 (m, 12 H, C(1)H_3 x 2 and C(14)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) 170.0 (O=*C* x 2), 169.1 (O=*C* x 2), 166.2 (*C*(15)), 142.3 (*C*(8)), 125.2 (*C*(9)), 61.9 (*C*(2) x 2), 61.8 (*C*(13) x 2), 56.3 (*C*(6)), 51. 6 (*C*(16)), 48.3 (*C*(4)), 36.7 (*C*(7)), 31.7 (*C*(5)), 14.0 (*C*(1) x 2), 14.0 (*C*(14) x 2) ppm; LRMS *m/z* (ESI^+) 431 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 453.17220, $C_{20}H_{30}O_{10}Na^+$ requires 453.17312; ν_{max} 2984 (w), 1724 (s, ester C=O), 1660 (w), 1440 (w), 1369 (w), 1273 (m), 1173 (m), 1095 (m), 1016 (m), 857 (m) cm^{-1}.

6.3.31 Preparation of (±)-344



Tetraethyl 4-(2-methoxy-2-oxoethyl)cyclopentane-1,1,3,3-tetracarboxylate: Obtained according to general procedure 3A using **343** (34 mg, 0.079 mmol) and Cs_2CO_3 (13 mg, 0.040 mmol). The title product was obtained following flash column chromatography (5:1 PE/EtOAc) as a clear, colourless oil (19 mg, 55%). Spectroscopic data match those reported for the enantioenriched product, **(+)-344**, below.

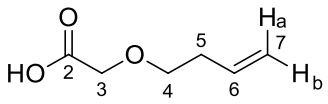
6.3.32 Preparation of (+)-344



(+)-Tetraethyl-4-(2-methoxy-2-oxoethyl)cyclopentane-1,1,3,3-tetracarboxylate: Obtained according to general procedure 3B using **343** (39 mg, 0.091 mmol), Cs_2CO_3 (15 mg, 0.045 mmol) and **C52** (3.5 mg, 0.0091 mmol) in toluene (0.69 mL). The title product was obtained following flash column chromatography (5:1 PE/EtOAc) as a clear, colourless oil (27 mg, 70%). The ee was determined by HPLC [Chiralpak AD-H, hexane/*iso*-propanol 95:5, λ 210 nm, 1.0 mL/min] t (minor) = 23.2 min., t (major) = 24.9 min. (11% ee). $[\alpha]_D^{20}$ = +5.4 (*c* 0.77, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.11-4.26 (m, 8 H, C(2)H_2 x 2 and C(13)H_2

x 2), 3.67 (s, 3 H, C(16)*H*$_3$), 3.01-3.09 (m, 1 H, C(8)*H*), 2.99 (d, *J* = 14.6 Hz, 1 H, C(9)*H'*H"), 2.87 (d, *J* = 14.6, 1 H, C(9)H'*H"*), 2.79-2.85 (m, 1 H, C(5)*H'*H"), 2.59 (dd, *J* = 13.7, 6.9 Hz, 1 H, C(7)*H'*H"), 2.17-2.29 (m, 2 H, C(5)H'*H"* and C(7)H'*H"*), 1.20-1.31 (m, 12 H, C(1)*H*$_3$ x 2 and C(14)*H*$_3$ x 2) ppm; δ_C (100 MHz, $CDCl_3$) 172.3 (O=*C*), 171.8 (O=*C*), 170.9 (O=*C*), 170.3 (O=*C*), 170.3 (O=*C*), 62.0 (*C*(2)'), 61.9 (*C*(2)"), 61.7 (*C*(13) x 2), 61.6 (*C*(4)), 57.9 (*C*(6)), 51.7 (*C*(16)), 41.3 (*C*(8)), 40.6 (*C*(9)), 38.4 (*C*(7)), 35.2 (*C*(5)), 14.0 (*C*(1) x 2), 13.9 (*C*(14) x 2) ppm; LRMS *m/z* (ESI^+) 431 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 431.18979, $C_{20}H_{31}O_{10}^+$ requires 431.19117; ν_{max} 2987 (w), 1727 (s, ester C=O), 1442 (w), 1370 (w), 1237 (m), 1201 (m), 1097 (m) cm^{-1}.

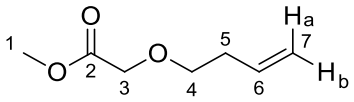
6.3.33 Preparation of 347



(But-3-en-1-yloxy)acetic acid:[193] The title compound was prepared using a known literature procedure.[193] 3-Buten-1-ol (950 µL, 11.0 mmol, 1.10 eq) was added dropwise to a stirred suspension of NaH (60% in mineral oil, 1.20 g, 30.0 mmol, 3.00 eq) in 16.5 mL anhydrous THF (16.5 mL) at 0 °C. After 15 min, a solution of bromoacetic acid (1.4 g, 10.0 mmol, 1.0 eq) in 2.7 mL THF (3.7 M) was added dropwise, then the solution was heated to reflux. After 2.5 h, 15 mL of H_2O was added and the aqueous layer was washed with Et_2O (2 x 15 mL). The aqueous layer was acidified to pH 1 with 2 M HCl, then extracted with Et_2O (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the title compound as a clear, colourless oil (1.175 g, 92%) used in the next step without further purification. δ_H (400 MHz, $CDCl_3$) 7.96 (br s, 1 H, O*H*), 5.80 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1 H, C(6)*H*), 5.11 (dd, *J* = 17.1, 1.5 Hz, 1 H, C(7)H_aH_b), 5.06 (d, *J* = 10.3 Hz, 1 H, C(7)H_aH_b), 4.12 (s, 2 H, C(3)*H*$_2$), 3.61 (t, *J* = 6.7 Hz, 2 H, C(4)*H*$_2$), 2.38 (app. q, *J*

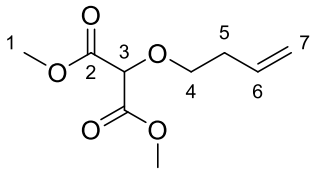
= 6.7 Hz, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 175.2 (*C*(2)), 134.6 (*C*(6)), 117.1 (*C*(7)), 71.2 (*C*(4)), 67.8 (*C*(3)), 34.0 (*C*(5)) ppm.

6.3.34 Preparation of 348



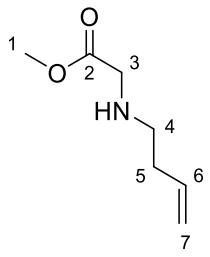
Methyl (but-3-en-1-yloxy)acetate:[194] DMAP (42 mg, 0.34 mmol, 5 mol%) and DCC (1.60 g, 7.75 mmol, 1.10 eq) were added sequentially to a solution of **347** (918 mg, 7.06 mmol, 1.00 eq) in CH_2Cl_2 (17.6 mL, 0.400 M) at 0 °C. The resulting cloudy, colourless suspension turned yellow after 5 min. Methanol (1.14 mL, 14.1 mmol, 2.0 eq) was added, and the yellow colour disappeared. The mixture was allowed to warm to ambient temperature overnight. After 15 h, the mixture was filtered, and the filtrate was concentrated *in vacuo* then purified by flash column chromatography (9:1 PE/EtOAc) to **348** as a clear, colourless oil (622 mg, 62%). δ_H (400 MHz, $CDCl_3$) 5.83 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1 H, C(6)*H*), 5.12 (d, *J* = 17.1 Hz, 1 H, C(7)H_aH$_b$), 5.06 (d, *J* = 10.3 Hz, 1 H, C(7)H$_a$$H_b$), 4.09 (s, 2 H, C(3)$H_2$), 3.75 (s, 3 H, C(1)$H_3$), 3.59 (t, *J* = 6.7 Hz, 2 H, C(4)H_2), 2.39 (app. q, *J* = 6.7 Hz, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 171.0 (*C*(2)), 134.8 (*C*(6)), 116.8 (*C*(7)), 71.2 (*C*(4)), 68.4 (*C*(3)), 51.9 (*C*(1)), 34.1 (*C*(5)) ppm.

6.3.35 Preparation of 349



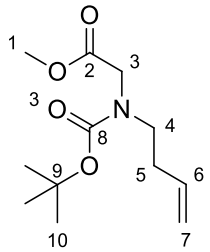
Dimethyl (but-3-en-1-yloxy)propanedioate: To a solution of LiHMDS (1 M in THF, 9.55 mL, 9.55 mmol, 2.40 eq) in anhydrous THF (20 mL) at −78 °C was added a solution of ester **348** (574 mg, 4.41 mmol, 1.00 eq) in anhydrous THF (20 mL) dropwise. The solution was stirred for 20 min, then methyl chloroformate (613 µL, 8.82 mmol, 2.00 eq) was added dropwise. The resultant mixture was allowed to warm to ambient temperature. After 12 h, a 1:1 solution of H_2O and sat. aq. NH_4Cl (20mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (9:1 PE/EtOAc) to give **349** as a clear, colourless oil (789 mg, 88%). δ_H (400 MHz, $CDCl_3$) 5.81 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1 H, C(6)*H*), 5.02-5.16 (m, 2 H, C(7)H_2), 4.53 (s, 1 H, C(3)*H*), 3.81 (s, 6 H, C(1)H_3 x 2), 3.64 (t, *J* = 6.8 Hz, 2 H, C(4)H_2), 2.43 (app. q, *J* = 6.8 Hz, 2 H, C(5)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 167.1 (*C*(2) x 2), 134.2 (*C*(6)), 117.2 (*C*(7)), 79.2 (*C*(3)), 70.9 (*C*(4)), 53.1 (*C*(1) x 2), 33.9 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 225 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 225.07313, $C_9H_{14}O_5Na^+$ requires 225.07334; ν_{max} 2958 (w), 1743 (s, ester C=O), 1641 (w), 1438 (m), 1294 (m), 1236 (m), 1134 (m), 1050 (m), 920 (m) cm^{-1}.

6.3.36 Preparation of 353



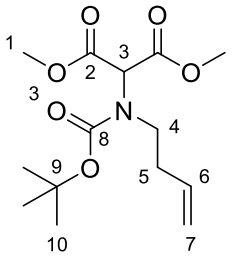
Methyl *N*-but-3-en-1-ylglycinate: Methyl bromoacetate (250 µL, 97%, 2.72 mmol, 1.00 eq) was added to a vigorously stirred suspension of homoallylamine (97%, 335 µL, 3.77 mmol, 1.40 eq) and K_2CO_3 (365 mg, 2.64 mmol, 1.00 eq) in 10.5 mL MeCN (0.25 M). After 16 hours, 10 mL H_2O was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (4:1 EtOAc/PE) to give the title compound as a clear, colourless oil (349 mg, 92%). δ_H (300 MHz, $CDCl_3$) 5.68-5.92 (m, 1 H, C(6)*H*), 4.97-5.19 (m, 2 H, C(7)*H*$_2$), 3.73 (s, 3 H, C(1)*H*$_3$), 3.43 (s, 2 H, C(3)*H*$_2$), 2.67 (t, *J* = 6.8 Hz, 2 H, C(4)*H*$_2$), 2.27 (app q, *J* = 6.8, 2 H, C(5)*H*$_2$), 1.87 (br s, 1 H, N*H*); δ_C (75 MHz, $CDCl_3$) 172.8 (*C*(2)), 136.0 (*C*(6)), 116.5 (*C*(7)), 51.7 (*C*(1)), 50.6 (*C*(3)), 48.4 (*C*(4)), 34.2 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 144 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 144.10182, $C_7H_{14}O_2N^+$ requires 144.10191; ν_{max} 2956 (br w, C-H and N-H stretch), 1730 (m, ester C=O), 1695 (m), 1651 (w), 1435 (w), 1197 (m), 1151 (m) cm^{-1}.

6.3.37 Preparation of 354



Methyl *N*-but-3-en-1-yl-*N*-(*tert*-butoxycarbonyl)glycinate: Methyl 3-(allylamino)propanoate **353** (223 mg, 1.56 mmol, 1.00 eq) and treithylamine (1.07 mL, 7.67 mmol, 4.90 eq) in CH_2Cl_2 (10 mL, 0.16 M) were cooled to 0 °C, and di-*tert*-butyl dicarbonate (504 mg, 2.30 mmol, 1.50 eq) was added in one portion. The resulting mixture was allowed to warm to ambient temperature. After 16 h, the mixture was concentrated *in vacuo* and the resulting crude product was purified by flash column chromatograph (8:1 PE/EtOAc) to give a clear, colourless oil (249 mg, 66%) characterized as a 1:1 mix of rotamers. δ_H (300 MHz, $CDCl_3$) peaks reported for approx. 1:1 mixture of rotamers: 5.64-5.87 (m, 1 H, C(6)*H*), 4.93-5.13 (m, 2 H, C(7)H_2), 3.95 (s, 1 H, C(3)H_2), 3.86 (s, 1 H, C(3)H_2), 3.72 (s, 3 H, C(1)H_3), 3.25-3.39 (m, 2 H, C(4)H_2), 2.23-2.31 (m, 2 H, C(5)H_2), 1.46 (s, 4.5 H, C(10)H_3 x 3), 1.40 (s, 4.5 H, C(10)H_3 x 3) ppm; δ_C (75 MHz, $CDCl_3$) visible peaks reported for approx. 1:1 mixture of rotamers: 170.7 (*C*(2)), 155.8 (*C*(8)), 155.2 (*C*(8)), 135.4 (*C*(6)), 116.9 (*C*(7)), 116.8 (*C*(7)), 80.4 (*C*(9)), 80.3 (*C*(9)), 52.1 (*C*(1)), 49.6 (*C*(3)), 48.94 (*C*(3)), 48.2 (*C*(4)), 48.0 (*C*(4)), 33.2 (*C*(5)), 32.8 (*C*(5)), 28.5 (*C*(10)), 28.4 (*C*(10)) ppm; LRMS *m/z* (ESI^+) 509 (100%, $[2M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 266.13554, $C_{12}H_{21}O_4NNa^+$ requires 266.13628; ν_{max} 2970 (w), 1743 (m, C=O), 1697 (m, C=O), 1366 (m), 1206 (m), 1147 (m) cm^{-1}.

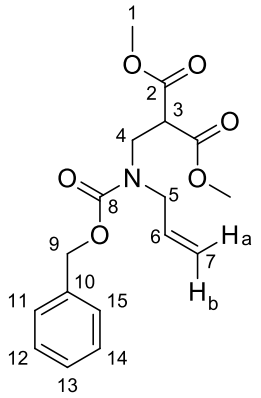
6.3.38 Preparation of 355



Dimethyl [but-3-en-1-yl(*tert*-butoxycarbonyl)amino]propanedioate: LiHMDS (1.0 M in THF, 2.23 mL, 2.23 mmol, 2.40 eq) was diluted with 4.6 mL THF (0.33 M) and cooled to −78 °C. A solution of **354** (226 mg, 0.930 mmol, 1.00 eq) in 4.6 mL THF (0.20 M) was added dropwise. The solution was stirred for 15 min, then methyl chloroformate (144 µL, 1.86 mmol, 2.00 eq) was added dropwise. The resulting solution was allowed to warm to ambient temperature. After 15 h, a 1:1 solution of H_2O and sat. aq. NH_4Cl (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (8:1 PE/EtOAc) to give the title compound as a clear colourless oil (180 mg, 64%) which was characterized as a 1:1 mixture of rotamers. δ_H (300 MHz, $CDCl_3$) peaks reported for approx. 1:1 mixture of rotamers: 5.48-5.72 (m, 1 H, C(6)*H*), 5.10 (s, 0.5 H, C(3)*H*), 4.80-4.98 (m, 2 H, C(7)H_2), 4.53 (s, 0.5 H, C(3)*H*), 3.64 (s, 6 H, C(1)H_3 x 2), 3.09-3.29 (m, 2 H, C(4)*H*), 2.16 (app. q, *J* = 7.2 Hz, 2 H, C(5)H_2), 1.33 (s, 4.5 H, C(10)H_3 x 3), 1.26 (s, 4.5 H, C(10)H_3 x 3) ppm; δ_C (75 MHz, $CDCl_3$) visible peaks reported for approx. 1:1 mixture of rotamers: 167.5 (*C*(2) x 2), 167.0 (C(*2*) x 2), 155.6 (*C*(8)), 154.4 (*C*(8)), 135.3 (*C*(6)), 135.2 (*C*(6)), 116.8 (*C*(7)), 116.6 (*C*(7)), 81.5 (*C*(9)), 81.3 (*C*(9)), 63.8 (*C*(3)), 62.3 (*C*(3)), 52.9 (*C*(1) x 2), 48.3 (*C*(4)), 47.3 (*C*(4)), 33.8 (*C*(5)), 33.0 (*C*(5)), 28.4 (*C*(10) x 3), 28.2 (*C*(10) x 3) ppm; LRMS *m/z* (ESI^+) 324 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found

$[M+Na]^+$ 324.14087, $C_{14}H_{23}O_6NNa^+$ requires 324.14176; ν_{max} 2979 (w), 1760 (s, C=O), 1697 (s, C=O), 1410 (m), 1296 (m), 1160 (s), 1026 (m), 775 (m) cm^{-1}.

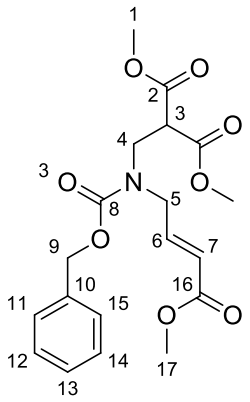
6.3.39 Preparation of 360



Dimethyl ({[(benzyloxy)carbonyl](prop-2-en-1-yl)amino}methyl)propanedioate: TMSCl (0.930 mL, 7.84 mmol, 3.00 eq) was added to a solution of benzyl allyl amine (463 mg, 2.62 mmol, 1.00 eq) and paraformaldehyde (109 mg, 3.92 mmol, 1.50 eq) in 6.3 mL CH_2Cl_2. The mixture was stirred at ambient temperature for 2 hours, then concentrated under a stream of nitrogen. In a separate vessel, dimethylmalonate (415 µL, 3.64 mmol, 1.40 eq) was added dropwise to a suspension of NaH (60% in mineral oil, 159 mg, 3.99 mmol, 1.50 eq) in THF (3.3 mL) and DMF (3.3 mL) at 0 °C. This mixture was stirred at ambient temperature for 45 min. Crude **359** was dissolved in 10.7 mL CH_2Cl_2 and added dropwise to the deprotonated malonate solution. The resultant mixture was stirred at ambient temperature for 13 h, then 4.4 mL 1 M HCl were added. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H_2O (2 x 10 mL) and brine (1 x 10 mL) then dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash column chromatography (2:1 PE/EtOAc) to give the title compound as a clear colourless oil (581 mg, 66% over 2 steps). δ_H (400 MHz, $CDCl_3$) peaks reported for approx. 1:1 mixture of rotamers: 7.27-7.54 (m, 5 H, C(Ar)*H* x 5), 5.74 (m, 1 H, C(6)*H*), 5.05-5.30 (m, 4 H, C(7)H_2 and C(9)H_2), 3.85-4.02 (m, 2.5 H, C(3)*H* and C(5)H_2), 3.74-3.82

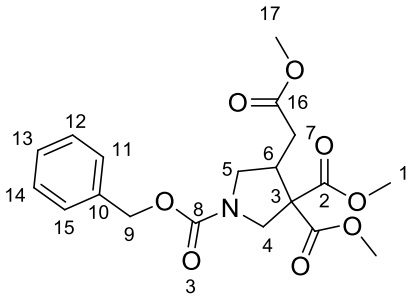
(m, 2.5 H, C(3)*H* and C(4)*H*), 3.72 (br s, 3 H, C(1)H_3 x 2), 3.67 (br s, 3 H, C(1)H_2 x 2) ppm; converged to a single compound at high temperature δ_H (500 MHz, 363 K, toluene-d8) 7.16-7.20 (m, 2 H, C(Ar)*H* x 2), 7.06-7.11 (m, 2 H, C(Ar)*H* x 2), 7.00-7.04 (m, 1 H, C(13)*H*), 5.62 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1 H, C(6)*H*), 5.01 (s, 2 H, C(9)H_2), 4.97 (d, *J* = 17.2 Hz, 1 H, C(7)H_a), 4.91 (d, *J* = 10.4 Hz, 1 H, C(7)H_b), 3.88-3.99 (m, 1 H, C(3)*H*), 3.79-3.86 (m, 4 H, C(5)H_2 and C(4)H_2), 3.33 (s, 6 H, C(1)H_3 x 2) ppm; δ_C (100 MHz, $CDCl_3$) visible peaks reported for approx. 1:1 mixture of rotamers: 168.6 (*C*(2) x 2), 168.4 (*C*(2) x 2), 156.2 (*C*(8)), 155.9 (*C*(8)), 136.6 (*C*(10)), 133.1 (*C*(10)), 128.6 (*C*(Ar)), 128.2 (*C*(Ar)), 128.1 (*C*(Ar)), 128.0 (*C*(Ar)), 127.9 (*C*(Ar)), 117.6 (*C*(7)), 117.0 (*C*(7)), 67.6 (*C*(9)), 67.4 (*C*(9)), 52.8 (*C*(1) x 2), 51.3 (*C*(3)), 51.1 (*C*(5)), 51.0 (*C*(5)), 50.6 (*C*(3)), 46.9 (*C*(4)), 45.7 (*C*(4)) ppm; LRMS *m/z* (ESI^+) 358 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 358.12522, $C_{17}H_{21}O_6NNa^+$ requires 358.12611; ν_{max} 2954 (w), 1734 (s, C=O), 1700 (s, C=O), 1467 (m), 1435 (m), 1241 (s), 1153 (m), 771 (m) cm^{-1}.

