An Ion-binding Approach to Asymmetric Allylation Reactions

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Declaration

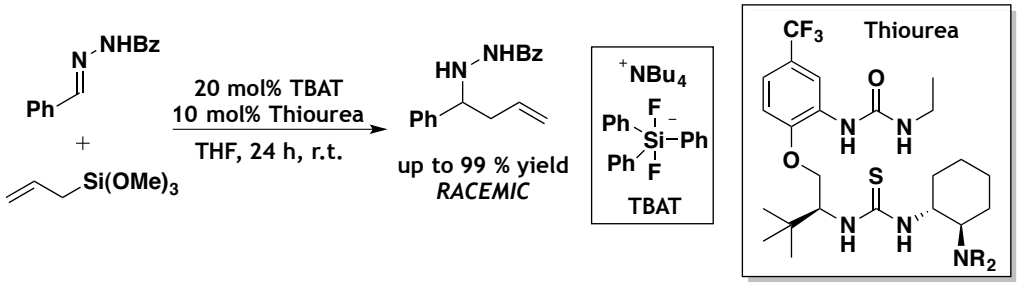
This dissertation describes work carried out in the Chemistry Research Laboratory between October 2009 and June 2013. The dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Caroline Stovold

Abstract

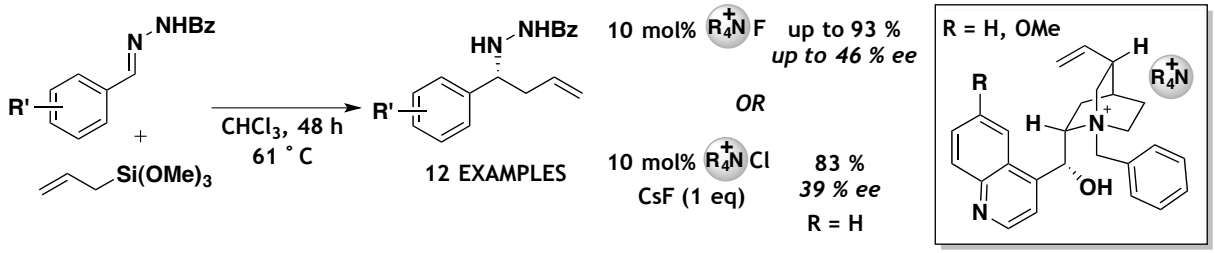
Ion-binding organocatalysis is an emerging field that has the potential to control the stereochemical outcome of any transformation that goes *via* charged intermediates. The aim of this project was to explore how this concept could be applied to an asymmetric allylation reaction.

Chapter 2 of this thesis discusses anion-binding catalysis and investigates a chiral cooperative thiourea catalyst that could bind to fluoride to control allylation using an allylsilane. Optimization using a non-chiral thiourea (Schreiner's catalyst) demonstrated that the reaction proceeded in high yield with TBAT onto an *N*-benzoylhydrazone. A chiral cooperative thiourea catalyst library was then synthesized but unfortunately, although the allylation using these catalysts proceeded in excellent yield, the product was isolated as the racemate (**Scheme 1**).



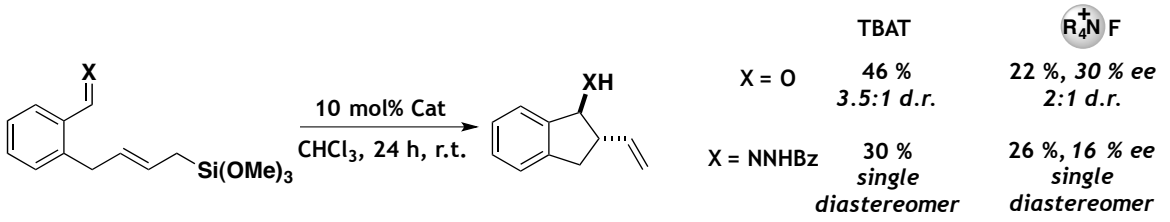
***Scheme 1**: Anion-binding catalysis gave allylated products in high yields but gave no stereocontrol*

Chapter 3 examines a chiral quaternary ammonium fluoride as an example of chiral cation-directed catalysis. We hypothesized that an allylsilane activated by fluoride would generate an allyl anion species that would associate with the chiral quaternary ammonium cation through electrostatic interactions. Extensive optimization found that the allylation reaction proceeded in good yield in chloroform at reflux with *N*-benzoylhydrazones. Different fluoride catalysts were prepared using an ion-exchange resin, and cinchonidine-derived catalysts performed the best. This methodology was extended to a phase-transfer catalyzed process, where solid cesium fluoride exchanged with chloride *in situ*, removing the need to synthesize and isolate ammonium fluoride catalysts (**Scheme 2**).



***Scheme 2**: Cation-directed asymmetric allylation*

In **Chapter 4** cation-directed asymmetric catalysis was extended to an intramolecular allylation reaction. Substrate synthesis was attempted by cross metathesis but the reaction was capricious and yields were low. Intramolecular allylation with these materials gave promising results (**Scheme 3**) but a lack of material prevented optimization.



***Scheme 3**: Intramolecular allylation results*

This thesis is dedicated to my Dad and Nan, who sadly are not here to celebrate the end of my DPhil. They would have been proud to call me Doctor!

Alan Stovold

14.01.1954 – 11.10.2011

Margaret Stovold

31.12.1921 – 29.02.2012

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This thesis would no doubt not be the same without all the wonderful people whom I have had the pleasure of working with over the past four years. I have many happy memories of my time in the Smith group and I am privileged to be able to call many of you friends.

My supervisor, Dr Martin Smith, has been an enthusiastic mentor. I am particularly grateful for his time and attention on how to create an aesthetically-pleasing presentation and the importance of selecting a good font. I look forward to beginning the tradition of leaving the group using his champagne sword.

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A project like this can't be done without the love and support of ones family, and I am lucky to have such a fantastic one.

A special mention must go to Dr Phil Woods, my love and my best friend. I can't wait to start life's next adventure together.

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Glossary of Terms

The following abbreviations are used in this thesis:

-ve	Negative
+ve	Positive
$[\alpha]_D$	Optical rotation
Å	Ångstroms
Ac	Acyl
Ar	*Denotes a generic aromatic system*
aq.	Aqueous
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
br.	Broad
Bu	Butyl
Bz	Benzoyl
c	Concentration
˚C	Degrees Celsius
CAN	Cerium Ammonium Nitrate
Cat	Catalyst/Catalytic
cod	1,5-Cyclooctadiene
COSY	Correlation Spectroscopy
δ	Chemical shift
d	Days
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCE	1,2-Dichloroethane
dba	Dibenzylideneacetone
dec.	Decomposition
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethyoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane

DMSO	Dimethylsulfoxide
d.r.	Diastereomeric ratio
ε	Dielectric constant
ε_0	Vacuum Permittivity
E	Potential Energy
ee	Enantiomeric excess
eq.	Equivalents
equiv.	Equivalents
e.r.	Enantiomeric ratio
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron-withdrawing group
FI	Field ionisation
FPP	4-Fluorophenylpiperazine
g	Grams
h	Hours
hfacac	Hexafluoroacetylacetonate
HG II	Hoveyda-Grubbs 2nd generation catalyst
HMBC	Heteronuclear multi-bond correlation spectroscopy
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation spectroscopy
i	*iso*
IPA	*iso*-Propylalcohol
IR	Infrared
J	Coupling constant
K	Equilibrium constant
K	Kelvin
KHMDS	Potassium bis(trimethylsilyl)amide
λ	Wavelength
L	Litre
LA	Lewis acid
LB	Lewis base
LDA	Lithium di-*iso*-propylamide
μ	Micro

m	*meta*
m	Metre
m	Milli
m	Multiplet
M	Molar concentration (mol dm^{-3})
Me	Methyl
MHz	Megahertz
min	Minutes
mol	Moles
m.p.	Melting point
MS	Molecular sieves
MW	Molecular weight
ν	Wavelength
n	Nano
Nap	Naphthyl
NMR	Nuclear magnetic resonance
n.r.	No reaction
Nu	Nucleophile
o	*ortho*
p	*para*
P	*Denotes a generic protecting group*
Ph	Phenyl
pin	Pinacol
pK_a	Acid dissociation constant
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
q	Charge
q	Quartet
quant.	Quantitative
quin	Quintet
R	*Denotes a generic substituent*
R_f	Retention factor
r.t.	Room temperature
s	Singlet
S_NAr	Nucleophilic aromatic substitution

S.M.	Starting material
SOMO	Singly occupied molecular orbital
t	*tertiary*
tert	*tertiary*
t_R	Retention time
t	Triplet
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TBAT	Tetra-*n*-butylammonium triphenyldifluorosilicate
TBME	Methyl *tert*-butyl ester
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
Temp	Temperature
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMAF	tetra-*n*-methylammonium fluoride
TMS	Trimethylsilyl
TRIP	3,3′-bis(2,4,6-Triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
TS	Transition state
Ts	Tosyl
UV	Ultraviolet
w	Wave
wt.%	Weight percent
X	Halide anion

1. Introduction

There are three principal branches of asymmetric catalysis predominantly used by synthetic organic chemists today – these are enzymatic catalysis, organometallic catalysis and organocatalysis.[1] Research into organocatalysis has boomed since the late 1990's, providing a practical and inexpensive approach. Organocatalysts offer a non-toxic alternative to complementary organometallic catalytic methods, and are often air and water stable.

In this thesis, we are primarily concerned with ion-binding (or ion-pairing) organocatalysis. Ion-binding organocatalysts can achieve stereocontrol in any transformation that proceeds *via* a charged intermediate and this project hoped to exploit this for an asymmetric allylation reaction. This introduction will first outline the field of ion-binding organocatalysis, and secondly present the different approaches towards catalytic asymmetric allylation.

1.1 Ion-binding Catalysis

"An ion pair is defined to exist when a cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy (RT) available to separate them. This means that the ions stay associated longer than the time required for Brownian motion to separate non-interacting species." [2]

Ion-binding catalysis is a burgeoning field, in which the stereochemical outcome of a reaction is controlled by the electrostatic forces between two ions.[3] The electrostatic interaction is described by Coulomb's law:

$$E = \frac{q_1 q_2}{4\pi\varepsilon\varepsilon_0 r}$$

where the potential energy (E) between two ions (q_1 and q_2) is inversely related to the distance between the two ions (r) and the dielectric constant of the medium they occupy (ε). Hence, strong ion-pairing is favoured by short distances and nonpolar solvents.[4]

Asymmetric reactions controlled by ion-pairing can be categorized into two general approaches. Firstly, we can consider a neutral chiral catalyst non-covalently binding to either an anion (**1**) or a metal cation (**2**) (**Figure 1.1 (a)**). Alternatively, chiral anionic or cationic catalysts can ion-pair with species of opposite charge (**3** and **4** respectively) (**Figure 1.1 (b)**).[3,4] Here, we briefly introduce each approach to demonstrate the breadth of application.

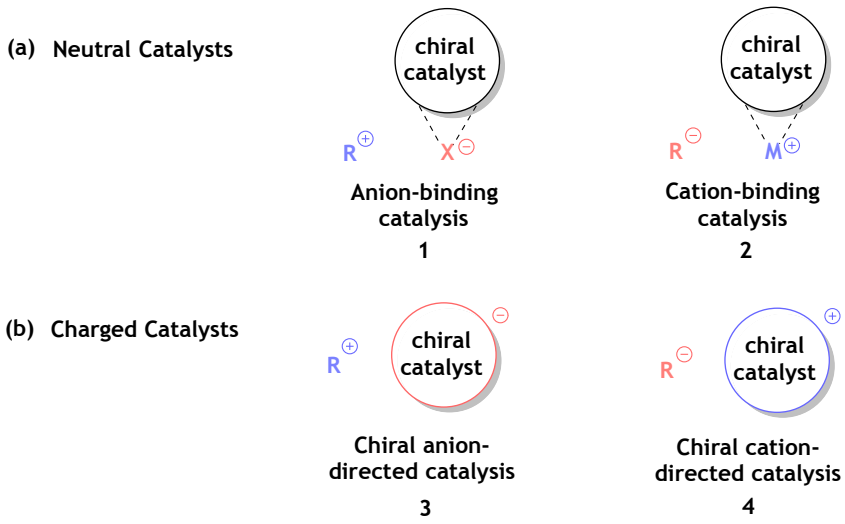


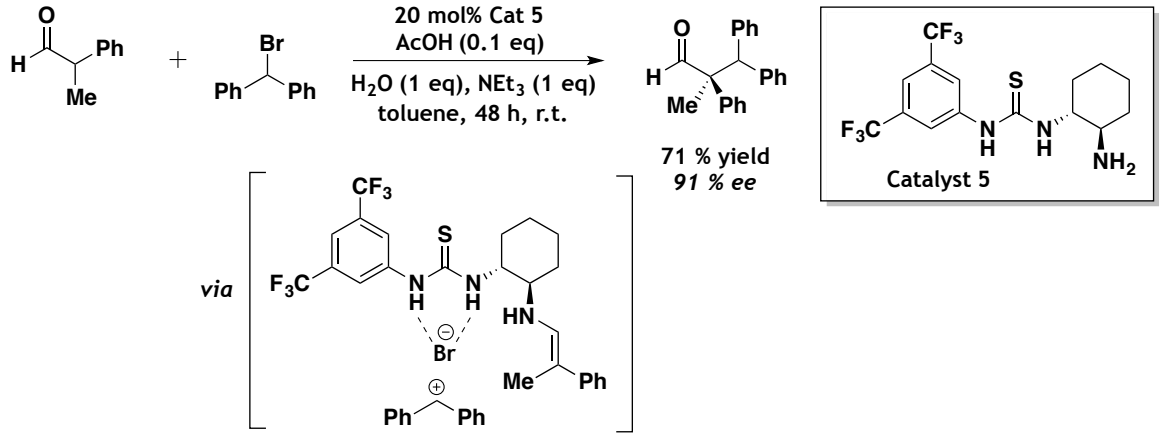
***Figure 1.1**: **(a)** Chiral neutral catalysts non-covalently binding to charged ion-pair intermediates and **(b)** counterion-pairing with charged, chiral catalysts*

1.1.1 Anion-binding Catalysis

This is a relatively new field that takes advantage of well-established anion-binding properties of (thio)urea catalysts.[5] Two distinct types of anion-binding catalysis have emerged thus far – (1) thio(urea) assisted anion extraction of reaction precursors and (2) thio(urea) anion-binding to ion-pair intermediates.[4] This methodology has already been applied using a wide range of anions including alkoxide,[6] cyanide,[7] carboxylate[8] and halide anions.[9]

For example, Jacobsen and coworkers disclosed that α-alkylation of aldehydes proceeds *via* an S_N1 pathway controlled by bromide anion-binding to thiourea **5** (**Scheme 1.1**).[10] Confirmation of this mechanism came from experimental evidence. Firstly, they showed that a secondary kinetic isotope effect occurred upon deuterium-substitution of the benzhydryl proton, indicating a change from sp^3 to sp^2 hybridization at the electrophilic carbon. A Hammett study also indicated that benzhydryl substrates that have electron-donating substituents react faster. Both of these results suggest a

transformation that proceeds *via* a carbocation intermediate formed by association with the catalyst. In addition, competition experiments between equimolar amounts of benzyl bromide and benzhydryl bromide, under the catalytic conditions, resulted in exclusive reactivity with benzhydryl bromide. This highlights the strong preference of these catalysts to promote an S_N1 pathway over an S_N2 pathway, resulting from catalyst **5**'s affinity for halide anions.

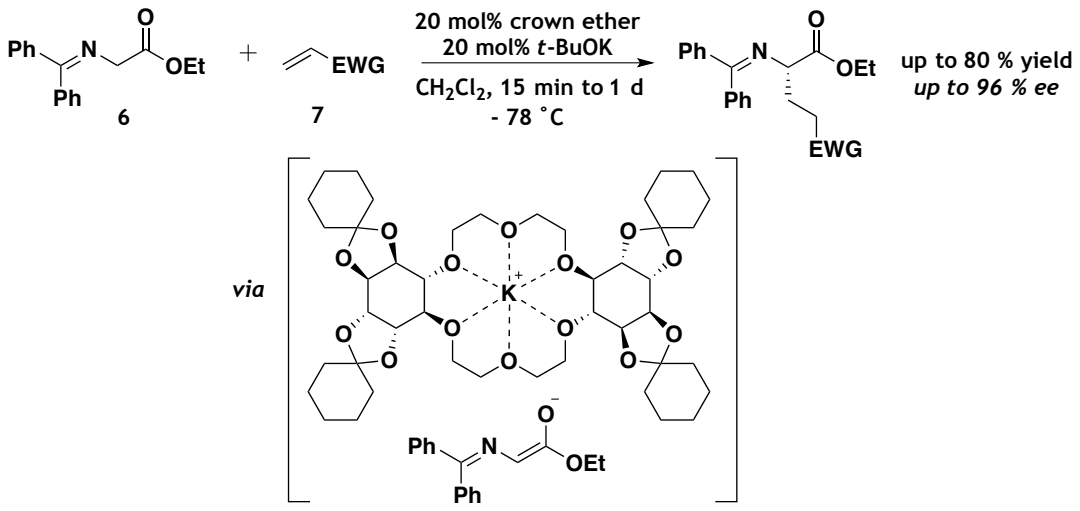


***Scheme 1.1**: α-Alkylation of aldehydes via an S_N1 mechanism*

1.1.2 Cation-binding Catalysis

The well-established metal-complexing abilities of polyethers make them potential cation-binding catalysts and these have been exploited in the field of phase-transfer catalysis. Crown ethers and other compounds with appropriately positioned heteroatoms, such as TADDOL and NOBIN, can successfully abstract an ion-pair into the organic phase by binding to the metal cation.[11] This method has been applied in asymmetric alkylation,[12] Michael[13] and Darzens[14] reactions.

Akiyama *et al.* used crown ethers derived from *chiro*-inositol (a carbohydrate) to perform an asymmetric Michael addition (**Scheme 1.2**).[15] The enolate formed, after deprotonation with potassium *tert*-butoxide of starting material **6**, complexes with the crown ether. Attack of different electrophiles **7** proceeded smoothly in good yields and high enantioselectivities (up to 96 % ee).



***Scheme 1.2**: Crown ether abstraction of an enolate intermediate in an asymmetric Michael addition*

1.1.3 Chiral Anion-directed Catalysis

Chiral counteranion-directed catalysis is a field that has blossomed over the last 10 years.[16,17] It is distinct from more traditional general Brønsted acid catalysis, where there is some hydrogen bonding character between an acid proton and the electrophile. The acid is fully dissociated and the chiral anion catalyst interacts with a cationic substrate primarily through electrostatic interactions (**Figure 1.2**).

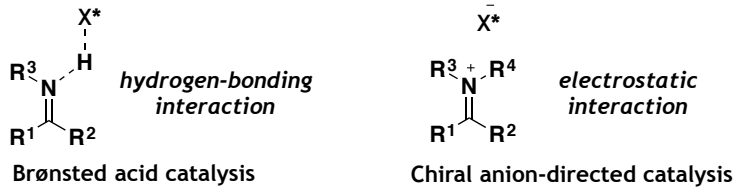
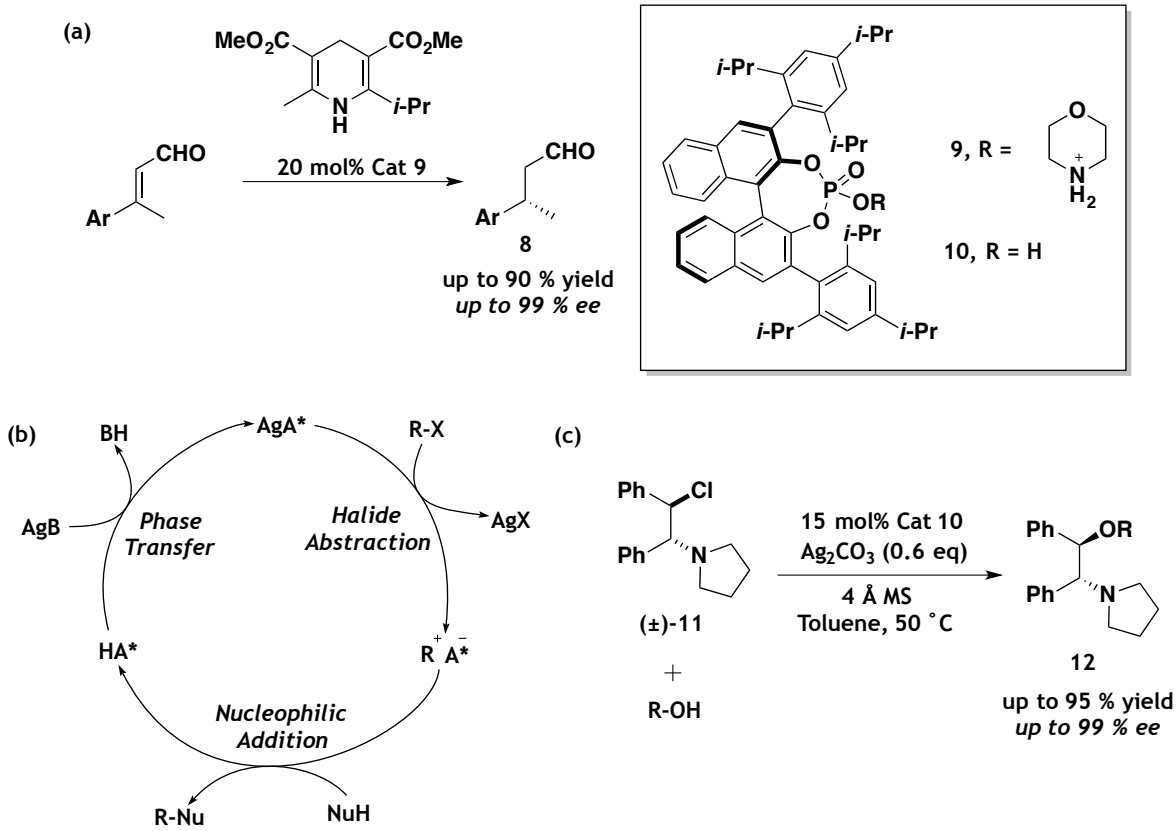


***Figure 1.2**: The difference between Brønsted acid catalysis and anion-directed catalysis*

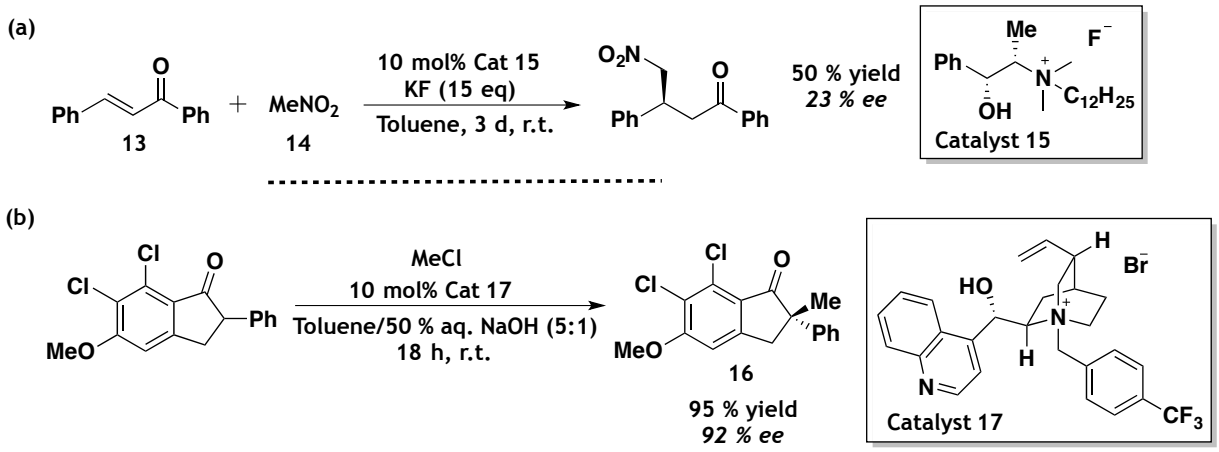
The use of chiral phosphate anions has dominated the topic of anion-directed catalysis since List and Mayer's work in 2006.[18] They designed TRIP-derived catalyst **9** for an asymmetric transfer hydrogenation reaction, which gave products **8** in exceptional enantioselectivities (**Scheme 1.3 (a)**). Another interesting development in the field is chiral anion phase-transfer catalysis (**Scheme 1.3 (b)**). Toste and coworkers realized that phosphoric acid **10** could abstract Ag^+ from aqueous solution, and in turn achieve chloride abstraction from substrate **11**. The ion-pair formed could then undergo nucleophilic addition in a controlled manner. This led to products **12** in up to 95 % yield and 99 % ee (**Scheme 1.3 (c)**).[19]



***Scheme 1.3**: **(a)** Transfer hydrogenation using a chiral anion catalyst, **(b)** mechanism for phase-transfer catalysis with chiral anions and **(c)** opening of an aziridinium intermediate controlled by a chiral phosphate*

1.1.4 Chiral Cation-directed Catalysis

Asymmetric induction invoked by a chiral cation was pioneered by Wynberg and coworkers in the late 1970s.[20,21] For example, quaternary onium catalyst **15** effected the Michael addition of nitromethane **14** to chalcone **13** with 23 % ee (**Scheme 1.4 (a)**). However, the true potential for chiral cation catalysis to access products with high enantioselectivity was first revealed by the Merck group in 1984.[22] They found that alkylation using *N*-benzylcinchoninium bromide **17** and aqueous NaOH solution afforded (+)-indacrinone **16** in 95 % yield and 92 % ee (**Scheme 1.4 (b)**).



***Scheme 1.4**: **(a)** Early example of a chiral cation employed for a Michael reaction and **(b)** the first highly stereoselective alkylation reaction directed by a chiral cation*

Since then, chiral catalytic phase-transfer reactions have dominated the research into cationic organocatalysts.[23,24] The majority of these have been based on a quaternary ammonium salt scaffold (**Figure 1.3**). Cinchona alkaloids are easily derivatized to catalysts such as **18** and **19**. Other successful catalyst frameworks designed and synthesized by chemists include Maruoka-type catalysts **20**[25] and Lygo-type catalysts **21**.[26] Shibasaki has also developed bisammonium salts **22** from tartrate.[27]

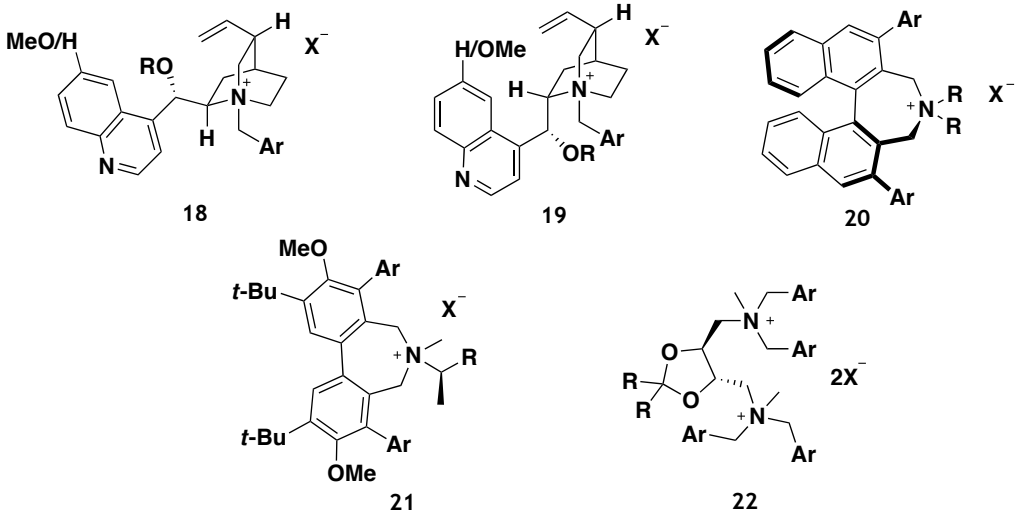
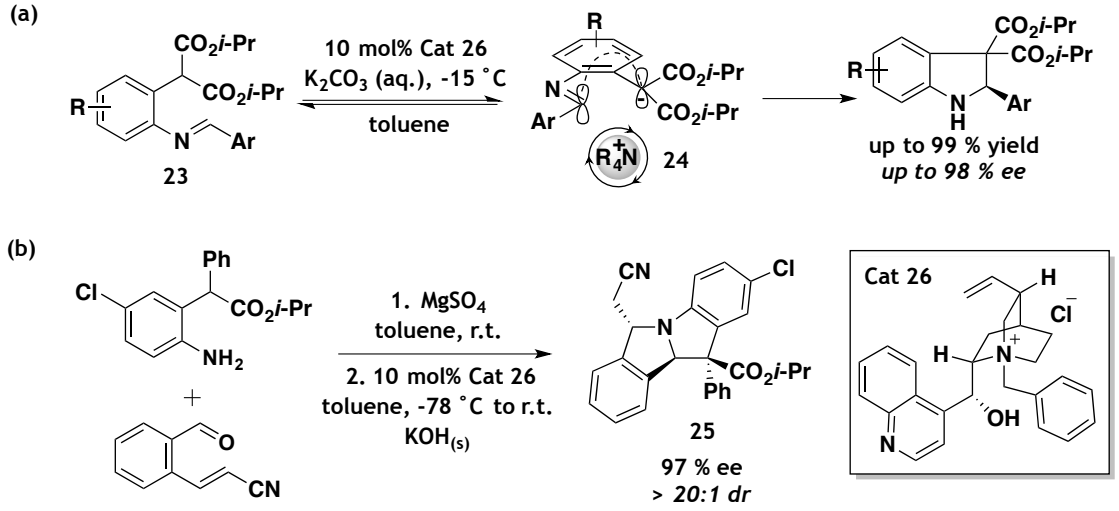


***Figure 1.3**: Range of chiral quaternary ammonium salt catalysts for phase-transfer reactions*

These quaternary ammonium salts have been used for phase-transfer catalysis to give exceptional yields and stereoselectivity for a range of reactions, under mild conditions. Most attention has been given to alkylation reactions, particularly of protected-glycine compounds for the synthesis of

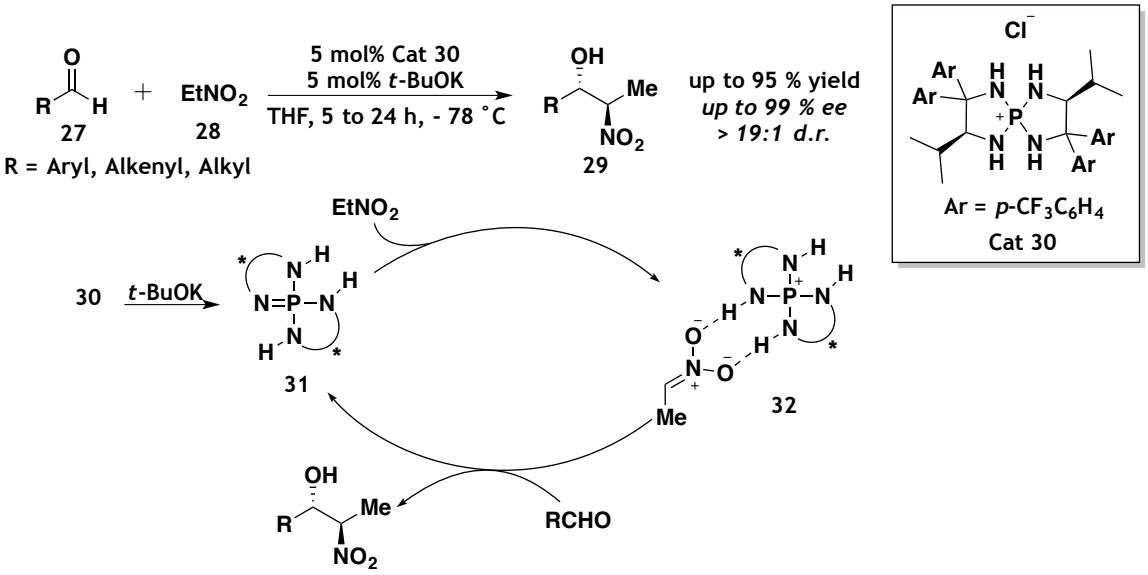
α-amino acids.[24, 28] However, other transformations, including (but not limited to) Michael additions,[29] Mannich reactions,[30] Darzens reactions[31] and cyclizations[32] have also been explored.

Previous work in the Smith group utilized this methodology for an asymmetric 6π electrocyclization reaction.[33] Deprotonation of starting material **23** leads to delocalized anion **24,** which, when closely bound to cinchonidine-derived cation **26**, undergoes 6π electrocyclization in up to 99 % yield and 98 % ee (**Scheme 1.5 (a)**). This work has also been extended to an electrocyclization-1,4-addition cascade process (**Scheme 1.5 (b)**).[34] This method can create complex polycycles, such as **25**, that contain three contiguous stereocentres, one of which is all-carbon. Chiral catalyst **26** constructs these compounds with impressive enantio- and diastereocontrol.



***Scheme 1.5**: **(a)** 6π Electrocyclization controlled by chiral catalyst **26** and **(b)** extension to an electrocyclization-1,4-addition cascade to make complex polycycles*

A recent innovation for chiral cation-directed catalysis is the advancement of chiral phosphonium salts, which have not only been employed as phase-transfer catalysts[35] but also as organic base catalysts.[36] For example, Ooi and coworkers developed chiral tetraaminophosphonium salt **30** for a Henry reaction.[37] Nitroethane **28** could be added to a range of aldehydes **27** to give alcohol products **29** with excellent enantio- and diastereocontrol (**Scheme 1.6**). They rationalized that *tert*-butoxide base would deprotonate the catalyst **30** to give triaminoiminophosphorane **31**. This would then participate in the catalytic cycle, by deprotonating the nitroethane, to create an ion-pair **32**, before addition onto the aldehyde **27**.



Scheme 1.6**: Henry reaction with phosphonium catalyst **30

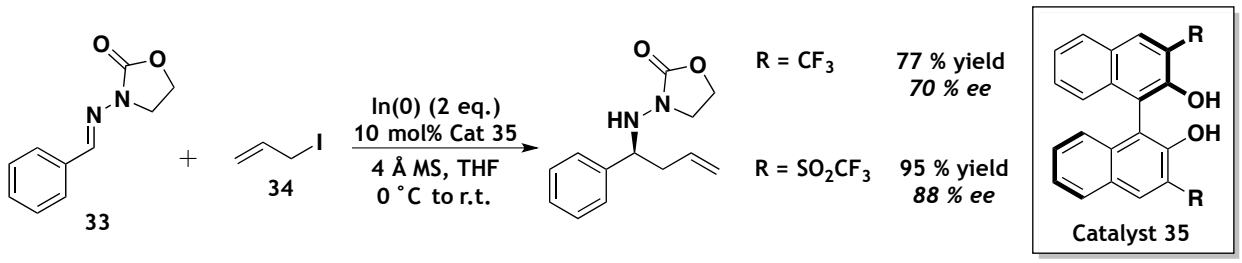
1.2 Allylation of Imino Compounds

Allylation of imines is a key reaction in synthetic chemistry because it simultaneously creates a carbon-carbon bond and a new stereocentre.[38] It also introduces an olefin group that can be subsequently elaborated and this attribute has been utilized in the total synthesis of a range of natural products.[39] However, although catalytic enantioselective allylation methods have been successfully applied for aldehydes and ketones, allylation of C=N electrophiles lags behind.[40] This is because the coordination of Lewis acid catalysts to imines, oximes and hydrazones is not fully understood causing stereoselectivties to be lower. In addition, the amine products frequently bind to Lewis acid catalysts, limiting their turnover.

Over the last decade, chemists have conceived a range of allylation strategies to develop catalytic asymmetric reactions to make homoallyl amines. These often employ chiral Lewis acids and metals, but there have also been some advances in organocatalysis. This section outlines some of the catalytic enantioselective allylation reactions that have been developed using allylic halides, allylic boranes, allylic alcohols and allylic silanes.

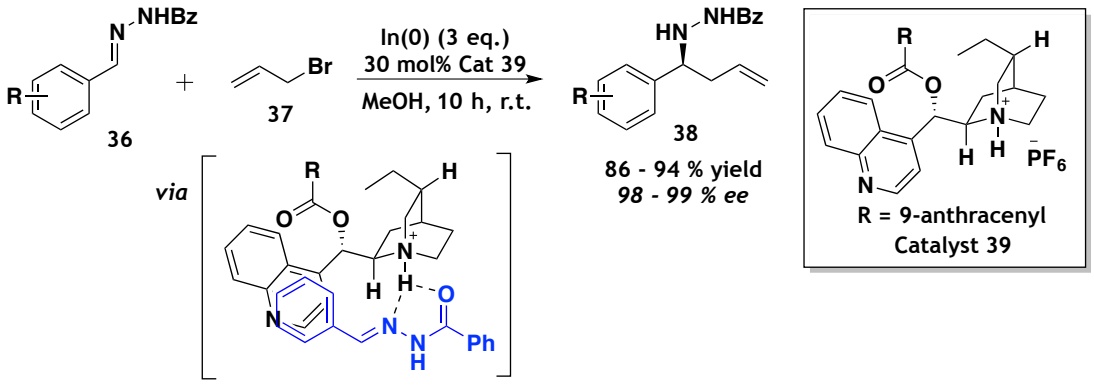
1.2.1 Allylic Halides

Allylic halides can be productively added to imines under Barbier-type conditions. The metal of choice for this is indium as it is regarded as having low toxicity and good stability.[41] Cook and Lloyd-Jones have used indium metal in combination with allyl iodide **34** or allyl bromide **37** for the allylation of hydrazones **33** derived from oxazolidinone (**Scheme 1.7**).[42] They developed a chiral BINOL catalyst **35** for this reaction, and found that the electronic properties of the catalyst were important for attaining high levels of enantioselectivity. When R is a trifluoromethyl substituent the best ee was 70 % but when the more electron-withdrawing group trifluoromethylsulfone was used the ee increased to 88 %.



***Scheme 1.7**: BINOL-catalyzed, In(0) mediated allyl iodide addition to hydrazones*

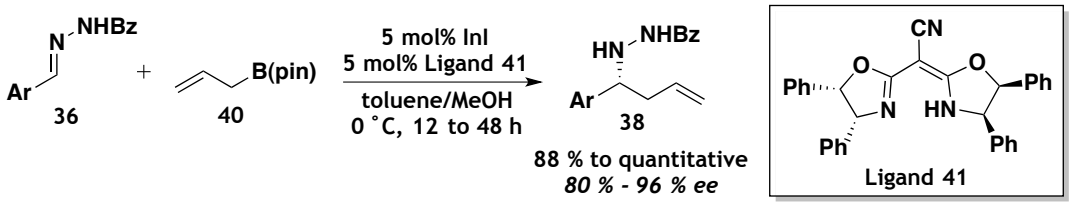
Kim and Jang utilized a chiral protonated amine **39** to catalyze In/allyl bromide **37** addition to hydrazones **36** under ambient conditions (**Scheme 1.8**).[43] They found that 99 % ee could be obtained for most aromatic-derived hydrazones that they tested. Interestingly, when they used the chiral amine alone (i.e. not protonated) they found the product was acquired racemically. They postulated from ^{1}H-NMR evidence that the hydrazone **36** interacts with the catalyst **39** *via* hydrogen bonding and π-π stacking, and that there is no association between the catalyst and the allylindium species.



***Scheme 1.8**: Chiral amine **39** interacts with hydrazone **36** for allylation with indium/allyl bromide.*

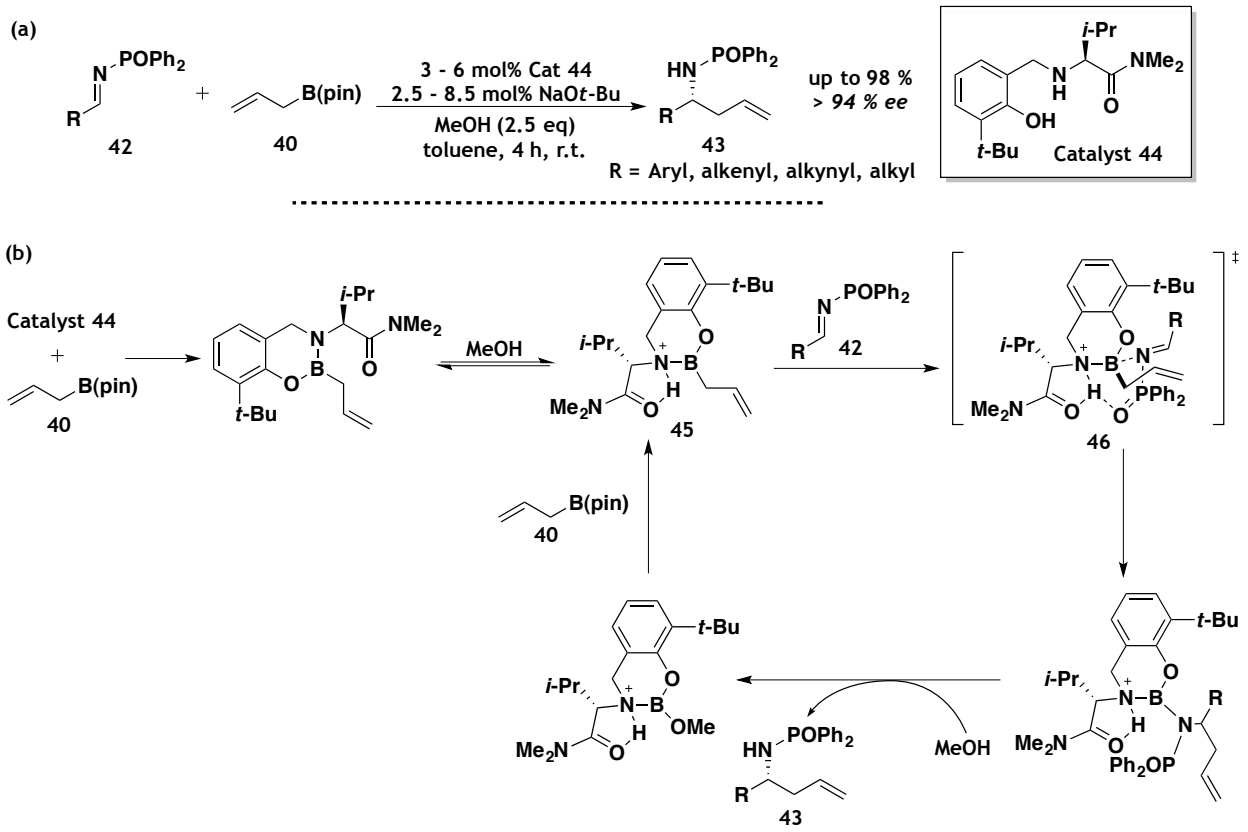
1.2.2 Allylic Boranes

Allylic boranes and boronates can react with imines efficiently when used in combination with metal catalysts, such as copper(I)[44] and zinc(II).[45] Kobayashi *et al.* have developed an indium(I)-catalyzed reaction that can achieve excellent results with bis(oxazoline) ligand **41**.[46] Allyl boronate pinocol ester **40** can react with hydrazones **36** in excellent yields and enantioselectivities (**Scheme 1.9**).



Scheme 1.9**: In(I)-mediated reaction of allyl boronate **40

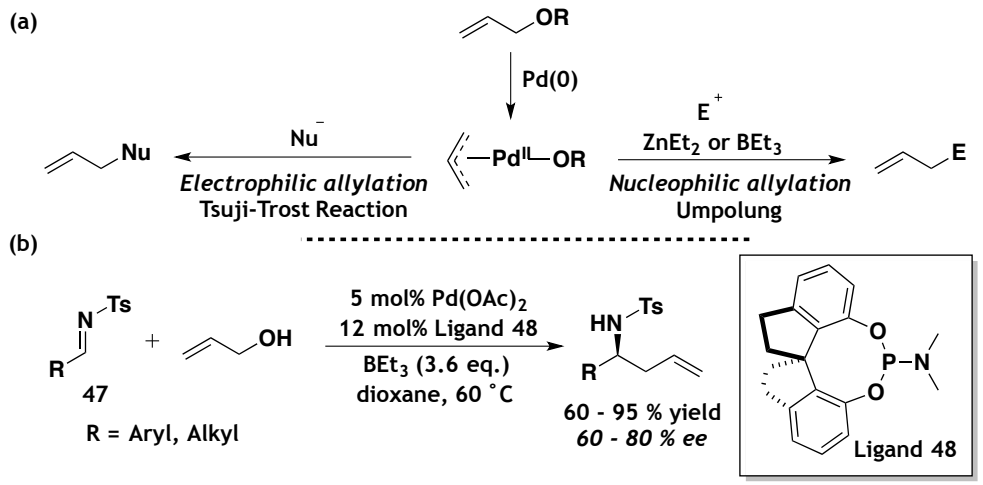
Reaction of allylic boranes without metals requires higher catalyst loadings and longer reaction times because ligand exchange is slow.[47] Recently, Hoveyda and coworkers reported an aminophenol organocatalyst **44** that can overcome these issues.[48] A wide range of *N*-phosphinoylimines **42** undergo allylation with allyl boronate **40** at low catalyst loadings to give the most general allylation procedure to date (**Scheme 1.10 (a)**). Conversion was found to be > 98 % in most cases and enantioselectivities were frequently > 94 %. Mechanistic work and computational studies revealed that a proton provided by methanol allows for hydrogen bonding within **45**, which increases the Lewis acidity of boron and facilitates substrate binding to make **46** (**Scheme 1.10 (b)**).



***Scheme 1.10**: **(a)** Allylation using allyl boronate **40** catalyzed by chiral amino phenol **44** and **(b)** mechanistic studies reveal internal hydrogen-bonding that increases the Lewis acidity of boron resulting in faster reaction turnover*

1.2.3 Allylic Alcohols

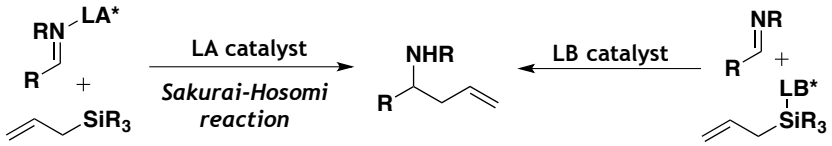
Allylic alcohols or acetates are stable, widely available and offer an alternative approach. Traditionally allyl alcohols can form π-allylpalladium species with Pd(0), which can react with nucleophiles in a Tsuji-Trost reaction. However, with the addition of either $ZnEt_2$ or BEt_3, the π-allylpalladium complex can react with electrophiles, demonstrating umpolung chemistry (**Scheme 1.11 (a)**).[49] There are limited examples of asymmetric allylations with imines, but Zhou *et al.* found that excellent yields (up to 95 %) and good enantioselectivties (up to 80 % ee) are achievable (**Scheme 1.11 (b)**).[50] They used chiral phosphoramidite ligand **48** and 5 mol% $Pd(OAc)_2$ to react with *N*-tosylimines **47** derived from aromatic and aliphatic aldehydes. They speculate that the mechanism goes *via* a η^3- to η^1-allylpalladium complex promoted by BEt_3, originally proposed by Feringa,[51] but state that the full mechanistic details are unclear.



***Scheme 1.11**: **(a)** Allylpalladium complexes can react with nucleophiles or electrophiles and **(b)** reaction with N-tosylimines gives good yields and enantioselectivities*

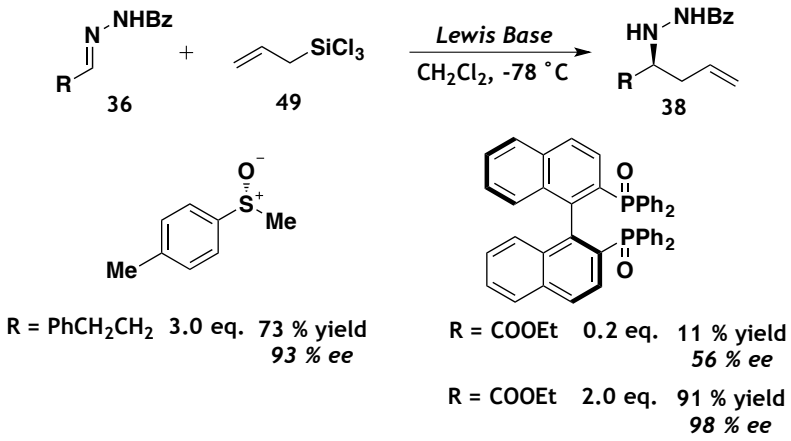
1.2.4 Allylic Silanes

There are two modes of operation to catalyze addition of allylsilanes to electrophiles. The Sakurai-Hosomi reaction involves a Lewis acid activating the electrophile to promote allylsilane addition (**Scheme 1.12)**. Alternatively, a Lewis base can directly activate the allylsilane, sometimes in combination with a Lewis acid.[52]



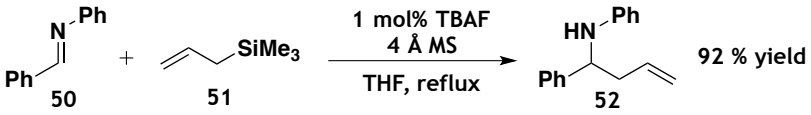
***Scheme 1.12**: Allylic silane additions can be controlled by either Lewis acid or Lewis base catalysis*

Research into chiral Lewis base activators stemmed from work by Kobayashi and coworkers, who noticed that DMF solvent could activate allyltrichlorosilane **49** and react with *N*-benzoylhydrazones **36**.[53] This led the group to develop chiral Lewis bases to perform an asymmetric allylation with hydrazones. Both chiral sulfoxides[54] and chiral phosphine oxides[55] gave excellent enantioselectivities and yields in dichloromethane at −78 °C (**Scheme 1.13**). However, the chiral Lewis base had to be used in stoichiometric quantities because the yield and ee significantly decreased when the chiral Lewis base was used as a catalyst.



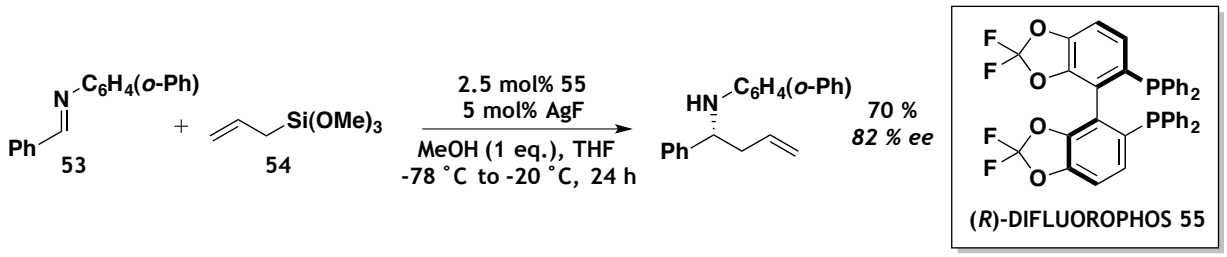
***Scheme 1.13**: Chiral Lewis base promoted allylsilane addition*

Fluoride anions can also promote the addition of allylsilanes to imino compounds. Hou *et al.* were first to demonstrate that TBAF could be used as a catalyst.[56] The reaction was performed using only 1 mol% of TBAF with allyltrimethylsilane **51** and benzylimine **50** (**Scheme 1.14**). The addition of 4 Å molecular sieves was essential; without it the product **52** was not observed. They carried out mechanistic studies to deduce that the reaction is initiated by fluoride and the reaction is autocatalytic in the product (See **Chapter 3.1.4**). Despite this, no asymmetric base-catalyzed reaction has been reported to date.



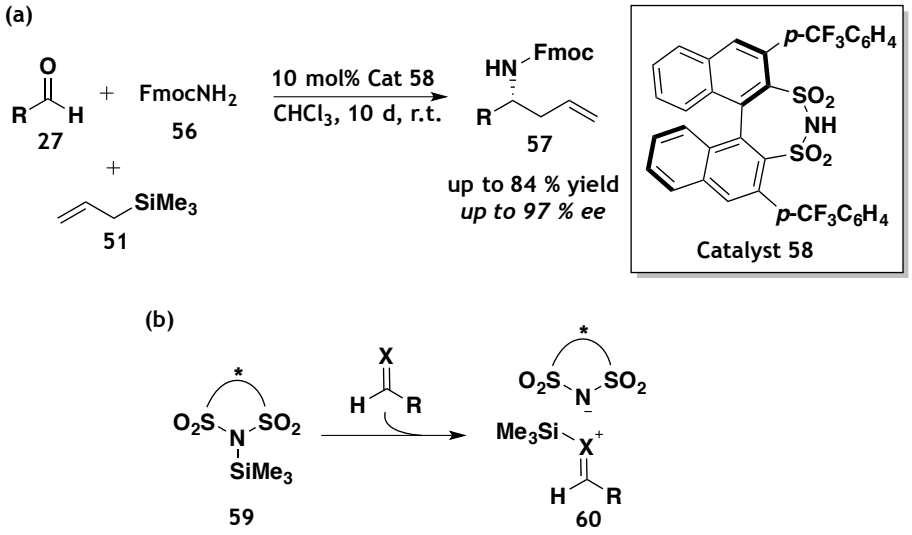
***Scheme 1.14**: Fluoride-catalyzed allylation reaction*

Several methods for allylic silane addition to imines catalyzed by Lewis acids have been realized. These include allylations catalyzed by π-allylpalladium(II),[57] ZnF_2[58] and $Cu(OTf)_2$.[59] For example, Yamamoto and coworkers have shown that catalytic silver fluoride and a phosphane ligand can be used effectively (2:1 ratio, respectively).[60] Good enantioselectivities were obtained with a range of phosphane ligands, with DIFLUROPHOS **55** performing the best. The yields were strongly dependent on the protecting group, with the *ortho*-$PhOC_6H_4$- imine **53** giving the best yield (70 %) (**Scheme 1.15**).



Scheme 1.15**: AgF-catalyzed allylation controlled by diphosphane ligand **55

An interesting example has recently been published by List and Gandhi that uses an organocatalyst.[61] In a one-pot procedure, an aldehyde **27** and benzyl carbamate **56** form an imine *in situ*, which is then allylated using allyltrimethylsilane **51** (**Scheme 1.16 (a)**). They use organocatalyst disulfonimide **58** and propose a mechanism that involves an ion-pair. They speculate that disulfonimide **58** is silylated under the reaction conditions (**59**), which can form an ion-pair with the electrophile (**60**) (**Scheme 1.16 (b)**).[62] This represents an example of counteranion-directed asymmetric catalysis. The homoallyl amine products **57** are obtained in excellent enantioselectivities for a range of aryl and alkyl substrates. Unfortunately, the reaction was rather sluggish as a reaction time of 10 days was required for reasonable yields.



***Scheme 1.16**: **(a)** One-pot imine formation-allylation reaction catalyzed by organocatalyst **58** and **(b)** proposed mechanism by chiral counteranion directed activation*

1.3 Aims of this Project

In this introduction, the first section gave a broad overview of ion-binding catalysis as a powerful concept to synthesize molecules with excellent stereocontrol. This mode of catalysis can direct any

reaction involving charged intermediates, making it applicable to a large number of transformations. There are plenty of examples of ion-binding to facilitate phase-transfer reactions, but other ion-pairing processes, namely anion-binding catalysis and chiral anion-directed catalysis, are areas of research that have emerged more recently. In the second section, catalytic asymmetric allylation of imino compounds was introduced. Chiral homoallyl amines are synthetically useful products but there is currently no general method to make them. There are only a limited number of examples that effect the reaction without employing a metal.

The aim of this project is to develop an asymmetric allylation reaction to make homoallyl amines, implementing an ion-binding organocatalyst. This thesis can be divided into two main sections; **Chapter 2** considers a fluoride-binding catalyst for asymmetric allylation and **Chapter 3** investigates a chiral cation-directed allylation process. **Chapter 4** will expand further a chiral cation-directed method for an intramolecular allylation reaction.

2. Cooperative Thiourea Catalysts for Asymmetric Allylation

2.1 Introduction

Until the last decade, the field of asymmetric catalysis has been focused predominantly on metal-mediated processes.[63] Whilst there have been formidable developments in creating organometallic catalysts that are highly tunable for efficient and selective reactions, organic chemists still strive to reach the near-perfect catalytic activity that enzymes demonstrate. Enzymes bind to substrates through manifold non-covalent interactions including hydrogen bonding and hydrophobic interactions. This has inspired organic chemists to design small organic molecules that emulate nature's catalysts and control reactivity and stereoselectivity of complex reactions *via* hydrogen bonding. [64,65] The hydrogen bond is defined as:

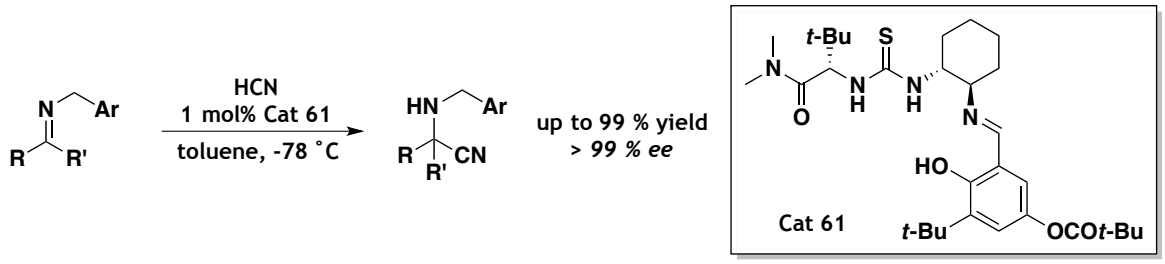
"An attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation." [66]

Previous research in the Smith group led to the development of a cooperative thiourea catalyst, in which hydrogen bonding was integral to its operation and efficiency as an organocatalyst (discussed further in **Chapter 2.1.2**). This project aimed to explore other asymmetric transformations utilizing this catalyst scaffold. On this basis, we devised a plan to investigate cooperative thiourea catalysts for an enantioselective allylation reaction. Our objective was to provide an alternative approach to the current handful of examples of organocatalyzed asymmetric allylation reactions in the literature.

This introduction first outlines a number of reactions where urea or thiourea organocatalysts have been successfully employed. It also describes the advantages of cooperative hydrogen bonding catalysts, and our strategy for employing them to asymmetric allylation.

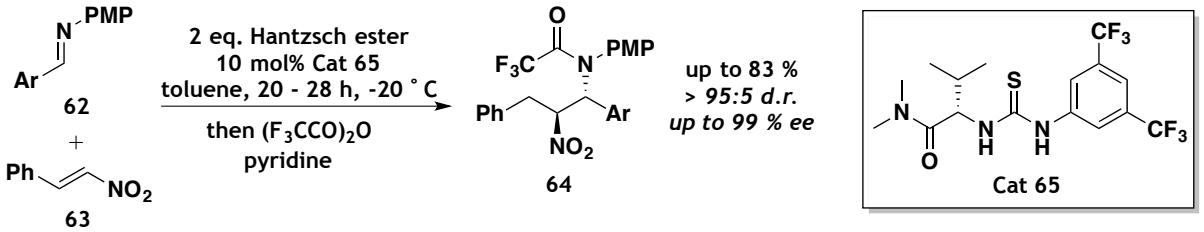
2.1.1 Chiral Urea and Thiourea Organocatalysts

Chiral urea and thiourea catalysts have been developed to catalyze a wide range of enantioselective processes.[67] For example the Strecker reaction, in which hydrocyanation of imines leads to the synthesis of α-amino acids, has been explored by Jacobsen *et al.* using both urea and thiourea catalysts.[68] Computational studies and NOE data led to a greater understanding of the interaction between the catalyst and the imine, allowing for the synthesis of more efficient and selective catalysts.[69] Optimization resulted in the development of thiourea **61**, which was capable of catalyzing the Strecker reaction at loadings of 1 mol% (**Scheme 2.1**). Both aromatic and aliphatic imines reacted to afford products in high yield, with enantioselectivities of > 99 %.



Scheme 2.1**: Asymmetric Strecker reaction catalyzed by thiourea **61

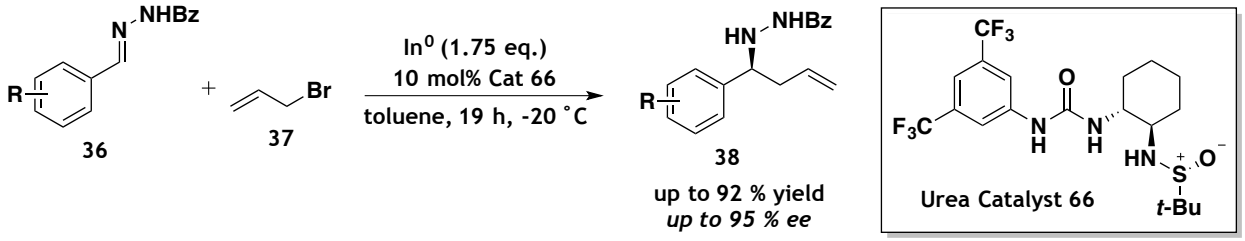
The nitro-Mannich reaction is another example of nucleophilic addition onto an imine that can be controlled by a thiourea catalyst.[70] A recent example by Anderson and coworkers showcased a novel tandem reductive nitro-Mannich process catalyzed by thiourea **65** (**Scheme 2.2**).[71] The nitroalkene **63** was reduced using a Hantzsch ester to generate the nucleophile, which could add to *N-para*-methoxyphenyl imines **62**. The product **64** was isolated in up to 83 % yield, with excellent diastereo- and enantioselectivities.



***Scheme 2.2**: Tandem reduction nitro-Mannich reaction*

Chiral ureas and thioureas have also been used to catalyze enantioselective allylation of hydrazones.[72] Tan and Jacobsen developed a process that generated an allylindium species *in situ*,

from allylbromide **37** and indium metal to effect the allylation of hydrazones (**Scheme 2.3**). They found that urea catalyst **66** was optimal and remarked on its structural simplicity and the necessity of a Lewis basic sulfonamide sidechain. They found the reaction proceeded in good yields (up to 92 %) and enantioselectivities (up to 95 % ee) with a variety of aromatic *N*-benzoylhydrazones **36**, but found the method was not easily applicable to aliphatic *N*-benzoylhydrazones. Interestingly, the analogous thiourea of **66** gave decreased enantioselectivity, which they hypothesized was because of competition between the allylindium and the hydrazone forming hydrogen bonds with the catalyst.



***Scheme 2.3**: Urea catalyzed allylation reaction using indium metal*

2.1.2 Cooperative Hydrogen Bonding Catalysts

Enzymes demonstrate the integral role that hydrogen bonding can play in terms of structure and catalysis. Binding to an enzyme's receptor can increase the effect of cooperative non-covalent interactions within the enzyme, and this has significant implications for catalysis. A positive cooperative effect can be defined as:

"Noncovalent interactions are said to interact with each other in a positively cooperative manner when the binding energy that is derived from them acting together is greater than would be derived from the sum of their acting separately." [73]

The Smith group have previously exploited the positive cooperative effect in their catalyst design (**Figure 2.1**).[74] They rationalized that conformationally well-defined but flexible thiourea catalysts, that benefit from cooperative ligand binding, would be highly efficient catalysts in asymmetric synthesis. The justification for this is two-fold – (1) preorganization of the catalyst structure by hydrogen bonding minimizes the entropic cost of transition state binding and (2) intramolecular

noncovalent interactions are strengthened upon ligand binding providing greater stabilization of charged intermediates and transition states.

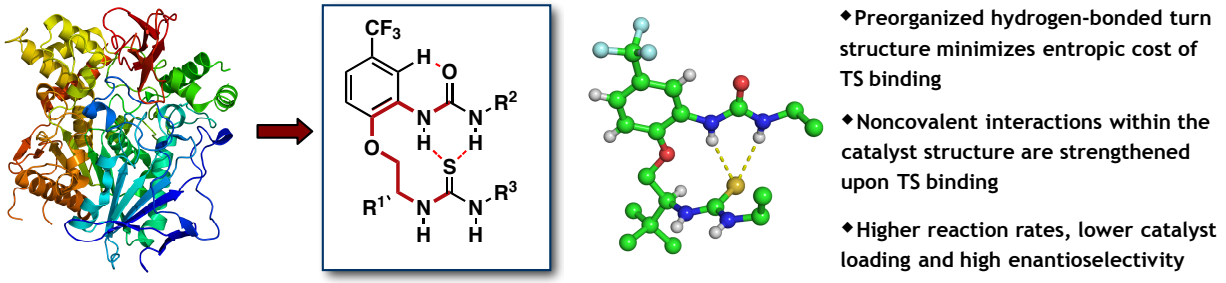
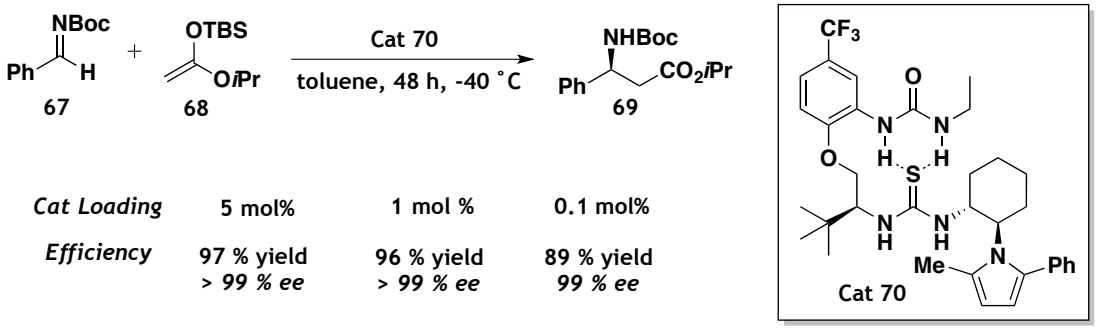


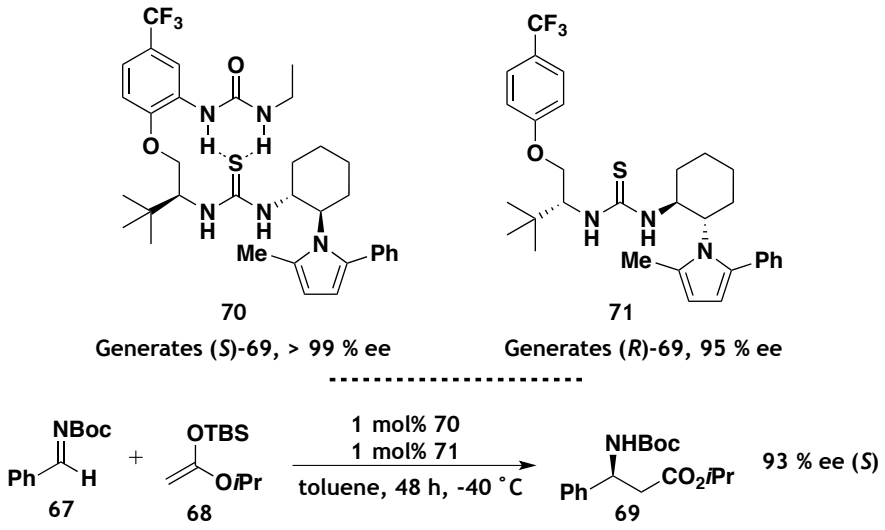
***Figure 2.1**: Rationale and structure of cooperative catalysts*

The catalyst construction incorporates a β-turn mimetic that ensures the structure is stabilized by intramolecular hydrogen bonding in the solution and solid states.[75] The potency of cooperative hydrogen bonding for asymmetric catalysis was first demonstrated in the context of a Mukaiyama-Mannich reaction.[74] The reaction of silyl ketene acetal **68** and *N-tert*-butoxycarbonyl (*N*-Boc) aldimine **67** substrates was examined. Optimization led to a thiourea catalyst **70** that could attain enantioselectivities of > 99 % ee at catalyst loadings as low as 0.1 mol% (**Scheme 2.4**).



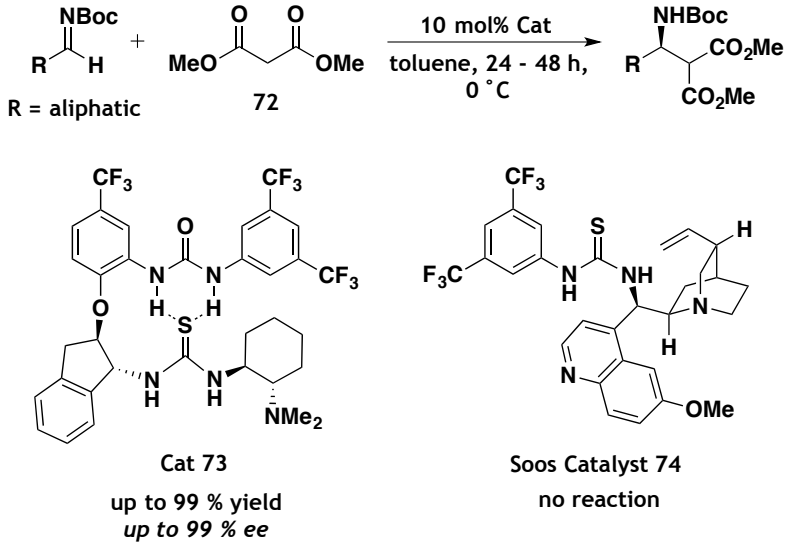
Scheme 2.4**: Mukaiyama-Mannich reaction with cooperative thiourea catalyst **70

Importantly, competition experiments revealed that the cooperative effect is valid in catalyst **70**. Deleted catalyst **71**, which generates the *R*-configured material **69**, was synthesized. When thiourea catalyst **70** (which generates the *S*-configured product **69**) and deleted catalyst **71** were used in the same pot, the product **69** was found to have an ee of 93 % (*S*) (**Scheme 2.5**). Thiourea **70** clearly outcompetes deleted catalyst **71** and this can be attributed to the noncovalent interactions within the structure, which are absent in **71**.



***Scheme 2.5**: Competition experiment*

Pikho *et al.* have also demonstrated the importance of cooperative hydrogen bonding.[76] They developed bifunctional thiourea catalyst **73** for a Mannich reaction between dialkyl malonate **72** and aldimines, for the synthesis of β-amino acids (**Scheme 2.6**). This is the first asymmetric hydrogen bonding catalyst that can activate aliphatic aldimines as electrophiles for the Mannich reaction. Alternative bifunctional thiourea catalysts, such as Soos catalyst **74**,[77] only effect the Mannich reaction with aromatic imines.[78,79]



***Scheme 2.6**: Mannich reaction with aliphatic aldimines*

Clearly, cooperative thiourea catalysts are a powerful class of organocatalysts that can give high reactivity and enantioselectivity, where other organocatalysts fail. We were keen to push this

methodology further, to find novel asymmetric transformations that benefited from the cooperative effect. This led us to develop a novel strategy for asymmetric allylation.

2.1.3 Cooperative Thiourea Catalysts for an Asymmetric Allylation Reaction

Allylation of imino compounds is an important synthetic transformation because of the creation of a carbon-carbon bond and a new stereocentre, whilst retaining the alkene functionality for subsequent elaboration.[80] However, the reaction is challenging and organic chemists are still striving to find better general catalytic enantioselective methods.[38]

We conceived a new approach that employed a cooperative thiourea catalyst to execute allylsilane addition onto an imine (**Figure 2.2 (a)**). It was envisaged that a cooperative thiourea catalyst could bind to a fluoride anion, which, in turn, could react with an allylsilane to form a "chiral ate-complex".[81] The enantioselective allylation reaction could then proceed with a suitable electrophile (**Figure 2.2 (b)**). Anion-binding to thioureas in catalytic asymmetric transformations is an emerging area in asymmetric catalysis.[4] There are currently no examples of this mode of catalysis for allylation reactions.

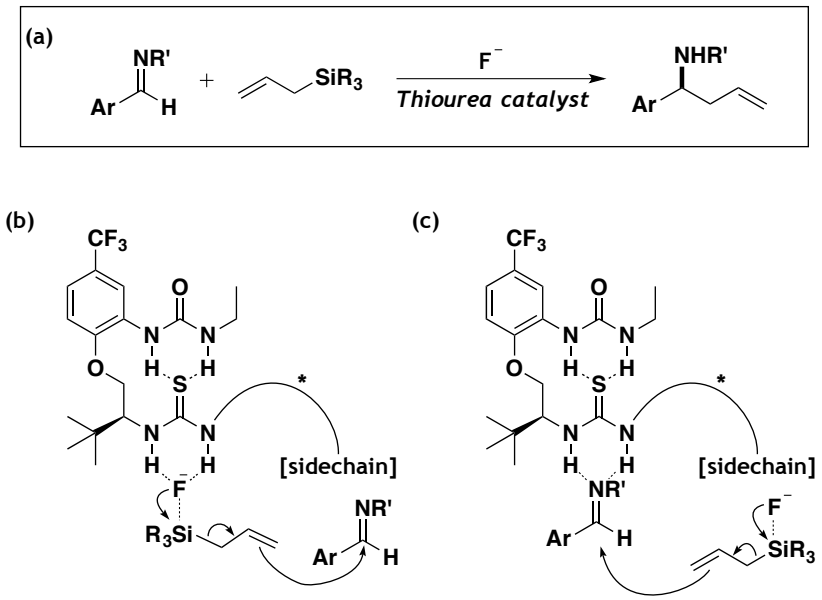


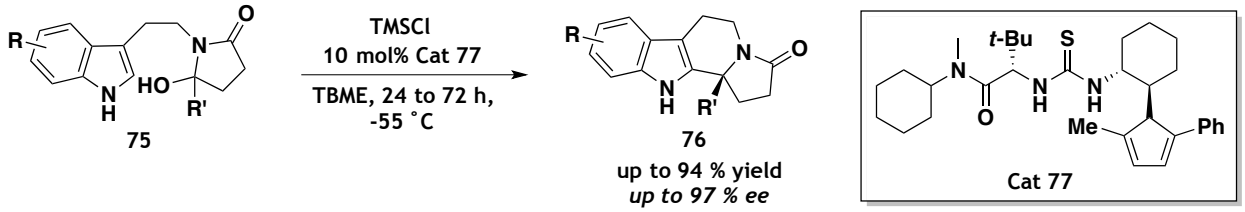
***Figure 2.2**: **(a)** Allylsilane addition to imines in the presence of fluoride and a thiourea catalyst, **(b)** forming a chiral ate-complex by anion-binding to the thiourea and **(c)** an alternative mode of operation, where the electrophile forms hydrogen bonds to the thiourea catalyst*

However, we rationalized that an alternative mode of reactivity could also operate. It is well known that imines can hydrogen bond to ureas and thioureas.[82] It is therefore possible that the electrophile will hydrogen bond to the cooperative catalyst and that fluoride attack of the allylsilane will occur independently (**Figure 2.2 (c)**). This would still lead to a stereocontrolled allylation reaction.

We hoped that a cooperative thiourea catalyst would achieve an efficient enantioselective allylation, with low catalyst loading and high enantioselectivities under mild, metal-free conditions. This would constitute a novel approach towards asymmetric allylation and, if successful, we hoped to probe the extent of fluoride-binding to the catalyst.

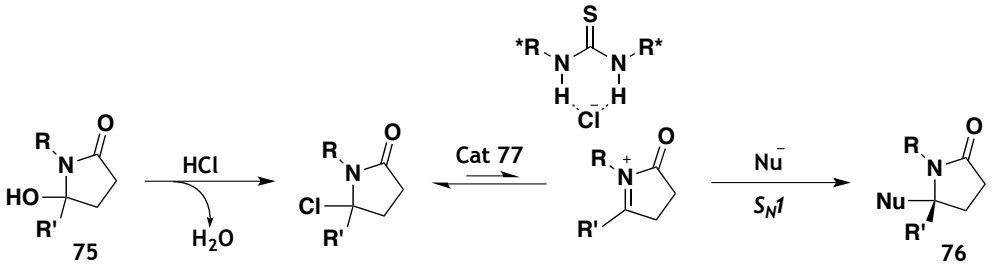
2.1.4 Anion-binding to Thiourea Catalysts

The concept of anion-binding to thiourea catalysts to accomplish asymmetric transformations was only recently developed by Jacobsen in 2007.[83] The authors developed an enantioselective Pictet-Spengler-type cyclization with thiourea catalyst **77** affording products in up to 94 % yield and 97 % ee (**Scheme 2.7**).



