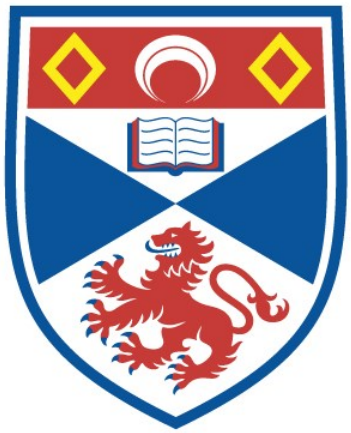
Isothiourea-catalyzed enantioselective reactions of imines with α,β-unsaturated esters employing α,β-unsaturated acyl ammonium intermediates

Jerson Lapetaje

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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The research described in this thesis has formed the basis of the following peer reviewed publications:

“Isothiourea-catalyzed formal enantioselective conjugate addition of benzophenone imines to β-fluorinated α,β-unsaturated esters”
J.E. Lapetaje, C.M. Young, C. Shu, and A.D. Smith, *Chem. Commun.,* **2022**, *58*, 6886-6889

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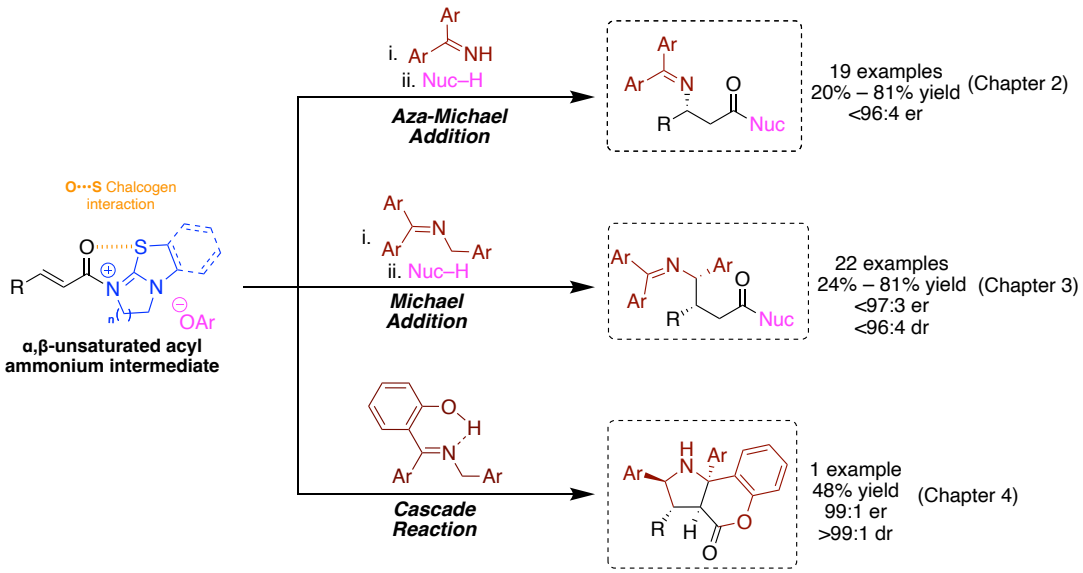
This was a good run for my academic career.

ABSTRACT

The use of isothioureas as Lewis base organocatalysts has been widely studied by the Smith group and shown to be effective in various Michael addition and annulation reactions, which is associated with the formation of the reactive α,β-unsaturated acyl ammonium intermediates. To further explore the reactivity of these reactive intermediates, this research project focuses on employing α,β-unsaturated acyl ammonium intermediates to perform various reactions such as (i) aza-Michael addition reactions, (ii) Michael addition reactions, and (iii) a Michael-addition-cyclisation-lactonisation cascade reactions using imines and other imine derivatives as nucleophiles to access a range of chiral compounds with important structural motifs (e.g. β-amino acids, γ-imino esters and amides, γ-lactam compounds, and pyrrolidine compounds) in high enantio- and diastereoselectivity.

In this work, successful protocols for the highly selective aza-Michael addition reaction and Michael addition reaction of imine nucleophiles to α,β-unsaturated ester substrates were established to obtain various β-imino esters, β-imino amides, various γ-imino amide and ester products *via* the access of the reactive α,β-unsaturated acyl ammonium intermediate using an enantiopure isothiourea organocatalyst showing moderate to excellent yield (20% – 81%) and enantio- and diastereoselectivity ((<97:3 er, <96:4 dr). A proof of concept for the highly enantio- and diastereoselective formation of a chromeno-pyrrolidine product was highlighted from the reaction of a Schiff base and α,β-unsaturated ester substrate using isothiourea organocatalyst showing moderate yield (48% yield) but with excellent selectivity (99:1 er, >99:1 dr). The reaction was deduced to follow a highly stereoselective Michael addition, followed by a 5-*endo*-*trig* cyclization reaction to generate the pyrrolidine core, and a subsequent lactonization reaction to form the chromeno-pyrrolidine product in excellent enantio- and diastereoselectivity.



ABBREVIATIONS

Å	Ångstrom(s) (1 x 10^{-10} m)
Ac	Acetyl
app.	Apparent
aq	Aqueous
Ar	Aromatic
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
br	Broad
BTM	Benzotetramisole
Bu	Butyl
c	Concentration
C	Celcius
cal	Calories
cat.	Catalyst
cm	Centimetre(s)
COSY	Correlation Spectroscopy
DABCO	1,4-diazobycyclo[2.2.2.]octane
d	Doublet
DMAP	4-*N,N*-Dimethylaminopyridine
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
equiv.	Equivalent molar quantity
er	Enantiomeric ratio
ES	Electrospray
ESI	Electrospray ionization
Et	Ethyl
g	Gram(s)
h	Hour(s)
HBTM	Homobenzotetramisole
HMDS	Hexamethyldisilazide
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry

HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i	*Iso*
IR	Infrared
k	Rate constant
LB	Lewis base
LG	Leaving group
Lit	Literature
LUMO	Lowest unoccupied molecular orbital
M	Molar (i.e. mol dm^{-3})
m	Multiplet
M. S.	Molecular sieves
m/z	Mass / Charge
MAL	Michael-Aldol-Lactonisation
Me	Methyl
Mes	Mesityl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
MML	Michael-Michael-Lactonisation
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry
o/n	Overnight
NCMAL	Nucleophile-Catalyzed Michael-Aldol-Lactonisation
NHC	N-heterocyclic carbene
ν_{max}	Frequency
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
NSI	Nanospray ionization
Nu	Nucleophile
o	*Ortho*
p	*Para*

PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
ppm	Parts per million
PPY	4-Pyrrolidinopyridine
Pr	Propyl
PS	Polymer supported
q	Quartet
quant.	Quantitative
quint	Quintuplet
R	Alkyl
recryst	Recrystallization/recrystallized
r.t.	Ambient (room) temperature
s	Singlet
sat.	Saturated
sept	Septet
SM	Starting material
SOMO	Singly Occupied Molecular Orbital
t	Triplet/time
T	Temperature
TBS	*Tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Tetramisole
TMS	Trimethylsilyl
TOF	Turnover frequency
Tol	Tolyl=Methylphenyl
TS	Transition state
Ts	Tosyl
V	Volume
µL	Microlitre(s)

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Health conditions such as the simple flu down to cancer are some of the main antagonists of human life, and the search for new ways to battle these diseases is one of the main goals worldwide. Research in the natural product area and the biomedical field have been the front runners for solving these problems in past decades. Many discoveries have been amassed, including the search and identification of drug-lead compounds, such as Dolastatin 11 **1** (activity against lymphocytic leukaemia),[1] NSL-93501 **2** (inhibition of platelet aggregation, possible antithrombotic agent),[2] Jasplakinolide **3** (insecticidal, anthelminthic, and antifungal properties),[3] and Methylphenidate **4** (treatment for the attention-deficit disorder)[4,5] (Figure 1). These advances range to the development of techniques and advanced technology such as Endoscopic Submucosal Dissection (ESD),[6] Flexible Bronchoscopy (FB) and transthoracic needle biopsy (TNB)[7] in the diagnosis of diseases. The contribution from these researchers has been overwhelming and laid the foundation of the medical field as it is today.

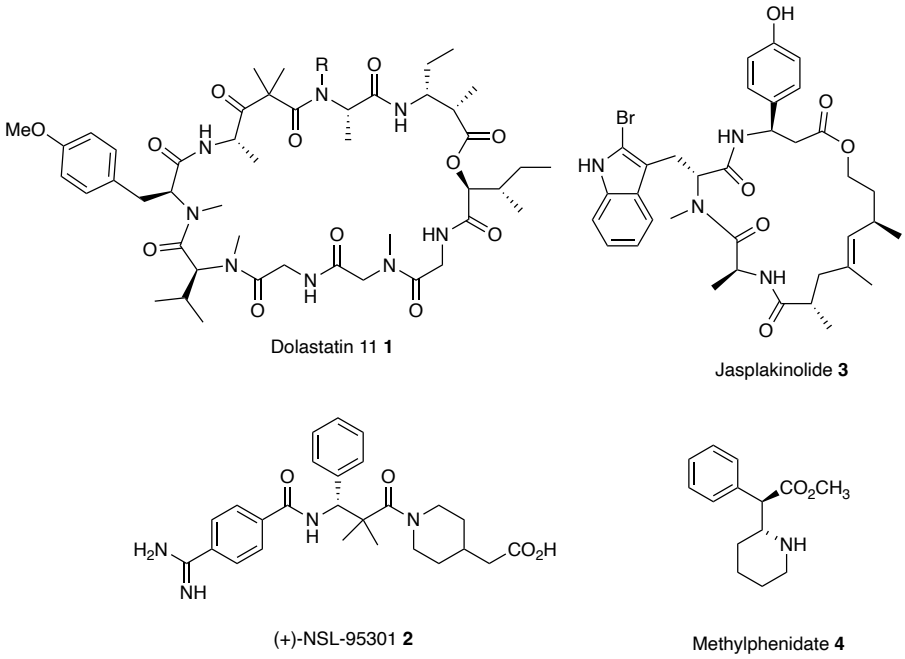


Figure 1. Drug-lead compounds.

As the intensity of the search and discovery of potent drug-lead components for different types of diseases increases, the inherent growth in the number of deaths caused by communicable and noncommunicable diseases likewise increases.[8] Thus, the search for new and innovative solutions in the medical field, especially in the development of unique and desirable chemical components derived from drug-lead compounds, has been an attractive field of research in synthetic chemistry.

One way in which synthetic chemistry can play a role is in the development and derivatisation of naturally occurring bioactive compounds. For example, a naturally occurring but weakly active antidiabetic drug (SGLT1 and SGLT2 inhibitor) Phlorizin **5** [9] was derivatised and led to the emergence of two classes of selective SGLT2 inhibitors: *O*- and *C*-aryl glucosides (Figure 2). Pharmacokinetic (PK) studies showed that all the clinical candidates of the *O*-aryl glucosides class, such as Sergliflozin **6** (GSK), showed suboptimal PK profiles. This problem was circumvented by an unanticipated discovery of the *C*-aryl glucoside class as a glucosylation side product led by medicinal chemists at Bristol-Myers Squibb Co.[10] Structure and activity relationship studies around the aglycone moiety of the *C*-aryl glucosides also lead to the discovery of clinically disclosed antidiabetic drugs such as Dapagliflozin (Forxiga®)[10] **7** and Ertugliflozin (PF-04971729) **8**.[11]

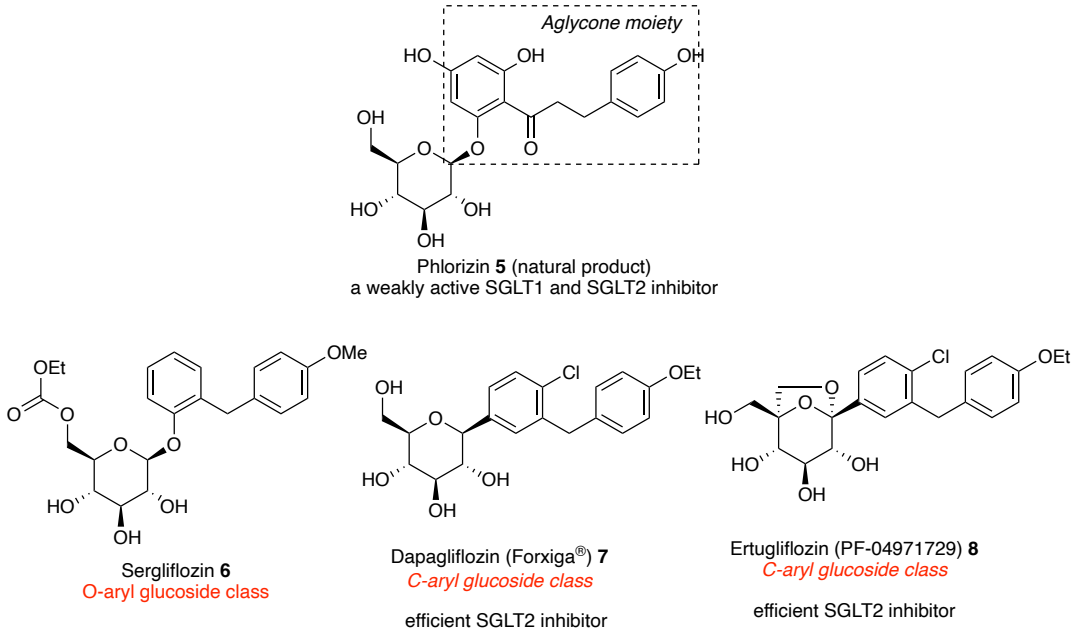
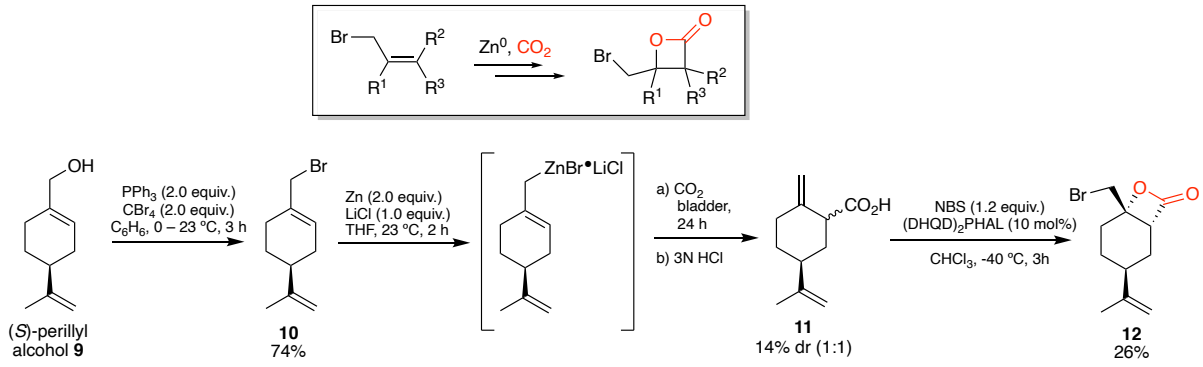