6.3.40 Preparation of 361



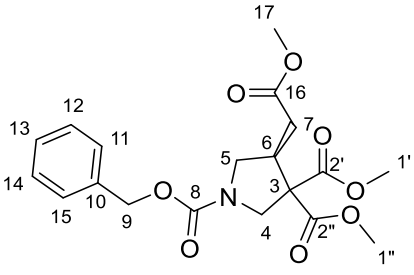
Dimethyl ({[(benzyloxy) carbonyl] [(2*E*)-4-methoxy-4-oxobut-2-en-1-yl]amino}methyl)propanedioate: Hoveyda-Grubbs II catalyst (8.3 mg, 0.013 mmol, 0.025 eq) was added to a solution of **360** (200 mg, 0.600 mmol, 1.00 eq) and methyl acrylate (216 µL, 2.40 mmol, 4.00 eq) in 6 mL CH_2Cl_2. After 9 h, the mixture was concentrated *in vacuo* and purified by flash column chromatography (4:1 PE/EtOAc) to give the title compound as a brown oil (156 mg, 66%). Spectroscopic data is reported for a mixture of rotamers. δ_H (400 MHz, $CDCl_3$ 7.28-7.41 (m, 5 H, C(Ar)*H* x 5), 6.77-6.89 (m, 1 H, C(6)*H*), 5.77-5.92 (m, 1 H, C(7)*H*), 5.10-5.20 (m, 2 H, C(9)H_2), 4.09 (br s, 2 H, C(5)H_2), 3.86-4.03 (m 1 H, C(3)*H*), 3.66-3.82 (m, 11 H, C(1)H_3 x 2, C(4)H_2 and C(17)H_3) ppm; δ_C (100 MHz, $CDCl_3$) visible peaks reported for a mixture of rotamers: 168.3 (O=*C*), 168.1 (O=*C*), 166.3 (O=*C*), 155.8 (*C*(8)), 143.6 (*C*(6)), 143.0 (*C*(6)), 136.1 (*C*(10)), 128.5 (*C*(Ar)), 128.5 (*C*(Ar)), 128.2 (*C*(Ar)), 128.1 (*C*(Ar)), 128.0 (*C*(Ar)), 122.2 (*C*(7)), 121.9 (*C*(7)), 67.9 (*C*(9)), 67.7 (*C*(9)), 52.8 (*C*(1) x 2), 51.6 (*C*(17)), 50.6 (*C*(3)), 49.6 (*C*(5)), 49.5 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 416 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 416.13082, $C_{19}H_{23}O_8NNa^+$ requires 416.13159; ν_{max} 3035 (w), 2955 (w), 1703 (s, C=O), 1456 (m), 1273 (m), 1170 (m), 735 (m), 699 (m) cm^{-1}.

6.3.41 Preparation of (±)-362



1-Benzyl 3,3-dimethyl 4-(2-methoxy-2-oxoethyl)pyrrolidine-1,3,3-tricarboxylate (racemate): Prepared according to general procedure 3A using **361** (26 mg, 0.065 mmol), Cs_2CO_3 (10.5 mg, 0.0325 mmol) and tetrabutylammonium bromide (2.0 mg, 0.0065 mmol) in toluene (0.5 mL). The title compound was isolated by flash column chromatography (4:1 PE/EtOAc) as a clear, colourless oil (13.4 mg, 52%). Spectroscopic data are identical to those reported for the enantioenriched sample, **(+)-362**, below.

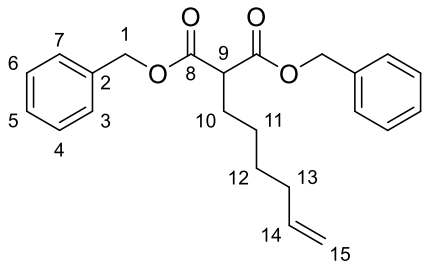
6.3.42 Preparation of (+)-362



(+)-1-Benzyl 3,3-dimethyl-4-(2-methoxy-2-oxoethyl)pyrrolidine-1,3,3-tricarboxylate: Obtained according to general procedure 3B using **361** (35 mg, 0.090 mmol), Cs_2CO_3 (15 mg, 0.045 mmol) and **C52** (3.5 mg, 0.0045 mmol) in toluene (0.69 mL). The title compound was isolated by flash column chromatography (4:1 PE/EtOAc) as a clear, colourless oil (8.0 mg, 23%). The ee was determined by HPLC [Chiralpak AD-H, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min] t (minor) = 35.0 min., t (major) = 49.0 min. (26% ee). $[\alpha]_D^{20}$ = +12.2 (*c* 0.430, $CHCl_3$); δ_H (500 MHz, 363 K, toluene-d8) 7.22-7.26 (m, 1 H, C(Ar)*H*), 7.01-7.13

(m, 4 H, C(Ar)*H* x 4), 5.09 (s, 2 H, C(9)*H*$_2$), 4.12 (d, *J* = 11.9 Hz, 1 H, C(4)*H'*H"), 3.91-3.98 (m, 1 H, C(5)*H'*H"), 3.74 (d, *J* = 11.9 Hz, 1 H, C(4)H'*H"*), 3.30-3.36 (m, 7 H, C(1)*H*$_3$ x 2 and C(5)H'*H"*), 3.27 (s, 3 H, C(17)*H*$_3$), 3.10-3.18 (m, 1 H, C(6)*H*), 2.84 (dd, *J* = 16.3, 3.9 Hz, 1 H, C(7)*H'*H"), 2.12 (dd, *J* = 16.3, 10.4 Hz, 1 H, C(7)H'*H"*) ppm; δ_C (125 MHz, 363 K, toluene-d8) 170.8 (*C*(16)), 168.9 (*C*(2)'), 168.6 (*C*(2)"), 153.9 (*C*(8)), 137.3 (*C*(10)), 128.6 (*C*(Ar)), 128.1 (*C*(Ar) x 2), 127. 7 (*C*(Ar) x 2), 76.9 (*C*(3)), 66.6 (*C*(9)), 51.8 (*C*(4)), 51.7 (*C*(17)), 51.4 (*C*(1)'), 50.5 (*C*(1)"), 50.4 (*C*(5)), 40.3 (*C*(6)), 33.7 (*C*(7)) ppm; LRMS *m/z* (ESI$^+$) 416 (100%, [M+Na]$^+$); HRMS *m/z* (ESI$^+$) found [M+Na]$^+$ 416.13041, $C_{19}H_{23}O_8NNa^+$ requires 416.13159; ν_{max} 2950 (w), 1735 (s, C=O), 1710 (s, C=O), 1447 (m), 1240 (m), 1160 (m) cm^{-1}.

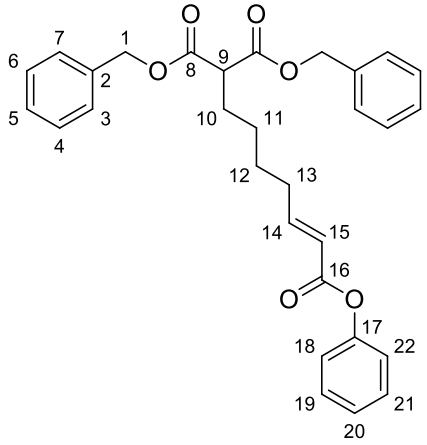
6.3.43 Preparation of 363



Dibenzyl hex-5-en-1-ylpropanedioate: Dibenzylmalonate (3.00 mL, 12.0 mmol, 1.00 eq) was added to a suspension of NaH (60% suspension in mineral oil, 552 mg, 13.8 mmol, 1.15 eq), in 11 mL anhydrous THF at 0 °C. The resulting mixture was allowed to warm to ambient temperature, then 6-bromo-1-hexene (1.92 mL, 14.4 mmol, 1.20 eq) and 11 mL anhydrous DMF were added sequentially. The solution was heated to reflux for 13 h, allowed to cool to ambient temperature, and then 15 mL 1 M HCl and 15 mL Et_2O were added. The layers were separated, and the aqueous layer was extracted Et_2O (2 x 15 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (1 x 15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by

flash column chromatography (25:1 PE/EtOAc) to give the title compound as a clear, colourless oil (2.70 g, 62%). δ_H (400 MHz, $CDCl_3$) 7.29-7.47 (m, 10 H, C(Ar)*H* x 10), 5.70-5.88 (m, 1 H, C(14)*H*), 5.19 (s, 4 H, C(1)H_2 x 2), 4.93-5.08 (m, 2 H, C(15)H_2), 3.42-3.55 (m, 1 H, C(9)*H*), 1.96-2.09 (m, 4 H, C(13)H_2 and C(10)H_2), 1.31.-1.49 (m, 4 H, C(11)H_2 and C(12)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 169.2 (*C*(8) x 2), 138.5 (*C*(14)), 135.5 (*C*(2) x 2), 128.6 (*C*(Ar) x 4), 128.2 (*C*(5) x 2), 128.2 (*C*(Ar) x 4), 114.7 (*C*(15)), 67.0 (*C*(1) x 2), 51.0 (*C*(9)), 33.4 (*C*(13)), 28.7 (*C*(10)), 28.4 (*C*(12)), 26.7 (*C*(11)) ppm; LRMS *m/z* (ESI^+) 367 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 389.17161, $C_{23}H_{26}O_4Na^+$ requires 389.17233; ν_{max} 3066 (w), 3033 (w), 2929 (w), 1732 (s, ester C=O), 1640 (w), 1455 (w), 1215 (m), 1145 (m), 735 (m), 695 (s) cm^{-1}.

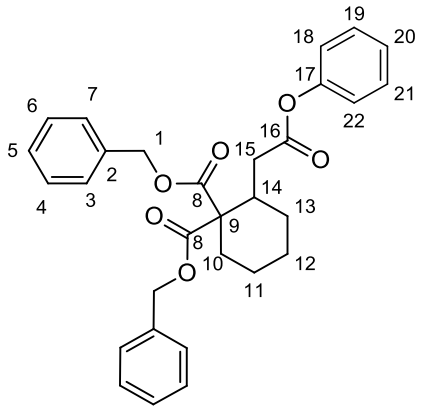
6.3.44 Preparation of 364



1,1-Dibenzyl 7-phenyl (6*E*)-hept-6-ene-1,1,7-tricarboxylate: Hoveyda-Grubbs II catalyst (14 mg, 0.022 mmol, 0.022 eq) was added to a solution of **363** (366 mg, 1.00 mmol, 1.00 eq) and phenyl acrylate (550 µL, 3.45 mmol, 3.50 eq) in 10.0 mL anhydrous CH_2Cl_2 (0.1 M) under N_2. The mixture was stirred at ambient temperature and, after 14 h, the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (8:1 PE/EtOAc) to yield the title compound as a clear, colourless oil (431 mg, 89%). δ_H (400 MHz, $CDCl_3$) 7.27-7.43 (m, 11 H, C(Ar)*H* x 11), 7.20-7.25 (m, 2 H,

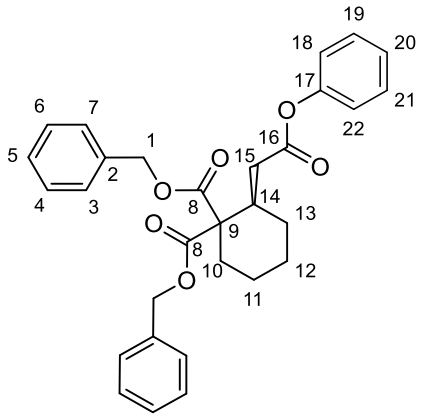
C(Ar)*H* x 2), 7.07-7.16 (m, 3 H, C(Ar)*H* x 2 and C(14)*H*), 5.99 (d, *J* = 15.7 Hz, 1 H, C(15)*H*), 5.16 (s, 4 H, C(1)H_2 x 2), 3.45 (t, *J* = 7.5 Hz, 1 H, C(9)*H*), 2.19-2.27 (m, 2 H, C(13)H_2), 1.97 (app q, *J* = 7.5 Hz, 2 H, C(10)H_2), 1.46-1.54 (m, 2 H, C(12)H_2), 1.31-1.41 (m, 2 H, C(11)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 169.2 (*C*(8) x 2), 165.0 (*C*(16)), 151.1 (*C*(14)), 150.9 (*C*(17)), 135.5 (*C*(2) x 2), 129.5 (*C*(Ar) x 2), 128.7 (*C*(Ar) x 4), 128.5 (*C*(Ar) x 2), 128.3 (*C*(Ar) x 4), 125.8 (*C*(20)), 121.8 (*C*(Ar) x 2), 121.0 (*C*(15)), 67.3 (*C*(1) x 2), 52.0 (*C*(9)), 32.2 (*C*(13)), 28.6 (*C*(10)), 27.7 (*C*(12)), 26.9 (*C*(11)) ppm; LRMS *m/z* (ESI^+) 509 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 509.19278, $C_{30}H_{30}O_6Na^+$ requires 509.19346; ν_{max} 3077 (w), 2963 (w), 1756 (s, ester C=O), 1739 (ester C=O), 1719 (s, ester C=O), 1440 (m), 1373 (s), 1227 (s) cm^{-1}.

6.3.45 Preparation of (±)-365



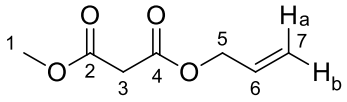
Dibenzyl 2-(2-oxo-2-phenoxyethyl)cyclohexane-1,1-dicarboxylate: Obtained according to general procedure 3A using **364** (63 mg, 0.13 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol) in toluene (1.0 mL). The title compound was isolated by flash column chromatography (8:1 PE/EtOAc) as a clear, colourless oil (41 mg, 65%). Spectroscopic data are identical to those reported for the enantioenriched product, **(−)-365**, below.

6.3.46 Preparation of (−)-365



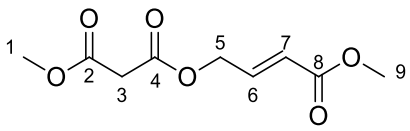
(−)-Dibenzyl 2-(2-oxo-2-phenoxyethyl)cyclohexane-1,1-dicarboxylate: Obtained according to general procedure 3B using **364** (63 mg, 0.13 mmol), Cs_2CO_3 (21 mg, 0.065 mmol) and **C52** (5 mg, 0.0065 mmol) in toluene (1.0 mL). The title compound was isolated by flash column chromatography (8:1 PE/EtOAc) as a clear, colourless oil (48 mg, 77%). [Chiralpak OD-H, hexane/*iso*-propanol 95:5, λ 210 nm, 1.0 mL/min] t (minor) = 12.5 min., t (major) = 15.2 min. (40% ee). $[\alpha]_D^{20} = -3.7$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.27-7.44 (m, 12 H, C(Ar)*H* x 12), 7.21-7.27 (m, 1 H, C(20)*H*), 7.07 (d, *J* = 8.2 Hz, 2 H, C(Ar)*H* x 2), 5.08-5.25 (m, 4 H, C(1)H_2 x 2), 2.68-2.87 (m, 3 H, C(15)H_2 and C(14)*H*), 2.29-2.38 (m, 1 H, C(10)*H'*H"), 1.87-2.05 (m, 2 H, C(10)H'*H"* and C(13)*H'*H"), 1.64-1.76 (m, 1 H, C(12)*H'*H"), 1.52-1.64 (m, 2 H, C(13)H'*H"* and C(11)*H'*H"), 1.41-1.52 (m, 2 H, C(11)H'*H"* and C(12)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 171.4 (*C*(8) x 2), 170.3 (*C*(16)), 150.9 (*C*(17)), 135.6 (*C*(2)'), 135.5 (*C*(2)"), 129.5 (*C*(Ar) x 2), 128.7 (*C*(Ar) x 2), 128.7 (*C*(Ar) x 2), 128.4 (*C*(5)'), 128.4 (*C*(5)"), 128.4 (*C*(Ar) x 2), 128.2 (*C*(Ar) x 2), 125.8 (*C*(20)), 121.7 (*C*(Ar) x 2), 67.3 (*C*(1)'), 67.0 (*C*(1)"), 58.8 (*C*(9)), 38.1 (*C*(14)), 36.9 (*C*(15)), 32.1 (*C*(10)), 28.3 (*C*(13)), 24.1 (*C*(12)), 22.5 (*C*(11)) ppm; LRMS *m/z* (ESI^+) 509 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 509.19260, $C_{30}H_{30}O_6Na^+$ requires 509.19346; ν_{max} 3033 (w), 2936 (w), 1757 (m, ester C=O), 1725 (m, ester C=O), 1493 (m), 1455 (m), 1246 (m), 1192 (m), 1133 (m), 747 (m), 696 (m) cm^{-1}.

6.3.47 Preparation of 368



Methyl prop-2-en-1-yl propanedioate:[195] Allyl alcohol (748 µL, 11.0 mmol, 1.10 eq) and triethylamine (2.09 mL, 15.0 mmol, 1.50 eq) were sequentially added to a stirred solution of methyl 3-chloro-3-oxopropanoate (1.07 mL, 10.0 mmol, 1.00 eq) in CH_2Cl_2 (28 mL, 0.36 M). After 5 h, 20 mL 1 M HCl was added and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (1 x 20 mL), H_2O (1 x 20 mL) and brine (1 x 20 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5:1 PE/EtOAc) to give a very pale yellow oil (1.126 g, 72%). δ_H (400 MHz, $CDCl_3$) 5.78-5.92 (m, 1 H, C(6)*H*), 5.22-5.31 (m, 1 H, C(7)H_aH_b), 5.14-5.22 (m, 1 H, C(7)H_a*H*$_b$), 2.53-4.62 (m, 2 H, C(5)*H*$_2$), 3.67 (s, 3 H, C(1)*H*$_3$), 3.34 (s, 2 H, C(3)*H*$_2$) ppm; δ_C (100 MHz, $CDCl_3$) 166.8 (O=*C*), 166.0 (O=*C*), 131.5 (*C*(6)), 118.5 (*C*(7)), 65.9 (*C*(5)), 52.4 (*C*(1)), 41.1 (*C*(3)) ppm.

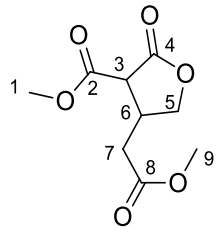
6.3.48 Preparation of 369



(2*E*)-4-Methoxy-4-oxobut-2-en-1-yl methyl propanedioate: Hoveyda-Grubbs II catalyst (33 mg, 0.053 mmol, 0.025 eq) was added to a solution of **368** (360 mg, 2.00 mmol, 1.00 eq) and methyl acrylate (386 µL, 4.29 mmol, 4.10 eq) in 20 mL CH_2Cl_2 (0.1 M). The resulting solution was stirred at ambient temperature. After 11 h, the solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography (7:2 PE/EtOAc) to yield the title compound as a clear, colourless oil (251 mg, 58%). δ_H

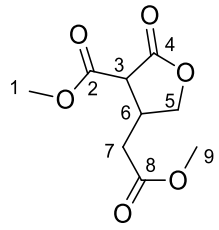
(400 MHz, $CDCl_3$) 6.90 (dt, *J* = 15.8, 4.5 Hz, 1 H, C(6)*H*), 6.03 (dt, *J* = 15.8, 1.9 Hz, 1 H, C(7)*H*), 4.79 (dd, *J* = 4.5, 1.9 Hz, 2 H, C(5)H_2), 3.73 (s, 3 H, C(9)H_3), 3.72 (s, 3 H, C(1)H_3), 3.43 (s, 2 H, C(3)H_2) ppm; δ_C (100 MHz, $CDCl_3$) 166.7 (O=*C*), 166.2 (O=*C*), 165.8 (O=*C*), 140.7 (*C*(6)), 122.2 (*C*(7)), 63.5 (*C*(5)), 52.7 (*C*(1)), 51.8 (*C*(9)), 41.1 (*C*(3)) ppm; LRMS *m/z* (ESI^+) 239 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 239.05244, $C_9H_{12}O_6Na^+$ requires 239.05244; ν_{max} 2956 (w, C-H stretch), 1721 (s, ester C=O stretch), 1667 (m), 1436 (m), 1273 (m), 1145 (s), 1017 (m) cm^{-1}.