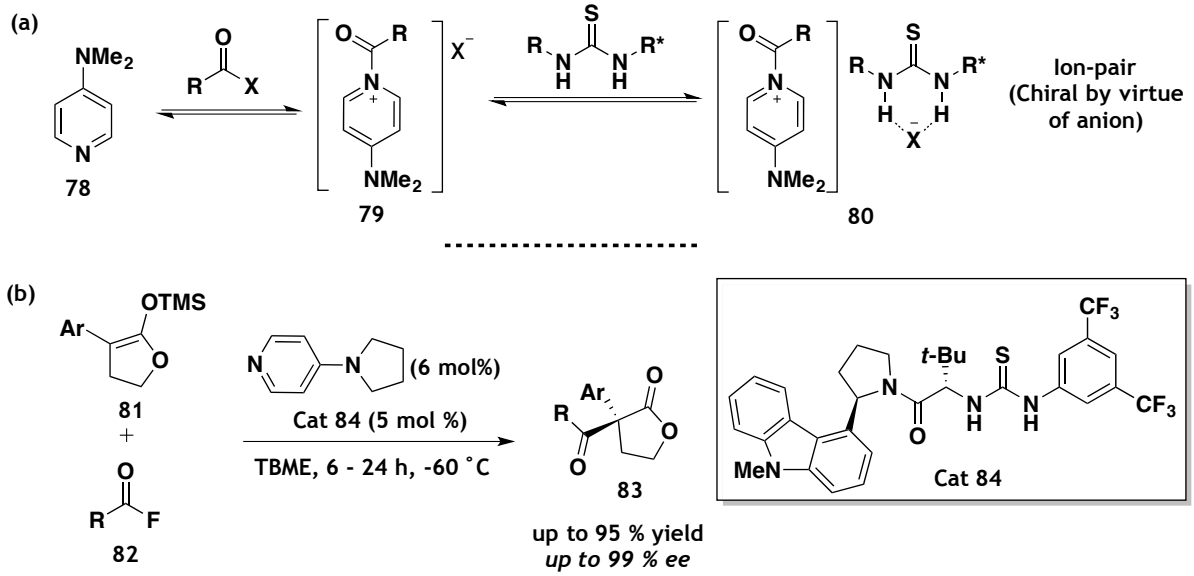
***Scheme 2.7**: Pictet-Spengler type cyclization of hydroxylactams*

Jacobsen and coworkers performed mechanistic investigations to discover the role of TMSCl in the reaction and learn how thiourea **77** is involved in the stereoselective bond-forming step. ^{1}H-NMR spectra revealed that chloride displaces water rapidly and irreversibly from hydroxylactam **75** first (**Scheme 2.8**). Jacobsen speculated that next the thiourea catalyst **77** promotes the *N*-acyliminium ion formation, by binding to the ejected chloride anion. The indole nucleophile can then attack the *N*-acyliminium ion to form the product in an S_N1-type manner. Evidence for this came from significant halide counterion effects; TMSCl additive affords the product **76** in 97 % ee, whereas TMSBr and TMSI furnish **76** in 68 % ee and 5 % ee respectively. Furthermore, non-polar aprotic solvents were required to attain high enantioselectivities.



***Scheme 2.8**: Anion-binding mechanism for asymmetric reaction*

The first and only example of fluoride anion-binding catalysis was also developed by Jacobsen and coworkers for an acyl transfer reaction.[84] A Lewis base catalyst such as DMAP **78** reacts with an acylating reagent to create an ion-pair **79**. This can coordinate to a chiral anion receptor such as a thiourea to generate a chiral ion-pair **80** (**Scheme 2.9 (a)**).[85] For the acylation of silyl ketene acetals **81**, acyl fluorides **82** were extremely effective for generating chiral ion-pairs, and afforded the β-keto lactone product **83** in up to 95 % yield and up to 99 % ee (**Scheme 2.9 (b)**).



***Scheme 2.9**: **(a)** Concept of anion-binding/nucleophilic cocatalysis of acyl transfer and **(b)** acylation of silyl ketene acetals by fluoride anion-binding*

Cooperative thiourea catalysts also exibit strong binding abilities to anions. Within the Smith group, the affinity of cooperative thiourea catalyst **85** for chloride anions compared to the deleted catalyst **86** has been examined,[74] revealing that the affinity of cooperative thiourea catalyst **85** had a $K_a = (550 \pm 85)\ M^{-1}$, whereas deleted catalyst **86** had a $K_a < 10\ M^{-1}$ – almost a hundred times smaller (**Figure 2.3**).

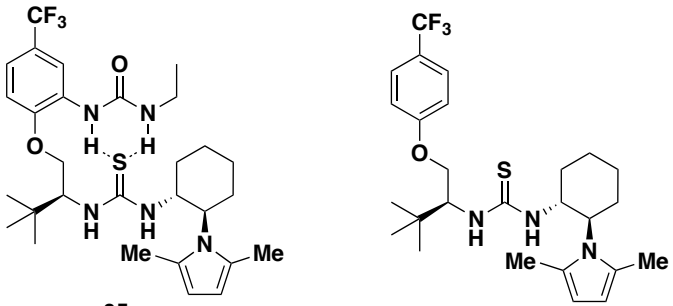


***Figure 2.3**: Chloride-binding affinity to catalysts **85** and **86** were measured*

Interestingly, Pikho *et al.* demonstrated the ability of cooperative thiourea catalysts to bind to anions by collecting X-ray diffraction data for crystals grown between cooperative thiourea catalyst **73** and different anions.[76] Co-crystallization between catalyst **73** and hexafluoroacetylacetonate (hfacac) resulted in the salt with the expected conformation (**Figure 2.4 (a)**). However, co-crystallisation between the catalyst and HCl presented an alternative binding mode, where the catalyst envelops the chloride anion with four stabilizing hydrogen bonds (**Figure 2.4 (b)**).

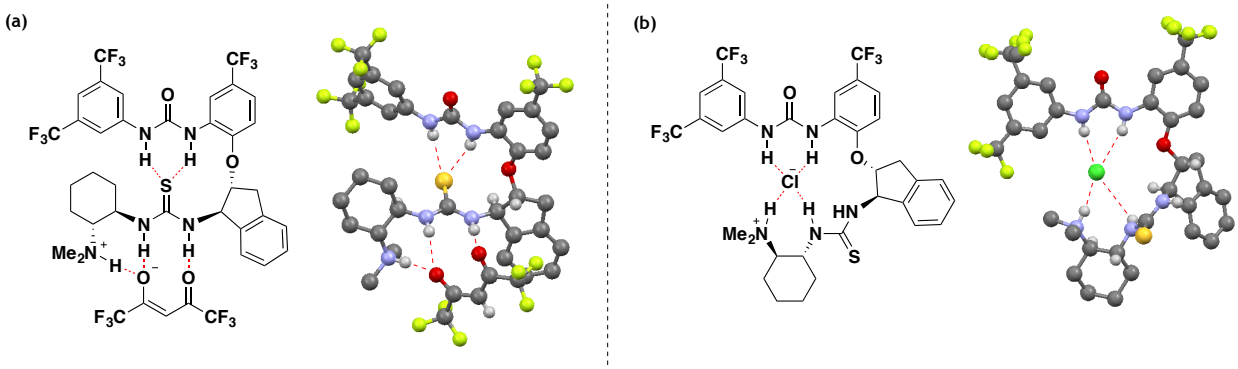


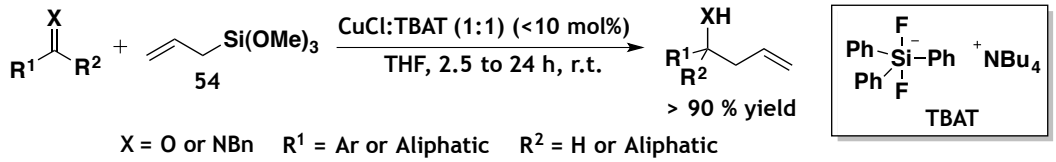
***Figure 2.4**: **(a)** Crystal structure of cooperative catalyst and hfacac and **(b)** crystal structure showing alternative binding-mode to chloride anion*

In summary, thioureas are excellent receptors for anions and recent examples in the literature show that this property can be utilized to develop novel asymmetric transformations. In addition, we have experimental evidence to show that cooperative thiourea catalysts also have a strong affinity for anion-binding. This gave us confidence that a cooperative thiourea catalyst and a fluoride anion could control an asymmetric allylation reaction.

2.1.5 Source of Fluoride Anion

An additional aim of this project was to develop relatively mild, metal-free reaction conditions, and use non-toxic, air stable reagents. With that in mind, careful consideration was made over the source of fluoride anion.

Tetrabutylammonium triphenyldifluorosilicate (TBAT) was chosen because it was reported in the literature to be a non-hygroscopic solid. In addition, it is air-stable and soluble in many solvents, and is available commercially.[86]Aldehydes, ketones and *N*-benzylimines have all undergone allylation catalyzed by TBAT in combination with copper (I) chloride (**Scheme 2.10**). Catalyst loading was as low as 1 mol% and the products were isolated in > 90 % yield in most cases. [87]



***Scheme 2.10**: TBAT and CuCl catalyzed allylation reaction*

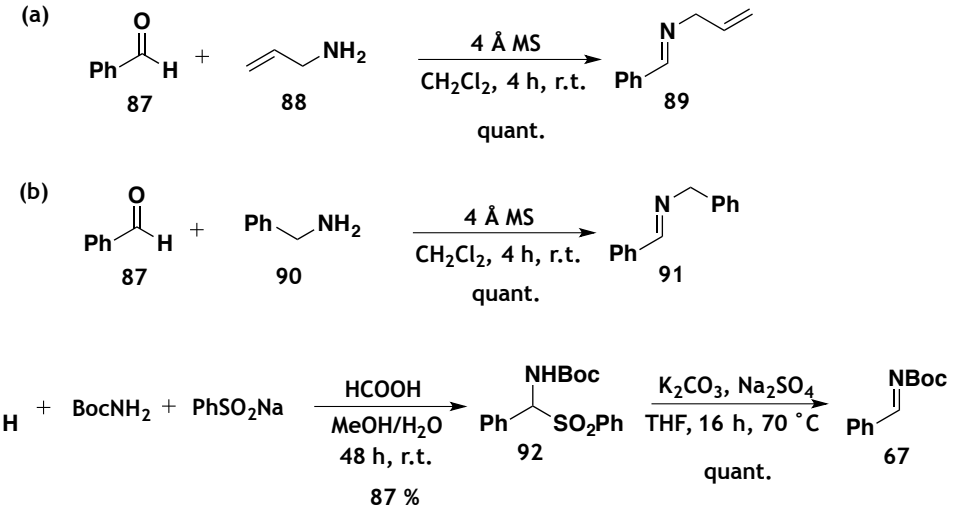
In summary, the aims of this project were to develop an asymmetric allylation reaction catalyzed by a cooperative thiourea catalyst. We envisaged that our catalyst could control fluoride attack of an allylsilane to generate an ate-complex, by hydrogen bonding to the anion. This would afford homoallyl amine products stereoselectively, using mild, metal-free conditions.

2.2 Results and Discussion

2.2.1 Allylation of Aldimines

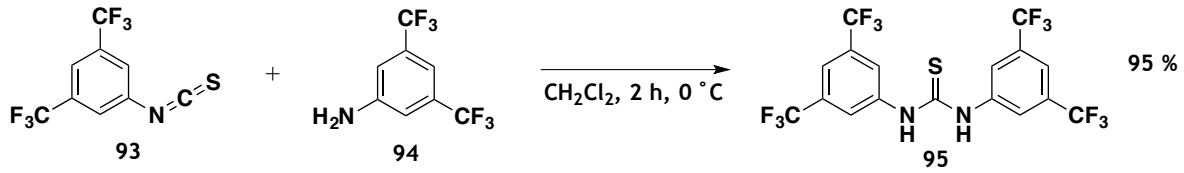
This project commenced with the preparation of *N*-protected imines, chosen because they are easy to prepare and can readily be deprotected after allylation to afford the homoallyl amine. Benzaldehyde **87** was protected as *N*-allyl aldimine **89**, *N*-benzyl aldimine **91**, and *N*-Boc aldimine **67** following literature procedures (**Scheme 2.11**).[68,88] Allylamine **88** and benzylamine **90** both reacted with benzaldehyde **87** in condensation reactions to yield aldimines **89** and **91** quantitatively.

The *N*-Boc aldimine **67** is more prone to hydrolysis and is not bench stable, so it was prepared from its precursor sulfone **92** when required.



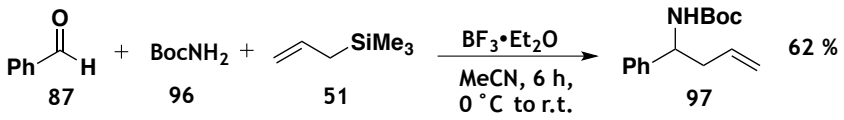
Scheme 2.11**: Preparation of **(a)** N-allyl aldimine **89** **(b)** N-benzyl aldimine **91** and **(c)** N-Boc aldimine **67

A key component of our strategy for an asymmetric allylation reaction was to utilize a thiourea catalyst. We synthesized Schreiner's catalyst **95**, as a suitable thiourea for racemic reactions. It was made by addition of aniline **94** onto isothiocyanate **93** in 95 % yield (**Scheme 2.12**).



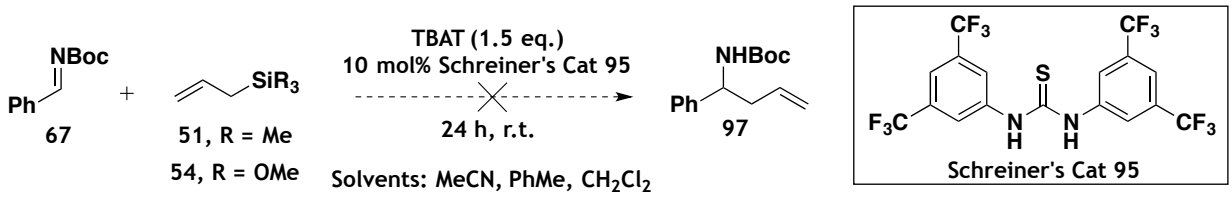
Scheme 2.12**: Preparation of Schreiner's catalyst **95

Our initial investigations were performed on *N*-Boc aldimine **67** because it was straightforward to prepare a sample of the product **97** following a literature procedure.[89] This would allow us to compare R_f on crude TLC and crude ^{1}H-NMR spectra with an authentic sample to quickly identify a successful reaction. Homoallyl amine **97** was prepared in 62 % yield by reaction of benzaldehyde **87**, *N*-Boc amine **96** and allyltrimethylsilane **51** with a Lewis acid (**Scheme 2.13**).



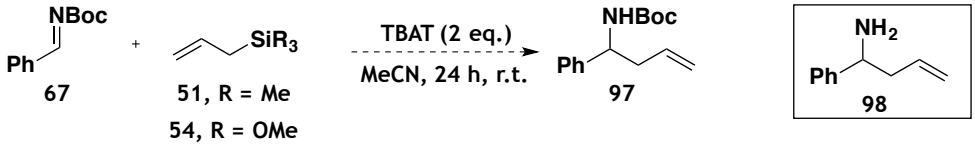
Scheme 2.13**: Literature preparation of homoallyl amine **97

Our initial studies started using 10 mol% Schreiner's catalyst **95** with allyltrimethylsilane **51** or allyltrimethoxysilane **54** (**Scheme 2.14**). We used stoichiometric TBAT because we were unsure whether the reaction would be catalytic in fluoride, and thought loadings could be lowered at a later stage. Unfortunately the product **97** was not isolated in any of the solvents used. Both TLC and crude ^{1}H-NMR spectra indicated the formation of new compounds but none corresponded with the sample of **97**, prepared above. Silica gel chromatography was performed to isolate the products, in the hope that we could understand what was happening. Alas, only trace amounts were cleanly separated and the ^{1}H-NMR spectra were indeterminable.



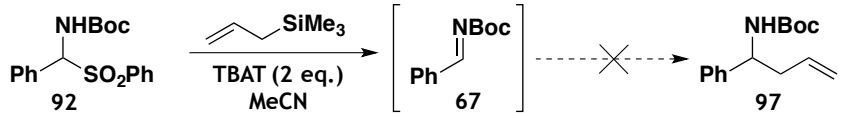
***Scheme 2.14**: Attempting allylation with Schreiner's catalyst **95** in different solvents*

Next, the allylation of *N*-Boc imine **67** was attempted without the Schreiner's catalyst **95** to determine the background reaction. Allyltrimethylsilane **51** and allyltrimethoxysilane **54** were both used, with two equivalents of fluoride in acetonitrile (**Scheme 2.15**). The results were similar; **97** was not identified and several new compounds appeared by TLC. This time purification of the crude mixture led to isolation of compound **98**. This suggests that some of the imine **67** is undergoing allylation, but problems might be arising due to the decomposition of the *N*-Boc group.



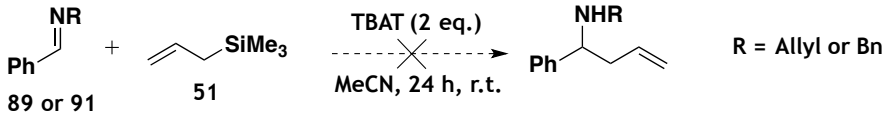
***Scheme 2.15**: Screening the background reaction*

We also attempted to generate imine **67** *in situ* from the corresponding sulfone **92** (**Scheme 2.16**). However, we found that the sulfone **92** could not be converted to the imine under these conditions and all the starting material was recovered.



***Scheme 2.16**: One-pot imine formation-allylation*

Finally, *N*-allyl imine **89** and *N*-benzyl imine **91** were subjected to allylation conditions. The reaction of *N*-benzyl imine **91** with allyltrimethylsilane **51** and 2 equivalents of TBAT did not proceed and starting material was fully recovered (**Scheme 2.17**). The *N*-allyl imine **89** was consumed but the product was not isolated. ^{1}H-NMR spectra of the material recovered showed that the allyl protecting group was no longer present. It was apparent that imines were not amenable for the allylation reaction, and so an alternative imine equivalent was sought.



***Scheme 2.17**: N-Allyl and N-benzyl imines did not react smoothly*

2.2.2 Allylation of Hydrazones

Hydrazones were an attractive alternative to aldimines for the allylation reaction, due to their high stability and precendent in allylation. Hydrazones are readily obtained by condensation between an aldehyde or a ketone with an acylhydrazine. They are usually crystalline, bench stable compounds, which can be simply purified by single recrystallization. Lewis acids can activate hydrazones by chelation, which makes them suitable electrophiles for a variety of reactions (**Figure 2.5**).[90] The resulting hydrazine can then be easily cleaved to the amine using samarium (II) iodide without racemization occurring.[91]

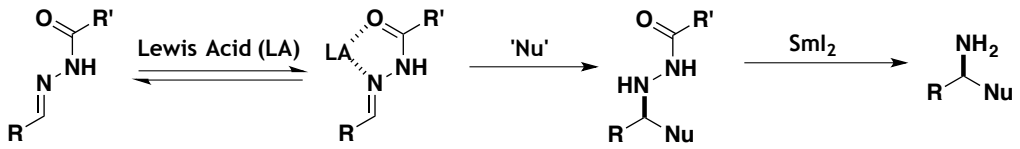
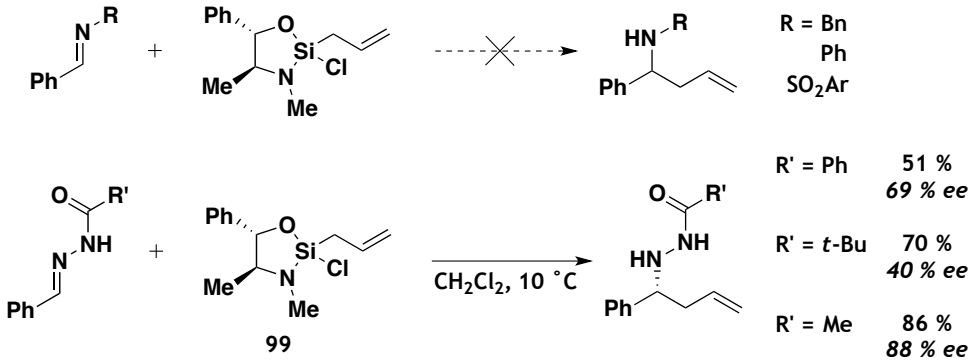


***Figure 2.5**: Hydrazones can be activated by Lewis acids towards nucleophilic attack, and deprotection leads to no racemization*

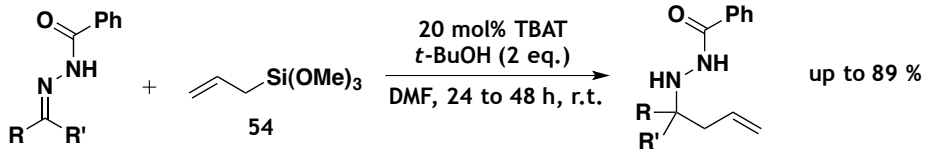
Although hydrazones have received less literature attention than imines as electrophiles in the past, they have already been used successfully in enantioselective allylation reactions. For example, Leighton *et al.* found during their study on chiral allylsilanes that imines were not reactive, but

hydrazones did undergo allylation (**Scheme 2.18**).[92] They found that *N*-acylhydrazone gave the best enantioselectivity (88 % ee) and yield (86 %) with strained silacycle **99**.



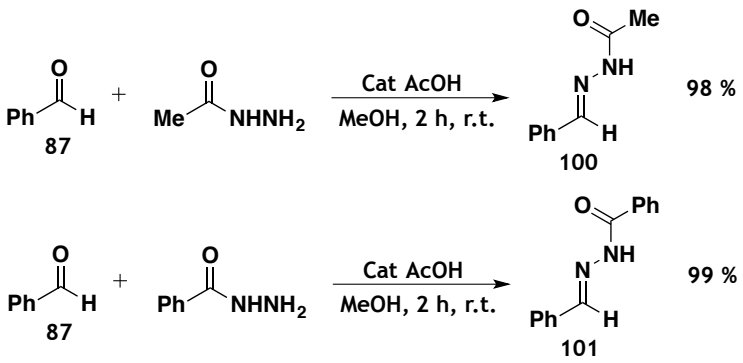
***Scheme 2.18**: Hydrazones react with chiral allylsilanes, but imines do not*

Allylation catalyzed by fluoride has also been demonstrated with hydrazones. Ding and Friestad showed that 20 mol% TBAT in DMF, in the presence of *tert*-butylalcohol additive, could effect allylation of *N*-benzoylhydrazones in up to 89 % yield (**Scheme 2.19**).[80] Therefore, we were confident that hydrazones would be appropriate electrophiles for this study because they are more stable than imines and they have demonstrated reactivity with allylsilanes and fluoride.



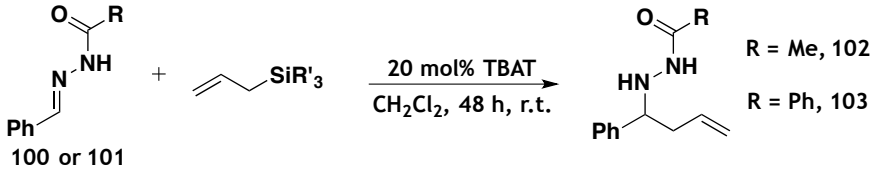
***Scheme 2.19**: Allyl addition onto N-benzoylhydrazones using catalytic fluoride*

First, *N*-acylhydrazone **100** and *N*-benzoylhydrazone **101** were prepared from benzaldehyde **87** (**Scheme 2.20**). Both were made in near quantitative amounts, by using methanol as a solvent and a catalytic quantity of acetic acid. Both hydrazones were very easy to purify by recrystallization from hot ethyl acetate.



***Scheme 2.20**: Preparation of hydrazones*

With the hydrazones **100** and **101** in hand, the allylation reactions with different allylsilanes and catalytic TBAT were investigated (**Table 2.1**). Allylation products **102** and **103** were obtained with both allyltrichlorosilane **49** and allyltrimethoxysilane **54**. No allylation occurred when allyltrimethylsilane **51** was employed.



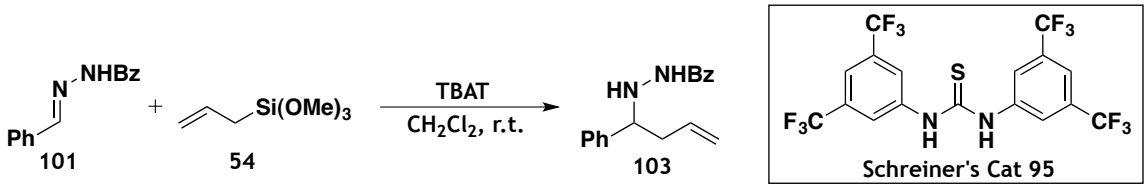
R = Me		R = Ph	
Allylsilane, R'	**Yield %**	**Allylsilane, R'**	**Yield %**
Cl	26	Cl	9
Me	0	Me	0
OMe	11	OMe	27

***Table 2.1**: Initial allylation results*

We decided, at this point, to concentrate our efforts on *N*-benzoylhydrazone **101** and allyltrimethoxysilane **54**. Although allyltrichlorosilane **49** was effective, we were keen to focus on allyltrimethoxysilane **54**, which can be stored at room temperature and does not fume in air. Allyltrimethoxysilane **54** has been reported as a good allylating reagent because it can easily form pentacoordinate silicate.[87]

We performed some basic reactions to test the allylation of *N*-benzoylhydrazone **101** with allyltrimethoxysilane **54** and TBAT (**Table 2.2**). The reaction proceeded in only 32 % yield when stoichiometric TBAT was used (entry 2). When the reaction was left to stir for 4 days with 20 mol% TBAT (entry 3) the reaction proceeded in a 45 % yield. This indicated to us that the reaction was

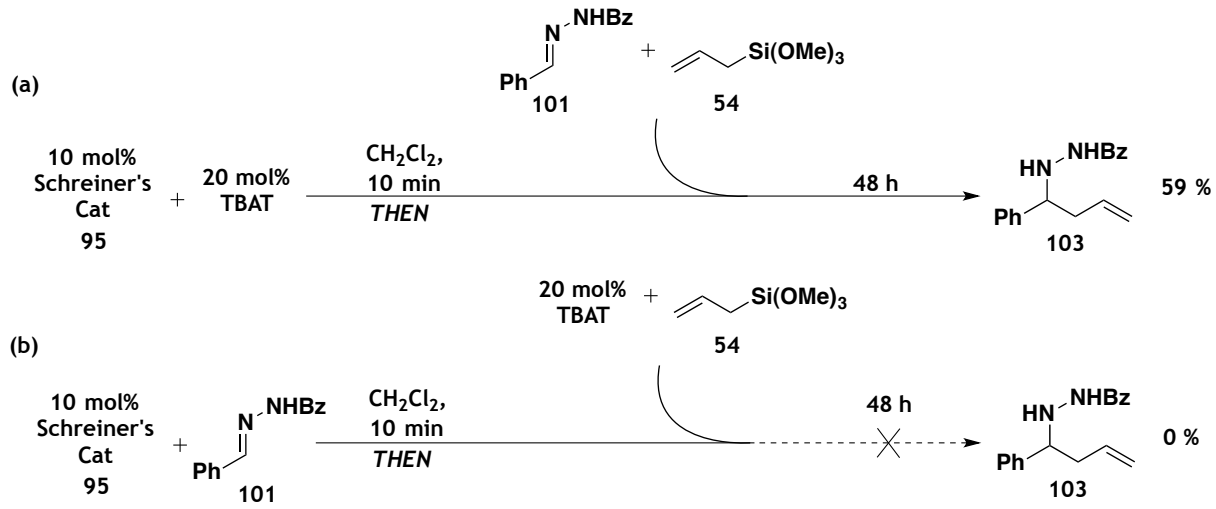
still turning-over with substoichiometric fluoride, but very slowly (c.f. entry 1 and entry 3). In line with our plan for an asymmetric reaction, a thiourea catalyst was added. The reaction did not proceed with Schreiner's catalyst **95** alone (entry 4) but, promisingly, the yield increased to 59 % when 20 mol% TBAT and 10 mol% Schreiner's catalyst **95** were used together (entry 5). This gave us confidence that optimization with TBAT and Schreiner's catalyst **95** would give us an efficient allylation reaction and that control of asymmetry using a chiral thiourea was a viable strategy.



	TBAT mol%	Additives	Time h	Yield %
1	20	-	48	27
2	100	-	48	32
3	20	-	96	45
4	0	**95** 10 mol%	48	0
5	20	**95** 10 mol%	48	59

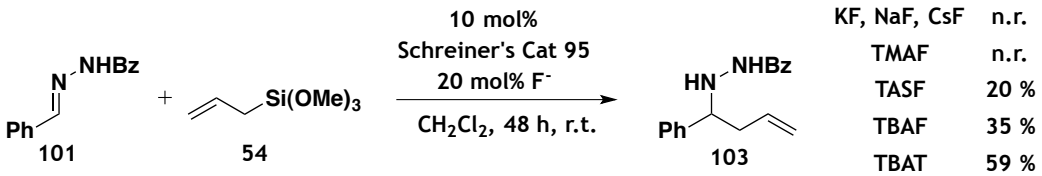
***Table 2.2**: Initial allyltrimethoxysilane reactions*

At this point, we made an interesting observation – the order of addition of the reagents was important. In the current system 59 % yield was obtained when the Schreiner's catalyst **95** and TBAT were stirred in dichloromethane for 10 min, before the addition of the other reagents (**Scheme 2.21 (a)**). However, if the hydrazone **101** and Schreiners's catalyst **95** were added to the flask and dissolved in dichloromethane before TBAT and allylsilane **54** were added, the reaction did not proceed (**Scheme 2.21 (b)**).



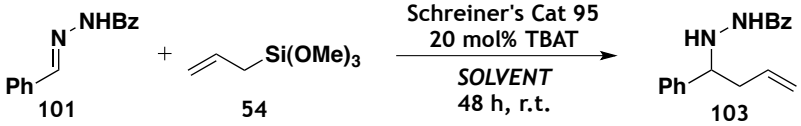
***Scheme 2.21**: **(a)** Reaction proceeds in 59 % yield but **(b)** changing the order of addition of the reagents prevents the reaction occurring*

To continue the optimization of the allylation reaction, we decided to consider different fluoride sources. We hoped to continue using TBAT because it is a non-hygroscopic solid and less toxic than some other fluoride reagents (discussed in **Chapter 2.1.5**), but it seemed prudent to check that this was the best reagent for the reaction. A screen of different fluoride sources was completed (**Scheme 2.22**) and showed that metal fluorides and tetramethylammonium fluoride (TMAF) did not initiate allylation, and returned starting materials. Tetrabutylammonium fluoride (TBAF) and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) both effected the allylation reaction, but in only a 35 % yield and 20 % yield respectively. Therefore, TBAT remained the best source of fluoride for the allylation reaction.



***Scheme 2.22**: Allylation reaction with different fluoride reagents*

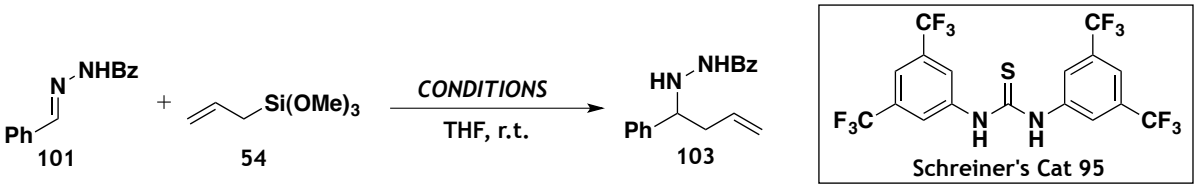
We next decided to do a solvent screen to determine if dichloromethane was the optimum solvent (**Scheme 2.23**). In toluene and anisole the reaction proceeded moderately in 31 % and 25 % yield respectively. However, when performed in THF, we noticed a significant improvement in reactivity and isolated the product **103** in 84 % yield. Using protic solvents was counter-productive and the reaction did not proceed in methanol or dichloromethane/water (9:1).



SOLVENT	Yield
CH_2CH_2	59 %
PhMe	31 %
Anisole	25 %
THF	84 %
MeOH	n.r.
CH_2Cl_2/H_2O (9:1)	n.r.

***Scheme 2.23**: Solvent optimization*

A further screen of allylation reaction conditions in THF was then performed (**Table 2.3**). The allylation reaction proceeded in 72 % yield over 24 h (entry 1) and this increased to an 84 % yield after another day (entry 2). Schreiner's catalyst **95** had a noticeable effect on reactivity as the reaction proceeded sluggishly in its absence (entries 3 and 4), demonstrating that it plays an integral role in catalyzing the reaction. The reaction did not proceed at all without TBAT (entry 5). This confirmed that both fluoride and thiourea catalysts were essential for effective catalysis of the allylation reaction.



	TBAT %	Schreiner's Cat 95 mol%	Time h	Yield %
1	20	10	24	72
2	20	10	48	84
3	20	-	24	19
4	20	-	48	41
5	-	10	48	0

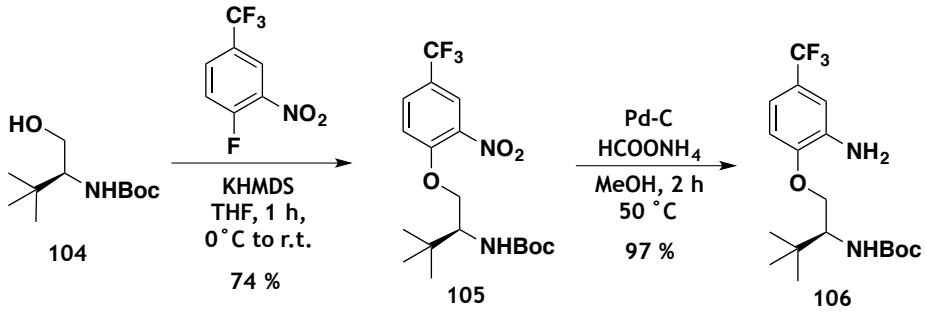
***Table 2.3**: Allylation reaction in THF*

Interestingly, when the order of addition of reagents was changed in THF the reaction did proceed, unlike the reaction in dichloromethane. When Schreiner's catalyst **95** and *N*-benzoylhydrazone **101** were dissolved in THF, before adding TBAT and allylsilane **54**, an 80 % yield was obtained after 48 h. The reaction was repeated and run in parallel with a reaction in dichloromethane, but there was no change in the outcome; the reaction in THF proceeded well whilst the reaction in dichloromethane returned starting material. The order of addition appears to not be a factor for the allylation reaction in THF.

Thus far, we had developed an allylation reaction with *N*-benzoylhydrazone **101** that required both fluoride and thiourea catalysts. We next wanted to test whether chiral thiourea catalysts could effect the reaction asymmetrically. We therefore set about designing and synthesizing a library of suitable thiourea catalysts. The catalyst scaffold was based on previous work done within the Smith group that incorporated a β-turn mimetic, where an intramolecular hydrogen bonding leads to a positive cooperative effect (**Chapter 2.1.2**).

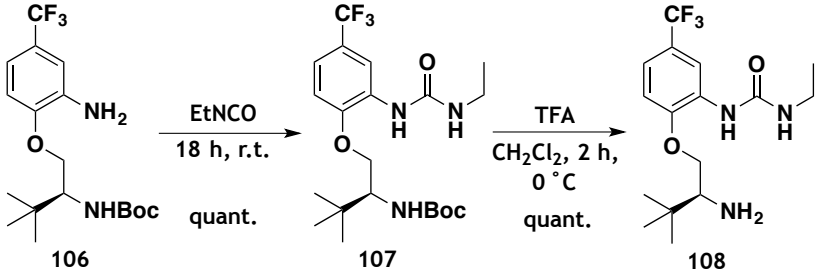
2.2.3 Catalyst Synthesis and Modifications

The design and synthesis for the β-turn mimetic is well established within the group.[74,75] Amino acids are used as chiral building blocks and our synthesis starts from *N*-Boc-L-*tert*-leucinol **104**, a derivative of amino acid leucine. It was decided that other amino acids could be considered at a later point. *N*-Boc-L-*tert*-leucinol **104** was coupled to 4-fluoro-3-nitrobenzotrifluoride in an S_NAr reaction and then reduced under transfer hydrogenation conditions to afford the β-turn linker **106** (**Scheme 2.24**). Both reactions proceed in excellent yields.



Scheme 2.24**: S_NAr reaction and reduction to aniline **106

Treatment of the aniline with ethyl isocyanate furnished the urea **107**, before *N*-Boc removal with trifluoroacetic acid afforded the turn precursor **108** in quantitative yield (**Scheme 2.25**).



Scheme 2.25**: Accessing turn precursor **108

At this point, it is easy to diversify the synthesis to access a range of catalysts from turn precursor **108**. Turn precursor **108** reacts with thiophosgene to form an isothiocyanate and then 1,2-diaminocyclohexane derivative can be added *in situ* to make a thiourea (**Figure 2.6**). (*R*,*R*)-(–)-1,2-Diaminocyclohexane **109** is a useful building block because it is easy to synthesize a range of derivatives to access catalysts with different functional groups.

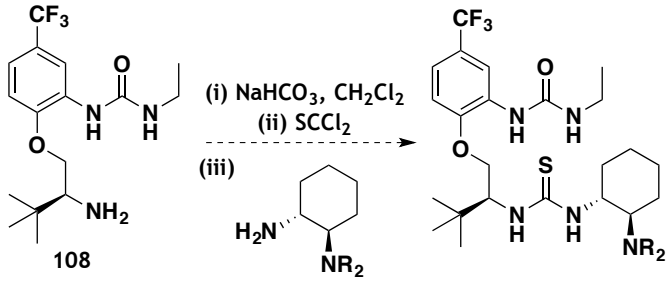
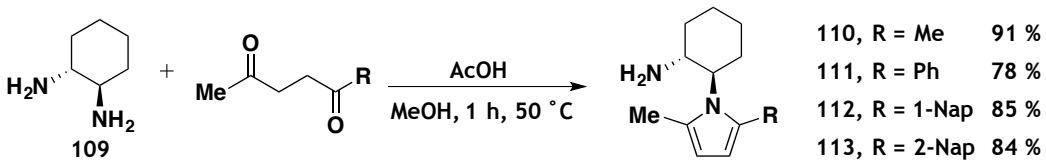


***Figure 2.6**: Thiourea formation with different amines to access a range of catalysts*

The first group of diamine derivatives that were synthesized was a range of pyrroles *via* a Paal-Knorr condensation (**Scheme 2.26**). These were made because they were known to be components of catalysts that react successfully with imines.



***Scheme 2.26**: Paal-Knorr condensation*

The relevant 1-napthyl and 2-napthyl derivatives of the 1,4-diketones (**117** and **118**) were not commercially available for the Paal-Knorr condensation. These were prepared by S_N2 reaction of the relevant lithium enolate of acetonaphthones **114** and **115** with chloroacetone **116** (**Scheme 2.27**).



***Scheme 2.27**: Synthesis of 1,4-diketones*

As well as the pyrroles, we also chose to elaborate (*R*,*R*)-(-)-1,2-diaminocyclohexane **109** to include Lewis basic functionality, because they are known to activate silicon.[93] Therefore we decided to synthesize sidechains containing acetamide (**119**), phosphinamide (**120**) and sulfonamide (**121** and

122) groups (**Figure 2.7**), as well as obtaining the catalyst with the free primary amine from **109**. This would give us a range of catalysts with different functionalities that could all be synthesized in a few synthetic steps. The sulfonamides **121** and **122** could be synthesized directly from the thiourea catalyst, whilst acetamide **119** and phosphinamide **120** were pre-prepared.

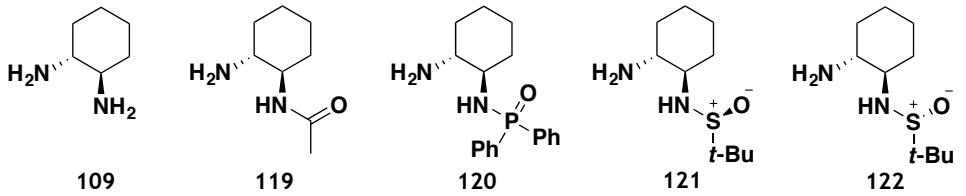
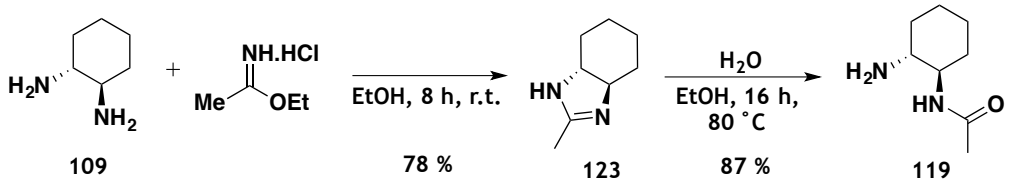


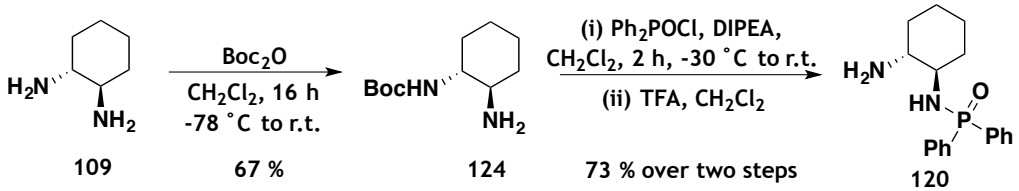
***Figure 2.7**: Lewis basic sidechains for thiourea catalysts*

Acetamide **119** was easily accessible in two high yielding steps under mild conditions (**Scheme 2.28**).[94] Condensation of diamine **109** with Pinner's salt made imidazoline **123** in 78 % yield**,** and this was followed by neutral hydrolysis to afford **119** in 87 % yield.



Scheme 2.28**: Synthesis of acetamide **119

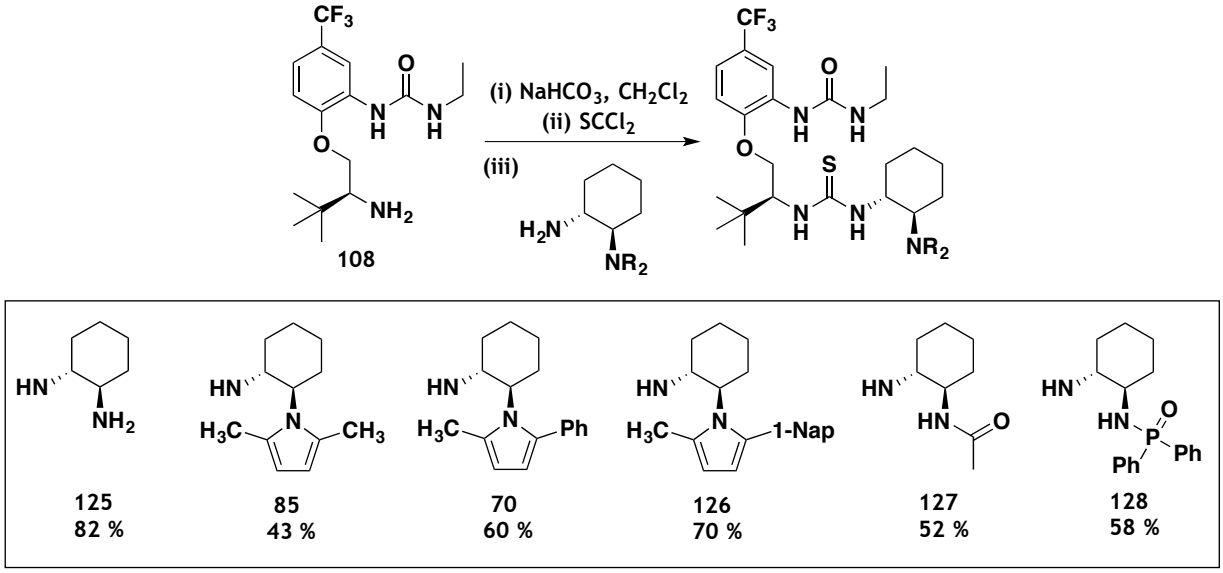
The phosphinamide **120** was made *via N*-Boc-protected diamine **124** (**Scheme 2.29**). The single *N*-Boc protected diamine **120** was tricky to obtain due to the presence of the doubly-protected diamine, but this was successfully removed by a careful acid work-up. *N*-Boc-protected diamine **124** was then successfully reacted with diphenylphosphinic chloride, before deprotection with trifluoroacetic acid led to the phosphinamide **120** in a 73 % yield, over the two steps.[72]



Scheme 2.29**: Preparing phosphinamide **120

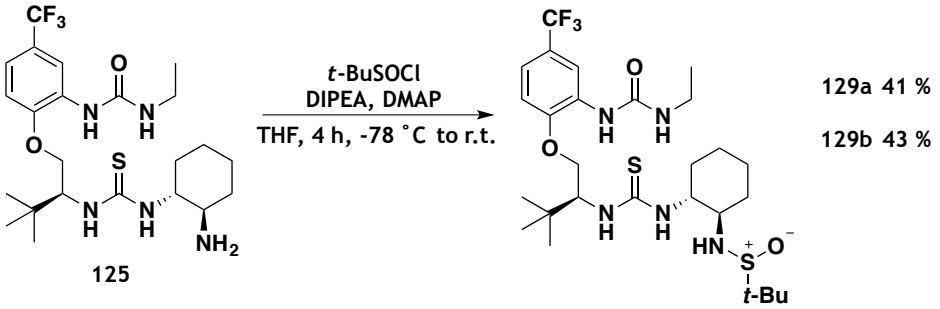
With a range of 1,2-diaminocylohexane derivatives in hand, we proceeded to couple them with turn precursor **108**. Sodium hydrogen carbonate solution was added to the turn precursor **108** stirring in dichloromethane to remove any acids before adding the thiophosgene. The thiophosgene addition

must be carefully added to the organic layer (stirring was stopped) or it could potentially react with water. Finally a brief work up was performed before adding the appropriate 1,2-diaminocyclohexane derivative to afford the thiourea catalysts, which were obtained in yields varying between 43 to 82 % (**Scheme 2.30**).



***Scheme 2.30**: Reaction with thiophosgene and diamines to make thiourea catalysts*

In addition, sulfonamide catalysts **129a** and **129b** were made from thiourea catalyst **125**.[72] These could both be accessed in the same step using racemic *tert*-butylsulfinyl chloride, diisopropylamine base and catalytic DMAP (**Scheme 2.31**). The two diastereomers were then separated by column chromatography and gave **129a** in 41 % yield and **129b** in 43 % yield (84 % overall). The relative stereochemistry of each diastereomer was not determined.

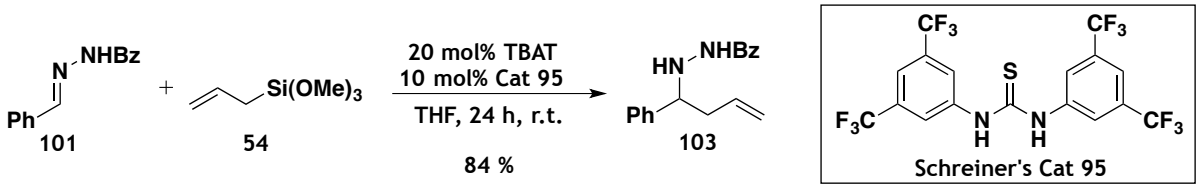


Scheme 2.31**: Accessing sulfonamides **129a** and **129b

We now had a sizable catalyst library in hand, and our attention was refocused on optimizing the asymmetric allylation reaction. Further catalyst modifications could be made at a later stage, if necessary.

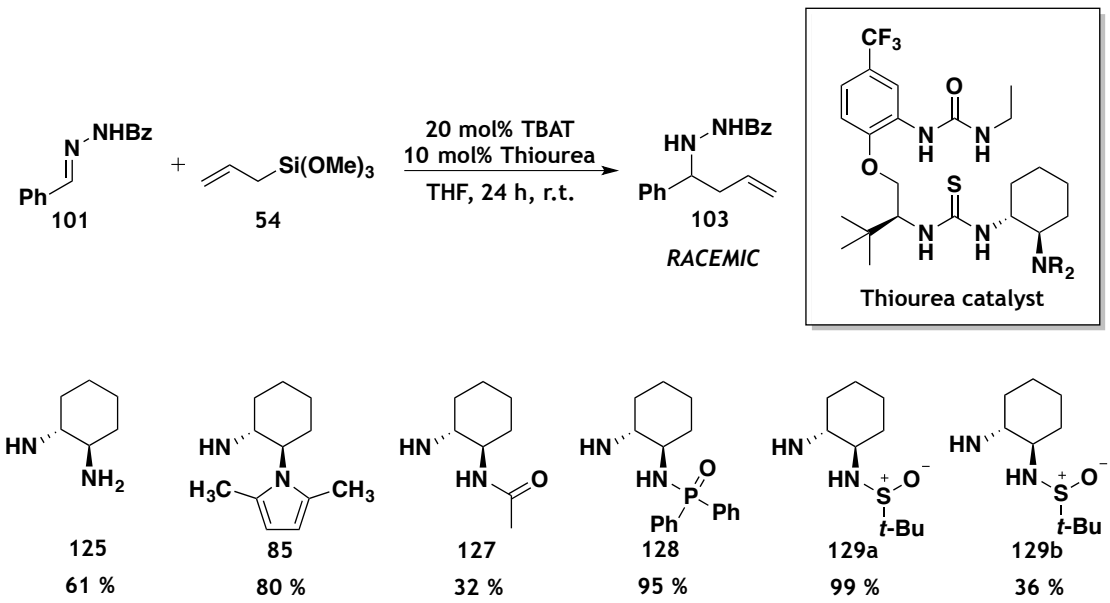
2.2.4 Allylation with Cooperative Thiourea Catalysts

As discussed in **Chapter 2.2.2**, we had developed an allylation reaction that was catalytic in both fluoride and thiourea. Allyltrimethoxysilane **54** and hydrazone **101** reacted in THF using 10 mol% Schreiner's catalyst **95** and 20 mol% TBAT in up to 84 % yield (**Scheme 2.32**).



Scheme 2.32**: Allylation catalyzed by TBAT and Schreiner's Cat **95

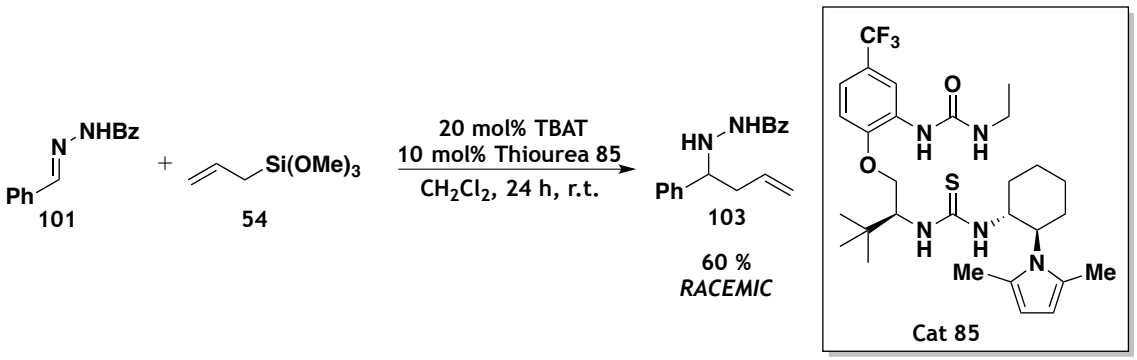
Next a systematic screen of cooperative thiourea catalysts using the same conditions was performed (**Scheme 2.33**). Yields varied significantly with different catalysts - amide catalyst **127** and sulfonamide catalyst **129b** performed the worst (only 32 % and 36 % yield respectively) for the allylation reaction. However phosphinamide catalyst **128** and sulfonamide catalyst **129a** effected the reaction in very high yields (95 % and 99 % respectively). Chiral HPLC analysis was performed on all products **103** using Chiralpak AD-H in an eluent system of 6 % IPA in hexane. Disappointingly, all of the reactions yielded product **103** as a racemate.



***Scheme 2.33**: Screening cooperative thiourea catalysts*

We were concerned that perhaps THF was a poor choice of solvent, and may be disrupting any hydrogen-bonding interactions between either the fluoride and the thiourea catalyst or hydrazone

101 and the thiourea catalyst. We therefore performed the allylation experiment in dichloromethane with catalyst **85** to determine whether homoallyl amine **103** could be made enantioselectively (**Scheme 2.34**). However the same result was obtained – the product **103** was only produced as the racemate and so we were forced to reconsider our strategy.



***Scheme 2.34**: Allylation in dichloromethane*

Next, we examined the interaction of fluoride with Schreiner's catalyst **95** to understand why our allylation reaction was proceeding in high yields with no asymmetric induction. TBAT and Schreiner's catalyst **95** were stirred in dichloromethane and crystals were grown by the slow evaporation of this solution. X-ray diffraction data was collected and to our surprise structure **130** was found (**Figure 2.8**).

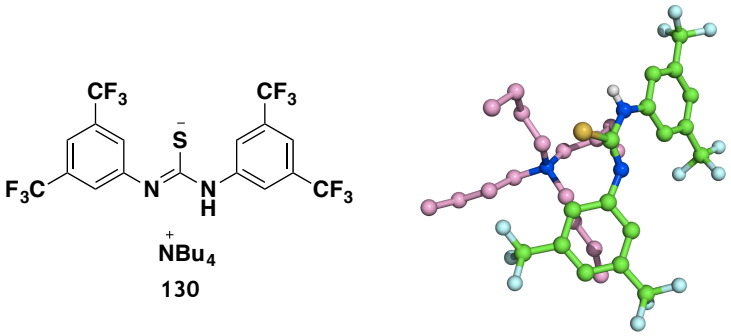


Figure 2.8**: Crystal structure of **130

Structure **130** shows that co-crystallization between the tetrabutylammonium cation and the thiourea anion has occurred. This suggests that fluoride is deprotonating the thiourea and generating HF *in situ*.[95] HF could subsequently act as a nucleophile to activate the allylsilane. This explains the excellent turnover observed and the fact that the reaction is racemic, since the catalyst is not coordinated during the bond-forming step.

Despite our best efforts, it was clear that using both fluoride and thiourea catalysts was unlikely to deliver an enantioselective allylation reaction. We hypothesized that an alternative mode of catalysis would be to deploy the cooperative thiourea catalysts as bifunctional organocatalysts.[96,97] The Lewis basic appendage of the cooperative thiourea catalyst could be used to coordinate to the allylsilane to make the ate-complex. At the same time the hydrazone could hydrogen bond to the thiourea, enhancing its electrophilicity for the allylation reaction (**Figure 2.9**). This would mean that allylation is accomplished without the use of fluoride.

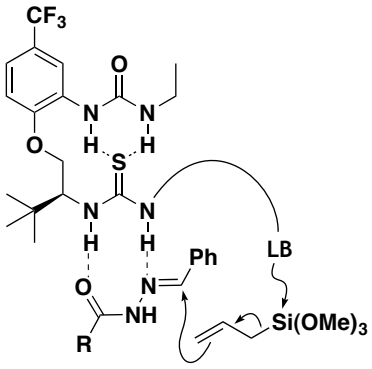
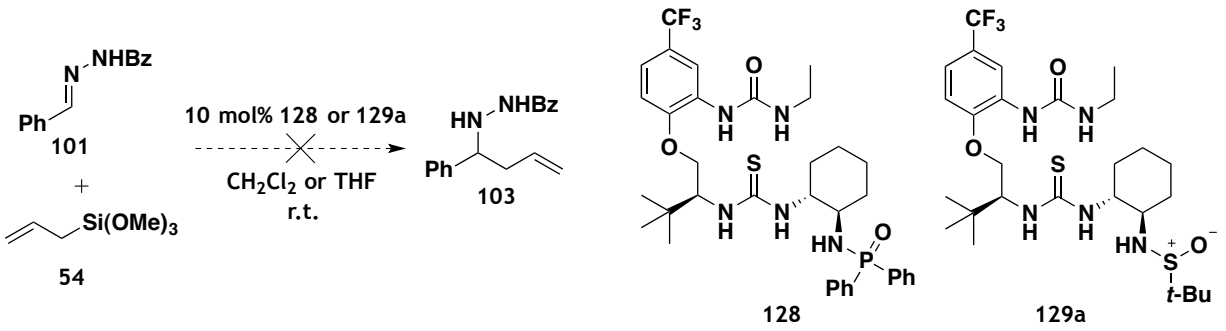


***Figure 2.9**: A bifunctional organocatalyst for asymmetric allylation*

Phosphinamide **128** and sulfonamide **129a** catalysts were examined to see if they exhibited any bifunctional activity for the allylation reaction. These catalysts were chosen because they had given the best yields in the system with fluoride. The catalysts **128** and **129a** were stirred with *N*-benzoylhydrazone **101** and allyltrimethoxysilane **54** (**Scheme 2.35**). Unfortunately the reaction did not proceed – in fact hydrazone **101** did not dissolve when these conditions were used. It appeared that phosphinamide **128** and sulfonamide **129a** were insufficiently powerful Lewis bases.

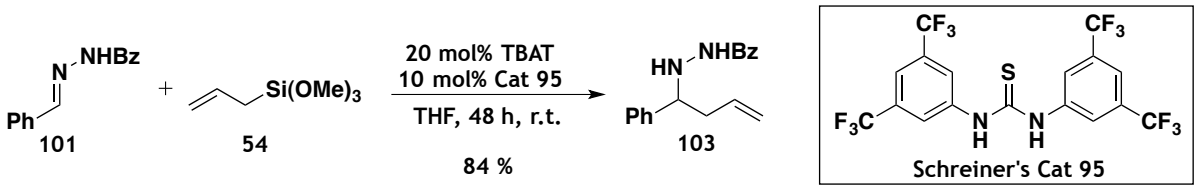


***Scheme 2.35**: Trying allylation under bifunctional catalyst conditions*

Regrettably, asymmetric allylation using catalytic fluoride and thiourea was unsuccessful. This appeared to be because the fluoride is able to deprotonate the thiourea, generating HF to catalyze the reaction. We decided to focus our efforts on an alternative strategy – exploring an ion-binding approach to asymmetric allylation (**Chapter 3**).

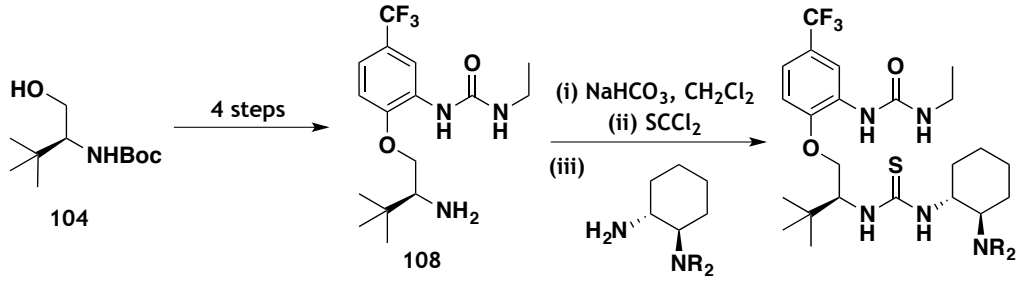
2.3 Conclusion

In this chapter, our aim was to develop an enantioselective allylation reaction using a cooperative thiourea catalyst and catalytic fluoride. We started this process by considering the racemic reaction with Schreiner's catalyst **95**. When *N*-Boc aldimine **67** was chosen as the substrate, allyl addition was not observed and it appeared the imine was decomposing before the reaction took place. Subsequently, *N*-benzoylhydrazone **101** was adopted as a more stable imine equivalent. We quickly found that allylation of *N*-benzoylhydrazone **101** was most successful using 20 mol% TBAT, 10 mol% Schreiner's catalyst **95** and allyltrimethoxysilane **54**. The reaction was performed at room temperature in THF and was stirred for 48 h to deliver product **103** in an 84 % yield (**Scheme 2.36**). The reaction did not proceed without fluoride and the reaction was sluggish without the thiourea.



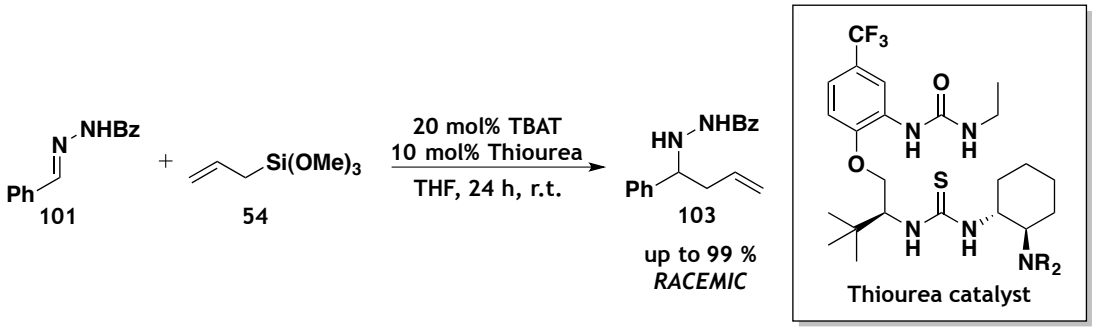
Scheme 2.36**: Optimized allylation reaction with TBAT and Schreiner's catalyst **95

Next, we successfully synthesized a range of cooperative thiourea catalysts. The turn precursor **108** was made in four high-yielding steps from *N*-Boc-L-*tert*-leucinol **104** (**Scheme 2.37**). The final step in the catalyst synthesis was reaction between turn precursor **108** and thiophosgene to make an isothiocyanate, and successively coupling to a (*R*,*R*)-(-)-1,2-diaminocyclohexane derivative. This allowed us to access catalysts with sidechains containing either pyrrole or Lewis basic functionality.



***Scheme 2.37**: Synthesis of cooperative thiourea catalysts*

With a sizable catalyst library in hand, we performed the allylation reaction using our optimized conditions with the cooperative thiourea catalysts. We found that some catalysts gave excellent yields (up to 99 %) but all furnished the homoallyl amine **103** as a racemate (**Scheme 2.38**).



***Scheme 2.38**: Allylation with cooperative thiourea catalysts were not enantioselective*

A possible explanation for the failure of this methodology is that the fluoride deprotonates the thiourea and produces HF *in situ*. Evidence of this effect came when crystals were successfully grown from TBAT stirring with Schreiner's catalyst **95** in dichloromethane. X-ray crystallography revealed that the thiourea anion had co-crystallized with the tetrabutylammonium cation (**Figure 2.8**). This suggests that the thiourea does not catalyze the allyl addition onto hydrazones, and so an asymmetric reaction cannot be achieved in this way. We decided to investigate an alternative approach towards enantioselective allylation reactions.

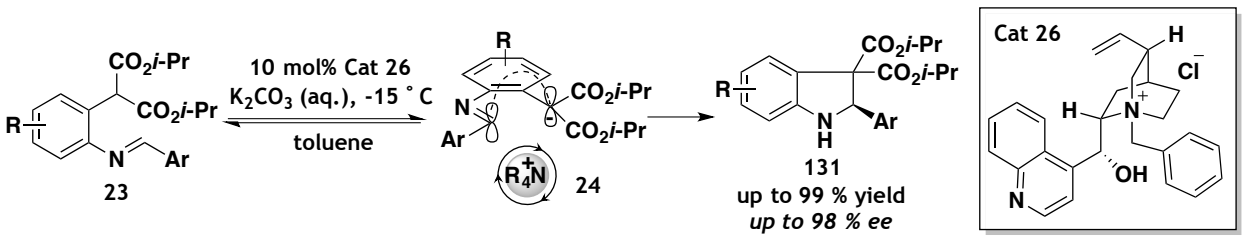
3. Cation-directed Asymmetric Allylation

3.1 Introduction

Ion-binding catalysis is a powerful tool in the field of organocatalysis. Transformations involving charged intermediates can be controlled by ion-pairing with chiral catalysts to deliver highly efficient and stereoselective processes. The reactions are operationally simple, employing mild conditions and inexpensive reagents.[4,23] In this chapter, we explore the possibility of chiral cation-directed catalysis as a novel approach towards an asymmetric allylation reaction (chiral cation-directed catalysis was introduced in **Chapter 1.1.4**).

3.1.1 Blueprint: Allylation Directed by a Chiral Cation

Research within the Smith group is focused on asymmetric organocatalytic reactions, with a specific emphasis on reactions that can be controlled by a counterion. A particularly successful project invoked a chiral cation to direct a 6π electrocyclization reaction.[33] This phase-transfer process took substrate **23** with potassium carbonate solution and *N*-benzylcinchonidinium salt **26** in toluene (**Scheme 3.1**). Deprotonation generates intermediate **24**, which has a 6π delocalized anionic system, and is tightly bound to the chiral *N*-benzylcinchonidinium cation by electrostatic and secondary non-covalent interactions. The electrocyclization reaction occurs in a disrotatory fashion away from the catalyst bulk to give indoline products **131** with high enantioselectivity.



***Scheme 3.1**: 6π asymmetric electrocyclization controlled by a countercation*

The success of this reaction led us to wonder whether similar levels of control could be achieved in other systems containing delocalized anions. The electrocyclization reaction exploits tight ion-pairing in an organic solvent, where close association of the quaternary ammonium cation to the 6π

anionic system leads to high levels of enantioselectivity. We envisaged an extension of this methodology to a 4π system, which could be applied in an allylation reaction (**Figure 3.1**).

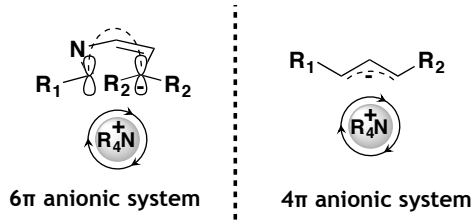
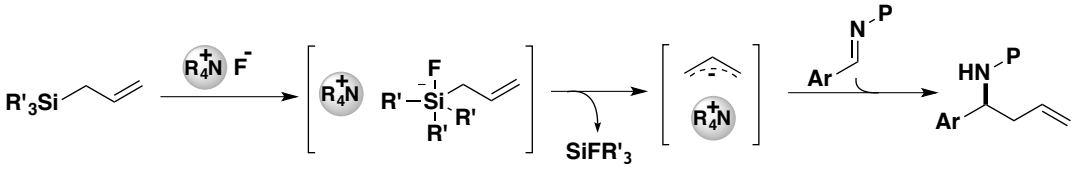


***Figure 3.1**: Using a chiral cation to control the reactivity of delocalized anions*

We reasoned that an allylsilane could act as an allyl anion surrogate, by reacting with fluoride *via* an ate-complex (**Scheme 3.2**). Therefore, our blueprint for this project was to use a chiral quaternary ammonium fluoride, which could activate an allylsilane, to generate an intermediate ion-pair. The resulting allyl anion could then react with imine electrophiles to yield protected homoallyl amines. We hoped that the tight ion-pair formed would lead to the reaction proceeding in a highly efficient and enantioselective manner.



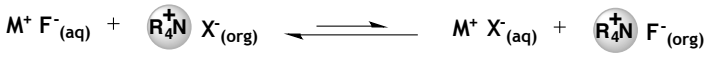
***Scheme 3.2**: Blueprint for allylation directed by a chiral ammonium fluoride catalyst*

3.1.2 Quaternary Ammonium Fluorides in Asymmetric Reactions

Quaternary ammonium fluorides are a convenient, organic soluble source of fluoride. The fluoride anion's strong affinity for silicon has been utilized in desilylation processes and in the generation of nucleophiles from organosilicon compounds.[98,99] Nevertheless, the application of chiral quaternary ammonium fluorides to catalytic asymmetric synthesis has only been explored to a limited extent, perhaps constrained by the fact that they are not commercially available.

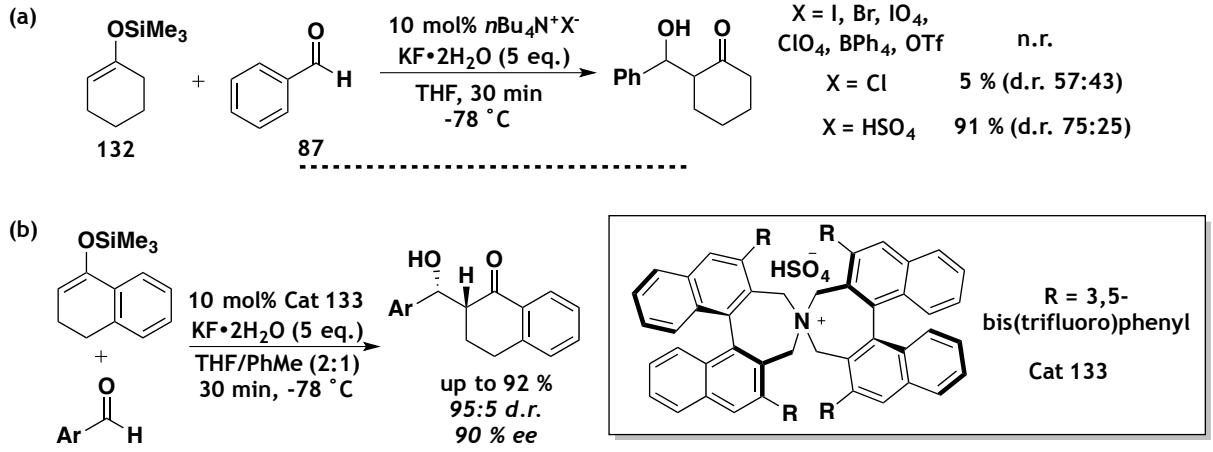
A practical solution to making quaternary ammonium fluorides is to generate them *in situ* by phase-transfer catalysis from the commercially-available quaternary ammonium halide and a metal fluoride salt. This process is not trivial, however, as the equilibrium of anions between the aqueous and organic phase is strongly dependent on the energy of hydration (**Scheme 3.3**).[100] Fluoride has a

very high hydration enthalpy of –474 kJ mol^{-1} compared to other halides (Cl^- = –338 kJ mol^{-1} and Br^- = –304 kJ mol^{-1}) and so the equilibrium favours fluoride in the aqueous phase.[101] Therefore phase-transfer of fluoride can be difficult and may require forcing conditions.



***Scheme 3.3**: Equilibrium favours the fluoride ion in the aqueous phase for X = Cl, Br, I, CN, SCN*

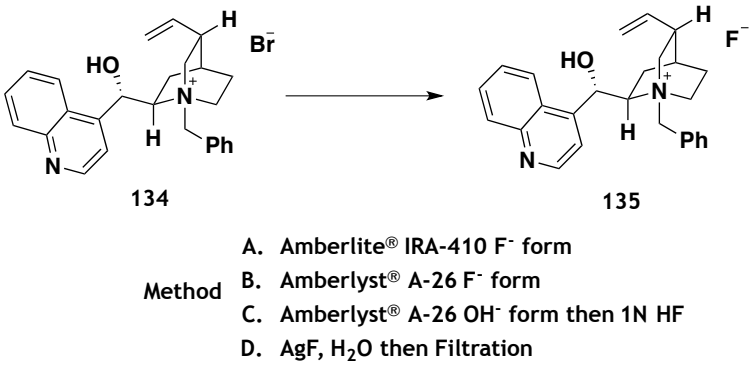
For example, Maruoka and coworkers investigated the effect of the counteranion of different tetrabutylammonium salts for a catalytic aldol reaction between enol silyl ether **132** and benzaldehyde **87**.[102] They found that the reaction did not proceed with most counterions, concluding that the anion exchange is inefficient. Their luck changed when they used hydrogensulfate as the anion instead, and the aldol reaction proceeded in 91 % yield (**Scheme 3.4 (a)**). They extended this research to an asymmetric process, and developed phase-transfer catalyst **133**. This afforded the aldol products in good yields and up to 90 % ee and 95:5 d.r. (**Scheme 3.4 (b)**). Unfortunately chiral quaternary ammonium hydrogensulfate salts are also not commercially available and require preparation prior to use.



***Scheme 3.4**: **(a)** Phase-transfer of KF•2H$_2$O with different tetrabutylammonium salts only gave a good reaction with HSO$_4^-$ as the counterion and **(b)** applying this methodology to an asymmetric aldol reaction*

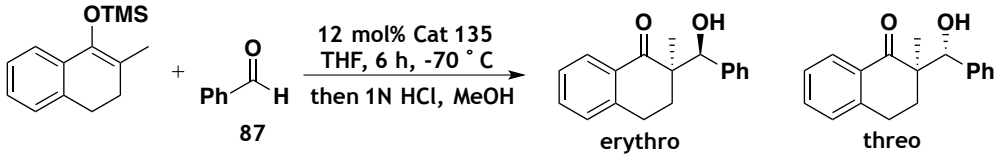
Shiori *et al.* embarked on a study to analyze different preparation methods for quaternary ammonium fluorides.[103] They considered four different techniques, three of which involved an ion exchange resin (Methods A – C) and one that employed silver fluoride (Method D) (**Scheme 3.5**). They noted that ^{1}H-NMR spectroscopy indicated no decomposition of the *N*-benzylcinchoninium

residue, and that ^{19}F-NMR revealed an F^- peak at –124 ppm (c.f. $CFCl_3$) in line with other literature reports.



Scheme 3.5**: Methods to prepare N-benzylcinchoninium fluoride **135

Shiori *et al.* then tested *N*-benzylcinchoninium fluoride catalysts synthesized by each method in a representative aldol reaction and compared the results (**Table 3.1**). The results showed that the yields varied little (63 – 74 %) and importantly that the diastereomeric ratio and ee were not dependent on which catalyst preparation method was used. Therefore they concluded that a chemist could choose which method they preferred for the preparation of quaternary ammonium fluorides and it would not effect the overall outcome of their investigations.

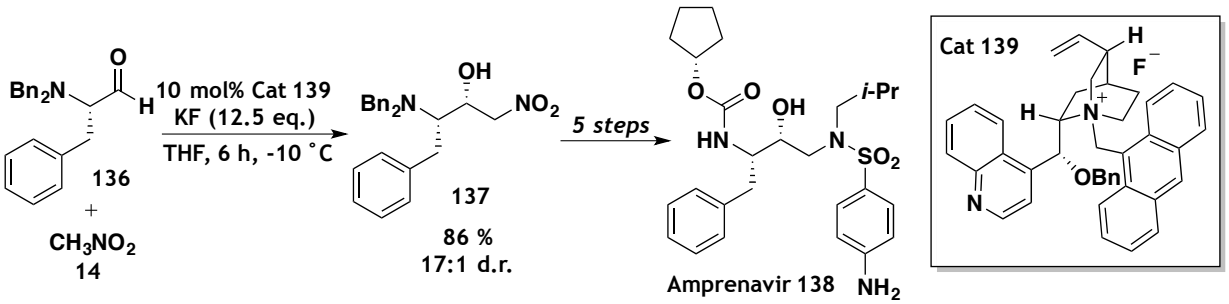


Catalyst Preparation Method	Yield %	Erythro/Threo	ee % (erythro)	ee % (Threo)
A	74	75/25	72	22
B	63	71/29	67	13
C	74	70/30	70	20
D	66	80/20	71	16

***Table 3.1**: Aldol reaction with catalyst **135** prepared by different methods*

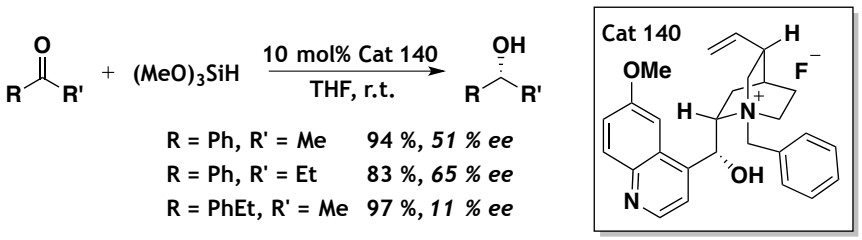
For example, Corey and Zhang used Method C to make quaternary ammonium salt **139** and applied it to a nitroaldol reaction as a key step towards the total synthesis of amprenavir, a HIV protease inhibitor (**Scheme 3.6**).[104] Nitromethane **14** was added to *N*,*N*-dibenzyl-(*S*)-phenylalaninal **136** in the first step, using quaternary ammonium salt **139** and excess KF in THF. This gave product **137** in 86 % yield, which was separable from its diastereomer by silica gel chromatography and confirmed a

d.r. of 17:1 (*syn*:*anti*). When TBAF was used for the same reaction the d.r. was only 4:1 (*syn*:*anti*). The total synthesis of amprenavir **138** was completed in five additional steps.



Scheme 3.6**: Nitroaldol reaction mediated by quaternary ammonium catalyst **139** in the total synthesis of amprenavir **138

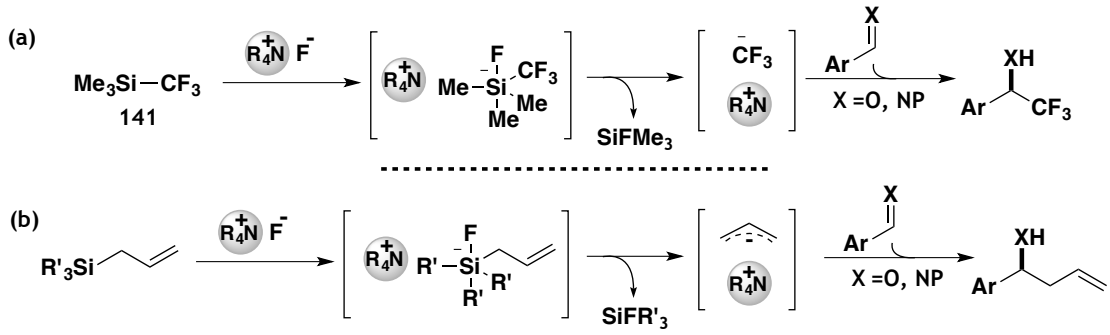
Lawrence *et al.* found that quaternary ammonium fluorides were good catalysts for the asymmetric reduction of ketones.[105] A range of different chiral quaternary ammonium salts were prepared by Method C. Hydrosilylation with trimethoxysilane and *N*-benzylquininium fluoride **140** proceeded with a range of ketone substrates, although the best enantioselectivities were obtained for bulkier groups (**Scheme 3.7**).