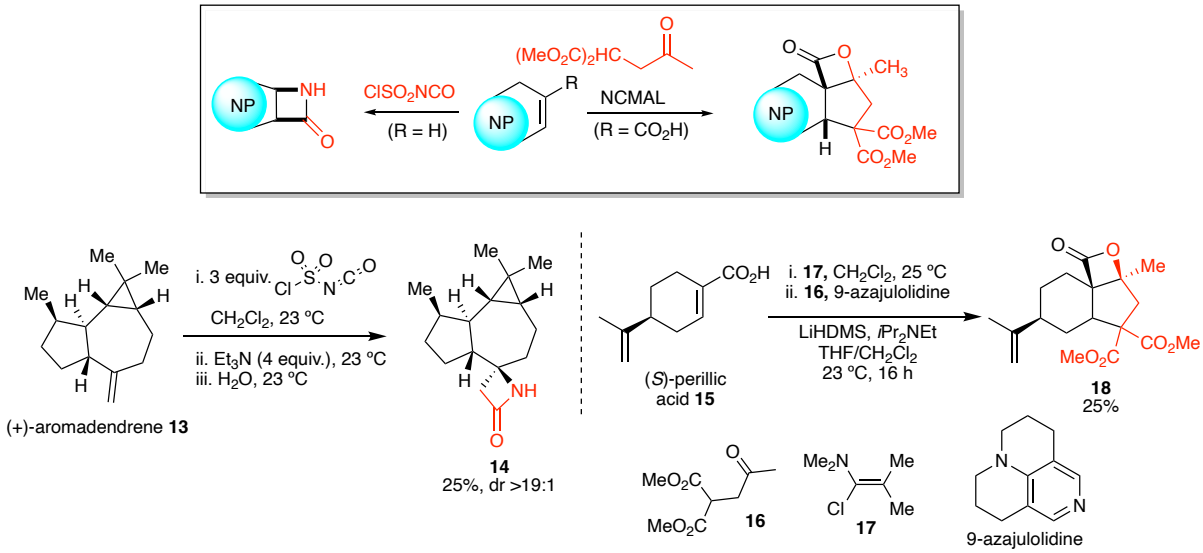
Figure 2. Development of Phlorizin **5,** Sergliflozin **6**, Dapagliflozin **7**, and Ertugliflozin **8.**

Another strategy aims to take natural products (NPs) and convert them to non-covalent bioactive NPs to act as covalent 'infinite' inhibitors, as described by Romo's group in 2019, through structural modification using different synthetic strategies.[12] One example is demonstrated by employing a β-lactone moiety onto (*S*)-perillyl alcohol **9** (antitumor NP). First, (*S*)-perillyl alcohol **9** was converted to its corresponding allylic bromide **10** via an Appel reaction.[13] Then a zinc-mediated carboxylation utilising CO_2 in a thick-walled rubber bladder was employed to obtain the intermediate **11**,[14] followed by a bromo-β-lactonization at a low temperature, first reported by Kan in 2012,[15] was employed (Scheme 1).[12]



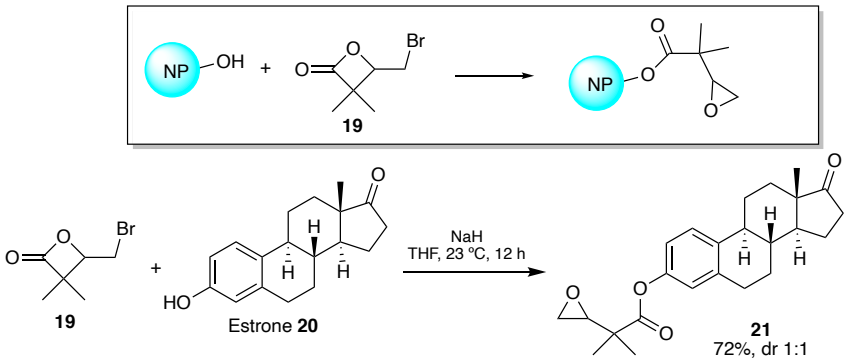
Scheme 1. Appel reaction followed by allylic Reformatzky-CO_2 capture and bromo-lactonization reaction sequence.

Another example is the incorporation of a spiro-β-lactam moiety onto an alkene-bearing NP such as (+)-aromadendrene **13** *via* net [2+2] cycloaddition with chlorosulfonyl isocyanate[16] (Scheme 2-left). A related strategy allows the incorporation of a cyclopentyl β-lactone moiety onto (*S*)-perillic acid **15** *via* a Nucleophile-Catalyzed Michael Aldol Lactonization approach (NCMAL) reaction reported by Romo in 2013[17] (Scheme 2-right).[12]



Scheme 2. Application of β-lactamization and nucleophile-catalyzed Michael aldol lactonization (NCMAL) strategies onto alkene-bearing natural product (NP).

Another one is the incorporation of epoxides from phenols (estrone **20**) through an acylation-cyclisation sequence using γ-bromo-β-lactone **19** (Scheme 3).[12] These are only a few of the many examples of research that highlight the immense capability of synthetic chemistry in the field of drug synthesis and design.



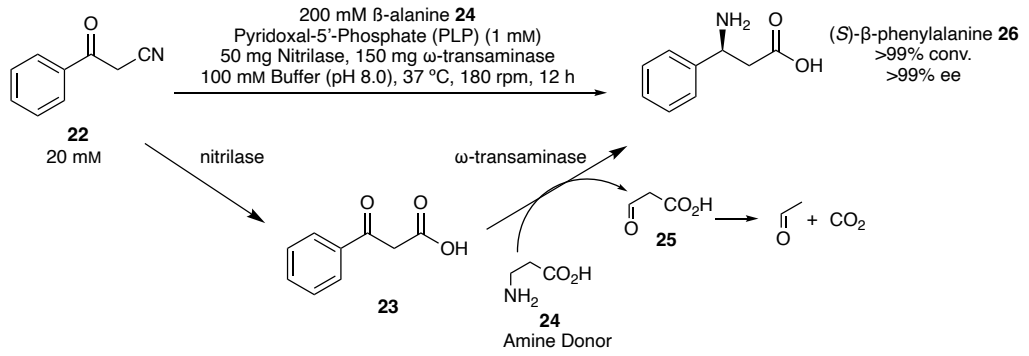
Scheme 3. Tagging of natural-product (Estrone **20**) with epoxides through an acylation-cyclisation sequence of phenols with γ-Bromo-β-lactone.

One important aspect of synthetic chemistry is the incorporation of chirality in the synthesis of specific compounds. Most of the drug-lead compounds and their derivatised counterparts previously highlighted either contain one or more stereogenic centres, and their synthesis in high enantiopurity is often required. Thus, researchers have focused on the development of highly selective methods for producing chiral bioactive compounds – this field is known as asymmetric synthesis.

1.2 ROLE OF ASYMMETRIC SYNTHESIS

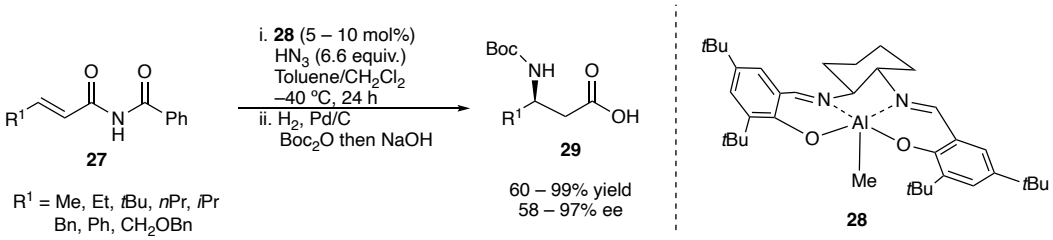
Asymmetric synthesis, taken from the core of Marckwald's definition in 1904,[18] is the conversion of an achiral compound to a chiral-nonracemic one with enantiocontrol.[19] Early asymmetric syntheses involved the application of chiral reagents or auxiliaries to impart stereoselectivity, but many of these have now been surpassed through the introduction of highly selective catalytic methods that allow the development of new chiral compounds in enantioenriched form with high yield and stereoselectivity. This area has been extensively explored for the development and design of structural motifs such as chiral β-amino acids, with enzymatic, metal and organocatalytic methods all explored.

As a representative biocatalytic example, the enzyme nitrilase from *Hoeflea phototrophica* DFL-43 has been coupled with ω-transaminase from *Polaromonas* sp. JS666 for a two-step one-pot synthesis of (*S*)-β-phenylalanine **26** from benzoyl acetonitrile **22** with excellent enantioselectivity (>99%) and conversion (>99%) (Scheme 4).[20]



Scheme 4. Nitrilase coupled with a ω-transaminase-catalyzed synthesis of (*S*)-β-phenylalanine **26.**

As a representative metal-catalyzed approach, in 1999, Jacobsen reported an asymmetric conjugate addition of hydrazoic acid to α,β-unsaturated imides **27** catalyzed by Al(III)-Salen complex **28**. Subsequent reduction and hydrolysis led to a range of β-amino acids **29** in high yield and enantioselectivity (Scheme 5). Excellent reactivity was observed despite the steric properties of the β-substituents (R^1) ranging from a simple methyl group to the sterically challenging *tert*-butyl group at −40 ºC. However, aryl R^1 groups were shown to be less reactive than alkyl groups, with a β-phenyl substituted imide showing poor yield and selectivity (60% yield and 58% ee) after 24 h at room temperature.[21]



Scheme 5. Al(III) Salen-catalyzed enantioselective conjugate addition of hydrazoic acid to α,β-unsaturated imides **27**.

Despite the promising reactivity of enzymes and organometallic complexes as chiral catalysts, these types of catalysts have some drawbacks associated with them. The production, extraction, and stability of most enzyme-derived catalysts, and their typical substrate specificity, together with the need for expensive and sophisticated instrumentation, is a significant drawback. Although extremely versatile, organometallic catalysts can be unstable to air and moisture and often require special inert glove-box conditions for their use and synthesis, making them expensive and difficult to use. An alternative to these traditional methods that are stable, cost-efficient, and generally easy to use and prepare is the use of organocatalysts.[22] Organocatalysis, a term popularised by MacMillan,[23] is classified as the acceleration of a chemical transformation by the introduction of a sub-stoichiometric quantity of an organic compound.[22] The use of organocatalysts for asymmetric synthesis has increased in the past two decades because of their experimental simplicity, catalyst stability,

and versatility, while imparting high stereoselectivity and its importance has been recognized by the award of the Nobel Prize in Chemistry in 2021. Despite their potential drawback (e.g. long reaction times, higher catalyst loading), asymmetric organocatalysis still provides an effective means of accessing chiral compounds.

1.3 ORGANOCATALYSIS: LEWIS BASE CATALYSIS

Organocatalysts can be classified as Lewis acids, Lewis bases, Brønsted acids, and Brønsted bases, with their generic catalytic cycles shown in Figure 3.[24]

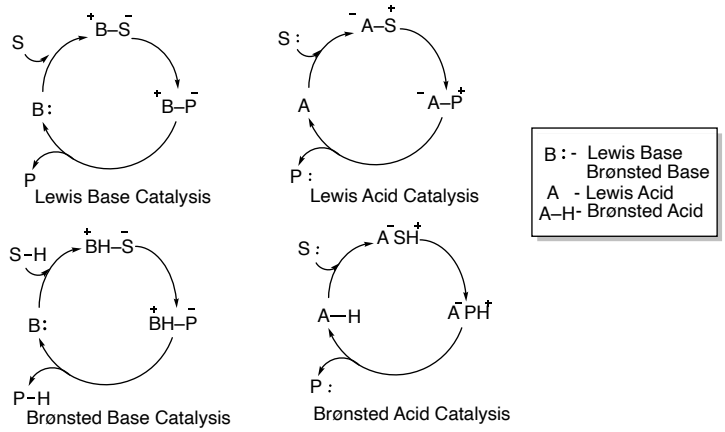
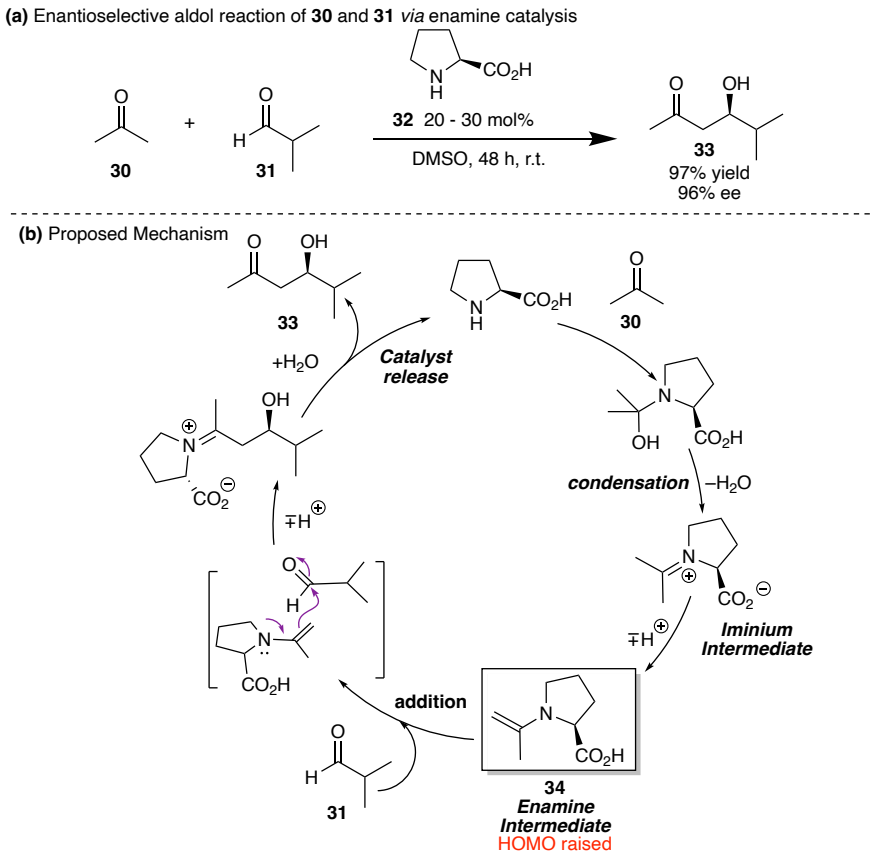


Figure 3. Generic catalytic cycles for Lewis acid, Lewis base, Brønsted acid, and Brønsted base organocatalysts.