6.3.49 Preparation of (±)-370



Methyl 4-(2-methoxy-2-oxoethyl)-2-oxotetrahydrofuran-3-carboxylate: Obtained according to general procedure 3A using **369** (28 mg, 0.13 mmol) and Cs_2CO_3 (21 mg, 0.065 mmol) in toluene (1.0 mL). The title compound was obtained *via* flash column chromatography (2:1 PE/EtOAc) as a clear, colourless oil (19 mg, 69%) and a mixture of diastereomers (9:1 dr). Spectroscopic data match those reported for sample **370**, below.

6.3.50 Attempted asymmetric preparation of 370



Methyl 4-(2-methoxy-2-oxoethyl)-2-oxotetrahydrofuran-3-carboxylate: Obtained according to general procedure 3B using **369** (28 mg, 0.13 mmol), Cs_2CO_3 (21 mg, 0.065 mmol) and **C52** (5.0 mg, 0.0065 mmol) in toluene (1.0 mL). The title compound was isolated as a clear colourless oil (8.1 mg, 29%) and a mixture of diastereomers (9:1 dr) using flash column chromatography (2:1 PE/EtOAc). The ee for the major diastereomer was determined by HPLC analysis [Chiralpak OD-H, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min] t_1 = 32.6 min., t_2 = 48.4 min. (0% ee). δ_H (400 MHz, $CDCl_3$) 4.65 (dd, *J* = 9.0, 7.5 Hz, 1 H, C(7)*H'*H"), 3.98-4.03 (m, 1 H, C(7)H'*H"*), 3.83 (s, 3 H, C(1)H_3), 3.70 (s, 3 H, C(9)H_3), 3.31-3.42 (m, 2 H, C(3)*H* and C(6)*H*), 2.64 (dd, *J* = 16.8, 6.1 Hz, 1 H, C(5)*H'*H"), 2.55 (dd, *J* = 16.8, 7.5 Hz, 1 H, C(5)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 171.1 (*C*=O), 170.9 (*C*=O), 167.4 (*C*(8)), 71.3 (*C*(7)), 53.2 (*C*(1)), 52.1 (*C*(9)), 51.4 (*C*(3)), 36.1 (*C*(6)), 35.8 (*C*(5)) ppm; LRMS *m/z* (ESI^+) 455 (100%, $[2M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 217.07043, $C_9H_{13}O_6^+$ requires 217.07066; ν_{max} 3081 (w), 2964 (w), 2856 (w), 1753 (s), 1720 (s), 1709 (s), 1443 (m), 1371 (s), 1205 (s) cm^{-1}.

6.4 Chapter 4 Experimental

6.4.1 General procedure 4A

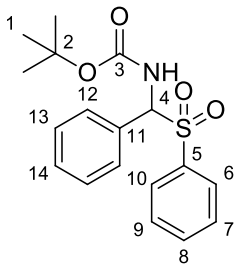
The corresponding amido sulfone (**414**, **417**-**438**) (0.144 mmol, 1.0 eq) was suspended in MTBE (1.4 mL) under an inert atmosphere. Nitroalkane (0.72 mmol, 5 eq) and catalyst **C51** (5.4 mg, 7.2 μmol, 5 mol%) were added sequentially, and the resulting mixture was cooled to −20 °C in a Thermo Scientific EK90 immersion cooler. Freshly ground KOH (40.4 mg, 0.720 mmol, 5.0 eq) was added and the resulting suspension was vigorously stirred at −20 °C. After 12 h, 5 mL sat. aq. $NaHCO_3$ was added and the solution was allowed to warm to ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), then the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography.

6.4.2 Determination of stereochemical configuration

The absolute stereochemical configuration of **411** was established by comparing its specific rotation to literature values[196] (reported for (*S*)-enantiomer, 82% ee: $[\alpha]_D^{20}$ = +18.9 (*c* 0.5, $CHCl_3$); measured for (*R*)-**411**, 89% ee: $[\alpha]_D^{20}$ = −24.0 (*c* 0.500, $CHCl_3$)). The absolute stereochemical configurations of **440**-**447** were determined by analogy.

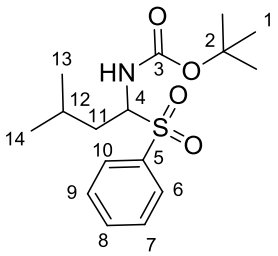
The relative stereochemistry of **373** was established by comparison of ^{1}H-NMR with the literature.[161] The relative stereochemical configurations of **464**-**476** were determined by analogy.

6.4.3 Preparation of 414



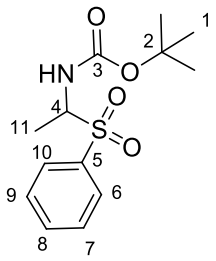
***tert*-Butyl [phenyl(phenylsulfonyl)methyl]carbamate:**[197] Sodium benzenesulfinate (14 g, 85 mmol, 2.0 eq) and *tert*-butyl carbamate (5.0 g, 43 mmol, 1.0 eq) were suspended in 41 mL methanol and 82 mL distilled water under air. Benzaldehyde (6.5 mL, 64 mmol, 1.5 eq) and formic acid (3.2 mL) were added sequentially and the mixture was stirred vigorously at ambient temperature for 3 days. The resulting suspension was filtered and the white precipitate was washed with water (3 x 10 mL) and diethyl ether (3 x 10 mL), then dried under vacuum. The title product was obtained as a white solid (9.7 g, 65%). MP 175-176 °C; δ_H (400 MHz, $CDCl_3$) 7.93 (d, *J* = 7.6 Hz, 2 H, C(Ar)*H* x 2), 7.65 (t, *J* = 7.3 Hz, 1 H, C(8)*H*), 7.54 (t, *J* = 7.6 Hz, 2 H, C(Ar)*H* x 2), 7.38-7.49 (m, 5 H, C(Ar)*H* x 5), 5.95 (d, *J* = 10.7 Hz, 1 H, C(4)*H*), 5.84 (d, *J* = 10.7 Hz, 1 H, N*H*), 1.26 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (100 MHz, $CDCl_3$) 153.4 (*C*(3)), 136.9 (*C*(5)), 133.9 (*C*(8)), 129.9 (*C*(Ar) x 2), 129.8 (*C*(Ar) x 2), 129.5 (*C*(Ar) x 2), 129.0 (*C*(Ar) x 2), 128.9 (*C*(Ar)), 128.8 (*C*(Ar)), 81.2 (*C*(2)), 73.9 (*C*(4)), 28.0 (*C*(1) x 3) ppm.

6.4.4 Preparation of 417



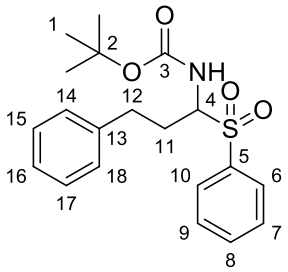
***tert*-Butyl [3-methyl-1-(phenylsulfonyl)butyl]carbamate:**[198] *tert*-Butyl carbamate (3.15 g, 26.9 mmol, 1.00 eq) was dissolved in THF (11 mL). Distilled water (27 mL), sodium benzenesulfinate (4.42 g, 26.9 mmol, 1.00 eq), isovaleraldehyde (3.2 mL, 29 mmol, 1.1 eq) and formic acid (6.5 mL) were added sequentially. The mixture was stirred vigorously at ambient temperature for 24 h, and the resulting white precipitate was collected via filtration. The solid was triturated from water, filtered, recrystallized twice from hexane/ethyl acetate (4:1), filtered, and dried under vacuum to give the title product as a white solid (3.2 g, 36%). MP 116-118 °C; δ_H (400 MHz, $CDCl_3$) 7.88-7.95 (m, 2 H, C(Ar)*H* x 2), 7.57-7.64 (m, 1 H, C(8)*H*), 7.48-7.57 (m, 2 H, C(Ar)*H* x 2), 5.16 (d, *J* = 10.8 Hz, 1 H, N*H*), 4.92 (td, *J* = 10.8, 3.0 Hz, 1 H, C(4)*H*), 1.93-2.05 (m, 1 H, C(11)*H'*H"), 1.68-1.84 (m, 2 H, C(11)H'*H"* and C(12)*H*), 1.18 (s, 9 H, C(1)H_3 x 3), 0.98 (d, *J* = 6.4 Hz, 3 H, C(13)H_3), 0.91 (d, *J* = 6.4 Hz, 3 H, C(14)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 153.6 (*C*(3)), 136.8 (*C*(5)), 133.7 (*C*(8)), 129.2 (*C*(Ar) x 2), 128.9 (*C*(Ar) x 2), 80.5 (*C*(2)), 69.5 (*C*(4)), 34.3 (*C*(11)), 27.9 (*C*(1) x 3), 24.6 (*C*(12)), 23.1 (*C*(13)), 21.0 (*C*(14)) ppm; LRMS *m/z* (ESI^+) 677 (100%, $[2M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 350.13923, $C_{16}H_{25}O_4NSNa^+$ requires 350.13965; ν_{max} 3243 (w, N-H stretch), 3143 (w), 2959 (w), 1705 (s, C=O), 1364 (m), 1144 (s) cm^{-1}.

6.4.5 Preparation of 418



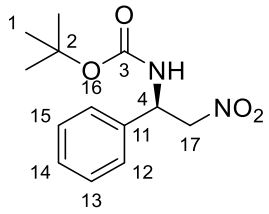
***tert*-Butyl [1-(phenylsulfonyl)ethyl]carbamate:**[199] *tert*-Butyl carbamate (3.15 g, 26.9 mmol, 1.00 eq) was dissolved in THF (11 mL). Distilled water (27 mL), sodium benzenesulfinate (4.42 g, 26.9 mmol, 1.00 eq), acetaldehyde (1.6 mL, 29 mmol, 1.1 eq) and formic acid (6.5 mL) were added sequentially. The mixture was stirred vigorously at ambient temperature for 40 h, and the resulting white precipitate was collected via filtration. The solid was triturated from water, filtered, triturated from diethyl ether, filtered, and dried under vacuum to give the title product as a white solid (3.52 g, 46%). MP 132.1-132.7 °C; δ_H (500 MHz, $CDCl_3$) 7.92 (d, *J* = 7.5 Hz, 2 H, C(Ar)*H* x 2), 7.64 (t, *J* = 7.5 Hz, 1 H, C(8)*H*), 7.55 (t, *J* = 7.5 Hz, 2 H, C(Ar)*H* x 2), 5.05-5.15 (m, 1 H, N*H*), 4.92-5.03 (m, 1 H, C(4)*H*), 1.63 (d, *J* = 6.9 Hz, 3 H, C(11)H_3), 1.22 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) 153.5 (*C*(3)), 136.8 (*C*(5)), 134.0 (*C*(8)), 129.5 (*C*(Ar) x 2), 129.2 (*C*(Ar) x 2), 81.0 (*C*(2)), 66.9 (*C*(4)), 28.1 (*C*(1) x 3), 13.1 (*C*(11)) ppm.

6.4.6 Preparation of 419



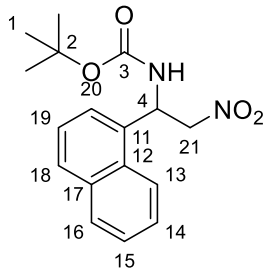
***tert*-Butyl [3-phenyl-1-(phenylsulfonyl)propyl]carbamate:** *tert*-Butyl carbamate (3.15 g, 26.9 mmol, 1.00 eq) was dissolved in THF (11 mL). Distilled water (27 mL), sodium benzenesulfinate (4.42 g, 26.9 mmol, 1.00 eq), 3-phenylpropanal (4.2 g, 29 mmol, 1.1 eq) and formic acid (6.5 mL) were added sequentially. The mixture was stirred vigorously at ambient temperature for 40 h, and the resulting white precipitate was collected via filtration. The solid was triturated from water, filtered, triturated from diethyl ether, filtered, and dried under vacuum to give the title product as a white solid (2.13 g, 21%). MP 129-131 °C; δ_H (400 MHz, $CDCl_3$) 7.85-8.01 (m, 2 H, C(Ar)*H* x 2), 7.63-7.73 (m, 1 H, C(8)*H*), 7.51-7.63 (m, 2 H, C(Ar)*H* x 2), 7.29-7.40 (m, 2 H, C(Ar)*H* x 2), 7.24-7.26 (m, 1 H, C(16)*H*), 7.19-7.24 (m, 2 H, C(Ar)*H* x 2), 5.19 (d, *J* = 10.8 Hz, 1 H, N*H*), 4.91 (td, *J* = 10.8, 3.2 Hz, 1 H, C(4)*H*), 2.85-3.03 (m, 1 H, C(12)*H'*H"), 2.71-2.85 (m, 1 H, C(12)H'*H"*), 2.56-2.71 (m, 1 H, C(11)*H'*H"), 2.03-2.24 (m, 1 H, C(11)H'*H"*), 1.27 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (100 MHz, $CDCl_3$) 153.6 (*C*(3)), 139.7 (*C*(13)), 136.7 (*C*(5)), 133.8 (*C*(8)), 129.2 (*C*(Ar) x 2), 129.0 (*C*(Ar) x 2), 128.6 (*C*(Ar) x 2), 128.4 (*C*(Ar) x 2), 126.4 (*C*(16)), 80.7 (*C*(2)), 70.2 (*C*(4)), 31.4 (*C*(12)), 28.0 (*C*(11)), 27.9 (*C*(1) x 3) ppm; LRMS *m/z* (ESI^+) 398 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 398.13906, $C_{20}H_{25}O_4NSNa^+$ requires 398.13965; ν_{max} 3350 (w, N-H stretch), 3053 (w), 2980 (w), 1691 (s, C=O), 1510 (m), 1318 (m), 1136 (s) cm^{-1}.

6.4.7 Preparation of (*R*)-411



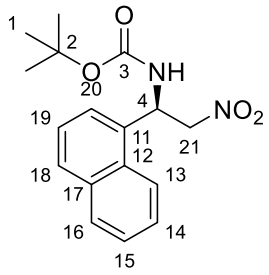
***tert*-Butyl [(1*R*)-2-nitro-1-phenylethyl]carbamate:**[165] Obtained according to general procedure 4A using **414** (50.0 mg, 0.144 mmol) and nitromethane (39 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (neat CH_2Cl_2) to yield 30.3 mg (79%) of product as a white solid. The ee was determined by HPLC [Chiralpak AD-H, hexane/*iso*-propanol 95:5, λ 210 nm, 0.8 mL/min] t (major) = 32.7 min., t (minor) = 31.4 min. (89% ee). $[\alpha]_D^{20}$ = –24.0 (*c* 0.500, $CHCl_3$); MP 98-99 °C; δ_H (500 MHz, $CDCl_3$) 7.41-7.29 (m, 5 H, C(Ar)*H* x 5), 5.37 (br s, 2 H, C(4)*H* and N*H*), 4.85 (br s, 1 H, C(17)*H'*H''), 4.78-4.62 (m, 1 H, C(17)H'*H''*), 1.44 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) 154.7 (*C*(3)), 136.8 (*C*(11)), 129.1 (*C*(Ar)*H* x 2), 128.7 (*C*(14)), 126.3 (*C*(Ar)*H* x 2), 80.6 (*C*(2)), 78.8 (*C*(17)), 52.8 (*C*(4)), 28.2 (*C*(1) x 3) ppm.

6.4.8 Preparation of (±)-444



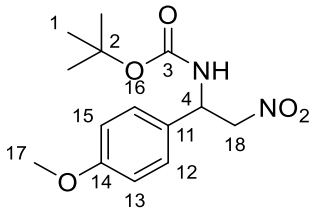
***tert*-Butyl [1-(naphthalen-1-yl)-2-nitroethyl]carbamate:** Amido sulfone **433** (119 mg, 0.300 mmol, 1.00 eq) was suspended in toluene (1.5 mL) in a microwave vial under N_2. Nitromethane (405 µL, 7.50 mmol, 25.0 eq) and TBAB (9.8 mg, 0.030 mmol, 0.10 eq) were added sequentially and the mixture was cooled to −66 °C. Ground KOH (84 mg, 1.5 mmol, 5.0 eq) was added and the vial was sealed and allowed to warm to −20 °C. After 12 h, 5 mL sat. aq. $NaHCO_3$ was added and the solution was allowed to warm to ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), then the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to give the title compound as a colourless solid (59 mg, 49%). All spectroscopic data are identical to the enantioenriched sample, **(*R*)-444**.

6.4.9 Preparation of (*R*)-444



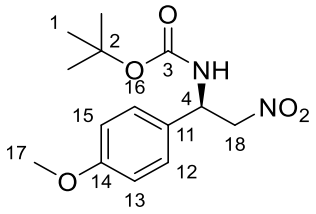
***tert*-Butyl [(1*R*)-1-(naphthalen-1-yl)-2-nitroethyl]carbamate:**[126] Obtained according to general procedure 4A using **433** (57.2 mg, 0.144 mmol) and nitromethane (39 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (neat CH_2Cl_2) to yield 42.2 mg (93%) of product as a white solid. The ee was determined by HPLC [Chiralpak AD-H, hexane/*iso*-propanol 95:5, λ 210 nm, 0.8 mL/min] t (major) = 32.7 min., t (minor) = 31.4 min. (86% ee). $[\alpha]_D^{20}$ = –10.9 (*c* 1.00, $CHCl_3$); MP 144-148 °C; δ_H (500 MHz, $CDCl_3$) 8.12 (d, *J* = 8.3 Hz, 1 H, C(Ar)*H*), 7.91 (d, *J* = 7.7 Hz, 1 H, C(Ar)*H*), 7.82-7.88 (m, 1 H, C(Ar)*H*), 7.51-7.66 (m, 2 H, C(Ar)*H* x 2), 7.43-7.48 (m, 2 H, C(Ar)*H* x 2), 6.22-6.34 (m, 1 H, C(4)*H*), 5.34 (d, *J* = 8.0 Hz, 1 H, N*H*), 4.82-4.95 (m, 2 H, C(21)H_2), 1.44 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) 154.7 (*C*(3)), 134.0 (*C*(Ar)), 132.6 (*C*(Ar)), 130.3 (*C*(Ar)), 129.5 (*C*(Ar)), 129.2 (*C*(Ar)), 127.3 (*C*(Ar)), 126.3 (*C*(Ar)), 125.2 (*C*(Ar)), 123.2 (*C*(Ar)), 122.1 (*C*(Ar)), 80.8 (*C*(2)), 78.3 (*C*(21)), 49.3 (*C*(4)), 28.2 (*C*(1) x 3) ppm.

6.4.10 Preparation of (±)-450



***tert*-Butyl [1-(4-methoxyphenyl)-2-nitroethyl]carbamate:** Amido sulfone **427** (151 mg, 0.400 mmol, 1.00 eq) was suspended in 4 mL toluene. Nitromethane (108 μL, 2.00 mmol, 5.00 eq), tetrabutylammonium bromide (13 mg, 0.040 mmol, 0.10 eq) and ground K_2CO_3 (276 mg, 2.00 mmol, 5.00 eq) were added sequentially and the resulting mixture was stirred at ambient temperature. After 24 h, 10 mL sat. aq. $NaHCO_3$ was added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (neat CH_2Cl_2) to yield 33.8 mg (29%) of **(±)-450**. Spectroscopic data are identical to those reported below for the enantioenriched sample, **(*R*)-450**.

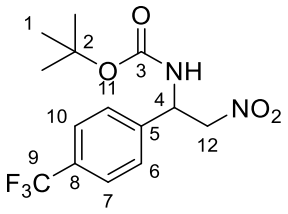
6.4.11 Preparation of (*R*)-450



***tert*-Butyl [(1*R*)-1-(4-methoxyphenyl)-2-nitroethyl]carbamate:**[152] Obtained according to general procedure 4A using *tert*-butyl [(4-methoxyphenyl)(phenylsulfonyl) methyl]carbamate **427** (54.4 mg, 0.144 mmol) and nitromethane (39 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2) to yield 35.4 mg (84%) of product as a white solid. The ee was determined by HPLC [Chiralpak AS,

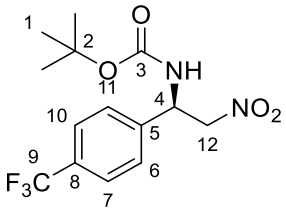
hexane/*iso*-propanol 90:10, λ 220 nm, 0.8 mL/min] t (minor) = 19.0 min., t (major) = 28.9 min. (90% ee). $[\alpha]_D^{20}$ = –33.3 (*c* 0.270, $CHCl_3$); MP 143-145 °C; δ_H (500 MHz, $CDCl_3$) δ 7.25-7.21 (m, 2 H, C(12)*H* and C(16)*H*), 6.92-6.87 (m, 2 H, C(13)*H* and C(15)*H*), 5.36-5.28 (m, 1 H, C(4)*H*), 5.24 (d, *J* = 7.5 Hz, 1 H, N*H*), 4.84 (br s, 1 H, C(18)*H'*H"), 4.67 (dd, *J* = 12.5, 5.5 Hz, 1 H, C(18)H'*H"*), 3.80 (s, 3 H, C(17)H_3), 1.44 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) δ 159.7 (*C*(14)), 154.7 (*C*(3)), 128.8 (*C*(11)), 127.6 (*C*(12) and *C*(16)), 114.5 (*C*(13) and *C*(15)), 80.5 (*C*(2)), 78.9 (*C*(18)), 55.3 (*C*(17)), 52.4 (*C*(4)), 28.2 (*C*(1) x 3) ppm.