Scheme 3.7**: Hydrosilylation of ketones catalyzed by N-benzylquininium fluoride **140

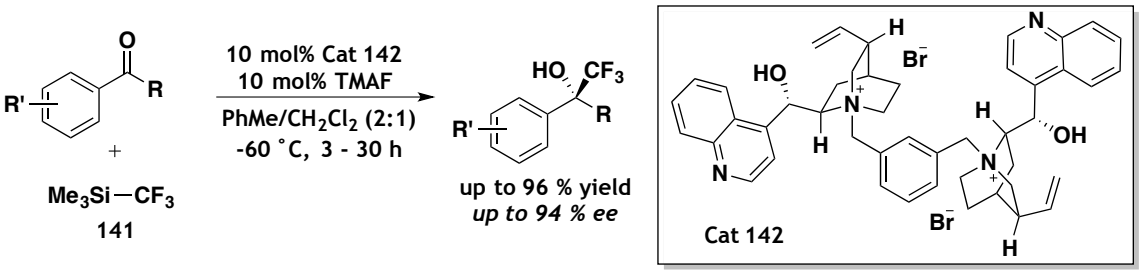
3.1.3 Enantioselective Trifluoromethylation with Quaternary Ammonium Salts

Perhaps the most interesting transformation that has been developed using quaternary ammonium fluorides is a nucleophilic trifluoromethylation reaction. In 1994, Kobayashi *et al.* first demonstrated that the Ruppert-Prakash reagent **141** is reactive with ketones, when catalyzed by chiral quaternary ammonium fluorides (although only modest ees were achieved).[106] There are several similarities between the nucleophilic trifluoromethylation reaction and our blueprint for allylation (**Scheme 3.8**). Both involve fluoride activation of a silane to form a pentacoordinate ate-complex.



***Scheme 3.8**: **(a)** Trifluoromethylation catalyzed by quaternary ammonium fluorides and **(b)** our blueprint for asymmetric allylation*

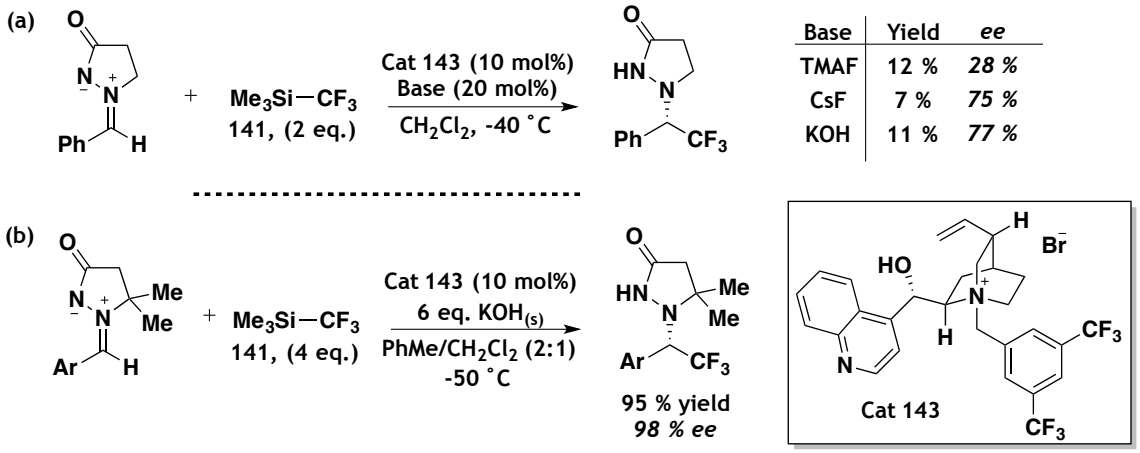
Shibata and coworkers were the first to obtain high enantioselectivities for trifluoromethylation catalyzed by cinchona alkaloid salts.[107] Their research aimed to find a phase-transfer method to eliminate the need to handle hygroscopic chiral fluoride salts. They found that the yield and enantioselectivity was strongly dependent on the fluoride source but tetramethylammonium fluoride (TMAF) gave pleasing results. Optimization found a solvent mixture of toluene/dichloromethane (2:1) and a temperature of –60 ˚C gave the best enantioselectivites in combination with bis(cinchona) catalyst **142** (**Scheme 3.9**). They demonstrated the scope of the reaction with a large number of aryl ketones, which gave consistently good results, and the highest ee obtained was 94 %.



***Scheme 3.9**: Trifluoromethylation of ketones by phase-transfer catalysis*

Since then, the same methodology has been employed to achieve the enantioselective trifluoromethylation of aryl aldehydes[108] and alkynyl ketones.[109] Furthermore, the first catalytic asymmetric trifluromethylation of imines was achieved by a similar procedure.[110] They found conventional imines, such as *N*-tosylimines, were poor substrates but azomethine imines proved more suitable. In this system TMAF was not selective as a phase-transfer reagent (only 28 % ee) but CsF and hydroxides such as KOH gave good enantioselectivities (75 % ee and 77 % ee respectively) (**Scheme 3.10 (a)**). The procedure was optimized with solid KOH and it was demonstrated that the

trifluoromethylation was general to many azomethine imines derived from aromatic aldehydes, with up to 94 % yield and 98 % ee attained (**Scheme 3.10 (b)**).

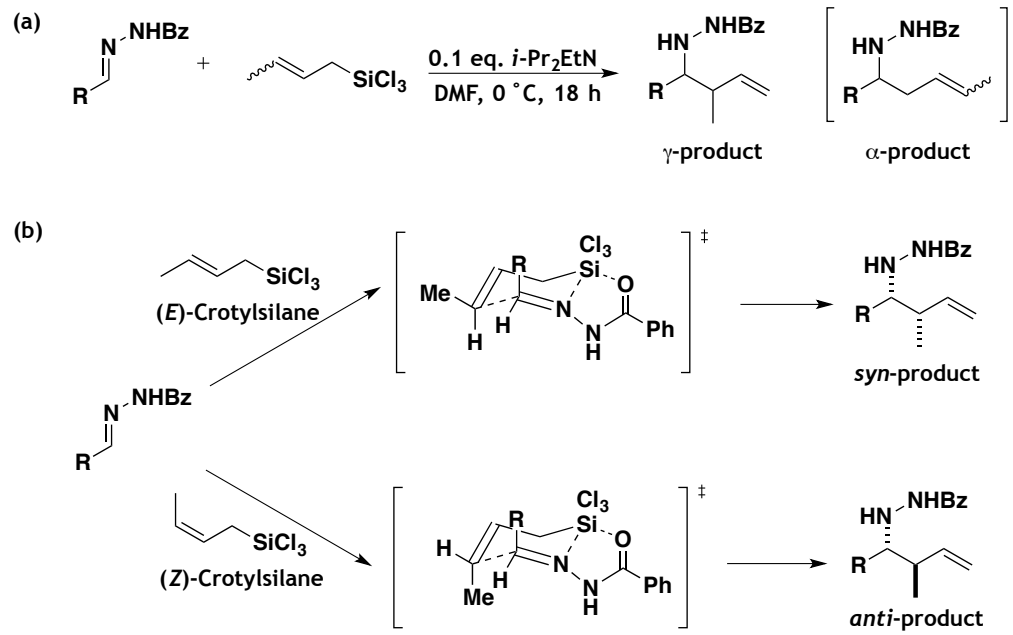


***Scheme 3.10**: **(a)** Trifluoromethylation of azomethine imines under phase-transfer conditions and **(b)** optimized results give excellent yields and enantioselectivities*

3.1.4 Mechanistic Considerations

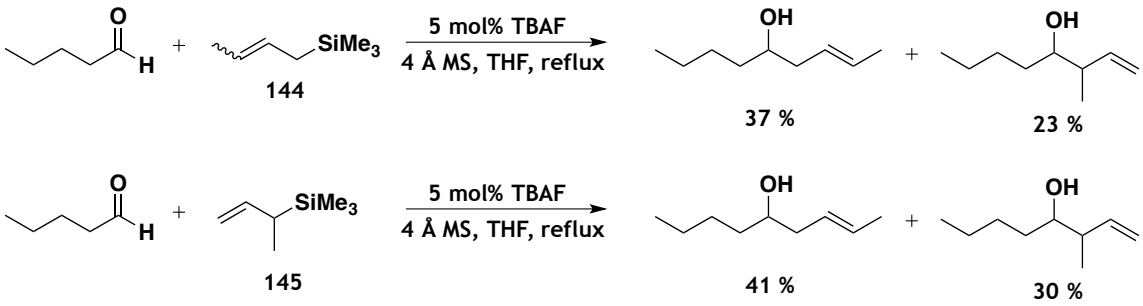
There are two important questions to consider for an allylation reaction catalyzed by an ammonium fluoride – (1) do the reaction conditions generate an allyl anion? And (2) is the reaction merely iniated by fluoride or does fluoride act as a true catalyst? Each of these are considered in turn.

The addition of an allylsilane, promoted by a Lewis base, to aldehydes or hydrazones has been well explored.[111,112] The reaction proceeds *via* a chair-like transition structure, as a two-step process, with the creation of a cationic intermediate. For the crotylation reaction, this leads to γ-products instead of α and the stereoselectivity depends on whether an (*E*)- or (*Z*)-crotylsilane was used (**Scheme 3.11**).[53]



***Scheme 3.11**: **(a)** Crotylation leads to the γ-products and **(b)** chair-like transition states give stereoselective reactions*

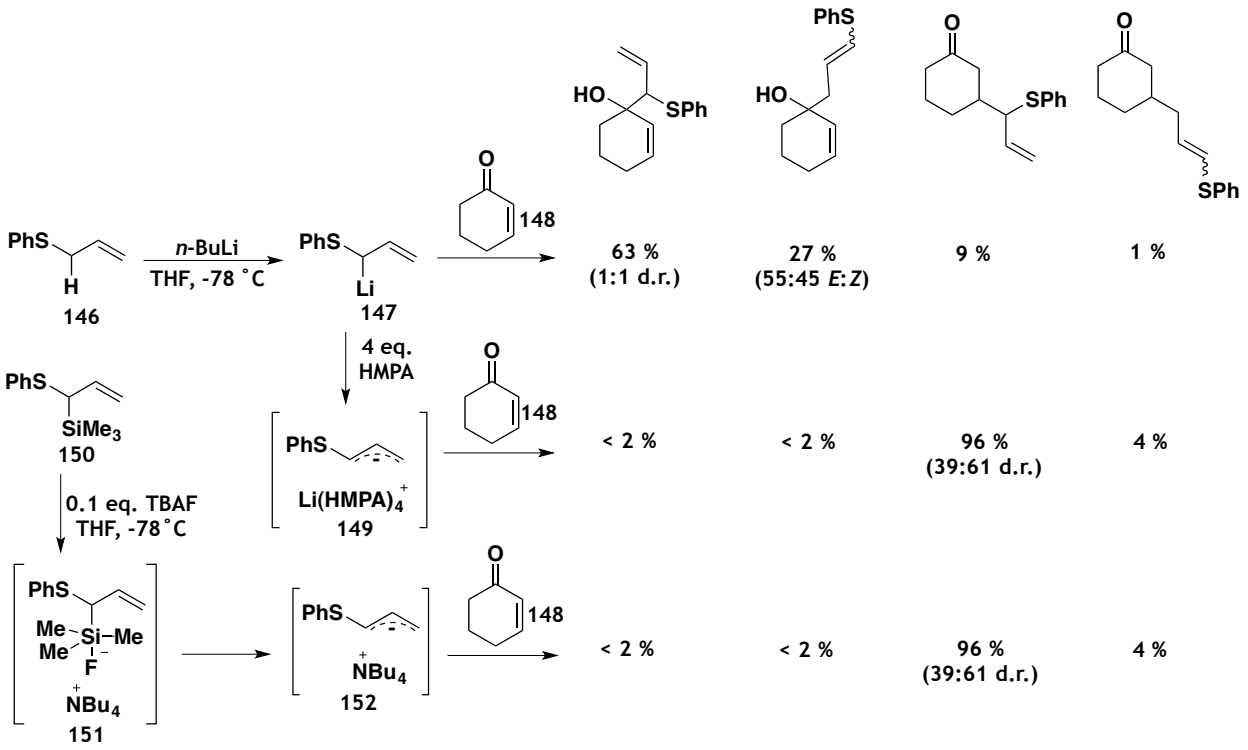
However, the scenario is less clear-cut when the allylation reaction is activated by fluoride.[93] This was noted as early as 1978 when the first Sakurai-Hosomi reaction was reported.[113] The reaction of crotylsilane **144**, with a catalytic amount of tetrabutylammonium fluoride (TBAF), gave a mixture of α- and γ-products (**Scheme 3.12**). Similarly, the isomeric 2-methylallylsilane **145** gave a comparable ratio of products, leading Sakurai to postulate that the mechanism involved an allyl anion species. Some criticized this theory because they thought the Brønsted basicity of an allyl anion would be too high.[114]



***Scheme 3.12**: Allylation leads to a mixture of α- and γ-products, suggesting an allyl anion is involved in the mechanism*

A recent study published by Biddle and Reich gives convincing supporting evidence that an allyl anion is the reactive species.[115] They compared the regio- and diastereoselectivities of the fluoride catalyzed reaction with well-defined solvent-separated lithium ion-pairs. When **146** reacts with

n-BuLi, it makes contact ion-pair **147**. This reacts with 2-cyclohexenone **148** primarily *via* 1,2-addition giving a ratio of α- and γ-products of 63:27 (**Scheme 3.13**). When co-solvent HMPA is added to **147** separated ion-pair **149** is generated. This primarily leads to 1,4-addition at the α-position, with a product d.r. of 39:61. They compared these results with the reaction of TBAF with allylsilane **150**. If the reactive intermediate is pentacoordinate **151** then the product ratio is predicted to be similar to the contact ion-pair **147**, whereas if an allyl anion **152** is generated, the reaction is expected to proceed like separated ion-pair **149**. They observed results that were near identical to the separated ion-pair **149**, observing 1,4-addition and a d.r. of 39:61. This strongly suggests that an intermediate resembling **152** is a key component of the catalytic cycle.

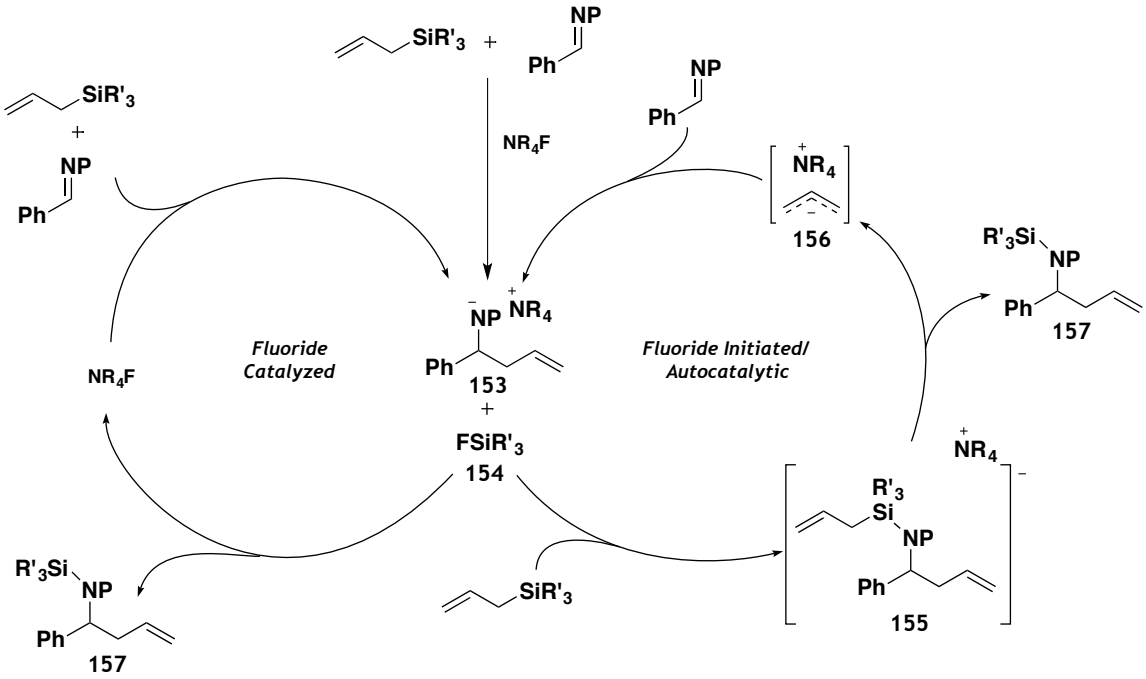


***Scheme 3.13**: The difference in reactivity of contact lithium ion-pairs and separated lithium ion-pairs is compared with fluoride-catalyzed allyl silane addition. Evidence strongly suggests an allyl anion is an intermediate*

Therefore, there is good evidence that an allyl anion is an intermediate in the fluoride promoted reaction. This fact is significant when considering our blueprint, because we have postulated that enantioselectivity is engendered by allyl anion addition in association with a chiral counterion.

The other interesting mechanistic consideration is whether the reaction is catalyzed or merely initiated by the fluoride ion. Two catalytic cycles have been proposed, as depicted in **Scheme 3.14**.[93]

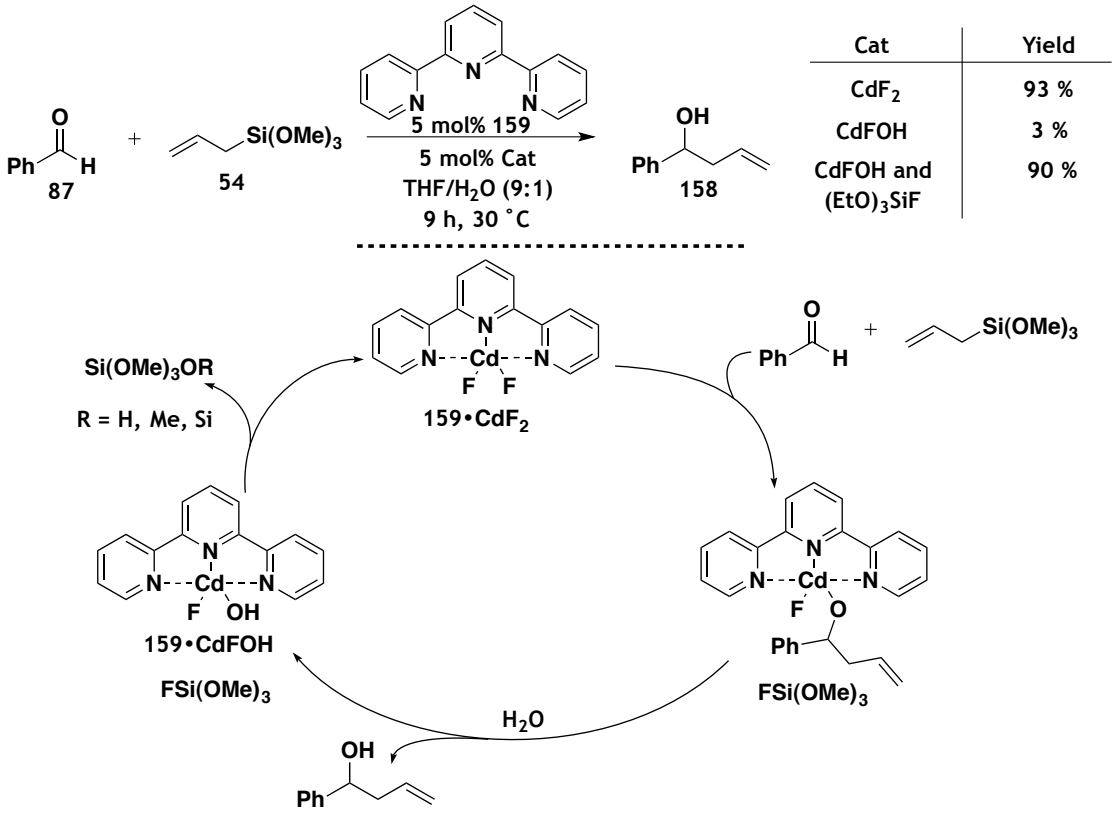
Both cycles begin in a similar manner, where the fluoride anion reacts with the allylsilane and adds to an imine electrophile, generating amide **153** and fluorosilane **154**. The fluoride-catalyzed mechanism then requires the amide **153** to break the Si-F bond of fluorosilane **154** to regenerate the quaternary ammonium fluoride catalyst. However the high bond strength of Si-F (561 kJ mol^{-1}) compared to the Si-N bond (316 kJ mol^{-1}) makes this pathway disputable.[116] It should also be noted that fluorosilane species like **154** often have low boiling points, for example $FSiMe_3$ boils at 16.4 ˚C. An alternative pathway is where amide **153** reacts with another moiety of allylsilane leading to intermediate ate-complex **155**. The ate-complex then decomposes to generate silylamine **157** and ion-pair **156**. The allyl anion intermediate **156** can then react with an imine to reproduce the amide **153**. Hence this pathway is fluoride-initiated and can be considered to be autocatalytic with respect to amide **153**.



***Scheme 3.14**: The mechanism could be fluoride catalyzed or fluoride initiated*

In some circumstances, such as the metal fluoride activated allylation reactions in protic solvents, the fluoride-catalyzed pathway is operational.[117] For example, Kobayashi *et al.* were first to demonstrate this with the CdF_2 and terpyridine **159** catalyzed reaction, which only proceeds if water is present (**Scheme 3.15**).[118] They found that complex **159•CdF_2** reacts with allylsilane **54** and benzaldehyde **87**, followed by hydrolysis to give product **158** and complex **159•CdFOH**. They

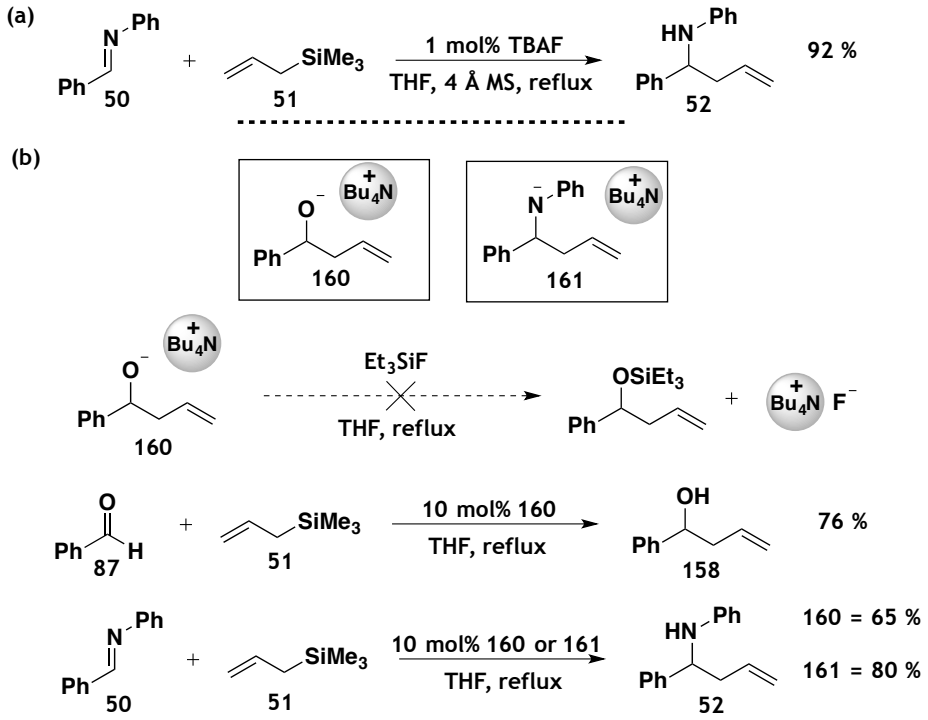
found that complex **159•CdFOH** alone was not able to catalyze the reaction, but if fluorotriethoxysilane was added that the reaction proceeded in high yield. Furthermore, ^{19}F-NMR evidence shows that a mixture of complex **159•CdFOH** and fluorotriethoxysilane produces primarily a new peak, whose chemical shift is the same as complex **159•CdF_2** (–125.8 ppm). This evidence suggests that the Si-F bond is broken to reform the catalyst.



***Scheme 3.15**: Example of a fluoride catalyzed allylation reaction*

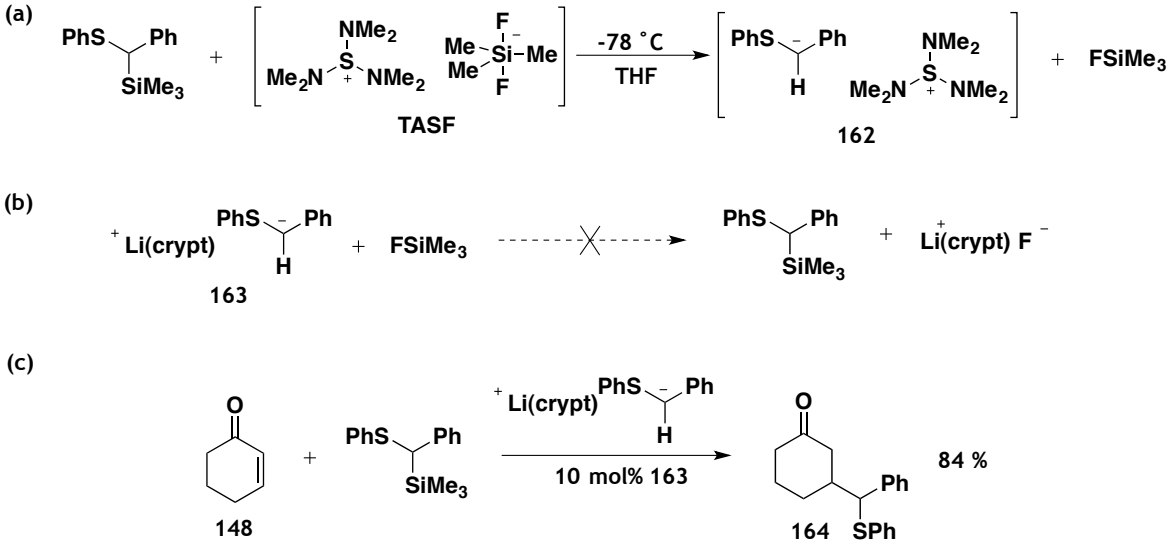
Conversely, the allylation reaction activated by ammonium fluorides in aprotic solvents appears to operate by the autocatalytic mechanism. This was investigated by Hou and coworkers, when they reported the first TBAF-catalyzed allylation of imines (**Scheme 3.16 (a)**).[56] The reaction of imine **50** and allylsilane **51** gave 92 % yield when 1 mol% of catalyst is used at reflux in THF. To probe the mechanism, they made the tetrabutylammonium salt of the product **161**, as well as the alkoxide salt **160** (**Scheme 3.16 (b)**). When alkoxide salt **160** was stirred at reflux with triethylfluorosilane, they found no evidence of the Si-F bond breaking to reform TBAF. However, when the allylation reaction was performed with either alkoxide salt **160** or amide salt **161** (i.e. no fluoride catalyst) the

reactions proceeded in good yields. This indicates that the reaction can be catalyzed by the product anion and suggests the reaction is fluoride initiated.



***Scheme 3.16**: **(a)** Allylation of imines using catalytic TBAF and **(b)** alkoxide and amide salts can also catalyze the reaction, indicating an autocatalytic pathway*

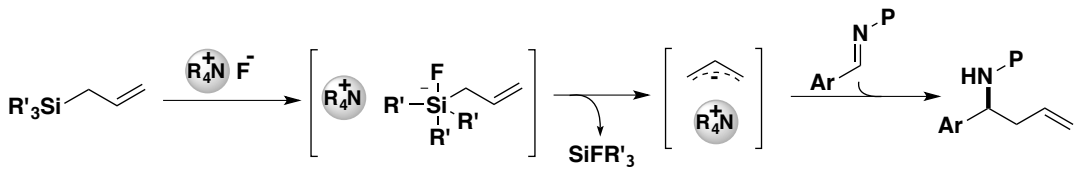
Biddle and Reich performed similar studies using separated lithium ion-pairs.[115] They found that TASF could create the anion **162** in THF at −78 °C, as observed by ^{13}C-NMR (**Scheme 3.17 (a)**). Furthermore they found the reverse reaction, where separated ion-pair **163** and trimethylfluorosilane were mixed, did not change by ^{13}C-NMR, despite the possibility of highly stable LiF being formed (**Scheme 3.17 (b)**). Finally, when they used separated ion-pair **163** to catalyze the reaction the product **164** was afforded as the 1,4-adduct in 84 % yield (**Scheme 3.17 (c)** c.f. to **Scheme 3.13**). They concluded that a fluoride initiated, autocatalytic pathway is the most likely, although they exercised caution and stated that in some cases the regeneration of the fluoride anion may compete.



***Scheme 3.17**: Separated lithium ion-pairs as allyl anion analogues give evidence for an autocatalytic pathway*

3.2 Results and Discussion

The objective of this project was to develop a catalytic enantioselective allylation reaction to make homoallyl amines. This is a synthetically useful transformation that creates a new stereocentre and carbon-carbon bond with the olefin group providing a functional handle for further elaboration. There are many different strategies for the synthesis of homoallyl amines, but currently there is no general organocatalytic method (see **Chapter 1.2**). This project aims to develop a new approach that invokes a chiral quaternary ammonium fluoride, and exploit tight ion-pairing to deliver the products with good enantioselectivities (**Scheme 3.18**). There are a limited number of examples of chiral quaternary ammonium fluorides being exploited in organocatalysis, making this strategy an intriguing challenge. If allylation is successful by this method, we additionally aim to develop a phase-transfer method, where the catalyst is generated *in situ*.



***Scheme 3.18**: Blueprint for allylation catalyzed by a chiral quaternary ammonium fluoride salt*

3.2.1 Catalyst Preparation

The quaternary ammonium fluorides are not commercially available, and so this project began by finding a suitable method to obtain them. We first considered the methods discussed by Shiori *et al.* (**Figure 3.2**).[103] For Methods A and B, the resins were not available in the fluoride form and required synthesis from the hydroxide form by passing aqueous HF through. Method C involves exchanging a quaternary ammonium bromide to the hydroxide using an ion-exchange resin, and then neutralizing with aqueous HF to afford the fluoride salt. These three methods require the use of aqueous HF, which is known to be extremely toxic. We wanted the catalyst preparation to be operationally simple and so decided to explore other methods first. Therefore we first chose to make the catalyst by Method D, employing silver fluoride.

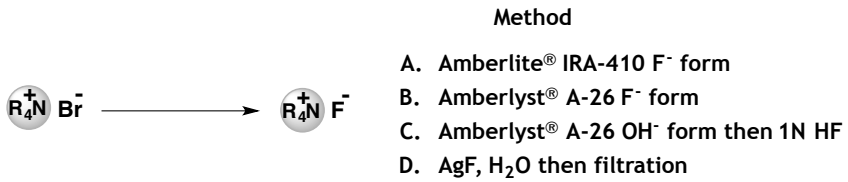
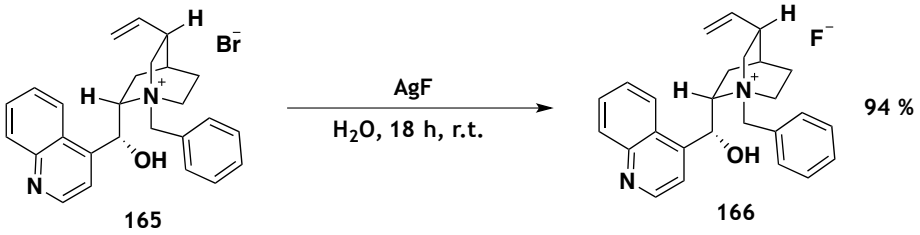


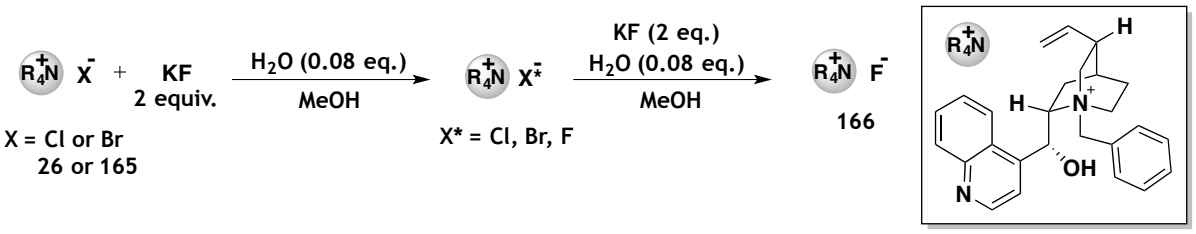
***Figure 3.2**: Ion exchange methods employed by Shiori and coworkers*

We started by using a cinchonidine-derived salt because the cinchona alkaloids are known to be general catalysts giving good enantioselectivites for a range of reactions.[119] The bromide **165** was dissolved in water with equimolar silver fluoride and stirred overnight (**Scheme 3.19**). The reaction was kept in the dark to avoid the decomposition of silver salts. Afterwards, the reaction was filtered to remove the silver bromide precipitate and the mixture was carefully dried by co-evaporation with acetonitrile.[120] The *N*-benzylcinchonidinium fluoride salt **166** showed no decomposition by ^{1}H-NMR and had a ^{19}F-NMR spectrum with a peak at –124.5 ppm, which matched literature reports.[121] However, when fluoride **166** was used in an allylation reaction, it was obvious that not all of the silver salts had been removed effectively. The reactions turned black and left a silvery sheen on the glassware. We therefore sought an alternative method because we did not want to risk the possibility of Ag(I) catalyzing the reaction - Ag(I) has been reported to catalyze allylsilane addition to ketones.[122]



***Scheme 3.19**: Ion exchange using silver fluoride*

We still hoped to find a method that did not employ aqueous HF, and a further search of the literature found that potassium fluoride in methanol could perform the desired ion exchange.[123] In this method either the bromide **165** or chloride **26** salts of *N*-benzylcinchonidinium were stirred with two equivalents of potassium fluoride (**Scheme 3.20**). After 15 minutes, the solids were filtered off, before resubmitting to the same reaction conditions. After a further 15 minutes, the reaction was filtered and the product was dried *in vacuo* (N.B. heating was avoided to prevent decomposition of the catalyst by Hofmann elimination). The literature reports that a 95 % conversion to the fluoride salt under these conditions.



***Scheme 3.20**: Anion exchange with potassium fluoride*

In our hands, this was not the case. We performed quantitative ^{19}F-NMR experiments to determine the percentage of fluoride salt within the catalyst (**Figure 3.3**). FPP was used as the internal standard, as it had a suitable chemical shift compared to our catalyst in d_6-DMSO. NMR analysis of the catalyst was carried out in duplicate, in the presence of a known quantity of the FPP standard, and the integration of the peaks was equated. We used the formula:

$$\text{Purity \%} = \frac{\text{Integral(Sample)} \times \text{Mol. Weight (Sample)} \times \text{Mass(Standard)}}{\text{Integral(Standard)} \times \text{Mol. Weight (Standard)} \times \text{Mass(Sample)}} \times 100$$

to determine the percentage of fluoride catalyst in the sample. The results showed that there was actually just 54 % (average) quaternary ammonium fluoride in the catalyst prepared by the potassium fluoride method.

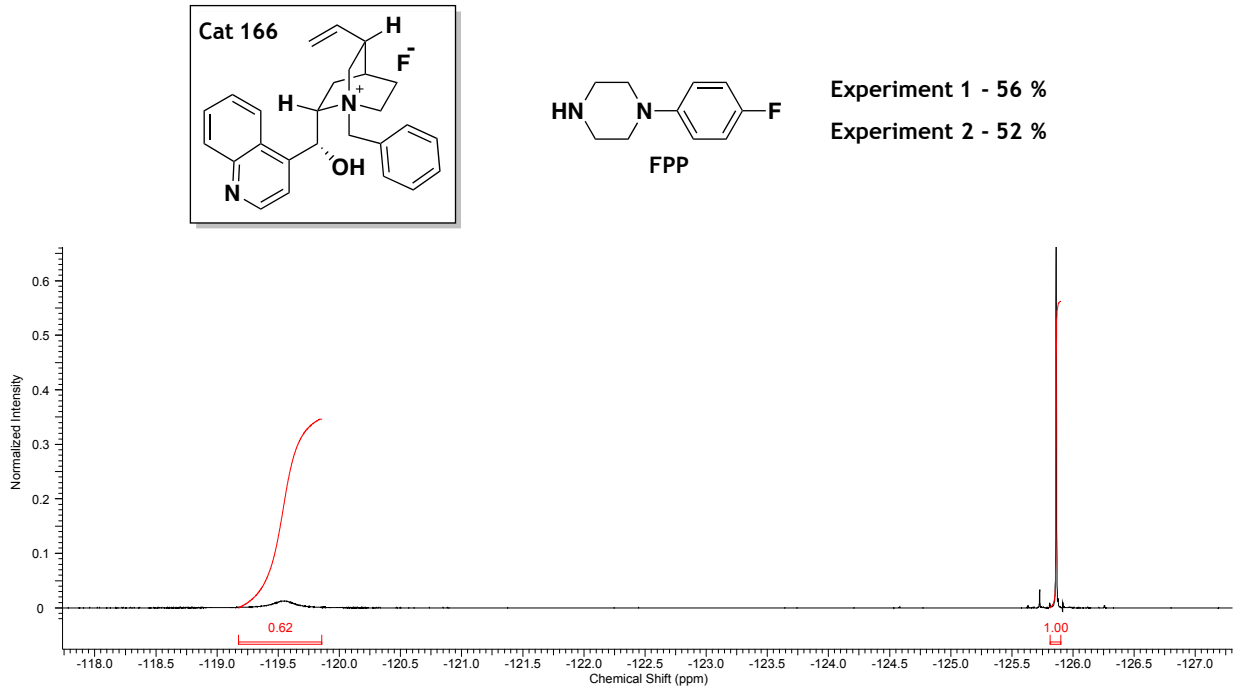
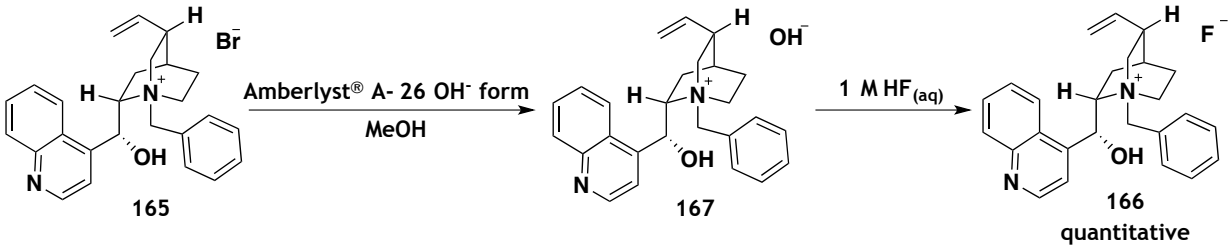


***Figure 3.3**: Quantitative ^{19}F-NMR assay for quaternary ammonium fluoride salts*

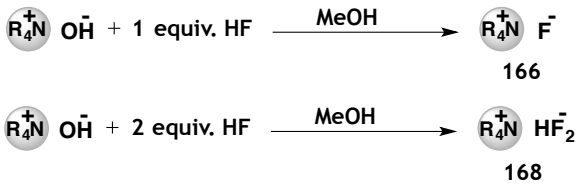
This is perhaps not surprising when we consider the scale on which the reaction was performed. The reaction must be performed with the correct ratios of quaternary ammonium salt, methanol and water. If there is no water present then the exchange does not occur but, conversely, too much water and the fluoride ion becomes solvated and is not exchanged.[124] The potassium fluoride exchange was carried out on a 3.0 mmol scale, requiring only 4 μL of water. Hence, even very small errors could cause a significant impact on the fluoride exchange. We were not confident that we could control the water content of these reactions, especially as there is probably some water in the potassium fluoride also contributing.[125] We also rationalized that, whilst *N*-benzylcinchonidinium bromide **165** can be bought relatively cheaply, other fluoride catalysts would need to be made from salts on a much smaller scale due to expense and availability. Therefore we needed to find a method that would be viable even on a <0.5 mmol scale.

Taking these issues into account, we decided to test Shiori's Method C. We slowly passed a solution of bromide **165** in methanol through a column of Amberlyst® A-26 OH^- form and flushed the column with methanol (**Scheme 3.21**). The hydroxide salt **167** formed was then neutralized with a 1 M HF solution to yield the fluoride **166** quantitatively, after drying overnight under vacuum.[126]



***Scheme 3.21**: Using an ion exchange column followed by neutralization with 1 M $HF_{(aq)}$ to render quaternary ammonium fluorides*

Although this method required extra precautions when handling aqueous HF, it proved to be much more effective than other methods. It could be performed easily at large or small scales and led to no decomposition of the cinchonidinium salt by ^{1}H-NMR spectra. Furthermore, we could use ^{19}F-NMR spectra to observe directly whether complete ion exchange had taken place. When an excess of aqueous HF is used the bifluoride salt **168** is obtained (**Scheme 3.22**). The HF_2^- ion has a distinctly different ^{19}F-NMR spectrum, typically with a peak at around –155 ppm. If this is observed in a spectrum then we know that the ion exchange was incomplete and that there is some bromide/chloride contaminating the catalyst. We therefore employed this method to make quaternary ammonium fluoride catalysts.

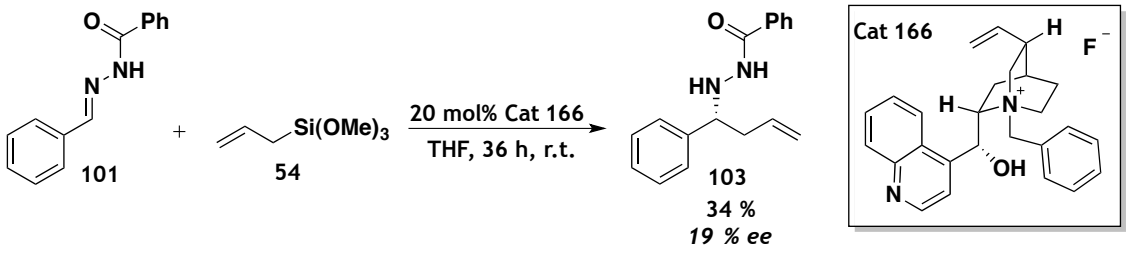


***Scheme 3.22**: Using an excess of $HF_{(aq)}$ leads to formation of a bifluoride salt*

3.2.2 Initial Results

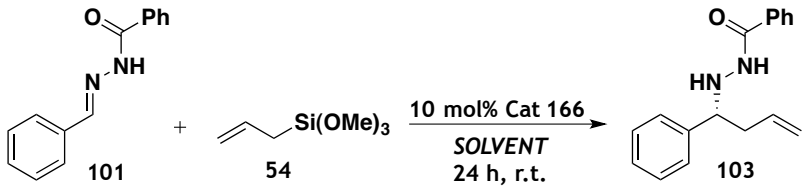
We started this project by considering the reaction of allyltrimethoxysilane **54** with *N*-benzoylhydrazone **101**. As discussed in **Chapter 2.2.2**, allyltrimethoxysilane is a good reagent because it can readily form pentacoordinate silicon with fluoride.[87] It is also a mild reagent that is stable at room temperature and does not fume in air. Similarly, *N*-benzoylhydrazone was chosen because we had already found it to be a good electrophile for allylation reactions. Its synthesis is simple, it can be purified by crystallization and is bench stable. The first reaction was carried out with a 20 mol% loading of *N*-benzylcinchonidinium fluoride **166** in THF (**Scheme 3.23**). Pleasingly,

this gave the product **103** in a 34 % yield and a 19 % ee. The enantiomeric excess was determined by chiral HPLC using a Chiralpak AD-H column and an eluent system of 6 % IPA in hexane. This was compared with a racemic sample, prepared using TBAT and Schreiner's catalyst (see **Chapter 2.2.2**). The absolute stereochemistry was determined to be the (*R*)-enantiomer, by comparison with optical rotation data in the literature.[43]



Scheme 3.23**: Initial allylation results with N-benzoylhydrazone **101** and allyltrimethoxysilane **54

This promising result was exciting but clearly significant optimization was required to increase turnover and improve enantioselectivity. We noted that the conversion to the product was clean, and that the remaining starting material could be recovered – there were no side products being formed. We first did a large solvent screen to see how this affected yield and ee, employing 10 mol% of catalyst **166** and stopping the reaction after 24 h (**Scheme 3.24**). We found THF gave the same enantioselectivity and a slightly reduced yield (25 %) under these conditions, whilst in diethyl ether and isopropyl ether gave no reaction. Non-polar solvents like toluene also returned starting material, and likewise the reaction did not proceed in protic solvent methanol. However, when chlorinated solvents like dichloromethane and chloroform were used, the reaction proceeded in low yield but gave an increased ee (39 % and 36 % respectively). Other chlorinated solvents like chlorobenzene and 1,1,2,2-tetrachloroethane were tried but gave no reactivity. We also found the reaction proceeded in polar aprotic solvent DMF, giving 19 % yield but the ee decreased to just 10 %. We suspect this is because of a background reaction that can occur, as DMF is Lewis basic and can activate the allylsilane.[127]

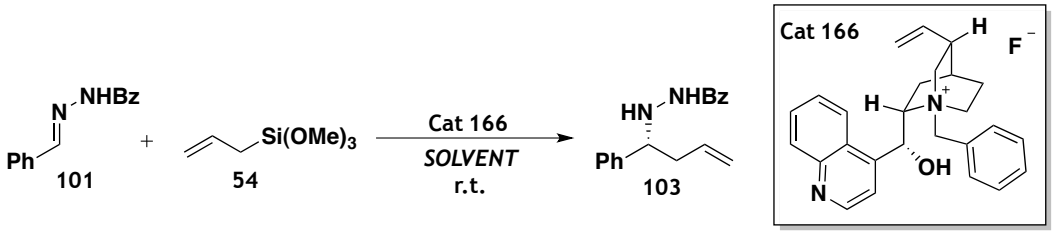


	Yield	*ee*
THF	25 %	*19 %*
CH_2Cl_2	12 %	*39 %*
$CHCl_3$	13 %	*36 %*
DMF	19 %	*10 %*

No reaction: Et_2O, *i*-Pr_2O, PhMe, MeCN, MeOH, chlorobenzene, 1,1,2,2-tetrachloroethane

***Scheme 3.24**: Initial solvent screen*

Therefore, we have established that polar non-protic solvents are required for the reaction and that chlorinated solvents give significantly better enantioselectivities. The catalyst appeared to be giving poor turnover, and so we compared the reaction when performed with stoichiometric amounts of ammonium fluoride **166** (**Table 3.2**). In THF the reaction only gave slightly improved yield after 24 h, but only gave a 12 % ee (entry 2). In dichloromethane the reaction also gave an improved yield of 36 %, and a similar ee (34 %) (entry 4 c.f. with entry 3). We also did a test reaction under catalytic conditions where the reaction was quenched after 2 h (entry 5). This gave only a 3 % yield, which indicates that the reaction does not start immediately and then stop turning over after a short time, but rather that the reaction is very sluggish to begin with.

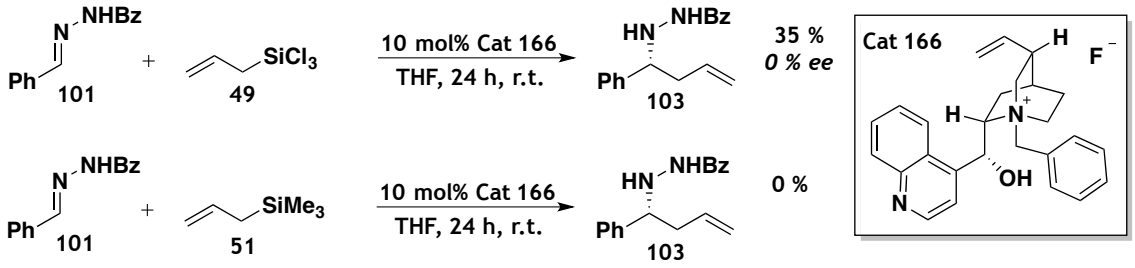


	Catalyst Loading mol%	Solvent	Time h	Yield %	ee %
1	20	THF	36	34	19
2	100	THF	24	39	12
3	20	CH_2Cl_2	24	25	35
4	100	CH_2Cl_2	24	36	34
5	10	CH_2Cl_2	2	3	34

***Table 3.2**: Initial results*

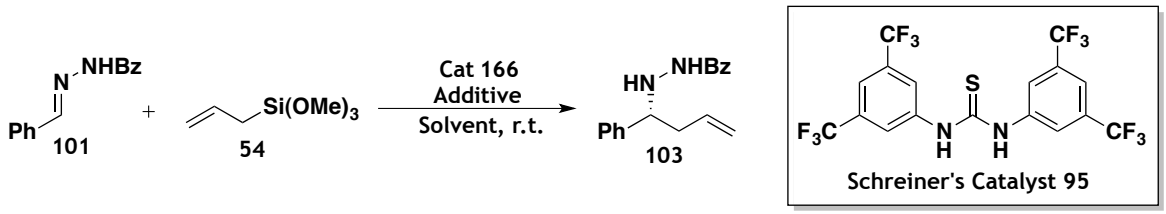
We were concerned, having observed low yields even under stoichiometric conditions that perhaps the catalyst was degrading in the reaction. To test this we set up two experiments, where the catalyst was left to stir overnight in THF and dichloromethane. After this time, the ^{1}H-NMR spectra of these samples showed no change, indicating that the catalyst was not going off in solution.

We also investigated what effect changing the allylsilane would have on the reaction (**Scheme 3.25**). Allyltrichlorosilane **49** reacted with hydrazone **101** using 10 mol% of the catalyst **166** and gave a 35 % yield but, unfortunately, the reaction was racemic. The reaction with allyltrimethylsilane **51** did not proceed at all, and no product was isolated. We concluded that allyltrimethoxysilane **54** was the best reagent to continue with.



***Scheme 3.25**: Allylation with different allylsilanes*

We next explored what effect different additives had on the reaction. The literature indicated that some allylation reactions require a proton source to regenerate the reactive species (see **Chapter 3.1.4**).[80,118] We also knew from our own research that a hydrogen bond donor can significantly increase the turnover of an allylation reaction (**Chapter 2.2.2**). The use of Schreiner's catalyst **95** as a hydrogen bond donor in THF with *N*-benzylcinchonidinium fluoride **166** gave the allylated product in 28 % yield and 22 % ee (**Table 3.3**, entry 1). Although the enantioselectivity had slightly increased, the turnover had not improved. Stoichiometric amounts of protic sources (*t*-BuOH entry 2 and AcOH entry 5) gave no reaction under these conditions. Using 10 mol% of acetic acid also caused the yield to decrease (entries 3 and 4) although, interestingly, in THF the ee improved under these conditions from 19 % to 27 %.

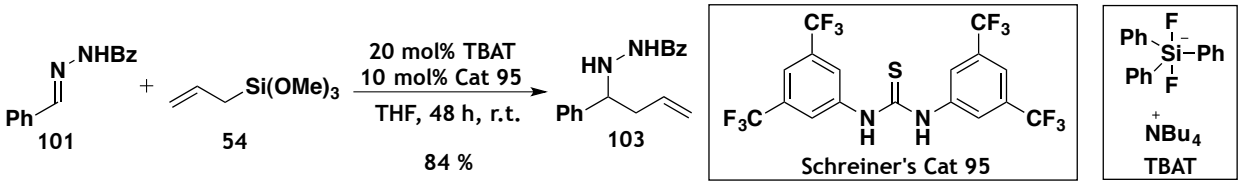


	Additive	Catalyst Loading mol%	Solvent	Yield %	ee %
1	10 mol% Schreiner's Cat **95**	20	THF	28	22
2	100 mol% *t*-BuOH	10	THF	0	N/A
3	10 mol% AcOH	10	CH_2Cl_2	5	31
4	10 mol% AcOH	20	THF	18	27
5	100 mol% AcOH	10	CH_2Cl_2	0	N/A

***Table 3.3**: Effect of different additives to the allylation reaction*

3.2.3 Triphenyldifluorosilicate as a Fluoride Source

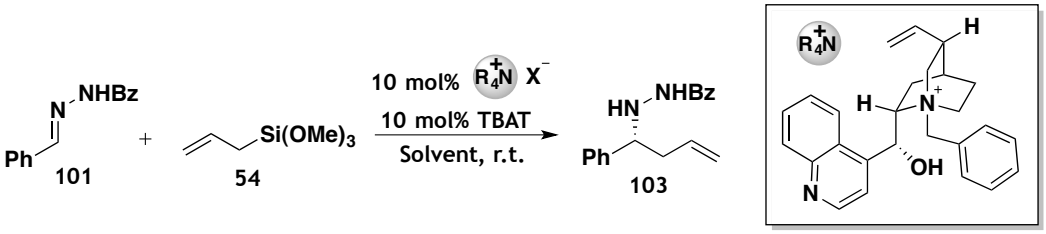
At this stage in the project we took inspiration from the work that had already been performed in the thiourea catalysis project (**Chapter 2**). We needed to find a way to increase turnover of the cinchonidine-derived catalyst **166** to make the reaction practical. TBAT (tetrabutylammonium triphenyldifluorosilicate) was an excellent fluoride source for promoting allylation reactions, with yields as high as 84 % (**Scheme 3.26**). Therefore triphenyldifluorosilicate was investigated as an alternative fluoride source.



***Scheme 3.26**: TBAT and thiourea **95** give high yields for the allylation reaction*

The first experiments performed were the *in situ* ion exchange of cinchona salts with TBAT. Although fluoride is known to be difficult to exchange with other anions under phase-transfer conditions, it was not known if the triphenyldifluorosilicate anion would behave similarly. Phase-transfer with 10 mol% *N*-benzylcinchonidinium chloride **26** in THF proceeded in 66 % yield, but was not stereoselective (**Table 3.4**, entry 1). When the solvent was changed to dichloromethane the yield was 57 % and the ee improved to 7 % (entry 2). Unfortunately, although these conditions were allowing catalysis to occur, there appeared to be significant background reaction occurring. When

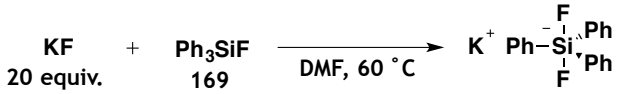
the bromide salt **165** was used instead the yield decreased to 34 % indicating that it did not catalyze the reaction as well as the chloride catalyst **26**.



	Catalyst	Solvent	Time h	Yield %	ee %
1	NR_4Cl, **26**	THF	24	66	0
2	NR_4Cl, **26**	CH_2Cl_2	24	57	7
3	NR_4Br, **165**	CH_2Cl_2	30	34	8

***Table 3.4**: Ion exchange with TBAT*

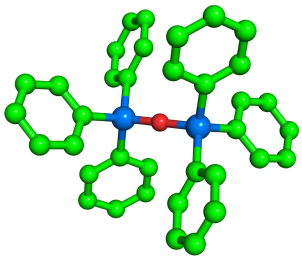
Next, we investigated the possibility of changing the triphenydifluorosilicate counterion. Instead of using the tetrabutylammonium salt, we thought that the potassium salt would be a good alternative because it would not catalyze the background reaction. The preparation of this salt has been reported by Mąkosza and Bujok.[128] Following their procedure, excess potassium fluoride was heated with triphenylsilyl fluoride **169** to 60 ˚C in DMF (**Scheme 3.27**). The solid produced was recrystallized from acetonitrile. However the product formed did not have ^{1}H-NMR data that matched the literature report and, furthermore, there was no peak in the ^{19}F-NMR spectrum.

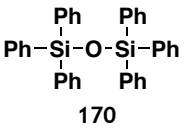


***Scheme 3.27**: Preparation of potassium triphenyldifluorosilicate*

Therefore X-ray crystallographic data was collected for the crystals. To our surprise, this revealed that the product was dimer hexaphenyldisiloxane **170** (**Scheme 3.28 (a)**). A search of the literature revealed that this product has been formed under similar conditions by other groups, when water was not effectively removed from either the solvent[129] or metal fluoride source[130] (**Scheme 3.28 (b)**).

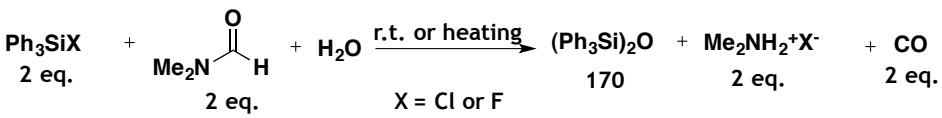
(a)





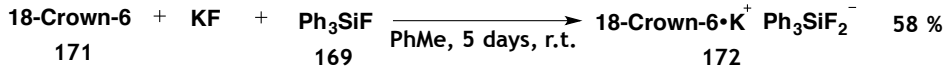
170

(b)



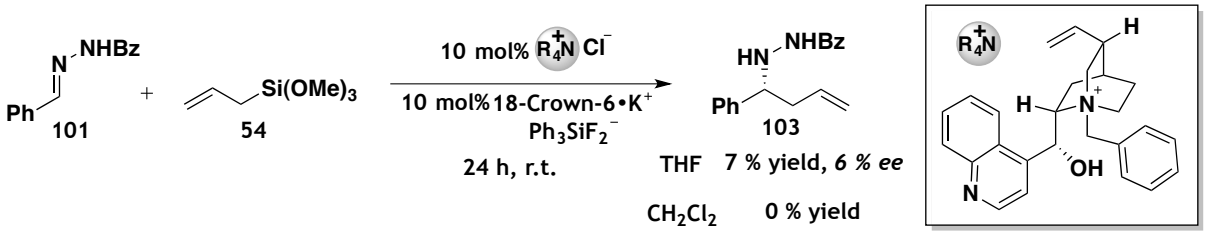
Scheme 3.28**: **(a)** Crystal structure of hexaphenylsiloxane and **(b)** reaction of triphenylchlorosilane in DMF with any water contaminants can produce the disiloxane **170

An alternative preparation for the 18-crown-6 potassium salt **172** was employed.[131] Triphenylsilyl fluoride **169**, potassium fluoride and 18-crown-6 ether **171** were stirred in toluene at room temperature (**Scheme 3.29**). The reaction was monitored by TLC analysis and it took 5 days for the triphenylsilyl fluoride **169** to be fully consumed. After filtering and washing the precipitate, the product was isolated in 58 % yield. It had a clear ^{19}F-NMR with the anion peak at –97.7 ppm (in d_6-DMSO c.f. $CFCl_3$).



***Scheme 3.29**: Formation of crown ether complex*

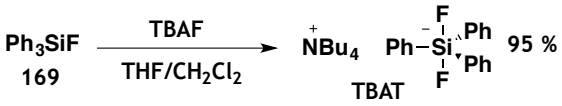
With the complex **172** in hand, we tested it under phase-transfer conditions. Unfortunately the allylation reaction did not proceed well using the 18-crown-6 complex. In THF the yield was only 7 % and in dichloromethane the reaction did not occur (**Scheme 3.30**). Therefore we did not pursue with the phase-transfer of triphenydifluorosilicate any further.



***Scheme 3.30**: Using 18-crown-6 complex **172** under phase-transfer conditions*

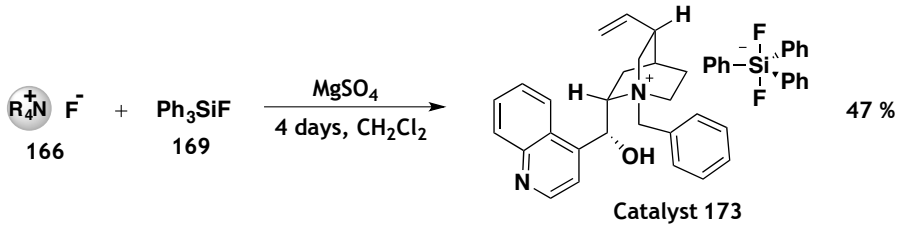
Instead, we attempted to synthesize the chiral quaternary ammonium salt where triphenyldifluorosilicate was the anion. DeShong *et al.* had reported the general synthesis of TBAT

from triphenylsilyl fluoride **169** by adding TBAF (**Scheme 3.31**)[132,133] and we believed that the quaternary ammonium salt could be prepared similarly.



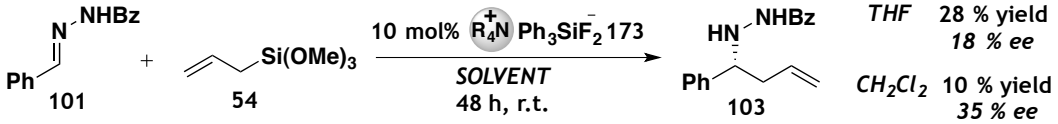
***Scheme 3.31**: Preparation of TBAT*

Pleasingly the catalyst **173** was successfully prepared using this method, although some precautions were required (**Scheme 3.32**). DeShong reported that when TBAF was added to triphenylsilyl fluoride **169** a mild exotherm was noticed, and the reaction was complete without stirring.[132] However, we found the reaction with *N*-benzylcinchonidinium fluoride **166** to be sluggish and incomplete after 4 days. We also found that traces of water in the reaction caused formation of hexaphenyldisiloxane byproduct **170**. The most practical method was to use $MgSO_4$ as a drying agent to prevent this. We were pleased to see by ^{19}F-NMR that the triphenylsilyl fluoride peak at –169.5 ppm was not present, and that the new peak at –97.7 ppm indicated the triphenyldifluorosilicate anion had been formed (in d_6-DMSO c.f. $CFCl_3$).



Scheme 3.32**: Making chiral quaternary ammonium salt **173

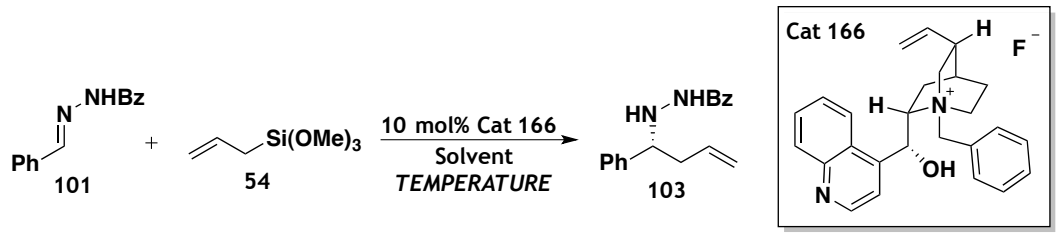
With catalyst **173** in hand, we investigated how it would perform in the allylation reaction. In THF the product was isolated in 28 % yield and 18 % ee and in dichloromethane the reaction gave **103** in 10 % yield and 35 % ee (**Scheme 3.33**). Unfortunately the triphenyldifluorosilicate anion does not effectively catalyze the reaction and these results were equivalent to using *N*-benzylcinchonidinium fluoride **166**. Therefore we did not pursue with this catalyst any further.



Scheme 3.33**: Allylation with quaternary ammonium triphenyldifluorosilicate catalyst **173

3.2.4 Further Optimization

At this stage, we returned to focusing on the allylation reaction with *N*-benzylcinchonidinium fluoride **166**. The reaction gave promising enantioselectivity in chlorinated solvents of up to 39 % ee, however the poor turnover of the catalyst still remained a significant challenge. We next investigated the effect temperature would have on both of these parameters (**Table 3.5**). We were cautious to observe changes in the enantioselectivity, because increasing the temperature can be detrimental if the rate of the background reaction changes. We noticed that when the allylation was carried out in refluxing dichloromethane the yield increased from 12 % to 37 % (entry 1 c.f. entry 2), although the ee decreased slightly to 32 %. When the temperature was increased further using chloroform as the solvent, a significant increase in the turnover of the reaction was observed. The yield boosted from 13 % at room temperature to 81 % at 61 ˚C (entry 3 and entry 4) and the ee had also marginally increased from 36 % to 39 %. In order to further raise the reaction temperature, we investigated the reaction in 1,2-dichloroethane (entries 5-7). The reaction proceeded well at reflux giving the product **103** in 67 % yield, but the enantioselectivity began to diminish. The ee at room temperature was 32 % in 1,2-dichloroethane, whereas at 84 ˚C the ee had lowered to 23 %.

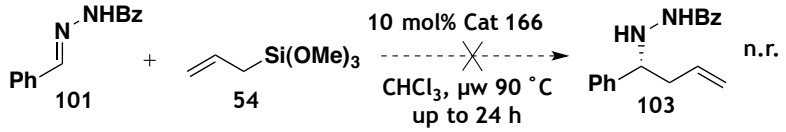


	Solvent	Temp. ˚C	Time h	Yield %	ee %
1	CH_2Cl_2	20	24	12	39
2	CH_2Cl_2	40	24	37	32
3	$CHCl_3$	20	48	13	36
4	$CHCl_3$	61	48	81	39
5	1,2-DCE	20	48	10	31
6	1,2-DCE	61	48	29	28
7	1,2-DCE	84	48	67	23

***Table 3.5**: Effect of changing the temperature*

We were happy with the improvement in yield that could be gained by performing the reaction in chloroform at reflux, although the experiments in 1,2-dichloroethane proved that there is a narrow

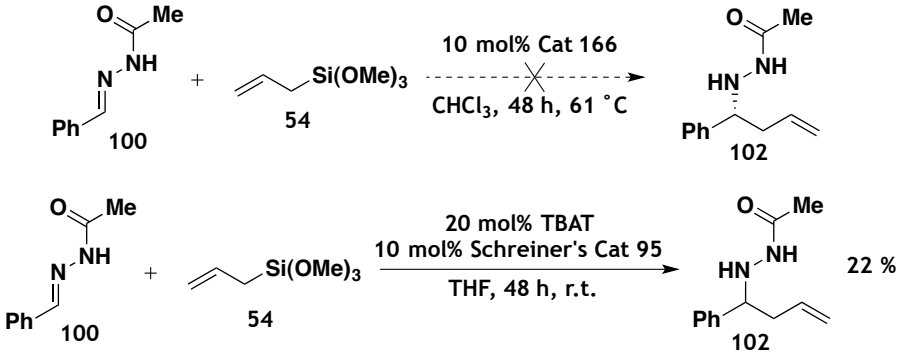
window of opportunity in which the reaction proceeds best. To investigate this further, the allylation reaction was carried out under microwave irradiation (**Scheme 3.34**). After 2 h at 90 ˚C, TLC analysis showed no trace of product, only starting materials, so the reaction was repeated for 24 h. Unfortunately no reaction had taken place after this time.



***Scheme 3.34**: Allylation did not proceed in the microwave*

3.2.5 Investigating Different Imine Substrates

The next aspect explored for optimization was the choice of hydrazone. Thus far, only *N*-benzoylhydrazone **101** had been used as a substrate with quaternary ammonium fluoride catalyst **166**. We conjectured that changing the protecting group might significantly affect the stereoselectivity of the reaction. This idea was first tested with *N*-acylhydrazone **100** (first synthesized in **Chapter 2.2.2**). To our surprise we discovered that this was a very poor substrate for the reaction (**Scheme 3.35**). With 10 mol% of catalyst **166**, only trace amounts of the product were observed in the crude ^{1}H-NMR and this could not be isolated. The racemic reaction with TBAT/Schreiner's catalyst **95** was also sluggish and the product **102** was isolated in only 22 % yield after 48 h. The remaining starting material could be regained by column chromatography and no byproducts were observed. Both of these results are in stark contrast to the reaction with *N*-benzoylhydrazone **101**.



***Scheme 3.35**: Allylation with N-acylhydrazone*

We postulated that perhaps this significant difference in reactivity is related to the pK_a of the hydrazones. The hydrazones **100** and **101**, to the best of our knowledge, have not had their pK_as measured but their parent hydrazides have (**Figure 3.4 (a)**).[134] The difference in the measured pK_as of these compounds is approximately 3 units. We rationalized that the stability of the product anion may be a significant factor in controlling the turnover of the allylation. If the product anion is not stabilized, we envisaged that the product would be difficult to form. Conversely, if the product anion is highly stabilized then this may significantly lower nucleophilicity, preventing catalytic turnover (See **Scheme 3.14**). We hypothesized that there would be a fine play-off between these two competing factors. This also raises the question of whether there is proton transfer in the product (**Figure 3.4 (b)**).

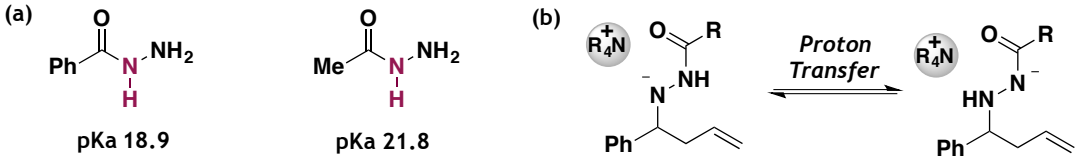
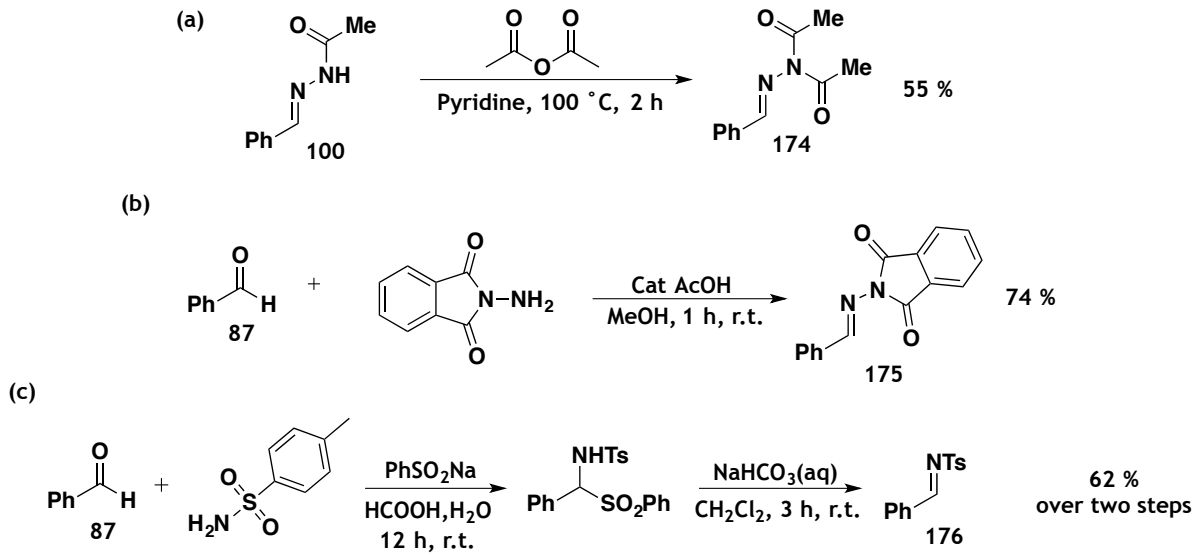


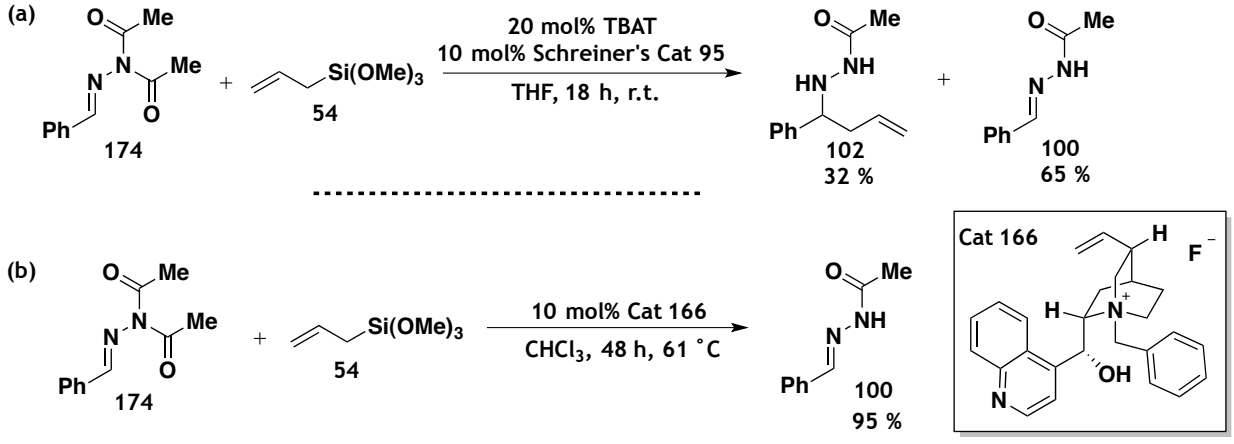
***Figure 3.4**: **(a)** pK_a of hydrazides and **(b)** proton transfer in the anionic product*

We started by designing two hydrazone substrates where proton transfer would not be possible. *N*-Acylhydrazone **100** was acylated using acetic anhydride in pyridine to yield *N*,*N*-diacylhydrazone **174** (**Scheme 3.36 (a)**). Phthalimide-derived hydrazone **175** was readily prepared from its hydrazide in 74 % yield after purification by recrystallization from ethanol (**Scheme 3.36 (b)**). *N*-Tosylimine **176** was also synthesized, in a two-step process, to provide an imine for comparison with the hydrazones (**Scheme 3.36 (c)**).



***Scheme 3.36**: Preparation of different substrates*

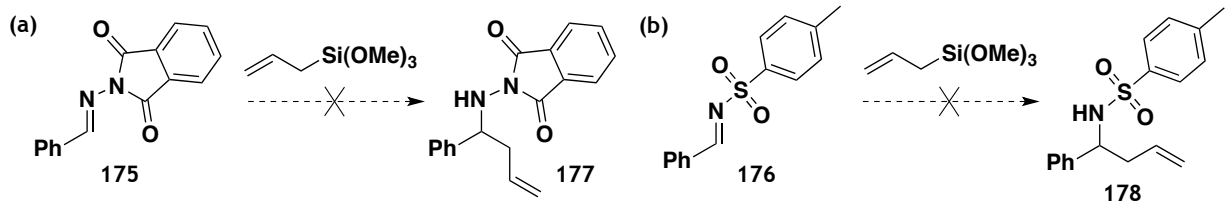
We first experimented with how *N*,*N*-diacylhydrazone **174** advanced under the standard reaction conditions. Regrettably, the reaction did not progress as expected under racemic or asymmetric conditions. Using TBAT/Schreiner's catalyst we observed a 32 % conversion to allylation product **102**. In addition, 65 % of the deacylation product was isolated (**Scheme 3.37 (a)**). The reaction catalyzed by *N*-benzylcinchonidinium fluoride **166** proceeded similarly and 95 % of the deacylation product **100** was sequestered (**Scheme 3.37 (b)**).



***Scheme 3.37**: Reaction of N,N-diacylhydrazone under standard allylation conditions*

Next, allylation of phthalimide hydrazone **175** was attempted. This was not a good substrate for allylation and no formation of the product **177** was observed by TLC analysis when the reactions were carried out under standard conditions (**Scheme 3.38 (a)**). We were interested to see how an imine would react by comparison but *N*-tosylimine **176** was also a poor substrate for allylation

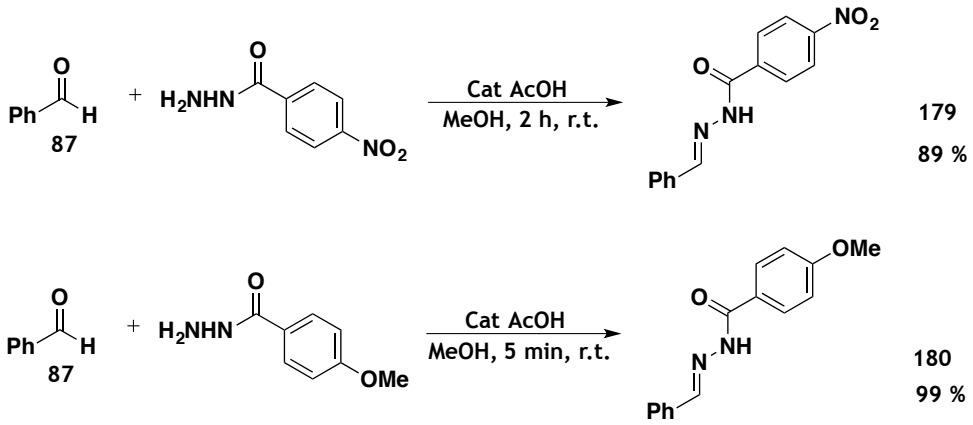
(**Scheme 3.38 (b)**). Although formation of a new compound was detected by TLC analysis, its structure could not be determined after it was isolated by silica gel chromatography. It was found that up to 85 % of imine **176** remained after the reaction. It is interesting that the allylation reaction does not proceed with any substrates that do not have a free amide N-H. This implies that this functionality possibly plays an important role in the mechanism.