Focusing on Lewis base catalysis as it is the central point of research in this thesis, this can be defined as the use of a Lewis base to enhance the rate of a chemical reaction by binding with an acceptor atom of a substrate without it being consumed or altered during the reaction. This binding may increase the nucleophilicity or electrophilicity of the intermediates formed.[25] These modes of activation can be classified as either the (i) highest occupied molecular orbital (HOMO) activation ; (ii) the lowest unoccupied molecular orbital (LUMO) activation; or (iii) singly occupied molecular orbital (SOMO) activation. Representative examples will be given for the aforementioned modes of activation.

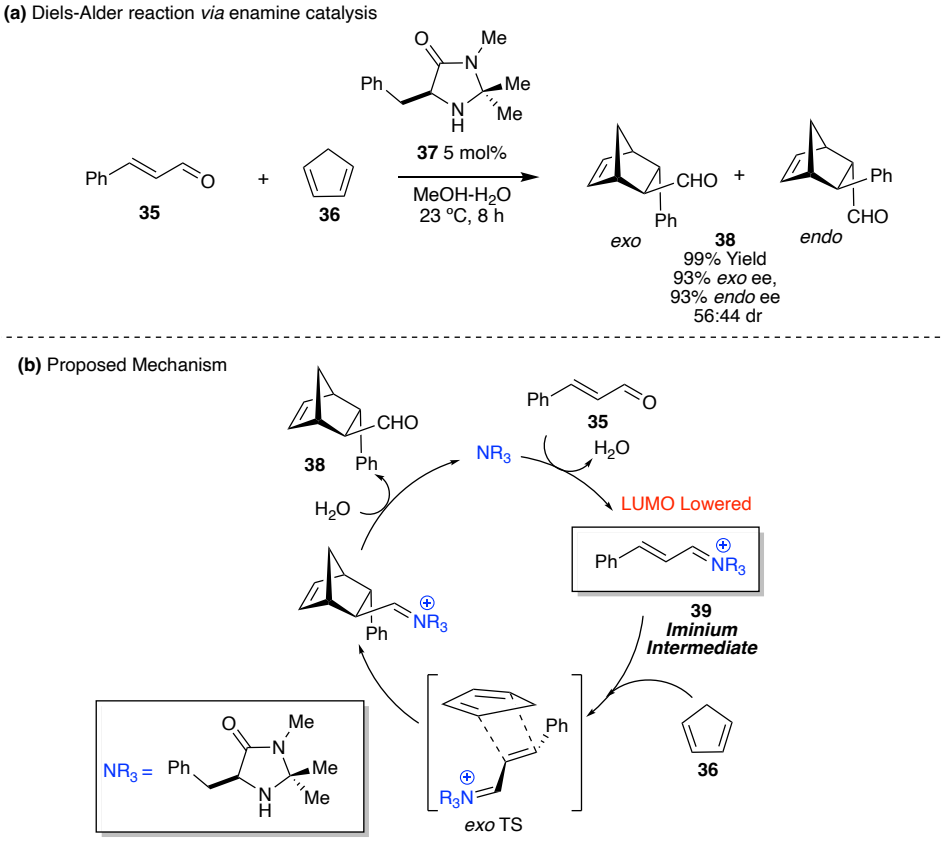
A HOMO activation mode typically enhances the nucleophilicity of the substrate upon binding of a Lewis base organocatalyst. An example is from the study of List showing the use of a HOMO-activating organocatalyst **32** to effectively carry out a stereoselective aldol reaction *via* enamine catalysis (Scheme 6a). A mechanism was proposed whereby the nucleophilic character of substrate **30** is enhanced by transformation to an enamine intermediate **34**,

followed by aldol reaction and hydration with the subsequent catalyst release via hydrolysis (Scheme 6b).[26]



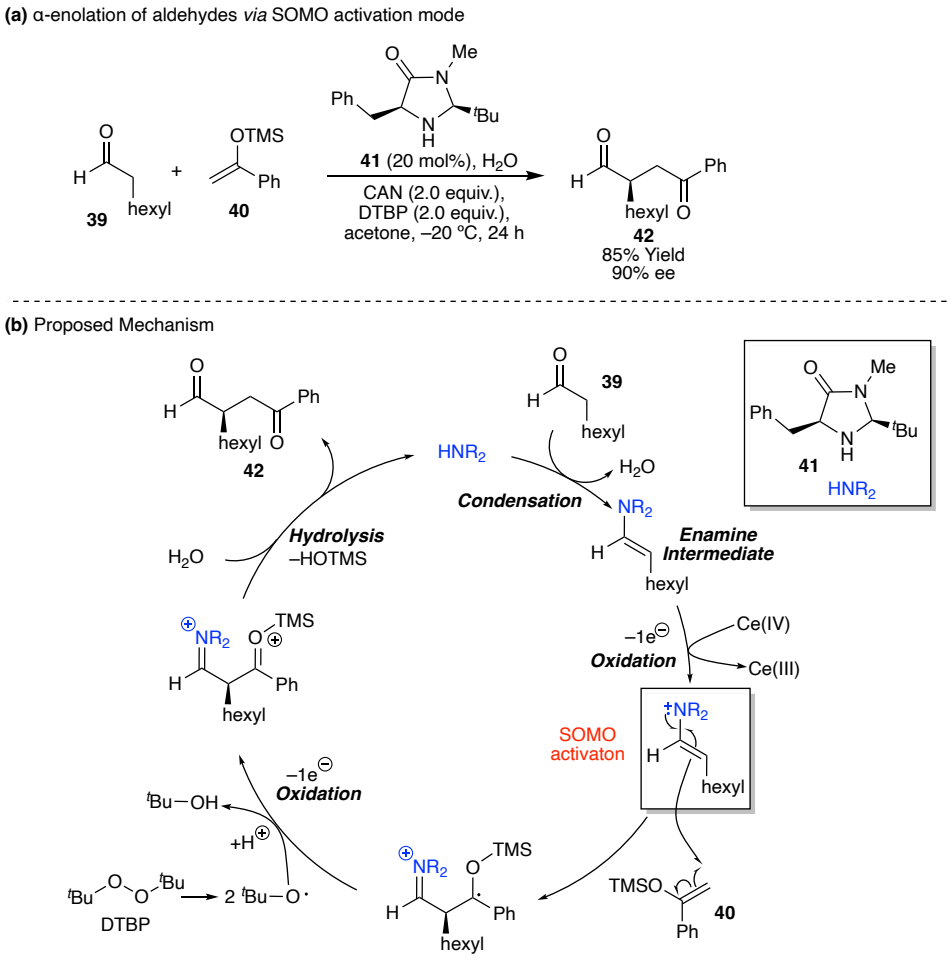
Scheme 6. Catalytic cycle for the HOMO activating enamine catalysis.

A LUMO activation mode, on the other hand, enhances the electrophilicity of the substrate upon binding with a Lewis base, as shown from the study of MacMillan describing the first highly enantioselective Diels-Alder reaction using the organocatalyst **37** (Scheme 7a). The LUMO lowering activation of α,β-unsaturated aldehyde **35** was demonstrated by the formation of iminium intermediate **39**, acting as an activated chiral dienophile. Subsequent cycloaddition onto diene **36** gave bicyclic structure **38** in excellent yield and high ee, albeit in low diastereoselectivity (Scheme 7b).[27]



Scheme 7. Catalytic cycle for LUMO activating iminium catalysis.

Lastly, a SOMO activation mode is the generation of a three-π-electron radical cation *via* a one-electron oxidation of a transient enamine species pioneered by MacMillan's group in 2007 for the first asymmetric aldehyde α-enolation to directly access the highly enantioenriched γ-ketoaldehydes in moderate to good yield and excellent enantioselectivity (Scheme 8a). The SOMO activation was demonstrated by the selective single-electron oxidation of the transient enamine intermediate followed by radical addition to the enolsilane **40** to generate the α-OTMS radical carbon center. Subsequent single-electron oxidation forms the oxocarbenium intermediate which then generates the α-substituted-γ-ketoaldehyde **42** upon hydrolysis of the silyl group (Scheme 8b).[28]



Scheme 8, Catalytic cycle for SOMO catalysis.

These are only a few of many organocatalysts shown to exploit either the HOMO, the LUMO, and the SOMO modes of activation through Lewis base catalysis.

1.4 ISOTHIOUREAS AS LEWIS BASE ORGANOCATALYST

One interesting class of asymmetric Lewis base organocatalysts is that of isothioureas. Isothiourea-based organocatalysts contain a heterocyclic core **43** (Figure 4) and were initially studied by Birman[29] and Okamoto[30] for their possible catalytic properties. Both initially demonstrated the utility of these Lewis base organocatalysts in acyl transfer reactions.

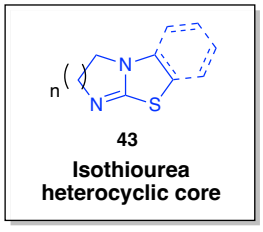
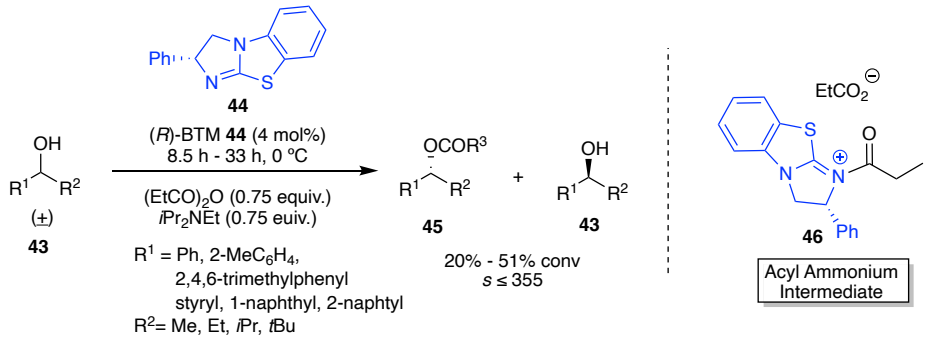


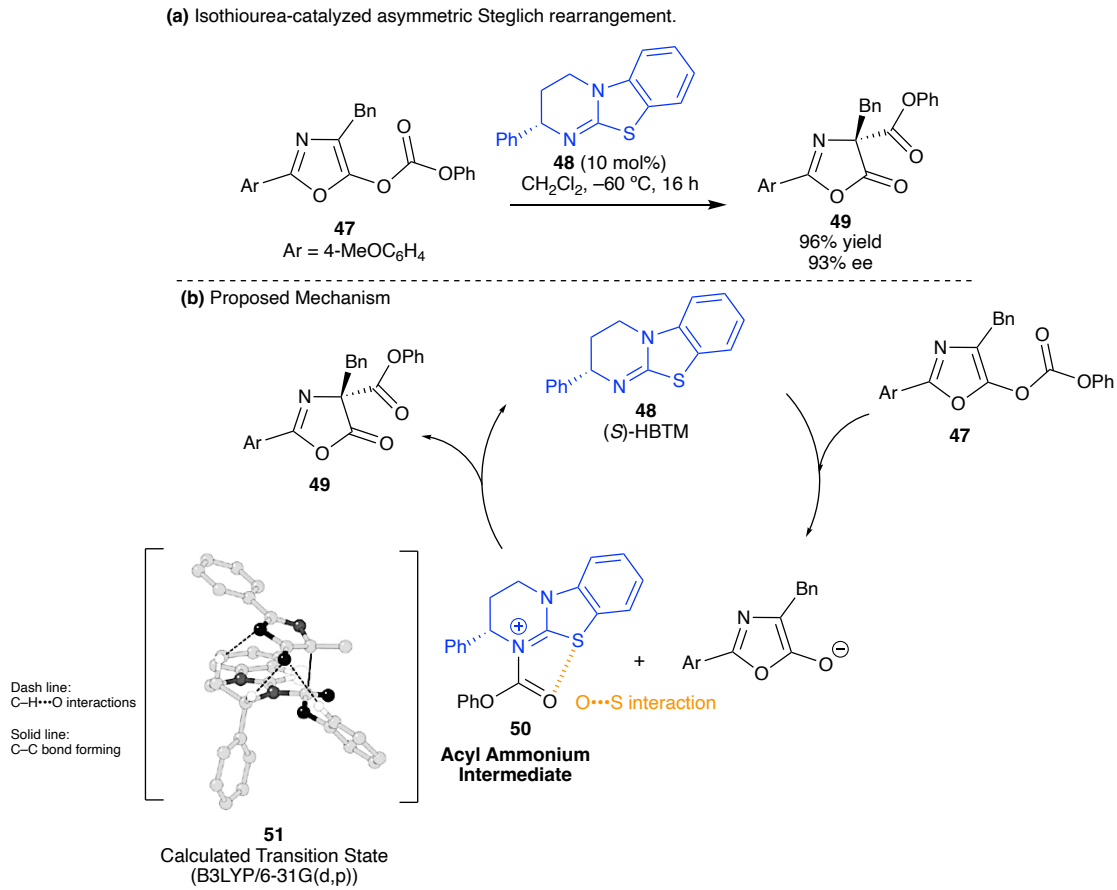
Figure 4. The general heterocyclic core of isothiourea-based organocatalysts.