6.4.12 Preparation of (±)-455



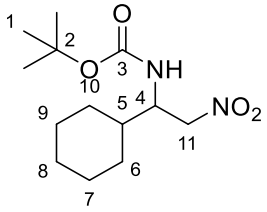
***tert*-Butyl {2-nitro-1-[4-(trifluoromethyl)phenyl]ethyl}carbamate:** Amido sulfone **423** (69 mg, 0.17 mmol, 1.0 eq) was suspended in 1.7 mL THF. Nitromethane (224 μL, 4.15 mmol, 24.0 eq) was added and the resulting mixture was cooled to 0 °C. Ground K_2CO_3 (115 mg, 0.830 mmol, 4.90 eq) was added and the mixture was maintained at 0 °C. After 36 h, 5 mL sat. aq. $NaHCO_3$ was added and the solution was allowed to warm to ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 10:1) to yield 50.9 mg (92%) of **(±)-455**. Spectroscopic data are identical to those reported for the enantioenriched product, **(*R*)-455**, below.

6.4.13 Preparation of (*R*)-455



***tert*-Butyl {(1*R*)-2-nitro-1-[4-(trifluoromethyl)phenyl]ethyl}carbamate:**[126] Obtained according to general procedure 4A using **432** (59.8 mg, 0.144 mmol) and nitromethane (39 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 6:1) to yield 31.3 mg (65%) of product as a white solid. The ee was determined by HPLC [Chiralpak AD, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min] t (major) = 17.0 min., t (minor) = 10.9 min. (91% ee). $[\alpha]_D^{20}$ = –8.1 (*c* 0.37, $CHCl_3$); MP 126-127 °C; δ_H (500 MHz, $CDCl_3$) 7.65 (d, *J* = 8.0 Hz, 2 H, C(7)*H* and C(10)*H*), 7.46 (d, *J* = 8.0 Hz, 2 H, C(6)*H* and C(11)*H*), 5.63-5.49 (m, 1 H, N*H*), 5.45 (br s, 1 H, C(4)*H*), 4.87 (br s, 1 H, C(12)*H'*H"), 4.79-4.67 (m, 1 H, C(12)H'*H"*), 1.45 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) 154.7 (*C*(3)), 140.9 (*C*(5)), 130.9 (q, J_{CF} = 32.0 Hz, *C*(8)), 126.8 (*C*(6) and *C*(11)), 126.1 (q, J_{CF} = 4.0 Hz, *C*(7) and *C*(10)), 123.7 (q, J_{CF} = 271.0 Hz, *C*(9)), 81.0 (*C*(2)), 78.5 (*C*(12)), 52.3 (*C*(4)), 28.2 (*C*(1) x 3) ppm.

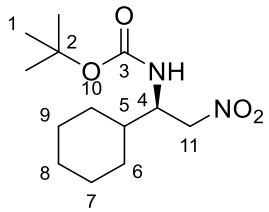
6.4.14 Preparation of (±)-456



***tert*-Butyl (1-cyclohexyl-2-nitroethyl)carbamate:** Amido sulfone **435** (106 mg, 0.300 mmol, 1.00 eq) was suspended in 3 mL toluene. Nitromethane (81 μL, 1.5 mmol, 5.0 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 0.10 eq) and ground K_2CO_3 (207 mg,

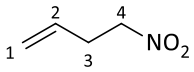
1.50 mmol, 5.0 eq) were added sequentially and the resulting mixture was stirred at ambient temperature. After 48 h, 10 mL sat. aq. $NaHCO_3$ was added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 6:1) to yield 62.6 mg (77%) of **(±)-456**. Spectroscopic data is identical to that obtained for the enantioenriched sample, **(*R*)-456**, below.

6.4.15 Preparation of (*R*)-456



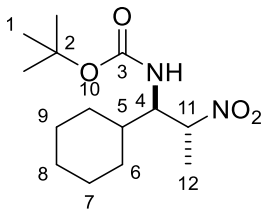
***tert*-Butyl [(1*R*)-1-cyclohexyl-2-nitroethyl]carbamate:**[126] Obtained according to general procedure 4A using **435** (50.9 mg, 0.144 mmol) and nitromethane (39 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 6:1) to yield 39.2 mg (100%) of product as a white solid. The ee was determined by HPLC analysis [Chiralpak AD-H, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min], t (major) = 7.2 min., t (minor) = 9.9 min. (84% ee). $[\alpha]_D^{20}$ = +5.1 (*c* 0.49, $CHCl_3$); MP 135-137 °C; δ_H (500 MHz, $CDCl_3$) 4.89 (d, *J* = 8.8 Hz, 1 H, N*H*), 4.58 (dd, *J* = 12.6, 6.3 Hz, 1 H, C(11)*H'*H"), 4.51 (dd, *J* = 12.6, 4.3 Hz, 1 H, C(11)H'*H"*), 4.00-3.90 (m, 1 H, C(4)*H*), 1.69-1.84 (m, 4 H, C(6)*H'*H", C(10)*H'*H", C(7)*H'*H" and C(9)*H'*H"), 1.61-1.68 (m, 1 H, C(8)*H'*H"), 1.47-1.57 (m, 1 H, C(5)*H*), 1.42 (s, 9 H, C(1)H_3 x 3), 1.10-1.25 (m, 3 H, C(7)H'*H"*, C(8)H'*H"* and C(9)H'*H"*), 0.94-1.07 (m, 2 H, C(6)H'*H"* and C(10)H'*H"*) ppm; δ_C (125 MHz, $CDCl_3$) 155.4 (*C*(3)), 80.1 (*C*(2)), 76.8 (*C*(11)), 54.0 (*C*(4)), 39.5 (*C*(5)), 29.9 (*C*(10)), 29.1 (*C*(6)), 28.4 (*C*(1) x 3), 26.1 (*C*(8)), 25.9 (*C*(7) and *C*(9)) ppm.

6.4.16 Preparation of 461



4-nitrobut-1-ene:[200] Silver nitrate (13.7 g, 88.8 mmol, 3.0 eq) was suspended in diethyl ether (40 mL). 4-Bromo-1-butene (3.01 mL, 29.6 mmol, 1.00 eq) was added and the mixture was heated to reflux. After 14 h, excess silver nitrate was removed via filtration and the filtrate was concentrated *in vacuo*. The crude oil was purified by distillation. The title compound was collected as a clear colourless oil (479 mg, 16%) at 26 °C (5.1 mbar). δ_H (500 MHz, $CDCl_3$) 5.76 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1 H, C(2)*H*), 5.10-5.23 (m, 2 H, C(1)H_2), 4.43 (t, *J* = 6.8 Hz, 2 H, C(4)H_2), 2.74 (q, *J* = 6.8 Hz, 2 H, C(3)H_2) ppm; δ_C (125 MHz, $CDCl_3$) 131.7 (*C*(2)), 118.8 (*C*(1)), 74.7 (*C*(4)), 31.3 (*C*(3)) ppm.

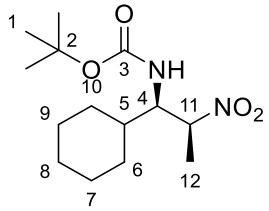
6.4.17 Preparation of (±)-469



***tert*-Butyl [(1*R**,2*R**)-1-cyclohexyl-2-nitropropyl]carbamate:** Amido sulfone **435** (106 mg, 0.300 mmol, 1.00 eq) was suspended in 3 mL toluene. Nitroethane (108 μL, 1.50 mmol, 5.00 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 5.00 eq) and ground K_2CO_3 (207 mg, 1.50 mmol, 5.00 eq) were added sequentially and the resulting mixture was stirred vigorously at ambient temperature. After 24 h, 10 mL sat. aq. $NaHCO_3$ was added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 10:1) to yield 71.9 mg (84%) of **(±)-469** as a mixture of diastereomers (dr = 1:4 (major *syn*), determined by ^{1}H-NMR analysis of the crude reaction mixture). NMR data only is reported

for the major (*syn*, 1*R**,2*R**) isomer. See below for full characterization of the *anti* diastereomer. δ_H (500 MHz, $CDCl_3$) 5.02 (d, *J* = 10.5 Hz, 1 H, N*H*), 4.90 (qd, *J* = 6.5, 4.0 Hz, 1 H, C(11)*H*), 3.64 (ddd, *J* = 10.5, 9.5, 4.0 Hz, 1 H, C(4)*H*), 1.85-1.69 (m, 4 H, C(6)*H'*H", C(7)*H'*H", C(9)*H'*H" and C(10)*H'*H"), 1.66-1.60 (m, 1 H, C(8)*H'*H"), 1.57 (d, *J* = 6.5 Hz, 3 H, C(12)H_3), 1.44 (s, 9 H, C(1)H_3 x 3), 1.37-1.28 (m, 1 H, C(5)*H*), 1.25-1.10 (m, 3 H, C(7)H'*H"*, C(8)H'*H"* and C(9)H'*H"*), 1.08-0.95 (m, 2 H, C(6)H'*H"* and C(10)H'*H"*) ppm; δ_C (125 MHz, $CDCl_3$) 156.3 (*C*(3)), 83.1 (*C*(2)), 79.8 (*C*(11)), 57.6 (*C*(4)), 40.0 (*C*(5)), 30.4 (*C*(10)), 29.4 (*C*(6)), 28.3 (*C*(1) x 3), 26.1 (*C*(8)), 25.8 (*C*(9)), 25.8 (*C*(7)), 17.2 (*C*(12)) ppm.

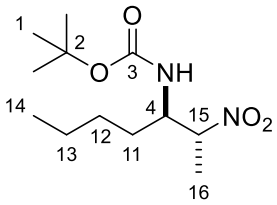
6.4.18 Preparation of (1*R*,2*S*)-469



***tert*-Butyl [(1*R*,2*S*)-1-cyclohexyl-2-nitropropyl]carbamate:**[128] Obtained according to general procedure 3A using **435** (50.9 mg, 0.144 mmol) and nitroethane (52 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 10:1) to yield 31.0 mg (75%) of product as a white solid and as a mixture of diastereomers (dr = 9:1, major *anti* (1*R*,2*S*), determined by ^{1}H NMR analysis of the crude reaction mixture). The ee was determined by HPLC analysis [Chiralpak IA, hexane/*iso*-propanol 97:3, λ 220 nm, 0.5 mL/min] ***major** (anti)*: t (major) = 28.2 min., t (minor) = 32.0 min. (95% ee), ***minor** (syn)*: t (major) = 14.4 min., t (minor) = 23.2 min. (36% ee). $[\alpha]_D^{20}$ = –4.1 (c 0.49, $CHCl_3$); MP 107-109 °C; δ_H (500 MHz, $CDCl_3$) 4.70-4.59 (m, 1 H, C(11)*H*), 4.46 (d, *J* = 10.0 Hz, 1 H, N*H*), 4.07-4.17 (m, 1 H, C(4)*H*), 1.83-1.71 (m, 3 H, C(6)*H'*H", C(7)*H'*H" and C(9)*H'*H"), 1.70-1.64 (m, 1 H, C(8)*H'*H"), 1.64-1.55 (m, 1 H, C(10)*H'*H"), 1.50 (d, *J* = 6.5

Hz, 3 H, C(12)H_3), 1.44 (s, 9 H, C(1)H_3 x 3), 1.39-1.30 (m, 1 H, C(5)*H*), 1.29-1.10 (m, 4 H, C(7)H'*H"*, C(8)H'*H"*, C(9)H'*H"* and C(10)H'*H"*), 1.05-0.94 (m, 1 H, C(6)H'*H"*) ppm; δ_C (125 MHz, $CDCl_3$) 155.6 (*C*(3)), 83.4 (*C*(11)), 80.2 (*C*(2)), 57.7 (*C*(4)), 39.3 (*C*(5)), 30.4 (*C*(10)), 28.4 (*C*(1) x 3), 27.8 (*C*(6)), 26.1 (*C*(8)), 26.0 (*C*(7)), 26.0 (*C*(9)), 14.7 (*C*(12)) ppm.

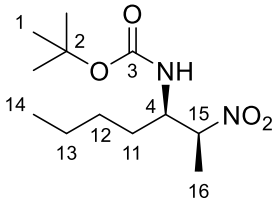
6.4.19 Preparation of (±)-472



***tert*-Butyl [(2*R**,3*R**)-2-nitroheptan-3-yl]carbamate:** Amido sulfone **437** (98 mg, 0.30 mmol, 1.0 eq) was dissolved in toluene (1.5 mL). Nitroethane (108 µL, 1.50 mmol, 5.00 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 0.10 eq), and ground anhydrous K_2CO_3 (207 mg, 1.50 mmol, 1.50 eq) were added sequentially and the mixture was stirred at ambient temperature. After 10 h, 5 mL sat. aq. $NaHCO_3$ was added; the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Integration of the crude ^{1}H NMR spectrum showed a dr of 1:1 (*anti*/*syn*). The crude reaction mixture was isolated as a 1:1 mixture of diastereomers by flash column chromatography (CH_2Cl_2) to give the product as a white solid (74 mg, 94%). A small sample of *syn*-enriched product was used to collect NMR data. NMR data is reported here for the *syn* (2*R**,3*R**) diastereomer only (see below for full characterization of the *anti*-addition product). δ_H (400 MHz, $CDCl_3$) 4.91 (br d, *J* = 9.9 Hz, 1 H, N*H*), 4.69-4.77 (m, 1 H, C(15)*H*), 3.85-3.95 (m, 1 H, C(4)*H*), 1.56 (d, *J* = 6.8 Hz, 3 H, C(16)H_3), 1.23-1.52 (m, 15 H, C(13)H_2, C(12)H_2, C(11)H_2 and C(1)H_3 x 3), 0.85-0.92 (m, 3 H, C(14)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 155.7 (*C*(3)), 85.6 (*C*(15)), 79.8 (*C*(2)),

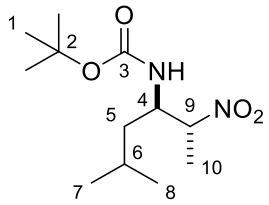
52.7 (*C*(4)), 31.9 (*C*(11)), 29.7 (*C*(12)), 28.3 (*C*(1) x 3), 22.2 (*C*(13)), 16.4 (*C*(16)), 13.8 (*C*(14)) ppm.

6.4.20 Preparation of (2*S*,3*R*)-472



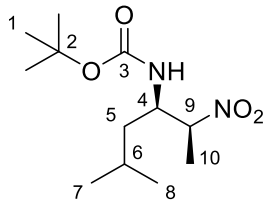
tert*-Butyl [(2*S*,3*R*)-2-nitroheptan-3-yl]carbamate:** Obtained according to general procedure 4A using **437** (47.2 mg, 0.144 mmol) and nitroethane (52 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2) to yield 31.0 mg (83%) of product as a white solid and as a mixture of diastereomers (dr = 11:1 (*anti*/*syn*), determined by ^{1}H NMR analysis of the crude reaction mixture). The ee was determined by HPLC analysis [Chiralpak AS-H, hexane/EtOH 99:1, λ 220 nm, 0.8 mL/min] ***major ***(anti)***: t (major) = 17.5 min., t (minor) = 21.0 min. (84% ee), ***minor*** ***(syn)***: t (minor) = 12.5 min., t (major) = 14.7 min. (40% ee). $[\alpha]_D^{20}$ = +27.9 (*c* 1.00, $CHCl_3$); MP 46-55 °C; δ_H (500 MHz, $CDCl_3$) 4.64-4.71 (m, 2 H, N*H* and C(15)*H*), 3.89-3.99 (m, 1 H, C(4)*H*), 1.52 (d, *J* = 6.9 Hz, 3 H, C(16)H_3), 1.44 (s, 9 H, C(1)H_3 x 3), 1.20-1.41 (m, 6 H, C(11)H_2, C(12)H_2 and C(13)H_2), 0.86-0.92 (m, 3 H, C(14)H_3) ppm; δ_C (125 MHz, $CDCl_3$) 155.4 (*C*(3)), 85.6 (*C*(15)), 80.0 (*C*(2)), 53.5 (*C*(4)), 29.3 (*C*(11)), 28.1 (*C*(12)), 28.3 (*C*(1) x 3), 22.2 (*C*(13)), 15.1 (*C*(16)), 13.8 (*C*(14)) ppm; LRMS *m/z* (ESI^+) 283 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 283.16225, $C_{12}H_{24}O_4N_2Na^+$ requires 283.16283; ν_{max} 3340 (w, N-H stretch), 2960 (w), 1693 (m, C=O), 1550 (m), 1391 (m), 1366 (m), 1248 (m), 1164 (m) cm^{-1}.

6.4.21 Preparation of (±)-473



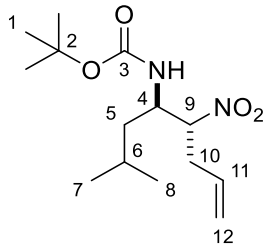
***tert*-Butyl [(2*R**,3*R**)-5-methyl-2-nitrohexan-3-yl]carbamate:** Amido sulfone **417** (98.2 mg, 0.300 mmol, 1.00 eq) was suspended in 1.5 mL toluene. Nitroethane (108 μL, 1.50 mmol, 5.00 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 0.10 eq) and ground K_2CO_3 (207 mg, 1.50 mmol, 5.00 eq) were added sequentially and the resulting mixture was stirred vigorously at ambient temperature. After 24 h, 10 mL sat. aq. $NaHCO_3$ was added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 15:1) to yield 31.5 mg (40%) of **(±)-473** as a mixture of diastereomers (dr = 1:1 (*anti*/*syn*), determined by ^{1}H NMR analysis of the crude reaction mixture). Selected NMR peaks corresponding to the *syn* diastereomer (2*R**,3*R**) reported only. See below for full characterization of the *anti* diastereomer. δ_H (400 MHz, $CDCl_3$) 4.89 (br d, *J* = 9.9 Hz, 1 H, N*H*), 4.66-4.74 (m, 1 H, C(9)*H*), 3.96-4.05 (m, 1 H, C(4)*H*), 1.62-1.75 (m, 1 H, C(6)*H*), 1.56 (d, *J* = 6.5 Hz, 3 H, C(10)H_3), 1.44 (s, 9 H, C(1)H_3 x 3), 1.33-1.41 (m, 1 H, C(5)*H'*H"), 1.22-1.31 (m, 1 H, C(5)H'*H"*), 0.89-0.97 (m, 6 H, C(7)H_3 and C(8)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 155.8 (*C*(3)), 86.2 (*C*(9)), 80.0 (*C*(2)), 51.0 (*C*(4)), 41.3 (*C*(5)), 28.4 (*C*(1) x 3), 25.0 (*C*(6)), 23.2 (*C*(7)), 22.0 (*C*(8)), 16.5 (*C*(10)) ppm.

6.4.22 Preparation of (2*S*,3*R*)-273



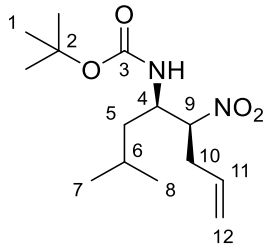
tert*-Butyl [(2*S*,3*R*)-5-methyl-2-nitrohexan-3-yl]carbamate:**[128] Obtained according to general procedure 4A using **417** (47.2 mg, 0.144 mmol) and nitroethane (52 μL, 0.72 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 15:1) to yield 37.5 mg (100%) of product as a white solid and as a mixture of diastereomers (dr = 13:1 (*anti*/*syn*), determined by HPLC analysis of the purified product (calibrated using the HPLC trace of the racemic product)). The ee was determined by HPLC [Chiralpak AS-H, hexane/EtOH 95:5, λ 220 nm, 0.9 mL/min] ***major *(anti)*: t (major) = 8.1 min, t (minor) = 9.4 min. (90% ee), ***minor*** *(syn)*: t (major) = 6.8 min., t (minor) = 6.2 min. (approx. 10% ee). $[\alpha]_D^{20}$ = +51.0 (*c* 0.49, $CHCl_3$) ; MP 90 °C; δ_H (400 MHz, $CDCl_3$) 4.62-4.72 (m, 2 H, N*H* and C(9)*H*), 3.96-4.05 (m, 1 H, C(4)*H*), 1.62-1.71 (m, 1 H, C(6)*H*), 1.50 (d, *J* = 6.8 Hz, 3 H, C(10)H_3), 1.44 (s, 9 H, C(1)H_3 x 3), 1.21-1.28 (m, 2 H, C(5)H_2), 0.88-0.94 (m, 6 H, C(7)H_3 and C(8)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 155.4 (*C*(3)), 86.0 (*C*(9)), 80.2 (*C*(2)), 52.0 (*C*(4)), 38.6 (*C*(5)), 28.4 (*C*(1) x 3), 24.8 (*C*(6)), 23.5 (*C*(7)), 21.4 (*C*(8)), 15.3 (*C*(10)) ppm.