Conditions: 20 mol% TBAT/10 mol% Schreiner's Cat 95, THF, 18 h, r.t.
OR 10 mol% Cat 166, $CHCl_3$ reflux

***Scheme 3.38**: **(a)** No reaction with N-phthalimide hydrazone under standard conditions and **(b)** N-tosylimine returned starting material under allylation conditions*

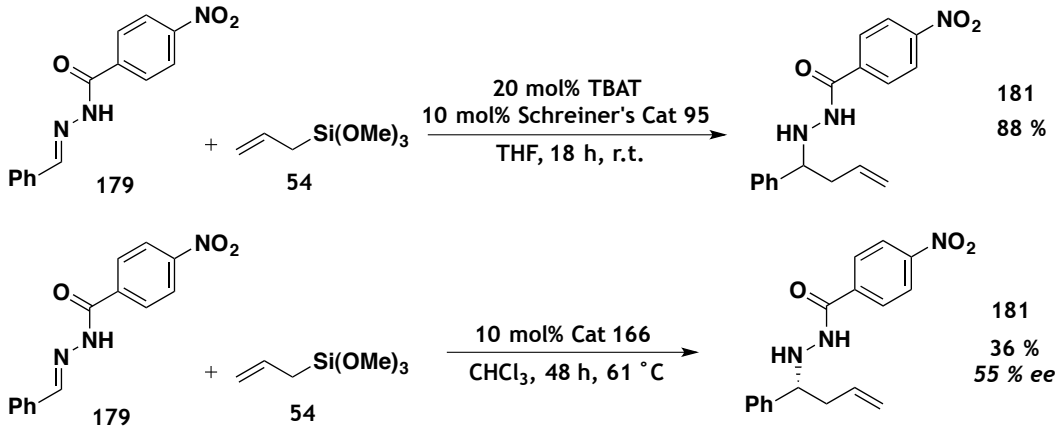
We were disappointed that none of the substrates tried, except for *N*-benzoylhydrazone **101**, were reactive under our standard allylation conditions. Therefore we next devised the synthesis of substituted *N*-benzoylhydrazones, one with an electron-withdrawing group and one with an electron-donating group. *N*-4-Nitrobenzoylhydrazone **179** and *N*-4-methoxybenzoylhydrazone **180** were readily made from commercially available starting materials in high yields (**Scheme 3.39**).



***Scheme 3.39**: Preparation of hydrazones*

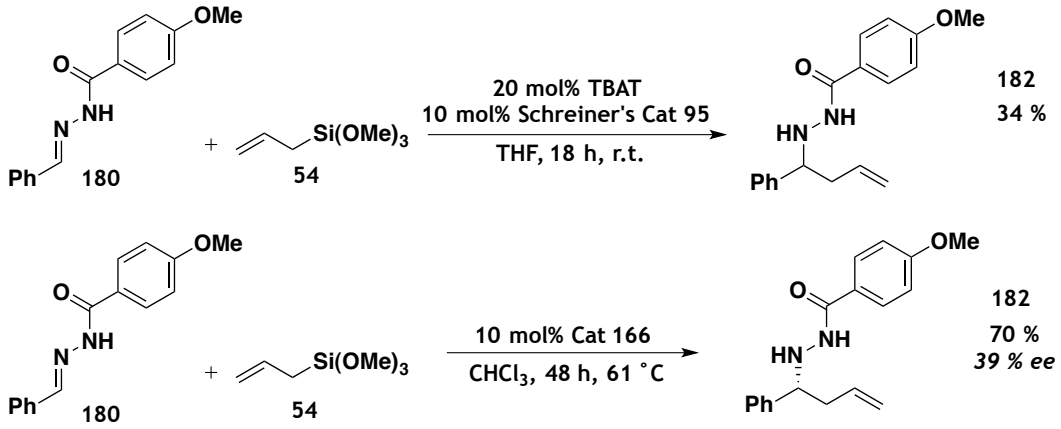
Allylation of *N*-4-nitrobenzoylhydrazone **179** under the racemic conditions proceeded smoothly, and the product **181** was furnished in 88 % yield (**Scheme 3.40**). When the reaction was carried out under asymmetric conditions the product was isolated in a 36 % yield. We were pleased to find that enantioselectivity had increased to 55 % ee, the best result yet. However, we also noticed formation

of a byproduct in this reaction, which was likely leading to a lower than anticipated yield. This byproduct was isolated and mass spectrometry revealed that it had a MW of two less than product **181**. The exact structure of the oxidized byproduct could not be solved by NMR spectroscopy.



Scheme 3.40**: Allylation of N-4-nitrobenzoylhydrazone **179

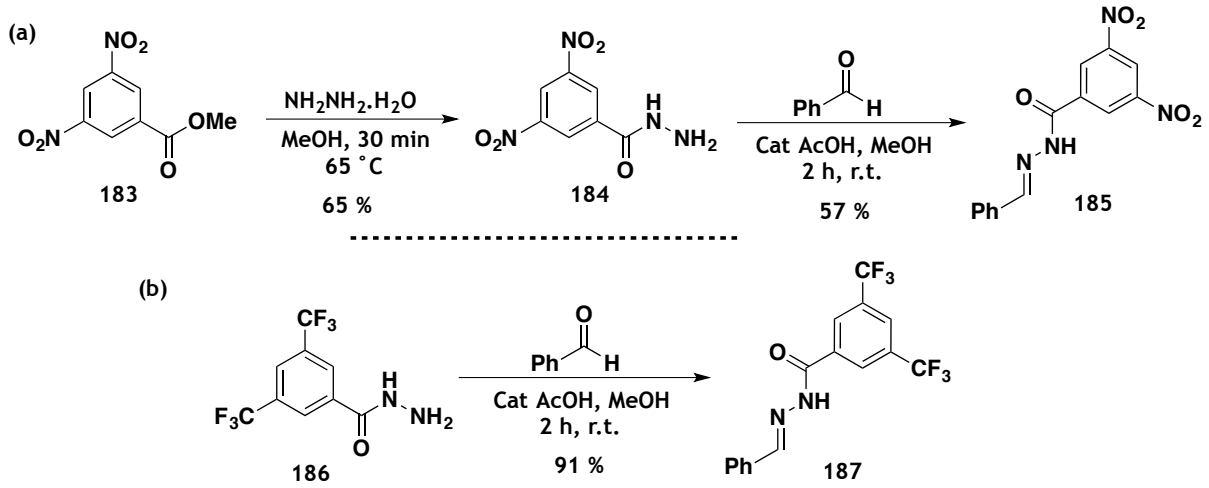
Conversely, the *N*-4-methoxybenzoylhydrazone **180** reacted poorly under the racemic allylation conditions (**Scheme 3.41**) and the product **182** was isolated in only a 34 % yield. However, we found that the reaction proceeded well with *N*-benzylcinchonidinium fluoride catalyst **166** and the product **182** was furnished in a 70 % yield. The ee was 39 %, which is the same as using the *N*-benzoyhydrazone **101** substrate.



Scheme 3.41**: Allylation of N-4-methoxybenzoylhydrazone **180

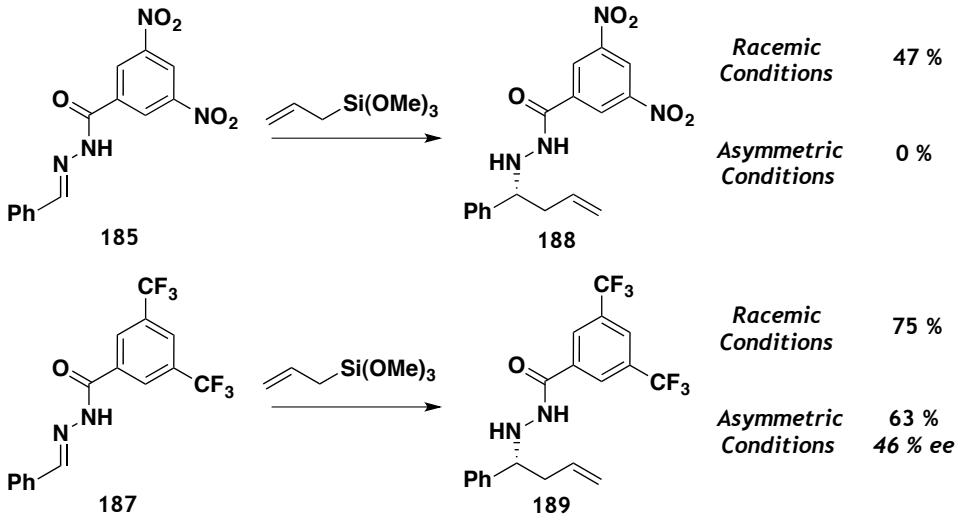
As the enantioselectivity had significantly improved to 55 % ee when an electron-withdrawing substituent was included on the benzoyl ring, we decided to investigate other hydrazones with electron-poor substituents, hoping that these would not lead to byproducts. 3,5-Dinitrobenzoylhydrazide **184** was not commercially available but was prepared from the methyl

ester **183** and hydrazine and, after recrystallization from ethanol, **184** was gained in 65 % yield (**Scheme 3.42 (a)**). The hydrazone **185** was then synthesized from benzaldehyde **87**, after stirring in methanol with a catalytic quantity of acetic acid. The 3,5-(bis)trifluoromethylbenzoylhydrazone **187** was prepared similarly from hydrazide **186** to give **187** in 91 % yield, after recrystallization (**Scheme 3.42 (b)**).



***Scheme 3.42**: Preparation of electron-poor hydrazones*

With the hydrazones **185** and **187** in hand, we performed the allylation reaction under both the standard racemic and asymmetric conditions (**Scheme 3.43**). We found that both reacted smoothly using TBAT and Schreiner's catalyst, producing 3,5-dinitro product **188** in 47 % yield and 3,5-(bis)trifluoromethyl product **189** in 75 % yield. No side products were observed in these reactions. However, when using quaternary ammonium salt **166** as the catalyst, the allylation reaction did not proceed as intended. 3,5-Dinitrobenzoylhydrazone **185** had been consumed after 48 h by TLC analysis, and the formation of two new products was observed. These could be separated and isolated after column chromatography, but neither had an ^{1}H-NMR spectrum that matched **188**. In fact, no allyl peaks were observed in the ^{1}H-NMR spectra. The reaction with 3,5-(bis)trifluoromethylbenoylhydrazone **187** also formed two products by TLC analysis. These were difficult to separate but the major product was found to be **189** and was obtained in 63 % yield and 46 % ee.



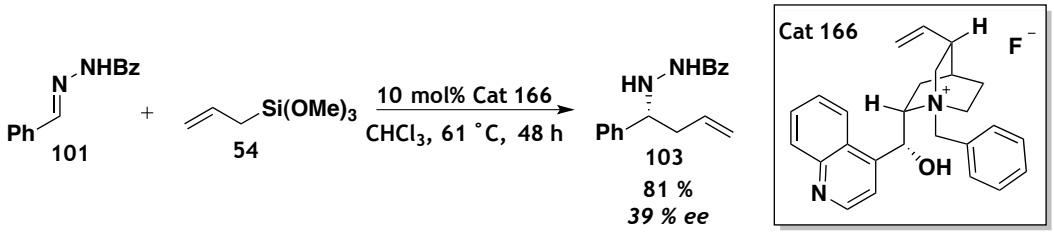
Racemic conditions: 20 mol% TBAT, 10 mol% Schreiner's Cat 95, THF
Asymmetric conditions: 10 mol% Cat 166, $CHCl_3$, 61 °C

***Scheme 3.43**: Allylation of electron-poor hydrazones*

At this stage, we reflected that whilst electron-poor substrates gave improved enantioselectivities (**181** up to 55 % and **189** up to 46 %), the allylation reaction with these substrates was less practical than with *N*-benzoylhydrazone **101**. The formation of unknown side-products was diminishing the yield and making purification difficult.

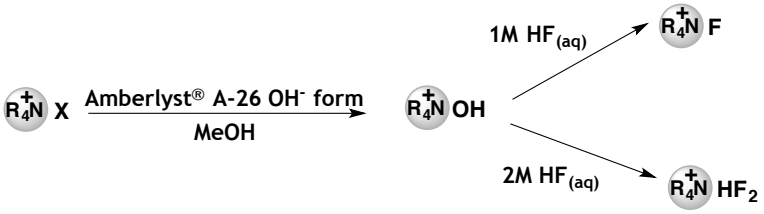
3.2.6 Catalyst Screen

Thus far, we had developed an efficient allylation reaction to make protected homoallyl amines, employing allyltrimethoxysilane with a chiral quaternary ammonium fluoride catalyst (**Scheme 3.44**). The reaction is operationally simple and has been optimized to provide the allylated product in 81 % yield and 39 % ee. We have probed a range of different hydrazone substrates, and although we have discovered electron-deficient hydrazones give improved enantioselectivities, the formation of byproducts is undesirable. Therefore, to improve the enantioselectivity of the allylation reaction with *N*-benzoylhydrazone **101**, a systematic catalyst screen was undertaken.



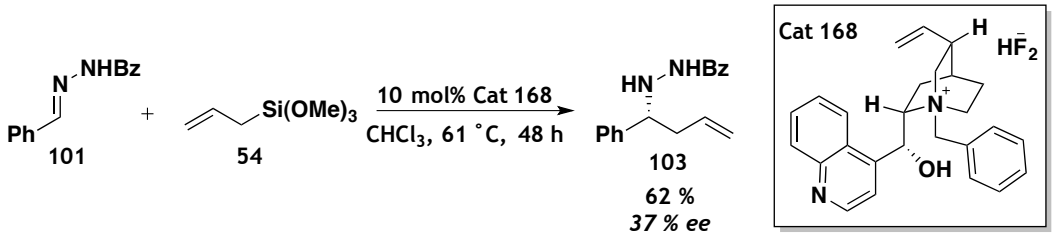
***Scheme 3.44**: Optimized allylation reaction conditions*

The catalysts are prepared using the same general method developed in **Chapter 3.2.1**. A quaternary ammonium salt is passed down an Amberlyst® A-26 OH^- resin column to make the hydroxide salt. This is then neutralized with one equivalent of aqueous HF to furnish the fluoride salt or two equivalents of aqueous HF will make the bifluoride salt (**Scheme 3.45**). The catalysts are generally obtained in near quantitative yields.



***Scheme 3.45**: Catalyst preparation*

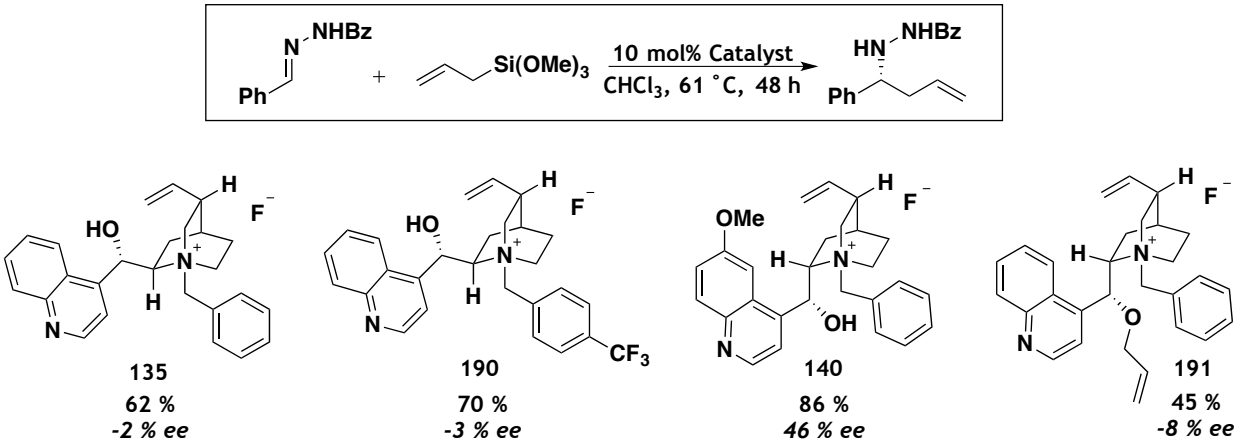
We started by wondering what effect the bifluoride salt has on the allylation reaction. If full ion exchange is not achieved on the Amberlyst® A-26 resin then some bifluoride is observed as a contaminant of the catalyst after addition of aqueous HF. However quaternary ammonium bifluorides have been shown to be good catalysts for some carbon-carbon bond forming reactions.[99,135] We therefore wanted to investigate the catalytic behaviour of the bifluoride catalyst in our allylation reaction. Under the standard reaction conditions, we found that bifluoride **168** catalyzed the allylation reaction affording product **103** in 62 % yield and 37 % ee (**Scheme 3.46**). Clearly the anion does not affect the enantioselectivity of the reaction, although the catalyst turnover was slightly poorer. We can therefore disregard the presence of small amounts of bifluoride after catalyst synthesis, since the bifluoride has minimal detrimental effect on asymmetric catalysis.



Scheme 3.46**: Allylation with quaternary ammonium bifluoride catalyst **168

Next, we took a selection of commercially available chiral quaternary ammonium salts and prepared their fluoride equivalents (**Scheme 3.47**). These were all tested under the standard reaction conditions and compared. Surprisingly, we found that pseudo-enantiomer *N*-benzylcinchoninium

fluoride **135** gave an entirely different stereoselectivity compared to its cinchonidine counterpart and the product was formed in only –2 % ee. Similarly cinchonine-derived catalyst **190**, which has a 4-trifluoromethylbenzyl substituent gave –3 % ee. Clearly, catalysts derived from cinchonine were poor at inducing facial selectivity in the reaction. When the allylation was performed with *N*-benzylquininium fluoride **140**, which has an additional methoxy group at the 6-position of quinoline, this delivered the product in 86 % yield and 46 % ee. We were delighted, as this is the best yield and ee gained from *N*-benzoylhydrazone **101** so far. Interestingly, when the *O*-allyl protected cinchonidine-derived catalyst **191** was used, the yield was 45 % and the ee was –8 %.



***Scheme 3.47**: Initial catalyst screen results*

The change in stereoselectivity when *O*-allyl-*N*-benzylcinchonidinium fluoride **191** was employed for the allylation intrigued us. We wondered whether a hydrogen bond was important for catalyst binding, which had been an important interaction in other reactions developed by our group.[136] We set about trying to prepare a range of catalysts that contained a urea moiety (**Figure 3.5**). Vexingly, this range of catalysts was not amenable to ion exchange and decomposed on the Amberlyst® A-26 OH^- form column.

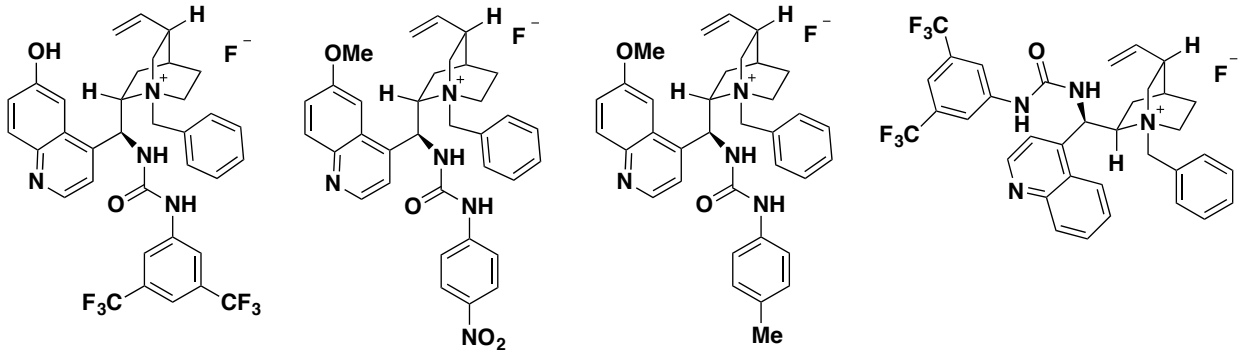
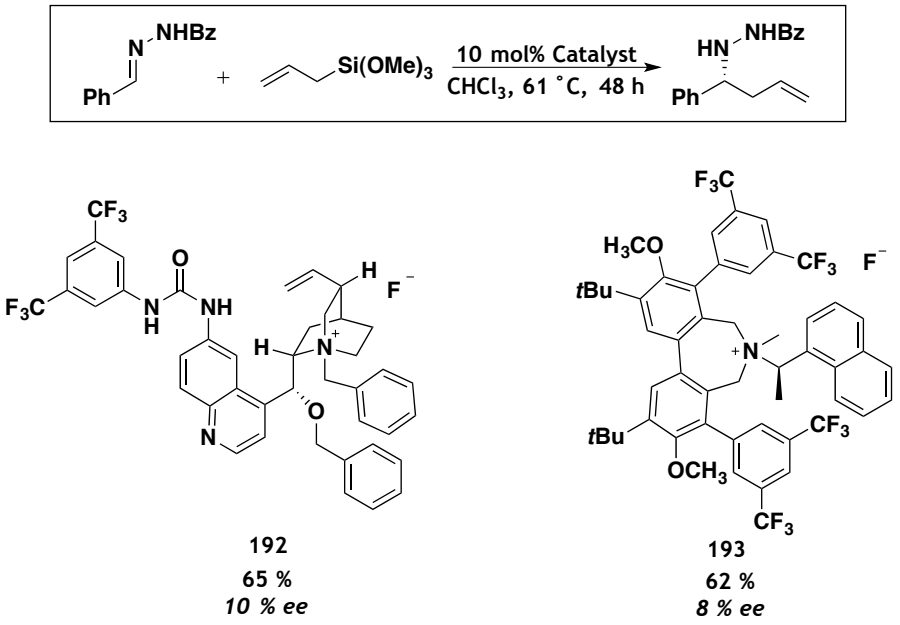


***Figure 3.5**: Urea-containing catalysts decomposed on Amberlyst® A-26 OH⁻ column*

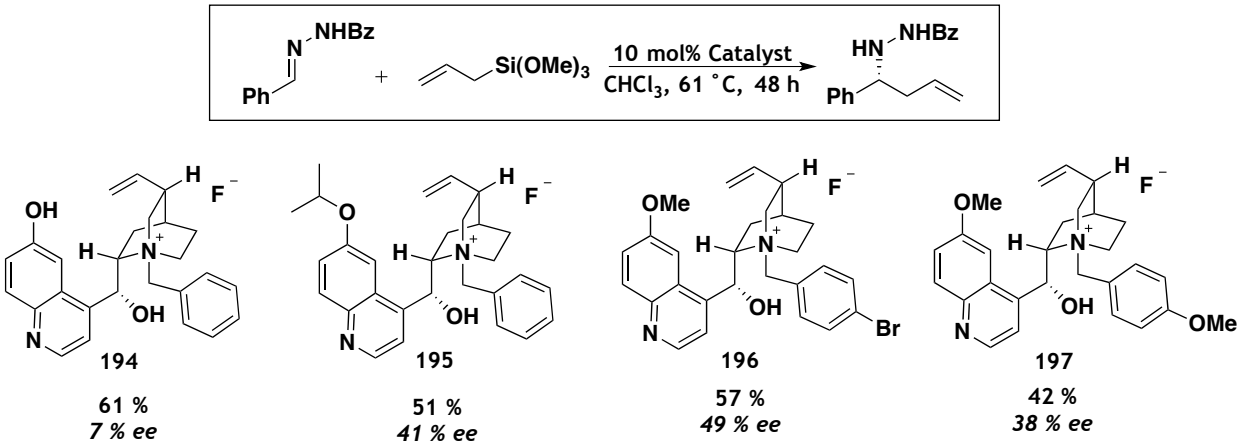
The only catalyst that was successfully prepared containing a urea was catalyst **192**, where the urea was positioned at C-6 of the quinoline. Unfortunately, deprotection of the *O*-Benzyl group was problematic and so only the protected catalyst was available for testing. The protection of this alcohol likely prevented sufficient binding of the substrate to the catalyst **192** giving the allylation product **103** in only 65 % yield and 10 % ee (**Scheme 3.48**). We also considered other catalyst scaffolds such as **193**, which is derived from the phase-transfer catalyst developed by Lygo.[26,137] However, catalyst **193** did not perform as well as we had hoped, and afforded the product **103** in 62 % yield and 8 % ee.



***Scheme 3.48**: Urea catalyst **192** and Lygo-type catalyst **193** gave low enantioselectivities*

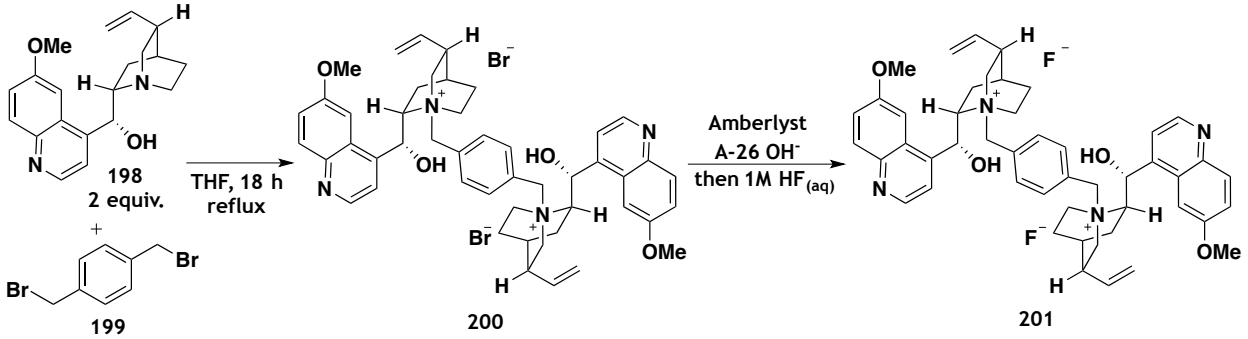
In an attempt to boost the enantioselectivity above 46 % ee, a range of quinine-derived catalysts were examined (**Scheme 3.49**). We found that de-methylated catalyst **194** gave poor

enantioselectivity, producing **103** in 7 % ee. Increasing the substituent bulk at this position from methoxy to *iso*-propyloxy catalyst **195** had little effect and the allylation proceeded to give **103** in 41 % ee. Substituents on the benzyl ring were also investigated, with electron-widthdrawing *para*-bromobenzyl catalyst **196** increasing the ee to 49 %, whereas electron-donating *para*-methoxybenzyl catalyst **197** decreased the ee slightly to 38 %.



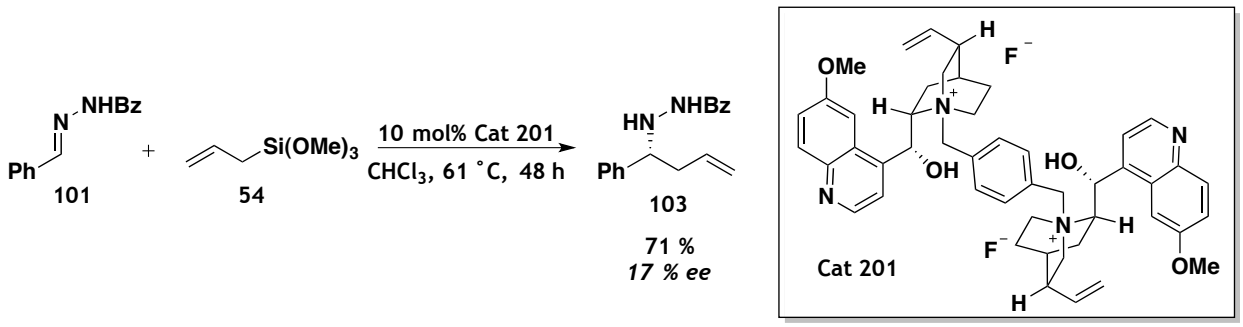
***Scheme 3.49**: Allylation with catalysts derived from quinine*

Finally, we examined the effect a bis(cinchona) salt would have on the enantioselectivity. Quinine **198** and *p*-xylylene-dibromide **199** were refluxed in THF to give dibromide salt **200** quantitatively, and then this was subjected to ion exchange to make the fluoride in the usual way to afford the catalyst **201** (**Scheme 3.50**).



Scheme 3.50**: Preparation of bis(cinchona) salt **201

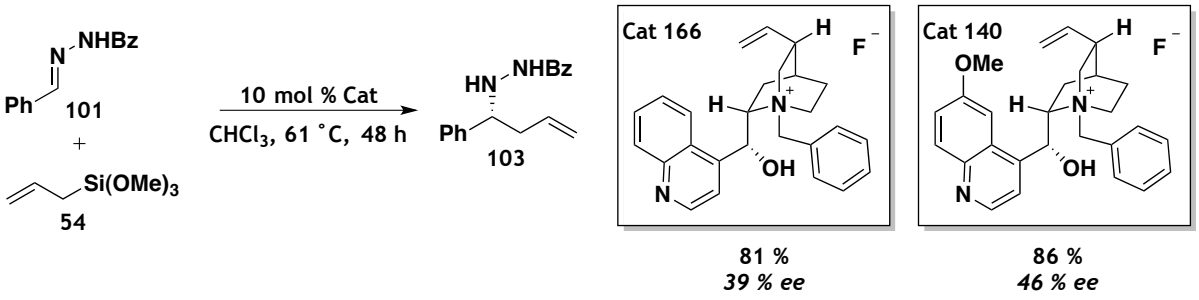
When bis(cinchona) salt **201** was used to catalyze the allylation reaction, the reaction proceeded smoothly and afforded the protected homoallyl amine **103** in 71 % yield. Disappointingly, the enantioselectivity had not improved, with an ee of 17 % (**Scheme 3.51**).



***Scheme 3.51**: Bis(cinchona) salt **201** catalyzed the reaction in 71 % yield and 17 % ee*

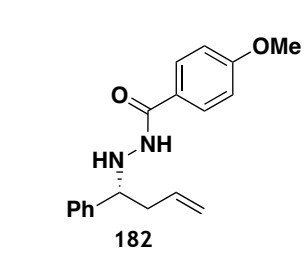
3.2.7 Substrate Scope

At this stage, we had developed a catalytic allylation reaction to afford protected homoallyl amine **103** in high yield. Regrettably, an extensive catalyst screen had not found a catalyst that could afford the product **103** in high enantiomeric excess – enantioselectivities were modest at best with *N*-benzylcinchonidinium fluoride **166** achieving 39 % ee and *N*-benzylquininium fluoride **140** reaching 46 % ee (**Scheme 3.52**). However, we wanted to demonstrate that this method was generally applicable to a range of hydrazone substrates, and probe the stereoselectivity that could be obtained with different substituents.



***Scheme 3.52**: Summary of optimized conditions and best catalysts*

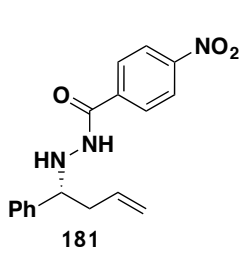
We started by looking at how the hydrazones prepared in **Chapter 3.2.5** fared, when allylation was catalyzed by *N*-benzylquininium fluoride **140**. These substrates were all prepared from benzaldehyde **87** and different benzoylhydrazides. Unsurprisingly, the reaction gave similar enantioselectivities for all substrates compared with those obtained with *N*-benzylcinchonidinium fluoride catalyst **166** (**Scheme 3.53**). The formation of byproducts was also observed in the formation of **181** and **189**, which affected the yield. 4-Nitrobenzoylhydrazone **179** gave the highest enantioselectivity, affording allylated product **181** in 52 % ee.



182

Cat 166 70 %, 39 % ee

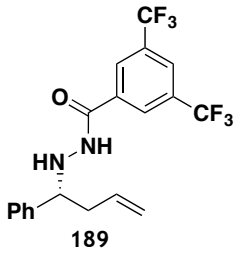
Cat 140 38 %, 40 % ee



181

Cat 166 36 %, 55 % ee

Cat 140 46 %, 52 % ee



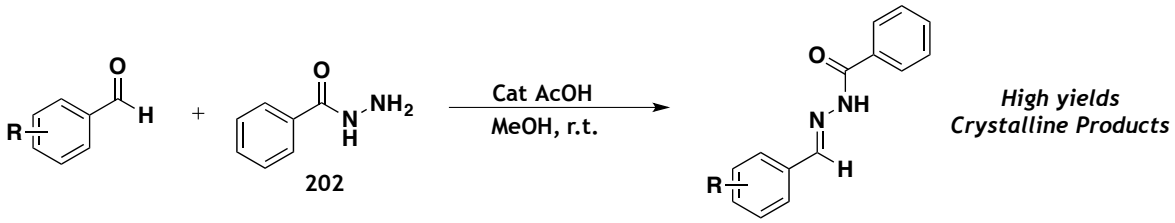
189

Cat 166 63 %, 46 % ee

Cat 140 43 %, 47 % ee

***Scheme 3.53**: Allylation with different hydrazones*

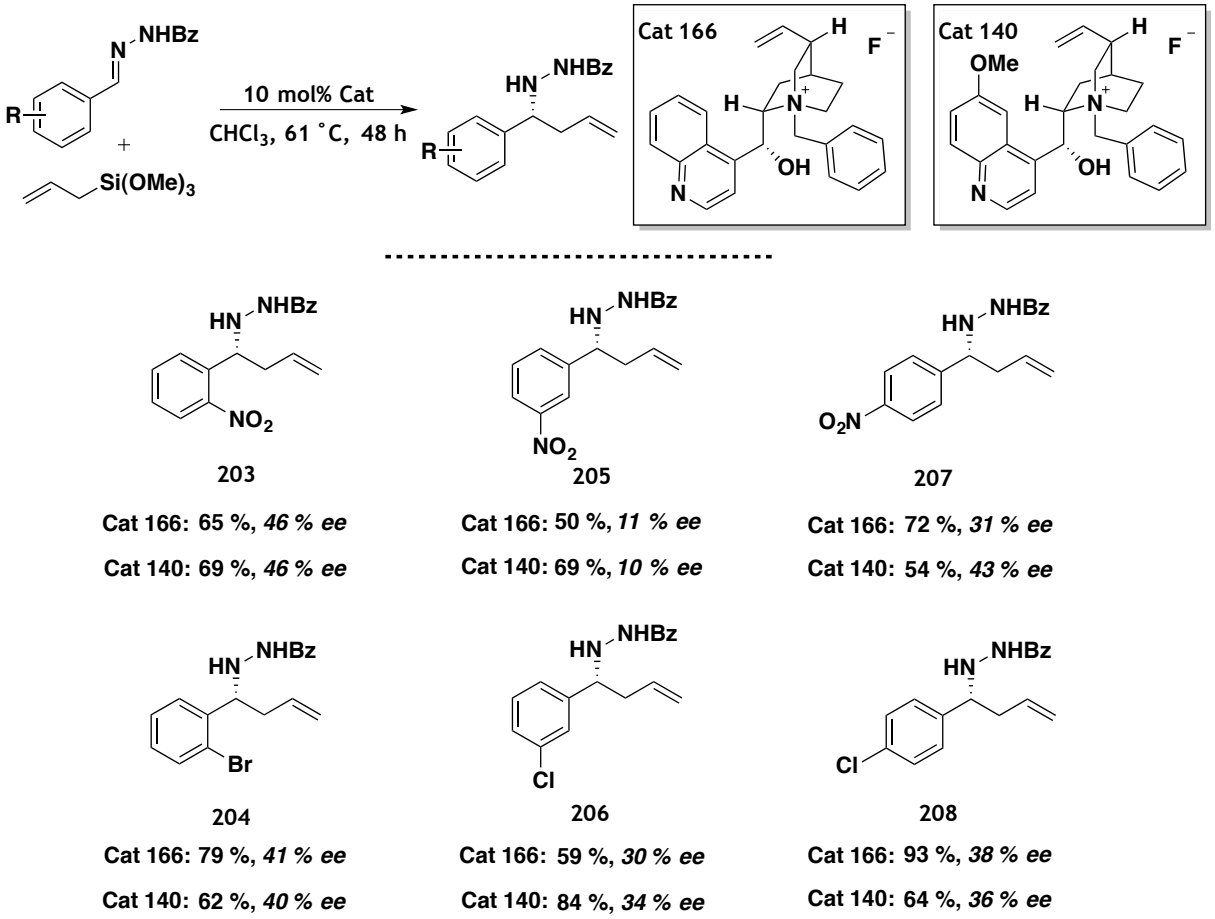
Next, a range of hydrazones derived from benzoylhydrazide **202** and different aldehydes were prepared according to a general procedure (**Scheme 3.54**). The reactants were stirred in methanol in the presence of a catalytic quantity of acetic acid at room temperature. In most cases, the hydrazone product precipitated out of the solvent, and was then filtered and recrystallized. Generally, all the hydrazones were attained in high yields as crystalline products.



***Scheme 3.54**: General formation of hydrazones*

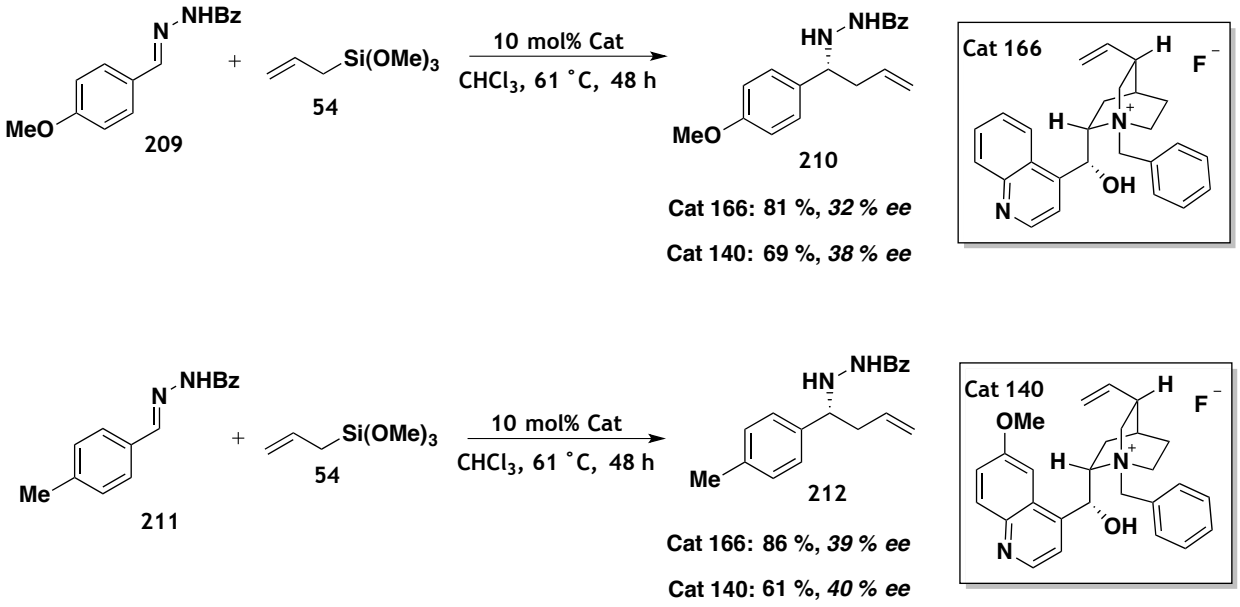
Each hydrazone was then exposed to the standard allylation conditions with both *N*-benzylcinchonidinium fluoride **166** and *N*-benzylquininium fluoride **140**. First, we examined hydrazones that had electron-withdrawing substituents at the *ortho*, *meta*, or *para* positions (**Scheme 3.55**). Generally these reactions proceeded smoothly with good yields and enantioselectivities, but we found that substituition at the *meta* position resulted in lower enantioselectivities. The *m*-chlorobenzene product **206** was attained with slightly lower enantioselectivities (30 % ee with **166** and 34 % ee with **140**) while the *m*-nitrobenzene product **205** had a significantly lower ee with both catalysts (10 % with **166** and 11 % with **140**). It transpires that substitution at the *ortho* position is best tolerated. *o*-Nitrobenzene **203** was furnished in 46 % ee with either chiral quaternary ammonium catalyst. There appears to be little correlation as to which catalyst is best for which substrate. The *p*-nitrobenzene **207** was furnished in 31 % ee with catalyst **166** but increased to

43 % ee with catalyst **140**. Conversely *p*-chlorobenzene **208** was acquired in 38 % ee with catalyst **140** but the ee decreased with catalyst **166** to 36 %.



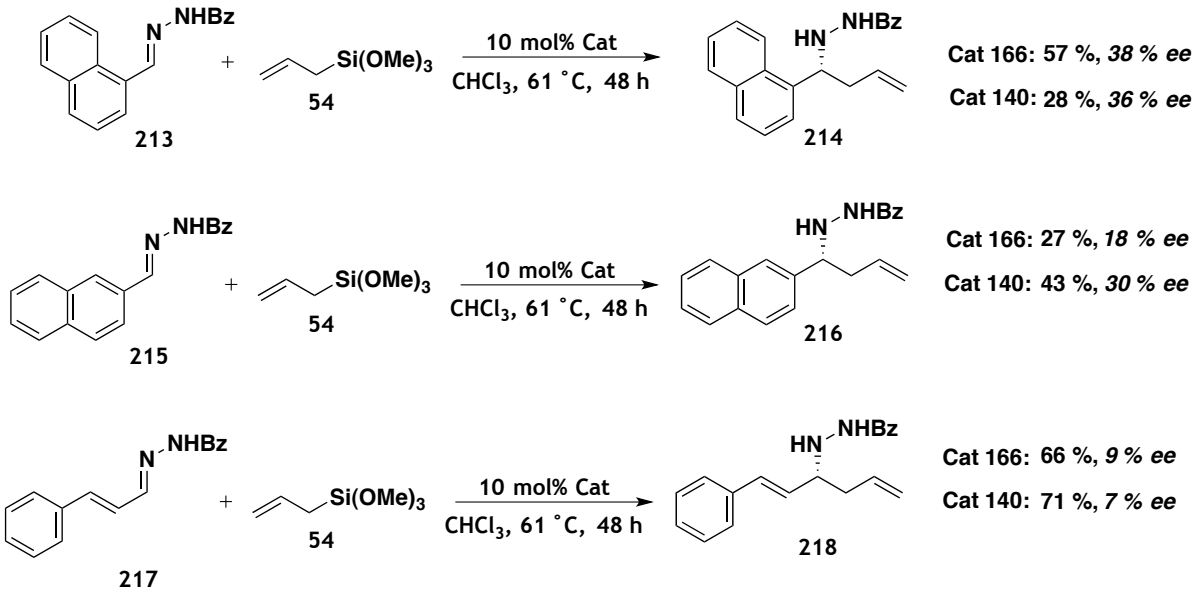
***Scheme 3.55**: Electron-withdrawing sustitution at ortho, meta and para positions*

We also looked at hydrazones containing electron-donating substituents at the *para* position. These reacted well under the standard allylation conditions (**Scheme 3.56**), giving yields of greater than 80 % with *N*-benzylcinchonidinium catalyst **166**. Catalyst **140** gave the highest enantioselectivity for *p*-methoxybenzene product **210**, reaching 38 % ee, whilst catalyst **166** gave the best ee for *p*-methylbenzene product **212** at 40 %. We were pleased to note that there appeared to be little difference in whether the hydrazone was electron-rich or electron-poor and that results were reasonably consistent (c.f **210** with **207** or **212** with **208**).



***Scheme 3.56**: Electron-donating substituents undergo allylation in high yields and good enantioselectivities*

Finally, the hydrazones derived from 1-naphthaldehyde **213**, 2-naphthaldehyde **215** and cinnamaldehyde **217** were prepared. These performed less well than substituted benzaldehyde derivatives under the standard allylation conditions (**Scheme 3.57**). Allylation of 1-naphthaldehyde-derivative **213** proceeded with good enantioselectivities with both chiral quaternary ammonium catalysts attaining 38 % ee with **166** and 36 % ee with **140**. Allylation of 2-naphthaldehyde-derivative **215** gave lower enantioselectivties with catalyst **140**, affording product **216** in 30 % ee and catalyst **166** giving just 18 % ee. Both hydrazones **213** and **215** reacted in much lower yields than normal for the allylation reaction, and the reaction was temperamental with these substrates. On the other hand, cinnamaldehyde derived hydrazone **217** reacted well with the chiral quateranary ammonium fluoride catalysts and product **218** was attained in good yields. However, allylation of this substrate gave much lower enantioselectivities (9 % ee using **166** and 7 % ee using **140**). This may be because any π-stacking interactions between the hydrazone and the catalyst are disrupted for the cinnamyl-hydrazone case due to the additional olefin group, projecting the arene further from the hydrazone.

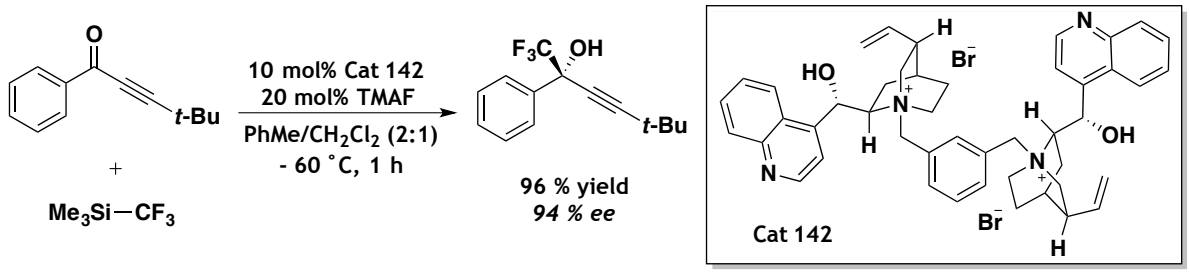


***Scheme 3.57**: Allylation of 1-naphthyl, 2-naphthyl and cinnamyl hydrazones*

In summary, we are pleased to have demonstrated that, in general, aromatic hydrazones, react well under the optimized allylation conditions and that substitution with electron-donating or electron-withdrawing groups is well tolerated. Enantioselectivities are particularly high when substitution is at the *ortho* position, whilst lower enantioselectivities can be seen when substitution is at the *meta* position.

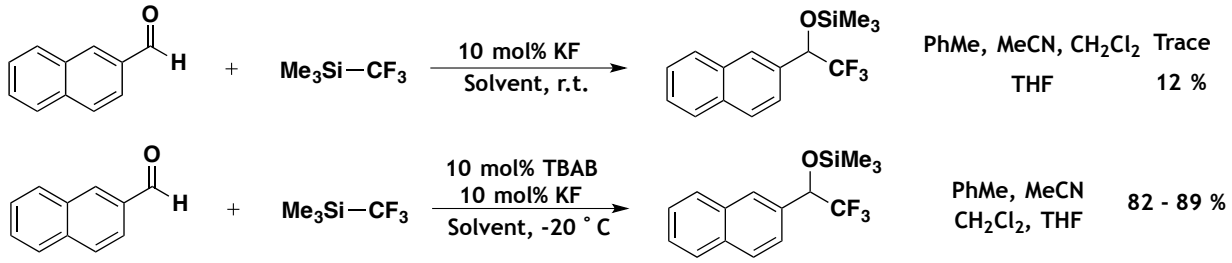
3.2.8 Phase-transfer of Fluoride

One original aim of this project was to develop a reaction where the fluoride anion could be exchanged *in situ* with a quaternary ammonium counterion. As previously discussed (**Chapter 3.1.2**), this can be very difficult because fluoride anions are less soluble in organic solvents than other anions. The advantages, however, of being able to perform the reaction from commercially available reagents and avoiding the need to prepare the quaternary ammonium fluoride salt make this a worthwhile endeavor. Successful phase-transfer with (bis)chinchona salts and TMAF (tetramethylammonium fluoride) for trifluoromethylation reactions have set the precedent for methods to be developed for other reactions.[107,108] For example, Shibata and coworkers developed the first trifluoromethylation of alkynyl ketones using 20 mol% TMAF and 10 mol% (bis)cinchona salt **142** (**Scheme 3.58**).[109] This reaction proceeded best in a mixture of toluene/dichloromethane (2:1) to give trifluoromethylated products in 96 % yield and 94 % ee.



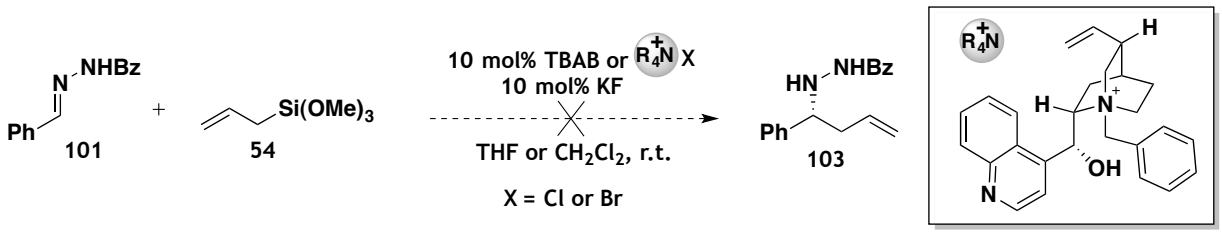
***Scheme 3.58**: Trifluoromethylation of alkynyl ketone under phase-transfer conditions*

We began our attempts to achieve phase-transfer of fluoride by following a literature example that found potassium fluoride could efficiently exchange with tetrabutylammonium salts.[138] Potassium fluoride does not catalyze the trifluoromethylation reaction at room temperature in a number of solvents (**Scheme 3.59**). However, when catalytic tetrabutylammonium bromide (TBAB) is added, ion exchange allows for the reaction to proceed in up to 89 % yield.



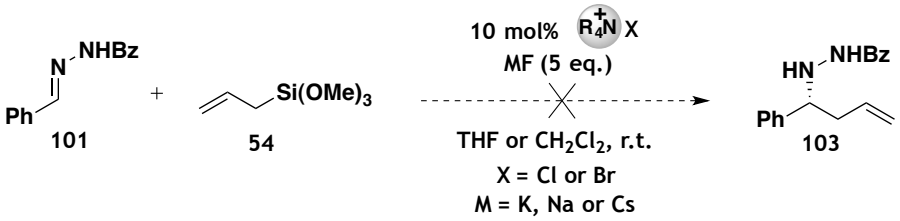
***Scheme 3.59**: Phase-transfer of potassium fluoride with TBAB*

Taking lead from this example, our first experiments were performed in a similar manner. *N*-benzoylhydrazone **101** and allyltrimethoxysilane **54** were stirred with a catalytic quantity of TBAB and potassium fluoride (**Scheme 3.60**). This was carried out in both THF and dichloromethane, but the reactions were unsuccessful and returned the starting materials. The *in situ* ion exchange was also attempted with the chiral cinchonidine-derived quaternary ammonium bromide and chloride salts but this lead to the same result.



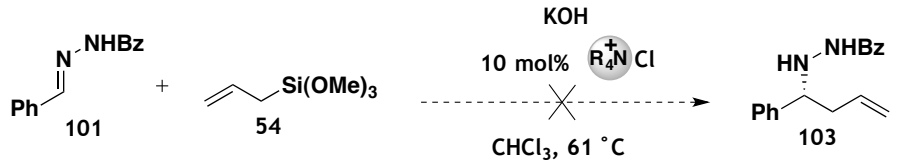
***Scheme 3.60**: First attempts at fluoride phase-transfer were unsuccessful*

Next, we attempted the reaction with a super-stoichiometric amount of potassium fluoride (5 equivalents), but in both dichloromethane and THF the reaction did not proceed (**Scheme 3.61**). Different metal fluorides were employed, such as sodium or cesium salts, but again the reaction failed.



***Scheme 3.61**: No allylation with stoichiometric potassium, sodium or cesium fluorides*

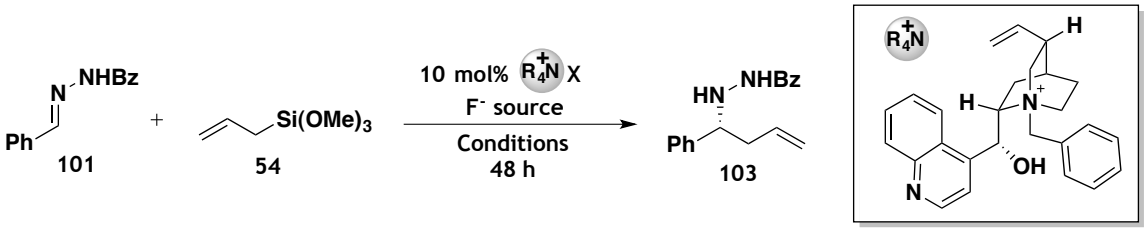
We subsequently investigated whether potassium hydroxide was a viable initiator for the reaction. Shibata and coworkers had found that trifluoromethylation of azomethine imines could be catalyzed by either fluoride or hydroxide anions (example discussed in **Chapter 3.1.3**).[110] Disappointingly, refluxing in chloroform with either 10 mol%, 1 equivalent or 6 equivalents of potassium hydroxide did not initiate the allylation reaction, and no product was formed (**Scheme 3.62**).



***Scheme 3.62**: Reaction with 10 mol% KOH, 1 equiv. KOH and 6 equiv. KOH were futile*

We next tried using TMAF as a source of fluoride for the exchange (**Table 3.6**). When the reaction was performed at room temperature in either a toluene/dichloromethane mixture or in neat dichloromethane, ion exchange did not take place (entries 1 and 2). Pleasingly, when the temperature was increased to 61 ˚C in chloroform we found that a small amount of product **103** could be attained in 22 % yield and 26 % ee (entry 3). When the quaternary ammonium catalyst was changed from the bromide salt **165** to the chloride salt **26** the exchange was even better, and the yield increased to 56 % (entry 4). Lowering the amount of TMAF from 20 mol% to 10 mol% resulted in a poorer turnover, with a yield of 33 % (entry 5). The reaction was also executed with TBAF and this gave a very high yield of 91 % but a reduced ee of 8 % (entry 6). Frustratingly, the background reaction with either tetramethylammonium cation or tetrabutylammonium cation was

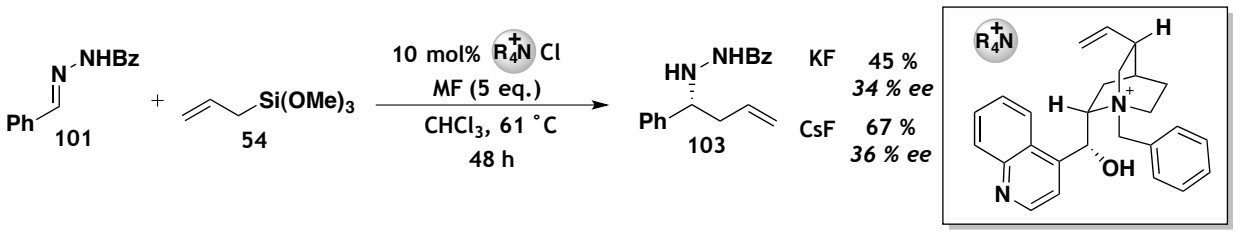
significantly impacting the enantioselectivity. We knew up to 39 % ee was attainable with *N*-benzylcinchonidinium catalyst and organic fluoride sources appeared unable to achieve that.



	TMAF mol%	NR_4X	Solvent	Temp ˚C	Yield %	ee %
1	20	Br	$PhMe/CH_2Cl_2$ (2:1)	20	0	-
2	20	Br	CH_2Cl_2	20	0	-
3	20	Br	$CHCl_3$	61	22	26
4	20	Cl	$CHCl_3$	61	56	27
5	10	Cl	$CHCl_3$	61	33	30
6	20 (TBAF)	Cl	$CHCl_3$	61	91	8

***Table 3.6**: Allylation with TMAF and quaternary ammonium salts*

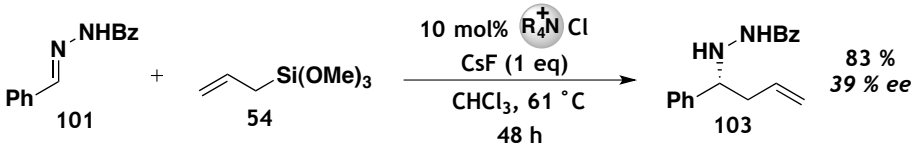
Once again, we focused on using metal fluorides to effect the allylation reaction by ion exchange. Since the phase-transfer of fluoride with TMAF has been successful in refluxing chloroform, we hoped to apply these conditions to the metal fluoride system and that the phase-transfer would be possible. Using potassium fluoride (5 equivalents) and chloride salt **26**, the product **103** was furnished in 45 % yield and 34 % ee (**Scheme 3.63**). Gratifingly, we found that cesium fluoride was even more effective and produced the product **103** in 67 % yield and 36 % ee.



***Scheme 3.63**: Efficacious fluoride exchange with KF and CsF*

We discovered that, after repeating the allylation with CsF, the reaction was capricious and high yields were not always obtainable under these conditions (as low as 28 %). We noticed that the large excess of cesium fluoride in the flask was forming clumps and preventing the reaction from stirring properly. This was rectified by decreasing the amount of cesium fluoride to just one equivalent. This system furnished the product in 83 % yield and 39 % ee, equivalent to using

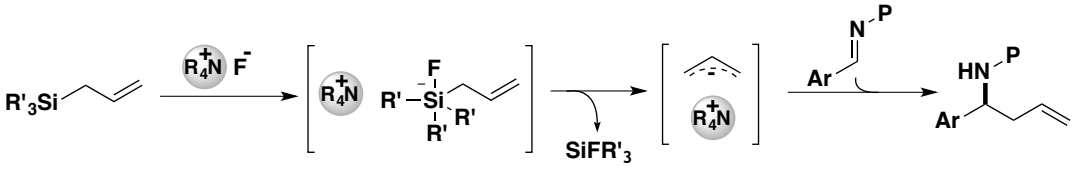
N-benzylcinchonidinium fluoride **166** as the catalyst (**Scheme 3.64**). We were delighted to have found an effective phase-transfer method for the allylation reaction, especially as this has only been done for a limited number of literature examples.



***Scheme 3.64**: Optimized conditions for successful phase-transfer of fluoride*

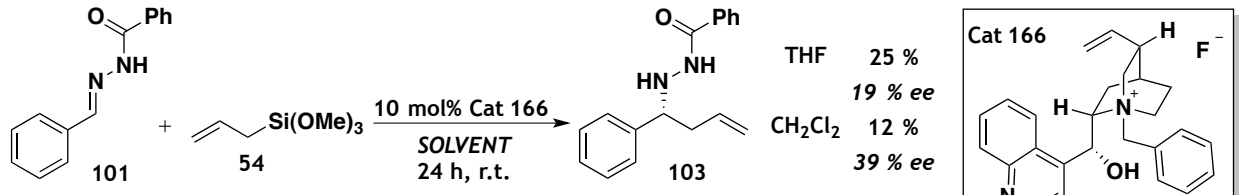
3.3 Conclusion

The aim of this project was to develop a catalytic enantioselective allylation reaction. We hoped to employ a novel cation-directed process generating protected homoallyl amines in high yields and enantioselectivities. We theorized that an allylsilane could act as an allyl anion surrogate when activated by fluoride to create a chiral ion-pair. This could then react with an imine electrophile (**Scheme 3.65**).



***Scheme 3.65**: Blueprint for asymmetric allylation*

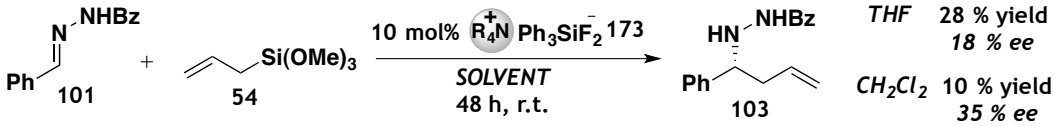
It was rapidly established that *N*-benzylcinchonidinium fluoride **166** effectively catalyzes the reaction between *N*-benzoylhydrazone **101** and allyltrimethoxysilane **54** (**Scheme 3.66**). The reaction did not proceed in a large range of solvents and the reaction was sluggish in either THF or dichloromethane at room temperature. We noted that enantioselectivities significantly improved in chlorinated solvents from 19 % to 39 % ee.



No reaction: Et_2O, *i*-Pr_2O, PhMe, MeCN, MeOH, chlorobenzene, 1,1,2,2-tetrachloroethane

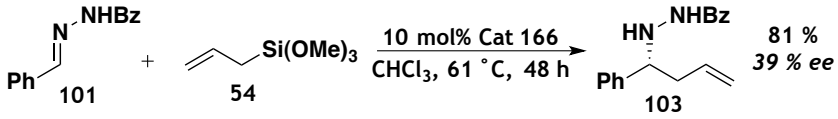
***Scheme 3.66**: Initial results*

Attempts to improve the yield of the reaction included making triphenydifluorosilicate compounds. Unfortunately, neither the potassium 18-crown-6 salt **172** or TBAT successfully underwent anion exchange with chiral quaternary ammonium chloride **26**. *N*-benzylcinchonidinium salt **173** was also prepared, but performed no better than using **166** (**Scheme 3.67**).



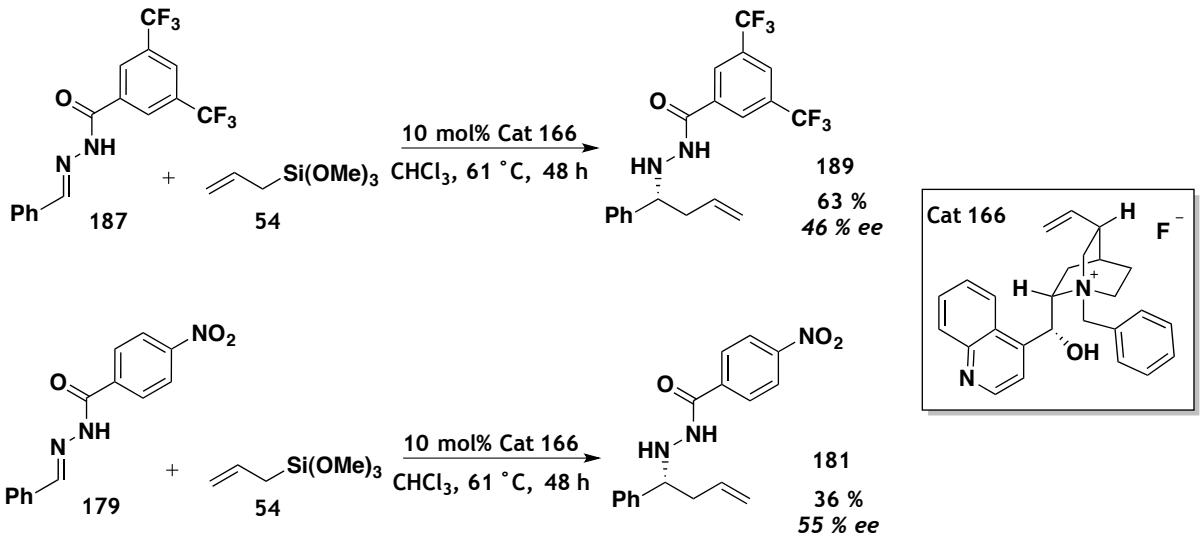
***Scheme 3.67**: Using triphenydifluorosilicate salts as catalysts*

Increasing the temperature to 61 ˚C and using chloroform as the solvent significantly improved the reaction outcome (**Scheme 3.68**). The yield had improved to 81 % and the ee remained at 39 %. The reaction was practical, employing mild and robust reagents.



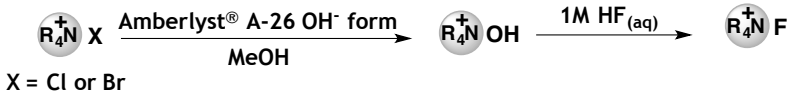
***Scheme 3.68**: Optimized reaction conditions*

A range of other substrates were prepared in the hope that a different imine-protecting group would give improved enantioselectivities, by offering better binding to the catalyst. To our surprise, a large number of substrates were unreactive under the standard conditions. We suspect this was due to the inability of the product amide to complete the catalytic cycle. *N*-Benzoylhydrazones with different substituents were examined, and found with electron-withdrawing substituents gave improved enantioselectivities (**Scheme 3.69**). The yields obtained with these substrates were low, however, due to the formation of side products in the reaction.



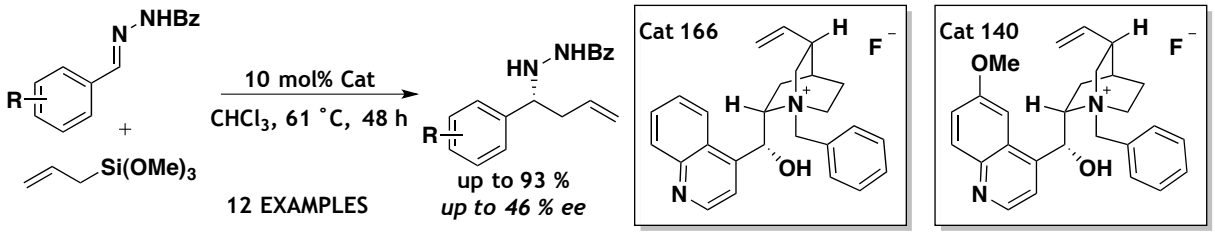
***Scheme 3.69**: Allylation with electron-withdrawing hydrazones*

A wide catalyst screen was also completed to find the best chiral quaternary ammonium fluoride for the allylation reaction with *N*-benzoylhydrazone **101**. The catalysts were prepared by ion exchange from either the chloride or bromide salts to the hydroxide down an Amberlyst® A-26 OH^- exchange resin. This was followed by neutralization with one equivalent of aqueous HF to afford the catalysts (**Scheme 3.70**). *N*-Benzylquininium fluoride **140** gave slightly improved results for the allylation, increasing the yield to 86 % and the ee to 46 %. Unfortunately we were unable to find a catalyst that gave exceptional enantiocontrol for the allylation reaction.



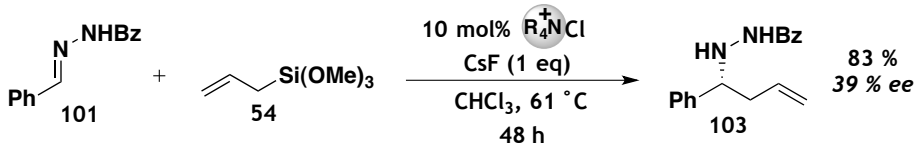
***Scheme 3.70**: General catalyst preparation method*

The substrate scope of the allylation reaction was demonstrated with both *N*-benzylcinchonidinium fluoride **166** and *N*-benzylquininium fluoride **140** (**Scheme 3.71**). Substitution was well tolerated at all positions for aromatic hydrazones, and similar results were obtained with either electron-donating or withdrawing groups. This method was exhibited with twelve examples.



***Scheme 3.71**: Allylation method applicable to a range of substrates*

In addition, we were pleased to develop a method that employed commercially available reagents. We found that one equivalent of cesium fluoride and a chiral quaternary ammonium chloride catalyst **26** were able to achieve the allylation reaction equally well (**Scheme 3.72**). Again, the optimal conditions were using chloroform as the solvent at 61 ˚C.



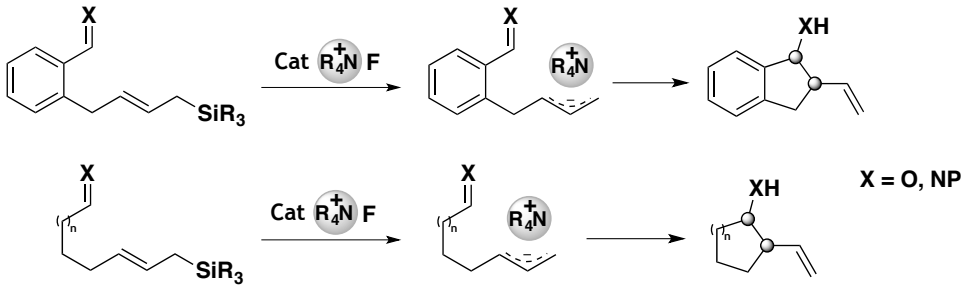
***Scheme 3.72**: Phase-transfer of fluoride with N-benzylcinchonidinium chloride*

In conclusion, we have developed a novel asymmetric allylation reaction. The method is operationally simple, employing mild conditions and robust air-stable reagents. This is the first example of a chiral quaternary ammonium fluoride being used to catalyze an enantioselective allylation reaction. We have demonstrated that high yields can be obtained for a range of *N*-benzoylhydrazones and that modest enantioselectivities are achieved. With greater understanding of the nature of interactions between the catalyst, the allyl anion and the substrate, the synthesis of a bespoke, rationally designed catalyst may be possible. Such a catalyst would undoubtedly deliver significantly better results.

4. Intramolecular Allylation

4.1 Introduction

The allylation reaction is an attractive transformation for synthetic organic chemists. This carbon-carbon bond forming process can create a new stereocentre, and the olefin provides a functional handle on which other chemistry can be performed. During our studies into a cation-directed asymmetric allylation, we saw a window of opportunity to extend this methodology to an intramolecular process (**Scheme 4.1**). An intramolecular allylation reaction would generate new cyclic compounds that contain two adjacent stereocentres, and we envisioned that both alcohols and amines could be synthesized. There is scope to incorporate heteroatoms in the molecular backbone to give access to heterocyclic products, and constructing rings of different sizes is possible through appropriate choice of tether length.

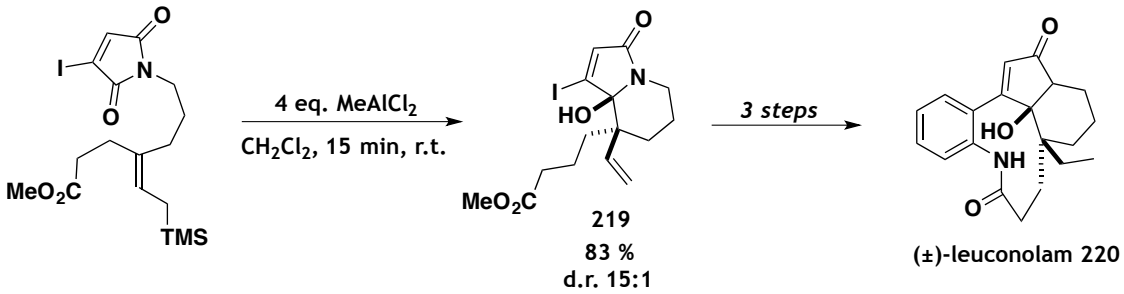


***Scheme 4.1**: Blueprint for intramolecular allylation induced by a chiral quaternary ammonium fluoride. This can construct cyclic compounds containing two adjacent stereocentres*

Developing a catalytic asymmetric intramolecular allylation would be a worthwhile endeavor as there are currently no literature examples either catalyzed by acid or by fluoride. Our blueprint involves initiation by a chiral quaternary ammonium fluoride, with ion-paring between the anionic intermediate and the chiral cation providing a source of asymmetric induction.

In 2013, the total synthesis of (±)-leuconolam **220** was completed by Izgu and Hoye and highlighted the current need for an asymmetric catalytic process.[139] Their total synthesis invoked an intramolecular allylation reaction as the critical step to create a ring containing two contiguous tetrasubstituted centres. A screen of conditions found that Lewis acid $MeAlCl_2$ (4 equivalents) was the best reagent to deliver bicycle **219** in good yield and high d.r. (15:1) (**Scheme 4.2**). While the

correct relative stereochemistry could be obtained using an intramolecular allylation reaction, the authors lamented that "an asymmetric variant of this transformation would be of interest, but has not yet been pursued."

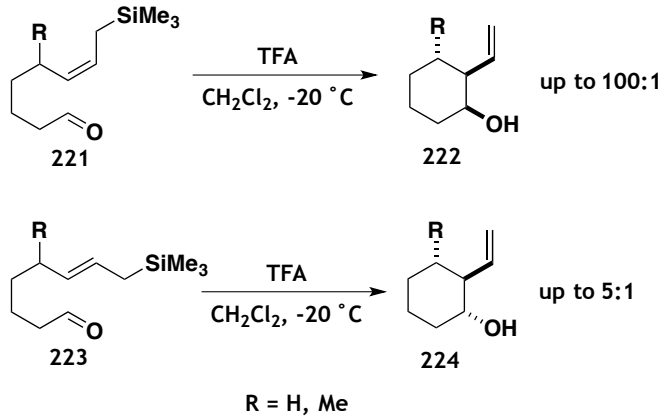


***Scheme 4.2**: The total synthesis of (±)-leuconolam was completed using an intramolecular allylation reaction*

This introduction aims to briefly outline the current methods available for intramolecular allylation. These methods can be divided into processes operated by either a Brønsted acid, Lewis acid or fluoride anion.[140] This introduction also hopes to highlight the breadth of reactivity and functional group diversity exhibited in these processes and demonstrate the power of intramolecular allylation through its application to total synthesis.

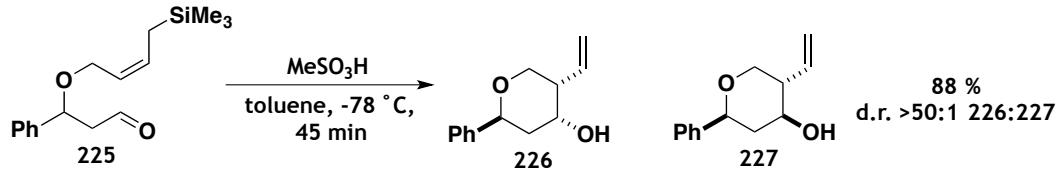
4.1.1 Intramolecular Allylation using Brønsted Acids

Brønsted acids have been used in stoichiometric quantities to successfully induce the intramolecular allylation of trimethylsilane compounds. The first intramolecular allylation of aldehydes under Brønsted acidic conditions led to highly stereospecific outcomes depending on the stereochemistry of the precursor.[141] The stereochemical outcome of this process was comprehensively examined by Schlosser and coworkers.[142] They found that (*Z*)-allylsilane **221** reacted to primarily give *syn* vinyl-alcohol product **222**, whilst the (*E*)-allylsilane **223** reacted to preferentially afford the *anti* vinyl-alcohol product **224** (**Scheme 4.3**). Interestingly, they also found that when a methyl group was included α- to the allylsilane, this resulted in the methyl group orientated *anti* with respect to the vinyl group in the product.



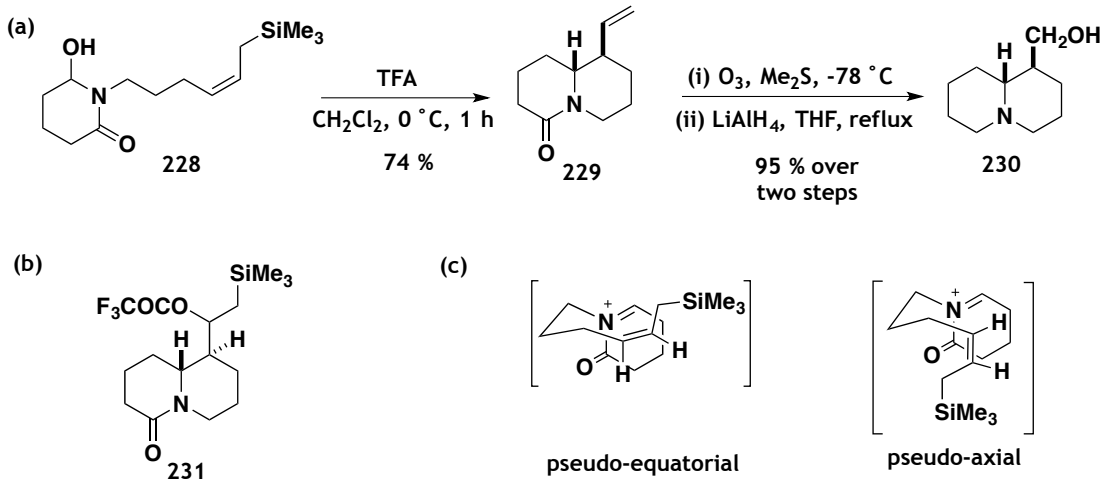
***Scheme 4.3**: Stereochemical outcome from (E) and (Z)-allylsilanes*

Brønsted acids have also been investigated for the intramolecular allylation to synthesize heterocycles, such as tetrahydropyrans.[143] Cox *et al.* employed a (*Z*)-allylsilane **225** to access 2,4,5-trisubstituted tetrahydropyrans with a preference for the *syn* vinyl alcohol diastereomer. The reaction was optimized to give diastereomeric ratio of >50:1 (**226**:**227**) when using methanesulfonic acid in toluene at –78 °C (**Scheme 4.4**).