In the initial studies by Birman,[29] isothiourea **44** – benzotetramisole (BTM) – was used as an effective acyl transfer organocatalyst harnessing an acyl ammonium intermediate to perform a kinetic resolution of secondary alcohols **43** (Scheme 9) with relatively good conversion and high selectivity (20% - 50% conv. and s ≤ 355). The reaction begins with a nucleophilic attack of (*R*)-BTM **44** onto propionic anhydride ($(EtCO)_2O$) to form acyl ammonium intermediate **46** followed by a preferential nucleophilic attack of one of the enantiomer of alcohol **43** at the carbonyl carbon of intermediate **46** to form product **45**.



Scheme 9. Kinetic resolution of secondary alcohols using (*R*)-BTM **44** as an efficient acyl transfer organocatalyst.

This was then followed by a study from the Smith group[31] that utilized isothiourea as an efficient organocatalyst for an enantioselective Steglich rearrangement that proceeded to give products (Scheme 10a) with excellent yield and enantioselectivity (96% yield, 93% ee). The proposed mechanism shows the formation of an acyl ammonium intermediate **50** and enolate ion pair by acylation of HBTM **48**, the lowest unoccupied molecular orbital (LUMO) of the acyl ammonium intermediate is lowered relative to the carbonyl substrate allowing a nucleophilic attack at the C(1) position,[22,32] then followed by C-carboxylation to produce (*R*)-**49** with the subsequent release of the catalyst. Catalyst stereocontrol is shown in the calculated transition state **51** (Scheme 10b).



Scheme 10. Proposed catalytic cycle for the isothiourea-catalysed Steglich rearrangement.

Building upon the results of Birman,[29] Okamoto,[30] and Smith's group,[31] Mayr and co-workers then studied the nucleophilicity, Lewis basicity, and nucleofugality of isothiourea derivatives and compared them to well-known organocatalysts. They concluded that the nucleophilicity and nucleofugality of isothioureas are in the region of the classical organocatalysts such as dimethylaminopyridine (DMAP) and 1-methyl-1*H*-imidazole (NMI), while their Lewis basicity is comparable to that of 1,4-diazobycyclo[2.2.2.]octane (DABCO),[33] benchmarking isothioureas as suitable Lewis-base organocatalysts. Typical examples of isothiourea organocatalysts are (*S*)-TM **52**, (*R*)-BTM **44**, (*S*)-HBTM **48**, and (2*S*,3*R*)-HyperBTM **53** as shown below (Figure 5).

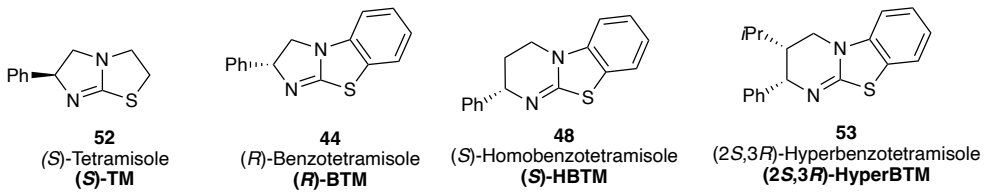


Figure 5. Examples of isothiourea-based asymmetric organocatalysts.

Having been demonstrated as an efficient acyl transfer catalysts, isothioureas as Lewis base organocatalysts were then further studied by different researchers and were shown to act through both the HOMO and the LUMO modes of activation, which can be accessed in the following types of Lewis base catalysis: ammonium enolate catalysis (Figure 6a), acyl ammonium catalysis (Figure 6b), and α,β-unsaturated acyl ammonium catalysis (Figure 6c). These different types of Lewis base catalysis offered by isothioureas are discussed in the following examples.

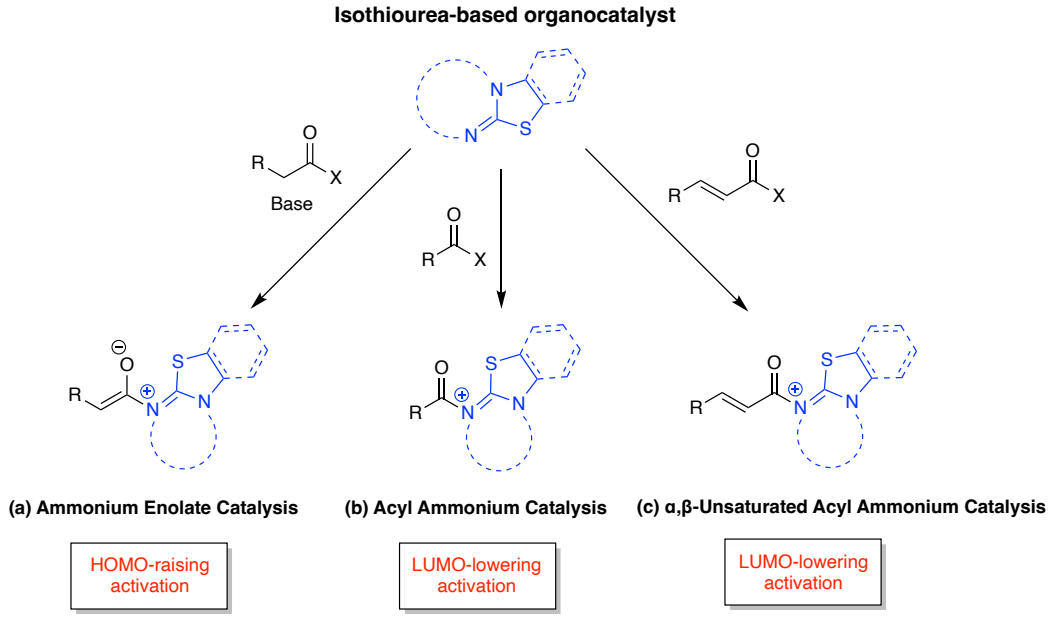
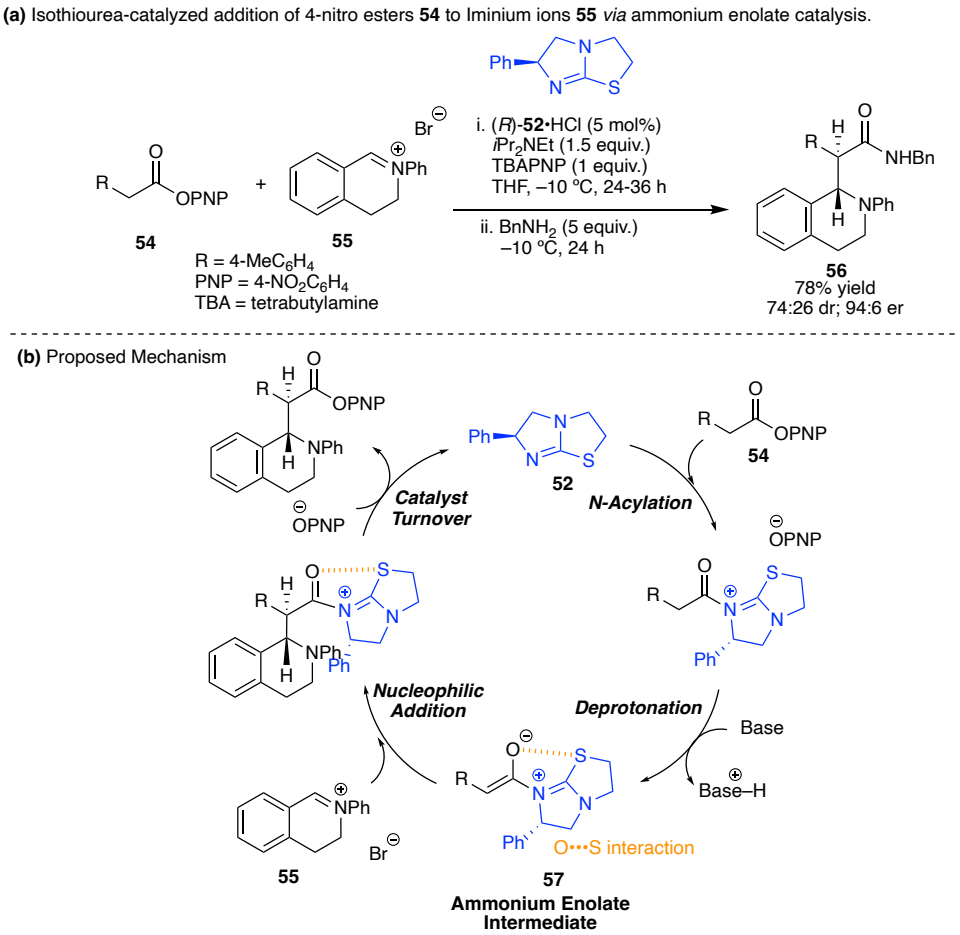


Figure 6. Different activation modes of isothiourea-based organocatalysts.

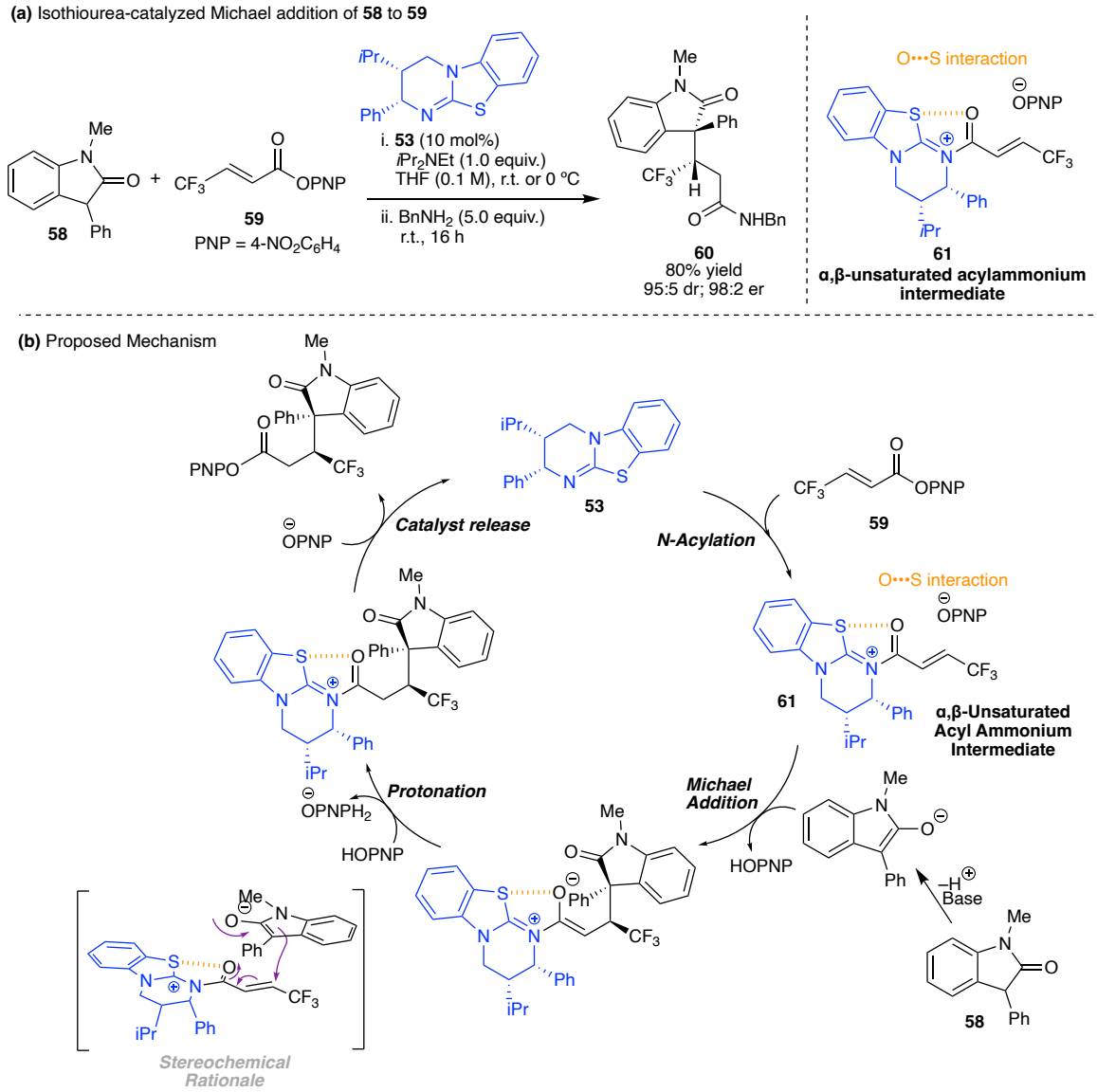
A representative example is the study from the Smith group using isothiourea **52** as a HOMO-activating organocatalyst *via* C(1)-ammonium enolate intermediates. They were able to carry out an enantioselective addition of 4-nitrophenyl ester **54** onto iminium ion **55** to form product **56** with satisfactory yield and stereoselectivity (78% yield, 74:26 dr, and 94:6 er) (Scheme 11a). The reaction starts with a nucleophilic attack of isothiourea **52** onto the substrate ester **54** followed by α-deprotonation to form the ammonium enolate intermediate **57**, effectively raising the HOMO energy of the ester substrate enabling a nucleophilic addition to iminium ion **56** followed by a catalyst release (Scheme 11b).[34]

A representative example for a LUMO-activating isothiourea organocatalyst *via* C(1)-acyl ammonium was previously highlighted in Scheme 10 by the Smith group via an isothiourea-catalysed enantioselective Steglich rearrangement.[31]



Scheme 11. Proposed catalytic cycle of the Isothiourea **53** in the addition of 4-nitrophenyl esters **55** to Iminium ions **56** *via* ammonium enolate catalysis.