6.4.23 Preparation of (±)-474



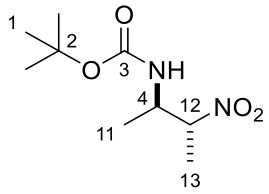
***tert*-Butyl [(4*R**,5*R**)-2-methyl-5-nitrooct-7-en-4-yl]carbamate:** Amido sulfone **417** (98.2 mg, 0.300 mmol, 1.00 eq) was suspended in 1.5 mL toluene. Nitrobutene (152 mg, 1.50 mmol, 5.00 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 0.10 eq) and ground K_2CO_3 (207 mg, 1.50 mmol, 5.00 eq) were added sequentially and the resulting mixture was stirred vigorously at ambient temperature. After 24 h, 5 mL sat. aq. $NaHCO_3$ were added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 10:1) to yield 79.2 mg (92%) of **(±)-474** as a mixture of diastereomers (dr = 1:3.4 (*anti*/*syn*), based on ^{1}H NMR of crude reaction mixture). NMR data reported for major (*syn*) isomer. See below for *anti* diastereomer. δ_H (500 MHz, $CDCl_3$) 5.67-5.79 (m, 1 H, C(11)*H*), 5.13-5.22 (m, 2 H, C(12)H_2), 4.94 (br d, *J* = 10.4 Hz, 1 H, N*H*), 4.59 (dt, *J* = 9.2, 4.5 Hz, 1 H, C(9)*H*), 4.03-4.12 (m, 1 H, C(4)*H*), 2.70-2.80 (m, 1 H, C(10)*H'*H"), 2.55-2.63 (m, 1 H, C(10)H'*H"*), 1.63-1.74 (m, 1 H, C(6)*H*), 1.45 (s, 9 H, C(1)H_3 x 3), 1.27-1.39 (m, 2 H, C(5)H_2), 0.90-0.94 (m, 6 H, C(7)H_3 and C(8)H_3) ppm; δ_C (125 MHz, $CDCl_3$) 155.7 (*C*(3)), 131.3 (*C*(11)), 119.9 (*C*(12)), 91.1 (*C*(9)), 80.1 (*C*(2)), 59.7 (*C*(4)), 41.7 (*C*(5)), 35.3 (*C*(10)), 28.4 (*C*(1) x 3), 24.7 (*C*(6)), 23.0 (*C*(7)), 22.0 (*C*(8)) ppm.

6.4.24 Preparation of (4*R*,5*S*)-474



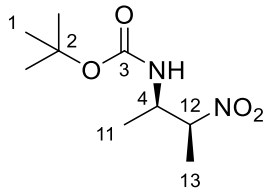
tert*-Butyl [(4*R*,5*S*)-2-methyl-5-nitrooct-7-en-4-yl]carbamate:** Obtained according to general procedure 4A using **417** (47.2 mg, 0.144 mmol) and nitrobutene (72.3 mg, 0.720 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 10:1) to yield 34.2 mg (83%) of product as a white solid and as a mixture of diastereomers (dr = 13:1, determined by ^{1}H NMR analysis of the crude reaction mixture). The ee was determined by HPLC analysis [Chiralpak AS-H, hexane/ethanol 95:5, λ 220 nm, 0.9 mL/min] ***major *(anti)*: t (major) = 7.1 min., t (minor) = 7.9 min. (88% ee), ***minor*** *(syn)*: not determined. $[\alpha]_D^{20}$ = +34.5 (*c* 0.610, $CHCl_3$); MP 81.1-83.2 °C; δ_H (500 MHz, $CDCl_3$) 5.65-5.77 (m, 1 H, C(11)*H*), 5.12-5.20 (m, 2 H, C(12)H_2), 4.65 (dt, *J* = 9.7, 4.8 Hz, 1 H, C(9)*H*), 4.55 (br d, *J* = 9.1 Hz, 1 H, N*H*), 3.99-4.09 (m, 1 H, C(4)*H*), 2.73-2.82 (m, 1 H, C(10)*H'*H"), 2.45-2.53 (m, 1 H, C(10)H'*H"*), 1.62-1.72 (m, 1 H, C(6)*H*), 1.44 (s, 9 H, C(1)H_3 x 3), 1.27-1.32 (m, 2 H, C(5)H_2), 0.92 (d, *J* = 6.6 Hz, 3 H, C(7)H_3), 0.89 (d, *J* = 6.6 Hz, 3 H, C(8)H_3) ppm; δ_C (125 MHz, $CDCl_3$) 155.4 (*C*(3)), 131.6 (*C*(11)), 119.7 (*C*(12)), 90.6 (*C*(9)), 80.3 (*C*(2)), 50.9 (*C*(4)), 38.6 (*C*(5)), 34.4 (*C*(10)), 28.4 (*C*(1) x 3), 24.8 (*C*(6)), 23.7 (*C*(7)), 21.3 (*C*(8)) ppm; LRMS *m/z* (ESI^+) 309 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 309.17778, $C_{14}H_{26}O_4N_2Na^+$ requires 309.17848; ν_{max} 3296 (w, N-H stretch), 2959 (w), 1679 (m, C=O), 1550 (s), 1524 (m), 1368 (m), 1161 (m), 920 (m) cm^{-1}.

6.4.25 Preparation of (±)-475



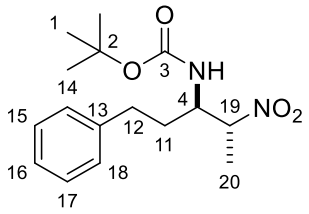
***tert*-Butyl [(2*R**,3*R**)-3-nitrobutan-2-yl]carbamate (racemate):** Amido sulfone **418** (85.6 mg, 0.300 mmol, 1.00 eq) was suspended in 1.5 mL toluene. Nitroethane (108 µL, 1.50 mmol, 5.00 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 0.10 eq) and ground K_2CO_3 (207 mg, 1.50 mmol, 5.00 eq) were added sequentially and the resulting mixture was stirred vigorously at ambient temperature. After 24 h, 5 mL sat. aq. $NaHCO_3$ were added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2) to yield 48.7 mg (74%) of **(±)-475** as a mixture of diastereomers (dr = 1:1 *anti*/*syn*, based on ^{1}H NMR of crude reaction mixture). NMR data collected on a mixture of diastereomers, but reported for *syn* (2*R**,3*R**) diastereomer only (see below for full characterization of *anti*-addition product). δ_H (500 MHz, $CDCl_3$) 4.94 (br s, 1 H, N*H*), 4.69 (br s, 1 H, C(12)*H*), 4.08 (br s, 1 H, C(4)*H*), 1.55 (d, *J* = 6.6 Hz, 3 H, C(13)H_3), 1.44 (s, 9 H, C(1)H_3 x 3), 1.22 (d, *J* = 6.6 Hz, 3 H, C(11)H_3) ppm; δ_C (125 MHz, $CDCl_3$) 155.4 (*C*(3)), 86.6 (*C*(12)), 80.1 (*C*(2)), 48.6 (*C*(4)), 28.4 (*C*(1) x 3), 17.8 (*C*(11)), 16.2 (*C*(13)) ppm.

6.4.26 Preparation of (2*R*,3*S*)-475



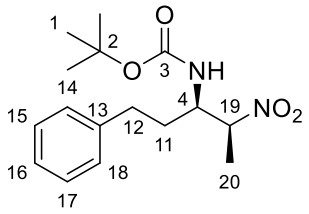
***tert*-Butyl [(2*R*,3*S*)-3-nitrobutan-2-yl]carbamate:** Obtained according to the general procedure using **418** (41.1 mg, 0.144 mmol) and nitroethane (51.7 µL, 0.720 mmol). The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2) to yield 31.4 mg (100%) of product as a white solid and as a mixture of diastereomers (dr = 10:1 (*anti*/*syn*), determined by ^{1}H NMR analysis of the crude reaction mixture). Data were collected on a mixture of diastereomers. NMR peaks are reported for the major (*anti*, 2*R*,3*S*) diastereomer only. The ee was determined by HPLC analysis [Chiralpak AS-H, hexane/ethanol 99:1, λ 220 nm, 0.9 mL/min] ***major** (anti)*: t (major) = 20.4 min., t (minor) = 25.5 min. (81% ee), ***minor** (syn)*: t (major) = 18.0 min., t (minor) = 18.9 min. (14% ee). $[\alpha]_D^{20}$ = +42.9 (*c* 0.530, $CHCl_3$); MP 99-100 °C; δ_H (500 MHz, $CDCl_3$) 4.81 (br s, 1 H, N*H*), 4.74 (br s, 1 H, C(12)*H*), 4.04 (br s, 1 H, C(4)*H*), 1.52 (d, *J* = 6.9 Hz, 3 H, C(13)H_3), 1.45 (s, 9 H, C(1)H_3 x 3), 1.17 (d, *J* = 6.6 Hz, 3 H, C(11)H_3) ppm; δ_C (125 MHz, $CDCl_3$) 155.1 (*C*(3)), 85.9 (*C*(12)), 80.3 (*C*(2)), 49.4 (*C*(4)), 28.4 (*C*(1) x 3), 15.6 (*C*(11)), 15.2 (*C*(13)) ppm; LRMS *m/z* (ESI^+) 241 (100%, $[M+Na]^+$); HRMS *m/z* (ESI^+) found $[M+Na]^+$ 241.11549, $C_9H_{18}O_4N_2Na$ requires 241.11588; ν_{max} 3341 (m, N-H stretch), 2980 (w), 1739 (m, C=O), 1678 (m), 1549 (m), 1546 (m), 1345 (w), 1166 (w) cm^{-1}.

6.4.27 Preparation of (±)-476



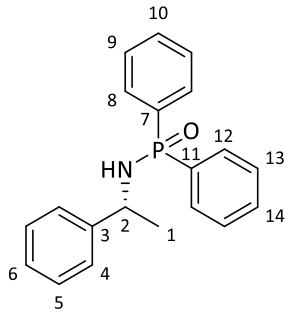
***tert*-Butyl [(3*R**,4*R**)-4-nitro-1-phenylpentan-3-yl]carbamate:** Amido sulfone **419** (113 mg, 0.300 mmol, 1.00 eq) was suspended in 1.5 mL toluene. Nitroethane (108 µL, 1.50 mmol, 5.00 eq), tetrabutylammonium bromide (9.8 mg, 0.030 mmol, 0.10 eq) and ground K_2CO_3 (207 mg, 1.50 mmol, 5.00 eq) were added sequentially and the resulting mixture was stirred vigorously at ambient temperature. After 36 h, 5 mL sat. aq. $NaHCO_3$ were added; the aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2) to yield 81.2 mg (88%) of **(±)-476** as a mixture of diastereomers (dr: 1:1.6 *anti*/*syn*). NMR data is reported here for the *syn* (3*R**,4*R**) diastereomer only (see below for full characterization of *anti*-addition product). δ_H (500 MHz, $CDCl_3$) 7.26-7.32 (m, 2 H, C(Ar)*H* x 2), 7.19-7.23 (m, 1 H, C(16)*H*), 7.14-7.19 (m, 2 H, C(Ar)*H* x 2), 5.02 (br d, *J* = 9.8 Hz, 1 H, N*H*), 4.68-4.75 (m, 1 H, C(19)*H*), 3.92-4.00 (m, 1 H, C(4)*H*), 2.59-2.82 (m, 2 H, C(12)H_2), 1.74-1.84 (m, 2 H, C(11)H_2), 1.55 (d, *J* = 6.6 Hz, 3 H, C(20)H_3), 1.48 (s, 9 H, C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) 155.7 (*C*(3)), 140.6 (*C*(13)), 128.5 (*C*(Ar) x 2), 128.3 (*C*(Ar) x 2), 126.2 (*C*(16)), 85.7 (*C*(19)), 79.9 (*C*(2)), 52.3 (*C*(4)), 34.0 (*C*(11)), 32.2 (*C*(12)), 28.2 (*C*(1) x 3), 16.3 (*C*(20)) ppm.

6.4.28 Preparation of (3*R*,4*S*)-476



***tert*-Butyl [(3*R*,4*S*)-4-nitro-1-phenylpentan-3-yl]carbamate:** Obtained according to general procedure 4A using **419** (41.1 mg, 0.144 mmol) and nitroethane (51.7 µL, 0.720 mmol). The crude reaction mixture was purified by flash column chromatography (6:1 PE/EtOAc) to yield 33.7 mg (84%) of product as a white solid and as a mixture of diastereomers (dr = 5:1 (*anti*/*syn*), determined by ^{1}H NMR analysis of the crude reaction mixture). Data were collected on a mixture of diastereomers. NMR peaks are reported for the major (*anti*, (3*R*,4*S*)) diastereomer only. The ee was determined by HPLC analysis [Chiralpak IA, hexane/*iso*-propanol 99:1, λ 220 nm, 0.8 mL/min] ***major** (anti)*: t (minor) = 39.4 min., t (major) = 51.0 min. (85% ee), ***minor** (syn)*: t (major) = 31.8 min., t (minor) = 43.1 min. (16% ee). $[\alpha]_D^{20}$ = +21.6 (*c* 1.00, $CHCl_3$); MP 91-93 °C; δ_H (500 MHz, $CDCl_3$) 7.26-7.32 (m, 2 H, C(Ar)*H* x 2), 7.19-7.23 (m, 1 H, C(16)*H*), 7.14-7.19 (m, 2 H, C(Ar)*H* x 2), 4.82 (br d, *J* = 9.1 Hz, 1 H, N*H*), 4.66-4.75 (m, 1 H, C(19)*H*), 3.93-4.01 (m, 1 H, C(4)*H*), 2.72-2.83 (m, 1 H, C(12)*H'*H"), 2.57-2.69 (m, 1 H, C(12)H'*H"*), 1.84-1.92 (m, 1 H, C(11)*H'*H"), 1.57-1.67 (m, 1 H, C(11)H'*H"*), 1.42-1.50 (m, 12 H, C(20)H_3 and C(1)H_3 x 3) ppm; δ_C (125 MHz, $CDCl_3$) 155.3 (*C*(3)), 140.5 (*C*(13)), 128.5 (*C*(Ar) x 2), 128.3 (*C*(Ar) x 2), 126.2 (*C*(16)), 85.5 (*C*(19)), 80.2 (*C*(2)), 53.2 (*C*(4)), 32.2 (*C*(12)), 31.3 (*C*(11)), 28.3 (*C*(1) x 3), 15.2 (*C*(20)) ppm; LRMS *m/z* (ESI$^+$) 331 (100%, $[M+Na]^+$); HRMS *m/z* (ESI$^+$) found $[M+Na]^+$ 331.16194, $C_{16}H_{24}O_4N_2Na^+$ requires 331.16283; ν_{max} 3371 (w, N-H stretch), 2924 (w), 1719 (s, C=O), 1603 (m), 1261 (s), 1099 (m), 729 (m) cm^{-1}.

6.4.29 Preparation of (*R*)-486



***P,P*-diphenyl-*N*-[(1*R*)-1-phenylethyl]phosphinic amide:**[201] Phosphoketimine **484** (30 mg, 0.094 mmol, 1.0 eq), catalyst **C34** (5.7 mg, 0.0094 mmol, 0.10 eq), and ground $CsOH \cdot H_2O$ (47.4 mg, 0.282 mmol, 3.00 eq) were dissolved in TBME (1.6 mL). Pinacolborane (41.0 µL, 0.282 mmol, 3.00 eq) was added and the reaction was stirred at ambient temperature. After 8 h, the mixture was diluted with CH_2Cl_2 (3 mL), and the organic layer was washed with NaOH (1 M, 10 mL) and H_2O (2 x 10 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (CH_2Cl_2/MeOH 40:1) to give the product as a white solid (5.2 mg, 17%). The ee was determined by HPLC [Chiralpak OD-H, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min] t (major) = 7.0 min., t (minor) = 9.5 min., (33%). $[\alpha]_D^{20}$ = +2.0 (c 0.64, $CHCl_3$); MP 136 °C; δ_H (400 MHz, $CDCl_3$) 7.91-7.86 (m, 2 H, C(5)*H* x 2), 7.83-7.78 (m, 2 H, C(4)*H* x 2), 7.49-7.20 (m, 11 H, C(6)*H*, C(8)*H* x 2, C(9)*H* x 2, C(10)*H*, C(12)*H* x 2, C(13)*H* x 2, and C(14)*H*), 4.40-4.35 (m, 1 H, N*H*), 3.20-3.16 (m, 1 H, C(2)*H*), 1.57 (d, *J* = 6.5 Hz, 3 H, C(1)H_3) ppm; δ_C (100 MHz, $CDCl_3$) 153.2 (*C*(Ar) x 2), 151.7 (*C*(Ar)), 145.2 (*C*(Ar) x 4), 133.3 (*C*(Ar) x 2), 132.4 (*C*(Ar) x 4), 128.6 (*C*(Ar) x 2), 127.3 (*C*(Ar)), 126.1 (*C*(Ar) x 2), 51.4 (*C*(2)), 26.4 (*C*(1)) ppm.

6.5 Preparation of Catalysts

6.5.1 General procedure CA

General procedure for the preparation of 9-amino(9-deoxy) epicinchona alkaloids: Diphenylphosphoryl azide (1.2 eq) was added to a suspension of cinchona alkaloid (1.0 eq) and triphenylphosphine (1.2 eq) in THF (0.17 M) at 0 °C. Diisopropyl azodicarboxylate (1.1 eq) was added dropwise and the resulting yellow solution was allowed to warm to ambient temperature. After 9 h, the solution was heated to 50 °C for 2 h, then allowed to cool to ambient temperature. To the azide formed *in situ* was added triphenylphosphine (1.2 eq). The resulting solution was heated to 50 °C for 2.5 h, then distilled water (8.6 eq) was added, and the solution was maintained at 50 °C for a further 3 h. The solvent was removed *in vacuo*, then the crude mixture was dissolved in 4 M HCl (4.6 mL/mmol cinchona alkaloid) and stirred for 10 min. The aqueous mixture was extracted with CH_2Cl_2 (4 x), then the aqueous layer was concentrated *in vacuo*. The resulting crude product was suspended in isopropyl alcohol (4mL/mmol cinchona alkaloid) and heated to 110 °C. After 10 min, the resulting thick white suspension was allowed to cool to ambient temperature and the product was collect *via* filtration and dried under vacuum to give a white solid.

6.5.2 General procedure CB

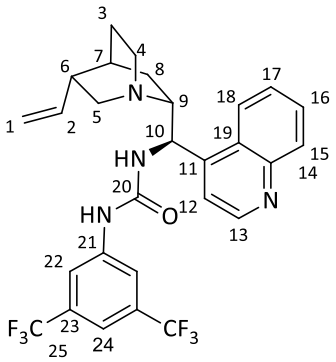
General procedure for the preparation of cinchona-derived tertiary amine/urea catalysts: The 3HCl salt of the corresponding 9-amino(9-deoxy) epicinchona alkaloid was dissolved in 1 M NaOH until pH 10 (approx. 6.5 mL/g amine salt). The aqueous mixture was extracted with CH_2Cl_2 (7 x volume of aqueous solution). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the free base amine as a thick yellow oil. The oil was suspended in CH_2Cl_2 (0.40 M) and the mixture was cooled to 0 °C. Isocyanate (1.0-1.1 eq) was added, and the solution was allowed to warm to ambient

temperature. After 10 h, the crude mixture was concentrated *in vacuo* and purified by flash column chromatography (CH_2Cl_2, then 100:2 EtOAc/MeOH or 9:1 CH_2Cl_2/MeOH) to give the urea as a white solid.

6.5.3 General procedure CC

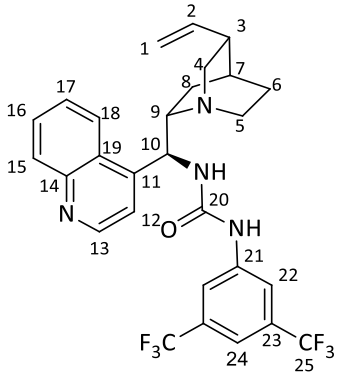
General procedure for the preparation of H-bond donor phase-transfer catatlysts: 9-Amino(9-deoxy) epicinchona-derived urea, amide, or sulphonamide (1.0 eq) was dissolved in anhydrous toluene. The corresponding aryl halide (1.0 eq) was added and the solution was heated to 65 °C. After 12 h, the mixture was allowed to cool to ambient temperature and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography to yield the desired phase-transfer catalyst (except for **C63** which was purified by trituration).