***Scheme 4.4**: Synthesis of trisubstituted 2,4,5-tetrahydropyrans*

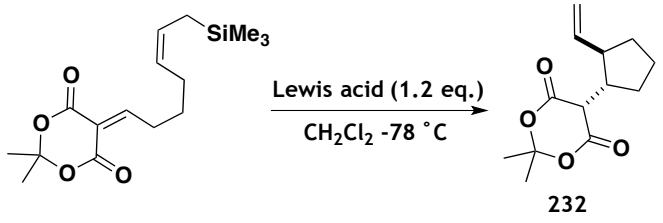
Speckamp *et al.* have utilized a Brønsted acid mediated intramolecular allylation to synthesize natural product indolizidines.[144] For example, (±)-epilupinine **230** was produced in three steps from allylsilane **228**, which, when subjected to stoichiometric trifluoroacetic acid, readily cyclized to bicycle **229** as a single diastereomer in 74 % yield (**Scheme 4.5 (a)**). Ozonolysis and reduction completed the synthesis of natural product **230**. Their studies alluded to a possible mechanism, by finding the formation of byproduct **231** after intramolecular allylation, along with bicycle **229** in a 9:1 mixture (**229**:**231**) (**Scheme 4.5 (b)**). This result implies that allylation occurs before desilylation and suggests the intermediate for the diastereomer observed would arise from a chair-like transition state, where the allylsilane preferentially sits in the pseudo-equatorial position over the pseudo-axial (**Scheme 4.5 (c)**).



***Scheme 4.5**: **(a)** Total synthesis of (±)-epilupinine **230**, **(b)** byproduct **231** and **(c)** chair-like transition state for intramolecular allylation*

4.1.2 Intramolecular Allylation using Lewis Acids

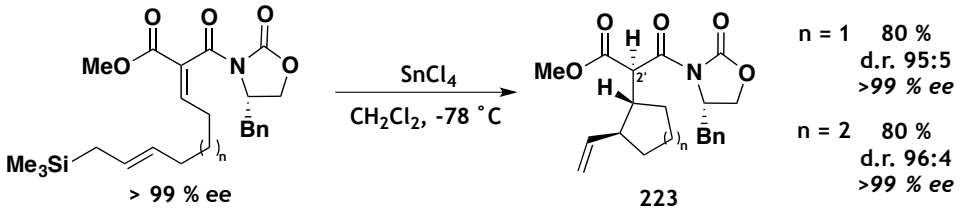
An alternative to using Brønsted acids is to employ a Lewis acid. Tietze and Ruther screened a range of different Lewis acids for the addition of (*Z*)-allylsilanes onto α,β-unsaturated dicarbonyls (**Scheme 4.6**).[145] They found that the construction of cyclopentane **232** proceeded with excellent diastereocontrol with all Lewis acids, with diastereoselectivities of > 90:10 in most cases. They noticed that the yield varied significantly depending on which Lewis acid was selected – BF_3•Et_2O afforded **232** in 77 % yield, whereas $ZnBr_2$ only gave **232** in 40 % yield.



Lewis acid	Yield %	d.r.
$TiCl_4$	75	90:10
BF_3•Et_2O	77	92:8
$ZnBr_2$	40	89:11
Me_2AlCl	69	92:8
$FeCl_3/Al_2O_3$	73	97:3
TMSOTf	45	95:5

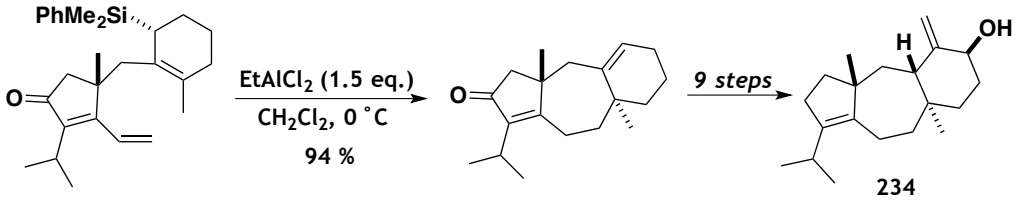
***Scheme 4.6**: 1,4-addition with different Lewis acids*

Lewis acids have also been employed in asymmetric intramolecular allylation reactions, by use of a chiral auxiliary. Tietze and coworkers extended their study of intramolecular allylation onto α,β-unsaturated dicarbonyls, and used oxazolidinone chiral auxiliaries to construct 1,2-disubstitued cyclopentanes and cyclohexanes diastereoselectively.[146] The best Lewis acid was $SnCl_4$, which gave only two products (of a possible eight), where the major was **233** and the minor was the epimer at the 2' position (**Scheme 4.7**). The compounds were furnished in 80 % yield and > 99 % ee.



***Scheme 4.7**: Enantioselective 1,4-addition*

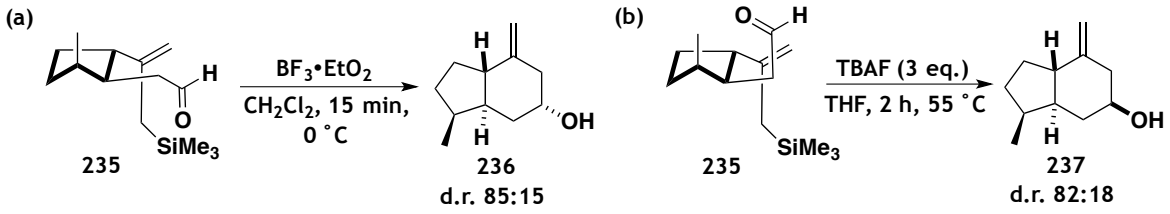
Lewis acids have also effected intramolecular allylation in a number of natural product syntheses. [147, 148] For example, Majetich *et al.* completed the stereoselective synthesis of (±)-14-deoxyisoamijol **234**, where intramolecular allylation was the key step to build the 5-7-6 fused ring system. [149] Lewis acid $EtAlCl_2$ achieved the reaction in a 94 % yield with complete diastereocontrol (**Scheme 4.8**).



Scheme 4.8**: Key step in the total synthesis of 14-deoxyisoamijol **234

4.1.3 Intramolecular Allylation using Fluoride

Fluoride has been demonstated to be effective at promoting the intramolecular allylation reaction, either in stoichiometric or catalytic quantities. Sarkar and Andersen performed an interesting study that compared the intramolecular allylation regulated by tetrabutylammonium fluoride (TBAF) with that of Lewis acids. [150] They reported that use of TBAF led to the complete reversal of stereochemical outcome compared with that of Lewis acids. The authors showed that aldehyde **235** reacts to give one diastereomer **236** with boron trifluoride ether complex (**Scheme 4.9 (a)**) and the other **237** with TBAF (**Scheme 4.9 (b)**).



***Scheme 4.9**: Stereochemical outcome under **(a)** Lewis acid conditions and **(b)** fluoride conditions*

The reversal in stereochemical outcome under Lewis acid and fluoride conditions was discussed further by Denmark *et al.*[151] A Lewis acid leads to the diastereomer resulting from the synclinical transition state, whereas the fluoride goes *via* an antiperiplanar transition state (**Figure 4.1**). This change in preference for different transition states is thought to be because there is a different mechanism operating. The synclinical arrangement lends itself to a concerted mechanism, where the carbon-carbon bond formation occurs at the same time as the carbon-silicon bond breaks. However, fluoride attack resulting in an anionic reactive species would prefer the antiperiplanar orientation because of a more favourable dipole arrangement (a "push-pull" mechanism). Interestingly, the size of the Lewis acid metal correlates with the observed stereoselectivity and a larger metal atom results in less of the synclinical product being observed. This is thought to be due to steric crowding for larger Lewis acid metals, inhibiting the synclinical arrangement ($SnCl_4$ gives a d.r. of 59:41 **236**:**237** for intramolecular allylation of **235** at –78 °C).[150]

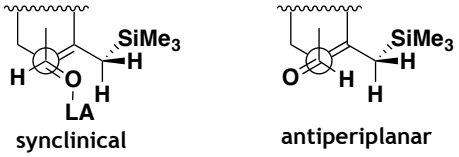
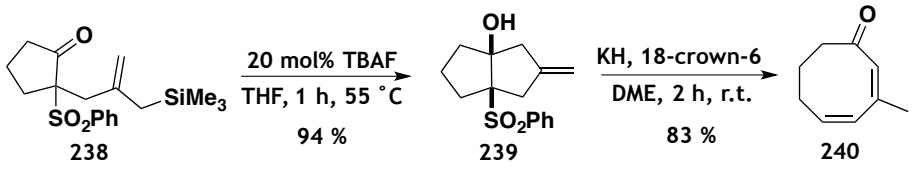


***Figure 4.1**: Synclinical and antiperiplanar transition states*

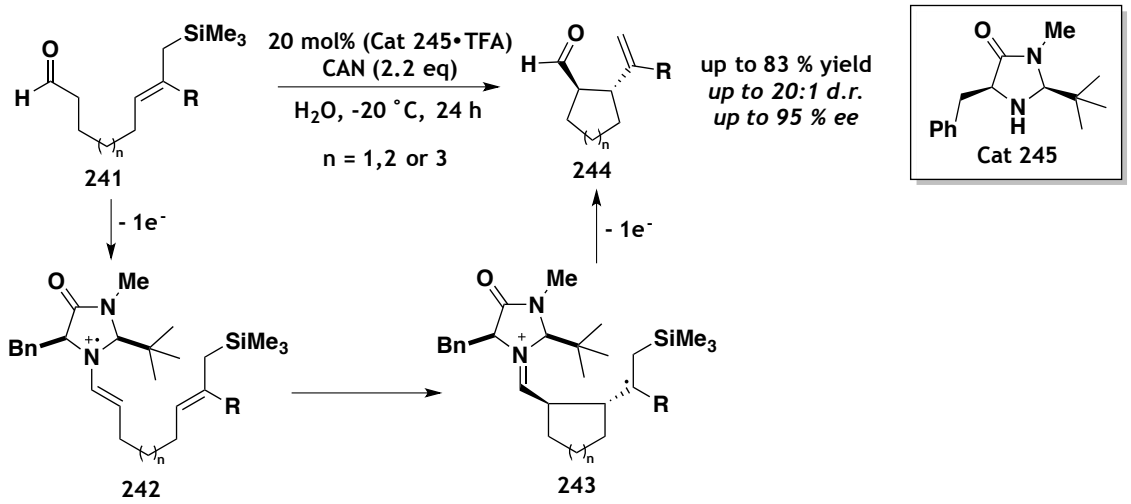
Fluoride has also been used in substoichiometric amounts to achieve intramolecular allylation. The reaction of allylsilanes, such as **238**, onto a ketone using catalytic TBAF in THF at 55 °C was reported by Trost and Vincent (**Scheme 4.10**).[152] The fused cyclopentane **239** was treated with potassium hydride to give the ring expansion product **240**. They found that Lewis acids did not work for the allyl addition. This methodology was later employed to the synthesis of muscone.



***Scheme 4.10**: Fluoride catalyzed intramolecular allylation followed by ring expansion*

4.1.4 Asymmetric Catalytic Intramolecular Allylation

Thus far, this introduction has outlined examples of intramolecular allylation induced by either Brønsted acids, Lewis acids or fluoride. None of these examples represented a catalytic asymmetric process. However, there is currently one example in the literature that achieves catalytic asymmetric intramolecular allylation by employing SOMO (singly occupied molecular orbital) catalysis.[153] This is distinctly different from those outlined above, as the allylsilane adds to the α-position to an aldehyde and is an example of umpolung chemistry. The amine catalyst **245** forms an imine with aldehyde **241**, which is followed by single electron oxidation and rearrangement to generate a radical enamine **242** (**Scheme 4.11**). This species undergoes intramolecular allylation *via* a radical mechanism to **243**, before another oxidation and loss of trimethylsilane to yield cyclized products **244**. As a result the aldehyde functionality is retained, unlike in other intramolecular allylation processes discussed. Five, six and seven membered carbocyles were all successfully made in up to 20:1 d.r. and 95 % ee.

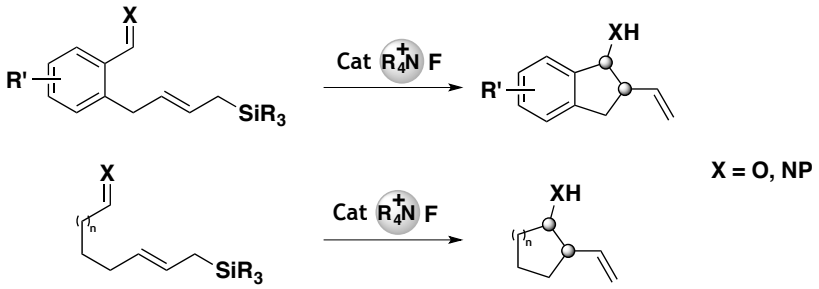


***Scheme 4.11**: SOMO catalysis for intramolecular allylation*

4.1.5 Design for a Intramolecular Allylation Reaction

The aim of this project was to develop the first catalytic asymmetric intramolecular allylation procedure, not *via* a radical mechanism. We hoped to employ chiral quaternary ammonium fluorides as catalysts to afford cyclic products containing two contiguous stereocentres (**Scheme 4.12**). A key factor of this project was designing an efficient substrate synthesis. It needed to be

flexible so that different ring sizes could be made, incorporating different functionalities, with the potential to extend the methodology to heterocycles.



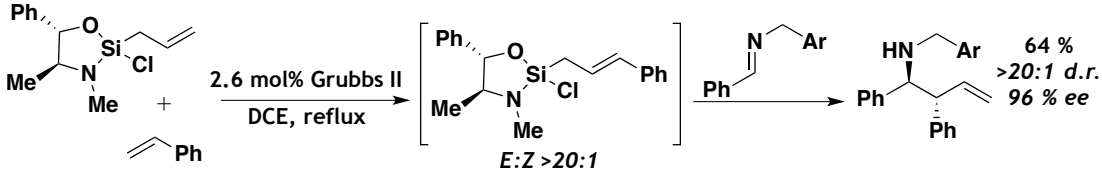
***Scheme 4.12**: Blueprint for intramolecular allylation forming carbocycles with two stereocenters*

Our first strategy envisioned a key cross metathesis step to insert the allylsilane (**Figure 4.2**). Allylsilanes have been shown to successfully undergo cross metathesis with vinyl- and alkyl-substitued alkenes.[154] The steric bulk of the silane helps drive the reaction and prevents self-metathesis.



***Figure 4.2**: Cross metathesis to introduce allylsilane.*

For example Leighton *et al.* have demonstrated that strained allyl-silacycles readily cross metathesize with styrenes (**Scheme 4.13**).[155] This was performed with Grubbs 2nd Generation catalyst in dichloroethane at reflux, and the resulting allyl-silcaycles have been employed in nucleophilic attack on imines to give substituted amines in high diastereo- and enantio- control.

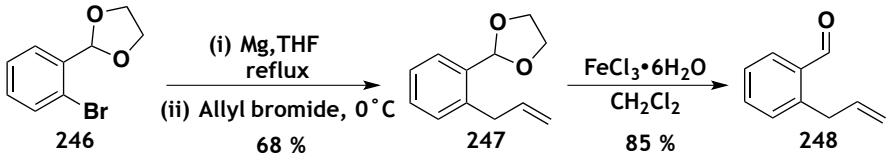


***Scheme 4.13**: Cross metathesis of silacycles, and reaction with imine.*

4.2 Results and Discussion

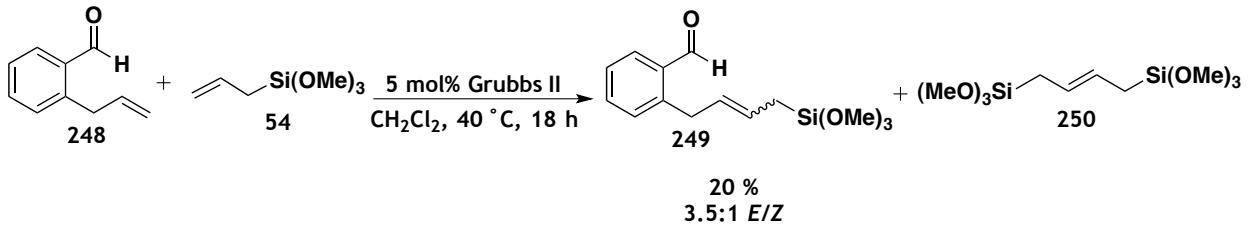
4.2.1 Synthesis of Allylsilanes by Cross Metathesis

The preparation of 2-allylbenzaldehyde **248** was performed in just two steps from commercially available starting materials (**Scheme 4.14**). Bromobenzene **246** was converted to the corresponding Gringard reagent by refluxing in THF with magnesium before reacting with allyl bromide.[156] The acetal-protecting group was then cleaved with ferric chloride hexahydrate to give 2-allylbenzaldehyde **248** in 85 % yield.[157]



Scheme 4.14**: Synthesis of 2-allylbenzaldehyde **248

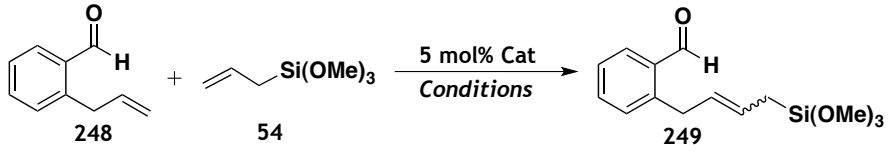
We then proceeded to investigate the key cross metathesis step. Our first reaction was based on literature conditions using Grubbs 2nd Generation catalyst.[158] Some conversion to the desired product **249** was observed, however there was a significant amount of the homodimerization product **250** (**Scheme 4.15**). Homodimerization byproduct **250** was difficult to remove by silica gel chromatography using petrol/ether eluents, but further attempts showed that dichloromethane eluent alone could be used to separate **250** from the products. ^{1}H-NMR spectra showed that a mixture of geometric isomers **249** were isolated in a 3.5:1 ratio, although whether *E* or *Z* was the major isomer could not be determined.



***Scheme 4.15**: Cross metathesis with Grubbs II in CH_2Cl_2*

Next, optimization was carried out to improve the yield of the allylsilane **249** and different solvents and temperatures were investigated (**Table 4.1**). Changing from dichloromethane to chloroform increased the yield to 31 % (entry 2) but 1,2-dichloroethane gave no reaction (entry 3). Toluene at

reflux also gave a lower yield (entry 4) and the reaction did not proceed under microwave irradiation (entry 5). We decided to investigate if using Hoveyda-Grubbs 2nd Generation catalyst (HG II) would be better for the cross metathesis as it is known to be more stable.[159] The reaction in chloroform at reflux showed no change in reactivity (entry 6) but the reaction in the microwave progressed in a 24 % yield (entry 7). The reaction was also carried out more concentrated in chloroform and 1,2-dichloroethane, both at reflux, and this gave yields around 30 % (entries 8 and 9).



248 54 249

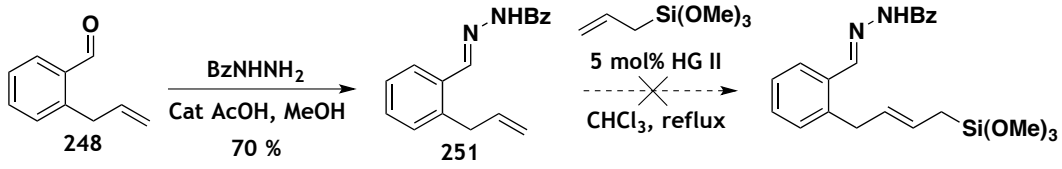
	Catalyst	Solvent	Conc M	Temp ˚C	Time h	Yield %
1	Grubbs II	CH_2Cl_2	0.05	40	18	20
2	Grubbs II	$CHCl_3$	0.05	61	18	31
3	Grubbs II	1,2-DCE	0.05	84	18	0
4	Grubbs II	Toluene	0.05	110	18	15
5	Grubbs II	CH_2Cl_2	0.50	70, μw	17	0
6	HG II	$CHCl_3$	0.05	61	18	31
7	HG II	CH_2Cl_2	0.33	70 μw	3	24
8	HG II	$CHCl_3$	0.20	61	18	34
9	HG II	1,2-DCE	0.20	84	18	30

***Table 4.1**: Cross metathesis conditions. E/Z ratios were not determined*

Unfortunately the reaction yield was not significantly improved under different cross metathesis conditions. Further attempts were made using only one equivalent of allyltrimethoxysilane **54** (compared to four equivalents in the other examples), and adding the allyltrimethoxysilane **54** dropwise over a 3 h period, but both of these strategies resulted in lower yields (18 % and 13 % respectively). Adding the Hoveyda-Grubbs 2nd Generation catalyst in two portions with a 5 h time gap had no effect on yield either. At this stage it was realized that the cross metathesis between 2-allylbenzaldehyde **248** and allyltrimethoxysilane **54** was not an effective method for accessing potential intramolecular allylation precursors, especially when the cost of the catalyst was considered.

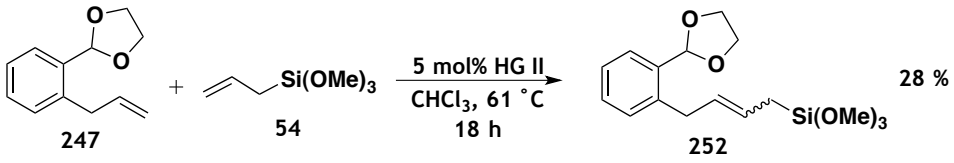
An alternative route where the hydrazone was made from 2-allylbenzaldehyde **248** before the cross metathesis reaction was next devised. The hydrazone **251** was prepared easily under standard

conditions (**Scheme 4.16**), however the cross metathesis reaction did not proceed and all of hydrazone **251** was returned.



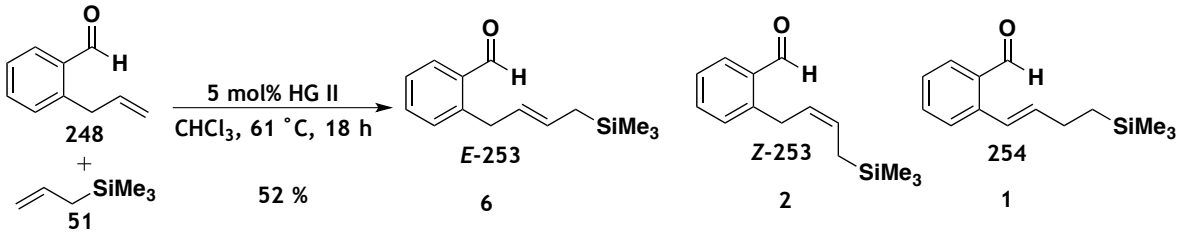
Scheme 4.16**: Cross metathesis of hydrazone **251

We decided to see if acetal **247** would be more reactive under cross metathesis conditions than aldehyde **248**. Acetal **247** did react to give the cross metathesis product **252** using Hoveyda Grubbs 2nd Generation catalyst, but the yield of the reaction was only 28 %, which was no improvement on aldehyde **248** under the same conditions (**Scheme 4.17**). The *E/Z* ratio could not be determined by ^{1}H-NMR.



Scheme 4.17**: Cross metathesis with acetal **247

The cross metathesis with allyltrimethylsilane **51** was also examined (**Scheme 4.18**). The reaction proceeded better, and gave a yield of 52 % and with an *E:Z* ratio of 3:1 by ^{1}H-NMR. The reaction also showed that some double bond migration had occurred and regioisomer **254** was found but could not be separated from **253**.

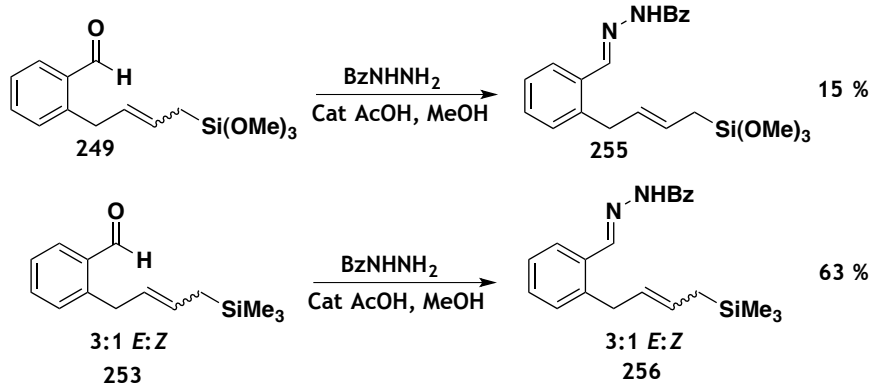


Scheme 4.18**: Cross metathesis with allylsilane **51

4.2.2 Intramolecular Allylation of Cross Metathesis Products

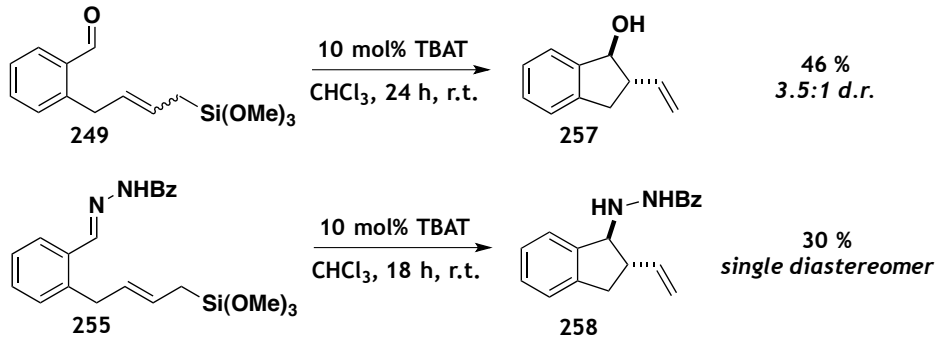
Although the cross metathesis route proved unreliable, we were keen to pursue with the material we had and probe the intramolecular allylation reaction. Aldehyde **249** was reacted with

benzoylhydrazine to make hydrazone **255** **(Scheme 4.19)**. Unfortunately hydrazone **255** was difficult to purify because it was an oil and so could not be recrystallized. Silica gel chromatography caused some decomposition but gave enough material to perform the intramolecular allylation. This problem did not arise when aldehyde **253** was made into hydrazone **256**, and **256** was found to retain the *E:Z* ratio present in the starting material.



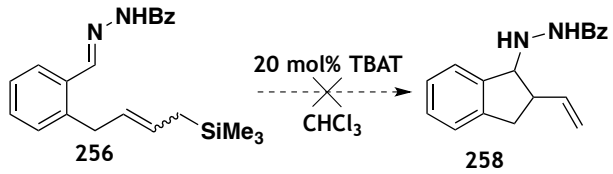
***Scheme 4.19**: Hydrazone formation*

The first attempts at the intramolecular allylation to cyclize both aldehyde **249** and hydrazone **255** were performed at room temperature using tetrabutylammonium triphenyldifluorosilicate (TBAT) (**Scheme 4.20**). Both reactions proceeded cleanly when followed by TLC. Pleasingly, **258** was made as a single diastereomer (diasteromers were assigned by comparison with literature compounds).[160]



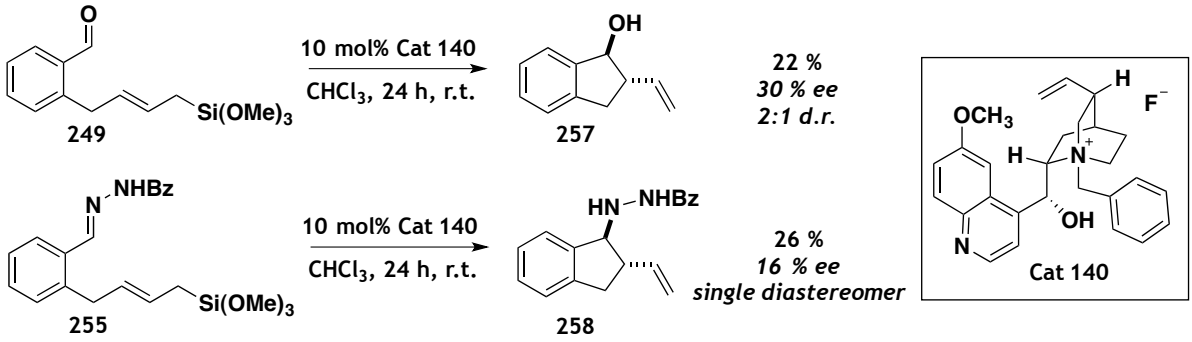
***Scheme 4.20**: Intramolecular allylation using 10 mol% TBAT.*

However, the intramolecular allylation reaction with hydrazone **256** did not proceed (**Scheme 4.21**). The reaction was attempted with 20 mol% TBAT in chloroform, but only starting material was recovered. The reaction was repeated at reflux but, again, only starting material was recovered.



Scheme 4.21**: Intramolecular allylation did not work with **256

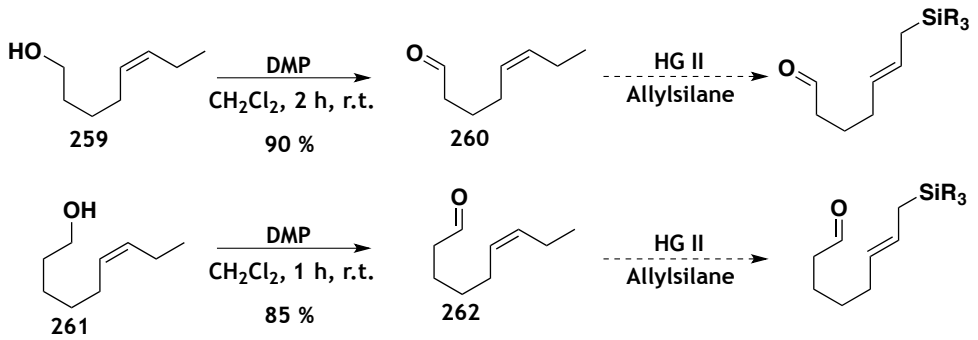
The success of the racemic reactions led us to attempt the intramolecular allylation reaction using *N*-benzylquininium fluoride catalyst **140** with aldehyde **249** and hydrazone **255** (**Scheme 4.22**). Alcohol **257** and amine **258** were obtained with a 30 % ee and 16 % ee respectively. These were promising first results but due to a lack of material we were unable to carry out optimization or a catalyst screen. We therefore planned to investigate alternative but related substrates that could be synthesized in greater quantity.



Scheme 4.22**: Intramolecular allylation using 10 mol% Cat **140

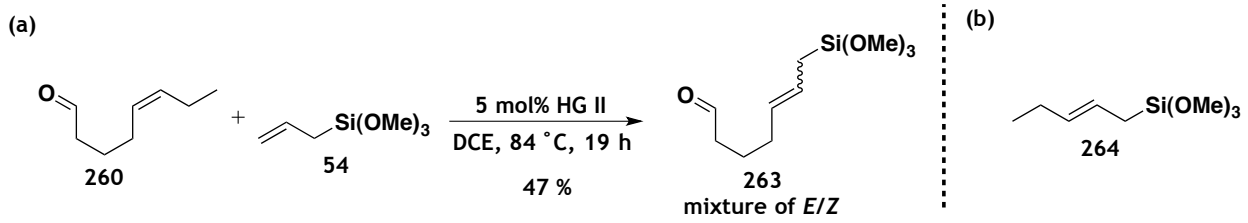
4.2.3 Other Allylsilanes Synthesized by Cross Metathesis

The original plan was to find a route to allylsilanes that would allow us to access functionalized carbocycles and heterocycles (**Chapter 4.1.5**). The cross metathesis precursors for cyclopentyl and cyclohexyl systems can be accessed from (*Z*)-oct-5-enol **259** and (*Z*)-non-6-enol **261** respectively by a Dess-Martin oxidation (**Scheme 4.23**). These starting materials were chosen over hex-5-enal or hept-6-enal, as they are commercially available. However the cross metathesis reaction was again found to not be trivial, despite there being literature precedent for these compounds to react under similar reaction conditions.[153]



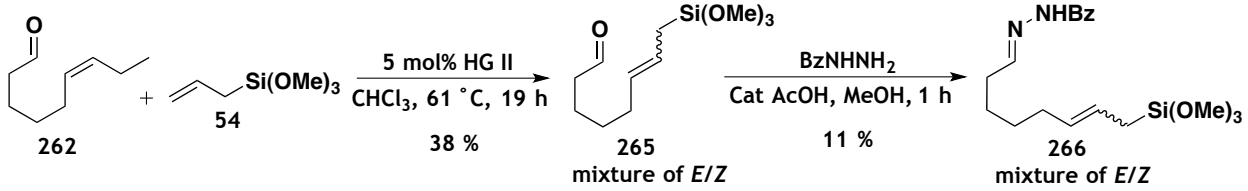
***Scheme 4.23**: Allylsilanes to make cyclopentanes and cyclohexanes*

(*Z*)-Oct-5-enal **260** was found to react with allyltrimethoxysilane **54** using Hoveyda-Grubbs II catalyst and 1,2-dichloroethane at reflux (**Scheme 4.24 (a)**). Reactions performed in chloroform at reflux gave only an 11 % yield, and the undesired cross metathesis product **264** was also isolated (**Scheme 4.24 (b)**). The allylsilane **263** was found to be a mixture of geometric isomers, although the exact ratio was indeterminable by ^{1}H-NMR.



***Scheme 4.24**: Cross metathesis of **(a)** (Z)-oct-5-enal and **(b)** undesired **264** formed in chloroform*

(*Z*)-Non-6-enal **262**, conversely, only gave trace product **265** when the reaction was performed in 1,2-dichloroethane at reflux, but did yield 38 % of cross metathesis product **265** in chloroform at reflux (**Scheme 4.25**). Repeating this experiment, however, gave varying yields as low as 6 %. The allylsilane **265** was taken onto the next step to make the hydrazone **266**, but problems were again encountered when the product was purified by silica gel chromatography and the hydrazone **266** was isolated in only an 11 % yield. Both **265** and **266** were a mixture of geometric isomers, whose ratios could not be determined by ^{1}H-NMR spectra.



***Scheme 4.25**: Cross metathesis of (Z)-non-6-enal*

As similar problems were arising with the cross metathesis reaction and the hydrazone purification, the procedures were not optimized further. A new route that did not involve cross metathesis to insert the allylsilane was sought.

4.2.4 Synthesis of Allylsilanes *via* a Heck Reaction

It was proposed that a slight modification to the allylsilane substrate would allow us to insert the allylsilane group adjacent to the aryl ring using palladium chemistry. The intramolecular allylation could then be performed in the same way and the indane products would still contain two new stereocentres (**Figure 4.3**).

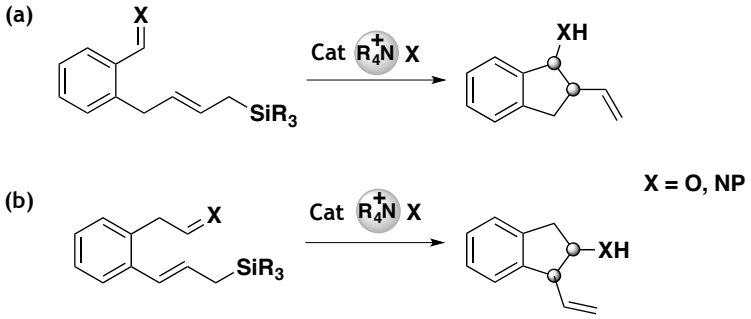
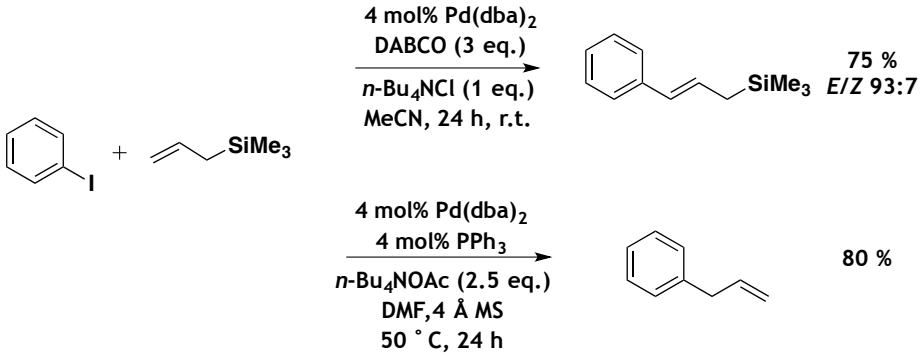


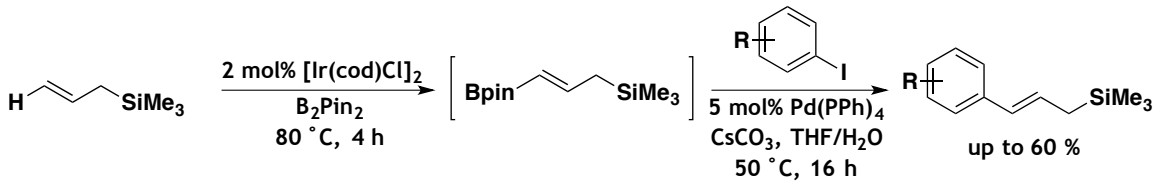
***Figure 4.3**: **(a)** Allylsilane made by cross metathesis and **(b)** allylsilane made by palladium chemistry*

A Heck reaction with allyltrimethylsilane **51** and aryl iodides was first demonstrated by Hallberg *et al.*,[161] however, they observed several byproducts. Double bond migration and β-trimethylsilyl elimination were observed, as well as regioselectivity issues in the β-hydride elimination step. Jeffery showed that these problems could be overcome by careful selection of base, solvent and also using a tetraalkylammonium salt additive (**Scheme 4.26**).[162]



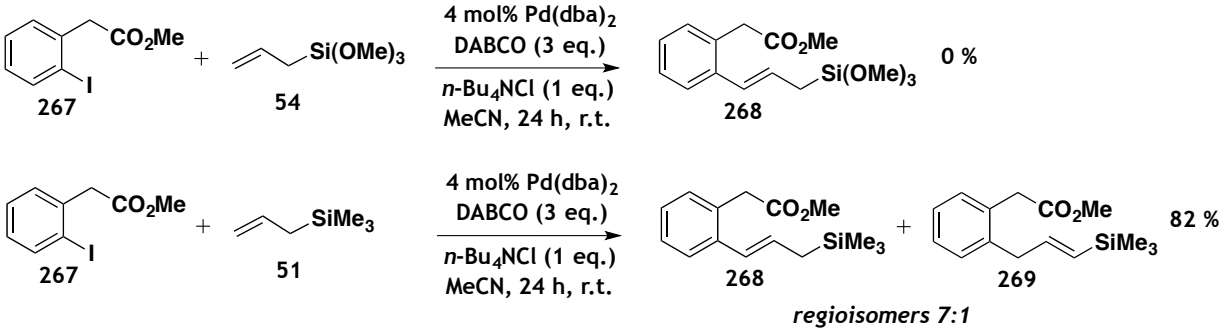
***Scheme 4.26**: Changing the base and solvent for a Heck reaction gives different products*

Alternatively, aryl iodides can react under Suzuki-Miyaura conditions.[163] The allylsilane must first undergo selective C-H borylation with an iridium catalyst. This can be carried out in one-pot to afford functionalized allylsilanes directly from the terminal allylsilane (**Scheme 4.27**). Importantly, there were no problems with the regioselectivity of the C-H functionalization step and only (*E*)-alkene products were observed.



***Scheme 4.27**: One-pot catalytic C-H borylation-Suzuki-Miyaura coupling sequence*

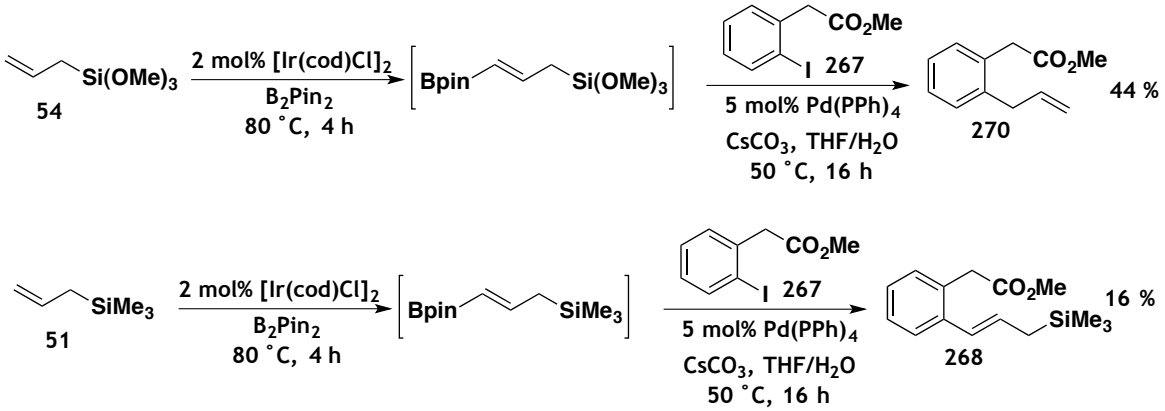
Given these literature examples we were confidant that we could make our functionalized allylsilanes using palladium chemistry. Commercially available 2-(iodophenyl)acetic acid was selected as an appropriate precursor and was protected as the methyl ester **267**. Jeffery's Heck reaction conditions[162] were first employed with methyl ester **267** and allylsilanes **54** and **51** (**Scheme 4.28**).



Scheme 4.28**: Heck reaction with aryl iodide **267

The Heck reaction with allyltrimethoxysilane **54** under these conditions showed the formation of several new products by TLC analysis. These compounds were isolated by column chromatography, but the ^{1}H-NMR spectra showed no traces of the desired allylsilane **268** and the compounds were not identified. Gratifyingly, the reaction with allyltrimethylsilane **51** proceeded smoothly and afforded the allylsilane **268** in 82 % yield (**Scheme 4.28**). ^{1}H-NMR analysis revealed that in fact there was a mixture of inseparable regioisomers, albeit in a ratio of **268**:**268** 7:1 in favour of the desired isomer.

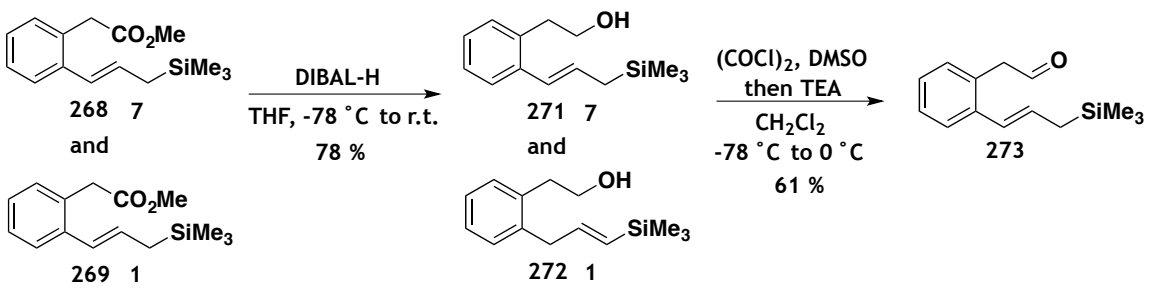
The C-H borylation-Suzuki-Miyaura coupling sequence[163] was also trialed with both allylsilanes **54** and **51** (**Scheme 4.29**). The reaction did proceed with allyltrimethoxysilane **54** but the main product formed, **270**, was the result of β-desilylation during C-C coupling with palladium. Unfortunately, the reaction of allyltrimethylsilane **51** under these conditions did not ensue as well as the Heck reaction had, and the allylsilane **268** was isolated in only 16 % yield.



Scheme 4.29**: C-H Borylation-Suzuki-Miyaura coupling sequence with aryl iodide **267

It was decided at this point to only continue the synthetic route with allylsilane **268** because it could be made efficiently on scale *via* the Heck reaction. This would allow us to experiment on the rest of the sequence and see if intramolecular allylation was successful. Although there was some of the other regioisomer **269**, it was hoped that this could be separated at a later step.

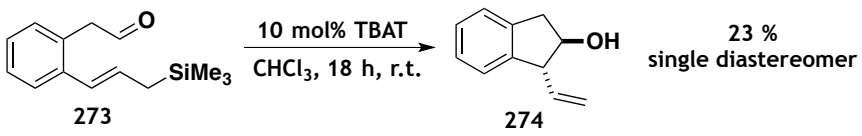
The next stage was to reduce the methyl ester **268** to the aldehyde **273**. DIBAL-H was used, but using just one equivalent gave only the alcohol **271** and returned starting material – no aldehyde **273** was detected. Therefore, all the methyl ester **268** was reduced using two equivalents of DIBAL-H to alcohol **271** in 78 % yield, which was obtained as a mixture of regioisomers (**271**:**272**, 7:1) (**Scheme 4.30**).



Scheme 4.30**: Reduction-oxidation sequence to prepare aldehyde **273

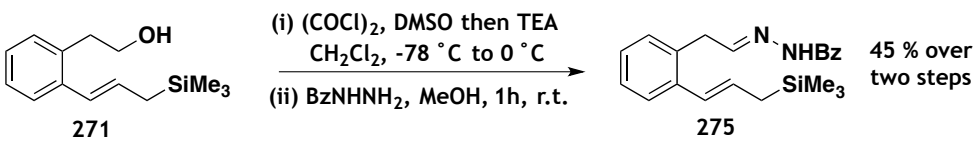
The aldehyde **273** could then be accessed by a single oxidation step. We first attempted a Dess-Martin oxidation, as this uses mild conditions, but the oxidation led to several products when followed by TLC. A Swern oxidation gave clean conversion, although the product underwent partial decomposition during purification. Nonetheless, aldehyde **273** was isolated cleanly in a 61 % yield; the other regioisomer was not observed. It was clear that aldehyde **273** is not stable at room temperature but it was felt that aldehyde **273** could be used without isolation for future steps.

Some of the purified aldehyde **273** was subjected to the intramolecular allylation conditions (**Scheme 4.31**). We were pleased to see that using TBAT at room temperature gave conversion to the indane **274** solely as the *anti*-diastereomer.[160] Unfortunately, the reaction could not be optimized, nor a catalyst screen performed with the chiral ammonium fluoride catalysts due to the instability of the aldehyde **273**.



Scheme 4.31**: Intramolecular allylation of aldehyde **273

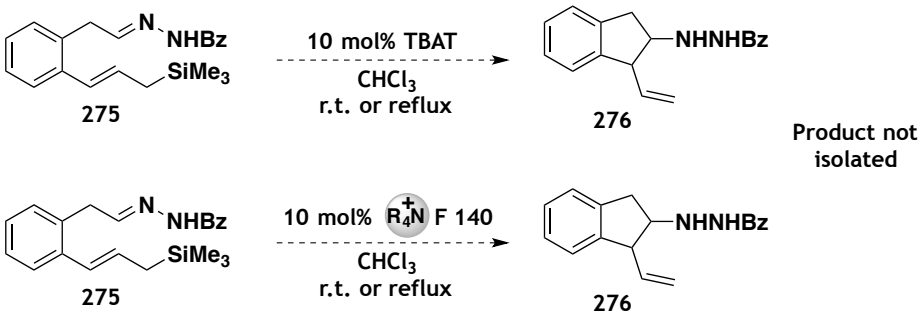
Our efforts were refocused on making hydrazone **275** to see whether this was stable and could be used to trial intramolecular allylation conditions. Alcohol **271** was oxidized under Swern conditions and, following a quick work-up, the crude aldehyde **273** was redisolved in methanol and exposed to benzoylhydrazine (**Scheme 4.32**). Thankfully, the hydrazone formation was fast and TLC analysis showed that minimal side-products were formed. The hydrazone **275** was purified by column chromatography with no decomposition issues (unlike similar hydrazones **255** and **266**, **Chapter 4.2.2**).



***Scheme 4.32**: Swern oxidation and hydrazone formation*

The first attempts to accomplish the intramolecular allylation reaction with hydrazone **275** were unsuccessful. Using catalytic TBAT or *N*-benzylquininium fluoride **140** at room temperature and at

reflux did not yield the indane **276** (**Scheme 4.33**). In the TBAT case, ^{1}H-NMR spectroscopic analysis of the crude reaction mixture showed that, although there were traces of a new product, the reactions were primarily returning starting material. It was clear that a more thorough screen of conditions for the intramolecular allylation was required.



Scheme 4.33**: Initial attempts at intramolecular allylation with hydrazone **275

The first results with TBAT showed that the allylsilane in hydrazone **275** was not susceptible to attack by catalytic fluoride. The reaction was also attempted with TBAF in catalytic and stoichiometric amounts at reflux (**Table 4.2**, entries 3 and 4). The reaction with stoichiometric TBAF did show formation of a new compound by crude ^{1}H-NMR, but this could not be isolated cleanly or identified. The conditions employed for the racemic reaction in **Chapter 2.2.2** were attempted (entry 5) but returned starting material and a new compound that could not be characterized. Given the literature on similar transformations, it seemed prudent to try Brønsted acid conditions. Trifluoroacetic acid did not affect hydrazone **275** under catalytic conditions (entry 7) but led to a complex mixture when used stoichiometrically (entry 8). We also examined diphenylphosphate (entry 9), since chiral phosphoric acids could provide an alternative asymmetric allylation methodology, but this just lead to several compounds by TLC analysis. Finally a less polar solvent, toluene, was considered with TBAT but at room temperature gave little reaction and heating to 85 ˚C caused the hydrazone **275** to decompose (entries 10 and 11).



275 276

	Reagent	Amount mol%	Solvent	Temp ˚C	Result
1	TBAT	10	$CHCl_3$	20	Returned S.M.
2	TBAT	10	$CHCl_3$	61	Returned S.M.
3	TBAF	10	$CHCl_3$	61	Returned S.M.
4	TBAF	100	$CHCl_3$	61	A new product observed – could not be isolated
5	TBAT/Schreiner's cat.	20/10	THF	20	A new product observed – could not isolate
6	Schreiner's cat.	10	$CHCl_3$	20	No reaction
7	TFA	20	$CHCl_3$	20	Returned S.M.
8	TFA	100	$CHCl_3$	20	Decomposition
9	Diphenylphosphate	10	$CHCl_3$	20	Decomposition
10	TBAT	10	Toluene	20	A new product observed – could not isolate
11	TBAT	10	Toluene	85	Decomposition

***Table 4.2**: Screen of intramolecular allylation conditions*

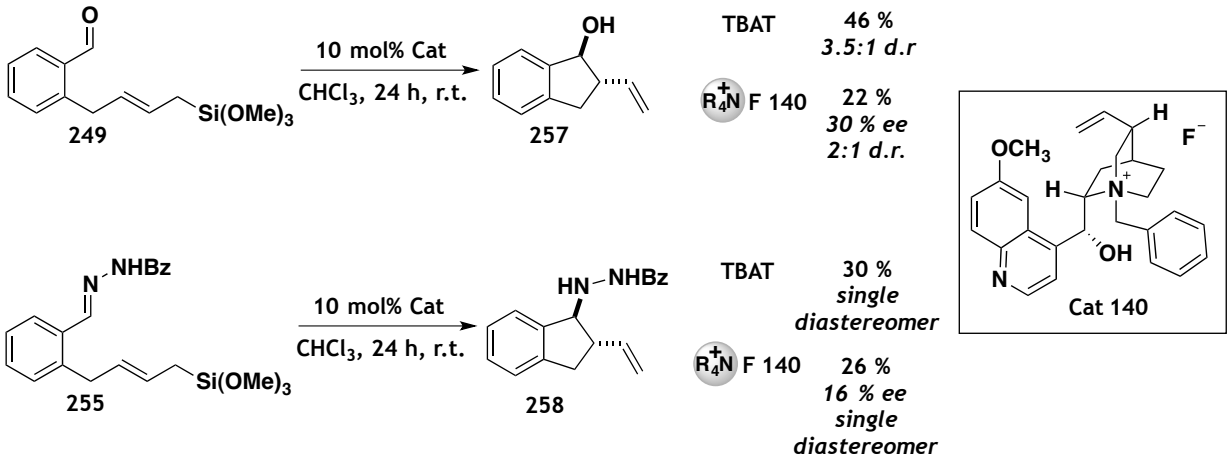
Regrettably, it was clear that hydrazone **275** could not readily undergo intramolecular allylation under a range of conditions. This is perhaps because desilylation would lead to an allyl anion species that would be highly stabilized, as it is in conjugation with the adjacent aromatic ring. This could potentially lead to side reactions and multiple products. Hydrazone **275** also contains an enolisable α-CH_2 and therefore it is possible reaction could occur at this position in acid or base. Furthermore, the likelihood of double bond isomerization to the other regioisomer also made substrate **275** problematic for this study.

4.3 Conclusion

This project aimed to establish the first example of catalytic asymmetric intramolecular allylation employing fluoride. This is an attractive transformation because it would generate carbocycles containing two contiguous stereocentres. The blueprint invoked a chiral quaternary ammonium fluoride catalyst and mild reaction conditions. Stereoselectivity would be garnered by the electrostatic association of the chiral quaternary ammonium cation with an allyl anion intermediate.

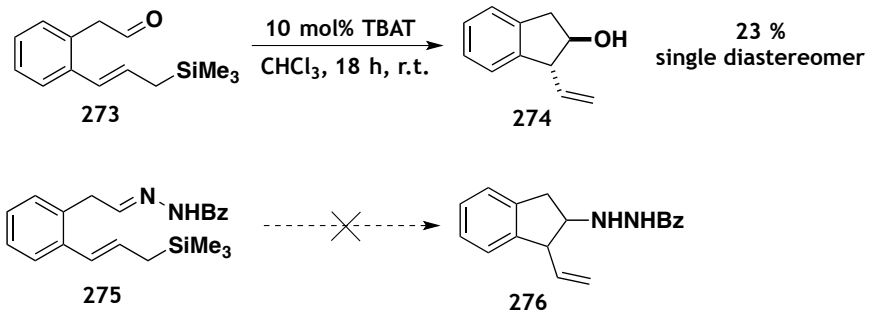
We hoped this method could be extended to synthesize different ring sizes and compounds with an array of substituents.

Our first approach to this project was to synthesize the allylsilanes *via* a cross metathesis reaction. This strategy only produced poor yields with allyltrimethoxysilane **54** (34 % at best) and so was not a feasible option for accessing these substrates in useful quantities. Nonetheless, the substrates attained by this method were subjected to the intramolecular allylation conditions using either TBAT or *N*-benzylquininium fluoride **140** (**Scheme 4.34**). Both aldehyde **249** and hydrazone **255** underwent intramolecular allylation with *N*-benzylquininium fluoride **140** and gave moderate enantioselectivities. Pleasingly we found that the amine **258** was formed as the *anti*-diastereomer only. Unfortunately, a lack of material impeded a comprehensive study to find optimal intramolecular allylation conditions.



***Scheme 4.34**: Summary of intramolecular allylations*

A new synthetic strategy involved installing the allylsilane in a Heck reaction, which proceeded with allyltrimethylsilane in 82 % yield. The resulting aldehyde **273** reacted using TBAT and gave a single diastereomer, but because the aldehyde **273** was not stable the reaction could not be optimized (**Scheme 4.35**). The hydrazone **275** was stable but intramolecular allylation did not proceed under a range of conditions. It was thought this was because of conjugation of the allyl anion to the arene ring and the possibility of side reactions at enolisable α-CH_2 position. It appeared that this structure was not amenable to intramolecular allylation.



***Scheme 4.35**: Summary of intramolecular cylization*

Our investigations into intramolecular allylation have been precluded by time restraints. Our ambition to find a synthesis of substrates that would be flexible, and allow for incorporation of different groups and sidechains, prevented us from building a suitable compound on which intramolecular allylation could be thouroughly tested. Finding a robust substrate synthesis would allow for a thorough examination of intramolecular allylation conditions. Development of an asymmetric catalytic process would be a worthwhile achievement.

5. Experimental Procedures and Data

5.1 General Experimental Details

General Information

Unless otherwise indicated, all reactions were carried out under a positive pressure of argon or nitrogen (balloon pressure) in washed and oven-dried glassware.

Solvents and Reagents

Tetrahydrofuran, dichloromethane, diethyl ether, methanol, toluene and acetonitrile were purified by pressurized filtration through activated silica columns, employing the method of Grubbs *et al.*[164] Unless otherwise indicated, other solvents were used as supplied (analytical or HPLC grade) without further purification. Where mixtures of solvents are specified, the stated ratios are volume:volume. Triethylamine was distilled over calcium hydride and stored over potassium hydroxide under an inert argon atmosphere. pH 7 buffer solution was prepared by the addition of sodium hydroxide (0.1 M aq., 291 mL) to potassium dihydrogen phosphate (0.1 M aq., 500 mL). Reagents were used directly as supplied by major chemical suppliers, or purified by procedures described by Perrin and Armarego.[165]

Chromatography

Flash column chromatography was performed using VWR silica gel (40 – 63 μm particle size). Thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} 0.25 mm precoated aluminium plates. Product spots were visualized under UV light (λ_{max} = 254 nm) and/or by staining with 1 % potassium permanganate (VII) or 0.3 % ninhydrin in *n*-butanol.

NMR Spectroscopy

NMR spectra were recorded on a Bruker AV400 (^{1}H: 400 MHz, ^{13}C: 101 MHz, ^{19}F: 377 MHz), AVIII400 (^{1}H: 400 MHz, ^{13}C: 101 MHz, ^{19}F: 377 MHz), Bruker AVII Cryo 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz), or Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) spectrometer. Chemical shifts are

quoted in ppm, based on appearance rather than interpretation, and are referenced to residual non-deuterated solvent peak. Signal splittings are abbreviated as follows: br. – broad, s – singlet, d – doublet, t – triplet, q – quartet, quin – quintet, m – mulitplet. All data was collected at 298 K, unless otherwise stated. Spectral assignment was aided by the results of DEPT, COSY, HMBC and HSQC experiments where appropriate.

IR Spectroscopy

Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorbtion maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

Mass Spectrometry

Mass spectra were recorded on a Micromass LCT Premier spectrometer under conditions of electrospray ionization (ESI). Accurate masses (HRMS) were recorded on Bruker MicroTOF and Micromass GCT spectrometers under conditions of ESI and field ionization (FI) respectively. Masses are reported in Daltons (Da).

Polarimetry

Optical rotations were recorded on Perkin-Elmer 241 and 341 polarimeters with a path length of 1 dm, and are reported in deg $dm^{-1}cm^{3}g^{-1}$. Values are measured at the sodium D line (589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

Melting Points

Melting points were measured in a Gallenkamp MF-370 melting point apparatus or a Reichert melting point stage, and are uncorrected.

HPLC

Analytical chiral HPLC was performed on a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode-array detector, equipped with the appropriate Daicel Chiralpak column

(dimensions: 0.46 cm × 25 cm) and corresponding guard column (0.4 cm × 1 cm). Wavelenghts (λ) are reported in nm and retention times (t_R) are reported in minutes.

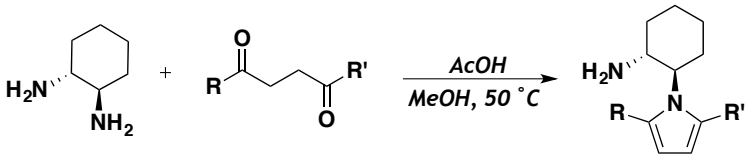
Naming, Numbering and Depiction of Compounds

Where given, systematic compound names are those generated by ChemBioDraw Ultra 13.1 following IUPAC conventions. The number of atoms for discussion and spectral assignment is arbitrary and not necessarily consistnent with IUPAC names.

Chiral nonracemic and racemic molecules are depicted according to the Maehr convention: absolute stereochemistry is indicated by solid wedged (▬) or hatched wedged (⋯) bonds, and relative stereochemistry is indicated by solid bold (▬) or hatched bold (⋯) bonds.[166]

5.2 General Procedures

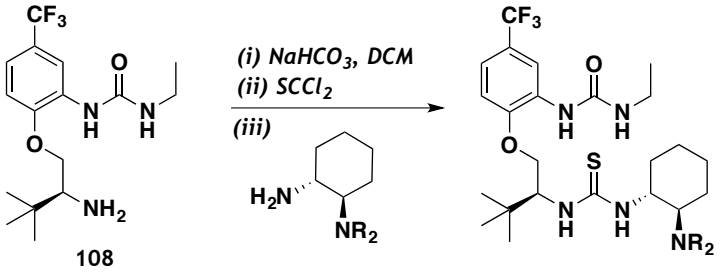
General Procedure for Pyrrole Formation



General Procedure A

This method is based on a literature procedure.[167] Acetic acid (1.0 eq.) and 1,4-diketone (1.0 eq.) were sequentially added to a stirring solution of (*R*,*R*)-(-)-1,2-diaminocyclohexane (1.0 eq) dissolved in methanol (0.2 M). The reaction was heated to 50 °C for 1 h and then allowed to cool to room temperature before removing solvent *in vacuo*. The residue was redissolved in dichloromethane and washed with aqueous NaOH solution (3M). The aqueous phase was back extracted with dichloromethane (× 2), and the combined organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography.

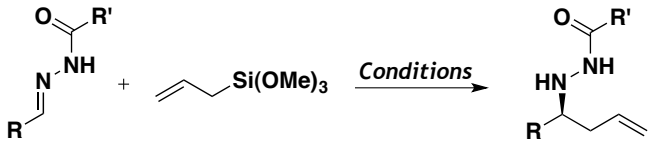
General Procedure for the Formation of Cooperative Thiourea Catalysts



General Procedure B

Amine **108** (1 eq.) was dissolved in dichloromethane (0.10 M) and saturated $NaHCO_3$ solution (0.10 M) and cooled to 0 °C. The solution was stirred for 10 min and then stirring was stopped. Thiophosgene (1.1 eq.) was added to the organic layer and stirring was continued for 30 min at 0 °C. The mixture was separated and the aqueous phase extracted with dichloromethane (× 2). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* and the residue was redissolved in dichloromethane (0.13 M). The appropriate cyclohexylamine (1 eq.) dissolved in dichloromethane (0.67 M) was added and the reaction stirred at room temperature for 16 h. The reaction was diluted with dichloromethane and washed with pH 7 buffer solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by silica gel chromatography.

General Procedures for the Allylation of Hydrazones



General Procedure C (racemic):

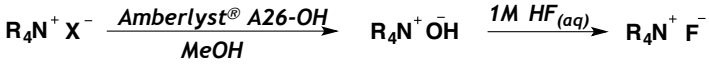
Tetrabutylammonium triphenyldifluorosilicate (10 mol%) and Schreiner's catalyst (20 mol%) were dissolved in THF (0.15 M) and stirred for 5 min. The appropriate hydrazone (1.0 eq.) and allyltrimethoxysilane (1.2 eq) were added and the reaction was stirred at r.t for 18 h. The reaction was then diluted with water and extracted with EtoAc (× 3), and the combined organics were

washed with brine. The organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo* and the crude was purified by silica gel chromatography.

General Procedure D (asymmetric):

Hydrazone (1.0 eq.) and chiral ammonium fluoride catalyst (10 mol%) were dissolved in chloroform (0.15 M). Allyltrimethoxysilane (2.0 eq) was added and the reaction was stirred at 61 ˚C for 48 h. The reaction was then cooled to r.t and diluted with water. The reaction was extracted with EtOAc (× 3) and the combined organics were washed with brine. The organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo* and the crude was purified by silica gel chromatography.

General Procedure for the Preparation of Ammonium Fluoride Catalysts



General Procedure E

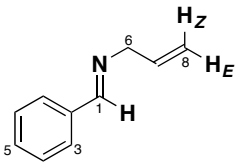
This procedure is based on a modified literature procedure.[126] Amberlyst® A26-OH resin (10 eq.) was placed in a thin glass column and washed with methanol (5mL/g). Chiral quaternary ammonium salt (chloride or bromide, 1 eq.) was dissolved in methanol (0.04 M) and passed slowly through the Amberlyst® resin and the column was further washed with methanol to remove all of the hydroxide salt. The eluent was then neutralized with aqueous 1 M hydrogen fluoride solution (1 eq.) and the solvent was removed *in vacuo*. The product was left to dry on a high vacuum line for at least 18 h.

N. B. WARNING – hydrofluoric acid is extremely toxic and a full COSHH assessment should be performed before carrying out any work.

5.3 Experimental Data

5.3.1 Experimental Data from Chapter 2: Cooperative Thiourea Catalysts for Asymmetric Allylation

***N*-Benzylideneprop-2-en-1-amine 89**



This compound was prepared according to a literature procedure.[68] 4 Å Molecular sieves (10 mg) were activated by vigorous heating *in vacuo*, in a round bottom flask. Dichloromethane (1.0 mL) and benzaldehyde (1 μL, 0.99 mmol) were added, followed by dropwise addition of allylamine (96 μL, 1.27 mmol). The resulting suspension was stirred at room temperature for 4 h, after which time the sieves were removed by filtration and washed with dichloromethane (2 × 10 mL). The filtrate was collected and solvent removed *in vacuo* to yield **89** as a colourless oil (0.14 g, quant.).

Data for **89**:

δ_H (400 MHz, $CDCl_3$): 8.30 (1H, s, C1), 7.78 (2H, dd, *J* 6.6, 2.8, H3), 7.42 (3H, m, H4 and H5), 6.10 (1H, ddt, *J* 16.8, 10.9, 5.6, H7), 5.23 - 5.30 (1H, m, H_Z(8)), 5.18 (1H, d, *J* 10.4 H_E(8)), 4.28 (2H, d, *J* 5.5, CH_2(6)).

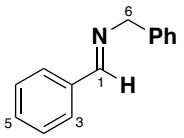
δ_C (101 MHz, $CDCl_3$): 162.0 (C1), 136.2 (C2), 135.9 (C7), 130.7, 128.6, 128.2 (ArCH), 116.1 (C8), 63.5 (C6).

ν_{max} (thin film): 1648 (C=N).

HRMS (ESI +ve) found: 146.0970 [$(M+H)^+$], $C_{10}H_{12}N$ requires: 146.0964.

This data is in accordance with the literature.[168]

***N*-Benzylidene-1-phenylmethanamine 91**



This compound was prepared according to a literature procedure.[68] 4 Å Molecular sieves (10 mg) were activated by vigorous heating *in vacuo*, in a round bottom flask. To this dichloromethane (1.0 mL) and benzylamine (110 μL, 0.99 mmol) were added, followed by dropwise addition of benzaldehyde (100 μL, 0.99 mmol). The reaction was stirred at room temperature for 4 h, after which the sieves were removed by filtration and washed with dichloromethane (2 × 10 mL). The filtrate was collected and solvent was removed *in vacuo* to afford **91** as a colourless oil (0.19 g, 99 %).

Data for **91**:

δ_H (400 MHz, $CDCl_3$): 8.43 (1H, s, H1), 7.83 (2H, m, ArH), 7.46 (3H, m, ArH), 7.39 (4H, d, *J* 4.3, ArH), 7.31 (1H, dq, *J* 8.7, 4.3, ArH), 4.87 (2H, s, CH_2(6)).

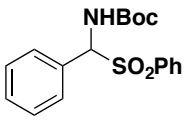
δ_C (101 MHz, $CDCl_3$): 162.0 (C1), 139.3 (ArC), 136.2 (ArC), 130.8, 128.7, 128.5, 128.4, 128.0, 127.0 (ArCH), 65.1 (C6).

ν_{max} (thin film): 1644 (C=N).

HRMS (ESI +ve) found: 196.1121 [$(M+H)^+$], $C_{14}H_{14}N$ requires: 196.1121.

This data is in accordance with the literature.[169]

***tert*-Butyl (phenyl(phenylsulfonyl)methyl)carbamate 92**



This compound was prepared according to a literature procedure.[88] *tert*-Butyl carbamate (1.17 g, 9.9 mmol) and benzenesulfinic acid sodium salt (3.27 g, 19.9 mmol) were dissolved in methanol (8.3 mL) and water (17 mL). Benzaldehyde (1.51 mL, 14.9 mmol) and formic acid (0.56 mL, 14.9 mmol) were added in one portion and the resulting solution stirred at room temperature for 48 h, over which time a white precipitate formed. The precipitate was collected by filtration and purified by trituration

with diethyl ether and water. No further purification was required and **92** was obtained as a white solid (3.01 g, 87 %).

Data for **92**:

m. p. 167 - 169 ˚C (Lit m. p. 169 – 170 ˚C).[170]

δ_H (400 MHz, $CDCl_3$): 7.92 (2H, d, *J* 7.3, ArH), 7.64 (1H, d, *J* 7.6, ArH), 7.54 (2H, t, *J* 7.7, ArH), 7.39 – 7.47 (5H, m, ArH), 5.86 – 5.99 (2H, m, CH & NH), 1.29 (9H, s, $C(CH_3)_3$).

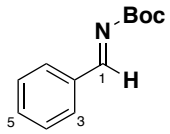
δ_C (101 MHz, $CDCl_3$): 153.5 (C=O), 136.9, 133.9, 129.8, 129.8, 129.5, 129.5, 129.0, 129.0, 128.9, 128.8 (12 × ArC), 81.2 ($\underline{C}(CH_3)_3$), 73.9 (CH), 28.0 ($C(\underline{C}H_3)_3$).

ν_{max} (thin film): 1693 (C=O), 1537 (Ar C=C).

HRMS (FI +ve) found: 347.1266 $[(M\bullet)^+]$, $C_{18}H_{21}NO_4S$ requires: 347.1191.

This data is in accordance with the literature.[88]

***tert*-Butyl benzylidenecarbamate 67**



This compound was prepared according to a literature procedure.[88] Potassium carbonate (0.60 g, 9.32 mmol) and sodium sulfate (0.61 g, 9.32 mmol) were activated by vigorous heating *in vacuo*. Once cooled, sulfone **92** (0.25 g, 0.72 mmol) and THF (6.0 mL) were added and the reaction was stirred at 70 ˚C for 16 h. The reaction was cooled to room tempertaure and and filtered to remove solids. The filtrate was concentrated *in vacuo* affording **67** as a colourless oil (0.15 g, quant.).

Data for **67**:

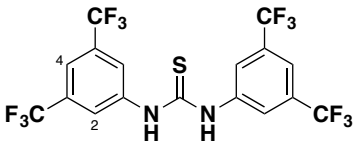
δ_H (400 MHz, C_6D_6): 8.75 (1H, s, H1), 7.69 (2H, d, *J* 7.3, H3), 7.10 (1H, t, *J* 7.2, H5), 7.02 (2H, t, *J* 7.1, H4), 1.56 (9H, s, $C(CH_3)_3$).

δ_C (101 MHz, C_6D_6): 168.2 (C1), 163.1 (C=O), 134.9, 132.9, 130.0, 128.8 (6 × ArC), 81.2 ($O\underline{C}(CH_3)_3$), 27.9 ($C(\underline{C}H_3)_3$).

ν_{max} (thin film): 1713 (C=O), 1630 (C=N).

This data is in accordance with the literature.[88]

1,3-Bis(3,5-bis(trifluoromethyl)phenyl)thiourea 95



3,5-Bis(trifluoromethyl)phenyl isothiocyanate (0.21 mL, 1.15 mmol) was added dropwise to a stirred solution of 3,5-bis(trifluoromethyl)aniline (0.17 mL, 1.00 mmol) in dichloromethane (5 mL) at 0 ˚C. After 2 h the reaction was washed with pH 7 buffer solution (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by silica gel chromatography to yield Schreiner's catalyst **95** as a white crystalline solid (0.475 g, 95 %).

Data for **95**:

m. p. 159 - 162˚C (Lit m. p. 172 – 173 ˚C).

δ_H (400 MHz, d_4-MeOD): 8.23 (4H, s, H2), 7.73 (2H, s, H4).

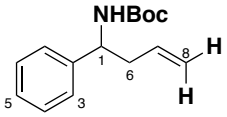
δ_C (101 MHz, d_4-MeOD): 181.1 (C=S), 141.6 (C1), 131.9 (q, $J_{C\text{-}F}$ 33.6, C3), 123.8 (C4), 123.7 (q, $J_{C\text{-}F}$ 271.6, CF_3), 117.9 (C4).

ν_{max} (thin film): 1556 (C=S), 1466 (Ar C=C).

HRMS (ESI -ve) found: 499.0141 [$(M\text{-}H^+)^-$], $C_{17}H_7F_{12}N_2S$ requires: 499.0144.

This data was in accordance with the literature.[6]

***tert*-Butyl (1-phenylbut-3-en-1-yl)carbamate 97**



This compound was prepared according to a literature procedure.[89] Benzaldehyde (102 μL, 1.00 mmol), allyltrimethylsilane (160 μL, 1.00 mmol) and *tert*-butyl carbamate (0.177 g, 1.00 mmol) were added to a flask containing acetonitrile (5.0 mL) and cooled to 0 ˚C. Boron trifluoride diethyl ether (74 μL, 0.06 mmol) was added in one portion that resulted in a white precipitate formed and then dissipated over a 30 min period. The reaction was warmed to room temperature and stirred for 6 h. The

reaction was poured into saturated aqueous sodium hydrogen carbonate solution (10 mL) and diluted with toluene (20 mL). The organic phase was washed with brine (2 × 20 mL) and then dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography to afford **97** as a white solid (0.154 g, 62 %).

Data for **97**:

m. p. 69 – 71 ˚C (Lit m. p. 74 – 76 ˚C).[170]

δ_H (400 MHz, $CDCl_3$): 7.31 – 7.37 (2H, m, H3), 7.23 – 7.30 (3H, m, H4 and H5), 5.70 (1H, ddt, *J* 17.2, 10.1, 7.2, H7), 5.06 – 5.17 (2H, m, CH_2(8)), 4.91 (1H, br. s, NH) 4.77 (1H, br. s, H1), 2.54 (2H, br. s, CH_2(6)), 1.44 (9H, br. s, $C(CH_3)_3$).

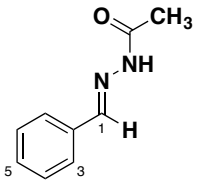
δ_C (101 MHz, $CDCl_3$): 155.2 (C=O), 142.0 (C2), 134.0 (C7), 128.5, 127.1, 126.2, (5 × ArCH), 118.2 (C8), 79.5 ($O\underline{C}(CH_3)_3$), 54.0 (C1), 41.2 (C6), 28.4 ($C(\underline{C}H_3)_3$).

ν_{max} (thin film): 1680 (C=O).

HRMS (ESI +ve) found: 270.1465 [$(M+Na)^+$], $C_{15}H_{21}NNaO_2$ requires: 270.1465.

This data was in accordance with the literature.[89]

_N_-Benzylidene acetohydrazide 100



Benzaldehyde (1.15 mL, 11.3 mmol) was added to a stirred solution of acethydrazide (0.84 g, 11.3 mmol) in ethanol (25 mL) at room temperature. The solution was stirred for 16 h, during which time a white solid precipitated. The solvent was removed *in vacuo* and the product was purified by crystallization from hot EtOAc that gave *N*-benzylidene acetohydrazide **100** as white needles (1.80 g, 98 %).

Data for **100**:

m. p. 117–120 ˚C (Lit. m. p. 133 ˚C).

δ_H (500 MHz, 363 K, d_6-DMSO): 10.93 (1H, br. s, NHCO), 8.06 (1H, br. s, H1), 7.67 (2H, m, ArH), 7.41 (3H, m, ArH), 2.20 (3H, br. s, CH_3).

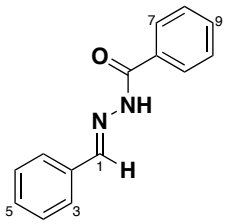
δ_C (126 MHz, d_6-DMSO): 172.6 (br., C=O), 143.6 (br., C1) 135.5 (ArC) 130.4 (ArCH), 129.5 (ArCH), 127.6 (ArCH), 20.9 (CH_3).

ν_{max} (thin film): 1674 (C=O), 1610 (C=N).

HRMS (ESI +ve) found: 185.0683 [$(M+Na)^+$], $C_9H_{10}N_2NaO$ requires: 185.0685.

This data is in accordance with the literature.[171]

(E)-*N'*-Benzylidenebenzohydrazide 101



Benzaldehyde (1.00 mL, 9.85 mmol) was added to a stirring solution of benzhydrazide (1.34 g, 9.85 mmol) in methanol (40 mL) at room temperature. A few drops of acetic acid were added and the solution stirred for 2 h, during which a white precipitate formed. The reaction mixture was concentrated *in vacuo* and *N*-benzilidene benzoylhydrazide **101** was recrystallized from hot EtOAc (2.18 g, 99 %) as white needles.

Data for **101**:

m. p. 202–203 ˚C (Lit m. p. 204 – 205 ˚C).

δ_H (400 MHz, d_6-DMSO): 11.86 (1H, s, NHCO), 8.47 (1H, s, C1), 7.92 (2H, d, *J* 7.3, H7), 7.74 (2H, d, *J* 6.3, H3), 7.60 (1H, m, H9), 7.53 (2H, m, H8), 7.46 (3H, m, H4 and H5).

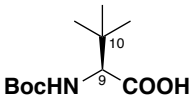
δ_C (101 MHz, d_6-DMSO): 164.0 (C=O), 148.6 (C1), 135.2 (C6), 134.3 (C2), 132.6 (ArCH), 131.0 (ArCH), 129.7 (ArCH), 129.41 (ArCH), 128.5 (C7), 128.0 (C3).

ν_{max} (thin film): 1640 (C=O), 1553 (C=N).

HRMS (ESI +ve) found: 225.1025 [$(M+H)^+$], $C_{14}H_{13}N_2O$ requires: 225.1022.