As a representative example of an isothiourea being harnessed as a LUMO activating organocatalyst the Michael addition of N-heterocyclic pro-nucleophile **58** onto α,β-unsaturated ester **59** to from the product **60** in very good yield and stereoselectivity (80% yield, 95:5 dr and 98:2 er) proceeding *via* an α,β-unsaturated acyl ammonium species was reported (Scheme 12a). The reaction starts with an attack of the isothiourea catalyst **49** at the carbonyl carbon of the α,β-unsaturated ester **59** to form an acyl ammonium intermediate **61** which has a lower LUMO than the ester substrate, making it susceptible to a nucleophilic attack by **58** at C(3) position. Protonation and aryloxide facilitated catalyst release complete the catalytic cycle (Scheme 12b).[35]



Scheme 12. Proposed catalytic cycle of isothiourea **53** for the Michael addition of pro-nucleophile **58** onto α,β-unsaturated aryl esters **59** *via* α,β-unsaturated Acyl ammonium catalysis.

1.5 ISOTHIOUREA AS CATALYSTS: REACTIVITY AND STEREOCONTROL

A key interaction that is harnessed to impart enantiocontrol when using isothiourea catalysts is an intramolecular chalcogen bond that is formed between the carbonyl group and the sulfur atom within acyl isothiouronium intermediates (1,5-O•••S interaction). This interaction is best constituted as orbital delocalisation between a lone-pair donor and an antibonding orbital acceptor ($n_O \rightarrow \sigma^*_{S\text{-}C}$) as highlighted in the X-ray structural analysis and computational study of isothiouronium intermediate **62** by the Smith and Cockroft research groups (Figure 7).[36]

Their results show the stabilising effect brought by the 1,5-O•••S chalcogen bond interaction (2.551 Å) and the preferred coplanar *syn* conformation of the intermediate **62** based on the X-ray crystal analysis and is supported by the (i) dispersion-corrected (ωB97X-D/6-311G*) energy minimization calculations ($\Delta E_{anti \rightarrow syn}$) highlighting the preference of the *syn* conformer of intermediate **62** and the (ii) stabilising interactions arising from the orbital delocalisation between the acyl lone pair (n) and the antibonding orbital ($\sigma^*_{S\text{-}C}$) based on the calculated natural bonding orbitals (NBOs) and the second order perturbation energies ($E^{(2)}$).[36]

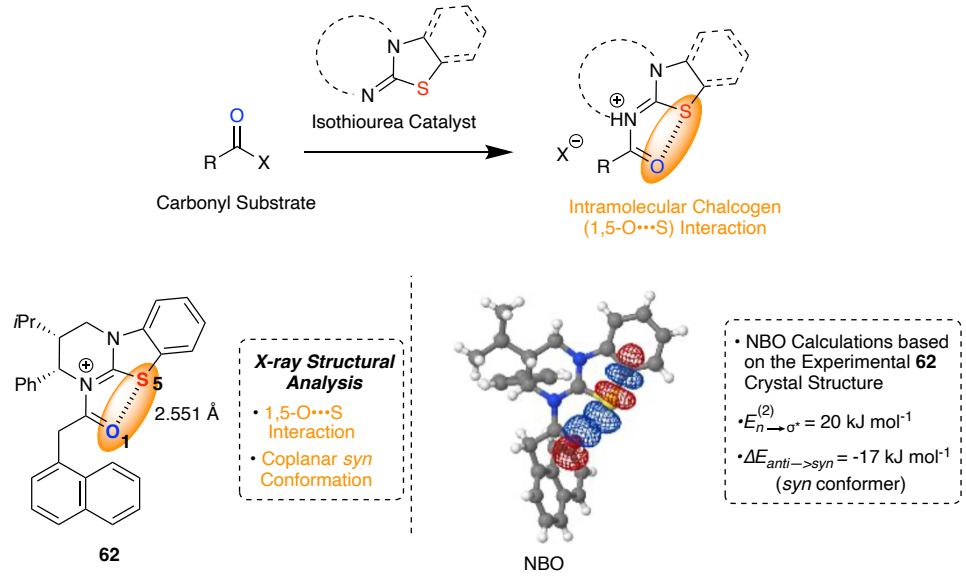
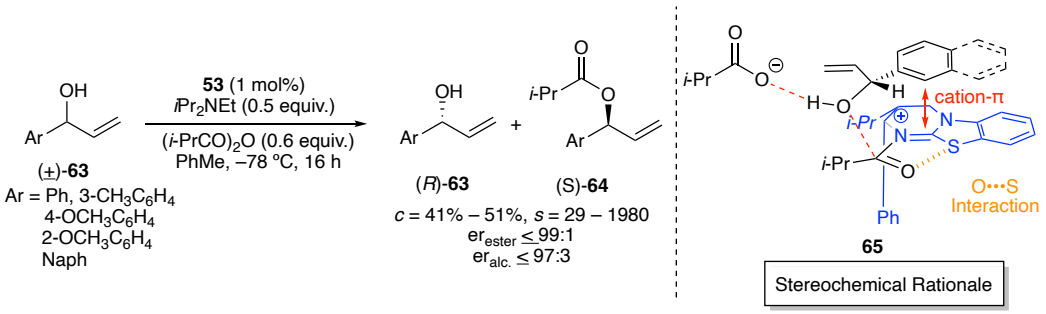


Figure 7. X-ray crystallographic geometry, natural bonding orbital (NBO), and Second-order perturbation theory output energies ($E^{(2)}_{n \rightarrow \sigma *}$) of *N*-naphthylacetyl isothiouronium hexafluorophosphate salt **62** (counterions omitted for clarity).

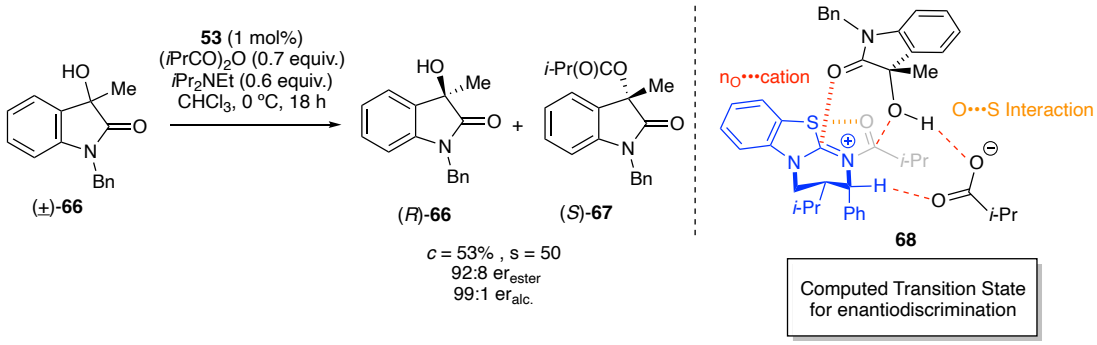
This intramolecular 1,5-O•••S chalcogen bond interaction, therefore, provides a plausible stabilising effect and conformational rigidity (*syn* conformer) within these intermediates together with the facial selectivity imposed by the stereodirecting group (chiral moiety) of the catalyst, thus, facilitating excellent stereocontrol. This interaction, along with additional factors related to the stereocontrol, was also demonstrated by chiral isothiourea catalysts, as shown in the following studies.

For example, a study by the Smith group proposed a stereochemical rationale for the transition state **64** in the kinetic resolution of secondary alcohols (Scheme 13). They proposed that the excellent stereocontrol of the reaction was result of a π-cation interaction between the acyl ammonium intermediate and the electron-rich aryl alcohols **63**, which is evident by the high selectivity of the reaction (*s* = 29 – 1980).[37]



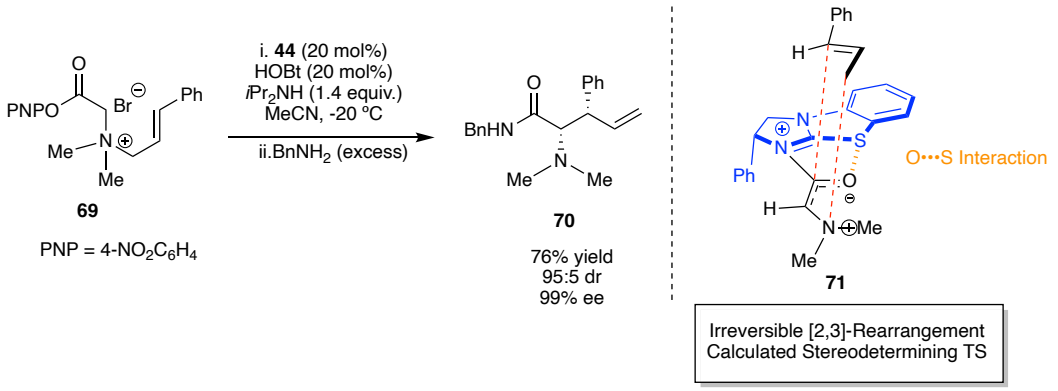
Scheme 13. HyperBTM (**53**)-catalyzed acylative kinetic resolution of aryl-substituted secondary alcohols.

Another example from Smith and co-workers shows different but significant stereocontrol, with the interaction of the carbonyl oxygen (n_O) of the tertiary alcohol **66** and the cationic region of the acyl ammonium intermediate (n_O•••cation) as shown in the calculated lowest-energy diastereomeric transition state structure **68** leading to very good selectivity for the kinetic resolution (*s* = 50) (Scheme 14).[38]



Scheme 14. HyperBTM(**53**)-catalyzed acylative kinetic resolution of tertiary alcohols.

Most notably, the mechanistic and computational study on the isothiourea-catalysed [2,3]-rearrangement of allylic quaternary ammonium ylides by Smith group showcased the utility of the 1,5-O•••S interaction together with the additional factors that facilitates the observed excellent selectivity of the rearrangement product **70**. Their work provided a computational study on the transition state (TS) **71** as shown in Scheme 15. The proposed stereocontrol model of the TS **71** showed that the (i) calculated favourable configuration with the chalcogen interaction (O•••S) of the acyl ammonium ylide (*Z* config. ΔΔG = 0.0 kcal•mol^{-1} vs *E* config. ΔΔG = 16.3 kcal•mol^{-1}) (Figure 8a), (ii) the facial selectivity associated by an O•••S interaction and the stereodirecting effect of the phenyl group of BTM which sterically biases the open enolate face (Figure 8b), (iii) the calculated Endo vs Exo [2,3]-sigmatropic rearrangement favours the Endo-TS (Endo-TS $\Delta\Delta G^{\ddagger}$ = 0.0 kcal•mol^{-1} vs Exo-TS ΔΔG = 0.9 kcal•mol^{-1}) (Figure 8c), and (iv) the preference of the major transition state is also reinforced by a π-cation interaction (Figure 8d).[39,40]



Scheme 15. BTM-catalyzed [2,3]-rearrangement of allylic quaternary ammonium ylides.

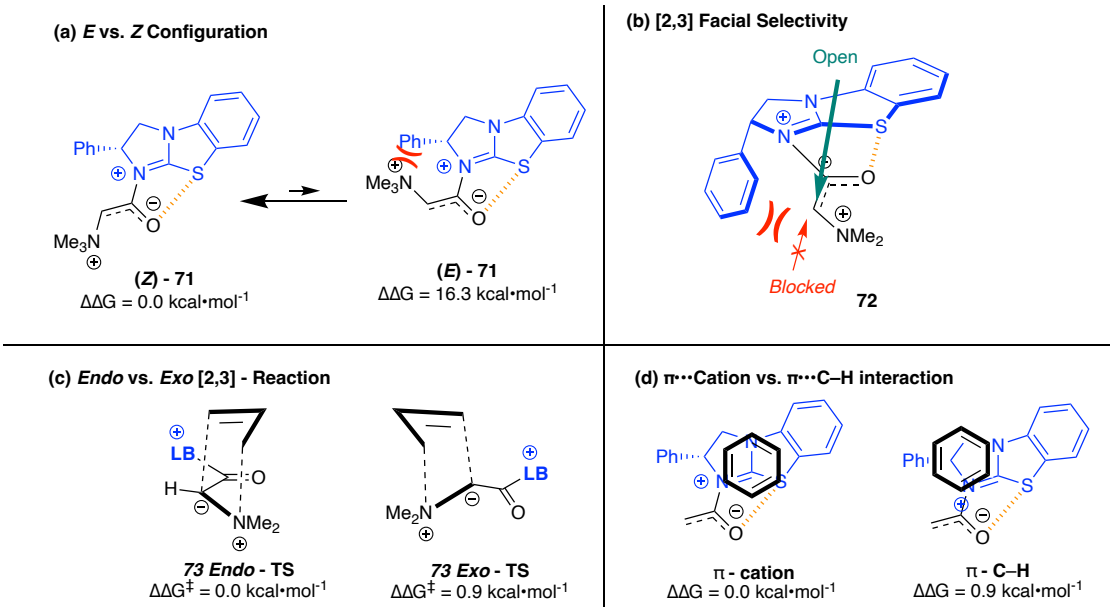


Figure 8. Proposed stereocontrol model for the transition state **71**.