6.5.4 Preparation of C12



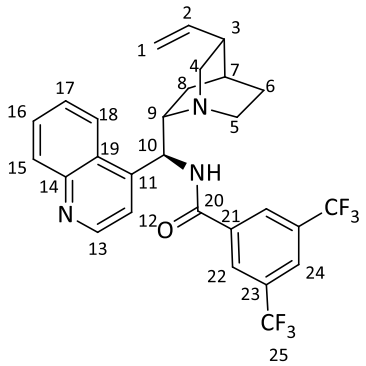
1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(8*R*,9*R*)-cinchonan-9-yl]urea:[202] General procedure CB was followed using 9-amino(9-deoxy) epicinchonine **C47** (983 mg, 3.35 mmol, 1.00 eq) and 3,5-bis(trifluoromethyl)phenyl isocyanate (580 µL, 3.35 mmol, 1.00 eq). Urea **C12** was obtained as a white solid (1.7 g, 93%). $[\alpha]_D^{20}$ = +82.6 (*c* 1.00, CH_3OH); MP 141-142 °C (decomp.); δ_H (300 MHz, CD_3OD) 8.83 (d, *J* = 4.7 Hz, 1 H, C(13)*H*), 8.50 (d, *J* = 8.5 Hz, 1 H, C(15)*H*), 8.06 (d, *J* = 8.4 Hz, 1 H, C(18)*H*), 7.89 (br s, 2 H, C(22)*H* x 2), 7.78 (app t, *J* = 7.4 Hz, 1 H, C(17)*H*), 7.69 (app t, *J* = 7.5 Hz, 1 H, C(16)*H*), 7.63 (d, *J* = 4.7 Hz, 1 H, C(12)*H*), 7.42 (s, 1 H, C(24)*H*), 5.92 (ddd, *J* = 17.2, 10.6, 6.4 Hz, 1 H, C(2)*H*), 5.53-5.72 (m, 1 H, C(10)*H*), 5.07-5.20 (m, 2 H, C(1)H_2), 3.08-3.29 (m, 2 H, C(5)*H'*H" and C(9)*H*), 2.93-3.06 (m, 3 H, C(4)H_2 and C(5)H'*H"*), 2.26-2.38 (m, 1 H, C(6)*H*),1.43-1.64 (m, 3 H, C(3)H_2 and C(7)*H*), 1.14-1.26 (m, 1 H, C(8)*H'*H"), 0.83-1.02 (m, 1 H, C(8)H'*H"*) ppm; δ_C (75 MHz, CD_3OD) 156.9 (*C*(20)), 151.1 (*C*(13)), 150.2 (*C*(19)), 149.2 (*C*(14)), 143.3 (*C*(21)), 141.6 (*C*(2)), 133.2 (q, J_{CF} = 33.0 Hz, *C*(23) x 2), 131.1 (*C*(17)), 130.2 (*C*(18)), 128.8 (*C*(11)), 128.3 (*C*(16)), 125.1 (*C*(15)), 124.9 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 120.8 (*C*(12)), 119.1 (*C*(22) x 2), 115.7 (*C*(24)), 115.5 (*C*(1)), 61.4 (*C*(9)), 50.4 (*C*(10)), 48.6 (*C*(4)), 48.3 (*C*(5)), 40.6 (*C*(6)), 29.1 (*C*(3)), 27.5 (*C*(7)), 26.5 (*C*(8)) ppm.

6.5.5 Preparation of C14



1-[3,5-bis(trifluoromethyl)phenyl]-3-[(8*S*,9*S*)-cinchonan-9-yl]urea:[203] General procedure CB was followed using 9-amino(9-deoxy) epicinchonidine **C45** (3.40 g, 11.6 mmol, 1.00 eq) and 3,5-bis(trifluoromethyl)phenyl isocyanate (2.25 mL, 12.8 mmol, 1.10 eq). Urea **C14** was obtained as a white solid (4.8 g, 75%). $[\alpha]_D^{20}$ = –6.8 (*c* 1.0, CH_3OH); MP 148-150 °C; δ_H (400 MHz, CD_3OD) 8.85 (d, *J* = 4.7 Hz, 1 H, C(13)*H*), 8.56 (d, *J* = 8.4 Hz, 1 H, C(15)*H*), 8.05-8.09 (m, 1 H, C(18)*H*), 7.90 (br s, 2 H, C(22)*H* x 2), 7.76-7.82 (m, 1 H, C(17)*H*), 7.69-7.74 (m, 1 H, C(16)*H*), 7.64 (d, *J* = 4.7 Hz, 1 H, C(12)*H*), 7.43 (br s, 1 H, C(24)*H*), 5.90 (ddd, *J* = 17.3, 10.0, 7.6 Hz, 1 H, C(2)*H*), 5.62 (br s, 1 H, C(10)*H*), 4.93-5.04 (m, 2 H, C(1)H_2), 3.34-3.42 (m, 3 H, C(4)*H'*H", C(5)*H'*H" and C(9)*H*), 2.75-2.85 (m, 2 H, C(4)H'*H"* and C(5)H'*H"*), 2.29-2.37 (m, 1 H, C(3)*H*), 1.55-1.73 (m, 3 H, C(6)H_2 and C(7)*H*), 1.36-1.45 (m, 1 H, C(8)*H'*H"), 0.83-0.91 (m, 1 H, C(8)H'*H"*) ppm; δ_C (100 MHz, CD_3OD) 156.8 (*C*(20)), 151.1 (*C*(13)), 150.0 (*C*(19)), 149.2 (*C*(14)), 143.3 (*C*(21)), 142.8 (*C*(2)), 133.2 (q, J_{CF} = 32.0 Hz, *C*(23) x 2), 131.1 (*C*(17)), 130.2 (*C*(18)), 129.0 (*C*(11)), 128.5 (*C*(16)), 125.2 (*C*(15)), 125.1 (q, J_{CF} = 271.0 Hz, *C*(25) x 2), 121.0 (*C*(12)), 119.1 (*C*(22) x 2), 115.7 (*C*(24)), 115.1 (*C*(1)), 61.3 (*C*(9)), 57.0 (*C*(4)), 52.3 (*C*(10)), 42.2 (*C*(5)), 41.0 (*C*(3)), 29.0 (*C*(7)), 28.7 (*C*(6)), 27.2 (*C*(8)) ppm.

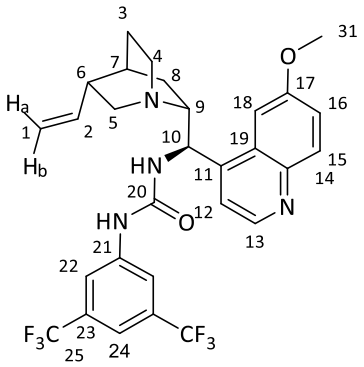
6.5.6 Preparation of C26



***N*-[(8*S*, 9*S*)-Cinchonan-9-yl]-3,5-bis(trifluoromethyl)benzamide**: 9-Amino(9-deoxy) epicinchonidine triple hydrochloride salt **C45** was suspended in CH_2Cl_2 (2 mL). 1 M NaOH was added to basify the solution. The aqueous solution was extracted with CH_2Cl_2 (7 x). The organic phases were combined and dried over Na_2SO_4. After filtration and concentration, 9-amino(9-deoxy) epicinchonidine free base was obtained and used directly without characterization. To a solution of the free base 9-amino(9-deoxy) epicinchonidine (298 mg, 1.01 mmol, 1.00 eq) in 10 mL CH_2Cl_2 was added triethylamine (704 µL, 5.05 mmol, 5.00 eq) and then 3,5-bis(trifluoromethyl)benzoyl chloride (183 µL, 1.01 mmol, 1.00 eq). The reaction was stirred at ambient temperature. After 10 h, the crude reaction mixture was concentrated *in vacuo* and purified by flash chromatography (neat CH_2Cl_2, then EtOAc/MeOH/Et_3N 100:2:0, then EtOAc/MeOH/Et_3N 100:10:3) to afford the desired pre-catalyst **C26** as a pale yellow solid (438 mg, 81%, reported yield based on the amount of free base amine used). $[\alpha]_D^{20}$ = –37.0 (*c* 1.00, MeOH); MP 116-118 °C; δ_H (400 MHz, $CDCl_3$) 8.89 (d, *J* = 4.5 Hz, 1 H, C(13)*H*), 8.46 (d, *J* = 8.5 Hz, 1 H, C(15)*H*), 8.23 (s, 2 H, C(22)*H* x 2), 8.10-8.19 (m, 2 H, C(18)*H* and N*H*), 7.95 (s, 1 H, C(24)*H*), 7.76 (t, *J* = 7.5 Hz, 1 H, C(17)*H*), 7.66 (t, *J* = 7.5 Hz, 1 H, C(16)*H*), 7.49 (d, *J* = 4.5 Hz, 1 H, C(12)*H*), 5.74 (ddd, *J* = 17.0, 10.0, 7.5, 1 H, C(2)*H*), 5.55 (br s, 1 H, C(10)*H*), 5.06-4.95 (m, 2 H, C(1)H_2), 3.36-3.19 (m, 2 H, C(9)*H* and C(4)*H'*H"), 3.11 (br s, 1 H, C(5)*H'*H"), 2.86-2.74 (m, 2 H,

C(4)H'*H"* and C(5)H'*H"*), 2.35 (br s, 1 H, C(3)*H*), 1.78-1.60 (m, 3 H, C(6)H_2 and C(7)*H*), 1.51-1.41 (m, 1 H, C(8)*H'*H"), 1.03 (dd, *J* = 13.0, 6.0 Hz, 1 H, C(8)H'*H"*) ppm; δ_C (100 MHz, $CDCl_3$) 164.6 (*C*(20)), 150.1 (*C*(13)), 148.6 (*C*(19)), 146.2 (*C*(14)), 140.9 (*C*(2)), 135.9 (*C*(21)), 132.0 (q, J_{CF} = 33.5 Hz, *C*(23) x 2), 130.6 (*C*(18)), 129.3 (*C*(17)), 127.5 (*C*(22) x 2), 127.2 (*C*(11)), 127.0 (*C*(16)), 125.2-124.9 (m, *C*(24)), 122.9 (*C*(15)), 122.8 (q, J_{CF} = 271.5 Hz, *C*(25) x 2), 119.1 (*C*(12)), 114.8 (*C*(1)), 60.1 (*C*(9)), 55.8 (*C*(4)), 51.8 (*C*(10)), 40.9 (*C*(5)), 39.4 (*C*(3)), 27.7 (*C*(6)), 27.2 (*C*(7)), 25.8 (*C*(8)) ppm; LRMS *m/z* (ESI^+) 534 (100%, $[M+H]^+$); HRMS *m/z* (ESI^+) found $[M+H]^+$ 534.1968, $C_{28}H_{26}ON_3F_6^+$ requires 534.1975; ν_{max} 3102 (w), 2950 (w), 1639 (m, C=O) cm^{-1}.

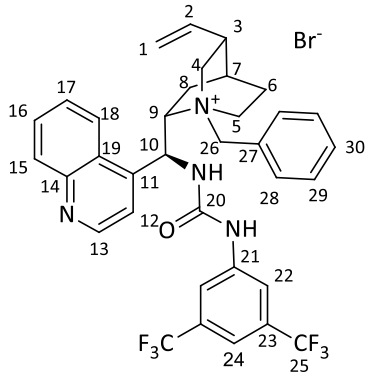
6.5.7 Preparation of C32



1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(8*R*,9*R*)-6'-methoxycinchonan-9-yl]urea bromide:[204] General procedure CB was followed using 9-epiamino-9-deoxyquinidine **C48** (783 mg, 2.42 mmol, 1.00 eq) and 3,5-bis(trifluoromethyl)phenyl isocyanate (420 µL, 2.42 mmol, 1.00 eq). Urea **C32** was obtained as a white solid (1.2 g, 86%). $[\alpha]_D^{20}$ = +90.9 (*c* 1.00, CH_3OH); MP 129-132 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.67 (d, *J* = 4.7 Hz, 1 H, C(13)*H*), 7.94 (d, *J* = 9.1 Hz, 1 H, C(15)*H*), 7.93 (br s, 2 H, C(22)*H* x 2), 7.78 (d, *J* = 2.7 Hz, 1 H, C(18)*H*), 7.57 (d, *J* = 4.7 Hz, 1 H, C(12)*H*), 7.41-7.45 (m, 2 H, C(16)*H* and C(24)*H*), 5.94 (ddd, *J* = 17.3, 10.6, 6.1 Hz, 1 H, C(2)*H*), 5.62 (br s, 1 H, C(10)*H*), 5.19 (dt, *J* = 17.3, 1.5 Hz, 1 H, C(1)H_aH$_b$), 5.12 (dt, *J* = 10.6, 1.5 Hz, 1 H, C(1)H$_a$$H_b$), 4.02 (s, 3 H, C(31)$H_3$),

3.19-3.30 (m, 2 H, C(5)*H'*H" and C(9)*H*), 2.98-3.07 (m, 3 H, C(4)H_2 and C(5)H'*H"*), 2.31-2.38 (m, 1 H, C(6)*H*), 1.60-1.65 (m, 3 H, C(3)H_2 and C(7)*H*), 1.18-1.24 (m, 1 H, C(8)*H'*H"), 1.06-1.13 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 159.9 (*C*(20)), 157.0 (*C*(17)), 148.4 (*C*(13)), 145.2 (*C*(19)), 143.4 (*C*(21)), 141.9 (*C*(2)), 133.2 (q, J_{CF} = 32.5 Hz, *C*(23) x 2), 131.5 (*C*(15)), 130.2 (*C*(14)), 124.9 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.0 (*C*(11)), 122.2 (*C*(16)), 120.8 (*C*(12)), 119.1-119.2 (m, *C*(22) x 2), 115.6-115.8 (m, *C*(24)), 115.4 (*C*(1)), 102.9 (*C*(18)), 61.1 (*C*(9)), 56.4 (*C*(31)), 50.4 (*C*(4)), 49.7 (*C*(10)), 48.2 (*C*(5)), 40.4 (*C*(6)), 29.0 (*C*(7)), 27.5 (*C*(3)), 26.9 (*C*(8)) ppm.

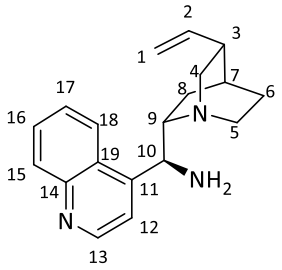
6.5.8 Preparation of C34



1-[(8*S*,9*S*)-1-benzylcinchonan-1-ium-9-yl]-3-[3,5-bis(trifluoromethyl)phenyl]urea bromide: Obtained according to general procedure CC using **C14** (1.60 g, 2.92 mmol) and benzyl bromide (350 μL, 2.92 mmol) in 35 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (Et_2O/MeOH 12:1, then CH_2Cl_2/MeOH 3:1) to yield 1.75 g (83%) of product as a pale yellow solid. $[\alpha]_D^{20}$ = –18.1 (c 1.00, $CHCl_3$); MP 175-178 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.99 (d, *J* = 4.5 Hz, 1 H, C(13)*H*), 8.46-8.55 (m, 1 H, C(15)*H*), 8.13-8.18 (m, 1 H, C(18)*H*), 8.00 (br s, 2 H, C(22)*H* x 2), 7.82-7.92 (m, 3 H, C(12)*H*, C(16)*H* and C(17)*H*), 7.61-7.67 (m, 2 H, C(29)*H* x 2), 7.53-7.58 (m, 4 H, C(28)*H* x 2 and C(30)*H*), 7.51 (br s, 1 H, C(24)*H*), 6.56 (br. s, 1 H, C(10)*H*), 5.90 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1 H, C(2)*H*), 5.18-5.29 (m, 2 H, C(1)H_2), 4.95-5.15 (m, 3

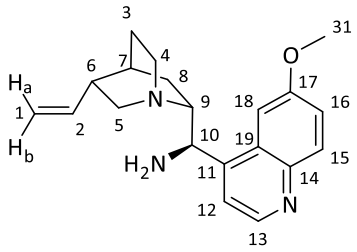
H, C(9)*H* and C(26)H_2), 4.48 (br s, 1 H, C(5)*H'*H"), 3.72-3.84 (m, 1 H, C(4)*H'*H"), 3.46-3.60 (m, 2 H, C(4)H'*H"* and C(5)H'*H"*), 2.75 (app q, *J* = 7.5 Hz, 1 H, C(3)*H*), 2.00-2.25 (m, 3 H, C(6)H_2 and C(8)*H'*H"), 1.93 (br s, 1 H, C(7)*H*), 1.14-1.27 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 155.8 (*C*(20)), 151.7 (*C*(13)), 149.7 (*C*(19)), 147.2 (*C*(14)), 142.5 (*C*(21)), 137.9 (*C*(2)), 134.8 (*C*(29) x 2), 133.2 (q, $^2J_{CF}$ = 32.0 Hz, *C*(23)), 131.9 (*C*(30)), 131.7 (*C*(17)), 130.8 (*C*(18)), 130.6 (*C*(28) x 2), 129.7 (*C*(16)), 129.0 (*C*(27)), 127.5 (*C*(11)), 124.8 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.7 (*C*(15)), 121.1 (*C*(12)), 119.4 (*C*(22) x 2), 118.4 (*C*(1)), 116.4 (*C*(24)), 69.4 (*C*(9)), 67.2 (*C*(26)), 61.8 (*C*(4)), 50.9 (*C*(5)), 50.7 (*C*(10)), 38.8 (*C*(3)), 28.6 (*C*(8)), 28.2 (*C*(7)), 25.7 (*C*(6) ppm; LRMS *m/z* (ESI^+) 639 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br^-]^+$ 639.2553, $C_{35}H_{33}F_6N_4O^+$ requires 639.2553; ν_{max} 3189 (w), 2979 (w), 1642 (m), 1387 (m), 1276 (m), 1175 (m), 1128 (m) cm^{-1}.

6.5.9 Preparation of C45



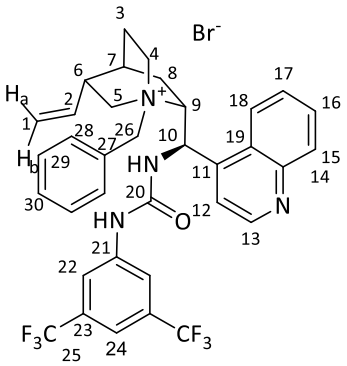
(9*S*)-Cinchonan-9-amine:[205] Obtained according to general procedure CA using cinchonidine (96% purity, 15.0 g, 48.9 mmol). The product was isolated as a white solid (19.8 g, 100%). Characterized as the 3HCl salt. $[\alpha]_D^{20} = -4.6$ (*c* 1.0, CH_3OH); MP 159-160 °C (decomp.); δ_H (400 MHz, D_2O) 9.18 (d, *J* = 5.9 Hz, 1 H, C(13)*H*), 8.61 (d, *J* = 8.6 Hz, 1 H, C(15)*H*), 8.27-8.31 (m, 1 H, C(18)*H*), 8.19 (td, *J* = 7.9, 1.1 Hz, 1 H, C(17)*H*), 8.16 (d, *J* = 5.9 Hz, 1 H, C(12)*H*), 8.06 (td, *J* = 7.9, 1.1 Hz, 1 H, C(16)*H*), 5.81 (ddd, *J* = 17.2, 10.7, 6.5 Hz, 1 H, C(2)*H*), 5.55 (d, *J* = 10.8, 1 H, C(10)*H*), 5.13-5.21 (m, 2 H, C(1)H_2), 4.21-4.30 (m, 1 H, C(9)*H*), 3.83-3.90 (m, 1 H, C(5)*H'*H"), 3.77 (dd, *J* = 13.4, 10.5 Hz, 1 H, C(4)*H'*H"), 3.40-3.50 (m, 2 H, C(4)H'*H"* and C(5)H'*H"*), 2.86 (br s, 1 H, C(3)*H*), 1.96-2.04 (m, 3 H, C(6)H_2 and C(7)*H*), 1.73-1.83 (m, 1 H, C(8)*H'*H"), 1.04-1.11 (m, 1 H, C(8)H'*H"*) ppm; δ_C (100 MHz, D_2O) 149.4 (*C*(11)), 144.6 (*C*(13)), 138.3 (*C*(14)), 137.0 (*C*(2)), 135.9 (*C*(17)), 131.8 (*C*(16)), 127.4 (*C*(19)), 123.9 (*C*(15)), 122.1 (*C*(18), 120.5 (*C*(12)), 116.8 (*C*(1)), 59.2 (*C*(9)), 53.8 (*C*(4)), 48.5 (*C*(10)), 42.3 (*C*(5)), 35.5 (*C*(3)), 25.2 (*C*(7)), 23.5 (*C*(8)), 23.1 (*C*(6)) ppm.