This data is in accordance with the literature.[171]

***N*-*t*-Butyl carbamate-L-*tert*-leucine 277**



Sodium hydroxide (0.35 g, 8.69 mmol) was added to a stirring solution of L-*tert*-leucine (1.04 g, 7.91 mmol) in dioxane (10 mL) and water (10 mL). The solution was cooled to 0 ˚C and di-*t*-butyl carbamate (1.90 g, 8.69 mmol) was added slowly. The reaction was warmed to room temperature and stirred for 4 h. The reaction mixture was cooled to 0 ˚C and acidified using 1 M HCl solution. The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The organic phase was then washed with 1M HCl solution (30 mL), brine (2 × 30 mL) and water (2 × 30 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give *N*-*t*-butyl carbamate-L-tert-leucine **277** as a crystalline solid (1.83 g, quant.).

Data for **277**:

m. p. 103 - 105 ˚C (Lit m. p. 105 – 106 ˚C).

δ_H (400 MHz, $CDCl_3$): 5.17 (1H, d, *J* 9.4, NH), 4.11 (1H, d, *J* 9.4, H9), 1.42 (9H, s, CH_3(Boc)), 1.00 (9H, s, $C(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 176.6 (COOH), 155.7 (CONH), 79.9 (C(Boc)), 61.6 (C9), 34.5 (C10), 28.3 (CH_3(Boc)), 26.5 ($C(CH_3)_3$).

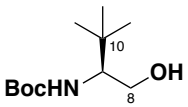
ν_{max} (thin film): 1721 (CO_2H), 1680 (CONH).

HRMS (ESI +ve) found: 254.1362 [$(M+Na)^+$], $C_{11}H_{21}NNaO_4$ requires: 254.1363.

$[\alpha]_D^{25}$: -3.8° (*c* 0.9 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -2.8° (*c* 1.1 in CH_2Cl_2)).

This data is in accordance with the literature.[172]

***N*-*t*-Butyl carbamate-L-*tert*-leucinol 104**



Triethylamine (0.32 mL, 2.27 mmol) was added to a stirring solution of *N*-*t*-butly carbamate-L-*tert*-leucine **277** (0.53 g, 2.27 mmol) in THF (6 mL) at –10 ˚C. Ethyl chloroformate

(0.22 mL, 2.27 mmol) was added dropwise and stirred for 20 min. The reaction mixture was warmed to 0 ˚C and sodium borohydride (0.26 g, 6.80 mmol) was added followed by dropwise addition of methanol (8 mL) over 10 min. After 2 h, the reaction was neutralized with 1 M HCl solution and organic solvents were removed under reduced pressure. The remaining aqueous phase was extracted with ethyl acetate (2 × 30 mL) and the combined organic phase was washed with 1 M HCl solution (30 mL), water (30 mL), aqueous $NaHCO_3$ solution (30 mL), and water (30 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Product was purified by silica gel chromatography to give *N-t*-butly carbamate-L-tert-leucinol **104** as a white solid (0.35 g, 71 %).

Data for **104**:

m. p. 100 - 102 ˚C (Lit m. p. 103 – 104 ˚C).

δ_H (400 MHz, $CDCl_3$): 4.66 (1H, d, *J* 5.8, NH), 3.85 (1H, d, *J* 3.8, H9), 3.50 (1H, m, H8), 3.45 (1H, m, H8), 1.46 (9H, s, CH_3(Boc)), 0.94 (9H, s, $C(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 157.2 (CONH), 79.6 (C(Boc)), 63.2 (C8), 61.0 (C9), 33.6 (C10), 28.4 (CH_3(Boc)), 26.8 ($C(CH_3)_3$).

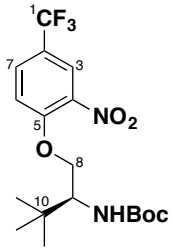
ν_{max} (thin film): 3355 (OH), 1681 (CONH).

HRMS (ESI +ve) found: 240.1569 [$(M+Na)^+$], $C_{11}H_{23}NNaO_3$ requires: 240.1570.

$[\alpha]_D^{25}$: -9.6° (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -5.5° (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[173]

(*S*)-*tert*-Butyl(3,3-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenoxy)butan-2-yl)carbamate 105



Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 8.80 mL, 4.00 mmol) was added dropwise over 1 h to a stirring solution of *N-t*-butly carbamate-L-tert-leucinol **104** (0.434 g, 2.00 mmol) and

4-fluoro-3-nitrobenzotrifluoride (0.840 mL, 6.00 mmol) in THF (15 mL). The solution was warmed to room temperature over 1 h and then diluted with dichloromethane (30 mL) and washed with aqueous ammonium chloride solution (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel chromatography yielded **105** as a yellow solid (0.601 g, 74 %).

Data for **105**:

m. p. 112 - 114 °C.

δ_H (400 MHz, $CDCl_3$): 8.16 (1H, d, *J* 1.3, H3), 7.80 (1H, dd, *J* 8.7, 1.6, H7), 7.21 (1H, d, *J* 8.8, H6), 5.05 (1H, d, *J* 9.9, NH), 4.34 (1H, dd, *J* 9.9, 4.3, H8), 4.24 (1H, dd, *J* 9.9, 4.3, H8), 3.83 (1H, dt, *J* 9.9, 3.8, H9), 1.44 (9H, s, CH_3(Boc)), 1.02 (9H, s, $C(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 155.8 (C=O), 154.5 (C5), 139.2 (C4), 131.1 (q, $J_{C\text{-}F}$ 3.2, C7), 124.3 (q, $J_{C\text{-}F}$ 270.0, C1), 123.6 (q, $J_{C\text{-}F}$ 3.2, C3), 123.1 (q, *J* 35.2, C2), 114.7 (C6), 79.6 (C(Boc)), 69.6 (C8), 56.8 (C9), 34.4 (C10), 28.4 (CH_3(Boc)), 27.1 ($C(CH_3)_3$).

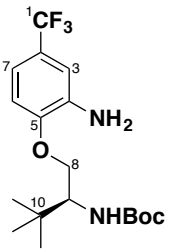
ν_{max} (thin film): 1697 (CONH), 1542 (NO_2).

HRMS (ESI +ve) found: 429.1607 [$(M+Na)^+$], $C_{18}H_{25}F_3N_2NaO_5$ requires: 429.1608.

$[\alpha]_D^{25}$: -10.2° (*c* 0.6 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -5.4° (*c* 0.3 in $CHCl_3$)).

This data is in accordance with the literature.[75]

(*S*)-*tert*-Butyl(1-(2-amino-4-(trifluoromethyl)phenoxy)-3,3-dimethylbutan-2-yl)carbamate 106



Starting material **105** (0.45 g, 1.11 mmol), ammonium formate (0.49 g, 7.79 mmol) and palladium (10 wt.% on carbon, 0.045 g) were dissolved in methanol (12.2 mL) and ethyl acetate (1.4 mL) and heated to 50 °C. After 2 h the reaction was cooled to room temperature and filtered through a pad of Celite® and the solids were washed through with methanol (50 mL). The solvent was removed *in vacuo* and the residue re-dissolved in dichloromethane (30 mL) and washed with brine (30 mL),

dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product **106** (0.41 g, 97 %) was isolated as a pale yellow solid and was used without further purification.

Data for **106**:

m. p. 96 - 97 °C.

δ_H (400 MHz, $CDCl_3$): 6.97 (1H, d, *J* 8.3, H7), 6.91 (1H, br. s, H3), 6.75 (1H, d, *J* 8.1, H6), 4.68 (1H, d, *J* 9.1, NHBoc), 4.21 (1H, m, H8), 3.98 (2H, br. s, NH_2), 3.87 – 3.95 (2H, m, H8 and H9), 1.45 (9H, s, CH_3(Boc)), 1.03 (9H, s, CH_3).

δ_C (101 MHz, $CDCl_3$): 156.3 (C=O), 148.5 (C5), 136.8 (C4), 124.5 (q, $J_{C\text{-}F}$ 269.5, C1), 123.5 (q, $J_{C\text{-}F}$ 31.9, C2), 115.0 (q, $J_{C\text{-}F}$ 3.2, C7), 110.9 (q, $J_{C\text{-}F}$ 3.2, C3), 110.3 (C6), 79.4 (C(Boc)), 68.7 (C8), 58.0 (C9), 33.6 (C10), 28.4 (CH_3(Boc)), 26.9 ($C(CH_3)_3$).

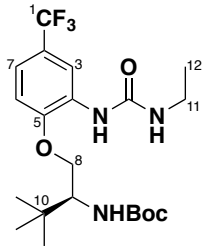
ν_{max} (thin film): 1697 (C=O), 1628 (N-H).

HRMS (ESI +ve) found: 399.1866 [$(M+Na)^+$], $C_{18}H_{27}F_3N_2NaO_3$ requires: 399.1866.

$[\alpha]_D^{20}$: -16.0° (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -14.5° (*c* 0.0 in $CHCl_3$)).

This data is in accordanve with the literature.[75]

(*S*)-*tert*-Butyl (1-(2-(3-ethylureido)-4-(trifluoromethyl)phenoxy)-3,3-dimethylbutan-2-yl) carbamate 107



Aniline **106** (0.41 g, 1.09 mmol) was dissolved in a minimum amount of ethyl isocyanate (1.0 mL) and stirred for 18 h at room temperature. The reaction was diluted with dichloromethane (10 mL) and washed with pH 7 buffer solution (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **107** as a white solid (0.486 g, quant.).

Data for **107**:

m. p. 83 - 84 ˚C (Lit m. p. 75 – 76 ˚C).

δ_H (500 MHz, $CDCl_3$): 8.63 (1H, d, *J* 1.9, H3), 8.09 (1H, s, ArNH), 7.11 (1H, dd, *J* 8.2, 1.6, H7), 6.77 (1H, d, *J* 8.2, H6), 5.51 (1H, t, *J* 5.0, EtNH), 4.76 (1H, d, *J* 10.1, NHBoc), 4.15 (1H, dd, *J* 8.8, 2.5, H8), 3.97 (1H, t, *J* 9.6 H8), 3.83 (1H, td, *J* 10.3, 2.8, H9), 3.32 (2H, m, CH_2(11)), 1.47 (9H, s, CH_3(Boc)), 1.19 (3H, t, *J* 7.3, CH_3(12)), 1.04 (9H, s, $C(CH_3)_3$).

δ_C (126 MHz, $CDCl_3$): 157.6 (carbamate C=O), 155.3 (urea C=O), 148.8 (C5), 131.1 (C4), 124.4 (q, $J_{C\text{-}F}$ 271.8, C1), 124.0 (q, $J_{C\text{-}F}$ 32.4, C2), 117.6 (q, $J_{C\text{-}F}$ 4.3, C7), 114.3 (q, *J* 3.9, C3), 110.7 (C6) 80.1 (C(Boc)), 70.7 (C8), 59.6 (C9), 34.6 (C11), 32.5 (C10), 28.5 (CH_3(Boc)), 26.8 ($C(CH_3)_3$), 15.4 (C12).

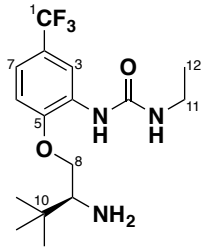
ν_{max} (thin film): 1678 (C=O), 1558 (Ar C=C).

HRMS (ESI +ve) found: 470.2246 [$(M+Na)^+$], $C_{21}H_{32}F_3N_3NaO_4$ requires: 470.2237.

$[\alpha]_D^{25}$: 75.1˚ (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: 110˚ (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[74]

(*S*)-1-(2-(2-Amino-3,3-dimethylbutoxy)-5-(trifluoromethyl)phenyl)-3-ethylurea 108



Protected amine **107** (0.40 g, 0.89 mmol) was dissolved in dichloromethane (1 mL) and TFA (1 mL) at 0˚C. After 2 h, solvent was removed *in vacuo*. The residue was redissolved in dichloromethane (25 mL) and washed with saturated $NaHCO_3$ solution (20 mL) and back extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Product **108** was isolated as pale yellow solid (0.31 g, quant.) and used without further purification.

Data for **108**:

m. p. 124 - 127 ˚C (Lit m p. 131 – 132 ˚C).

δ_H (500 MHz, $CDCl_3$): 8.53 (1H, d, *J* 1.9, H3), 8.03 (1H, s, ArNH), 7.11 (1H, dd, *J* 8.4, 1.4, H7), 6.82 (1H, d, *J* 8.2, H6), 5.54 (1H, br. s, EtNH), 4.24 (1H, dd, *J* 9.6, 3.0, H8), 3.76 (1H, t, *J* 9.8 H8), 3.29 (2H, m, CH_2(11)), 2.99 (1H, dd, *J* 9.8, 2.8, H9), 2.50 (2H, br. s, NH_2), 1.17 (3H, t, *J* 7.3, CH_3(12)), 1.02 (9H, s, $C(CH_3)_3$).

δ_C (126 MHz, $CDCl_3$): 155.5 (C=O), 148.8 (C5), 130.6 (C4), 124.2 (q, $J_{C\text{-}F}$ 271.8, C1), 124.1 (q, $J_{C\text{-}F}$ 32.5, C2), 118.4 (q, $J_{C\text{-}F}$ 4.3, C7), 115.7 (q, *J* 3.8, C3), 112.0 (C6), 70.7 (C8), 59.4 (C9), 34.9 (C11), 32.4 (C10), 26.3 ($C(CH_3)_3$) 15.3 (C12).

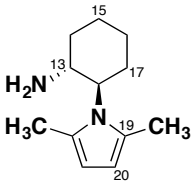
ν_{max} (thin film): 3356 (N-H), 1665 (C=O).

HRMS (ESI +ve) found: 348.1896 [$(M+H)^+$], $C_{16}H_{25}F_3N_3O_2$ requires: 348.1893.

$[\alpha]_D^{20}$: 25.1° (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: 28.3° (*c* 1.1 in $CHCl_3$)).

This data is in accordance with the literature.[74]

(1*R*,2*R*)-2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)cyclohexanamine 110



Prepared according to General Procedure A on a 1.32 mmol scale. Product **110** was isolated as a yellow oil (0.23 g, 91%).

Data for **110**:

δ_H (400 MHz, $CDCl_3$): 5.79 (1H, br. s, H20), 5.75 (1H, br. s, H20), 3.61 (1H, td, *J* 10.8, 4.9, H18), 3.27 (1H, td, *J* 10.5, 4.0, H13), 2.37 (3H, br. s, CH_3), 2.24 (3H, br. s, CH_3), 2.05 (1H, m, CH_2), 1.76 – 1.96 (4H, m, CH_2 and NH_2), 1.31 – 1.46 (3H, m, CH_2), 1.16 – 1.28 (2H, m, CH_2).

δ_C (101 MHz, $CDCl_3$): 129.8 (C19), 126.8 (C19), 107.9 (C20), 105.3 (C20), 63.7 (C18), 53.0 (C13), 35.4 (CH_2), 31.3 (CH_2), 26.3 (CH_2), 25.1 (CH_2), 15.2 (CH_3), 13.7 (CH_3).

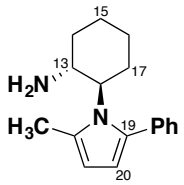
ν_{max} (thin film): 2932 (C-H), 1607 & 1559 (Ar C=C).

HRMS (ESI +ve) found: 193.1700 [$(M+H)^+$], $C_{12}H_{21}N_2$ requires: 193.1699.

$[\alpha]_D^{20}$: -44.3° (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -24.6° (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[74]

(1*R*,2*R*)-2-(2-Methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexanamine 111



Prepared according to General Procedure A on a 1.00 mmol scale. Product **111** was isolated as a brown oil (0.20 g, 78 %).

Data for **111**:

δ_H (400 MHz, $CDCl_3$): 7.25 – 7.43 (5H, m, ArH), 6.07 (1H, br. s, H20), 6.00 (1H, br. s, H20), 3.75 – 3.84 (1H, m, H18), 3.23 (1H, t, *J* 8.8, H13), 2.48 (1H, br. s, CH_3), 1.94 – 2.08 (3H, m, CH_2), 1.68 – 1.87 (2H, m, CH_2), 1.18 – 1.37 (2H, m, CH_2), 0.93 – 1.05 (3H, m, CH_2).

δ_C (101 MHz, $CDCl_3$): 137.1, 134.6, 129.6, 129.0, 128.6, 128.3, 128.1, 126.7 (8 × ArC), 109.6 (C20), 107.9 (C20), 64.5 (C18), 53.3 (C13), 35.3 (CH_2), 31.8 (CH_2), 26.0 (CH_2), 25.1 (CH_2), 15.4 (CH_3).

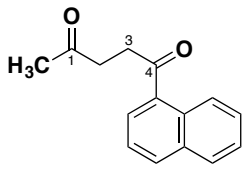
ν_{max} (thin film): 2934 & 2857 (C-H), 1601 (N-H), 1513 (Ar C=C).

HRMS (ESI +ve) found: 255.1857 [$(M+H)^+$], $C_{17}H_{23}N_2$ requires: 255.1856.

$[\alpha]_D^{20}$: -69.1° (*c* 1.2 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -80.2° (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[74]

1-(Naphthalen-1-yl)pentane-1,4-dione 117



n-Butyl lithium (0.53 mL, 2.5 M in hexane, 1.32 mmol) was added dropwise to a solution of diisopropylamine (0.19 mL, 1.32 mmol) in THF (6.0 mL) at 0 ˚C and stirred for 20 min. The solution was cooled to –78 ˚C and 1-acetonapthone (0.18 mL, 1.20 mmol) was added slowly and stirred for a further 20 min. The solution was allowed to warm to 0 ˚C, before cooling to –78 ˚C and adding chloroacetone (0.11 mL, 1.32 mmol). After 20 min, the solution was warmed over an hour to

room temperature. The reaction was diluted with brine (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to afford 1,4-diketone **117** as a colourless oil (0.23 g, 83 %).

Data for **117**:

δ_H (400 MHz, $CDCl_3$): 8.58 (1H, d, *J* 8.6, ArH), 7.93 – 7.99 (2H, m, ArH), 7.87 (1H, d, *J* 7.8, ArH), 7.47 – 7.61 (3H, m, ArH), 3.32 (2H, dd, *J* 6.6, 5.8 CH_2(3)), 2.95 (2H, t, *J* 6.2, CH_2(2)), 2.29 (3H, s, CH_3).

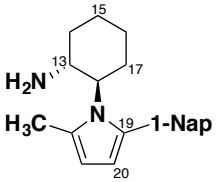
δ_C (101 MHz, $CDCl_3$): 207.3 (C=O), 202.8 (C=O), 135.8, 133.9, 132.6, 130.1, 128.4, 127.9, 127.5, 126.4, 125.8, 124.4 (10 × Ar C), 37.5 (C2), 35.8 (C3), 30.1 (CH_3).

ν_{max} (thin film): 1715 & 1680 (C=O).

HRMS (ESI +ve) found: 249.0883 [$(M+Na)^+$], $C_{15}H_{14}NaO_2$ requires: 249.0886.

This data is in accordance with the literature.[74]

(1*R*,2*R*)-2-(2-Methyl-5-(naphthalen-1-yl)-1*H*-pyrrol-1-yl)cyclohexanamine 112



Prepared according to General Procedure A on a 0.67 mmol scale. Product **112** was isolated as a brown oil (0.17 g, 85%).

Data for **112**:

δ_H (500 MHz, $CDCl_3$): 7.85 – 7.91 (3H, m, ArH), 7.41 – 7.50 (4H, m, ArH), 6.15 (1H, br. s, H20), 6.08 (1H, br. s, H20), 3.36 (1H, m, H18), 3.21 (1H, m, H13), 2.50 (3H, br. s, CH_3), 1.95 – 2.02 (2H, m, CH_2), 1.49 – 1.66 (3H, m, CH_2 & NH_2), 1.16 – 1.34 (4H, m, CH_2), 0.71 (1H, m, CH_2).

δ_C (126 MHz, $CDCl_3$): *major rotamer* - 134.2, 133.7, 133.4, 133.0, 132.6, 129.6, 128.6, 128.2, 128.0, 126.4, 125.9, 124.9 (12 × ArC), 109.5 (C20), 109.4 (C20), 64.9 (C18), 53.6 (C13), 35.2 (CH_2), 32.3 (CH_2), 25.9 (CH_2), 25.1 (CH_2), 15.3 (CH_3).

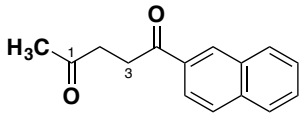
ν_{max} (thin film): 3055 (N-H), 2934 & 2857 (C-H), 1592 (Ar C=C).

HRMS (ESI +ve) found: 305.2013 [$(M+H)^+$], $C_{21}H_{25}N_2$ requires: 305.2012.

$[\alpha]_D^{20}$: -22.5° (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -26.0° (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[74]

1-(Naphthalen-2-yl)pentane-1,4-dione 118



n-Butyl lithium (0.58 mL, 2.5 M in hexane, 1.45 mmol) was added dropwise to a solution of diisopropylamine (0.21 mL, 1.45 mmol) in THF (6.0 mL) at 0 ˚C and stirred for 20 min. The solution was cooled to –78 ˚C and 2-acetonapthone (0.20 mL, 1.32 mmol) was added slowly and stirred for a further 20 min. The solution was allowed to warm to 0 ˚C, before cooling to –78 ˚C and adding chloroacetone (0.12 mL, 1.45 mmol). After 20 min, the solution was warmed over an hour to room temperature. The reaction was diluted with brine (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to afford 1,4-diketone **118** as a white solid (0.23 g, 69 %).

Data for **118**:

m. p. 73 - 74 ˚C (Lit m. p. 79 – 80 ˚C).

δ_H (400 MHz, $CDCl_3$): 8.53 (1H, s, ArH), 8.04 (1H, dd, *J* 8.6, 1.5, ArH), 7.97 (1H, d, *J* 7.8, ArH), 7.86 – 7.92 (2H, m, ArH), 7.54 – 7.63 (2H, m, ArH), 3.43 (2H, t, *J* 6.3, CH_2(3)), 2.96 (2H, t, *J* 6.4, CH_2(2)), 2.30 (3H, s, CH_3).

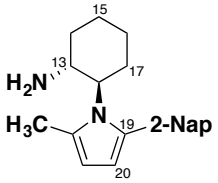
δ_C (101 MHz, $CDCl_3$): 207.4 (C=O), 198.5 (C=O), 135.6, 134.0, 132.5, 129.8, 129.6, 128.5, 128.4, 127.8, 126.8, 123.8 (10 × ArC), 37.2 (C2), 32.5 (C3), 30.1 (CH_3).

ν_{max} (thin film): 1715 & 1680 (C=O).

HRMS (ESI +ve) found: 249.0883 [$(M+Na)^+$], $C_{15}H_{14}NaO_2$ requires: 249.0886.

This data is in accordance with the literature.[74]

(1*R*,2*R*)-2-(2-Methyl-5-(naphthalen-2-yl)-1*H*-pyrrol-1-yl)cyclohexanamine 113



Prepared according to General Procedure A on a 0.62 mmol scale. Product **113** was isolated as a brown oil (0.16 g, 84 %).

Data for **113**:

δ_H (500 MHz, $CDCl_3$): 7.83 – 7.89 (4H, m, ArH), 7.46 – 7.53 (3H, m, ArH), 6.16 (1H, br. s, H20), 6.03 (1H, br. s, H20), 3.88 (1H, m, C18), 3.24 (1H, m, C13), 2.50 (3H, br. s, CH_3), 2.04 – 2.16 (2H, m, CH_2), 1.97 (1H, m, CH_2), 1.73 – 1.88 (3H, m, CH_2 & NH_2), 1.18 – 1.38 (3H, m, CH_2), 0.95 (1H, m, CH_2).

δ_C (126 MHz, $CDCl_3$): 137.1, 133.4, 132.2, 131.9, 129.3, 128.0, 127.8 (× 3), 127.6, 126.2, 125.8 (12 × ArC), 109.9 (C20), 108.4 (C20), 64.5 (C18), 53.4 (C13), 35.1 (CH_2), 31.9 (CH_2), 26.0 (CH_2), 25.1 (CH_2), 15.4 (CH_3).

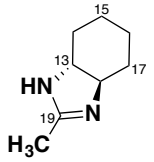
ν_{max} (thin film): 2934 (C-H), 1601 (Ar C=C).

HRMS (ESI +ve) found: 305.2014 [$(M+H)^+$], $C_{21}H_{25}N_2$ requires: 305.2012.

$[\alpha]_D^{25}$: -36.0° (*c* 0.8 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: -56.0° (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[74]

(3a*R*,7a*R*)-2-Methyl-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*]imidazole 123



This compound was prepared according to a literature procedure.[94] Ethyl acetimidate hydrochloride (0.14 g, 1.14 mmol) was dissolved in ethanol (3.0 mL) and cooled to 0 °C. (*R*,*R*)-(–)-1,2-Diaminocyclohexane (0.13 g, 1.14 mmol) was added and the solution was stirred at room temperature for 8 h. 1 M Sodium hydroxide solution (10 mL) was added and the mixture extracted with 5% MeOH in dichloromethane (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 filtered and concentrated to afford **123** as a yellow oil (0.14 g, 78%).

Data for **123**:

δ_H (400 MHz, $CDCl_3$): 2.91 - 3.00 (2H, m, H13 and H18), 2.13 - 2.20 (2H, m, CH_2), 1.98 (3H, s, CH_3), 1.75 – 1.82 (2H, m, CH_2), 1.38 – 1.48 (2H, m, CH_2), 1.24 – 1.33 (2H, m, CH_2).

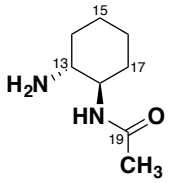
δ_c (101 MHz, $CDCl_3$): 165.6 (C19), 69.5 (C13 and C18), 30.7 (CH_2), 24.9 (CH_2), 16.2 (CH_3).

ν_{max} (thin film): 3275 (C-H), 1640 (C=N).

HRMS (ESI +ve) found: 139.1226 [$(M+H)^+$], $C_8H_{15}N_2$ requires: 139.1230.

This data is in accordance with the literature.[94]

***N*-((1*R*,2*R*)-2-Aminocyclohexyl)acetamide 119**



This compound was prepared according to a literature procedure.[94] Imidazole **123** (70 mg, 0.51 mmol) was dissolved in water (1.5 mL) and ethanol (1.5 mL) and heated under reflux at 80 °C for 16 h. Solvent was removed *in vacuo* to afford **119** as a light brown solid (69 mg, 87 %).

Data for **119**:

δ_H (400 MHz, $CDCl_3$): 6.09 (1H, d, *J* 8.3, CONH), 3.42 - 3.53 (1H, m, H18), 2.38 (1H, td, *J* 10.3, 3.9, H13), 1.90 - 2.05 (4H, m, CH_2), 1.97 (3H, s, CH_3), 1.64 – 1.71 (2H, m, CH_2), 1.03 – 1.34 (4H, m, CH_2 & NH_2).

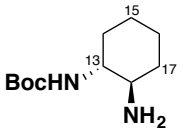
δ_C (101 MHz, $CDCl_3$): 170.5 (C=O), 55.8 (C18), 55.3 (C13), 35.2 (CH_2), 32.5 (CH_2), 25.0 (CH_2), 25.0 (CH_2), 23.5 (CH_3).

ν_{max} (thin film): 1637 (C=O),

HRMS (ESI +ve) found: 157.1332 [$(M+H)^+$], $C_8H_{17}N_2O$ requires: 157.1335.

This data is in accordance with the literature.[174]

tert-Butyl ((1*R*,2*R*)-2-aminocyclohexyl)carbamate 124



This compound was prepared according to a literature procedure.[175] (*R*,*R*)-(-)-1,2-Diaminocyclohexane (0.46 g, 4.0 mmol) were dissolved in dichloromethane (3.0 mL) and cooled to -78 ˚C. Di-*tert*-butyl dicarbonate (0.29 g, 1.4 mmol) dissolved in dichloromethane (3.0 mL) was added dropwise over 30 min. The reaction was warmed to room temperature and stirred for 16 h, during which time a precipitate formed. Water (3 mL) and dichloromethane (3 mL) were added to dissolve the precipitate and, after separation, the organic phase was concentrated *in vacuo*. The residue was redissolved in diethyl ether (15 mL) and water (15 mL) and the mixture was acidified with 1 M HCl solution to pH 5. The doubly-protected amine was removed by extraction with diethyl ether (3 × 15 mL). The aqueous phase was then basified with 1 M sodium hydroxide solution to pH 11 and extracted with EtOAc (6 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield **124** (0.15 g, 67% based on Boc_2O) as a pale yellow crystalline solid.

Data for **124**:

m. p. 98 - 100 ˚C (Lit m. p. 109 – 111 ˚C).

δ_H (400 MHz, d_6-DMSO): 6.63 (1H, d, *J* 7.1, NHBoc), 2.88 (1H, d, *J* 7.6 H13), 2.33 (1H, br. s, H18), 1.76 (2H, a-d, *J* 10.1, CH_2), 1.59 (2H, a-d, *J* 8.1, CH_2), 1.38 (9H, s, $C(CH_3)_3$), 0.96 – 1.24 (4H, m, CH_2).

δ_c (101 MHz, d_6-DMSO): 156.4 (C=O), 78.1 ($O\underline{C}(CH_3)_3$), 57.9 (C13), 54.6 (C18), 35.3 (CH_2), 33.0 (CH_2), 29.1 ($OC(\underline{C}H_3)_3$), 25.7 (CH_2), 25.6 (CH_2).

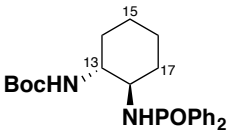
ν_{max} (thin film): 1688 (C=O).

HRMS (ESI +ve) found: 215.1763 [$(M+H)^+$], $C_{11}H_{23}N_2O_2$ requires: 215.1754.

$[\alpha]_D^{20}$: -33.4° (*c* 0.9 in $CHCl_3$) (Lit $[\alpha]_D^{20}$: -31.0° (*c* 0.5 in $CHCl_3$)).

This data is in accordance with the literature.[175]

tert-Butyl ((1*R*,2*R*)-2-((diphenylphosphoryl)amino)cyclohexyl)carbamate 278



This compound was prepared according to a literature procedure.[72] Amine **124** (0.12 g, 0.57 mmol) was dissolved in dichloromethane (4.4 mL) and cooled to – 30 ˚C. *N*,*N*-diisopropylethylamine (0.18 mL, 1.03 mmol) and diphenylphosphinic chloride (0.12 mL, 0.63 mmol) were added and the reaction was warmed to room temperature and stirred for 2.5 h. The reaction was diluted with dichloromethane (10 mL) and washed with 1M HCl solution (10 mL), saturated $NaHCO_3$ solution (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to yield **278** as an off-white solid (0.17 g, 73 %).

Data for **278**:

m. p. 159 - 161 ˚C.

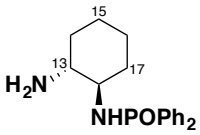
δ_H (500 MHz, $CDCl_3$): 7.87 - 7.92 (2H, m, ArH), 7.78 (2H, dd, *J* 12.0, 7.3, ArH), 7.34 - 7.49 (6H, m, ArH), 5.42 (1H, d, *J* 7.3, $NHPOPh_2$), 3.26 - 3.35 (2H, m, H18 and NHBoc), 2.75 - 2.85 (1H, m, H13), 2.00 - 2.15 (2H, m, CH_2), 1.57 - 1.65 (2H, m, CH_2), 1.45 (9H, s, $C(CH_3)_3$), 1.18 – 1.34 (2H, m, CH_2), 1.02 - 1.14 (2H, m, CH_2).

δ_C (126 MHz, $CDCl_3$): 156.6 (C=O), 133.1 (d, $J_{C\text{-}P}$ 130.7, ArC), 133.0 (d, $J_{C\text{-}P}$ 126.8, ArC), 132.2 (ArCH), 132.2 (ArCH), 131.6 - 131.8 (m, ArCH), 128.4 (d, $J_{C\text{-}P}$ 2.9, ArCH) 128.3 (d, $J_{C\text{-}P}$ 2.9, ArCH), 79.1 ($O\underline{C}(CH_3)_3$), 55.7 (d, *J* 5.7, C18), 55.4 (C13), 36.1 (d, *J* 2.9, CH_2), 33.1 (CH_2), 28.5 ($OC(\underline{C}H_3)_3$), 25.0 (CH_2), 24.8 (CH_2).

ν_{max} (thin film): 1704 (C=O), 1174 (P=O).

HRMS (ESI +ve) found: 437.1960, $C_{23}H_{31}N_2NaO_3P$ requires: 437.1965.

((1*R*,2*R*)-2-Aminocyclohexyl)diphenylphosphine oxide 120



This compound was prepared following a literature procedure.[72] Trifluoroacetic acid (0.57 mL, 7.71 mmol) was added to a stirring solution of phosphinamide **278** (0.16 g, 0.39 mmol) and dichloromethane (4.5 mL) at room temperature. After 30 min the reaction was cooled to 0 ˚C and triethylamine (1.5 mL) was added carefully. The reaction was diluted with dichloromethane (20 mL) and washed with water (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography to yield **120** as a pale yellow oil (0.12 g, quant.).

Data for **120**:

δ_H (400 MHz, $CDCl_3$): 7.85 (4H, td, *J* 12.1, 7.9, ArH), 7.34 - 7.50 (6H, m, ArH), 5.14 (1H, br. s, NH_2), 4.23 (1H, t, *J* 8.6, $NHPOPh_2$), 2.70 - 2.77 (2H, m, H13 and H18), 1.93 - 2.03 (2H, m, CH_2), 1.60 (2H, d, *J* 8.8, CH_2), 1.01 – 1.38 (4H, m, CH_2).

δ_C (101 MHz, $CDCl_3$): 132.3 (d, *J* 129.5, ArC), 132.1 (d, *J* 132.6, ArC), 132.4, 132.3, 131.9, 131.8, 131.7, 128.6, 128.4 (ArCH), 56.8 (C13), 56.1 (d, *J* 3.2, C18), 35.0 (d, *J* 4.8, CH_2), 33.1 (CH_2), 25.1 (CH_2), 24.6 (CH_2).

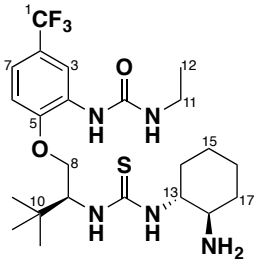
ν_{max} (thin film): 2935 (N-H), 1175 (P=O).

HRMS (ESI +ve) found: 315.1624 [$(M+H)^+$], $C_{18}H_{24}N_2OP$ requires: 315.1621.

$[\alpha]_D^{20}$: 7.2˚ (*c* 0.5 in $CHCl_3$).

This data is in accordance with the literature.[72]

1-(2-((*S*)-2-(3-((1*R*,2*R*)-2-Aminocyclohexyl)thioureido)-3,3-dimethylbutoxy)-5-(trifluoromethyl)phenyl)-3-ethylurea 125



Prepared according to General Procedure B. Amine **108** (69 mg, 0.20 mmol) and *R*,*R*)-(–)-1,2-diaminocyclohexane (25 mg, 0.20 mmol) were reacted to give thiourea **125** as a pale yellow crystalline solid (82 mg, 82 %).

Data for **125**:

m. p. 170 - 173 ˚C.

δ_H (400 MHz, $CDCl_3$): 9.34 (1H, br. s, NH), 8.50 (1H, br. s, H3), 8.00 (1H, s, ArNH), 7.11 (1H, d, *J* 8.1, H7), 6.77 (1H, d, *J* 8.3, H6), 6.59 (1H, br. s, EtNH), 5.82 (1H, br. s, NH), 4.92 (1H, br. s, H9), 4.35 (1H, d, *J* 5.8, H8), 3.85 (1H, br. s, H8), 3.24 (2H, a-quin, *J* 6.7, CH_2(11)), 2.46 (2H, br. s, H13 and H18), 1.73 - 1.90 (2H, m, CH_2), 1.61 (2H, br. s, CH_2), 1.13 (3H, t, *J* 7.2, CH_3(12)), 1.05 (9H, s, $C(CH_3)_3$), 0.85 – 1.25 (6H, m, CH_2 and NH_2).

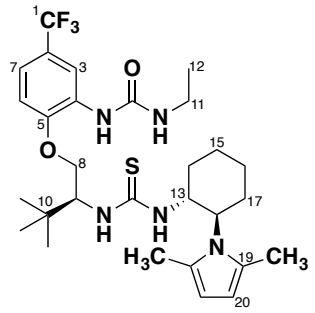
δ_C (101 MHz, $CDCl_3$): 184.3 (C=S), 155.8 (C=O), 149.0 (C5), 130.1 (C4), 126.6 (q, *J* 271.7, C1), 124.6 (q, *J* 32.0, C2), 118.1 (br. m, C7), 115.2 (br. m, C3), 109.8 (C6), 69.4 (br. C8), 64.0 (br. C9 and C13), 55.9 (br. C18), 34.7 (C11), 34.1 (CH_2), 33.4 ($\underline{C}(CH_3)_3$), 32.2 (CH_2), 27.1 ($C(\underline{C}H_3)_3$), 24.6 (CH_2), 24.4 (CH_2), 15.5 (C12).

ν_{max} (thin film): 1670 (C=O), 1555 (C=S).

HRMS (ESI +ve) found: 504.2613 [$(M+H)^+$], $C_{23}H_{37}F_3N_5O_2S$ requires: 504.2615.

$[\alpha]_D^{20}$: -18.6˚ (*c* 0.9 in $CHCl_3$).

1-(2-((*S*)-2-(3-((1*R*,2*R*)-2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)cyclohexyl)thioureido)-3,3-dimethylbutoxy)-5-(trifluoromethyl)phenyl)-3-ethylurea 85



Prepared according to General Procedure B. Amine **108** (83 mg, 0.24 mmol) and cyclohexylamine **110** (46 mg, 0.24 mmol) were reacted to give thiourea **85** as a pale crystalline solid (110 mg, 60 %).

Data for **85**:

m. p. 109 - 111 ˚C (Lit m. p. 109 – 110 ˚C).

δ_H (500 MHz, $CDCl_3$): 8.62 (1H, br. s, H3), 7.77 (1H, br. s, ArNH), 7.10 (1H, dd, *J* 8.4, 1.6, H7), 6.78 (1H, br. s, H6), 6.25 (1H, br. s, NH), 6.02 (1H, br. s, NH), 5.76 (1H, d, *J* 6.8, H20), 5.70 (1H, d, *J* 6.8, H20), 5.69 (1H, br. s, NH), 4.99 (1H, m, H9), 4.29 (1H, d, *J* 6.4, H18), 4.19 (1H, br. s, H8), 3.81 (1H, m, H13), 3.67 (1H, br. s, H8), 3.26 (2H, q, *J* 7.2, CH_2(11)), 2.57 (1H, br. m, CH_2), 2.30 (3H, s, CH_3), 2.18 (3H, s, CH_3), 1.93 (1H, m, CH_2), 1.86 (1H, m, CH_2), 1.79 (1H, m, CH_2), 1.35 - 1.41 (2H, m, CH_2), 1.24 (3H, t, *J* 7.2, CH_3(12)), 1.21 (1H, m, CH_2), 0.93 (9H, s, $C(CH_3)_3$), 0.85 (1H, m, CH_2).

δ_C (126 MHz, $CDCl_3$): 183.5 (C=S), 155.4 (C=O), 148.7 (C5), 135.9 (C19), 134.8 (C19), 130.4 (C4), 124.3 (q, *J* 270.1, C1), 123.2 (br. m, C2), 118.0 (br. m, C7), 114.6 (br. m, C3), 109.3 (C6), 108.6 (C20), 106.2 (C20), 69.2 (C8), 62.5 (C9), 59.5 (C13), 56.9 (C18), 34.8 (C11), 34.1 (CH_2), 33.5 (C10), 32.1 (CH_2), 26.6 ($C(\underline{C}H_3)_3$), 25.8 (CH_2), 24.6 (CH_2), 15.6 (C12), 14.9 (CH_3), 13.3 (CH_3).

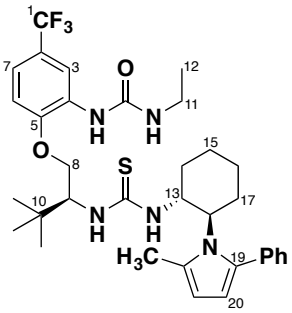
ν_{max} (thin film): 1663 (C=O), 1548 (C=S).

HRMS (ESI +ve) found: 604.2909 [$(M+Na)^+$], $C_{29}H_{42}F_3N_5NaO_2S$ requires: 604.2904.

$[\alpha]_D^{25}$: 5.0˚ (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: 5.2˚ (*c* 1.0 in $CHCl_3$)).

This data is in accordance with the literature.[74]

1-(2-((*S*)-3,3-Dimethyl-2-(3-((1*R*,2*R*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thioureido)butoxy)-5-(trifluoromethyl)phenyl)-3-ethylurea 70



Prepared according to General Procedure B. Amine **108** (98 mg, 0.28 mmol) and cyclohexylamine **111** (72 mg, 0.28 mmol) were reacted to give thiourea **70** as a pale crystalline solid (109 mg, 60 %).

Data for **70**:

m. p. 123 – 125 ˚C (Lit m. p. 121 – 122 ˚C).

δ_H (500 MHz, $CDCl_3$): 8.64 (1H, s, H3), 7.36 – 7.41 (2H, m, ArH), 7.25 – 7.34 (3H, m, ArH), 7.12 (1H, d, *J* 8.2, H7), 6.78 (1H, br. s, H6), 5.97 (1H, br. s, H20), 5.79 (1H, br. s, H20), 5.59 (1H, br. s, NH), 5.45 (1H, br. s, NH), 4.27 – 4.34 (2H, m, CH_2(8)), 4.06 (1H, m, H18), 3.65 (1H, br. s, H9), 3.19 – 3.30 (2H, m, CH_2(11)), 2.44 (3H, br. s, CH_3), 2.33 (1H, br. s, CH_2), 2.16 – 2.21 (3H, br. m, H13 & CH_2), 1.88 (1H, m, CH_2), 1.73 (1H, a-d, *J* 12.3, CH_2), 1.15 (3H, t, *J* 7.3, CH_3(12)), 1.02 – 1.10 (2H, m, CH_2), 0.98 (9H, s, $C(CH_3)_3$), 0.87 – 0.94 (1H, m, CH_2).

δ_C (126 MHz, $CDCl_3$): 182.9 (C=S), 155.6 (C=O), 148.4 (C5), 134.9 (ArC), 134.5 (ArC), 133.8 (ArC), 130.8 (C4), 129.0 (ArCH), 128.8 (ArCH), 127.2 (ArCH), 124.4 (q, $J_{C\text{-}F}$ 274.0, C1), 123.8 (q, $J_{C\text{-}F}$ 33.4, C2), 117.8 (br. m, C7), 114.9 (br. m, C3), 110.6 (C20), 109.9 (C6), 108.8 (C20), 69.2 (C8), 59.9 (C18), 59.4 (C9), 34.8 (C11), 33.6 (CH_2), 32.3 (C10), 32.6 (CH_2), 30.9 (C13), 25.7 ($C(CH_3)_3$), 25.5 (CH_2), 24.5 (CH_2), 15.6 (C12), 15.2 (CH_3).

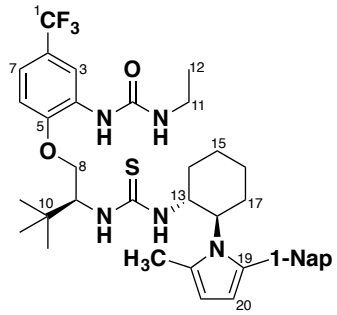
ν_{max} (thin film): 1673 (C=O), 1556 (C=S).

HRMS (ESI +ve) found: 644.3240 [$(M+H)^+$], $C_{34}H_{45}F_3N_5O_2S$ requires: 644.3241.

$[\alpha]_D^{25}$: 9.0˚ (*c* 0.9 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: 5.3˚ (*c* 0.8 in $CHCl_3$)).

This data is in accordance with the literature.[74]

1-(2-((*S*)-3,3-Dimethyl-2-(3-((1*R*,2*R*)-2-(2-methyl-5-(naphthalen-1-yl)-1*H*-pyrrol-1-yl)cyclohexyl)thioureido)butoxy)-5-(trifluoromethyl)phenyl)-3-ethylurea 126



Prepared according to General Procedure B. Amine **108** (92 mg, 0.27 mmol) and cyclohexylamine **112** (80 mg, 0.27 mmol) were reacted to give thiourea **126** as a pale crystalline solid (128 mg, 67 %).

Data for **126**:

m. p. 125 – 127 ˚C (Lit m. p. 126 – 127 ˚C).

δ_H (500 MHz, $CDCl_3$): 8.65 (1H, d, *J* 8.8, H3), 7.88 – 7.98 (3H, m, ArH), 7.43 – 7.67 (4H, m, ArH), 7.14 (1H, d, *J* 7.3, H7), 6.80 (1H, br. s, H6), 6.06 (1H, a-t, *J* 5.3, NH), (*two rotamers generated two peaks for the majority of subsequent resonances*) 6.01, 5.95 & 5.88 (2H, br. s, H20), 5.70, 5.47, 5.36 & 5.01 (2H, br. s, NH), 4.85 & 4.49 (1H, m, H18), 4.37 & 4.31 (1H, m, CH_2(8)), 3.87 – 3.97 (1H, m, CH_2(8)), 3.73 & 3.40 (1H, m, H9), 3.16 – 3.26 (2H, m, CH_2(11)), 2.50 (3H, br. s, CH_3), 2.10 – 2.20 (3H, m, CH_2 & H13), 1.84 (1H, a-d, *J* 13.2, CH_2), 1.51 – 1.69 (3H, m, CH_2), 1.14 (3H, t, *J* 7.3, CH_3(12)), 1.04 & 0.98 (9H, s, $C(CH_3)_3$) 0.63 – 0.75 (2H, m, CH_2).

δ_C (126 MHz, $CDCl_3$): 182.8 (C=S), 155.2 (C=O), 148.5 (C5), 134.2, 133.7, 133.6, 133.5, 133.4, 132.0, 131.4, 129.5, 129.1, 129.0, 128.9, 128.8, 128.3, 128.1, 127.6, 126.7, 126.5, 126.3, 126.0, 125.7, 125.6, 125.5, 125.4, 125.3 (*two rotamers generated 24 peaks from 12 ×* ArC), 130.7 (C4), 123.3 (m, C2), 124.4 (q, $J_{C\text{-}F}$ 274.0, C1), 117.7 (br. m, C7), 115.0 (br. m, C3), 110.4 (C20), 109.4 (C6), 109.4 (C20), (*two rotamers generated two peaks for the majority of subsequent resonances*) 70.7 & 69.2 (C8), 60.3 (br. C18), 59.7 (br. C13), 60.0 & 59.7 (C9), 34.7 (C11), 33.7 & 33.3 (CH_2), 33.3 & 33.2 (C10), 32.1 & 31.4 (CH_2), 26.8 & 26.7 ($C(CH_3)_3$), 26.9 & 25.5 (CH_2), 25.3 & 24.4 (CH_2), 15.4 (C12), 15.6 & 15.2 (CH_3).

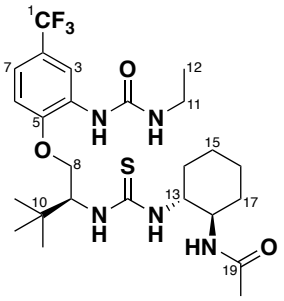
ν_{max} (thin film): 1667 (C=O), 1552 (C=S).

HRMS (ESI +ve) found: 694.3240 [$(M+H)^+$], $C_{38}H_{47}F_3N_5O_2S$ requires: 694.3397.

$[\alpha]_D^{20}$: 48.4° (*c* 1.0 in $CHCl_3$) (Lit $[\alpha]_D^{25}$: 57.2° (*c* 1.0 in $CHCl_3$)).

This data was in accordance with the literature.[74]

_N_-((1_R_,2_R_)-2-(3-((_S_)-1-(2-(3-Ethylureido)-4-(trifluoromethyl)phenoxy)-3,3-dimethylbutan-2-yl)thioureido)cyclohexyl)acetamide 127



Prepared according to General Procedure B. Amine **108** (101 mg, 0.29 mmol) and cyclohexylamine **119** (45 mg, 0.29 mmol) were reacted to give thiourea **127** as a pale crystalline solid (80 mg, 51 %).

Data for **127**:

m. p. 149 - 151 °C.

δ_H (500 MHz, $CDCl_3$): 8.53 (1H, br. s, H3), 8.13 (1H, br. s, ArNH), 7.36 (1H, d, *J* 5.7, NH), 7.09 (1H, d, *J* 7.3, H7), 6.95 (1H, d, *J* 9.5, NH), 6.68 (1H, d, *J* 7.9, H6), 6.41 (1H, br. s, EtNH), 6.08 (1H, d, *J* 8.8, NH), 5.03 (1H, t, *J* 8.8, H9), 4.34 (1H, dd, *J* 8.8, 2.8, H8), 4.19 - 4.27 (1H, m, H18), 3.58 - 3.71 (2H, m, H8 and H13), 3.43 (1H, dd, *J* 12.8, 6.1, H11), 3.24 - 3.30 (1H, m, H11), 2.39 (1H, d, *J* 10.4, CH_2), 1.98 (1H, d, *J* 12.0, CH_2), 1.81 (2H, br. s, CH_2), 1.35 (3H, br. s, CH_3), 1.28 (3H, t, *J* 7.4, CH_3(12)), 1.13 - 1.37 (4H, m, CH_2), 1.01 (9H, s, $C(CH_3)_3$).

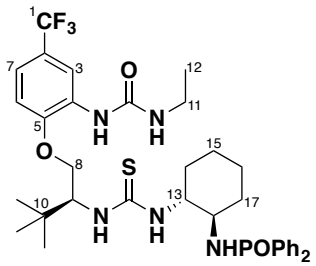
δ_C (101 MHz, $CDCl_3$): 184.0 (C=S), 171.8 (C=O 19), 155.8 (C=O urea), 148.7 (C5), 129.9 (C4), 124.4 (q, $J_{C\text{-}F}$ 271.5, C1), 123.4 (q, $J_{C\text{-}F}$ 32.8, C2), 118.3 (q, $J_{C\text{-}F}$ 4.2, C7), 114.5 (br. C3), 109.8 (br. C6), 69.2 (C8), 61.6 (C9), 58.1 (br. C18), 52.9 (C13), 35.1 (C11), 33.2 (C10), 33.0 (CH_2), 32.9 (CH_2), 26.8 ($C(\underline{C}H_3)_3$), 25.0 (CH_2), 24.6 (CH_2), 22.5 (CH_3), 15.5 (C12).

ν_{max} (thin film): 1686 (C=O urea), 1644 (C=O amide), 1556 (C=S).

HRMS (ESI +ve) found: 546.2721 [(M+H)$^+$], $C_{25}H_{39}F_3N_5O_3S$ requires: 546.2720.

$[\alpha]_D^{20}$: 1.2° (*c* 0.6 in $CHCl_3$).

1-(2-((*S*)-2-(3-((1*R*,2*R*)-2-((Diphenylphosphoryl)amino)cyclohexyl)thioureido)-3,3-dimethylbutoxy)-5-(trifluoromethyl)phenyl)-3-ethylurea 128



Prepared according to General Procedure B. Amine **108** (65 mg, 0.19 mmol) and cyclohexylamine **120** (59 mg, 0.19 mmol) were reacted to give thiourea **128** as a pale crystalline solid (76 mg, 58 %).

Data for **128**:

m. p. 110 - 113 °C.

δ_H (500 MHz, $CDCl_3$): 8.36 (1H, s, H3), 8.05 (1H, br. s, ArNH), 7.95 (1H, s, $NHPOPh_2$), 7.85 (2H, dd, *J* 12.3, 7.3, ArH), 7.55 (1H, m, ArH), 7.49 (2H, td, *J* 7.5, 3.3, ArH), 7.25 - 7.30 (2H, m, ArH), 7.05 - 7.13 (2H, m, H7 and ArH), 6.92 (1H, d, *J* 9.8, NH), 6.82 (2H, br. s, ArH), 6.61 (1H, d, *J* 8.2, H6), 6.28 (1H, t, *J* 4.9, EtNH), 4.98 - 5.03 (1H, m, H9), 4.28 (1H, dd, *J* 8.8, 3.5, H8), 3.92 - 3.99 (1H, m, H18), 3.82 (1H, t, *J* 9.3, H8), 3.24 - 3.40 (2H, m, CH_2(11)), 2.95 - 3.00 (1H, m, NH), 2.80 - 2.90 (1H, m, H9), 2.53 (1H, d, *J* 12.3, CH_2), 1.98 (1H, d, *J* 12.0, CH_2), 1.72 (2H, d, *J* 12.6 CH_2), 1.28 - 1.40 (2H, m, CH_2), 1.24 (3H, t, *J* 7.4, CH_3(12)), 1.10 - 1.15 (2H, m, CH_2), 1.08 (9H, s, $C(CH_3)_3$).

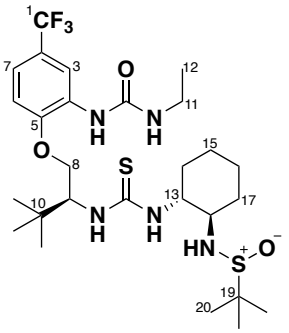
δ_C (126 MHz, $CDCl_3$): 184.7 (C=S), 155.5 (C=O), 148.4 (C5), 132.7 (ArCH), 132.6 (ArCH), 132.4 (d, $J_{C\text{-}P}$ 2.9, ArCH), 132.3 (d, $J_{C\text{-}P}$ 1.9, ArCH), 130.9 (d, $J_{C\text{-}P}$ 135.4, ArC), 130.6 (d, $J_{C\text{-}P}$ 125.9, ArC), 129.9 (ArCH), 129.8 (C4), 128.8 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 124.5 (q, $J_{C\text{-}F}$ 271.5, C1), 123.1 (q, $J_{C\text{-}F}$ 32.1, C2), 117.9 (q, $J_{C\text{-}F}$ 4.1, C7), 114.5 (br. C3), 108.9 (br. C6), 68.2 (C8), 61.3 (C9), 60.9 (br. C18), 54.8 (C13), 35.4 (br. CH_2), 34.9 (C11), 33.6 (C10), 33.0 (br. CH_2), 27.0 ($C(\underline{C}H_3)_3$), 25.4 (br. CH_2), 24.5 (br. CH_2), 15.6 (C12).

ν_{max} (thin film): 1692 (C=O), 1548 (C=S), 1167 (P=O).

HRMS (ESI +ve) found: 726.2803 [$(M+Na)^+$], $C_{35}H_{45}F_3N_5NaO_3PS$ requires: 726.2825.

$[\alpha]_D^{25}$: -22.3° (*c* 0.6 in $CHCl_3$).

***N*-((1*R*,2*R*)-2-(3-((*S*)-1-(2-(3-Ethylureido)-4-(trifluoromethyl)phenoxy)-3,3-dimethylbutan-2-yl)thioureido)cyclohexyl)-2-methylpropane-2-sulfinamide 129a & 129b**



This compound was prepared following a modified literature procedure.[72] A round bottom flask charged with THF (2.8 mL) was cooled to –78 ˚C and *tert*-butylsulfinyl chloride (35 μL, 0.28 mmol), diisopropylethylamine (58 μL, 0.33 mmol) and 4-dimethylaminopyridine (6 mg, 0.05 mmol) were added. After stirring for 5 min, thiourea **125** (128 mg, 0.26 mmol) was added and the reaction was stirred for 4 h at –78 ˚C. The reaction was then warmed to room temperature over 5 h. The reaction was diluted with methanol (5 mL) and solvent was removed *in vacuo*. The residue was redissolved in EtOAc (10 mL) and washed with 1 M HCl solution (7.5 mL) and aqueous sodium bicarbonate solution (7.5 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography to yield **129a** (63 mg, 41 %) and **129b** (66 mg, 43 %), both as pale yellow crystalline solids.

Data for **129a**:

m. p. 127 - 131 ˚C.

δ_H (500 MHz, $CDCl_3$): 8.59 (1H, d, *J* 1.6, H3), 8.00 (1H, br. s, ArNH), 7.24 (1H, d, *J* 7.3, NHSO*t*-Bu), 7.11 (2H, dd, *J* 8.2, 1.6, H7), 6.71 (2H, d, *J* 8.5, NH and H6), 6.14 (1H, br. s, EtNH), 4.99 (1H, t, *J* 8.7, H9), 4.30 (1H, dd, *J* 8.8, 2.8, H8), 4.05 - 4.12 (1H, m, H18), 3.76 (1H, t, *J* 9.5, H8), 3.61 (1H, br. s, NH), 3.31 (2H, quin, *J* 6.6, CH_2(11)), 2.98 - 3.05 (1H, m, H13), 2.45 (1H, br. s, CH_2), 2.12

(1H, d, *J* 9.8, CH_2), 1.80 (2H, t, *J* 13.9, CH_2), 1.26 - 1.40 (3H, m, CH_2), 1.22 (3H, t, *J* 7.3, CH_3(12)), 1.08 - 1.17 (1H, m, CH_2), 1.00 (9H, s, $C(CH_3)_3$(20)), 0.88 (9H, s, $C(CH_3)_3$).

δ_c (126 MHz, $CDCl_3$): 184.6 (C=S), 155.4 (C=O), 148.6 (C5), 130.3 (C4), 124.4 (q, *J* 271.5, C1), 123.4 (q, *J* 32.9, C2), 117.9 (m, C7), 114.7 (m, C3), 109.1 (C6), 68.8 (C8), 61.5 (C9), 58.6 (C13), 58.5 (C18), 55.5 (C19), 34.7 (C11), 34.0 (CH_2), 33.4 (C10), 32.9 (CH_2), 26.8 ($C(CH_3)_3$(20)), 24.7 (CH_2), 24.5 (CH_2), 21.9 ($C(CH_3)_3$), 15.6 (C12).

ν_{max} (thin film): 1654 (C=O), 1550 (C=S).

HRMS (ESI +ve) found: 608.2914 [$(M+H)^+$], $C_{27}H_{45}F_3N_5O_3S_2$ requires: 608.2910.

$[\alpha]_D^{20}$: -82.7° (*c* 1.0 in $CHCl_3$).

Data for **129b**

m. p. 144 - 147 °C.

δ_H (500 MHz, d_4-MeOD): 8.45 (1H, d, *J* 2.2, H3), 7.22 (1H, dd, *J* 8.4, 1.4, H7), 7.04 (1H, d, *J* 8.5, H6), 4.99 (1H, d, *J* 8.2, H9), 4.40 (1H, dd, *J* 9.1, 2.2, H8), 4.15 (1H, br. s, H18), 3.88 - 3.94 (1H, m, H8), 3.24 - 3.35 (2H, m, CH_2(11)), 3.05 (1H, td, *J* 10.8, 4.3, H13), 2.16 (2H, m, CH_2), 1.72 - 1.82 (2H, m, CH_2), 1.46 - 1.54 (1H, m, CH_2), 1.33 - 1.40 (2H, m, CH_2), 1.25 (3H, t, *J* 7.2, CH_3(12)), 1.18 - 1.22 (1H, m, CH_2), 1.09 (9H, s, $C(CH_3)_3$), 0.96 & 0.91 (9H, s, $C(CH_3)_3$(20)).

δ_C (126 MHz, d_4-MeOD): 184.6 (C=S), 157.5 (C=O), 150.8 (C5), 131.3 (C4), 126.1 (q, *J* 270.8, C1), 124.0 (q, *J* 32.8, C2), 119.6 (m, C7), 115.3 (m, C3), 111.9 (C6), 70.9 (C8), 62.0 (C9), 59.9 (C13), 57.1 (C18), 49.6 (C19), 36.5 (C10), 35.8 (CH_2), 34.7 (C11), 33.9 (CH_2), 27.2 ($C(\underline{C}H_3)_3$), 26.2 (CH_2), 25.6 (CH_2), 22.8 ($C(CH_3)_3$(20)), 15.8 (C12).

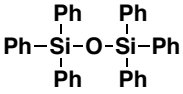
ν_{max} (thin film): 1668 (C=O), 1555 (C=S).

HRMS (ESI +ve) found: 630.2728 [$(M+Na)^+$], $C_{27}H_{44}F_3N_5NaO_3S_2$ requires: 630.2730.

$[\alpha]_D^{20}$: -2.8° (*c* 0.8 in $CHCl_3$).

5.3.2 Experimental Data from Chapter 3: Cation-directed Asymmetric Allylation

Hexaphenyldisiloxane 170



Triphenylsilyl fluoride **169** (0.28 g, 1.00 mmol), potassium fluoride (1.06 g, 20.0 mmol) and DMF (2.5 mL) were added to a round bottom flask. The reaction was heated to 60 ˚C and stirred for 24 h. The reaction was then cooled to room temperature and filtered and washed with DMF (3 × 4 mL). The filtrate was then concentrated under reduced pressure and the solid was recrystallized from acetonitrile to yield a white crystalline solid **170** (0.149 g, 56 %).

This compound was unambiguously identified by single crystal X-ray diffraction. See **Appendices** for full details.

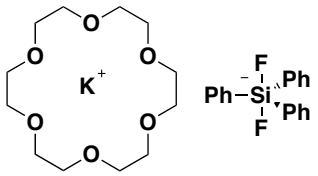
Data for **170**:

δ_H (400 MHz, $CDCl_3$): 7.48 (12H, m, ArH), 7.39 (6H, m, ArH), 7.27 (12H, m, ArH).

δ_C (101 MHz, $CDCl_3$): 135.4 (ArC), 135.2 (ArC), 129.8 (ArC), 127.7 (ArC).

This data is in accordance with the literature.[176]

18-Crown-6 potassium Triphenyldifluorosilicate 172



This compound was prepared according to a literature procedure.[131] Triphenyfluorosilane **169** (0.48 g, 1.73 mmol) potassium fluoride (0.10 g, 1.73 mmol) and 18-crown-6 (0.46 g, 1.73 mmol) were dissolved in toluene (3.5 mL) and stirred at room temperature. After 5 days, a precipitate had formed, which was filtered and washed with diethyl ether (50 mL). The product **172** was found to be a white crystalline material (0.69 g, 68 %).

Data for **172**:

m. p. 134 – 137 °C.

δ_H (500 MHz, d_6-acetone): 8.10 (6H, d, *J* 6.6, ArH), 7.03 – 7.15 (9H, m, ArH), 3.63 (24H, s, CH_2).

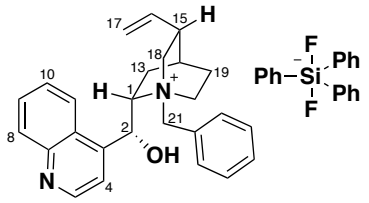
δ_C (126 MHz, d_6-acetone): 138.5 (ArC), 137.6 (ArC), 136.3 (ArC), 135.9 (ArC), 135.7 (ArCH), 131.0 (ArC), 130.5 (ArC), 128.7 (ArC), 128.6 (ArC), 126.7 (ArC), 71.0 (CH_2).

δ_F (377 MHz, d_6-acetone): - 99.9 (Si-F).

ν_{max} (thin film): 1110 (C-O-C).

This data is in accordance with the literature.[131]

_N_-Benzylcinchonidinium triphenyldifluorosilicate 173



Triphenylfluorosilane (34 mg, 0.12 mmol) was dissolved in dichloromethane (1 mL) and magnesium sulfate (10 mg) was added to dry the solution. *N*-benzylcinchonidinium fluoride **166** (50 mg, 0.12 mmol) was added and the solution was stirred for 4 days at room temperature. After this time, the slurry was filtered and the filtrate was concentrated *in vacuo* to yield **173** as a solid (40 mg, 47 %).

Data for **173**:

δ_H (500 MHz, d_6-DMSO): 8.97 (1H, d, *J* 4.4, H5), 8.25 (1H, d, *J* 8.2, H8/11), 8.11 (1H, dd, *J* 8.5, 1.3, H8/11), 7.80 – 7.90 (8H, m, 2 × ArH and 6 × Ph_3SiF_2), 7.67 – 7.77 (3H, m, ArH), 7.56 (3H, m, ArH), 7.06 – 7.15 (9H, m, Ph_3SiF_2), 6.54 (1H, s, H2), 5.67 (1H, ddd, *J* 17.2, 10.6, 6.5, H16), 5.26 (1H, d, *J* 12.0, H21), 5.14 (1H, dt, *J* 17.3, 1.3, H_Z(17)), 4.90 – 4.98 (2H, m, H_E(17) and H21), 4.36 (1H, t, *J* 11.3, H20), 3.87 (1H, t, *J* 8.7, H1), 3.68 (1H, m, H18), 3.27 (1H, m, H18), 3.19 (1H, m, H20), 2.68 (1H, br. s, H15), 1.97 – 2.14 (3H, m, H13, H14 and H19), 1.80 (1H, m, H19), 1.26 (1H, m, H13).

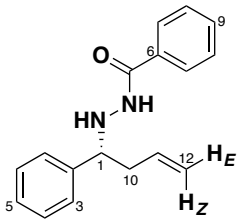
δ_C (126 MHz, d_6-DMSO): 150.5(t, $J_{C\text{-}F}$ 0.5, Ph_3SiF_2), 150.2 (C5), 147.6 (C3/7), 145.8 (C3/7), 138.2 (C16), 137.0 (t, $J_{C\text{-}F}$ 0.1, Ph_3SiF_2), 134.5 (ArCH), 130.0 (ArCH), 129.9 (ArCH), 129.3 (ArC), 128.9

(ArCH), 128.0 (ArCH), 127.8 (ArC), 126.2 (Ph_3SiF_2), 126.0 (Ph_3SiF_2), 124.4 (ArC), 123.5 (ArC), 120.2 (ArC), 116.3 (C17), 67.9 (C1), 64.1 (C2), 62.7 (C21), 59.2 (C18), 50.4 (C20), 36.9 (C15), 25.9 (C14), 24.2 (C19), 20.9 (C13).

δ_F (377 MHz, d_6-DMSO): -97.7 ($Ph_3SiF_2^-$).

HRMS (ESI +ve) found: 385.2276 [$(M)^+$], $C_{26}H_{29}N_2O^+$ requires: 385.2274.

(R)-*N*'-(1-Phenylbut-3-en-1-yl)benzohydrazide 103



Racemic: Prepared using general procedure C. Hydrazone **101** (192 mg, 0.89 mmol) reacted to give product **103** (190 mg, 84 %) as a white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **101** (100 mg, 0.45 mmol) reacted to give product **103** (96 mg, 81 %, 39 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **101** (98 mg, 0.44 mmol) reacted to give product **103** (100 mg, 86 %, 46 % ee).

N.B. The absolute stereochemistry was defined by comparison of the optical rotation with data in the literature.[43] The HPLC data also matched that reported for the (*R*)-enantiomer.[46,177] All other compounds prepared by general procedure D have been assumed to be the (*R*)-enantiomer by analogy.

Data for **103**:

m. p. 76 - 80 ˚C (Lit m. p. 93 – 94 ˚C).

δ_H (500 MHz, $CDCl_3$): 7.60 (2H, dd, *J* 8.4, 1.4, ArH), 7.46 - 7.50 (1H, m, ArH), 7.34 - 7.42 (7H, m, ArH and CONH), 7.31 (1H, m, ArH), 5.82 - 5.91 (1H, m, H11), 5.29 (1H, br. s, NH), 5.20 (1H, dq, *J* 17.0, 1.6, H_Z(12)), 5.14 (1H, m, H_E(12)), 4.19 (1H, t, *J* 7.0, H1), 2.48 - 2.58 (2H, m, CH_2(10)).

δ_C (126 MHz, $CDCl_3$): 167.1 (C=O), 141.6 (C2), 134.4 (C11), 132.8 (C6), 131.8, 128.6, 128.6, 127.7, 126.8 (ArCH), 118.1 (C12), 63.9 (C1), 40.4 (C10).

ν_{max} (thin film): 3282 (N-H), 1640 (C=O).

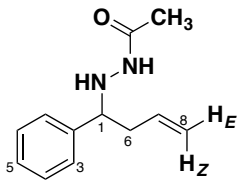
HRMS (ESI +ve) found: 289.1313 [$(M+Na)^+$], $C_{17}H_{18}N_2NaO$ requires: 289.1311.

$[\alpha]_D^{20}$: 58.6° (*c* 0.9 in $CHCl_3$).

HPLC (Chiralpak AD-H, 6 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 17.1, t_R minor = 21.1; *Racemic*: t_R major = 17.1, t_R minor = 21.2.

This data is in accordance with the literature.[43]

_N_'-(1-Phenylbut-3-en-1-yl)acetohydrazide 102



Racemic: Prepared using general procedure C. Hydrazone **100** (156 mg, 0.96 mmol) reacted to give product **102** (43 mg, 22 %) as a white solid.

Data for **102**:

m. p. 81 – 84 °C.

δ_H (500 MHz, $CDCl_3$): 7.34 - 7.37 (4H, m, ArH), 7.27 - 7.32 (1H, m, ArH), 6.75 (1H, br. s, CONH), 5.79 (1H, ddt, *J* 17.2, 10.1, 7.0, H7), 5.14 (1H, dd, *J* 17.0, 1.3, H_Z(8)), 5.09 (1H, d, *J* 10.1, H_E(8)), 4.99 - 5.06 (1H, br. s, NH), 4.07 (1H, t, *J* 7.3, H1), 2.43 (2H, a-t, *J* 2.4, CH_2(6)), 1.85 (3H, s, CH_3).

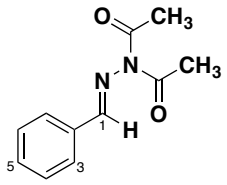
δ_C (126 MHz, $CDCl_3$): 169.4 (C=O), 141.8 (ArC), 134.3 (C7), 128.6 (× 2), 127.7 (× 3) (ArCH), 118.1 (C8), 63.7 (C1), 40.6 (C6), 21.2 (CH_3).

ν_{max} (thin film): 3279 (C-H), 1635 (C=O).

HRMS (ESI +ve) found: 227.1154 [$(M+Na)^+$], $C_{12}H_{16}N_2NaO$ requires: 227.1155.

This data is in accordance with the literature.[92]

(*E*)-*N*-acetyl-*N'*-benzylideneacetohydrazide 174



Hydrazone **100** (286 mg, 1.77 mmol) was stirred in a solution of acetic anhydride (1.50 mL) and pyridine (1.50 mL) and heated to 100 ˚C. After 2 h the reaction mixture was cooled to r.t. and diluted with water (10 mL). The reaction was extracted with dichloromethane (3 × 10 mL) and the combined organics were dried ($MgSO_4$) filtered and reduced *in vacuo*. The crude was purified by silica gel chromatography to yield hydrazone **174** (199 mg, 55 %) as a white solid.

Data for **174**:

m. p. 76 – 79 ˚C.

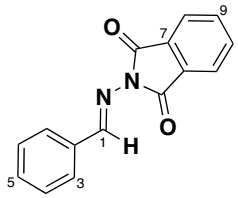
δ_H (400 MHz, $CDCl_3$): 8.50 (1H, s, H1), 7.78 (2H, m, H3), 7.47 (3H, m, H4 and H5), 2.50 (6H, s, CH_3).

δ_C (101 MHz, $CDCl_3$): 171.3 (C=O), 164.6 (C1), 133.1 (C2), 132.0 (C5), 128.9 (C4), 128.4 (C3), 26.4 (CH_3).

ν_{max} (thin film): 1722 (C=O), 1699 (C=N).

HRMS (ESI +ve) found: 227.0791 [$(M+Na)^+$], $C_{11}H_{12}N_2NaO_2$ requires: 227.0791.

(*E*)-2-(Benzylideneamino)isoindoline-1,3-dione 175



N-Aminophthalimide (0.48 g, 2.96 mmol) and benzaldehyde (0.36 mL, 3.53 mmol) were dissolved in methanol (12 mL). Acetic acid (few drops) was added the solution was stirred for 1 h. The solvent was removed under reduced pressure and the product was purified by crystallization from ethanol, yielding pale yellow needles of **175** (0.55 g, 74 %).

Data for **175**:

m. p. 164 – 168 ˚C (Lit m. p. 162 – 165 ˚C).

δ_H (400 MHz, $CDCl_3$): 9.41 (1H, s, H1), 7.89 – 7.95 (4H, m, H3 and H8), 7.79 (2H, dd, *J* 5.4, 3.2, H9), 7.44 – 7.52 (3H, m, H4 and H5).

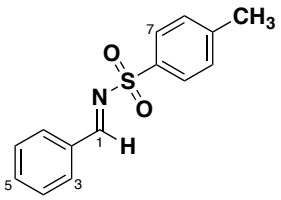
δ_C (101 MHz, $CDCl_3$): 165.1 (C6), 158.6 (C1), 134.6 (C9), 133.6 (C2/7), 131.7 (C5), 130.3 (C2/7), 128.8 (C4), 128.4 (C3), 123.8 (C8).

ν_{max} (thin film): 1710 (C=O), 1600 (C=N).

HRMS (ESI +ve) found: 273.0633 [$(M+Na)^+$], $C_{15}H_{10}N_2NaO_2$ requires: 273.0634.

This data is in accordance with the literature.[178]

_N_-Benzylidene-4-methylbenzenesulfonamide 176



This compound was prepared according to a literature procedure.[179] Benzaldehyde (1.20 mL, 11.8 mmol), *p*-toluenesulfonamide (2.03 g, 11.8 mmol) and benzenesulfinic acid sodium salt (2.15 g, 13.0 mmol) were dissolved in water (17 mL) and formic acid (17 mL). The reaction was stirred for 12 h at room temperature and a white precipitate formed. The white precipitate was filtered and washed with water (2 × 15 mL) and pentane (15 mL) and then re-dissolved in dichloromethane (100 mL). Saturated $NaHCO_3$ solution (70 mL) was added and the mixture and stirred for 3 h. The phases were then separated and the aqueous phase was extracted with dichloromethane (100 mL) and the combined organics were dried ($NaHCO_3$), filtered and concentrated under reduced pressure to yield **176** as a white solid (1.60 g, 62 %).

Data for **176**:

m. p. 83 – 86 ˚C.

δ_H (400 MHz, $CDCl_3$): 9.04 (1H, s, H1), 7.92 (4H, m, H3 and H7), 7.62 (1H, m, H5), 7.49 (2H, m, H4), 7.35 (2H, d, *J* 7.8, H8), 2.44 (3H, s, CH_3).

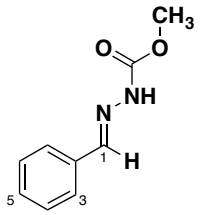
δ_C (101 MHz, $CDCl_3$): 170.3 (C1), 144.7 (ArC), 135.1 (ArC), 135.0 (C5), 132.4 (ArC), 131.3 (C3/7), 129.9 (C8), 129.2 (C4), 128.1 (C3/7), 21.7 (CH_3).

ν_{max} (thin film): 1598 (C=N), 1301 and 1157 (S=O).

HRMS (ESI +ve) found: 282.0557 [$(M+Na)^+$], $C_{14}H_{13}NNaO_2S$ requires: 282.0559.

This data is in accordance with the literature.[179]

(*E*)-Methyl 2-benzylidenehydrazinecarboxylate 279



Benzaldehyde (1.90 mL, 18.9 mmol) and methyl hydrazinocarboxylate (1.50 g, 16.7 mmol) were dissolved in methanol (80 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **279** (2.40 g, 81 %) as white crystalline solid.

Data for **279**:

m. p. 138 – 141 ˚C (Lit m. p. 140 – 142 ˚C).

δ_H (400 MHz, d_6-DMSO): 11.11 (1H, br. s, NHCO), 8.03 (1H, s, H1), 7.62 (2H, dd, *J* 7.7, 1.6, H3), 7.35 – 7.44 (3H, m, H4 and H5), 3.69 (3H, s, OCH_3).

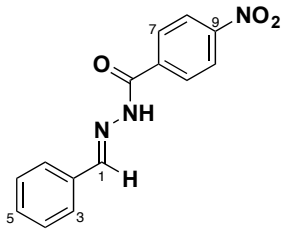
δ_C (101 MHz, $CDCl_3$): 154.8 (C=O), 144.7 (C1), 135.2 (C2), 130.4 (C5), 129.6 (C4), 127.5 (C3), 52.8 (OCH_3).

ν_{max} (thin film): 1718 (C=O), 1549 (C=N).

HRMS (ESI +ve) found: 201.0633 [$(M+Na)^+$], $C_9H_{10}N_2NaO_2$ requires: 201.0634.

This data is in accordance with the literature.[180]

(*E*)-*N*'-Benzylidene-4-nitrobenzohydrazide 179



Benzaldehyde (1.88 mL, 18.5 mmol) and 4-nitrobenzhydrazide (2.74 g, 15.1 mmol) were dissolved in methanol (80 mL). Acetic acid (few drops) was added and the reaction was stirred for 2 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **179** (3.62 g, 89 %) as a pale yellow crystalline solid.