These studies exemplify the excellent reactivity and the stereocontrol brought by isothioureas as organocatalysts exploiting various modes of Lewis base catalysis.

1.6 CATALYSIS USING α,β – UNSATURATED ACYL AMMONIUM INTERMEDIATES

As the main focus of research in this thesis will be on α,β-unsaturated acyl ammonium intermediates, this mode of catalysis will be discussed in this section in further detail. Development of isothiourea catalysts' LUMO-activating capability was performed by the Smith and Romo group through the further development of processes that proceed *via* α,β-unsaturated acyl ammonium intermediates. This process begins with the nucleophilic attack of a chiral isothiourea catalyst onto the carbonyl unit of the reactive α,β-unsaturated carboxylic

acid equivalent **74** (*i.e.* esters, anhydrides, acyl halides) to form an α,β-unsaturated acyl ammonium intermediate **75** (Figure 9).

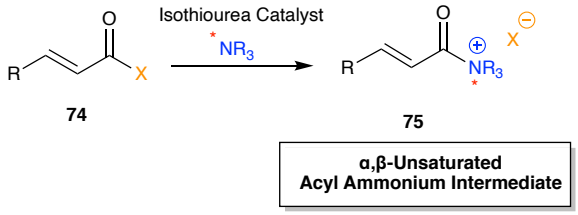
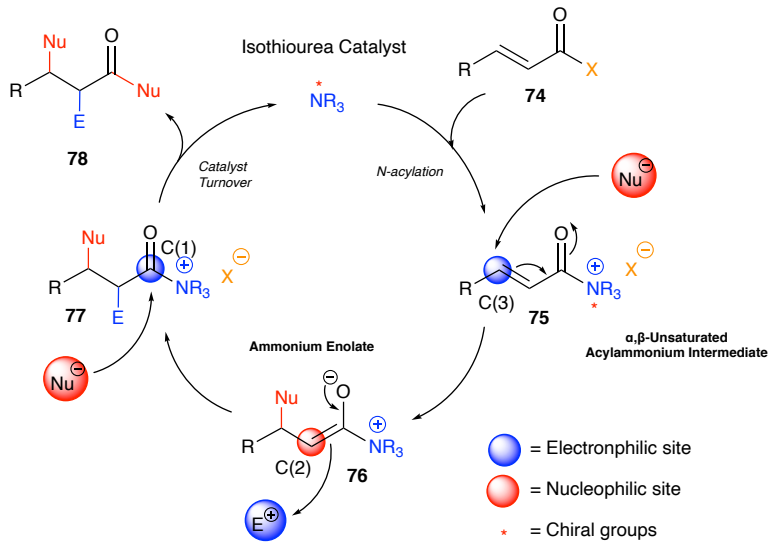


Figure 9. Formation of an α,β-unsaturated acyl ammonium intermediate.

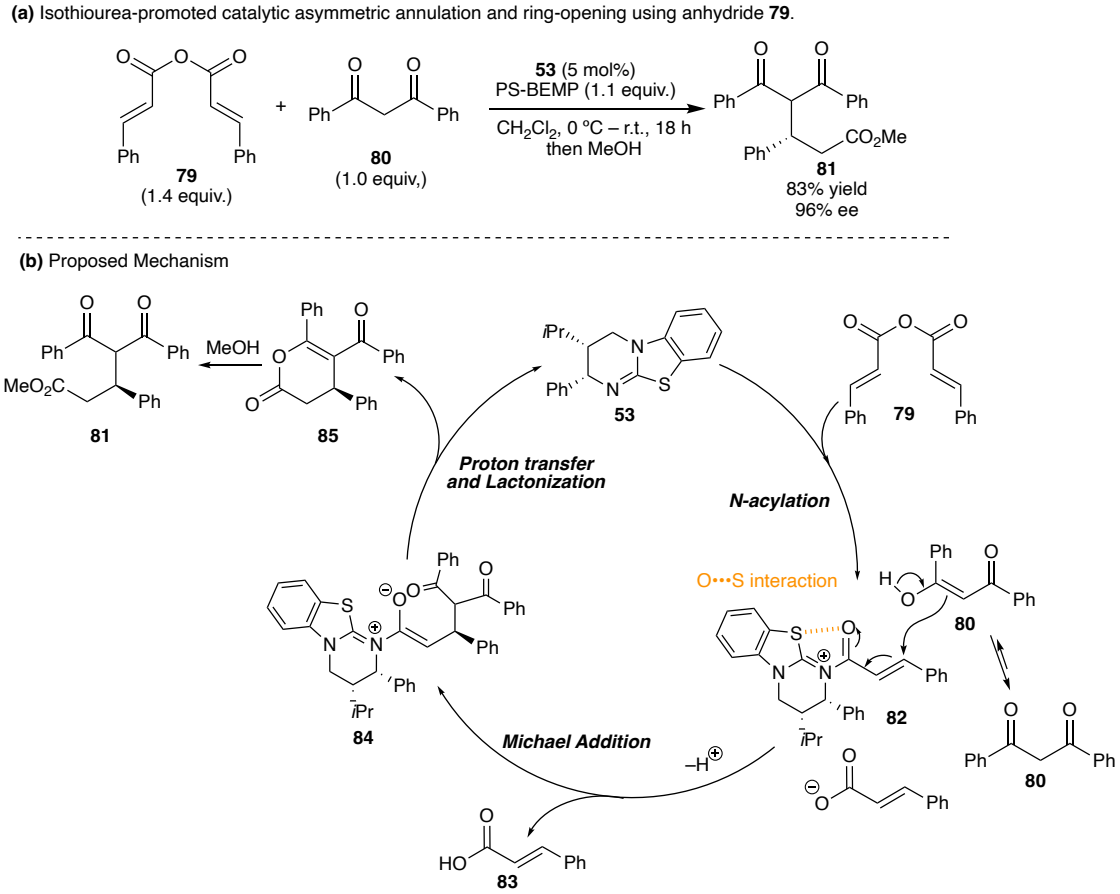
The lowest unoccupied molecular orbital (LUMO) of the unsaturated acylammonium intermediate **75** is lowered relative to its unsaturated carbonyl substrate and in principle allows reactivity at three sites of the unsaturated intermediate (at C(1), C(2), and C(3) positions). This reactivity first leads to a Michael addition at C(3) to form an ammonium enolate intermediate **76**, followed by an α-addition of an electrophile (*e.g.* proton) to generate acyl ammonium intermediate **77**. Subsequent nucleophilic acyl substitution at C(1) facilitates catalyst turnover. This generic catalytic cycle leads to overall functionalisation at C(1), C(2), and C(3) positions of the unsaturated carbonyl compound **78** (Scheme 16).[17]



Scheme 16. General catalytic cycle and reactivity of α,β-unsaturated acyl isothiourionium ions.

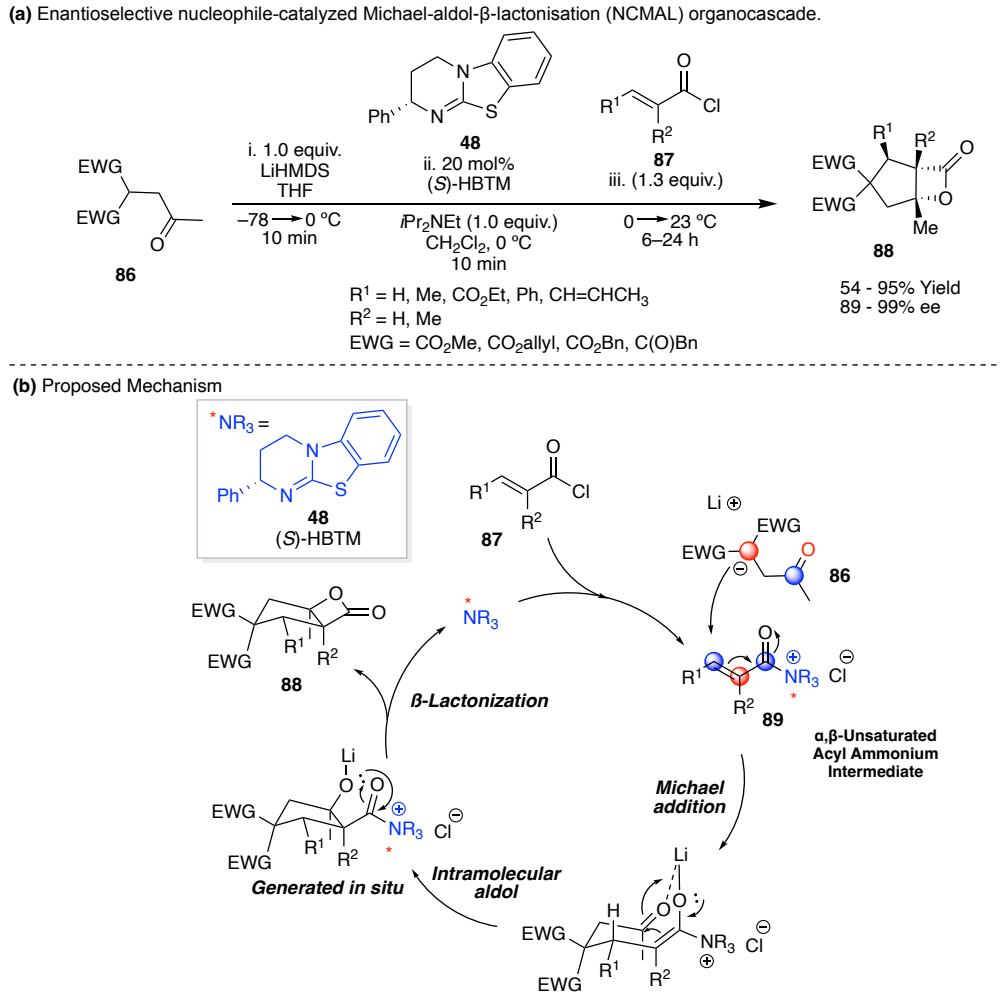
Within this model, α,β-unsaturated carboxylic acid derivatives provide an excellent opportunity for nucleophilic additions at the C(3) position using isothioureas as catalysts and will be discussed more thoroughly in the following examples. In 2013, the Smith group first reported the reactivity of α,β-unsaturated acyl ammonium intermediates in an isothiourea-catalysed enantioselective annulation process using α,β-unsaturated anhydride **79** and diketone **80** to provide products such as **81** in excellent yield (83%) and enantioselectivity (95% ee) after

ring-opening with methanol (Scheme 17a). The reaction is proposed to proceed through a mechanism which involves the formation of α,β-unsaturated acyl ammonium intermediate **82** followed a Michael addition of the enol tautomer **80**. A subsequent lactonisation process forms **85**, which is followed by the addition of methanol to obtain the final product **81** (Scheme 17b).[41]



Scheme 17. Proposed mechanism for isothiourea-promoted catalytic asymmetric annulation *via* a Michael addition reaction.

In the same year, the Romo group reported related reactivity of α,β-unsaturated acyl ammonium intermediates and successfully carried out a nucleophile-catalysed Michael-aldol-β-lactonization (NCMAL) using α,β-unsaturated acyl chlorides **87** and ketone substrates **86** with good to excellent yield and excellent enantioselectivity for the lactone products **88** (Scheme 18a).[17] The proposed mechanism (Scheme 18b) shows the formation of α,β-unsaturated acyl ammonium intermediate **99** by nucleophilic attack of HBTM **46** onto **87**, followed by a Michael addition of **86** at C(3) position of the acyl ammonium intermediate, then a β-lactonization process (*via* an intramolecular aldol reaction and cyclisation) to form the product with subsequent release of the catalyst **46.**

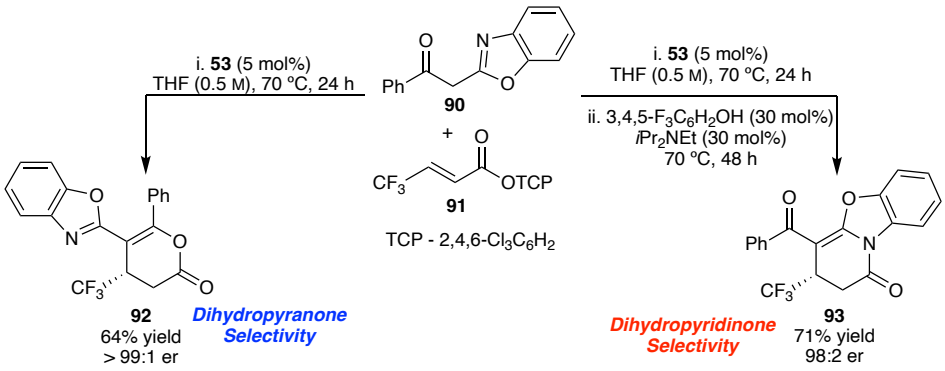


Scheme 18. Proposed catalytic cycle for the nucleophile-catalysed Michael-aldol-β-lactonisation (NCMAL).

To further develop the reactivity of α,β-unsaturated acyl ammonium intermediates, the Smith group used different α,β-unsaturated esters and various nucleophiles to carry out various isothiourea-promoted stereoselective addition and annulation reactions successfully.