6.5.10 Preparation of C48



(9*R*)-6'-Methoxycinchonan-9-amine:[206] Obtained according to general procedure CA using quinidine (5.29 g, 16.0 mmol). The product was isolated as a white solid (5.70 g, 81%). $[\alpha]_D^{20}$ = +55.3 (*c* 0.170, $CHCl_3$); MP 91-93 °C; δ_H (400 MHz, D_2O) 8.96 (d, *J* = 5.8 Hz, 1 H, C(13)*H*), 8.19 (d, *J* = 9.3 Hz, 1 H, C(15)*H*), 8.10 (d, *J* = 5.8 Hz, 1 H, C(12)*H*), 7.92 (dd, *J* = 9.3, 2.3 Hz, 1 H, C(16)*H*), 7.69 (d, *J* = 2.3 Hz, 1 H, C(18)*H*), 5.74-5.91 (m, 1 H, C(2)*H*), 5.52 (d, *J* = 11.0 Hz, 1 H, C(1)H_aH_b), 5.24-5.27 (m, 1 H, C(10)*H*), 5.20 (d, *J* = 6.4 Hz, 1 H, C(1) H_aH_b), 4.13-4.28 (m, 1 H, C(9)*H*), 4.04 (s, 3 H, C(31)H_3), 3.43-3.76 (m, 4 H, C(4)H_2 and C(5)H_2), 2.77-2.91 (m, 1 H, C(6)*H*), 1.82-2.08 (m, 3 H, C(3)H_2 and C(7)*H*), 1.38-1.53 (m, 1 H, C(8)*H*'H"), 1.23-1.36 (m, 1 H, C(8)H'*H"*) ppm; δ_C (100 MHz, D_2O) 160.9 (*C*(17)), 150.0 (*C*(11)), 141.4 (*C*(13)), 136.6 (*C*(2)), 135.1 (*C*(14)), 129.3 (*C*(19)), 127.9 (*C*(16)), 124.1 (*C*(15), 120.3 (*C*(12), 116.9 (*C*(1)), 102.1 (*C*(18)), 60.8 (*C*(9)), 56.6 (*C*(31)), 49.3 (*C*(4)), 48.7 (*C*(10)), 46.4 (*C*(5)), 35.3 (*C*(6)), 25.4 (*C*(7)), 23.0 (*C*(8)), 22.1 (*C*(3)) ppm.

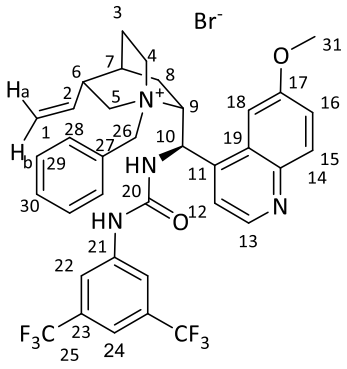
6.5.11 Preparation of C50



1-[(8*R*,9*R*)-1-Benzylcinchonan-1-ium-9-yl]-3-[3,5-bis(trifluoromethyl)phenyl]urea bromide: Obtained according to general procedure CC using **C12** (0.30 g, 0.55 mmol) and benzyl bromide (65 μL, 0.55 mmol) in 6 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (two consecutive columns: 1. Et_2O/MeOH 12:1, then Et_2O/MeOH 6:1; 2. CH_2Cl_2/MeOH 20:1) to yield 115 mg (29%) of product as a pale yellow solid. $[\alpha]_D^{20}$ = +52.7 (*c* 0.360, $CHCl_3$); MP 172-173 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.92 (d, *J* = 3.0 Hz, 1 H, C(13)*H*), 8.74 (br s, 1 H, C(15)*H*), 8.09 (d, *J* = 8.0 Hz, 1 H, C(18)*H*), 7.96 (br s, 1 H, C(12)*H*), 7.88-7.76 (m, 4 H, C(16)*H*, C(17)*H* and C(22)*H* x 2), 7.75-7.67 (m, 2 H, C(29)*H* x 2), 7.53-7.46 (m, 3 H, C(28)*H* x 2 and C(30)*H*), 7.34 (br s, 1 H, C(24)*H*), 6.69 (br s, 1 H, C(10)*H*), 5.75-5.63 (m, 1 H, C(2)*H*), 5.31 (d, *J* = 17.5 Hz, 1 H, C(1)H_aH_b), 5.26-5.04 (m, 3 H, C(1) H_aH_b, C(9)*H* and C(26)*H'*H"), 4.96-4.87 (m, 1 H, C(26)H'*H"*), 4.17-3.92 (m, 2 H, C(4)*H'*H" and C(5)*H'*H"), 3.88-3.75 (m, 1 H, C(5)H'*H"*), 3.30-3.22 (m, 1 H, C(4)H'*H"*), 2.68-2.60 (m, 1 H, C(6)*H*), 2.13-2.03 (m, 1 H, C(3)*H'*H"), 1.97-1.87 (m, 1 H, C(3)H'*H"*), 1.83 (br s, 1 H, C(7)*H*), 1.62-1.53 (m, 1 H, C(8)*H'*H"), 1.33 (br s, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 155.6 (*C*(20)), 151.5 (*C*(13)), 149.3 (*C*(19)), 148.2 (*C*(14)), 142.5 (*C*(21)), 137.3 (*C*(2)), 135.0 (*C*(29) x 2), 133.1 (q, $^2J_{CF}$ = 33.0 Hz, *C*(23) x 2), 131.9 (*C*(30)), 131.7 (*C*(17)), 130.6 (*C*(28) x 2), 130.5 (*C*(18)), 129.4 (*C*(16)), 129.0 (*C*(27)), 128.1 (*C*(11)), 125.1 (*C*(15)), 124.7 (q, J_{CF} = 270.0 Hz, *C*(25) x 2),

121.5 (*C*(12)), 119.4-119.2 (m, *C*(22) x 2), 118.2 (*C*(1)), 116.3-116.1 (m, *C*(24)), 70.4 (*C*(9)), 66.2 (*C*(26)), 57.8 (*C*(5)), 53.5 (*C*(4)), 48.9 (*C*(10)), 38.3 (*C*(6)), 28.7 (*C*(8)), 28.0 (*C*(7)), 24.5 (*C*(3)) ppm; LRMS *m/z* (ESI^+) 639 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br^-]^+$ 639.2556, $C_{35}H_{33}F_6N_4O^+$ requires 639.2553; ν_{max} 3039 (w), 1692 (m), 1567 (m), 1386 (w), 1277 (m), 1175 (m), 1128 (m) cm^{-1}.

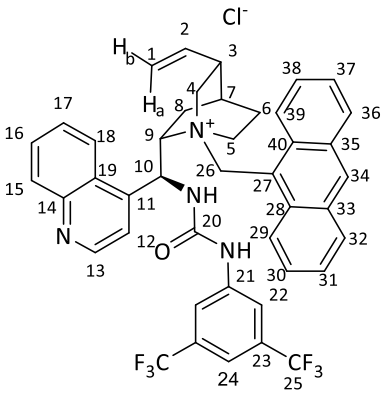
6.5.12 Preparation of C51



1-[(9*R*)-1-Benzyl-6'-methoxycinchonan-1-ium-9-yl]-3-[3,5-bis(trifluoromethyl)phenyl] urea bromide: Obtained according to general procedure CC, using **C32** (200 mg, 0.346 mmol) and benzyl bromide (41 μL, 0.35 mmol) in 3.8 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (two consecutive columns: 1. Et_2O/MeOH 20:1; 2. CH_2Cl_2/MeOH 40:1) to yield 129 mg (50%) of product as a pale yellow solid. $[\alpha]_D^{20}$ = +37.6 (c 1.00, $CHCl_3$); MP 173-174 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.85-8.75 (m, 1 H, C(13)*H*), 8.02 (d, *J* = 9.0 Hz, 1 H, C(15)*H*), 7.96-7.90 (m, 2 H, C(22)*H* x 2), 7.81-7.77 (m, 1 H, C(18)*H*), 7.76 (d, *J* = 4.5 Hz, 1 H, C(12)*H*), 7.70-7.64 (m, 2 H, C(29)*H* x 2), 7.57-7.51 (m, 4 H, C(16)*H*, C(28)H_2 x 2 and C(30)*H*), 7.47 (br s, 1 H, C(24)*H*), 6.54-6.43 (m, 1 H, C(10)*H*), 5.87-5.75 (m, 1 H, C(2)*H*), 5.37 (d, *J* = 17.5 Hz, 1 H, C(1)H_aH_b), 5.26 (d, *J* = 10.5 Hz, 1 H, C(1)H_aH_b), 5.08-4.98 (m, 1 H, C(26)*H'*H"), 4.98-4.87 (m, 2 H, C(9)*H* and C(26)H'*H"*), 4.10 (br s, 4 H, C(5)*H'*H" and C(31)H_3), 3.92-3.79 (m, 2 H, C(4)*H'*H" and C(5)H'*H"*), 3.43-3.34 (m, 1 H, C(4)H'*H"*), 2.73 (br s, 1 H, C(6)*H*), 2.13-

2.04 (m, 1 H, C(3)*H'*H"), 1.99-1.90 (m, 2 H, C(3)H'*H"* and C(7)*H*), 1.80-1.71 (m, 1 H, C(8)*H'*H"), 1.45-1.35 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 160.8 (*C*(20)), 156.2 (*C*(17)), 148.7 (*C*(13)), 146.0 (*C*(19)), 145.7 (*C*(14)), 142.6 (*C*(21)), 137.9 (*C*(2)), 134.9 (*C*(29) x 2), 133.3 (q, J_{CF} = 31.0 Hz, *C*(23) x 2), 132.2 (*C*(15)), 132.0 (*C*(30)), 130.6 (*C*(28) x 2), 129.0 (*C*(27)), 129.0 (*C*(11)), 124.8 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.4 (*C*(16)), 121.1 (*C*(12)), 119.5 (*C*(22) x 2), 118.1 (*C*(1)), 116.5 (*C*(24)), 102.8 (*C*(18)), 70.3 (*C*(9)), 66.7 (*C*(26)), 58.1 (*C*(4)), 56.7 (*C*(31)), 53.8 (*C*(5)), 49.8 (*C*(10)), 38.2 (*C*(6)), 29.3 (*C*(8)), 27.5 (*C*(7)), 24.8 (*C*(3)) ppm; LRMS *m/z* (ESI^+) 669 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br^-]^+$ 669.2663, $C_{36}H_{35}F_6N_4O_2^+$ requires 669.2659; ν_{max} 3211 (w), 3005 (w), 2360 (w), 1689 (m), 1564 (m), 1474 (w), 1386 (w), 1276 (m), 1174 (m), 1127 (w), 702 (m), 680 (m) cm^{-1}.

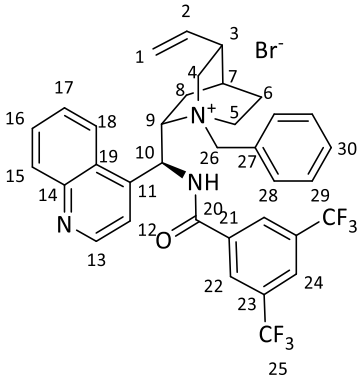
6.5.13 Preparation of C52



1-[(8*R*,9*R*)-1-(anthracen-9-ylmethyl)cinchonan-1-ium-9-yl]-3-[3,5-bis (trifluoromethyl)phenyl] urea chloride: Obtained according to general procedure CC using **C14** (500 mg, 0.911 mmol) and 9-(chloromethyl)anthracene (210 mg, 0.911 mmol) in 10 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (two consecutive columns: 1. Et_2O/MeOH 10:1; 2. CH_2Cl_2/MeOH 20:1) to yield 246 mg (35%) of product as a yellow solid. $[\alpha]_D^{20}$ = –3.7 (c 1.0, $CHCl_3$); MP 206-207 °C (decomp.); δ_H (500 MHz, CD_3OD) 9.09 (d, *J* = 4.5 Hz, 1 H, C(13)*H*), 8.77 (s, 1 H,

C(34)*H*), 8.73 (d, *J* = 9.0 Hz, 1 H, C(Ar)*H*), 8.64 (d, *J* = 8.0 Hz, 1 H, C(Ar)*H*), 8.51 (d, *J* = 8.5 Hz, 1 H, C(15)*H*), 8.19 (d, *J* = 7.5 Hz, 1 H, C(18)*H*), 8.16 (d, *J* = 8.0 Hz, 1 H, C(Ar)*H*), 8.14-8.08 (m, 4 H, C(12)*H*, C(22)*H* x 2 and C(Ar)*H*), 7.95-7.86 (m, 2 H, C(Ar)*H* x 2), 7.74-7.68 (m, 1 H, C(Ar)*H*), 7.60-7.45 (m, 4 H, C(16)*H*, C(17)*H*, C(24)*H* and C(Ar)*H*), 6.85 (d, *J* = 10.5 Hz, 1 H, C(10)*H*), 6.45 (d, *J* = 14.5 Hz, 1 H, C(26)*H'*H"), 5.98 (d, *J* = 14.5 Hz, 1 H, C(26)H'*H"*), 5.79 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1 H, C(2)*H*), 5.63-5.55 (m, 1 H, C(9)*H*), 5.08 (d, *J* = 10.5 Hz, 1 H, C(1)H$_a$*H$_b$*), 5.00 (d, *J* = 17.0 Hz, 1 H, C(1)*H$_a$*H$_b$), 4.92-4.83 (m, 1 H, C(5)*H'*H"), 3.77-3.70 (m, 1 H, C(4)*H'*H"), 3.30-3.20 (m, 2 H, C(4)H'*H"* and C(5)H'*H"*), 2.39-2.31 (m, 1 H, C(3)*H*), 2.29-2.18 (m, 2 H, C(6)*H'*H" and C(8)*H'*H"), 1.93-1.84 (m, 1 H, C(6)H'*H"*), 1.81 (br s, 1 H, C(7)*H*), 1.30-1.23 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 156.6 (*C*(20)), 151.8 (*C*(13)), 149.9 (*C*(19)), 147.3 (*C*(14)), 142.6 (*C*(21)), 137.5 (*C*(2)), 135.1 (*C*(Ar)), 134.7 (*C*(Ar)), 134.1 (*C*(Ar)), 133.4 (q, J_{CF} = 33.0 Hz, *C*(23) x 2), 133.2 (*C*(Ar)), 133.0 (*C*(Ar)), 132.0 (*C*(17)), 131.4 (*C*(Ar)), 131.2 (*C*(Ar)), 130.9 (*C*(18)), 129.9 (*C*(16)), 129.5 (*C*(Ar)), 129.2 (*C*(Ar)), 127.5 (*C*(11)), 126.6 (*C*(Ar)), 126.5 (*C*(Ar)), 125.5 (*C*(Ar)), 124.8 (*C*(Ar)), 124.8 (q, J_{CF} = 271.0 Hz, *C*(25) x 2), 124.6 (*C*(15)), 120.8 (*C*(12)), 119.7 (*C*(22) x 2), 119.4 (*C*(Ar)), 118.2 (*C*(1)), 116.7 (*C*(24)), 71.7 (*C*(9)), 61.8 (*C*(4)), 60.6 (*C*(26)), 51.8 (*C*(5)), 51.5 (*C*(10)), 38.8 (*C*(3)), 29.2 (*C*(8)), 27.4 (*C*(7)), 25.9 (*C*(6)) ppm; LRMS *m/z* (ESI$^+$) 739 (100%, [M-Cl]$^+$); HRMS *m/z* (ESI$^+$) found [M-Cl]$^+$ 739.2873, $C_{43}H_{37}F_6N_4O^+$ requires 739.2866; ν_{max} 3016 (w), 2970 (w), 1739 (m), 1472 (m), 1275 (m), 1133 (m) cm^{-1}.

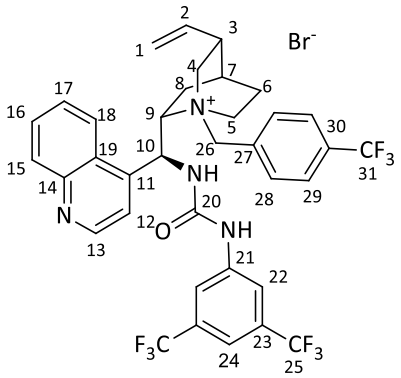
6.5.14 Preparation of C60



***N*-[(8*S*, 9*S*)-1-benzylcinchonan-1-ium-9-yl]-3,5-bis(trifluoromethyl)benzylamide bromide:** Obtained according to general procedure CC using **C26** (49 mg, 0.092 mmol) and benzyl bromide (12 μL, 0.10 mmol) in 1.5 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (two consecutive columns: 1. Et_2O/MeOH 30:1, then Et_2O/MeOH 5:1; 2. CH_2Cl_2/MeOH 30:1) to yield 14 mg (22%) of product as a pale yellow solid. $[\alpha]_D^{20}$ = –103 (*c* 0.290, $CHCl_3$); MP 230-242 °C (decomp. began at 145 °C); δ_H (500 MHz, CD_3OD) 8.99 (d, *J* = 4.5 Hz, 1 H, C(13)*H*), 8.63 (d, *J* = 8.0 Hz, 1 H, C(15)*H*), 8.47 (br s, 2 H, C(22)*H* x 2), 8.15 (dd, *J* = 8.0, 1.5 Hz, 1 H, C(18)*H*), 8.13 (br s, 1 H, C(24)*H*), 7.93 (d, *J* = 4.5 Hz, 1 H, C(12)*H*), 7.87-7.92 (m, 1 H, C(17)*H*), 7.83-7.87 (m, 1 H, C(16)*H*), 7.58-7.65 (m, 2 H, C(29)*H* x 2), 7.53-7.57 (m, 3 H, C(30)*H* and C(28)*H* x 2), 6.92 (br s, 1 H, C(10)*H*), 5.96 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1 H, C(2)*H*), 5.23-5.35 (m, 2 H, C(1)H_2), 5.14 (br s, 1 H C(9)*H*), 4.83-4.97 (m, 2 H, C(26)H_2), 4.32 (br s, 1 H, C(5)*H'*H"), 3.55-3.78 (m, 3 H, C(4)H_2 and C(5)H'*H"*), 2.72-2.79 (m, 1 H, C(3)*H*), 2.06-2.18 (m, 2 H, C(6)*H'*H" and C(8)*H'*H"), 2.02 (br s, 1 H, C(6)H'*H"*), 1.92-1.96 (m, 1 H, C(7)*H*), 1.20-1.27 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 166.2 (*C*(20)), 151.5 (*C*(13)), 149.6 (*C*(19)), 146.4 (*C*(14)), 138.0 (*C*(2)), 136.4 (*C*(21)), 134.8 (*C*(29) x 2), 133.4 (q, J_{CF} = 34.0 Hz, *C*(23) x 2), 132.1 (*C*(30)), 131.9 (*C*(17)), 130.9 (*C*(18)), 130.7 (*C*(28) x 2), 129.8 (*C*(16)), 129.6 (*C*(22) x 2), 128.5 (*C*(27)), 127.9 (*C*(11)), 127.1 (*C*(24)), 124.6

(*C*(15)), 124.5 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 121.6 (*C*(12)), 118.5 (*C*(1)), 69.7 (*C*(9)), 67.0 (*C*(26)), 61.9 (*C*(4)), 50.7 (*C*(5)), 50.7 (*C*(10)), 38.7 (*C*(3)), 29.0 (*C*(8)), 28.0 (*C*(7)), 25.7 (*C*(6)) ppm; LRMS *m/z* (ESI^+) 624 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br]^+$ 624.2451, $C_{35}H_{32}F_6N_3O^+$ requires 624.2444; ν_{max} 3164 (w), 2925 (w), 1737 (w), 1668 (w), 1535 (w), 1457 (w), 1279 (m), 1182 (w), 1133 (m), 761 (m), 701 (m), 681 (m) cm^{-1}.

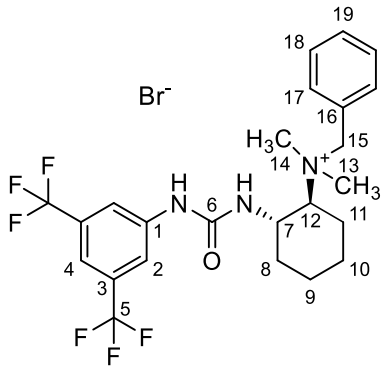
6.5.15 Preparation of C63



1-[(8*S*, 9*S*)-1-(4-Trifluoromethylbenzyl)-6'-methoxycinchonan-1-ium-9-yl]-3-[3,5-bis(trifluoromethyl)phenyl]urea bromide: Obtained according to general procedure CC using **C14** (200 mg, 0.365 mmol) and 4-trifluoromethylbenzyl bromide (56 μL, 0.37 mmol) in 4 mL anhydrous toluene. The concentrated crude reaction mixture was dissolved in minimal CH_2Cl_2, then triturated with PE to yield 62 mg (22%) of product as a white solid. $[\alpha]_D^{20}$ = –2.9 (*c* 1.0, $CHCl_3$); MP >350 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.99 (d, *J* = 3.5 Hz, 1 H, C(13)*H*), 8.51 (br s, 1 H, C(15)*H*), 8.17-8.14 (m, 1 H, C(18)*H*), 7.99 (br s, 2 H, C(22)*H* x 2), 7.92-7.81 (m, 7 H, C(12)*H*, C(16)*H*, C(17)*H*, C(28)*H* x 2 and C(29)*H* x 2), 7.50 (br s, 1 H, C(24)*H*), 6.56 (br s, 1 H, C(10)*H*), 5.90 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1 H, C(2)*H*), 5.26 (d, *J* = 17.5 Hz, 1 H, C(1)*H'*H"), 5.22 (d, *J* = 10.5 Hz, 1 H, C(1)H'*H"*), 5.12 (br s, 2 H, C(26)H_2), 4.99 (br s, 1 H, C(9)*H*), 4.51 (br s, 1 H, C(5)*H'*H"), 3.76 (br s, 1 H, C(4)*H'*H"), 3.62-3.53 (m, 2 H, C(4)H'*H"* and C(5)H'*H"*), 2.80-2.72 (m, 1 H, C(3)*H*), 2.26-1.98 (m, 3 H, C(6)H_2 and C(8)*H'*H"), 1.96-1.91 (m, 1 H, C(7)*H*), 1.30-1.12 (m, 1 H,

C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 156.0 (*C*(20)), 151.5 (*C*(13)), 149.7 (*C*(19)), 146.8 (*C*(14)), 142.4 (*C*(27)), 137.6 (*C*(2)), 135.6 (*C*(21)), 133.7 (q, J_{CF} = 32.0 Hz, (*C*(23) x 2), 133.2 (q, J_{CF} = 32.0 Hz, *C*(30)), 133.3 (*C*(29) x 2), 131.8 (*C*(17)), 130.8 (*C*(18)), 129.7 (*C*(16)), 127.5 (*C*(11)), 127.3 (*C*(28) x 2), 125.2 (q, J_{CF} = 270.0 Hz, *C*(31)), 124.7 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.4 (*C*(15)), 120.6 (*C*(12)), 119.5 (*C*(22) x 2), 118.4 (*C*(1)), 116.6 (*C*(24)), 69.3 (*C*(9)), 66.2 (*C*(26)), 62.3 (*C*(4)), 51.3 (*C*(5)), 51.1 (*C*(10)), 38.7 (*C*(3)), 28.6 (*C*(8)), 28.0 (*C*(7)), 25.6 (*C*(6)) ppm; LRMS *m/z* (ESI^+) 707 (100 %, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br]^+$ 707.2425, $C_{36}H_{32}F_9N_4O^+$ requires 707.2427; ν_{max} 3071 (w), 2849 (w), 1645 (w), 1532 (w), 1275 (m), 1129 (m) cm^{-1}.