Data for **179**:

m. p. 258 – 259 °C (Lit m. p. 255 – 257 °C).

δ_H (400 MHz, d_6-DMSO): 12.15 (1H, br. s, NHCO), 8.48 (1H, s, H1), 8.37 (2H, d, *J* 8.6, H7/8), 8.16 (2H, d, *J* 8.6, H7/8), 7.76 (2H, m, H3/4), 7.47 (3H, m, H3/4/5).

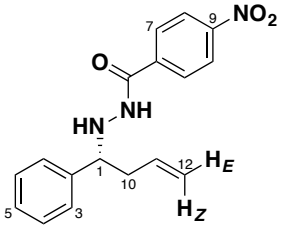
δ_C (101 MHz, d_6-DMSO): 162.4, (C=O), 150.1 (C9), 149.8 (C1), 139.9 (ArC), 134.9 (ArC), 131.2 (C5), 130.0 (C7/8), 129.8 (C3/4), 128.1 (C3/4), 124.5 (C7/8).

ν_{max} (thin film): 1685 (C=O), 1583 (C=N).

HRMS (ESI +ve) found: 292.0697 [$(M+Na)^+$], $C_{14}H_{11}N_3NaO_3$ requires: 292.0693.

This data is in accordance with the literature.[181]

(R)-4-Nitro-*N*'-(1-phenylbut-3-en-1-yl)benzohydrazide 181



Racemic: Prepared using general procedure C. Hydrazone **179** (97 mg, 0.36 mmol) reacted to give product **181** (99 mg, 88 %) as an orange crystalline solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **179** (100 mg, 0.37 mmol) reacted to give product **181** (34 mg, 36 %, 55 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **179** (108 mg, 0.40 mmol) reacted to give product **181** (58 mg, 46 %, 52 % ee).

Data for **181**:

m. p. 104 – 106 ˚C.

δ_H (400 MHz, $CDCl_3$): 8.22 (2H, m, H8), 7.75 (2H, d, *J* 8.6, H7), 7.62 (1H, br. s, NHCO), 7.28 – 7.41 (5H, m, H3, H4 and H5), 5.78 – 5.90 (1H, m, H11), 5.20 – 5.40 (1H, br. s, NH), 5.20 (1H, *a*dq, *J* 17.2, 1.5, H_Z(12)), 5.15 (1H, d, *J* 10.4, H_E(12)), 4.17 (1H, t, *J* 6.9, H1), 2.52 (2H, m, CH_2(10)).

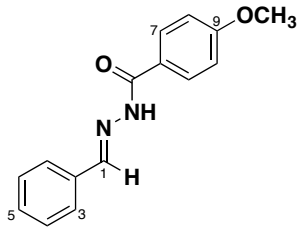
δ_C (101 MHz, $CDCl_3$): 165.1 (C=O), 149.7 (C9), 141.3 (ArC), 138.4 (ArC), 134.2 (C11), 128.7 (ArCH), 128.1 (ArCH), 127.9 (C5), 127.6 (ArCH), 123.8 (C8), 118.3 (C12), 63.9 (C1), 40.5 (C10).

ν_{max} (thin film): 1674 (C=O).

HRMS (ESI +ve) found: 334.1148 [$(M+Na)^+$], $C_{17}H_{17}N_3NaO_3$ requires: 334.1162.

HPLC (Chiralpak IC, 20 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 9.2, t_R minor = 15.4; *Racemic*: t_R major = 9.2, t_R minor = 15.4.

(*E*)-*N*'-Benzylidene-4-methoxybenzohydrazide 180



Benzaldehyde (0.33 mL, 3.24 mmol) and 4-methoxybenzhydrazide (0.53 g, 3.20 mmol) were dissolved in methanol (15 mL). Acetic acid (few drops) was added and the reaction was stirred for 5 min, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **180** (0.81 g, 99 %) as white needles.

Data for **180**:

m. p. 193 – 196 ˚C.

δ_H (400 MHz, d_6-DMSO): 11.75 (1H, br. s, NHCO), 8.46 (1H, s, H1), 7.92 (2H, d, *J* 8.8, H7), 7.72 (2H, d, *J* 6.6, H3), 7.45 (3H, m, H4 and H5), 7.06 (2H, d, *J* 8.6, H8), 3.86 (3H, s, OCH_3).

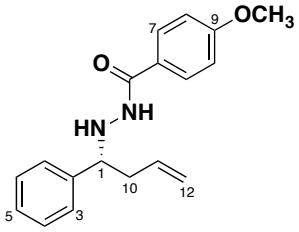
δ_C (101 MHz, d_6-DMSO): 163.4, 162.9 (C=O and C9), 148.0 (C1), 135.3 (C2), 130.8 (C7), 130.4 (C5), 129.7 (C3), 126.3 (C6), 114.6 (C8), 56.3 (OCH_3).

ν_{max} (thin film): 1642 (C=O), 1557 (C=N).

HRMS (ESI +ve) found: 277.0940 [$(M+Na)^+$], $C_{15}H_{14}N_2NaO_2$ requires: 277.0947.

This data is in accordance with the literature.[182]

(R)-4-Methoxy-*N*'-(1-phenylbut-3-en-1-yl)benzohydrazide 182



Racemic: Prepared using general procedure C. Hydrazone **180** (38 mg, 0.15 mmol) reacted to give product **182** (15 mg, 34 %) as a white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **180** (97 mg, 0.38 mmol) reacted to give product **182** (78 mg, 70 %, 39 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **180** (117 mg, 0.46 mmol) reacted to give product **182** (52 mg, 38 %, 40 % ee).

Data for **182**:

m. p. 82 – 85 ˚C.

δ_H (400 MHz, $CDCl_3$): 7.57 (2H, m, H7), 7.28 – 7.42 (6H, m, H3, H4, H5 and NHCO), 6.87 (2H, m, H8), 5.86 (1H, m, H11), 5.10 – 5.30 (3H, m, NH and CH_2(12)), 4.17 (1H, t, *J* 7.1, H1), 3.82 (3H, s, OCH_3), 2.46 – 2.58 (2H, m, CH_2(10)).

δ_C (101 MHz, $CDCl_3$): 166.8, 162.4 (C=O and C9), 141.8 (ArC), 134.5 (C10), 128.6 (ArCH), 128.5 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 125.0 (ArC), 118.0 (C12), 113.8 (C8), 63.9 (C1), 55.4 (OCH_3), 40.4 (C10).

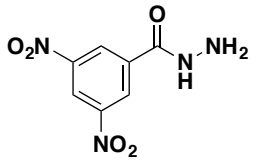
ν_{max} (thin film): 3281 (N-H), 1633 (C=O).

HRMS (ESI +ve) found: 319.1416 [$(M+Na)^+$], $C_{18}H_{20}N_2NaO_2$ requires: 319.1417.

HPLC (Chiralpak AD-H, 12 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 19.1, t_R minor = 23.7; *Racemic*: t_R major = 19.0, t_R minor = 23.6.

This data is in accordance with the literature. [54]

3,5-Dinitrobenzohydrazide 184



This compound was made according to a modified literature procedure.[183] Methyl 3,5-dinitrobenzoate (2.22 g, 9.82 mmol) was dissolved in methanol (3 mL) and hydrazine monohydrate (0.95 mL, 19.6 mmol) was added carefully. The reaction was heated to 65 ˚C and stirred for 30 min before cooling to r.t. The resulting precipitate was filtered was washed with water (25 mL) and the product was recrystallized from EtOH to yield **184** as a yellow crystalline solid (1.45 g, 65 %).

Data for **184**:

m. p. 146 – 148 ˚C.

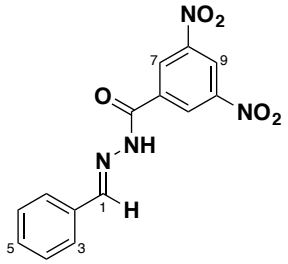
δ_H (400 MHz, d_6-DMSO): 10.51 (1H, br. s, NHCO), 9.00 (2H, d, *J* 2.0, *ortho*-H), 8.93 (1H, m, *para*-H), 4.75 (2H, br. s, NH_2).

δ_C (101 MHz, d_6-DMSO): 161.8 (C=O), 148.7 (C-NO_2), 136.4 (ArC), 127.6 (*ortho*-C), 121.1 (*para*-C).

ν_{max} (thin film): 1630 (C=O), 1539 and 1346 (NO_2).

HRMS (ESI -ve) found: 225.0262 [$(M-H^+)^-$], $C_7H_5N_4O_5$ requires: 225.0265.

(*E*)-*N*'-Benzylidene-3,5-dinitrobenzohydrazide 185



Benzaldehyde (0.67 mL, 6.6 mmol) and hydrazide **184** (1.36 g, 6.0 mmol) were dissolved in methanol (20 mL). Acetic acid (few drops) was added and the reaction was stirred for 2 h. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography to yield hydrazone **185** (1.07 g, 57 %) as a pale yellow solid.

Data for **185**:

m. p. 268 – 272 ˚C.

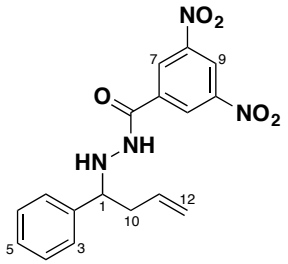
δ_H (400 MHz, d_6-DMSO): 12.41 (1H, br. s, NHCO), 9.13 (2H, d, *J* 2.3, H7), 9.00 (1H, t, *J* 2.0, H9), 8.51 (1H, s, H1), 7.77 (2H, m, H3/4), 7.49 (3H, m, H3/4/5).

δ_C (101 MHz, d_6-DMSO): 159.9, (C=O), 150.5 (C1), 149.1 (C8), 136.8 (ArC), 134.7 (ArC), 131.4 (C5), 129.8 (C3/4), 128.8 (C7), 128.2 (C3/4), 122.1 (C9).

ν_{max} (thin film): 1661 (C=O), 1542 and 1343 (NO_2), 1535 (C=N).

HRMS (ESI +ve) found: 337.0546 [$(M+Na)^+$], $C_{14}H_{10}N_4NaO_5$ requires: 337.0543.

3,5-Dinitro-*N*'-(1-phenylbut-3-en-1-yl)benzohydrazide 188



Racemic: Prepared using general procedure C. Hydrazone **185** (236 mg, 0.75 mmol) reacted to give product **188** (126 mg, 47 %) as an orange oil.

Data for **188**:

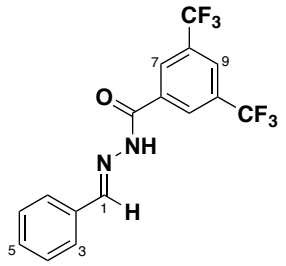
δ_H (400 MHz, $CDCl_3$): 9.10 (1H, t, *J* 1.9, H9), 8.80 (2H, d, *J* 2.60, H7), 7.95 – 8.45 (1H, br. s, NHCO), 7.25 – 7.41 (5H, m, H3, H4 and H5), 5.84 (1H, ddt, *J* 17.1, 10.1, 7.0, H11), 5.19 (2H, m, CH_2(12)), 4.18 (1H, t, *J* 6.9, H1), 2.54 (2H, m, CH_2(10)).

δ_C (101 MHz, $CDCl_3$): 162.6 (C=O), 148.6 (C8), 141.0 (ArC), 136.2 (ArC), 134.1 (C11), 128.7 (C3/4), 128.0 (C5), 127.6 (C3/4), 127.2 (C7), 121.2 (C9), 118.5 (C12), 64.0 (C1), 40.4 (C10).

ν_{max} (thin film): 1643 (C=O), 1541 and 1344 (NO_2).

HRMS (ESI +ve) found: 379.1006 [$(M+Na)^+$], $C_{17}H_{16}N_4NaO_5$ requires: 379.1013.

(*E*)-*N*'-Benzylidene-3,5-bis(trifluoromethyl)benzohydrazide 187



Benzaldehyde (0.84 mL, 8.3 mmol) and 3,5-bis(trifluoromethyl)benzoic acid hydrazide (1.88 g, 6.9 mmol) were dissolved in methanol (40 mL). Acetic acid (few drops) was added and the reaction was stirred for 2 h. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **187** (2.26 g, 91 %) as a white crystalline solid.

Data for **187**:

m. p. 205 – 207 ˚C.

δ_H (400 MHz, d_6-DMSO): 12.21 (1H, br. s, NHCO), 8.57 (2H, s, H7), 8.48 (1H, s, H1), 8.37 (1H, s, H9), 7.77 (2H, m, H3), 7.48 (3H, m, H4/5).

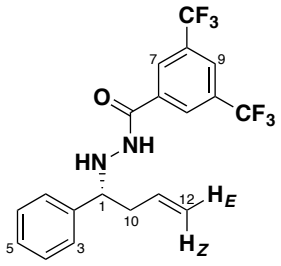
δ_F (377 MHz, d_6-DMSO): - 61.3, (CF_3).

δ_C (101 MHz, d_6-DMSO): 161.1 (C=O), 150.1 (C1), 136.6 (ArC), 134.8 (ArC), 131.4 (q, *J* 33.6, C8), 131.3 (C5), 129.8 (C4), 129.3 (q, *J* 3.2, C7), 128.2 (C3), 126.2 (q, *J* 3.3, C9), 123.9 (q, *J* 273.4, CF_3).

ν_{max} (thin film): 1655 (C=O), 1569 (C=N).

HRMS (ESI +ve) found: 383.0587 [$(M+Na)^+$], $C_{16}H_{10}F_6N_2NaO$ requires: 383.0590.

(R)-*N'*-(1-Phenylbut-3-en-1-yl)-3,5-bis(trifluoromethyl)benzohydrazide 189



Racemic: Prepared using general procedure C. Hydrazone **187** (198 mg, 0.55 mmol) reacted to give product **189** (166 mg, 75 %) as a white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **187** (134 mg, 0.37 mmol) reacted to give product **189** (94 mg, 63 %, 46 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **187** (141 mg, 0.39 mmol) reacted to give product **189** (68 mg, 43 %, 47 % ee).

N.B. Careful purification required (often two columns) because an unidentified byproduct is formed.

Data for **189**:

m. p. 82 – 86 ˚C.

δ_H (400 MHz, $CDCl_3$): 8.03 (2H, s, H7), 7.98 (1H, s, H9), 7.71 (1H, br. s, NHCO), 7.28 – 7.41 (5H, m, H3, H4 and H5), 5.85 (1H, ddt, *J* 17.1, 10.2, 7.1, H11), 5.21 – 5.38 (1H, br. s, NH) 5.21 (1H, dd, *J* 17.2, 1.5, H_Z(12)), 5.15 (1H, d, *J* 10.1, H_E(12)), 4.18 (1H, t, *J* 7.1, H1), 2.53 (2H, m, CH_2(10)).

δ_F (377 MHz, $CDCl_3$): -63.0 (CF_3).

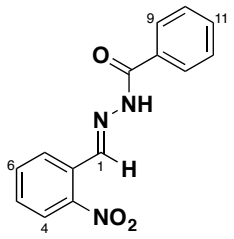
δ_C (101 MHz, $CDCl_3$): 164.4 (C=O), 141.2 (ArC), 134.9 (ArC), 134.3 (C11), 132.2 (q, *J* 34.4, C8), 128.7 (C3/4), 128.0 (C5), 127.6 (C3/4), 127.2 (q, *J* 3.2, C7), 122.7 (CF_3), 118.3 (C12), 63.9 (C1), 40.4 (C10).

ν_{max} (thin film): 3269 (N-H), 1644 (C=O).

HRMS (ESI +ve) found: 425.1065 [$(M+Na)^+$], $C_{19}H_{16}F_6N_2NaO$ requires: 425.1059.

HPLC (Chiralpak AD-H, 2 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 9.3, t_R minor = 14.1; *Racemic*: t_R major = 9.3, t_R minor = 14.1.

(*E*)-*N*'-(2-nitrobenzylidene)benzohydrazide 280



2-Nitrobenzaldehyde (0.87 g, 5.75 mmol) and benzhydrazide (0.68 g, 5.00 mmol) were dissolved in methanol (20 mL). Acetic acid (few drops) was added and the reaction was stirred for 10 min, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **280** (1.21 g, 90 %) as yellow needles.

Data for **280**:

m. p. 196 – 199 ˚C.

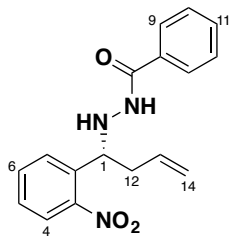
δ_H (400 MHz, d_6-DMSO): 12.22 (1H, s, NHCO), 8.89 (1H, s, H1), 8.14 (1H, d, *J* 7.6, H4/7), 8.08 (1H, d, *J* 8.1, H4/7), 7.95 (2H, d, *J* 7.3, H9), 7.82 (1H, t, *J* 7.5, H5/6), 7.68 (1H, t, *J* 7.7, H5/6), 7.61 (1H, m, H11), 7.54 (2H, m, H10).

δ_C (101 MHz, d_6-DMSO): 164.2 (C=O), 149.1 (C3), 143.8 (C1), 134.6 (C5/6), 133.9 (ArC), 132.9 (C11), 131.5 (C5/6), 129.6 (ArC), 129.4 (C10), 128.8, 128.6 (C9 and C4/7), 125.5 (C4/7).

ν_{max} (thin film): 1645 (C=O), 1565 (C=N), 1524 and 1343 (NO_2).

HRMS (ESI +ve) found: 292.0694 [$(M+Na)^+$], $C_{14}H_{11}N_3NaO_3$ requires: 292.0693.

(R)-*N*'-(1-(2-nitrophenyl)but-3-en-1-yl)benzohydrazide 203



Racemic: Prepared using general procedure C. Hydrazone **280** (221 mg, 0.82 mmol) reacted to give product **203** (200 mg, 78 %) as an orange solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **280** (133 mg, 0.49 mmol) reacted to give product **203** (125 mg, 82 %, 46 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **280** (112 mg, 0.42 mmol) reacted to give product **203** (89 mg, 69 %, 47 % ee).

Data for **203**:

m. p. 56 – 58 ˚C.

δ_H (400 MHz, $CDCl_3$): 7.91 (1H, d, *J* 7.3, H4/7), 7.77 (1H, dd, *J* 8.1, 1.0, H4/7), 7.54 – 7.63 (4H, m, H5/6, H9 and NHCO), 7.32 – 7.48 (4H, m, H5/6, H10 and H11), 5.92 (1H, m, H13), 5.33 (1H, br. s, NH), 5.20 (2H, m, CH_2(14)), 4.69 (1H, dd, *J* 8.3, 5.1, H1), 2.67 (1H, m, CH_2(12)), 2.49 (1H, m, CH_2(12)').

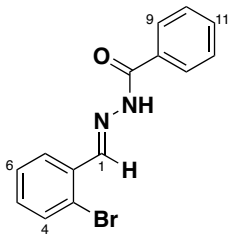
δ_C (101 MHz, $CDCl_3$): 167.4 (C=O), 150.2 (C3), 136.5 (ArC), 133.8 (C13), 132.8 (C5/6), 132.5 (ArC), 131.9 (C11), 129.1 (C4/7), 128.6 (C10), 128.2 (C5/6), 126.8 (C9), 124.1 (C4/7), 118.8 (C14), 58.9 (C1), 39.9 (C12).

ν_{max} (thin film): 3283 (N-H), 1638 (C=O).

HRMS (ESI +ve) found: 334.1166 [$(M+Na)^+$], $C_{17}H_{17}N_3NaO_3$ requires: 334.1162.

HPLC (Chiralpak AD-H, 10 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 43.5, t_R minor = 48.3; *Racemic*: t_R major = 43.5, t_R minor = 48.3.

(*E*)-*N*'-(2-Bromobenzylidene)benzohydrazide 281



2-Bromobenzaldehyde (1.35 mL, 11.4 mmol) and benzhydrazide (1.41 g, 10.4 mmol) were dissolved in methanol (40 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **281** (2.89 g, 92 %) as white needles.

Data for **281**:

m. p. 186 – 190 ˚C.

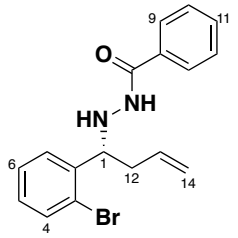
δ_H (400 MHz, d_6-DMSO): 12.13 (1H, s, NHCO), 8.84 (1H, s, H1), 8.02 (1H, d, *J* 7.6, H7), 7.95 (2H, d, *J* 7.3, H9), 7.70 (1H, d, *J* 7.8, H4), 7.45 – 7.63 (4H, m, H6, H10 and H11), 7.37 (1H, m, H5).

δ_C (101 MHz, d_6-DMSO): 164.1 (C=O), 146.9 (C1), 134.0 (C2 and C8), 134.0 (C4), 132.8 (C11), 132.6 (C5), 129.4 (C6/10), 129.0 (C6/10), 128.6 (C9), 128.1 (C7), 124.5 (C3).

ν_{max} (thin film): 1650 (C=O), 1556 (C=N).

HRMS (ESI +ve) found: 324.9948 [$(M+Na)^+$], $C_{14}H_{11}Br^{79}N_2NaO$ requires: 324.9947.

(R)-*N*'-(1-(2-Bromophenyl)but-3-en-1-yl)benzohydrazide 204



Racemic: Prepared using general procedure C. Hydrazone **281** (109 mg, 0.36 mmol) reacted to give product **204** (103 mg, 83 %) as a pale yellow solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **281** (127 mg, 0.42 mmol) reacted to give product **204** (114 mg, 79 %, 41 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **281** (115 mg, 0.38 mmol) reacted to give product **204** (66 mg, 62 %, 40 % ee).

Data for **204**:

m. p. 56 – 60 ˚C (Lit m. p. 76 – 77 ˚C).[184]

δ_H (400 MHz, $CDCl_3$): 7.68 (1H, d, *J* 7.6, H7), 7.61 (2H, d, *J* 7.3, H9), 7.55 (1H, d, *J* 7.6, H4), 7.47 (1H, m, H11), 7.38 (4H, m, H6, H10 and CONH), 7.14 (1H, td, *J* 7.7, 1.5, H5), 5.95 (1H, m, H13), 5.33 (1H, br. s, NH), 5.20 (2H, m, CH_2(14)), 4.72 (1H, dd *J* 8.3, 5.1, H1), 2.57 (1H, m, CH_2(12)), 2.41 (1H, m, CH_2(12)').

δ_C (101 MHz, $CDCl_3$): 167.3 (C=O), 140.8 (C2), 134.1 (C13), 133.0 (C4), 132.8 (C8), 131.8 (C11), 128.8 (C5), 128.6 (C10), 128.3 (C6/7), 127.7 (C6/7), 126.9 (C9), 124.6 (C3), 118.5 (C14), 62.1 (C1), 39.3 (C12).

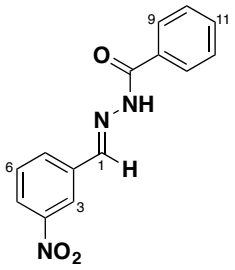
ν_{max} (thin film): 3282 (N-H), 1639 (C=O).

HRMS (ESI +ve) found: 367.0407 [$(M+Na)^+$], $C_{17}H_{17}Br^{79}N_2NaO$ requires: 367.0416.

HPLC (Chiralpak AD-H, 9 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 17.8, t_R minor = 20.8; *Racemic*: t_R major = 17.8, t_R minor = 20.8.

This data is in accordance with the literature.[72]

(*E*)-*N*'-(3-Nitrobenzylidene)benzohydrazide 282



3-Nitrobenzaldehyde (312 mg, 2.07 mmol) and benzhydrazide (256 mg, 1.88 mmol) were dissolved in methanol (7 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **282** (219 mg, 43 %) as white needles.

Data for **282**:

m. p. 189 – 192 ˚C.

δ_H (400 MHz, d_6-DMSO): 12.12 (1H, br. s, NHCO), 8.56 (2H, ad, *J* 6.8, H1 and H3), 8.26 (1H, d, *J* 7.8, H5/7), 8.16 (1H, d, *J* 7.6, H5/7), 7.93 (2H, d, *J* 7.6, H9), 7.75 (1H, t, *J* 8.0, H6), 7.50 – 7.65 (3H, m, H10 and H11).

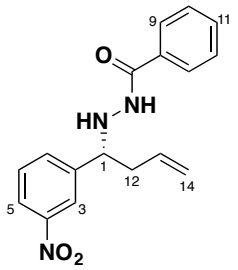
δ_C (101 MHz, d_6-DMSO): 164.3 (C=O), 149.1 (C4), 146.2 (C1), 137.1 (ArC), 134.3 (C5/7), 134.0 (ArC), 132.8 (C10/11), 131.3 (C6), 129.4 (C10/11), 128.6 (C9), 125.1 (C5/7), 121.8 (C3).

ν_{max} (thin film): 1650 (C=O), 1565 (C=N), 1532 (NO_2).

HRMS (ESI +ve) found: 292.0692 [$(M+Na)^+$], $C_{14}H_{11}N_3NaO_3$ requires: 292.0693.

This data is in accordance with the literature.[185]

(R)-*N*'-(1-(3-Nitrophenyl)but-3-en-1-yl)benzohydrazide 205



Racemic: Prepared using general procedure C. Hydrazone **282** (59 mg, 0.22 mmol) reacted to give product **205** (49 mg, 72 %) as a white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **282** (60 mg, 0.22 mmol) reacted to give product **205** (35 mg, 50 %, 11 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **282** (50 mg, 0.19 mmol) reacted to give product **205** (40 mg, 69 %, 10 % ee).

Data for **205**:

m. p. 77 – 80 ˚C.

δ_H (400 MHz, $CDCl_3$): 8.31 (1H, s, H3), 8.13 (1H, d, *J* 8.1, H5), 7.70 (1H, d, *J* 7.6, H7), 7.61 (3H, d, *J* 7.3, CONH and H9), 7.50 (2H, aq, *J* 7.7, H6 and H11), 7.38 (2H, m, H10), 5.83 (1H, td, *J* 16.8, 7.8, H13), 5.13 – 5.25 (3H, m, NH and CH_2(14)), 4.34 (1H, t, *J* 6.9, H1), 2.44 – 2.59 (2H, m, CH_2(12)).

δ_C (101 MHz, $CDCl_3$): 167.7 (C=O), 148.5 (C4), 144.3 (C2), 134.2 (C7), 133.4 (C13), 132.4 (C8), 132.1 (C6/11), 129.4 (C6/11), 128.7 (C10), 126.8 (C9), 122.7 (C3/5), 122.5 (C3/5), 119.0 (C14), 63.2 (C1), 40.5 (C12).

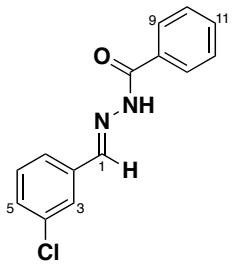
ν_{max} (thin film): 3287 (N-H), 1640 (C=O), 1528 (NO_2)

HRMS (ESI +ve) found: 334.1154 [$(M+Na)^+$], $C_{17}H_{17}N_3NaO_3$ requires: 334.1162.

HPLC (Chiralpak AD-H, 8 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 36.9, t_R minor = 39.1; *Racemic*: t_R major = 37.1, t_R minor = 39.2.

This data is in accordance with the literature.[186]

(*E*)-*N*'-(3-Chlorobenzylidene)benzohydrazide 283



3-Chlorobenzaldehyde (0.90 mL, 7.91 mmol) and benzhydrazide (1.02 g, 7.42 mmol) were dissolved in methanol (30 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **283** (1.57 g, 83 %) as white needles.

Data for **283**:

m. p. 182 – 185 ˚C.

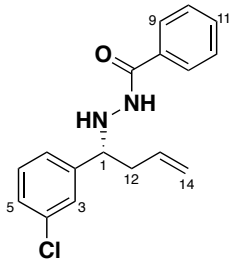
δ_H (500 MHz, d_6-DMSO): 12.01 (1H, br. s, NHCO), 8.46 (1H, s, H1), 7.94 (2H, d, *J* 7.3, H9), 7.80 (1H, s, H3), 7.70 (1H, m, H5/6/7), 7.61 (1H, m, H11), 7.55 (2H, m, H10), 7.50 (2H, m, H5/6/7).

δ_C (126 MHz, d_6-DMSO): 163.3 (C=O), 146.1 (C1), 136.6 (ArC), 133.7 (ArC), 133.2 (ArC), 131.9 (C11), 130.8 (C5/6/7), 129.7 (C5/6/7), 128.5 (C10), 127.7 (C9), 126.3 (C3), 125.8 (C5/6/7).

ν_{max} (thin film): 1650 (C=O), 1553 (C=N).

HRMS (ESI +ve) found: 281.0451 [$(M+Na)^+$], $C_{14}H_{11}Cl^{35}N_2NaO$ requires: 281.0452.

(R)-*N*'-(1-(3-Chlorophenyl)but-3-en-1-yl)benzohydrazide 206



Racemic: Prepared using general procedure C. Hydrazone **283** (124 mg, 0.48 mmol) reacted to give product **206** (106 mg, 74 %) as pale yellow needles.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **283** (115 mg, 0.45 mmol) reacted to give product **206** (79 mg, 59 %, 30 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **283** (113 mg, 0.44 mmol) reacted to give product **206** (110 mg, 84 %, 34 % ee).

Data for **206**:

m. p. 64 – 68 ˚C (Lit m. p. 65 – 66 ˚C).[184]

δ_H (500 MHz, $CDCl_3$): 7.61 (2H, m, H9), 7.55 (1H, br. s, CONH), 7.48 (1H, m, H11), 7.43 (1H, s, H3), 7.38 (2H, m, H10), 7.25 (3H, m, H5/6/7), 5.82 (1H, m, H13), 5.12 – 5.25 (3H, m, NH and CH_2(14)), 4.17 (1H, t, *J* 6.9, H1), 2.48 (2H, m, CH_2(12)).

δ_C (126 MHz, $CDCl_3$): 167.9 (C=O), 144.5 (C2), 134.9 (C4/8), 134.4 (C13), 133.1 (C4/8), 132.4 (C11), 130.3 (C5/6/7), 129.1 (C10), 128.3 (C5/6/7), 128.1 (C3), 127.3 (C9), 126.5 (C5/6/7), 118.9 (C14), 63.9 (C1), 40.9 (C12).

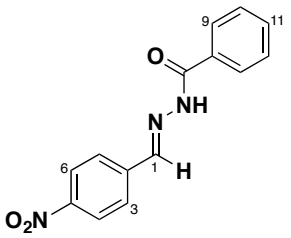
ν_{max} (thin film): 3278 (N-H), 1636 (C=O).

HRMS (ESI +ve) found: 323.0910 [$(M+Na)^+$], $C_{17}H_{17}Cl^{35}N_2NaO$ requires: 323.0922.

HPLC (Chiralpak AD-H, 6 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 19.2, t_R minor = 24.8; *Racemic*: t_R major = 19.3, t_R minor = 24.8.

This data is in accordance with the literature.[43]

(*E*)-*N*'-(4-Nitrobenzylidene)benzohydrazide 284



4-Nitrobenzaldehyde (1.74 g, 11.5 mmol) and benzhydrazide (1.36 g, 10.0 mmol) were dissolved in methanol (40 mL). Acetic acid (few drops) was added and the reaction was stirred for 10 min, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOH to yield hydrazone **284** (1.68 g, 63 %) as yellow needles.

Data for **284**:

m. p. 238 – 240 ˚C.

δ_H (400 MHz, d_6-DMSO): 12.16 (1H, br. s, NHCO), 8.55 (1H, s, H1), 8.30 (2H, d, *J* 8.3, H4 and H6), 7.87 – 8.03 (4H, m, H3, H7 and H9), 7.50 – 7.64 (3H, m, H10 and H11).

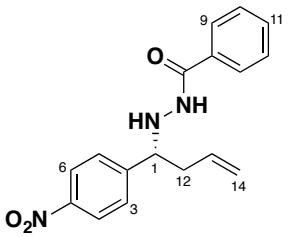
δ_C (101 MHz, d_6-DMSO): 164.3 (C=O), 148.7 (C5), 146.1 (C1), 141.5 (ArC), 133.9 (ArC), 132.9 (C11), 129.4 (C10), 128.9, 128.6 (C3/7 and C9), 124.9 (C4/6).

ν_{max} (thin film): 1654 (C=O), 1540 (C=N), 1512 and 1344 (NO_2).

HRMS (ESI +ve) found: 292.0689 [$(M+Na)^+$], $C_{14}H_{11}N_3NaO_3$ requires: 292.0693.

This data is in accordance with the literature.[80]

(R)-*N*'-(1-(4-Nitrophenyl)but-3-en-1-yl)benzohydrazide 207



Racemic: Prepared using general procedure C. Hydrazone **284** (237 mg, 0.88 mmol) reacted to give product **207** (176 mg, 64 %) as a yellow solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **284** (133 mg, 0.49 mmol) reacted to give product **207** (110 mg, 72 %, 31 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **284** (118 mg, 0.39 mmol) reacted to give product **207** (74 mg, 54 %, 43 % ee).

Data for **207**:

m. p. 123 – 125 ˚C (Lit m. p. 128 – 129 ˚C).

δ_H (400 MHz, $CDCl_3$): 8.16 (2H, d, *J* 8.6, H4 and H6), 7.71 (1H, s, NHCO), 7.61 (2H, m, H9), 7.55 (2H, d, *J* 8.6, H3 and H7), 7.48 (1H, m, H11), 7.37 (2H, m, H10), 5.73 – 5.86 (1H, m, H13), 5.11 – 5.25 (3H, m, NH and CH_2(14)), 4.32 (1H, t, *J* 7.1, H1), 2.41 – 2.56 (2H, m, CH_2(12)).

δ_C (101 MHz, $CDCl_3$): 167.7 (C=O), 149.6 (C5), 147.4 (ArC), 133.3 (C13), 132.3 (ArC), 132.1 (C11), 128.7 (C10), 128.6 (C3/7), 126.8 (C9), 123.7 (C4/6), 119.0 (C14), 63.4 (C1), 40.4 (C12).

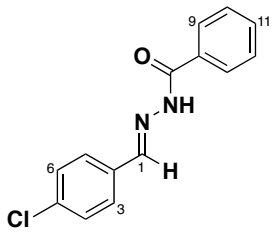
ν_{max} (thin film): 3280 (N-H), 1638 (C=O), 1516 and 1342 (NO_2).

HRMS (ESI +ve) found: 334.1159 [$(M+Na)^+$], $C_{17}H_{17}N_3NaO_3$ requires: 334.1159.

HPLC (Chiralpak AD-H, 8 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 40.3, t_R minor = 46.0; *Racemic*: t_R major = 40.3, t_R minor = 46.0.

This data is in accordance with the literature.[43]

(*E*)-*N'*-(4-Chlorobenzylidene)benzohydrazide 285



4-Chlorobenzaldehyde (457 mg, 3.26 mmol) and benzhydrazide (402 mg, 2.95 mmol) were dissolved in methanol (15 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **285** (667 mg, 88 %) as white crystalline solid.

Data for **285**:

m. p. 167 – 170 ˚C.

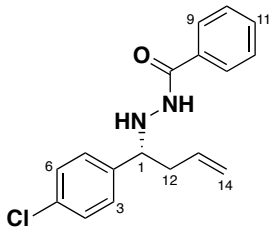
δ_H (400 MHz, d_6-DMSO): 11.93 (1H, s, NHCO), 8.45 (1H, s, H1), 7.92 (2H, d, *J* 7.6, H9), 7.76 (2H, d, *J* 8.1, H3/7), 7.30 – 7.63 (5H, m, H4/6, H10 and H11).

δ_C (101 MHz, d_6-DMSO): 164.0 (C=O), 147.3 (C1), 135.4 (ArC), 134.2 (ArC), 132.7 (C11), 129.8 (ArC), 129.8, 129.6, 129.4 (C4/6, C3/7 and C10), 128.5 (C9).

ν_{max} (thin film): 1650 (C=O), 1552 (C=N).

HRMS (ESI +ve) found: 281.0457 [$(M+Na)^+$], $C_{14}H_{11}Cl^{35}N_2NaO$ requires: 281.0452.

(R)-*N*'-(1-(4-Chlorophenyl)but-3-en-1-yl)benzohydrazide 208



Racemic: Prepared using general procedure C. Hydrazone **285** (98 mg, 0.38 mmol) reacted to give product **208** (109 mg, 96 %) as a white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **285** (109 mg, 0.42 mmol) reacted to give product **208** (119 mg, 93 %, 38 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **285** (116 mg, 0.45 mmol) reacted to give product **208** (86 mg, 64 %, 36 % ee).

Data for **208**:

m. p. 106 – 108 ˚C (Lit m. p. 102 – 103 ˚C).

δ_H (400 MHz, $CDCl_3$): 7.59 (3H, m, CONH and H9), 7.48 (1H, m, H11), 7.38 (2H, m, H10), 7.31 (4H, s, H3/4/6/7), 5.80 (1H, m, H13), 5.10 – 5.34 (3H, m, NH and CH_2(14)), 4.16 (1H, t, *J* 7.1, H1), 2.47 (2H, m, CH_2(12)).

δ_C (101 MHz, $CDCl_3$): 167.4 (C=O), 140.2 (ArC), 134.0 (C13), 133.3 (ArC), 132.6 (ArC), 131.9 (C11), 129.1, 128.7 (C3/7 and C4/6), 128.7 (C10), 126.8 (C9), 118.4 (C14), 63.2 (C1), 40.4 (C12).

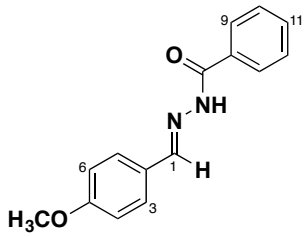
ν_{max} (thin film): 3279 (N-H), 1638 (C=O).

HRMS (ESI +ve) found: 323.0917 [$(M+Na)^+$], $C_{17}H_{17}Cl^{35}N_2NaO$ requires: 323.0922.

HPLC (Chiralpak AD-H, 6 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 21.6, t_R minor = 24.6; *Racemic*: t_R major = 21.6, t_R minor = 24.6.

This data is in accordance with the literature.[43]

(*E*)-*N*'-(4-Methoxybenzylidene)benzohydrazide 209



p-Anisaldehyde (1.40 mL, 11.5 mmol) and benzhydrazide (1.36 g, 10.0 mmol) were dissolved in methanol (40 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **209** (1.46 g, 57 %) as white needles.

Data for **209**:

m. p. 146 – 151 ˚C.

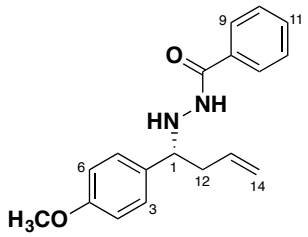
δ_H (400 MHz, d_6-DMSO): 11.74 (1H, s, NHCO), 8.42 (1H, s, H1), 7.92 (2H, d, *J* 7.3, H9), 7.68 (2H, d, *J* 8.8, H3 and H7), 7.47 – 7.60 (3H, m, H10 and H11), 7.02 (2H, d, *J* 8.6, H4 and H6), 3.80 (3H, s, OCH_3).

δ_C (101 MHz, d_6-DMSO): 163.9 (C=O), 161.7 (C5), 148.6 (C1), 134.5 (C8), 132.5 (C11), 129.6 (C3/7), 129.3 (C10), 128.4 (C9), 127.8 (C2), 115.2 (C4/6), 56.2 (OCH_3).

ν_{max} (thin film): 1654 (C=O), 1540 (C=N), 1512 and 1344 (NO_2).

HRMS (ESI +ve) found: 255.1131 [$(M+H)^+$], $C_{15}H_{15}N_2O_2$ requires: 255.1128.

(R)-*N*'-(1-(4-methoxyphenyl)but-3-en-1-yl)benzohydrazide 210



Racemic: Prepared using general procedure C. Hydrazone **209** (203 mg, 0.80 mmol) reacted to give product **210** (161 mg, 68 %) as a white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **209** (132 mg, 0.52 mmol) reacted to give product **210** (124 mg, 81 %, 32 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **209** (129 mg, 0.51 mmol) reacted to give product **210** (103 mg, 69 %, 38 % ee).

Data for **210**:

m. p. 88 – 90 ˚C.

δ_H (400 MHz, $CDCl_3$): 7.71 (1H, s, NHCO), 7.61 (2H, d, *J* 7.3, H9), 7.46 (1H, m, H11), 7.36 (2H, m, H10), 7.28 (2H, d, *J* 8.6, H3 and H7), 6.87 (2H, d, *J* H4 and H6), 5.80 (1H, m, H13), 5.06 – 5.31 (3H, m, NH and CH_2(14)), 4.11 (1H, t, *J* 7.1, H1), 3.78 (3H, s, OCH_3), 2.49 (2H, m, CH_2(12)).

δ_C (101 MHz, $CDCl_3$): 167.2 (C=O), 159.1 (C5), 134.6 (C13), 133.5 (ArC), 132.9 (ArC), 131.7 (C11), 128.8 (C3/7), 128.6 (C10), 126.9 (C9), 117.9 (C14), 113.9 (C4/6), 63.3 (C1), 55.2 (OCH_3), 40.2 (C12).

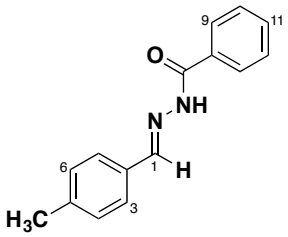
ν_{max} (thin film): 3281 (N-H), 1639 (C=O).

HRMS (ESI +ve) found: 319.1417 [$(M+Na)^+$], $C_{18}H_{20}N_2NaO_2$ requires: 319.1417.

HPLC (Chiralpak AD-H, 8 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 21.6, t_R minor = 24.6; *Racemic*: t_R major = 21.6, t_R minor = 24.6.

This data is in accordance with the literature.[43]

(*E*)-*N*'-(4-Methylbenzylidene)benzohydrazide 211



p-Tolualdehyde (1.33 mL, 11.2 mmol) and benzhydrazide (1.39 g, 10.2 mmol) were dissolved in methanol (40 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **211** (2.19 g, 90 %) as white needles.

Data for **211**:

m. p. 147 – 150 ˚C.

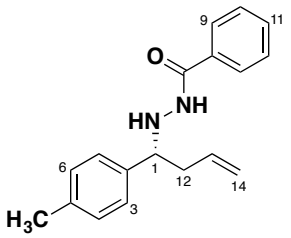
δ_H (400 MHz, d_6-DMSO): 11.80 (1H, s, NHCO), 8.43 (1H, s, H1), 7.92 (2H, d, *J* 7.3, H9), 7.63 (2H, d, *J* 8.1, H3/7), 7.58 (1H, d, *J* 7.1, H11), 7.53 (2H, m, H10), 7.27 (2H, d, *J* 7.8, H4/6), 2.34 (3H, s, CH_3).

δ_C (101 MHz, d_6-DMSO): 163.9 (C=O), 148.7 (C1), 140.8 (C5), 134.4 (C2/8), 132.6 (C2/8), 132.5 (C11), 130.3 (C4/6), 129.3 (C10), 128.5 (C9), 127.9 (C3/7), 21.9 (CH_3).

ν_{max} (thin film): 1646 (C=O), 1555 (C=N).

HRMS (ESI +ve) found: 261.1003 [$(M+Na)^+$], $C_{15}H_{14}N_2NaO$ requires: 261.0998.

(R)-*N*'-(1-(*p*-Tolyl)but-3-en-1-yl)benzohydrazide 212



Racemic: Prepared using general procedure C. Hydrazone **211** (114 mg, 0.48 mmol) reacted to give product **212** (103 mg, 77 %) as a pale yellow solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **211** (129 mg, 0.54 mmol) reacted to give product **212** (131 mg, 86 %, 39 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **211** (115 mg, 0.48 mmol) reacted to give product **212** (83 mg, 61 %, 40 % ee).

Data for **212**:

m. p. 74 – 77 ˚C (Lit m. p. 67 – 69 ˚C).[46]

δ_H (400 MHz, $CDCl_3$): 7.61 (3H, m, CONH and H9), 7.47 (1H, m, H11), 7.77 (2H, m, H10), 7.27 (2H, d, *J* 7.8, H3/7), 7.16 (2H, d, *J* 7.6, H4/6), 5.84 (1H, m, H13), 5.26 (1H, br. s, NH), 5.18 (1H, d, *J* 17.2, H_Z(14)), 5.12 (1H, d, *J* 10.1, H_Z(14)), 4.14 (1H, t *J* 7.1, H1), 2.50 (2H, m, CH_2(12)), 2.35 (3H, s, CH_3).

δ_C (101 MHz, $CDCl_3$): 167.1 (C=O), 138.5 (ArC), 137.3 (ArC), 134.6 (C13), 132.9 (ArC), 131.7 (C11), 129.3 (C4/6), 128.6 (C10), 127.6 (C3/7), 126.9 (C9), 117.9 (C14), 63.6 (C1), 40.3 (C12), 21.1 (CH_3).

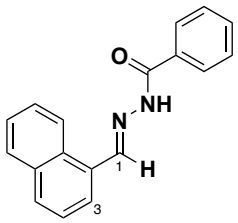
ν_{max} (thin film): 3279 (N-H), 1638 (C=O).

HRMS (ESI +ve) found: 303.1461 [$(M+Na)^+$], $C_{18}H_{20}N_2NaO$ requires: 303.1468.

HPLC (Chiralpak AD-H, 6 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 18.5, t_R minor = 22.3; *Racemic*: t_R major = 18.5, t_R minor = 22.3.

This data is in accordance with the literature.[54]

(*E*)-*N*'-(Naphthalen-1-ylmethylene)benzohydrazide 213



1-Naphthaldehyde (0.35 mL, 2.58 mmol) and benzhydrazide (0.39 g, 2.56 mmol) were dissolved in methanol (12 mL). Acetic acid (few drops) was added and the reaction was stirred for 1 h, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **213** (0.51 g, 75 %) as white needles.

Data for **213**:

m. p. 171 – 173 ˚C.

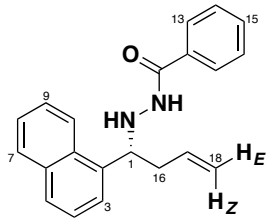
δ_H (500 MHz, d_6-DMSO): 11.95 (1H, s, NHCO), 9.13 (1H, s, H1), 8.89 (1H, d, *J* 8.5, H3), 8.04 (2H, t, *J* 7.1, ArH), 7.97 (3H, m, ArH), 7.70 (1H, m, H4), 7.55 – 7.66 (5H, m, ArH).

δ_C (126 MHz, d_6-DMSO): 163.1 (C=O), 147.7 (C1), 133.6 (ArC), 133.4 (ArC), 131.8 (ArCH), 130.6 (ArCH), 130.2 (ArC), 129.6 (ArC), 128.8 (ArCH), 128.6 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.4 (C4), 126.3 (ArCH), 125.6 (ArCH), 124.2 (C3).

ν_{max} (thin film): 1645 (C=O), 1552 (C=N).

HRMS (ESI +ve) found: 297.0989 [$(M+Na)^+$], $C_{18}H_{14}N_2NaO$ requires: 297.0998.

(R)-*N*'-(1-(naphthalen-1-yl)but-3-en-1-yl)benzohydrazide 214



Racemic: Prepared using general procedure C. Hydrazone **213** (44 mg, 0.16 mmol) reacted to give product **214** (38 mg, 75 %) as a crystalline white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **213** (41 mg, 0.15 mmol) reacted to give product **214** (27 mg, 57 %, 38 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **213** (120 mg, 0.50 mmol) reacted to give product **214** (60 mg, 43 %, 36 % ee).

Data for **214**:

m. p. 59 – 61 ˚C.

δ_H (500 MHz, $CDCl_3$): 8.27 (1H, br. s, ArH), 7.89 (1H, m, ArH), 7.82 (2H, d, *J* 8.2, ArH), 7.41 – 7.56 (7H, m, NHCO and ArH), 7.33 (2H, m, ArH), 5.98 (1H, m, H17), 5.47 (1H, d, *J* 3.5, NH), 5.26 (1H, dd, *J* 17.0, 1.3, H_Z(18)), 5.18 (1H, d, *J* 10.1, H_E(18)), 5.08 (1H, br. s, H1), 2.77 (1H, m, CH_2(16)), 2.64 (1H, m, CH_2(16)).

δ_C (126 MHz, $CDCl_3$): 167.3 (C=O), 137.3 (ArC), 134.6 (C17), 134.0 (ArC), 132.7 (ArC), 131.7 (ArCH), 131.7 (ArC), 128.9 (ArCH), 128.6 (ArCH), 128.0 (ArCH), 126.8 (ArCH), 126.1 (ArCH), 125.6 (ArCH), 125.5 (ArCH), 124.3 (br., ArCH), 123.2 (br. ArCH), 118.2 (C18), 59.5 (br., C1), 40.0 (C16).

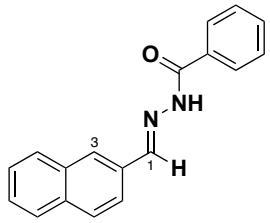
ν_{max} (thin film): 3296 (N-H), 1640 (C=O).

HRMS (ESI +ve) found: 339.1464 [$(M+Na)^+$], $C_{21}H_{20}N_2NaO$ requires: 339.1468.

HPLC (Chiralpak AD-H, 9 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 16.2, t_R minor = 19.9; *Racemic*: t_R major = 16.2, t_R minor = 19.9.

This data is in accordance with the literature.[72]

(*E*)-*N*'-(Naphthalen-2-ylmethylene)benzohydrazide 215



2-Naphthaldehyde (0.48 g, 3.08 mmol) and benzhydrazide (0.42 g, 3.07 mmol) were dissolved in methanol (15 mL). Acetic acid (few drops) was added and the reaction was stirred for 5 min, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **215** (0.63 g, 75 %) as white needles.

Data for **215**:

m. p. 210 – 212 ˚C (Lit m. p. 212 ˚C).

δ_H (500 MHz, d_6-DMSO): 11.96 (1H, s, NHCO), 8.63 (1H, s, H1), 8.17 (1H, s, H3), 7.93 – 8.05 (6H, m, ArH), 7.53 – 7.65 (5H, m, ArH).

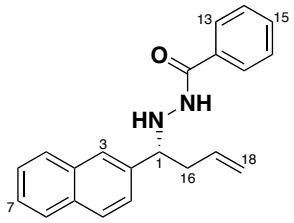
δ_C (126 MHz, d_6-DMSO): 163.2 (C=O), 147.7 (C1), 133.8 (ArC), 133.5 (ArC), 132.9 (ArC), 132.1 (ArC), 131.8 (ArCH), 128.7 (C3), 128.5 (2 × ArCH), 128.3 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 122.7 (ArCH).

ν_{max} (thin film): 1645 (C=O), 1551 (C=N).

HRMS (ESI +ve) found: 297.0995 [$(M+Na)^+$], $C_{18}H_{14}N_2NaO$ requires: 297.0998.

This data is in accordance with the literature.[187]

(R)-*N*'-(1-(Naphthalen-2-yl)but-3-en-1-yl)benzohydrazide 216



Racemic: Prepared using general procedure C. Hydrazone **215** (99 mg, 0.36 mmol) reacted to give product **216** (88 mg, 77 %) as a crystalline white solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **215** (54 mg, 0.20 mmol) reacted to give product **216** (15 mg, 27 %, 18 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **215** (126 mg, 0.50 mmol) reacted to give product **216** (63 mg, 43 %, 30 % ee).

Data for **216**:

m. p. 86 – 90 ˚C (Lit m. p. 106 – 107 ˚C).

δ_H (400 MHz, $CDCl_3$): 7.81 – 7.89 (4H, m, NHCO and ArH), 7.57 (3H, m, ArH), 7.42 – 7.53 (4H, m, ArH), 7.34 (2H, m, ArH), 5.89 (1H, m, H17), 5.25 – 5.55 (1H, br. s, NH), 5.22 (1H, dd, *J* 17.2, 1.5, H_Z(18)), 5.15 (1H, d, *J* 10.1, H_E(18)), 4.36 (1H, t, *J* 6.9, H1), 2.60 (2H, m, CH_2(16)).

δ_C (101 MHz, $CDCl_3$): 167.2 (C=O), 139.2 (ArC), 134.3 (C17), 133.4 (ArC), 133.1 (ArC), 132.7 (ArC), 131.8 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 127.9 (ArCH), 127.7 (ArCH), 126.8 (2 × ArCH), 126.1 (ArCH), 125.9 (ArCH), 125.5 (ArCH), 118.2 (C18), 64.1 (C1), 40.4 (C16).

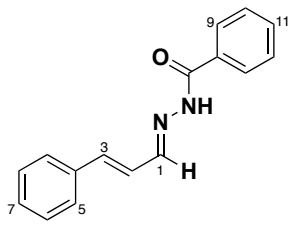
ν_{max} (thin film): 3284 (N-H), 1639 (C=O).

HRMS (ESI +ve) found: 339.1459 [$(M+Na)^+$], $C_{21}H_{20}N_2NaO$ requires: 339.1468.

HPLC (Chiralpak AD-H, 9 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 17.0, t_R minor = 20.5; *Racemic*: t_R major = 17.0, t_R minor = 20.5.

This data is in accordance with the literature.[46]

_N_'-((1_E_,2_E_)-3-Phenylallylidene)benzohydrazide 217



trans-Cinnamaldehyde (1.45 mL, 11.5 mmol) and benzhydrazide (1.36 g, 10.0 mmol) were dissolved in methanol (40 mL). Acetic acid (few drops) was added and the reaction was stirred for 5 min, after which time a suspension had formed. The solvent was removed under reduced pressure and the crude was recrystallized from hot EtOAc to yield hydrazone **217** (2.15 g, 86 %) as white needles.

Data for **217**:

m. p. 182 – 184 ˚C.

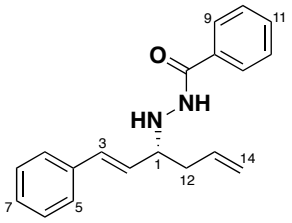
δ_H (400 MHz, d_6-DMSO): 11.75 (1H, s, NHCO), 8.25 (1H, d, *J* 7.1, H1), 7.91 (2H, d, *J* 7.3, H9), 7.49 – 7.65 (5H, m, H5, H10 and H11), 7.30 – 7.42 (3H, m, H6 and H7), 7.07 (2H, m, H2 and H3).

δ_C (101 MHz, d_6-DMSO): 163.4 (C=O), 150.6 (C1), 139.9 (C3), 136.8 (ArC), 134.3 (ArC), 132.6 (C5/10/11), 129.7 (C6 and C7), 129.3 (C5/10/11), 128.5 (C9), 127.9 (C5/10/11), 126.6 (C2).

ν_{max} (thin film): 1647 (C=O), 1543 (C=N).

HRMS (ESI +ve) found: 273.1005 [$(M+Na)^+$], $C_{16}H_{14}N_2NaO$ requires: 273.0998.

(R)-(*E*)-*N'*-(1-Phenylhexa-1,5-dien-3-yl)benzohydrazide 218



Racemic: Prepared using general procedure C. Hydrazone **217** (235 mg, 0.94 mmol) reacted to give product **218** (150 mg, 55 %) as a white crystalline solid.

Asymmetric: Prepared using catalyst **166** and general procedure D - hydrazone **217** (130 mg, 0.52 mmol) reacted to give product **218** (100 mg, 66 %, 9 % ee). Prepared using catalyst **140** and general procedure D - hydrazone **217** (127 mg, 0.51 mmol) reacted to give product **218** (105 mg, 71 %, 7 % ee).

Data for **218**:

m. p. 83 – 87 ˚C (Lit m. p. 91 ˚C).

δ_H (400 MHz, $CDCl_3$): 8.08 (1H, s, NHCO), 7.73 (2H, m, H9), 7.49 (1H, m, H11), 7.22 – 7.43 (7H, m, ArH), 6.56 (1H, d, *J* 15.7, H3), 6.12 (1H, dd, *J* 15.9, 8.6, H2), 5.90 (1H, ddt, *J* 17.1, 10.1, 7.0, H13), 5.11 – 5.25 (3H, m, NH and CH_2(14)), 3.76 (1H, m, H1), 2.41 (2H, m, CH_2(12)).

δ_C (101 MHz, $CDCl_3$): 167.3 (C=O), 136.7 (ArC), 134.2 (C13), 133.1 (C3), 132.9 (ArC), 131.8 (C11), 129.9 (C2), 128.7 (ArCH), 128.6 (ArCH), 127.7 (C7), 126.9 (C9), 126.5 (ArCH), 118.0 (C14), 62.5 (C1), 38.4 (C12).

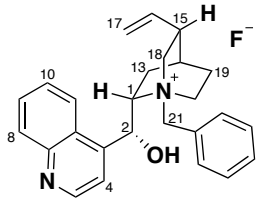
ν_{max} (thin film): 3277 (N-H), 1638 (C=O).

HRMS (ESI +ve) found: 315.1469 [$(M+Na)^+$], $C_{19}H_{20}N_2NaO$ requires: 315.1468.

HPLC (Chiralpak AD-H, 8 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 21.0, t_R minor = 23.0; *Racemic*: t_R major = 21.0, t_R minor = 23.0.

This data is in accordance with the literature.[53]

_N_-Benzylcinchonidinium fluoride 166



Prepared according to General Procedure E. *N*-Benzylcinchonidinium chloride (0.80 mmol) was passed down Amberlyst® A26-OH resin (2.0 g) and neutralized with 1M HF solution (0.80 mmol) to yield fluoride catalyst **166** (323 mg, quant) as an amorphous solid.

Data for **166**:

m. p. 144 – 147 ˚C.

δ_H (400 MHz, d_6-DMSO): 8.89 (1H, d, *J* 4.5, H5), 8.21 (1H, d, *J* 8.3, H11), 8.07 (1H, d, *J* 8.1, H8), 7.80 (2H, m, H4 and H9), 7.68 (3H, m, H10 and ArH), 7.51 (3H, m, ArH), 6.46 (1H, s, H2), 5.63 (1H, ddd, *J* 17.2, 10.6, 6.3, H16), 5.30 (1H, d, *J* 12.1, H21), 5.13 (1H, d, *J* 17.2, H_Z(17)), 4.94 (2H, dd, *J* 17.9, 11.4, H_E(17) and H21), 4.38 (1H, m, H20), 3.86 (1H, t, *J* 8.8, H1), 3.71 (1H, d, *J* 12.4, H18), 3.27 (1H, t, *J* 11.6, H18), 3.13 (1H, td, *J* 11.1, 4.3, H20), 2.65 (1H, br. s, H15), 2.06 (2H, m, H13 and H19), 1.95 (1H, br. s, H14), 1.76 (1H, br. s, H19), 1.17 (1H, m, H13).

δ_C (101 MHz, d_6-DMSO): 150.9 (C5), 148.4 (C3/7), 146.9 (C3/7), 139.1 (C16), 134.6 (ArCH), 130.9 (C8), 130.7 (C22), 130.1 (C4/9), 129.7 (ArCH), 129.0 (ArCH), 127.9 (C10), 125.2 (C12), 124.3

(C11), 121.1 (C4/9), 117.9 (C17), 65.0 (C1), 63.3 (C2), 60.1 (C21), 55.8 (C18), 51.1 (C20), 37.7 (C15), 26.7 (C14), 25.1 (C19), 21.9 (C13).

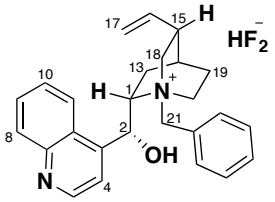
δ_F (377 MHz, d_6-DMSO): -124.5 (F^-).

ν_{max} (thin film): 2957 (OH), 753 (C-H aromatic).

HRMS (ESI +ve) found: 385.2277 [$(M)^+$], $C_{26}H_{29}N_2O^+$ requires: 385.2274.

$[\alpha]_D^{20}$: -149.5° (*c* 1.0 in $CHCl_3$).

_N_-Benzylcinchonidinium bifluoride 168



Prepared according to General Procedure E, modified by using 2 eq. of 1M HF solution. *N*-Benzylcinchonidinium chloride (0.40 mmol) was passed down Amberlyst® A26-OH resin (1.0 g) and neutralized with 1M HF solution (0.80 mmol) to yield fluoride catalyst **168** (176 mg, quant) as an amorphous solid.

Data for **168**:

m. p. 190 ˚C (dec).

δ_H (400 MHz, d_6-DMSO): 10.67 (1H, br. s, HF_2^-), 8.95 (1H, d, *J* 4.3, H5), 8.21 (1H, d, *J* 8.3, H8/11), 8.10 (1H, d, *J* 8.3, H8/11), 7.68 – 7.85 (5H, m, H4, H9, H10 and ArH), 7.52 (3H, m, ArH), 6.73 (1H, m, H2), 5.69 (1H, ddd, *J* 17.2, 10.5, 6.6, H16), 5.38 (1H, d, *J* 11.1, H21), 5.11 (1H, d, *J* 17.4, H_Z(17)), 4.95 (1H, d, *J* 10.6, H_E(17)), 4.85 (1H, d, *J* 11.6, H21), 4.37 (1H, br. s, H20), 3.86 (1H, t, *J* 8.5, H1), 3.62 (1H, dd, *J* 12.0, 3.9, H18), 3.30 (1H, t, *J* 11.6, H18), 3.12 (1H, m, H20), 2.67 (1H, br. s, H15), 2.13 (2H, m, H13 and H19), 1.96 (1H, d, *J* 2.0, H14), 1.77 (1H, t, *J* 9.9, H19), 1.33 (1H, t, *J* 11.5, H13).

δ_C (101 MHz, d_6-DMSO): 151.0 (C5), 148.5 (C3/7), 146.9 (C3/7), 139.0 (C16), 134.8 (ArCH), 130.8 (C8/11), 130.7 (ArC), 130.2 (ArC), 129.6 (ArCH), 129.1 (ArCH), 127.9 (ArCH), 125.3 (C12), 124.4

(C8/11), 120.9 (ArCH), 117.2 (C17), 69.0 (C1), 64.5 (C2), 63.6 (C21), 59.9 (C18), 51.2 (C20), 37.8 (C15), 26.9 (C14), 25.0 (C19), 21.4 (C13).

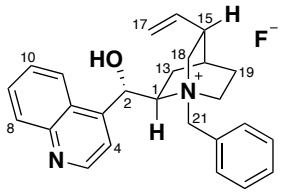
δ_F (377 MHz, d_6-DMSO): -146.0 (br. HF_2^-).

ν_{max} (thin film): 3316 (OH), 747 (C-H aromatic).

HRMS (ESI +ve) found: 385.2278 [$(M)^+$], $C_{26}H_{29}N_2O^+$ requires: 385.2274.

$[\alpha]_D^{20}$: -156.5° (*c* 1.0 in MeOH).

_N_-Benzylcinchoninium fluoride 135



Prepared according to General Procedure E. *N*-Benzylcinchoninium chloride (0.82 mmol) was passed down Amberlyst® A26-OH resin (2.0 g) and neutralized with 1M HF solution (0.82 mmol) to yield fluoride catalyst **135** (340 mg, quant) as an amorphous solid.

Data for **135**:

m. p. 134 – 137 °C.

δ_H (500 MHz, d_6-DMSO): 8.89 (1H, d, *J* 4.4, H5), 8.22 (1H, d, *J* 8.2, H8/11), 8.07 (1H, d, *J* 8.5, H8/11), 7.80 (2H, m, H4 and H9/10), 7.62 – 7.71 (3H, m, H9/10 and ArH), 7.45 – 7.54 (3H, m, ArH), 6.38 (1H, m, H2), 6.02 (1H, ddd, *J* 17.0, 10.7, 7.3, H16), 5.42 (1H, d, *J* 12.3, H21), 5.22 (2H, m, CH_2(17)), 4.96 (1H, d, *J* 12.3, H21), 4.45 (1H, t, *J* 9.3, H18), 3.74 – 3.89 (2H, m, H1 and H20), 3.33 (1H, m, H18), 2.88 – 2.98 (1H, m, H20), 2.60 (1H, m, H15), 2.28 (1H, m, H13), 1.66 – 1.85 (3H, m, H14 and CH_2(19)), 0.92 (1H, m, H13).

δ_C (126 MHz, d_6-DMSO): 150.1 (C5), 147.6 (C3/7), 146.5 (C3/7), 137.2 (C16), 133.7 (ArCH), 129.9 (C22), 129.8 (ArCH), 129.1 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 126.7 (ArCH), 124.5 (C8/11), 123.6 (C12), 120.3 (ArCH), 116.9 (C17), 67.8 (C1), 64.5 (C2), 61.8 (C21), 55.9 (C20), 53.4 (C18), 36.8 (C15), 26.4 (C14), 23.1 (C19), 20.7 (C13).

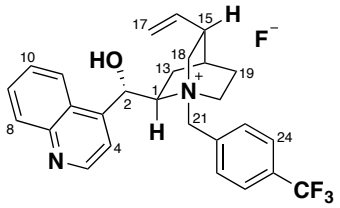
δ_F (470 MHz, d_6-DMSO): -118.8 (F^-).

ν_{max} (thin film): 2957 (OH), 753 (C-H aromatic).

HRMS (ESI +ve) found: 385.2272 [$(M)^+$], $C_{26}H_{29}N_2O^+$ requires: 385.2274.

$[\alpha]_D^{20}$: 118.4° (*c* 1.0 in $CHCl_3$).

_N_-[4-(Trifluoromethyl)benzyl]cinchoninium fluoride 190



Prepared according to General Procedure E. *N*-[4-(Trifluoromethyl)benzyl]cinchoninium bromide (0.38 mmol) was passed down Amberlyst® A26-OH resin (1.0 g) and neutralized with 1 M HF solution (0.38 mmol) to yield fluoride catalyst **190** (192 mg, 97 %) as an amorphous solid.

Data for **190**:

m. p. 141 – 143 °C.

δ_H (500 MHz, d_6-DMSO): 8.92 (1H, d, *J* 4.4, H5), 8.25 (1H, d, *J* 8.2, H8/11), 8.07 (1H, dd, *J* 8.5, 0.9, H8/11), 7.92 (2H, d, *J* 8.2, H23), 7.81 (4H, m, H4 H9/10 and H24), 7.67 (1H, m, H9/10), 6.41 (1H, m, H2), 6.00 (1H, ddd, *J* 17.5, 10.2, 7.3, H16), 5.46 (1H, d, *J* 12.0, H21), 5.20 (2H, m, CH_2(17)), 5.08 (1H, d, *J* 12.3, H21), 4.41 (1H, t, *J* 9.3, H18), 3.77 – 3.92 (2H, m, H1 and H20), 3.31 (1H, m, H18), 2.89 – 3.03 (1H, m, H20), 2.60 (1H, q, *J* 8.4, H15), 2.20 – 2.31 (1H, m, H13), 1.69 – 1.85 (3H, m, H14 and CH_2(19)), 0.95 (1H, m, H13).

δ_C (126 MHz, d_6-DMSO): 150.1 (C5), 147.6 (C3/7), 146.0 (C3/7), 137.2 (C16), 134.6 (C23), 133.0 (ArCH), 130.1 (q, *J* 32.1 C25), 129.8 (C8/11), 129.1 (C22), 126.9 (ArCH), 125.5 (q, *J* 3.8, C24), 124.5 (ArCH), 124.0 (q, *J* 273.7, CF_3), 123.6 (ArCH), 120.2 (ArCH), 116.9 (C17), 68.0 (C1), 64.5 (C2), 61.0 (C21), 56.0 (C20), 53.6 (C18), 36.8 (C15), 26.3 (C14), 23.1 (C19), 20.6 (C13).

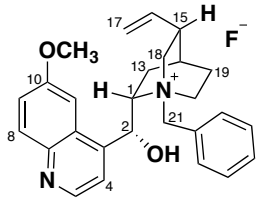
δ_F (377 MHz, d_6-DMSO): -61.3 (CF_3), -124.0 (F^-).

ν_{max} (thin film): 2963 (OH), 1327 (C-F), 755 (C-H aromatic).

HRMS (ESI +ve) found: 453.2147 [$(M)^+$], $C_{27}H_{28}F_3N_2O^+$ requires: 453.2148.

$[\alpha]_D^{20}$: 124.0° (*c* 1.0 in $CHCl_3$).

***N*-Benzylquininium fluoride 140**



Prepared according to General Procedure E. *N*-Benzylquininium chloride (0.40 mmol) was passed down Amberlyst® A26-OH resin (1.0 g) and neutralized with 1 M HF solution (0.40 mmol) to yield fluoride catalyst **140** (185 mg, quant) as an amorphous solid.

Data for **140**:

m. p. 136 – 138 ˚C.

δ_H (500 MHz, d_6-DMSO): 8.76 (1H, d, *J* 4.4, H5), 8.00 (1H, d, *J* 9.1, H8), 7.75 (1H, d, *J* 4.4, H4), 7.68 (2H, dd, *J* 7.4, 1.7, H23), 7.50 – 7.56 (3H, m, H24 and H25), 7.47 (1H, dd, *J* 9.1, 2.5, H9), 7.37 (1H, d, *J* 2.5, H11), 6.55 (1H, s, H2), 5.73 (1H, ddd, *J* 17.3, 10.4, 6.9, H16), 5.57 (1H, d, *J* 12.3, H21), 5.10 (1H, dt, *J* 17.3, 1.3, H_Z(17)), 5.00 (1H, dt, *J* 10.4, 1.3, H_E(17)), 4.64 (1H, d, *J* 12.3, H21), 4.45 (1H, t, *J* 11.2, H20), 3.98 (3H, s, OCH_3), 3.79 (1H, dd, *J* 9.9, 7.1, H1), 3.62 (1H, ddd, *J* 12.7, 5.8, 2.7, H18), 3.31 (1H, m, H18), 3.11 (1H, td, *J* 11.4, 6.1, H20), 2.68 (1H, d, *J* 8.5, H15), 2.10 – 2.23 (2H, m, H13 and H19), 1.98 (1H, d, *J* 2.5, H14), 1.79 (1H, td, *J* 11.3, 2.0, H19), 1.37 (1H, m, H13).

δ_C (126 MHz, d_6-DMSO): 157.3 (C10), 147.4 (C5), 144.9 (C3/7), 143.6 (C3/7), 138.2 (C16), 133.6 (C23), 131.4 (C8), 130.1 (C22), 128.9 (C24), 128.1 (C25), 125.4 (C12), 121.3 (C9), 120.4 (C4), 116.5 (C17), 102.0 (C11), 68.7 (C1), 63.5 (C2), 63.0 (C21), 59.2 (C18), 55.4 (OCH_3), 50.3 (C20), 37.0 (C15), 26.0 (C14), 24.2 (C19), 20.5 (C13).

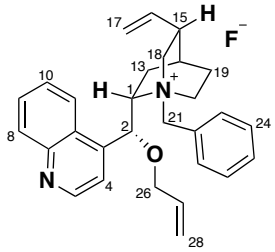
δ_F (377 MHz, d_6-DMSO): -118.7 (F^-).

ν_{max} (thin film): 2949 (OH), 750 (C-H aromatic).

HRMS (ESI +ve) found: 415.2380 [$(M)^+$], $C_{27}H_{31}N_2O_2^+$ requires: 415.2380.

$[\alpha]_D^{20}$: -191.8˚ (*c* 1.0 in $CHCl_3$).

***O*-Allyl-*N*-benzylcinchonidinium fluoride 191**



Prepared according to General Procedure E. *O*-Allyl-*N*-benzylcinchonidinium bromide (0.40 mmol) was passed down Amberlyst® A26-OH resin (1.0 g) and neutralized with 1 M HF solution (0.40 mmol) to yield fluoride catalyst **191** (190 mg, 98 %) as an amorphous solid.

Data for **191**:

m. p. 158 – 160 ˚C.

δ_H(500 MHz, d_6-DMSO): 9.02 (1H, d, *J* 4.4, H5), 8.24 (1H, d, *J* 8.2, H8/11), 8.15 (1H, dd, *J* 8.4, 1.1, H8/11), 7.89 (1H, ddd, *J* 8.3, 7.0, 1.1, H9/10), 7.80 (1H, ddd, *J* 8.3, 6.9, 1.3, H9/10), 7.72 (3H, m, H4 and H23), 7.60 (3H, m, H24 and H25), 6.43 (1H, s, H2), 6.17 (1H, ddt, *J* 17.2, 10.7, 5.4, H27), 5.70 (1H, ddd, *J* 17.3, 10.6, 6.8, H16), 5.47 (1H, dq, *J* 17.3, 1.6, H_Z(28)), 5.31 (1H, dq, *J* 10.6, 1.7, H_E(28)), 5.09 – 5.18 (2H, m, H_Z(17) and H21), 4.98 (1H, dt, *J* 10.6, 1.1, H_E(17)), 4.91 (1H, d, *J* 12.3, H21), 4.34 (1H, ddt, *J* 12.6, 5.4, 1.4, H26), 3.95 – 4.07 (3H, m, H1, H20 and H26), 3.67 (1H, m, H18), 3.31 (2H, m, H18 and H20), 2.69 (1H, br. s, H15), 2.29 (1H, m, H13), 2.07 – 2.20 (2H, m, H14 and H19), 2.03 (1H, dd, *J* 5.5, 2.7, H19), 1.86 (1H, t, *J* 12.1, H13).

δ_C (126 MHz, d_6-DMSO): 150.3 (C5), 148.0 (C3/7), 141.2 (C3/7), 137.9 (C16), 134.2 (C28), 133.8 (C23), 130.2 (C8/11), 130.0 (C9/10), 129.7 (C25), 129.0 (C24), 127.7 (C22), 127.4 (C9/10), 125.0 (C12), 123.4 (C8/11), 119.6 (C4), 117.7 (C28), 116.5 (C17), 71.9 (br. C2), 69.3 (C26), 67.7 (C1), 63.6 (C21), 59.0 (C18), 50.9 (C20), 36.8 (C15), 25.9 (C14), 24.2 (C19), 20.8 (C13).

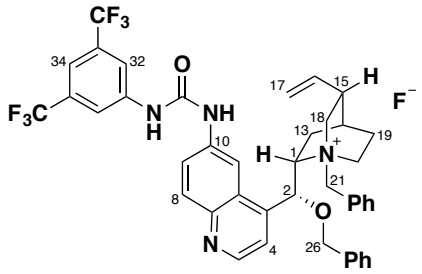
δ_F (470 MHz, d_6-DMSO): -123.5 (F^-).

ν_{max} (thin film): 2948 (OH), 763 (C-H aromatic).

HRMS (ESI +ve) found: 425.2586 [$(M)^+$], $C_{29}H_{33}N_2O^+$ requires: 425.2587.

$[\alpha]_D^{20}$: -149.1˚ (*c* 1.0 in $CHCl_3$).

1-Benzyl-2-((*R*)-(benzyloxy)(6-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium fluoride 192



Prepared according to General Procedure E. The parent quaternary ammonium bromide[136, 188] (0.12 mmol) was passed down Amberlyst® A26-OH resin (0.3 g) and neutralized with 1 M HF solution (0.12 mmol) to yield fluoride catalyst **192** (98 mg, quant.) as an amorphous solid.

Data for **192**:

m. p. 167 – 170 ˚C.

δ_H (500 MHz, d_6-DMSO): 10.32 (1H, br. s, NH), 10.12 (1H, br. s, NH), 8.89 (1H, d, *J* 4.4, H5), 8.70 (1H, br. s, H34), 8.09 (1H, d, *J* 9.1, H8), 8.03 (2H, s, H32), 7.77 (1H, dd, *J* 9.0, 2.0, H9), 7.71 (1H, d, *J* 4.4, H4), 7.52 – 7.64 (6H, m, ArH), 7.44 – 7.50 (4H, m, ArH), 7.40 (1H, m, ArH), 6.50 (1H, br. s, H2), 5.72 (1H, ddd, *J* 17.2, 10.4, 6.8, H16), 5.50 (1H, d, *J* 11.3, H21), 5.08 (1H, d, *J* 17.3, H_Z(17)), 4.97 (2H, d, *J* 10.7, H_E(17) and H26), 4.84 (1H, d, *J*, 12.3, H21), 4.54 (1H, d, *J* 10.7, H26), 4.07 (1H, dd, *J* 10.9, 5.5, H1), 3.93 (1H, t, *J* 11.7, H20), 3.51 (1H, ddd, *J* 12.2, 6.7, 2.2, H18), 3.26 (2H, m, H18 and H20), 2.64 (1H, m, H15), 2.33 (1H, d, *J* 11.7, H13), 1.95 – 2.06 (2H, m, H14 and H19), 1.77 (1H, t, *J* 10.6, H19), 1.55 (1H, t, *J* 12.0, H13).