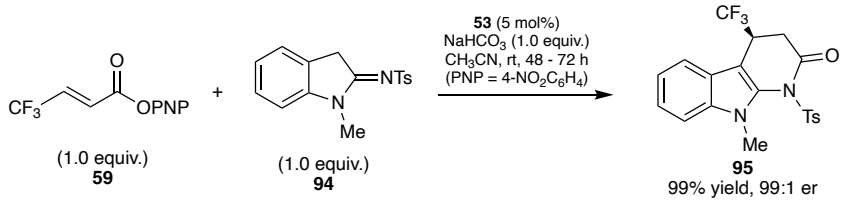
For example, Michael addition-annulation of **90** onto α,β-unsaturated acyl ester **91** generates excellent selectivity in the formation of either a dihydropyranone product **92** when only in the presence of HyperBTM catalyst **53** at 70ºC for 24 h (*via* a lactonization process) or a dihydropyridinone product **93** in the presence of catalyst **53**, 3,4,5-trifluorophenol, and base (*via* a phenol-promoted Brønsted-acid activation lactamization process). Key to developing the reactivity in this process was the multiple-role capability of the aryloxide as a (i) good leaving group during *N*-acylation reaction of the catalyst **53** to generate the α,β-unsaturated acyl ammonium intermediate, (ii) a sufficient Brønsted base to deprotonate substrate **90** at the C(2) position to form the enolate nucleophile, and (iii) as an effective Lewis-base catalyst to selectively promote the isomerization of product **92** to the dihydropyridinone product **93**

(Scheme 19),[42] which further extends the idea of using α,β-unsaturated acyl ammonium intermediates in various annulation processes.



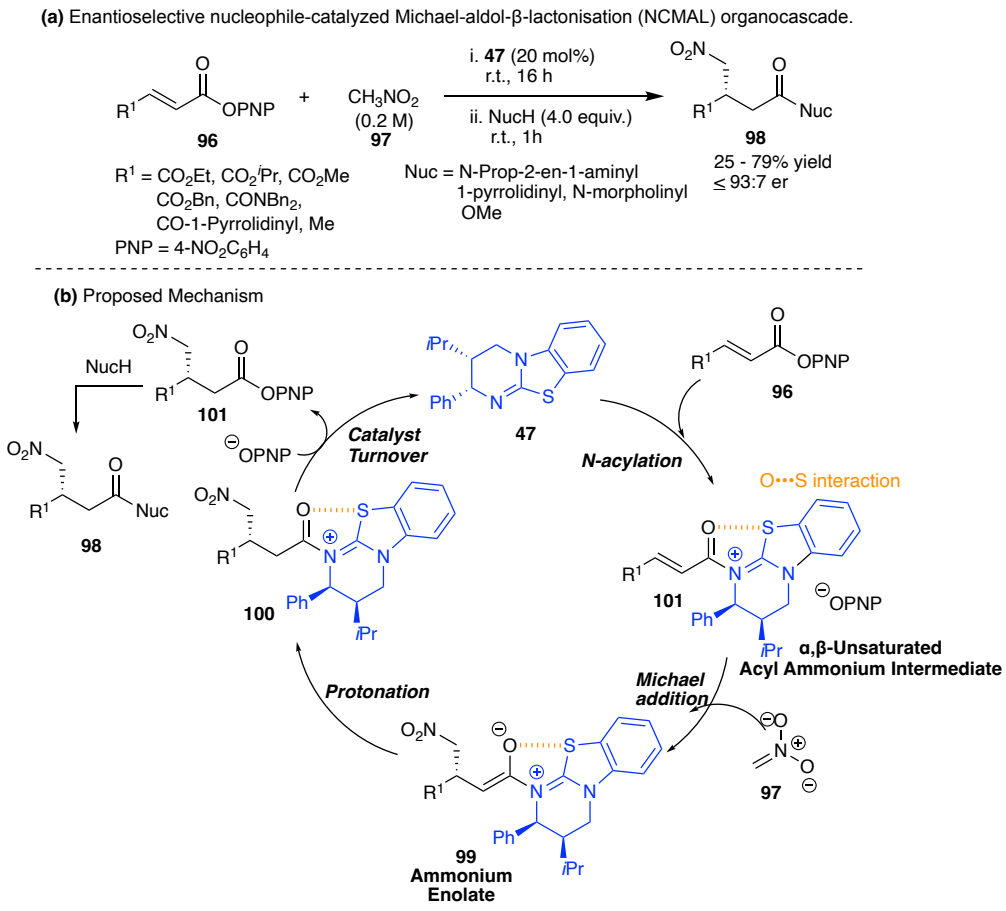
Scheme 19. Michael addition-annulation of **90** and unsaturated ester **91**: selective formation of dihydropyranone **92** or dihydropyridinone **93** products.

Recent work within the group used indoline-2-imines **94** as pro-nucleophiles to carry out enantioselective annulation (*via* lactamization process) reaction for the synthesis of tetrahydro-α-carbolinone **95** with excellent yield and enantioselectivity (99% yield, 97:3 er) (Scheme 20).[43]



Scheme 20. Isothiourea-catalyzed enantioselective annulation to give tetrahydro-α-carbolinone **95.**

In a further development, the isothiourea-catalyzed Michael addition of nitromethane **96** to α,β-unsaturated ester **96** to give product **98** (Scheme 21a) with good yields and enantioselectivity (23 – 79% yield, ≤ 93:7 er) was reported. The proposed mechanism, which is similar to the conducted research in this thesis, follows an *N*-acylation of the unsaturated ester **96**, Michael addition of the nitromethane **97**, protonation of the enolate and an aryloxide-facilitated catalyst turnover before amidation to form product **98** (Scheme 21b).[44]



Scheme 21. Proposed mechanism for isothiourea-catalysed Michael addition of nitromethane **97** to α,β-unsaturated ester **96**.

1.7 RESEARCH OBJECTIVES

With the established reactivity of the α,β-unsaturated acylammonium intermediates at the C(3) position generated from the *N*-acylation reaction of α,β-unsaturated esters using isothiourea-based organocatalysts, this project aims to utilise the specific reactivity at the C(3) position of these intermediates to perform various Michael addition and cascade reactions such as (i) the enantioselective aza-Michael addition reactions of imines to α,β-unsaturated esters to obtain enantioenriched β-amino acid compounds and their derivatives, (ii) the highly selective Michael addition of Schiff bases to α,β-unsaturated esters to obtain γ-imino ester and amide compounds and γ-lactam compounds, and (iii) perform a highly selective Michael-addition-cyclisation-lactonisation cascade reaction of Schiff bases to α,β-unsaturated esters to access various pyrrolidine compounds. This research project will provide an interesting route in the synthesis of chiral compounds with important structural motifs through the access of one reactive intermediate, the α,β-unsaturated acylammonium intermediate.

This Project: Isothiourea-Catalysed Enantioselective Reactions of Imines with α,β-Unsaturated Esters Employing α,β-Unsaturated Acyl Ammonium Intermediates

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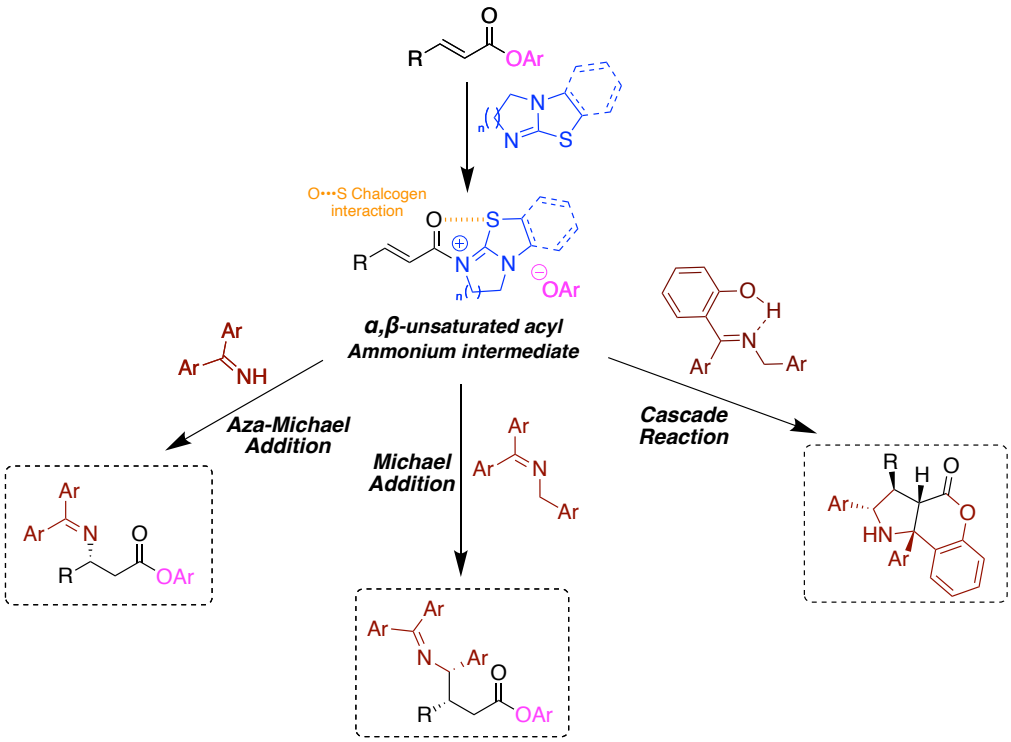

CHAPTER 2: ENANTIOSELECTIVE AZA-MICHAEL ADDITION REACTIONS EMPLOYING α,β-UNSATURATED ACYL AMMONIUM INTERMEDIATES

2.1 PROJECT OVERVIEW

2.1.1 β-Amino Acids

The synthesis of natural product-derived compounds has been one of the main goals of research in recent decades. Notably, nitrogen-containing compounds have been of particular interest due to their prevalence in proteins, vitamins, and hormones vital for supporting life,[1] and 59% of US FDA-approved small-molecule drugs contain a nitrogen heterocycle.[46]

β-Amino acids are a class of nitrogen-containing compounds that share the same functional groups as α-amino acids; however, the amino group is attached at the β-position with respect to the carbonyl carbon **102** (Figure 10). Unlike α-amino acids, β-amino acids are non-proteinogenic, meaning they are not naturally encoded in the genetic code, and thus, are not readily abundant in nature.[47] β-Amino acid moieties have been incorporated into bioactive compounds, for example, Cryptophycin **103** (potent antitumor),[48] β-quinoline-β-alanine derivative RWJ-53033 **104** (nonpeptide integrin antagonist),[49] and cyclic peptide Asterin **105** (potential antitumor)[50] are all examples of bioactive materials that contain this motif (Figure 11). These moieties are considered potential lead structures and are essential to develop.[51]

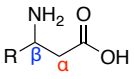

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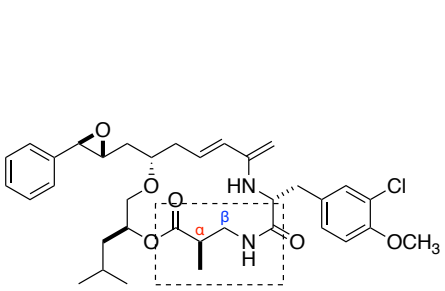
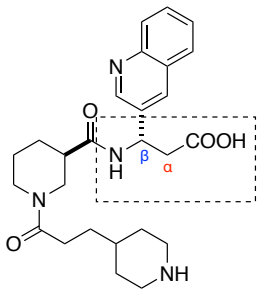
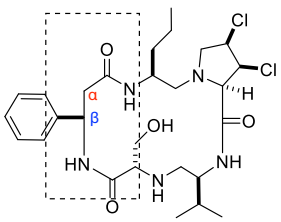
Figure 10. The general structure of β-amino acids.



Cryptophycin **103**
(Potent Antitumor Compound)



RWJ-53033 **104**
(Nonpeptide Integrin Antagonist)



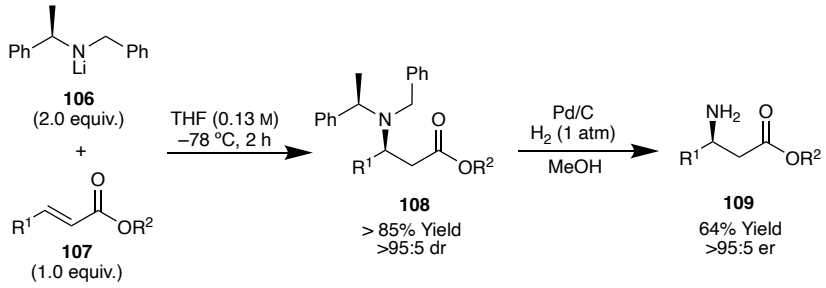
Asterin **105**
(Potential Antitumor Compound)

Figure 11. Compounds with potential bioactivity containing a β-amino acid moiety.

Given the interest in nitrogen-containing molecules and particularly β-amino acids, the ability to develop and selectively design methodology to allow the synthesis of structural analogues is an essential target for synthetic chemists.