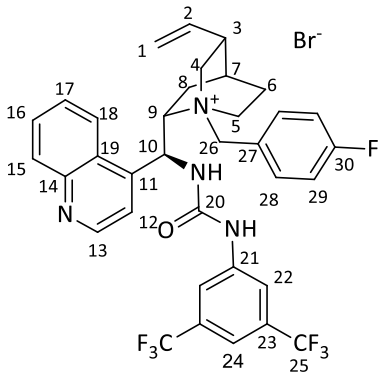
6.5.16 Preparation of C64



(1*S*,2*S*) - *N* – Benzyl - 2 - ({[3,5-bis(trifluoromethyl)phenyl] carbamoyl}amino) - *N*,*N* - dimethylcyclohexanaminium bromide: Takemoto's urea (1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)urea) **C29** (55 mg, 0.14 mmol, 1.0 eq) was suspended in anhydrous toluene (1.5 mL). Benzyl bromide (16 µL, 0.14 mmol, 1.0 eq) was added and the mixture was heated to 65 °C. After 12 h, the solution was allowed to cool to ambient temperature and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (Et_2O/MeOH 10:1, then CH_2Cl_2/MeOH 10:1) to afford the title compound as a pale yellow solid (48 mg, 0.084 mmol, 61%). $[\alpha]_D^{20}$ = – 4.1 (*c* 0.99, $CHCl_3$); MP >350 °C (decomp.); δ_H (400 MHz, CD_3OD) 8.13 (br s, 2 H, C(4)*H*

and C(19)*H*), 7.46-7.60 (m, 6 H, C(2)*H* x 2, C(17)*H* x 2 and C(18)*H* x 2), 4.81 (br s, 1 H, C(15)*H'*H"), 4.78 (br s, 1 H, C(15)H'*H"*), 4.35-4.45 (m, 1 H, C(7)*H*), 3.78-3.87 (m, 1 H, C(12)*H*), 3.14 (br s, 3 H, C(13)H_3), 3.09 (br s, 3 H, C(14)H_3), 2.51-2.59 (m, 1 H, C(11)*H'*H"), 2.05-2.14 (m, 1 H, C(8)*H'*H"), 1.97-2.04 (m, 1 H, C(10)*H'*H"), 1.68-1.87 (m, 3 H, C(8)H'*H"*, C(9)*H'*H" and C(11)H'*H"*), 1.45-1.57 (m, 2 H, C(9)H'*H"* and C(10)H'*H"*) ppm; δ_C (100 MHz, CD_3OD) 156.3 (*C*(6)), 143.1 (*C*(1)), 134.5 (*C*(Ar) x 2), 133.3 (q, J_{CF} = 32.0 Hz, *C*(3) x 2), 132.0 (*C*(19)), 130.4 (*C*(Ar) x 2), 129.2 (*C*(16)), 124.9 (q, J_{CF} = 270.0 Hz, *C*(5) x 2), 119.4-119.5 (m, *C*(2) x 2), 116.1-166.3 (m, *C*(4)), 78.2 (*C*(12)), 67.0 (*C*(15)), 51.4 (*C*(7)), 51.3 (*C*(13)), 50.5 (*C*(14)), 36.6 (*C*(8)), 27.7 (*C*(11)), 26.1 (*C*(9)), 25.4 (*C*(10)) ppm; LRMS *m/z* (ESI^+) 488 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br]^+$ 488.2125, $C_{24}H_{28}F_6N_3O^+$ requires 488.2131.

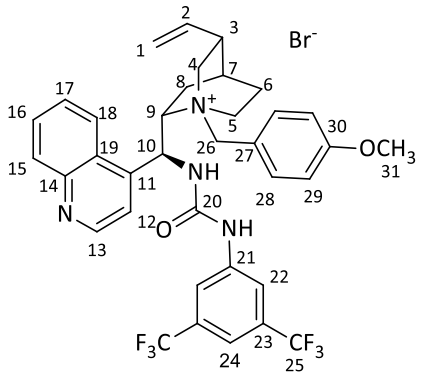
6.5.17 Preparation of C69



1-[(8*S*,9*S*)-1-(4-Fluorobenzyl)-6'-methoxycinchonan-1-ium-9-yl]-3-[3,5-bis (trifluoromethyl) phenyl] urea bromide: Obtained according to general procedure CC using **C14** (200 mg, 0.360 mmol) and 4-fluorobenzyl bromide (46.8 µL, 0.360 mmol) in 4 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (Et_2O/MeOH 20:1-9:1) to yield 158 mg (59%) of product as a pale yellow solid. $[\alpha]_D^{20}$ = +30.5 (*c* 1.00, CH_3OH); MP 161-162 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.96 (br s, 1 H, C(18)*H*), 8.53-8.64 (m, 1 H, C(15)*H*), 8.11 (d, *J* = 7.9 Hz, 1 H, C(13)*H*),

7.98 (br s, 3 H, C(22)*H* x 2 and C(Ar)*H*), 7.79-7.88 (m, 2 H, C(Ar)*H* x 2), 7.69-7.76 (m, 2 H, C(Ar)*H* x 2), 7.43 (br s, 1 H, C(24)*H*), 7.19-7.27 (m, 2 H, C(Ar)*H* x 2), 6.59 (br s, 1 H, C(10)*H*), 5.93 (ddd, *J* = 17.1, 10.3, 6.9 Hz, 1 H, C(2)*H*), 4.96-5.36 (m, 5 H, C(1)H_2, C(9)*H* and C(26)H_2), 4.43 (br s, 1 H, C(5)*H'*H"), 3.69 (br s, 2 H, C(4)H_2), 3.53-3.62 (m, 1 H, C(5)H'*H"*), 2.70-2.79 (m, 1 H, C(3)*H*), 1.95-2.19 (m, 3 H, C(6)H_2 and C(8)*H'*H"), 1.86-1.93 (m, 1 H, C(7)*H*), 1.14-1.25 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 165.6 (d, J_{CF} = 248.8 Hz, *C*(30)), 155.9 (*C*(20)), 151.7 (*C*(13)), 149.7 (*C*(14)), 147.3 (*C*(19)), 142.6 (*C*(16)), 137.9 (*C*(2)), 137.1 (*C*(28) x 2), 133.2 (q, J_{CF} = 33.8 H, *C*(23) x 2), 131.7 (*C*(Ar)), 130.8 (*C*(18)), 129.7 (*C*(15)), 127.7 (*C*(Ar)), 125.1 (*C*(17)), 124.7 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.6 (*C*(Ar)), 121.2 (*C*(Ar)), 119.4 (*C*(22) x 2), 118.4 (*C*(1)), 117.5 (d, J_{CF} = 22.5 Hz, *C*(29) x 2), 116.4 (*C*(24)), 69.4 (*C*(9)), 66.3 (*C*(26)), 61.7 (*C*(4)), 51.8 (*C*(10)), 51.7 (*C*(5)), 38.8 (*C*(3)), 28.6 (*C*(7)), 28.2 (*C*(6)), 25.7 (*C*(8)) ppm; LRMS *m/z* (ESI^+) 657 (100%, $[M-Br]^+$); HRMS *m/z* (ESI^+) found $[M-Br]^+$ 657.24438, $C_{35}H_{32}ON_4F_7^+$ requires 657.24589; ν_{max} 3354 (w, N-H stretch), 2960 (w), 1738 (w), 1413 (w), 1279 (m), 1181 (m), 1121 (m), 974 (m) cm^{-1}.

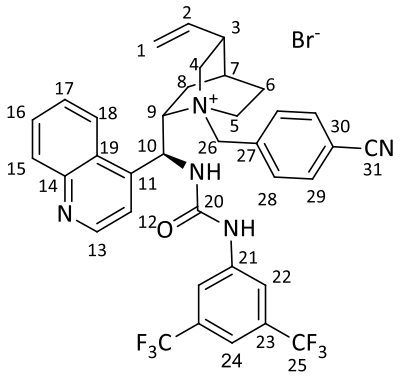
6.5.18 Preparation of C70



1-[(8*S*,9*S*)-1-(4-Methoxybenzyl)-6'-methoxycinchonan-1-ium-9-yl]-3-[3,5-bis (trifluoromethyl)phenyl]urea bromide: Obtained according to general procedure CC using **C14** (200 mg, 0.360 mmol) and *para*-methoxybenzyl bromide (50.4 μL, 0.360 mmol) in 4 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (Et_2O/MeOH 12:1-9:1) to yield 151 mg (59%) of product as a pale yellow solid. $[\alpha]_D^{20}$ = +25.7 (*c* 1.00, CH_3OH); MP 196-197 °C (decomp); δ_H (500 MHz, CD_3OD) 8.97 (br s, 1 H, C(13)*H*), 8.52 (br s, 1 H, C(15)*H*), 8.14 (d, *J* = 8.2 Hz, 1 H, C(18)*H*), 7.99 (br s, 2 H, C(22)*H* x 2), 7.79-7.92 (m, 3 H, C(12)*H*, C(16)*H* and C(17)*H*), 7.54 (d, *J* = 7.7 Hz, 2 H, C(28)*H* x 2), 7.48 (br s, 1 H, C(24)*H*), 7.05 (d, *J* = 7.7 Hz, 2 H, C(29)*H* x 2), 6.53 (br s, 1 H, C(10)*H*), 5.84-5.94 (m, 1 H, C(2)*H*), 5.18-5.30 (m, 2 H, C(1)H_2), 4.94 (br s, 3 H, C(26)H_2 and C(9)*H*), 4.37 (br s, 1 H, C(5)*H'*H"), 3.83 (s, 3 H, C(31)H_3), 3.68-3.78 (m, 1 H, C(4)*H'*H"), 3.46-3.56 (m, 2 H, C(4)H'*H"* and C(5)H'*H"*), 2.69-2.77 (m, 1 H, C(3)*H*), 1.96-2.19 (m, 3 H, C(6)H_2 and C(8)*H'*H"), 1.91 (br s, 1 H, C(7)*H*), 1.13-1.24 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 163.1 (*C*(30)), 156.0 (*C*(20)), 151.7 (*C*(13)), 149.8 (*C*(18)), 145.9 (*C*(14)), 142.6 (*C*(11)), 138.0 (*C*(2)), 136.2 (*C*(28) x 2, *C*(21)), 133.3 (q, J_{CF} = 32.5 Hz, C(23) x 2), 131.8 (*C*(15)), 130.9 (*C*(17)), 129.8 (*C*(27)), 126.3 (*C*(19)), 124.8 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.7 (*C*(16)), 120.5 (*C*(12)), 119.5 (*C*(22) x 2), 118.3 (*C*(1)), 116.5 (*C*(24)), 115.9 (*C*(29) x 2), 69.2 (*C*(9)), 67.1 (*C*(26)), 61.8 (*C*(4)), 56.1 (*C*(31)), 51.0 (*C*(10)),

51.5 (*C*(5)), 38.9 (*C*(3)), 28.6 (*C*(7)), 28.3 (*C*(6)), 25.8 (*C*(8)) ppm; LRMS *m/z* (ESI^+) 669 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br]^+$ 669.26431, $C_{36}H_{35}O_2N_4F_6^+$ requires 669.26587; ν_{max} 3353 (w, N-H stretch), 2977 (w), 1682 (m, C=O), 1572 (m), 1517 (m), 1276 (s), 1178 (m), 1128 (s) cm^{-1}.

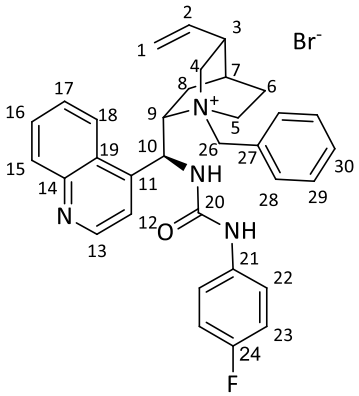
6.5.19 Preparation of C71



1-[(8*S*,9*S*)-1-(4-Cyanobenzyl)-6'-methoxycinchonan-1-ium-9-yl]-3-[3,5-bis (trifluoromethyl)phenyl]urea bromide: Obtained according to general procedure CC using **C14** (200 mg, 0.360 mmol) and 4-(bromomethyl)benzonitrile (72.7 mg, 0.360 mmol) in 4 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography (Et_2O/MeOH 12:1 to 9:1) to yield 152 mg (56%) of product as a yellow solid. $[\alpha]_D^{20}$ = +21.2 (*c* 0.750, CH_3OH); MP 188-189 °C (decomp.); δ_H (500 MHz, CD_3OD) 8.98 (br s, 1 H, C(13)*H*), 8.53-8.62 (m, 1 H, C(15)*H*), 8.14 (d, *J* = 7.9 Hz, 1 H, C(18)*H*), 7.98 (br s, 2 H, C(22)*H* x 2), 7.81-7.95 (m, 7 H, C(Ar)*H* x 7), 7.46 (br s, 1 H, C(24)*H*), 6.51-6.66 (m, 1 H, C(10)*H*), 5.94 (ddd, *J* = 17.2, 10.2, 7.3 Hz, 1 H, C(2)*H*), 5.04-5.38 (m, 5 H, C(1)H_2, C(9)*H* and C(26)H_2), 4.40-4.56 (m, 1 H, C(5)*H'*H"), 3.57-3.80 (m, 3 H, C(4)H_2 and C(5)H'*H"*), 2.74-2.80 (m, 1 H, C(3)*H*), 1.97-2.21 (m, 3 H, C(6)H_2 and C(8)*H'*H"), 1.93 (br s, 1 H, C(7)*H*), 1.14-1.25 (m, 1 H, C(8)H'*H"*) ppm; δ_C (125 MHz, CD_3OD) 155.9 (*C*(20)), 151.7 (*C*(13)), 149.7 (*C*(Ar)), 145.9 (*C*(Ar)), 142.6 (*C*(Ar)), 137.8 (*C*(2)), 135.8 (*C*(29) x 2), 134.2 (*C*(28) x 2), 139.3 (*C*(Ar)), 133.2 (q, J_{CF} = 32.5 Hz, C(23) x 2), 131.8 (*C*(18)), 130.9

(*C*(Ar)), 129.8 (*C*(Ar)), 126.3 (*C*(15)), 124.8 (q, J_{CF} = 270.0 Hz, *C*(25) x 2), 124.6 (*C*(Ar)), 121.5 (*C*(Ar)), 119.5 (*C*(22) x 2), 119.0 (*C*(31)), 118.5 (*C*(1)), 116.5 (*C*(24)), 115.7 (*C*(30)), 69.7 (*C*(9)), 66.2 (*C*(26)), 62.2 (*C*(4)), 51.3 (*C*(10)), 51.0 (*C*(5)), 38.9 (*C*(3)), 28.6 (*C*(7)), 28.0 (*C*(6)), 25.8 (*C*(8)) ppm; LRMS *m/z* (ESI^+) 664 (100%, $[M\text{-}Br]^+$); HRMS *m/z* (ESI^+) found $[M\text{-}Br]^+$ 664.24885, $C_{36}H_{32}ON_5F_6^+$ requires 664.25056; ν_{max} 3240 (w, N-H stretch), 2962 (w), 1692 (w), 1567 (w), 1387 (w), 1276 (m), 1174 (m), 1127 (m) cm^{-1}.

6.5.20 Preparation of C72



1-[(8*S*,9*S*)-1-Benzyl-6'-methoxycinchonan-1-ium-9-yl]-3-(4-fluorophenyl) urea bromide: Obtained according to general procedure CC using 1-[4-fluoro-phenyl]-3-[(8*S*,9*S*)-cinchonan-9-yl]urea (157 mg, 0.360 mmol) and benzyl bromide (43.4 µL, 0.360 mmol) in 4 mL anhydrous toluene. The crude reaction mixture was purified by flash column chromatography using two consecutive columns (1. Et_2O/MeOH 20:1 to 9:1 then 2. MeOH/CH_2Cl_2 9:1) to yield 113 mg (51%) of product as a pale yellow solid. $[\alpha]_D^{20} = -14.7$ (*c* 1.00, $CHCl_3$); MP 165-166 °C (decomp.); δ_H (400 MHz, CD_3OD) 9.01 (d, *J* = 4.2 Hz, 1 H, C(13)*H*), 8.55 (d, *J* = 8.3 Hz, 1 H, C(15)*H*), 8.18 (d, *J* = 8.3 Hz, 1 H, C(18)*H*), 7.83-7.96 (m, 3 H, C(12)*H*, C(16)*H* and C(17)*H*), 7.65-7.72 (m, 2 H, C(29)*H* x 2), 7.55-7.62 (m, 3 H, C(28)*H* x 2 and C(30)*H*), 7.31-7.39 (m, 2 H, C(22)*H* x 2), 6.94-7.03 (m, 2 H, C(23)*H* x 2), 6.55 (br s, 1 H, C(10)*H*), 5.94 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 1 H, C(2)*H*), 5.21-5.35 (m, 2 H, C(1)H_2), 5.12 (br s, 3 H, C(9)*H* and C(26)H_2), 4.48 (br s, 1 H, C(5)*H*'H"), 3.74-3.87 (m, 1

H, C(4)*H'*H"), 3.61-3.73 (m, 1 H, C(4)H'*H"*), 3.49-3.60 (m, 1 H, C(5)*H'*H"), 2.71-2.82 (m, 1 H, C(3)*H*), 1.98-2.24 (m, 3 H, C(6)H_2 and C(8)*H'*H"), 1.94 (br s, 1 H, C(7)*H*), 1.14-1.29 (m, 1 H, C(8)H'*H"*) ppm; δ_C (100 MHz, CD_3OD) 160.4 (d, J_{CF} = 239.0 Hz, *C*(24)), 156.6 (*C*(20)), 151.7 (*C*(13)), 149.8 (*C*(Ar)), 147.3 (*C*(Ar)), 137.8 (*C*(2)), 136.2 (*C*(21)), 134.8 (*C*(29) x 2), 131.9 (*C*(30)), 131.8 (*C*(17)), 130.9 (*C*(18)), 130.7 (*C*(28) x 2), 129.7 (*C*(16)), 129.0 (*C*(27)), 127.5 (*C*(11)), 124.7 (*C*(15)), 122.6 (d, J_{CF} = 8.0 Hz, *C*(22) x 2), 121.0 (*C*(12)), 118.4 (*C*(1)), 116.4 (d, J_{CF} = 23.0 Hz, *C*(23) x 2), 69.5 (*C*(9)), 67.3 (*C*(26)), 61.9 (*C*(4)), 51.3 (*C*(10)), 50.7 (*C*(5)), 38.8 (*C*(3)), 28.5 (*C*(8)), 28.3 (*C*(7)), 25.7 (*C*(6)) ppm; LRMS *m/z* (ESI^+) 521 (100%, $[M-Br]^+$); HRMS *m/z* (ESI^+) found $[M-Br]^+$ 521.26970, $C_{33}H_{34}ON_4F^+$ requires 521.27112; ν_{max} 3460 (w, N-H stretch), 3018 (w), 2961 (w), 1741 (m, C=O), 1668 (m), 1507 (s), 1450 (m), 1373 (m), 1219 (m) cm^{-1}.

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