δ_C (126 MHz, d_6-DMSO): 152.8 (C=O), 148.2 (C5), 144.6 (ArC), 141.8 (ArC), 140.1 (ArC), 138.2 (ArC), 137.7 (C16), 137.3 (ArC), 133.5 (ArCH), 130.6 (q, *J* 32, C33), 130.6 (C8), 130.1 (ArC), 128.8 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.6 (ArCH), 125.7 (ArC), 123.1 (q, *J* 273.1, CF_3), 122.9 (ArCH), 119.6 (br., ArCH), 117.6 (q, *J* 2.0, C32), 116.6 (C17), 114.4 (br., ArCH), 108.0 (br., C34), 71.6 (C2), 70.3 (C26), 68.5 (C1), 64.4 (C21), 58.7 (C18), 50.6 (C20), 37.0 (C15), 26.1 (C14), 24.0 (C19), 20.1 (C13).

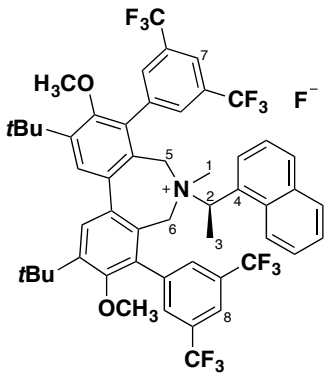
δ_F (377 MHz, d_6-DMSO): -61.7 (CF_3), -121.3 (F^-).

ν_{max} (thin film): 1712 (C=O), 1278 (C-F), 756 (C-H aromatic).

HRMS (ESI +ve) found: 745.2977 [$(M)^+$], $C_{42}H_{39}F_6N_4O_2^+$ requires: 745.2972.

$[\alpha]_D^{20}$: -220.2° (*c* 1.0 in $CHCl_3$).

(*R*)-4,8-bis(3,5-bis(Trifluoromethyl)phenyl)-2,10-di-*tert*-butyl-3,9-dimethoxy-6-methyl-6-(1-(naphthalen-1-yl)ethyl)-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-6-ium fluoride 193



Prepared according to General Procedure E. Lygo's catalyst[26,137] (0.40 mmol) was passed down Amberlyst® A26-OH resin (1.0 g) and neutralized with 1 M HF solution (0.40 mmol) to yield fluoride catalyst **193** (365 mg, 93 %) as an amorphous solid.

Data for **193**:

m. p. 150 – 152 °C.

δ_H (500 MHz, d_6-DMSO): 8.50 (1H, s, H7/8), 8.39 (1H, s, H7/8), 8.20 (3H, m, ArH), 8.05 (2H, d, *J* 8.2, ArH), 7.67 (3H, m, ArH), 7.57 (2H, m, ArH), 7.34 (2H, dt, *J* 14.7, 7.5, ArH), 6.98 (1H, d, *J* 8.8, ArH), 5.07 (1H, d, *J* 6.9, H2), 4.59 (1H, d, *J* 14.2, H5/6), 3.86 (1H, d, *J* 14.2, H5/6), 3.28 (1H, d, *J* 13.6, H5/6), 3.20 (3H, s, OCH_3), 2.98 (3H, s, OCH_3), 2.84 (1H, d, *J* 13.6, H5/6), 2.50 (3H, s, CH_3(1)), 1.60 (9H, s, $C(CH_3)_3$), 1.45 (9H, s, $C(CH_3)_3$), 0.84 (3H, d, *J* 6.6, CH_3(3)).

δ_C (126 MHz, d_6-DMSO): 157.5 (COMe), 157.3 (COMe), 146.6 (C*t*Bu), 145.4 (C*t*Bu), 137.8 (ArC), 137.5 (ArC), 137.0 (ArC), 136.1 (ArC), 135.2 (ArC), 134.7 (ArC), 133.7 (ArC), 132.8 (br. C7/8), 132.4 (br. ArCH), 131.7 (q, *J* 33.8, CCF_3), 131.4 (ArCH), 131.3 (ArCH), 131.1 (ArC), 131.0 (br. ArCH), 130.4 (q, *J* 34.0, CCF_3), 130.4 (q, *J* 33.8, CCF_3), 130.2 (ArCH), 128.8 (ArCH), 128.3 (q, *J* 34.1, CCF_3), 127.8 (ArCH), 127.6 (ArCH), 127.5 (C4), 127.0 (ArCH), 126.3 (ArCH), 125.6 (ArC),

125.0 (ArCH), 124.6 (ArC), 123.2 (q, *J* 273.4, CF_3), 123.0 (q, *J* 273.3, CF_3), 122.9 (q, *J* 272.9, CF_3), 122.8 (br. C7/8), 122.7 (q, *J* 273.0, CF_3), 121.8 (ArCH), 119.5 (ArCH), 61.4 (C2), 61.1 (OCH_3), 60.8 (OCH_3), 57.7 (C5/6), 57.4 (C5/6), 42.0 (C1), 35.5 ($C(CH_3)_3$), 35.2 ($C(CH_3)_3$), 30.7 ($C(CH_3)_3$), 30.6 ($C(CH_3)_3$), 14.7 (C3).

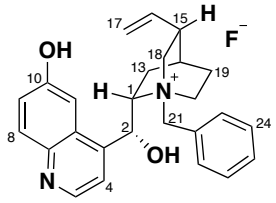
δ_F (377 MHz, d_6-DMSO): -61.3 (CF_3), -123.9 (F^-).

ν_{max} (thin film): 1280 (C-F), 755 (C-H aromatic).

HRMS (ESI +ve) found: 960.3647 [$(M)^+$], $C_{53}H_{50}F_{12}NO_2^+$ requires: 960.3644.

$[\alpha]_D^{20}$: 91.0° (*c* 1.0 in $CHCl_3$).

Demethyl-*N*-benzylquininium fluoride 194



Prepared according to General Procedure E. Demethyl-*N*-benzylquininium bromide[136] (0.22 mmol) was passed down Amberlyst® A26-OH resin (0.6 g) and neutralized with 1 M HF solution (0.22 mmol) to yield fluoride catalyst **194** (100 mg, quant.) as an amorphous solid.

Data for **194**:

m. p. 204 – 206 °C.

δ_H (500 MHz, d_6-DMSO): 8.71 (1H, d, *J* 4.4, H5), 7.92 (1H, d, *J* 8.8, H8), 7.73 (2H, br. s, ArH), 7.66 (1H, d, *J* 4.4, H4), 7.56 (3H, m, ArH), 7.43 (1H, s, H11), 7.34 (1H, d, *J* 8.8, H9), 6.84 (1H, br. s, OH), 6.38 (1H, br. s, H2), 5.72 (1H, ddd, *J* 17.3, 10.5, 6.6, H16), 5.25 (1H, d, *J* 12.0, H21), 5.17 (1H, d, *J* 17.3, H_Z(17)), 4.99 (1H, d, *J* 10.7, H_E(17)), 4.90 (1H, d, *J* 11.7, H21), 4.26 (1H, t, *J* 10.1, H20), 4.13 (1H, br. s, OH), 3.91 (1H, t, *J* 8.4, H1), 3.72 (1H, dd, *J* 11.7, 3.8, H18), 3.30 (1H, m, H18), 3.19 (1H, m, H20), 2.68 (1H, br. s, H15), 2.06 – 2.20 (2H, m, H13 and H19), 1.99 (1H, d, *J* 2.5, H14), 1.81 (1H, t, *J* 11.2, H19), 1.36 (1H, m, H13).

δ_C (126 MHz, d_6-DMSO): 156.6 (C10), 146.3 (C5), 143.1 (C3/7), 142.8 (C3/7), 138.1 (C16), 133.9 (ArCH), 131.4 (C8), 130.1 (C22), 128.9 (ArCH), 128.0 (ArCH), 125.8 (C12), 122.0 (C9), 119.8 (C4),

116.4 (C17), 104.0 (C11), 67.8 (C1), 63.9 (C2), 63.0 (C21), 58.9 (C18), 50.4 (C20), 36.9 (C15), 26.0 (C14), 24.2 (C19), 20.5 (C13).

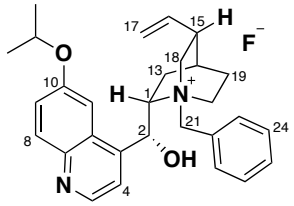
δ_F (377 MHz, d_6-DMSO): -123.4 (F^-).

ν_{max} (thin film): 2961 (OH), 748 (C-H aromatic).

HRMS (ESI +ve) found: 401.2224 [$(M)^+$], $C_{26}H_{29}N_2O_2^+$ requires: 401.2224.

$[\alpha]_D^{20}$: -189.0° (*c* 1.0 in MeOH).

(1*S*,2*S*,4*S*,5*R*)-1-Benzyl-2-((*R*)-hydroxy(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium fluoride 195



Prepared according to General Procedure E. The parent quaternary ammonium bromide[136] (0.10 mmol) was passed down Amberlyst® A26-OH resin (0.3 g) and neutralized with 0.5 M HF solution (0.10 mmol) to yield fluoride catalyst **195** (41 mg, 92 %) as an amorphous solid.

Data for **195**:

m. p. 144 – 148 °C.

δ_H (500 MHz, d_4-MeOD): 8.78 (1H, d, *J* 4.7, H5), 8.07 (1H, d, *J* 9.5, H8), 7.88 (1H, d, *J* 4.7, H4), 7.70 (2H, dd, *J* 7.1, 2.4, ArH), 7.60 (3H, m, ArH), 7.57 (1H, dd, *J* 9.5, 2.5, H9), 7.46 (1H, d, *J* 2.5, H11), 6.61 (1H, s, H2), 5.75 (1H, ddd, *J* 17.3, 10.4, 6.9, H16), 5.37 (1H, d, *J* 12.3, H21), 5.14 (1H, d, *J* 17.0, H_Z(17)), 5.06 (1H, d, *J* 10.4, H_E(17)), 4.95 (1H, m, OCH), 4.72 (1H, d, *J* 12.3, H21), 4.45 (1H, m, H20), 3.89 (1H, t, *J* 8.8, H1), 3.55 (1H, m, H18), 3.49 (1H, m, H18), 3.39 (1H, td, *J* 11.3, 4.9, H20), 2.73 (1H, d, *J* 7.3, H15), 2.28 – 2.41 (2H, m, H13 and H19), 2.10 (1H, m, H14), 1.90 (1H, t, *J* 9.8, H19), 1.55 (1H, m, H13), 1.44 (6H, dd, *J* 9.8, 6.0, CH_3).

δ_C (126 MHz, d_4-MeOD): 158.2 (C10), 148.3 (C5), 146.1 (C3/7), 144.6 (C3/7), 138.7 (C16), 134.8 (ArCH), 132.0 (C8), 131.9 (C25), 130.5 (ArCH), 128.7 (C12/22), 127.6 (C12/22), 123.5 (C9), 121.6

(C4), 117.6 (C17), 105.5 (C11), 71.8 (OCH), 70.3 (C1), 66.1 (C2), 65.8 (C21), 62.1 (C18), 52.8 (C20), 39.3 (C15), 28.2 (C14), 25.9 (C19), 22.4 (CH_3), 22.3 (CH_3), 22.2 (C13).

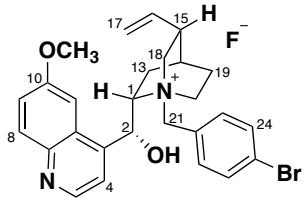
δ_F (377 MHz, d_4-MeOD): -133.1 (F^-).

ν_{max} (thin film): 2977 (OH), 751 (C-H aromatic).

HRMS (ESI +ve) found: 443.2679 [$(M)^+$], $C_{29}H_{35}N_2O_2^+$ requires: 443.2693.

$[\alpha]_D^{20}$: -169.5° (*c* 0.8 in $CHCl_3$).

_N_-4-Bromobenzylquininium fluoride 196



Prepared according to General Procedure E. *N*-4-Bromobenzylquininium bromide (0.22 mmol) (compound prepared by a coworker following the procedure of Dixon *et al.*[188]) was passed down Amberlyst® A26-OH resin (0.6 g) and neutralized with 0.5 M HF solution (0.22 mmol) to yield fluoride catalyst **196** (108 mg, 96 %) as an amorphous solid.

Data for **196**:

m. p. 188 – 190 °C.

δ_H (500 MHz, d_6-DMSO): 8.75 (1H, d, *J* 4.7, H5), 7.91 (1H, d, *J* 9.1, H8), 7.75 (1H, d, *J* 4.4, H4), 7.71 (2H, m, H23/24), 7.65 (2H, m, H23/24), 7.46 (1H, dd, *J* 9.1, 2.5, H9), 7.34 (1H, d, *J* 2.2, H11), 6.45 (1H, s, H2), 5.71 (1H, ddd, *J* 17.3, 10.5, 6.6, H16), 5.64 (1H, d, *J* 12.3, H21), 5.09 (1H, d, *J* 17.3, H_Z(17)), 4.98 (1H, dt, *J* 10.4, H_E(17)), 4.49 – 4.61 (2H, m, H20 and H21), 3.98 (3H, s, OCH_3), 3.72 (1H, m, H1), 3.59 (1H, ddd, *J* 12.5, 5.3, 2.4, H18), 3.33 (1H, m, H18), 3.05 (1H, td, *J* 11.0, 6.0, H20), 2.65 (1H, m, H15), 2.07 – 2.17 (2H, m, H13 and H19), 1.96 (1H, d, *J* 2.5, H14), 1.76 (1H, m, H19), 1.30 (1H, m, H13).

δ_C (126 MHz, d_6-DMSO): 157.3 (C10), 147.4 (C5), 145.2 (C3/7), 143.6 (C3/7), 138.2 (C16), 135.7 (C23/24), 131.8 (C23/24), 131.4 (C8), 127.6 (ArC), 125.5 (ArC), 123.9 (ArC), 121.2 (C9), 120.5

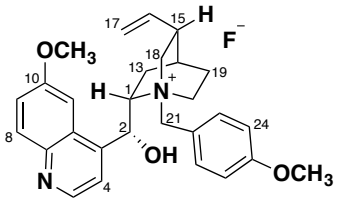
(C4), 116.4 (C17), 102.0 (C11), 68.8 (C1), 63.4 (C2), 61.9 (C21), 59.2 (C18), 55.4 (OCH_3), 50.1 (C20), 37.0 (C15), 26.0 (C14), 24.3 (C19), 20.7 (C13).

δ_F (377 MHz, d_6-DMSO): -117.6 (F^-).

ν_{max} (thin film): 2953 (OH), 721 (C-H aromatic).

HRMS (ESI +ve) found: 493.1487 [$(M)^+$], $C_{27}H_{30}Br^{79}N_2O_2^+$ requires: 493.1485.

_N_-4-Methoxybenzylquininium fluoride 197



Prepared according to General Procedure E. *N*-4-Methoxybenzylquininium chloride (0.10 mmol) (compound prepared by a coworker following the procedure of Dixon *et al.*[188]) was passed down Amberlyst® A26-OH resin (0.3 g) and neutralized with 0.5 M HF solution (0.10 mmol) to yield fluoride catalyst **197** (46 mg, quant.) as an amorphous solid.

Data for **197**:

m. p. 135 ˚C (dec).

δ_H (500 MHz, d_6-DMSO): 8.76 (1H, d, *J* 4.4, H5), 8.00 (1H, d, *J* 9.1, H8), 7.74 (1H, d, *J* 4.4, H4), 7.59 (2H, d, *J* 8.5, H23), 7.46 (1H, dd, *J* 9.1, 2.5, H9), 7.34 (1H, d, *J* 2.5, H11), 7.03 (2H, d, *J* 8.5, H24), 6.55 (1H, br. s, H2), 5.72 (1H, ddd, *J* 17.4, 10.4, 7.0, H16), 5.55 (1H, d, *J* 12.0, H21), 5.09 (1H, d, *J* 17.3, H_Z(17)), 4.99 (1H, d, *J* 10.4, H_E(17)), 4.58 (1H, d, *J* 12.0, H21), 4.42 (1H, br. s, H20), 3.97 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.74 (1H, m, H1), 3.55 (1H, m, H18), 3.30 (1H, m, H18), 3.07 (1H, m, H20), 2.66 (1H, d, *J* 2.1, H15), 2.09 – 2.22 (2H, m, H13 and H19), 1.97 (1H, d, *J* 2.5, H14), 1.77 (1H, m, H19), 1.37 (1H, m, H13).

δ_C (126 MHz, d_6-DMSO): 160.4 (C10/25), 157.3 (C10/25), 147.4 (C5), 145.1 (C3/7), 143.6 (C3/7), 138.2 (C16), 134.9 (C23), 131.4 (C8), 125.5 (C12), 121.3 (C9), 120.4 (C4), 119.7 (C22), 116.4 (C17), 114.2 (C24), 101.9 (C11), 68.4 (C1), 63.4 (C2), 62.6 (C21), 58.8 (C18), 55.3 (OCH_3), 55.3 (OCH_3), 49.9 (C20), 37.0 (C15), 26.1 (C14), 24.2 (C19), 20.4 (C13).

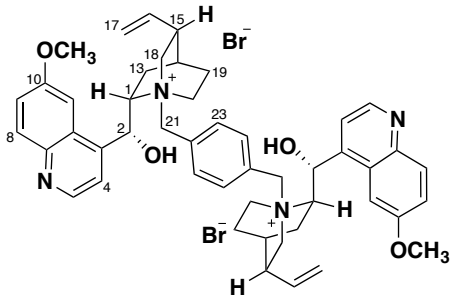
δ_F (377 MHz, d_6-DMSO): -119.3 (F^-).

ν_{max} (thin film): 2927 (OH), 754 (C-H aromatic).

HRMS (ESI +ve) found: 445.2484 [$(M)^+$], $C_{28}H_{33}N_2O_3^+$ requires: 445.2486.

$[\alpha]_D^{20}$: -135.6° (*c* 0.5 in $CHCl_3$).

Bis-*N*-Benzylquininium dibromide 200



Quinine (0.49 g, 1.51 mmol) and *p*-xylylene-di-bromide (0.16 g, 0.60 mmol) were dissolved in tetrahydrofuran (6.0 mL) and was heated to reflux and stirred for 18 h. The reaction was then cooled to room temperature and the yellow precipitate was filtered off. The precipitate was further washed with diethyl ether (25 mL) and the product **200** required no further purification (0.54 g, quant.).

Data for **200**:

m. p. 220 °C (dec).

δ_H (500 MHz, d_6-DMSO): 8.83 (2H, d, *J* 4.4, H5), 8.04 (2H, d, *J* 9.5, H8), 7.85 (4H, s, H23), 7.79 (2H, d, *J* 4.4, H4), 7.52 (2H, dd, *J* 9.1, 2.5, H9), 7.42 (2H, d, *J* 2.5, H11), 6.70 (2H, d, *J* 4.4, H2), 6.64 (2H, br. s, OH), 5.76 (2H, ddd, *J* 17.3, 10.3, 6.8, H16), 5.51 (2H, d, *J* 11.7, H21), 5.13 (2H, d, *J* 17.3, H_Z(17)), 5.02 (2H, d, *J* 10.4, H_E(17)), 4.80 (2H, d, *J* 11.7, H21), 4.23 (2H, m, H20), 4.05 (6H, s, OCH_3), 3.86 (2H, m, H1), 3.72 (4H, br. s, CH_2(18)), 3.48 (2H, d, *J* 5.4, H20), 2.87 (2H, d, *J* 7.3, H15), 2.24 (2H, br. s, H13), 2.10 (2H, br. s, H19), 2.02 (2H, br. s, H14), 1.69 (2H, m, H19), 1.45 (2H, t, *J* 11.3, H13).

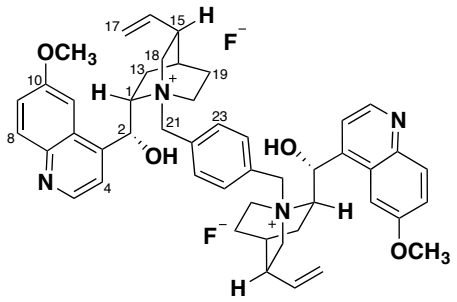
δ_C (126 MHz, d_6-DMSO): 157.4 (C10), 147.5 (C5), 143.9 (C3/7), 143.7 (C3/7), 138.3 (C16), 134.0 (C23), 131.5 (C8), 129.8 (C22), 125.4 (C12), 121.5 (C9), 120.3 (C4), 116.5 (C17), 102.1 (C11), 68.3

(C1), 63.7 (C2), 62.6 (C21), 59.1 (C18), 55.6 (OCH_3), 50.6 (C20), 36.8 (C15), 26.1 (C14), 24.0 (C19), 20.5 (C13).

ν_{max} (thin film): 2925 (C-H alkyl), 735 (C-H aromatic).

$[\alpha]_D^{20}$: -177.6° (*c* 0.5 in MeOH).

Bis-*N*-Benzylquininium difluoride 201



Prepared according to General Procedure E. Bis-*N*-Benzylquininium dibromide **200** (0.27 mmol) was passed down Amberlyst® A26-OH resin (1.0 g) and neutralized with 1.0 M HF solution (0.54 mmol) to yield fluoride catalyst **201** (210 mg, 98 %) as an amorphous solid.

Data for **201**:

m. p. 202 – 205 ˚C.

δ_H (500 MHz, d_6-DMSO): 8.82 (2H, d, *J* 4.4, H5), 8.04 (2H, d, *J* 9.1, H8), 7.85 (4H, s, H23), 7.78 (2H, d, *J* 4.4, H4), 7.52 (2H, dd, *J* 9.1, 2.5, H9), 7.34 (2H, d, *J* 2.5, H11), 6.61 (2H, s, H2), 5.77 (2H, ddd, *J* 17.1, 10.3, 6.9, H16), 5.50 (2H, d, *J* 12.3, H21), 5.13 (2H, d, *J* 17.0, H_Z(17)), 5.04 (2H, d, *J* 10.4, H_E(17)), 4.74 (2H, d, *J* 12.3, H21), 4.32 (2H, t, *J* 11.0, H20), 4.02 (6H, s, OCH_3), 3.86 (2H, m, H1), 3.70 (4H, dd, *J* 12.1, 3.3, H18), 3.42 (2H, m, H18), 3.24 (2H, d, *J* 5.0, H20), 2.71 (2H, d, *J* 7.3, H15), 2.13 – 2.30 (4H, m, H13 and H19), 2.03 (2H, d, *J* 2.2, H14), 1.85 (2H, br. s, H19), 1.47 (2H, t, *J* 11.7, H13).

δ_C (126 MHz, d_6-DMSO): 157.4 (C10), 147.5 (C5), 144.1 (C3/7), 143.7 (C3/7), 138.1 (C16), 134.1 (C23), 131.5 (C8), 129.8 (C22), 125.3 (C12), 121.4 (C9), 120.3 (C4), 116.7 (C17), 102.0 (C11), 68.6 (C1), 63.6 (C2), 62.6 (C21), 59.2 (C18), 55.4 (OCH_3), 50.7 (C20), 37.1 (C15), 26.1 (C14), 24.2 (C19), 20.3 (C13).

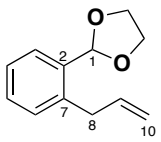
δ_F (377 MHz, d_6-DMSO): -157.8 (F^-).

ν_{max} (thin film): 2941 (OH), 725 (C-H aromatic).

$[\alpha]_D^{20}$: -110.6° (*c* 0.5 in $CHCl_3$).

5.3.3 Experimental Data for Chapter 4: Intramolecular Allylation

2-(2-Allylphenyl)-1,3-dioxolane 247



This compound was prepared according to a literature procedure.[156] Magnesium turnings (0.72 g, 29.6 mmol) were added to a dried schlenk tube and stirred under an argon atmosphere for one hour. In a separate dried flask, 2-bromobenzaldehyde ethylene acetal (3.70 mL, 24.8 mmol) and iodine (1 grain) were dissolved in THF (15 mL). Part of this solution (1.5 mL) was added slowly to the schlenk tube containing the magnesium turnings and was stirred until the colour suddenly faded. The rest of the solution was then added dropwise, *via* cannula, and heated to reflux for 2 h. The reaction was then cooled to 0 ˚C and allyl bromide (3.30 mL, 37.5 mmol) was added dropwise. The reaction was stirred for 2 h, by which time it had warmed to room temperature. The reaction was quenched with saturated NH_4Cl solution (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography yielded the product **247** as a colourless oil (3.25 g, 68 %).

Data for **247**:

δ_H (400 MHz, $CDCl_3$): 7.59 (1H, dd, *J* 7.6, 1.0 ArH), 7.19 – 7.35 (3H, m, ArH), 5.95 – 6.07 (2H, m, H1 and H9), 5.06 (2H, m, 2 × H10), 4.02 – 4.17 (4H, m, CH_2acetal), 3.56 (2H, d, *J* 6.3, CH_2(8)).

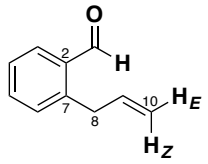
δ_C (101 MHz, $CDCl_3$): 138.4 (ArC), 137.2 (C9), 135.2 (ArC), 129.9 (ArCH), 129.2 (ArCH), 126.3 (ArCH), 126.1 (ArCH), 101.6 (C1), 65.2 (CH_2acetal), 63.6 (CH_2acetal), 36.5 (C8).

ν_{max} (thin film): 757 (C-H aromatic)

HRMS (ESI +ve) found: 213.0888 [$(M+Na)^+$], $C_{12}H_{14}NaO_2$ requires: 213.0886.

This data is in accordance with the literature.[156]

2-Allylbenzaldehyde 248



This compound was prepared according to a literature procedure.[157] Acetal **247** (1.47 g, 7.72 mmol) and iron (III) chloride hexahydrate (7.31 g, 27.0 mmol) were dissolved in dichloromethane (110 mL). The resulting suspension was stirred at room temperature for 1 h and was then quenched with saturated $NaHCO_3$ solution (200 mL). The aqueous layer was extracted (3 × 100 mL) and the combined organics were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by flash column chromatography to afford the product **248** (0.98 g, 85 %) as a colourless oil.

Data for **248**:

δ_H (400 MHz, $CDCl_3$): 10.26 (1H, s, CHO), 7.86 (1H, dd, *J* 7.6, 1.0 H3/6), 7.54 (1H, td, *J* 7.5, 1.3, H4/5), 7.41 (1H, m, H4/5), 7.31 (1H, d, *J* 7.6, H3/6), 6.05 (1H, ddt, *J* 16.9, 10.4, 6.1, H9), 5.10 (1H, dd, *J* 10.2, 1.4, H10(*E*)), 4.99 (1H, dd, *J* 17.1, 1.6, H10(*Z*)), 3.83 (2H, d, *J* 6.1, CH_2(8)).

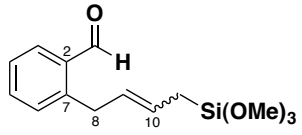
δ_C (101 MHz, $CDCl_3$): 192.4 (CHO), 142.3 (ArC), 136.9 (C9), 134.0 (C4/5), 133.8 (ArC), 131.6 (C3/6), 131.1 (C3/6), 126.9 (C4/5), 116.4 (C10), 36.5 (C8).

ν_{max} (thin film): 1695 (CHO)

HRMS (ESI +ve) found: 169.0619 [$(M+Na)^+$], $C_{10}H_{10}NaO$ requires: 169.0624.

This data is in accordance with the literature.[156]

(2-(4-(Trimethoxysilyl)but-2-en-1-yl)benzaldehyde 249



2-Allylbenzaldehyde **248** (153 mg, 1.05 mmol) was dissolved in chloroform (4.2 mL) in a two-necked round bottom flask, with reflux condenser attached, under a N_2 atmosphere. Allyltrimethoxysilane (0.70 mL, 4.20 mmol) was added, followed by Hoveyda-Grubbs 2nd

Generation catalyst (33 mg, 0.05 mmol) dissolved in chloroform (1.0 mL). The reaction mixture was heated to reflux (61 ˚C) for 18 h and then cooled to room temperature. The reaction solvent was removed under reduced pressure and the crude was passed through a silica plug using dichloromethane as the eluent. The solution was concentrated *in vacuo* and the crude was purified by flash column chromatography to afford the product **249** (99 mg, 34 %) as an oil. Product **249** was found to be a mixture of geometric isomers (*E*:*Z*, 3.5:1).

N.B. The solvent used for flash column chromatography was dichloromethane because petrol/ether eluents did not separate **249** from byproduct **250**.

Data for **249 (**major geometric isomer):

δ_H (400 MHz, $CDCl_3$): 10.28 (1H, s, CHO), 7.83 (1H, d, *J* 7.6, ArH), 7.51 (1H, m, ArH), 7.26 – 7.39 (2H, m, ArH), 5.40 – 5.65 (2H, m, H9 and H10), 3.76 (2H, d, *J* 6.3, CH_2(8)), 3.53 (9H, s, $Si(OCH_3)_3$), 1.61 (2H, d, *J* 7.6, CH_2(11)).

δ_C (101 MHz, $CDCl_3$): 192.3 (CHO), 143.4 (ArC), 133.9 (ArCH), 133.7 (ArC), 131.1 (ArCH), 130.8 (ArCH), 128.9 (C9/10), 126.7 (ArCH), 125.6 (C9/10), 50.7 ($Si(OCH_3)_3$), 35.5 (C8), 15.3 (C11).

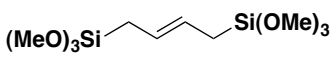
ν_{max} (thin film): 1694 (CHO), 1051 (Si – OCH_3)

HRMS (ESI +ve) found: 303.1021 [$(M+Na)^+$], $C_{14}H_{20}NaO_4Si$ requires: 303.1023.

Selected data for minor geometric isomer:

δ_H (400 MHz, $CDCl_3$): 3.84 (2H, d, *J* 6.6, CH_2(8)), 3.59 (9H, s, $Si(OCH_3)_3$), 1.75 (2H, d, *J* 7.8, CH_2(11)).

(*E*)-1,4-Bis(trimethoxysilyl)but-2-ene 250



Data for **250**:

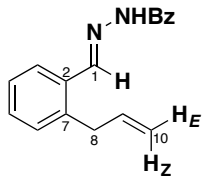
δ_H (200 MHz, $CDCl_3$): 5.41 (2H, m, CH), 3.58 (18H, s, $Si(OCH_3)_3$), 1.62 (4H, m, CH_2).

δ_C (101 MHz, $CDCl_3$): 125.9 (CH), 50.7 ($Si(OCH_3)_3$), 15.2 (CH_2).

ν_{max} (thin film): 1083 (Si – OCH_3).

HRMS (ESI +ve) found: 319.0993 [(M+Na)$^+$], $C_{10}H_{24}NaO_6Si_2$ requires: 319.1004.

(*E*)-*N*'-(2-Allylbenzylidene)benzohydrazide 251



Aldehyde **248** (197 mg, 1.32 mmol) and benzoylhydrazine (181 mg, 1.32 mmol) were dissolved in methanol (5 mL). Acetic acid (small drop) was added and the resulting mixture was stirred for 1 h. The methanol was then removed under reduced pressure and the product **251** was crystallized from hot EtOAc (249 mg, 70%) as a white solid.

Data for **251**:

m. p. 146 – 149 ˚C.

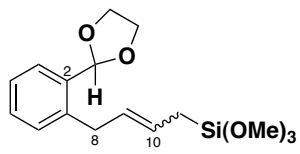
δ_H (500 MHz, DMSO-d_6): 11.85 (1H, s, NH), 8.75 (1H, s, H1), 7.92 (3H, m, H3 and ArH), 7.61 (1H, m, ArH), 7.55 (2H, m, ArH), 7.39 (1H, m, H4/5), 7.33 (1H, m, H4/5), 7.28 (1H, d, *J* 7.6, H6), 6.02 (1H, ddt, *J* 16.8, 10.3, 6.1, H9), 5.07 (1H, d, *J* 10.1, H10(*E*)), 5.00 (1H, dd, *J* 17.2, 1.4, H10(*Z*)), 3.58 (2H, d, *J* 6.0, CH_2(8)).

δ_C (126 MHz, DMSO-d_6): 163.0 (CONH), 146.0 (C1), 138.7 (C7), 137.4 (C9), 133.4 (ArC), 132.2 (C2), 131.8 (ArCH), 130.4 (C6), 130.0 (C4/5), 128.5 (ArCH × 2), 127.6 (ArCH × 2), 126.7 (C4/5), 126.0 (C3), 116.1 (C10), 36.4 (C8).

ν_{max} (thin film): 1645 (C=O), 1557 (C=N).

HRMS (ESI +ve) found: 287.1146 [(M+Na)$^+$], $C_{17}H_{16}N_2NaO$ requires: 287.1155.

(4-(2-(1,3-Dioxolan-2-yl)phenyl)but-2-en-1-yl)trimethoxysilane 252



2-(2-Allylphenyl)-1,3-dioxolane **247** (137 mg, 0.72 mmol) was dissolved in chloroform (3.0 mL) in a two-necked round bottom flask, with reflux condenser attached, under a N_2 atmosphere.

Allyltrimethoxysilane (0.48 mL, 2.88 mmol) was added, followed by Hoveyda-Grubbs 2nd Generation catalyst (23 mg, 0.04 mmol) dissolved in chloroform (0.6 mL). The reaction mixture was heated to reflux (61 ˚C) for 18 h and then cooled to room temperature. The reaction solvent was removed under reduced pressure and the crude was passed through a silica plug using dichloromethane as the eluent. The solution was concentrated *in vacuo* and the crude was purified by flash column chromatography to afford the product **252** (65 mg, 28 %) as an oil. Product **252** was found to be a mixture of geometric isomers (*E*/*Z* ratio could not be determined by ^{1}H-NMR).

Data for **252** (major geometric isomer):

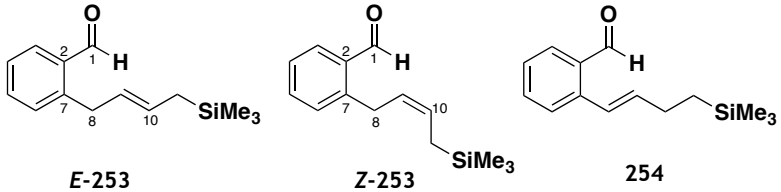
δ_H (400 MHz, $CDCl_3$): 7.56 (1H, d, *J* 7.8, ArH), 7.16 – 7.36 (3H, m, ArH), 6.02 (1H, m, H1), 5.35 – 5.63 (2H, m, H9 and H10), 4.00 – 4.19 (4H, m, CH_2(acetal)), 3.54 – 3.62 (9H, m, $Si(OCH_3)_3$), 3.50 (2H, m, CH_2(8)), 1.64 (2H, dd, *J* 7.6, 1.0, CH_2(11)).

δ_C (101 MHz, $CDCl_3$): 139.4 (ArC), 135.0 (ArC), 129.6 (ArCH), 129.1 (ArCH), 129.1 (C9/10), 126.1 (ArCH), 125.9 (ArCH), 124.7 (C9/10), 101.5 (C1), 65.2 (CH_2acetal), 50.7 ($Si(OCH_3)_3$), 35.4 (C8), 15.2 (C11).

ν_{max} (thin film): 1073 (Si-OCH_3).

m/z (ESI +ve): 347 ($[M+Na]^+$, 100 %), 379 ($[M+MeOH+Na]^+$, 30 %).

(*E*)-2-(4-(Trimethylsilyl)but-2-en-1-yl)benzaldehyde 253 and (*Z*)-2-(4-(Trimethylsilyl)but-2-en-1-yl)benzaldehyde 253



E-253 *Z*-253 254

2-Allylbenzaldehyde **248** (109 mg, 0.75 mmol) was dissolved in chloroform (2.75 mL) in a two-necked round bottom flask, with reflux condenser attached, under a N_2 atmosphere. Allyltrimethylsilane (0.48 mL, 2.98 mmol) was added, followed by Hoveyda-Grubbs 2nd Generation catalyst (23 mg, 0.04 mmol) dissolved in chloroform (1.0 mL). The reaction mixture was heated to reflux (61 ˚C) for 18 h and then cooled to room temperature. The reaction solvent was removed

under reduced pressure and the crude was passed through a silica plug using dichloromethane as the eluent. The solution was concentrated *in vacuo* and the crude was purified by flash column chromatography (Petrol 40-60/Ether) to afford an oil (90 mg, 52 %) as a mixture of geometric isomers **253** as well as regioisomer **254** (6:2:1, ***E*-253**: ***Z*-253**: **254**).

Data for ***E*-253 (**major geometric isomer):

δ_H (400 MHz, $CDCl_3$): 10.31 (1H, s, CHO), 7.85 (1H, dd, *J* 7.7, 1.4, H3/6), 7.53 (1H, td, *J* 7.6, 1.5, H4/5), 7.37 (1H, t, *J* 7.8, H4/5), 7.30 (1H, dd, *J* 7.6, 0.5, H3/6), 5.36 – 5.50 (2H, m, H9 and H10), 3.76 (2H, d, *J* 5.6, CH_2(8)), 1.44 (2H, d, *J* 6.8, CH_2(11)), -0.04 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 192.3 (CHO), 144.4 (C7), 135.3 (C2), 133.9 (C4/5), 130.8 (C3 and C6), 128.8 (C9/10), 126.8 (C4/5), 126.6 (C9/10), 35.5 (C8), 22.8 (C11), -2.0 ($Si(CH_3)_3$).

ν_{max} (thin film): 1696 (CHO), 1247 (Si – CH_3)

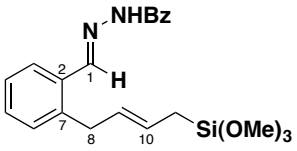
HRMS (ESI +ve) found: 255.1165 [$(M+Na)^+$], $C_{14}H_{20}NaOSi$ requires: 255.1176.

Selected data for minor geometric isomer:

δ_H (400 MHz, $CDCl_3$): 10.30 (1H, s, CHO), 5.57 – 5.64 (2H, m, H9 and H10), 3.78 (2H, d, *J* 7.1, CH_2(8)), 1.60 (2H, d, *J* 8.6, CH_2(11)), 0.05 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 192.5 (C=O), 30.1 (C8), 18.8 (C11), -1.3 ($Si(CH_3)_3$).

(*E*)-*N*'-(2-((*E*)-4-(Trimethoxysilyl)but-2-en-1-yl)benzylidene)benzohydrazide 255



Aldehyde **249** (307 mg, 1.09 mmol) and benzoylhydrazine (149 mg, 1.09 mmol) were dissolved in methanol. To the reaction, a couple of drops of acetic acid were added and the reaction was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography, to yield hydrazone **255** as a colourless oil (62 mg, 15 %).

Data for **255**:

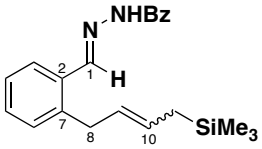
δ_H (500 MHz, $CDCl_3$): 9.97 (1H, br. s, NH), 8.64 (1H, br. s, H1), 8.19 (1H, d, *J* 6.0, H6), 7.96 (2H, d, *J* 7.3, ArH), 7.53 (1H, m, ArH), 7.45 (2H, m, ArH), 7.31 (1H, m, H5), 7.25 (1H, m, H4), 7.16 (1H, d, *J* 7.3, H3), 5.38 – 5.57 (2H, m, H9 and H10), 3.46 – 3.58 (11H, m, CH_2(8) and $Si(OCH_3)_3$), 1.64 (2H, d, *J* 7.6, CH_2(11)).

δ_C (126 MHz, $CDCl_3$): 164.2 (CONH), 146.9 (C1), 139.1 (C7), 133.4 (ArC), 132.2 (C2), 131.8 (ArCH), 130.4 (C5), 130.3 (C3), 129.2 (C10), 128.5 (ArCH × 2), 127.5 (ArCH × 2), 127.0 (C6), 126.9 (C4), 125.1 (C9), 50.6 ($Si(OCH_3)_3$), 37.4 (C8), 14.6 (C11).

ν_{max} (thin film): 1647 (C=O), 1556 (C=N), 1081 (Si-OCH_3).

HRMS (ESI +ve) found: 421.1552 [$(M+Na)^+$], $C_{21}H_{26}N_2NaO_4Si$ requires: 421.1554.

***N*'-*N*'-(2-(4-(Trimethylsilyl)but-2-en-1-yl)benzylidene)benzohydrazide 256**



Aldehyde **253** (160 mg, 0.69 mmol) was dissolved in methanol (3 mL) and then benzoylhydrazine (93 mg, 0.69 mmol) and acetic acid (drop) were added. The reaction was stirred at room temperature for 1 h and then was diluted with water (10 mL). The mixture was then extracted with EtOAc (2 × 10mL) and the combined organics were washed with brine (10 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* and the crude was purified by flash column chromatography to yield **256** (151 mg, 63 %) as an amorphous white solid, which was a mixture of geometric isomers (3:1).

Data for **256** (major geometric isomer):

m.p. 32 – 34 ˚C.

δ_H (500 MHz, d_6-DMSO): 11.80 (1H, s, NH), 8.78 (1H, s, H1), 7.91 (3H, d, *J* 7.6, ArH), 7.52 – 7.65 (3H, m, ArH), 7.23 – 7.39 (3H, m, ArH), 5.40 (2H, m, H9 and H10), 3.49 (2H, br. s, CH_2(8)), 1.41 (2H, d, *J* 5.7, CH_2(11)), -0.08 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, d_6-DMSO): 164.4 (CONH), 147.5 (C1), 141.6 (ArC), 135.0 (ArC), 133.2 (ArCH), 131.6 (ArCH), 131.4 (ArCH), 130.0 (ArCH × 2), 129.0 (ArCH × 2), 128.5 (C9 and C10), 128.0 (ArCH), 127.1 (ArCH), 36.9 (C8), 23.7 (C11), -0.5 ($Si(CH_3)_3$).

ν_{max} (thin film): 1647 (C=O), 1557 (C=N), 1287 (Si-CH_3)

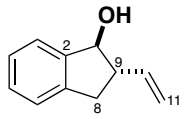
HRMS (ESI +ve) found: 373.1701 [$(M+Na)^+$], $C_{21}H_{26}N_2NaOSi$ requires: 373.1707.

Selected data for minor geometric isomer:

δ_H (500 MHz, d_6-DMSO): 11.84 (1H, s, NH), 8.80 (1H, s, H1), 5.52 (1H, m, H9/10), 3.53 (2H, d, *J* 6.9 CH_2(8)), 1.65 (2H, d, *J* 8.5, CH_2(11)), 0.02 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, d_6-DMSO): 31.3 (C8), 19.6 (C11), -0.2 ($Si(CH_3)_3$).

2-Vinyl-2,3-dihydro-1*H*-inden-1-ol 257



Racemic: Aldehyde **249** (38 mg, 0.135 mmol) and tetrabutylammonium triphenyldifluorosilicate (7 mg, 0.014 mmol) were dissolved in chloroform (1.0 mL) and stirred at r.t. for 24 h. The reaction was then quenched with water (10 mL) and extracted with dichlromethane (2 × 10 mL). The combined organics were dried ($MgSO_4$) and purified by flash column chromatography to yield indane **257** (10 mg, 46 %) as a white solid, which was a mixture of diastereomers (*anti*:*syn*, 3.5:1).

Asymmetric: Aldehyde **249** (40 mg, 0.142 mmol) and *N*-benzylquininium fluoride (6 mg, 0.014 mmol) were dissolved in chloroform (1.0 mL) and stirred at r.t. for 24 h. The reaction was then quenched with water (10 mL) and extracted with dichlromethane (2 × 10 mL). The combined organics were dried ($MgSO_4$) and purified by flash column chromatography to yield indane **257** (5 mg, 22 %, 30 % ee), which was a mixture of diastereomers (*anti*:*syn*, 2:1).

N.B. The relative stereochemistry is defined by comparison with literature data for the *syn*-diastereomer.[160]

Data for the *anti*-diastereomer **257** (major):

m. p. 52 – 56 ˚C.

δ_H (500 MHz, $CDCl_3$): 7.38 – 7.44 (1H, m, ArH), 7.21 – 7.28 (3H, m, ArH), 6.04 (1H, ddd, *J* 17.4, 10.0, 7.6, H10), 5.24 – 5.31 (1H, m, H11), 5.16 (1H, m, H11), 4.97 (1H, d, *J* 7.6, H1), 3.12 (1H, dd, *J* 15.3, 7.7, H8), 2.85 (1H, m, H9), 2.75 (1H, m, H8'), 1.63 (1H, br. s, OH).

δ_C (126 MHz, $CDCl_3$): 144.2 (ArC), 141.1 (ArC), 139.2 (C10), 128.1 (ArCH), 126.8 (ArCH), 124.6 (ArCH), 123.8 (ArCH), 116.0 (C11), 80.7 (C1), 55.6 (C9), 35.8 (C8).

ν_{max} (thin film): 3348 (OH).

HRMS (FI +ve) found: 160.0884 $[(M\bullet)^+]$, $C_{11}H_{12}O$ requires: 160.0888.

HPLC (Chiralpak AD-H, 10 % IPA in hexane, 1.0 mL min^{-1}, λ = 272) *Asymmetric*: t_R major = 6.8, t_R minor = 7.4; *Racemic*: t_R major = 6.8, t_R minor = 7.4.

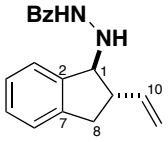
Data for the *syn*-diastereomer **257** (minor):

δ_H (500 MHz, $CDCl_3$): 7.38 – 7.44 (1H, m, ArH), 7.21 – 7.28 (3H, m, ArH), 5.98 (1H, ddd, *J* 17.3, 10.4, 7.9, H10), 5.24 – 5.31 (2H, m, H11), 5.11 (1H, d, *J* 6.0, H1), 3.15 – 3.21 (1H, m, H9), 3.01 (2H, d, *J* 6.9, H8), 1.93 (1H, br. s, OH).

δ_C (126 MHz, $CDCl_3$): 142.6 (ArC), 136.8 (C10), 128.5 (ArCH), 125.0 (ArCH), 124.7 (ArCH), 117.9 (C11), 77.1 (C1), 49.5 (C9), 35.2 (C8).

This data is in accordance with the literature.[160]

***anti-N'*-(2-Vinyl-2,3-dihydro-1*H*-inden-1-yl)benzohydrazide 258**



Racemic: Hydrazone **255** (30 mg, 0.075 mmol) was dissolved in chloroform (0.75 mL) and tetrabutylammonium triphenyldifluorosilicate (4 mg, 0.007 mmol) was added. The reaction was stirred at room temperature for 18 h. The reaction was diluted with dichloromethane (5 mL) and washed with water (5 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated *in*

vacuo. The crude was purified by flash column chromatography to yield indane **258** (7 mg, 33 %, single diastereomer) as a yellow oil.

Asymmetric: Hydrazone **255** (44 mg, 0.110 mmol) was dissolved in chloroform (1.0 mL) and *N*-benzylquininium fluoride (5 mg, 0.011 mmol) was added. The reaction was stirred at room temperature for 24 h. The reaction was diluted with dichloromethane (5 mL) and washed with water (5 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography to yield indane **258** (8 mg, 26 %, 16 % ee, single diastereomer).

N.B. The anti-diastereomer was assigned by comparison with a literature compound.[160]

Data for **258**:

δ_H (500 MHz, $CDCl_3$): 7.73 (2H, m, ArH and CONH), 7.54 (1H, m, ArH), 7.47 (4H, m, ArH), 7.29 (2H, m, ArH), 7.23 (1H, m, ArH), 6.26 (1H, ddd, *J* 17.3, 10.3, 7.1, H10), 5.36 (2H, m, H11 × 2), 4.90 – 5.20 (1H, br. s, NH), 4.57 (1H, d, *J* 5.7, H1), 3.20 (2H, m, H9 and H8), 2.99 (1H, m, H8').

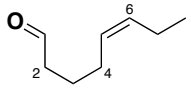
δ_C (126 MHz, $CDCl_3$): 167.0 (CONH), 143.9 (ArC), 142.4 (ArC), 137.5 (C10), 132.9 (ArC), 131.9 (ArCH), 128.8 (ArCH × 2), 128.4 (ArCH), 126.7 (ArCH × 2), 126.5 (ArCH), 125.3 (ArCH), 124.9 (ArCH), 117.3 (C11), 67.4 (C1), 48.4 (C9), 35.7 (C8).

ν_{max} (thin film): 1641 (C=O), 910 (C-H alkene)

HRMS (ESI +ve) found: 301.1311 [$(M+Na)^+$], $C_{18}H_{18}N_2NaO$ requires: 301.1311.

HPLC (Chiralpak AD-H, 15 % IPA in hexane, 1.0 mL min^{-1}, λ = 272): *Asymmetric*: t_R major = 10.3, t_R minor = 14.3; *Racemic*: t_R major = 10.6, t_R minor = 14.5.

(*Z*)-Oct-5-enal 260



(*Z*)-5-Octen-1-ol (0.60 mL, 4.0 mmol) was dissolved in dichloromethane (20 mL) and Dess-Martin periodinane (2.6 g, 6.0 mmol) was added. The resulting suspension was stirred at r.t. for 2 h and then diluted with dichloromethane (30 mL) and quenched with saturated aqueous sodium

thiosulfate (30 mL). The organic layer was then separated and washed with 10 % aqueous sodium bicarbonate (30 mL). The combined aqueous washings were extracted with dichloromethane (3 × 30 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography to yield product **260** (0.45 g, 90 %) as a colourless oil.

Data for **260**:

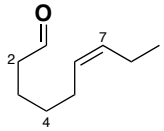
δ_H (400 MHz, $CDCl_3$): 9.78 (1H, t, *J* 1.8, CHO), 5.39 – 5.47 (1H, m, H5/6), 5.25 – 5.33 (1H, m, H5/6), 2.44 (2H, td, *J* 7.3, 1.8, CH_2(2)), 1.99 – 2.13 (4H, m, CH_2(4) and CH_2(7)), 1.70 (2H, a. quin., *J* 7.3, CH_2(3)), 0.96 (3H, t, *J* 7.6, CH_3).

δ_C (101 MHz, $CDCl_3$): 202.7 (CHO), 133.0 (C5/6), 127.6 (C5/6), 43.3 (C2), 26.3 (C4/7), 22.0 (C3), 20.5 (C4/7), 14.3 (CH_3).

ν_{max} (thin film): 1725 (CHO)

HRMS (FI +ve) found: 126.1047 [$(M\bullet)^+$], $C_8H_{14}O$ requires: 126.1045.

(*Z*)-Non-6-enal 262



(*Z*)-6-Nonen-1-ol (0.67 mL, 4.0 mmol) was dissolved in dichloromethane (25 mL) and Dess-Martin periodinane (2.6 g, 6.0 mmol) was added. The resulting suspension was stirred at r.t. for 1 h and then diluted with dichloromethane (30 mL) and quenched with saturated aqueous sodium thiosulfate (30 mL). The organic layer was then separated and washed with 10 % aqueous sodium bicarbonate (30 mL). The combined aqueous washings were extracted with dichloromethane (3 × 30 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography to yield product **262** (0.48g, 85 %) as a colourless oil.

Data for **262**:

δ_H (400 MHz, $CDCl_3$): 9.77 (1H, t, *J* 1.8, CHO), 5.27 – 5.43 (2H, m, H6 and H7), 2.44 (2H, td, *J* 7.3, 1.8, CH_2(2)), 2.05 (4H, m, CH_2(5) and CH_2(8)), 1.66 (2H, dt, *J* 15.3, 7.5, CH_2(3)), 1.40 (2H, m, CH_2(4)), 0.96 (3H, t, *J* 7.5, CH_3).

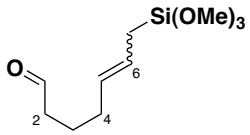
δ_C (101 MHz, $CDCl_3$): 202.8 (CHO), 132.2 (C6/7), 128.3 (C6/7), 43.8 (C2), 29.2 (C4), 26.6 (C5/8), 21.6 (C3), 20.5 (C5/8), 14.3 (CH_3).

ν_{max} (thin film): 1726 (CHO)

HRMS (FI +ve) found: 140.1203 [$(M\bullet)^+$], $C_9H_{16}O$ requires: 140.1201.

This data is in accordance with the literature.[189]

7-(Trimethoxysilyl)hept-5-enal 263



Oct-5-enal **260** (106 mg, 0.840 mmol) was dissolved in 1,2-dichloroethane (4.2 mL), in a two-necked round bottom flask with condenser attached, under a N_2 atmosphere. Allyltrimethoxysilane (0.56 mL, 3.44 mmol) was added and the solution was heated to 84 °C. Hoveyda-Grubbs 2nd Generation catalyst (26 mg, 0.042 mmol) was added and the reaction was stirred for 19 h and then cooled to rt. The solution was concentrated under reduced pressure and then purified by flash column chromatography (neat dichloromethane) to yield product **263** (91 mg, 47 %) as a colourless oil, which is a mixture of geometric isomers (*E*/*Z* ratio not determinable by ^{1}H NMR).

Data for **263** (only major geometric isomer quoted):

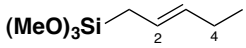
δ_H (400 MHz, $CDCl_3$): 9.76 (1H, t, *J* 1.6, CHO), 5.28 – 5.56 (2H, m, H5 and H6), 3.56 (9H, s, $Si(OCH_3)_3$), 2.42 (2H, td, *J* 7.4, 1.6, CH_2(2)), 2.00 – 2.13 (2H, m, CH_2(4)), 1.70 (2H, m, CH_2(3)), 1.59 (2H, d, *J* 7.3, CH_2(4)).

δ_C (101 MHz, $CDCl_3$): 202.7 (CHO), 129.6 (C5/6), 123.4 (C5/6), 50.7 ($Si(OCH_3)_3$), 43.1 (C2), 32.0 (C4), 21.9 (C3), 15.0 (C7).

ν_{max} (thin film): 1723 (CHO), 1081 (Si – OCH_3)

HRMS (ESI +ve) found: 255.1022 [$(M+Na)^+$], $C_{10}H_{20}NaO_4Si$ requires: 255.1023.

(*E*)-Trimethoxy(pent-2-en-1-yl)silane 264



The following byproduct was observed when the reaction to make 7-(trimethoxysilyl)hept-5-enal **263** was performed in chloroform.

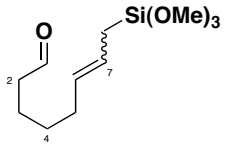
Data for **264**:

δ_H (500 MHz, $CDCl_3$): 5.37 – 5.50 (2H, m, H2 and H3), 3.58 (9H, s, $Si(OCH_3)_3$), 2.03 (2H, m, CH_2(4)), 1.59 (2H, dd, *J* 7.3, 0.9, CH_2(1)), 0.96 (3H, t, *J* 7.4, CH_3).

δ_C (101 MHz, $CDCl_3$): 132.9 (C2/3), 121.6 (C2/3), 50.7 ($Si(OCH_3)_3$), 25.7 (C4), 15.0 (C1), 14.0 (CH_3).

ν_{max} (thin film): 1085 (Si – OCH_3)

8-(Trimethoxysilyl)oct-6-enal 265



(*Z*)-Non-6-enal **262** (120 mg, 0.860 mmol) was dissolved in chloroform (5.0 mL), in a two-necked round bottom flask with condenser attached, under a N_2 atmosphere. Allyltrimethoxysilane (0.57 mL, 3.44 mmol) was added and the solution was heated to 61 °C. Hoveyda-Grubbs 2nd Generation catalyst (27 mg, 0.043 mmol) was added and the reaction was stirred for 19 h and then cooled to room temperature. The solution was concentrated under reduced pressure and then purified by flash column chromatography (neat dichloromethane) to yield product **265** (81 mg, 38 %) as a colourless oil, which is a mixture of geometric isomers (*E*/*Z* ratio not determinable by ^{1}H-NMR).

Data for **265** (only major geometric isomer quoted for ^{13}C NMR):

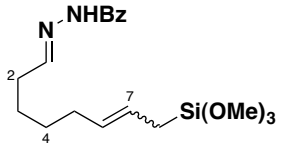
δ_H (400 MHz, $CDCl_3$): 9.76 (1H, m, CHO), 5.30 – 5.46 (2H, m, H6 and H7), 3.57 (9H, m, $Si(OCH_3)_3$), 2.43 (2H, m, CH_2(2)), 1.99 – 2.11 (2H, m, CH_2(5)), 1.58 – 1.70 (4H, m, CH_2(3) and CH_2(8)), 1.40 (2H, m, CH_2(4)).

δ_C (101 MHz, $CDCl_3$): 202.8 (CHO), 130.4 (C6/7), 123.5 (C6/7), 50.7 ($Si(OCH_3)_3$), 43.8 (C2), 32.4 (C5), 29.0 (C4), 21.5 (C3/8), 15.0 (C3/8).

ν_{max} (thin film): 1723 (CHO), 1078 (Si – OCH_3)

HRMS (ESI +ve) found: 269.1172 [$(M+Na)^+$], $C_{11}H_{22}NaO_4Si$ requires: 269.1180.

_N_'-(8-(Trimethoxysilyl)oct-6-en-1-ylidene)benzohydrazide 266



Aldehyde **265** (50 mg, 0.20 mmol) was dissolved in methanol (1 mL). Benzoylhydrazine (28 mg, 0.20 mmol) and acetic acid (small drop) was added and the reaction was stirred at r.t. for 1 h. The reaction was then diluted with dichloromethane (10 mL) and washed with water (10 mL). The aqueous phase was then extracted with dichloromethane (2 × 5 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by flash column chromatography to yield hydrazone **266** as a pale solid (8 mg, 11 %), which is a mixture of geometric isomers (*E*/*Z* ratio not determinable by ^{1}H NMR).

Data for **266** (only major geometric isomer quoted for ^{13}C NMR):

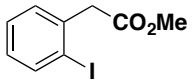
δ_H (500 MHz, $CDCl_3$): 9.07 (1H, m, CONH), 7.73 – 7.91 (2H, m, ArH), 7.30 – 7.62 (4H, m, ArH and H1), 5.30 – 5.49 (2H, m, H6 and H7), 3.57 (9H, m, $Si(OCH_3)_3$), 2.42 (1H, m, CH_2(2)), 2.02 (1H, m, CH_2(2)'), 1.32 – 1.68 (8H, m, CH_2(3), CH_2(4), CH_2(5) and CH_2(8)).

δ_C (126 MHz, $CDCl_3$): 164.0 (CONH), 152.7 (C1), 133.2 (ArC), 131.9 (ArCH), 130.6 (C6/7), 128.7 (2 × ArCH), 127.2 (2 × ArCH), 123.3 (C6/7), 50.7 ($Si(OCH_3)_3$), 32.2 (C2), 29.1 (CH_2), 25.9 (CH_2), 14.9 (CH_2), 11.1 (CH_2).

ν_{max} (thin film): 1631 (CONH), 1578 (C=N), 1075 (Si – OCH_3)

HRMS (ESI +ve) found: 387.1707 [$(M+Na)^+$], $C_{18}H_{28}N_2NaO_4Si$ requires: 387.1711.

Methyl 2-(2-iodophenyl)acetate 267



This compound was prepared following a literature procedure.[190] Sulfuric acid (2.5 mL) was added to a stirring solution of 2-(iodophenyl)acetic acid (5.02 g, 19.2 mmol) in methanol (8 mL). The solution was stirred at reflux for 2.5 h at 65 ˚C. The reaction was cooled to r.t. and quenched with CH_2Cl_2 (200 mL) and water (200 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were washed with water (200 mL) and brine (200 mL). The organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was then purified by flash column chromatography to yield **267** as a colourless oil (5.34 g, quantitative).

Data for **267**:

δ_H (400 MHz, $CDCl_3$): 7.86 (1H, d, *J* 7.8, ArH), 7.26 – 7.36 (2H, m, ArH), 6.95 – 7.00 (1H, m, ArH), 3.82 (2H, s, CH_2), 3.73 (3H, s, OCH_3).

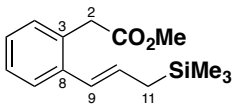
δ_C (101 MHz, $CDCl_3$): 171.0 (C=O), 139.5 (ArCH), 137.7 (C3), 130.6 (ArCH), 128.9 (ArCH), 128.5 (ArCH), 101.0 (C8), 52.2 (OCH_3), 46.1 (CH_2).

ν_{max} (thin film): 1737 (C=O)

HRMS (ESI +ve) found: 298.9534 [$(M+Na)^+$], $C_9H_9INaO_2$ requires: 298.9539

This data is in accordance with the literature.[190]

(*E*)-Methyl 2-(2-(3-(trimethylsilyl)prop-1-en-1-yl)phenyl)acetate 268



This compound was prepared following a modified literature procedure.[162] Aryl iodide **267** (5.29 g, 19.2 mmol) and allyltrimethylsilane (6.1 mL, 38.3 mmol) were added to a stirring suspension of DABCO (5.37 g, 47.9 mmol), *n*-tetrabutylammonium chloride (5.33 g, 19.2 mmol) and bis(dibenzylideneacetone)palladium(0) (0.44 g, 0.77 mmol) in acetonitrile (50 mL). The reaction mixture was stirred at room temperature for 24 h. The mixture was filtered over celite® and eluted

with diethyl ether (300 mL). The filtrate was then washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude was purified by flash column chromatography to yield **268** and **269** as a colourless oil (4.13 g, 82 %; **268**:**269**, 7:1).

Data for **268**:

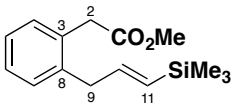
δ_H (400 MHz, $CDCl_3$): 7.44 (1H, d, *J* 7.6, ArH), 7.15 – 7.29 (3H, m, ArH), 6.44 (1H, d, *J* 15.4, H9), 6.16 (1H, dt, *J* 15.5, 8.3, H10), 3.71 (2H, s, CH_2(2)), 3.70 (3H, s, OCH_3), 1.73 (2H, dd, *J* 8.2, 1.1, CH_2(11)), -0.09 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 172.0 (C=O), 138.2 (ArC), 130.8 (C10), 130.7 (ArC), 130.5 (ArCH), 127.5 (ArCH), 126.6 (ArCH), 126.0 (ArCH), 125.4 (C9), 52.0 (OCH_3), 39.0 (C2), 24.4 (C11), -1.9 ($Si(CH_3)_3$).

ν_{max} (thin film): 1737 (C=O), 1247 (Si-CH_3).

HRMS (ESI +ve) found: 285.1274 [$(M+Na)^+$], $C_{15}H_{22}NaO_2Si$ requires: 285.1281.

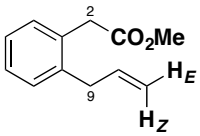
(*E*)-methyl 2-(2-(3-(trimethylsilyl)allyl)phenyl)acetate 269



Selected data for **269**:

δ_H (400 MHz, $CDCl_3$): 5.64 (1H, dt, *J* 18.4, 1.6, H11), 3.47 (2H, m, CH_2(9)), -0.06 (9H, s, $Si(CH_3)_3$).

Methyl 2-(2-allylphenyl)acetate 270



This compound was prepared following a modified literature procedure.[163] Bis(1,5-cyclooctadiene)diiridium(I) dichloride (6 mg, 0.009 mmol) and bis(pinacolato)diboron (114 mg, 0.45 mmol) were dissolved in allyltrimethoxysilane (0.3 mL) and was stirred at 80 °C for 4 h. The reaction was then cooled to room temperature and diluted with THF/water (10:1, 1.1 mL). Aryl iodide **267** (124 mg, 0.45 mmol), tetrakis(triphenylphosphine)palladium(0) (26 mg, 0.02 mmol),

and cesium carbonate (338 mg, 0.90 mmol) were added and the reaction was heated to 55 ˚C and stirred overnight. The reaction was cooled and the crude was purified by silica gel chromatography to afford undesired product **270** (38 mg, 44 %) as a colourless oil.

Data for **270**:

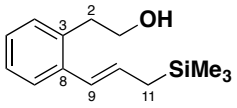
δ_H (400 MHz, $CDCl_3$): 7.10 – 7.17 (4H, m, ArH), 5.87 (1H, ddt, *J* 16.9, 10.3, 6.2, H10), 4.99 (1H, *a*dq, *J* 10.2, 1.6, H11(*E*)), 4.90 (1H, *a*dq, *J* 17.1, 1.6, H11(*Z*)), 3.61 (3H, s, OCH_3), 3.59 (2H, s, CH_2(2)), 3.34 (2H, dt, *J* 6.3, 1.5, CH_2(9)).

δ_C (101 MHz, $CDCl_3$): 172.1 (C=O), 138.4 (ArC), 136.6 (C10), 132.6 (ArC), 130.7 (ArCH), 129.9 (ArCH), 127.6 (ArCH), 126.7 (ArCH), 116.0 (C11), 52.1 (OCH_3), 38.5 (C2) 37.4 (C9).

ν_{max} (thin film): 1737 (C=O).

HRMS (ESI +ve) found: 213.0884 [$(M+Na)^+$], $C_{12}H_{14}NaO_2$ requires: 213.0886.

(*E*)-2-(2-(3-(trimethylsilyl)prop-1-en-1-yl)phenyl)ethanol 271



Diisobutylaluminium hydride (1M in toluene, 33.5 mL) was added carefully to a stirring solution of ester **268** (4.00 g, 15.2 mmol) in THF (80 mL) at -78 ˚C. The reaction was warmed to room temperature over 1.5 h and then cooled to 0 ˚C. Methanol (25 mL) was added carefully and then sat. Rochelle's solution (100 mL) and the resulting mixture was stirred at room temperature for 1.5 h. The layers were separated and the organic layer was washed with sat. Rochelle's solution (2 × 50 mL) and the combined aqueous layers were extracted with diethyl ether (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude was purified by flash column chromatography to yield **271** as a colourless oil (2.75 g, 78 %), which was inseparable from its regioisomer **272 (271**:**272**, 7:1).

Data for **271**:

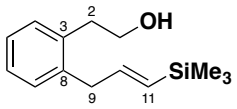
δ_H (400 MHz, $CDCl_3$): 7.35 (1H, d, *J* 7.3, ArH), 6.96 – 7.15 (3H, m, ArH), 6.42 (1H, d, *J* 15.7, H9), 6.07 (1H, m, H10), 3.76 (2H, t, *J* 6.8, CH_2(1)), 2.89 (2H, t, *J* 6.8, CH_2(2)), 1.64 (2H, d, *J* 8.3, CH_2(11)), 1.41 – 1.48 (1H, br. s, OH), 0.00 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 139.7 (ArC), 136.4 (ArC), 132.0 (ArCH), 131.9 (C10), 128.7 (ArCH), 128.3 (ArCH), 127.8 (ArCH), 127.3 (C9), 64.9 (C1), 38.4 (C2), 26.2 (C11), 0.0 ($Si(CH_3)_3$).

ν_{max} (thin film): 3338 (OH), 1247 (Si-CH_3).

HRMS (ESI +ve) found: 257.1340 [$(M+Na)^+$], $C_{14}H_{22}NaOSi$ requires: 257.1332.

(*E*)-2-(2-(3-(trimethylsilyl)allyl)phenyl)ethan-1-ol 272

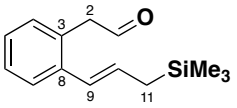


Selected NMR data for regioisomer **272**:

δ_H (400 MHz, $CDCl_3$): 5.55 (1H, d, *J* 18.6, H11), 3.83 – 3.88 (2H, m, CH_2(1)), 3.43 (2H, dd, *J* 5.7, 1.6 CH_2(9)), 2.83 (2H, t, *J* 6.8, CH_2(2)), - 0.02 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 133.2 (C11), 131.8 (C10), 61.3 (C1), 42.0 (C9), 37.7 (C2), 0.56 ($Si(CH_3)_3$).

(*E*)-2-(2-(3-(Trimethylsilyl)prop-1-en-1-yl)phenyl)acetaldehyde 273



Oxalylchloride (0.11 mL, 1.29 mmol) was added dropwise to a solution of dimethylsulfoxide (0.20 mL, 2.59 mmol) in dichloromethane (2.50 mL) at -78 ˚C. The solution was left to stir for 10 min and then alcohol **271** (0.20 g, 0.86 mmol) dissolved in dichloromethane (0.50 mL) was added *via* cannula. The solution was stirred at -78 ˚C for 1 h and then triethylamine (0.36 mL, 2.59 mmol) was added and the reaction was warmed to 0 ˚C over 30 min. The reaction was quenched with water (10 mL) and dichloromethane (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 10 mL) and the combined organics were dried ($MgSO_4$) and reduced *in vacuo*. Typically, the aldehyde was used crude due to its unstable

nature, however purification by flash column chromatography was performed for characterization purposes to yield the aldehyde **273** as a colourless oil (0.12 g, 61 %).

Data for **273**:

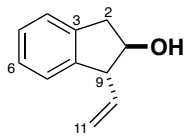
δ_H (400 MHz, $CDCl_3$): 9.69 (1H, t, *J* 2.4, CHO) 7.45 (1H, d, *J* 7.6, ArH), 7.27 (1H, m, ArH), 7.21 (1H, td, *J* 7.5, 1.4, ArH), 7.15 (1H, m, ArH), 6.31 (1H, d, *J* 15.4, H9), 6.15 (1H, dt, *J* 15.4, 8.2, H10), 3.74 (2H, d, *J* 2.2, CH_2(2)), 1.70 (2H, dd, *J* 8.5, 1.3, CH_2(11)), 0.06 (9H, s, $Si(CH_3)_3$).

δ_C (101 MHz, $CDCl_3$): 199.8 (CHO), 138.6 (ArC), 131.5 (C10), 130.8 (ArCH), 128.6 (ArC), 127.9 (ArCH), 126.9 (ArCH), 126.3 (ArCH), 125.0 (C9), 48.5 (C2), 24.5 (C11), -1.9 ($Si(CH_3)_3$).

ν_{max} (thin film): 1724 (C=O), 1248 (Si-CH_3).

HRMS (ESI +ve) found: 255.1169 [$(M+Na)^+$], $C_{14}H_{20}NaOSi$ requires: 255.1176.

(±)-*anti*-1-Vinyl-2,3-dihydro-1*H*-inden-2-ol 274



Aldehyde **273** (63 mg, 0.27 mmol) and tetrabutylammonium triphenyldifluorosilicate (15 mg, 0.03 mmol) were dissolved in chloroform (2.0 mL) and were stirred for 18 h. The reaction was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL) and the combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by flash column chromatography to yield indane **274** (10 mg, 23 %) as a single diastereomer.

N.B. The relative stereochemistry was assigned by comparison with literature data for the *syn*-diastereomer.[160]

Data for **274**:

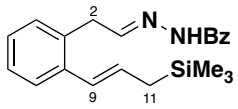
δ_H (500 MHz, $CDCl_3$): 7.21 (3H, m, ArH), 7.13 (1H, m, ArH), 5.87 (1H, m, H10), 5.27 (2H, m, H11), 4.37 (1H, *a*q, *J* 6.9, H1), 3.64 (1H, *a*t, *J* 7.4, H9), 3.26 (1H, dd, *J* 15.4, 6.9, H2), 2.90 (1H, dd, *J* 15.4, 7.3, H2'), 1.85 (1H, br. s, OH).

δ_C (126 MHz, $CDCl_3$): 142.5 (ArC), 139.9 (ArC), 137.9 (C10), 127.3 (ArCH), 126.9 (ArCH), 124.7 (ArCH), 124.6 (ArCH), 117.8 (C11), 79.1 (C1), 58.5 (C9), 40.1 (C2).

ν_{max} (thin film): 3344 (OH).

HRMS (FI +ve) found: 160.0892 [$(M\bullet)^+$], $C_{11}H_{12}O$ requires: 160.0888.

(*E*)-*N*'-(2-(2-((*E*)-3-(Trimethylsilyl)prop-1-en-1-yl)phenyl)ethylidene)benzohydrazide 275



Oxalylchloride (0.47 mL, 5.60 mmol) was added dropwise to a solution of dimethylsulfoxide (0.79 mL, 11.2 mmol) in dichloromethane (10 mL) at -78 ˚C. The solution was left to stir for 10 min and then alcohol **271** (0.87 g, 3.74 mmol) dissolved in dichloromethane (2 mL) was added *via* cannula. The solution was stirred at -78 ˚C for 1 h and then triethylamine (1.55 mL, 11.2 mmol) was added and the reaction was warmed to 0 ˚C over 30 min. The reaction was quenched with water (30 mL) and dichloromethane (30 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 30 mL) and the combined organics were dried ($MgSO_4$) and reduced *in vacuo*. The crude aldehyde **273** was then redissolved in methanol (20 mL) and benzoylhydrazine (0.50 g, 3.70 mmol) and acetic acid (few drops) were added. The reaction was stirred for 1 h and then diluted with water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography to yield hydrazone **275** (0.59 g, 45 %, over 2 steps) as an amorphous solid.

Data for **275**:

m. p. 45 – 48 ˚C.

δ_H (500 MHz, *d*6-DMSO): 11.46 (1H, s, NH) 7.76 – 7.85 (3H, m, H1 and ArH), 7.45 – 7.58 (4H, m, ArH), 7.16 – 7.24 (3H, m, ArH), 6.54 (1H, d, *J* 15.4, H9), 6.21 (1H, m, H10), 3.67 (2H, d, *J* 5.4, CH_2(2)), 1.72 (2H, d, *J* 8.2, CH_2(11)), 0.04 (9H, s, $Si(CH_3)_3$).

δ_C (126 MHz, *d*6-DMSO): 162.8 (C=O), 150.4 (C1), 133.5 (ArC), 133.0 (ArC), 131.6 (ArCH), 130.6 (ArC), 129.9 (ArCH), 129.9 (C10), 128.4 (2 × ArCH), 127.5 (2 × ArCH), 127.1 (ArCH), 126.6 (ArCH), 125.4 (ArCH), 125.0 (C9), 36.2 (C2), 23.8 (C11), -1.8 ($Si(CH_3)_3$).

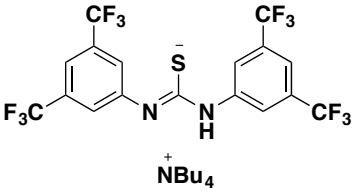
ν_{max} (thin film): 1651 (C=O), 1550 (C=N), 1247 ($Si-CH_3$).

HRMS (ESI +ve) found: 373.1703 [$(M+Na)^+$], $C_{21}H_{26}N_2NaOSi$ requires: 373.176.

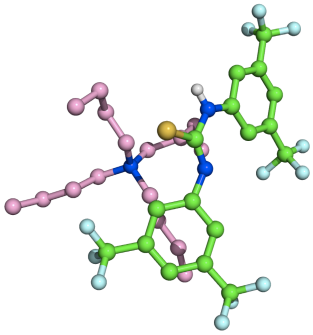
6. Appendices

6.1 X-Ray Crystallography Data

Tetra-*n*-butylammonium (*Z*)-*N*,*N*'-bis(3,5-bis(trifluoromethyl)phenyl)carbamimidothioate salt 130



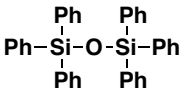
130

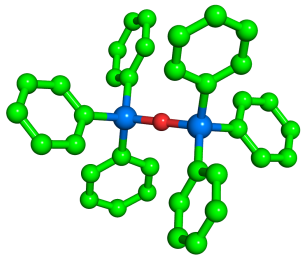


Empirical formula	$C_{33}H_{43}N_3SF_{12}$
Formula weight	741.77
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P 2_1/c
a (Å)	12.5379
b (Å)	8.7642
c (Å)	32.5107
α (°)	90
β (°)	93.332
γ (°)	90
Cell Volume (Å^3)	3566.4
Z	2
Calculated density (Mg/m^3)	1.381
Absorption coefficient (mm^{-1})	0.181
F_{000}	1544.00
Crystal size (mm)	0.26 × 0.09 × 0.09
θ range for data collected	5.123 to 27.473
Index ranges	-16≥ h ≥16, -11≥ k≥ 8, -40≥ l ≥40
Reflections collected	10663
Independent reflections	7686
Completeness to θ = 27.47°	94.0%

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.60
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	7686/0/443
Goodness-of-fit on F^2	0.9685
Final R indices [I>2σ(I)]	R1=0.0931, wR2=0.1958
R indicies (all data)	R1=0.1671, wR2=0.2501

Hexaphenyldisiloxane 170





Empirical formula	$C_{36}H_{30}OSi_2$
Formula weight	534.81
Temperature (K)	150
Wavelength (Å)	1.54180
Crystal system	Triclinic
Space group	P -1
a (Å)	8.6125
b (Å)	9.4880
c (Å)	11.0060
α (°)	95.910
β (°)	111.755
γ (°)	113.363
Cell Volume ($Å^3$)	733.13
Z	2
Calculated density (Mg/m^3)	1.211
Absorption coefficient (mm^{-1})	1.296
F_{000}	282
Crystal size (mm)	0.12 × 0.22 × 0.04
θ range for data collected	4.524 to 76.571
Index ranges	-10≥ h ≥10, -11≥ k≥ 10, 0≥ l ≥13
Reflections collected	12263
Independent reflections	3030
Completeness to θ = 76.57°	98.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.95 and 0.86
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3029/0/178
Goodness-of-fit on F^2	0.9560
Final R indices [I>2σ(I)]	R1=0.0336, wR2=0.0934
R indicies (all data)	R1=0.0374, wR2=0.0977

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