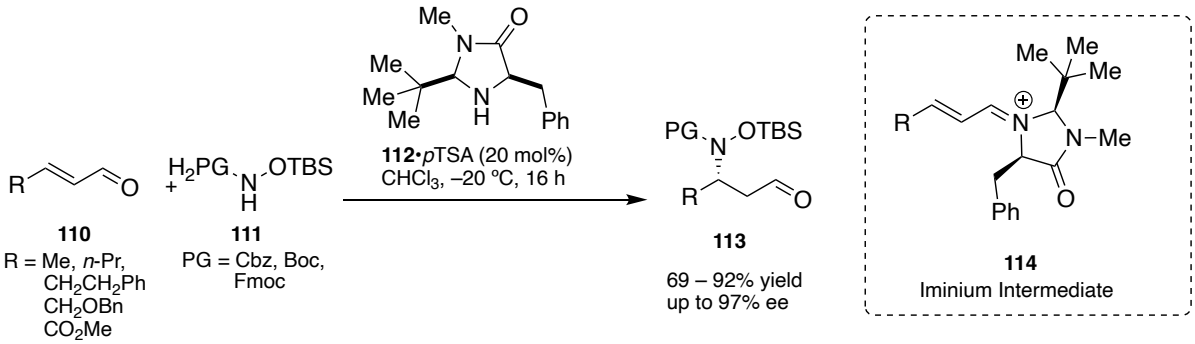
2.1.2 Organocatalytic Aza-Michael Addition Reactions

Different strategies have been applied to synthesise chiral β-amino acids and their derivatives. A direct reaction route can be achieved through an asymmetric aza-Michael addition of amine nucleophiles at the C(3)-position of α,β-unsaturated esters and was first showcased by Davies and Ichihara in 1991 by employing a conjugate addition of lithium *N*-benzyl-*N*-α-methylbenzylamine **106** to α,β-unsaturated ester **107** to give the corresponding β-amino ester **108** with high diastereoselectivity (>95:5 dr). Subsequent hydrogenolysis revealed the corresponding free β-amino ester **109** (Scheme 22).[52]



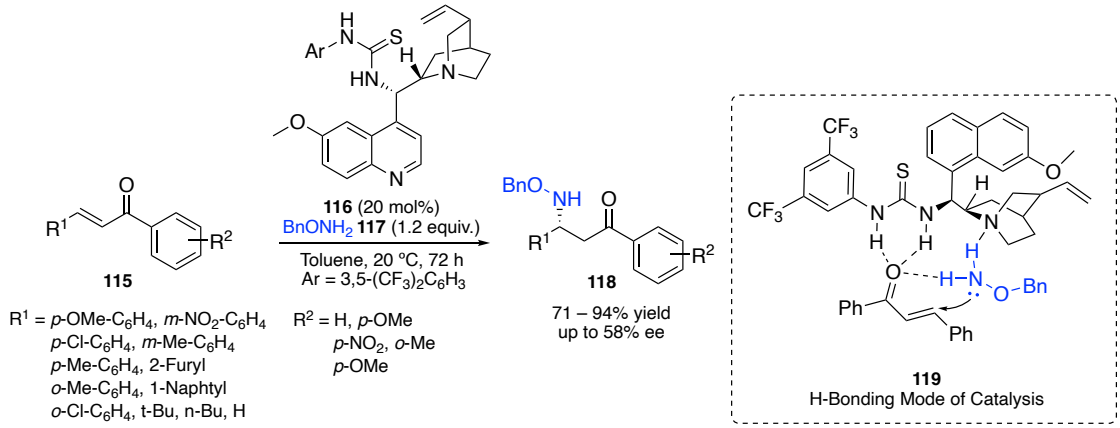
Scheme 22. Amine conjugate addition of lithium *N*-benzyl-*N*-α-methylbenzylamine **106** to of α,β-unsaturated ester **107.**

Over the last two decades, several enantioselective organocatalytic aza-Michael addition reactions have been explored. A particular example is from MacMillan and co-workers in 2006, where they were able to carry out an aza-Michael addition of carbamate **111** onto α,β-unsaturated aldehydes **110** *via* iminium catalysis with good to excellent yield and enantioselectivity (69% – 92% yield, 97% ee) of the β-amino aldehyde product **113** (Scheme 23). In this study, the authors strategically designed carbamates as nucleophilic amines by incorporating silyl ether groups such as OTBS (*tert*-butyldimethylsilyl ether) to enhance the nitrogen nucleophilicity of **111** *via* the α-effect.[53] At the same time, they used α,β-unsaturated aldehydes as electrophiles and effectively lowered the LUMO energy *via* iminium catalysis through the formation of the iminium intermediate **114**.[54]



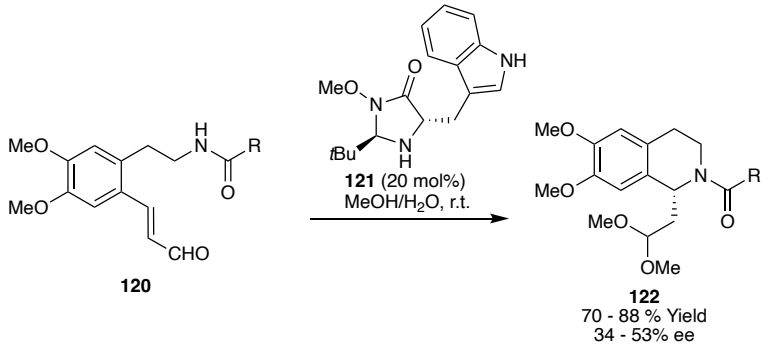
Scheme 23. Enantioselective organocatalytic conjugate amination of α,β-unsaturated aldehydes *via* iminium catalysis.

Another example is a study of Ricci and co-workers, who utilised *O*-benzylhydroxylamine **117** as a nucleophilic amine to carry out aza-Michael addition onto α,β-unsaturated ketones **115** with good to excellent yield but moderate enantioselectivity (71% – 94% yield, ≤ 58% ee) of the corresponding β-amino phenyl ketone **118** product at a slightly higher catalyst loading of **116** at 20 mol% (Scheme 24). They proposed a non-covalent hydrogen-bonding mode of catalysis and stereocontrol, with the catalyst **116** binding to the substrate *via* its thiourea moiety, combined with the stereodirecting effect of the quinuclidine nitrogen by hydrogen bonding to the amine nucleophile as shown in stereochemical model **114**.[55]



Scheme 24. Asymmetric organocatalytic aza-Michael addition of *O*-benzylhydroxylamine **117** to chalcones **115**.

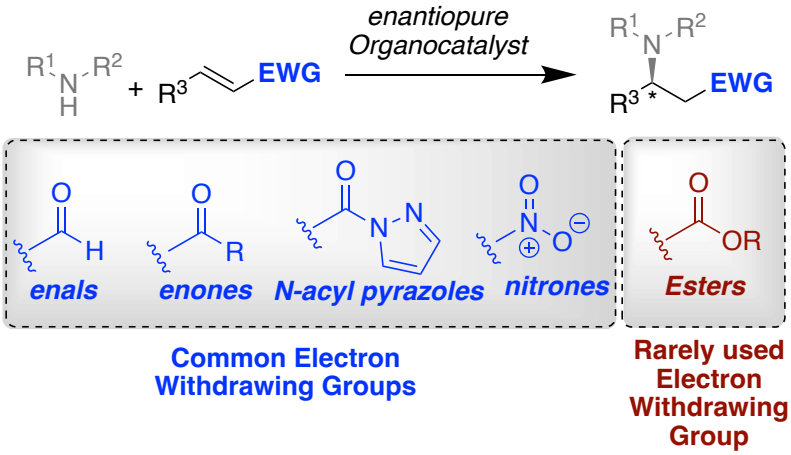
An alternative example that highlights an organocatalytic intramolecular aza-Michael addition reaction was first reported by Ihara and co-workers in 2003 that utilizes the dopamine derivative **120** and undergoes an iminium-catalysed intramolecular cyclisation reaction to form the tetrahydroquinoline product **122** in excellent yield but with poor enantioselectivity (70 – 88% yield, <53% ee) as shown in Scheme 25.[56] This work was then expanded by various researchers and is highlighted in a review for organocatalysed intramolecular aza-Michael addition reactions by Roselló in 2014.[57]



Scheme 25. Organocatalysed intramolecular aza-Michael addition *via* iminium catalysis.

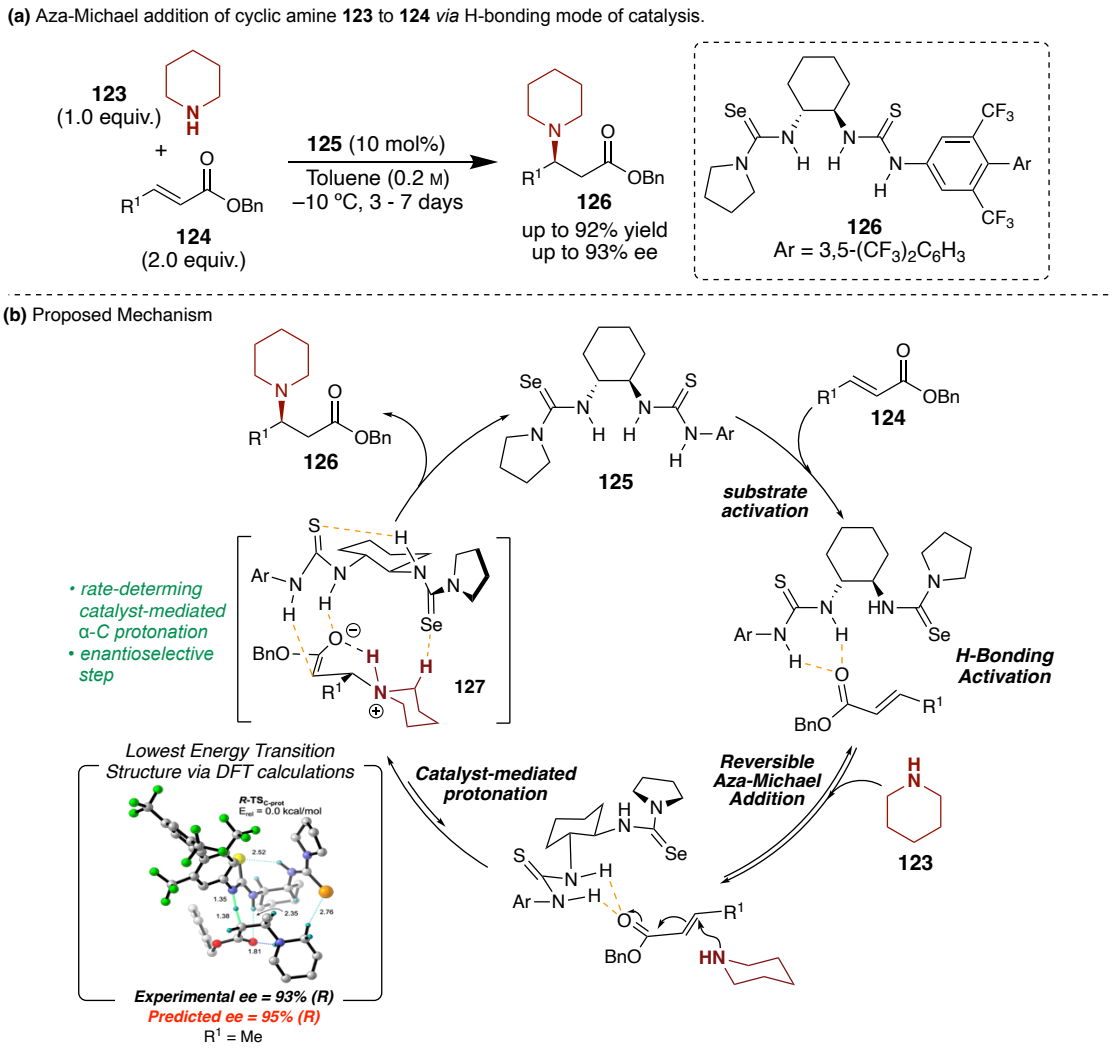
To date, most of these successful aza-Michael addition reactions mostly rely on the use of reactive α,β-unsaturated carbonyl compounds such as enals,[54,58–60] enones,[55,61,62] *N*-acyl

pyrazoles,[63–65] and nitro-olefins[66–69] as reactive Michael acceptors. Reactivity in these systems relies on either covalent modes of catalysis such as iminium catalysis which uses Lewis basic pyrrolidine organocatalysts,[54,58–60] or *via* a non-covalent mode of catalysis such as H-bonding catalysis using bifunctional thiourea[55,64,70–74] or squaramide organocatalysts[55,62,65,72,73,75,76] (Scheme 26). However, catalytic aza-Michael additions of amines utilising α,β-unsaturated esters as Michael acceptors are rarely encountered due to the poor electron-withdrawing effect of the ester group resulting in diminished electrophilicity at the C(3) position of α,β-unsaturated esters which lead to poor reactivity in most conjugate addition reactions as compared to α,β-unsaturated aldehydes and ketones Michael acceptors.



Scheme 26. Commonly used Michael acceptors for aza-Michael addition reactions with esters as rarely used electron-withdrawing groups.

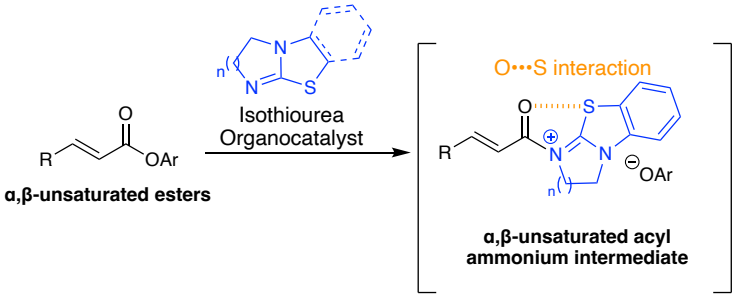
To date, the most recent catalytic approach that utilises α,β-unsaturated esters as Michael acceptors has been demonstrated by Seidel and co-workers [77] through the aza-Michael addition of cyclic amines **123** to α,β-unsaturated benzyl esters **124** using a selenourea-thiourea catalyst **126** (Scheme 27a) in high yields and enantioselectivity (up to 92% yield, up to 93% ee). In their proposed mechanism, the reaction is initiated by activating the α,β-unsaturated benzyl ester **124** by the selenourea-thiourea catalyst **125** *via* H-bonding, followed by a reversible conjugate addition of the cyclic amine nucleophile to form the zwitter-ionic intermediate **127**. Intermediate **127**, supported by kinetic isotope effect (KEI) experiments and DFT calculations of the transition states, then undergoes a rate-determining and enantio-determining catalyst-mediated α-C protonation of the zwitterionic intermediate **127** to produce the desired enantioenriched product **126** (Scheme 27).



Scheme 27. Proposed Mechanism for the Aza-Michael addition of amine **123** to α,β-unsaturated benzyl ester **124** *via* H-bonding mode of catalysis.

Despite this straightforward approach for the aza-Michael addition reaction (Scheme 27), certain drawbacks were still observed for the reaction, such as the use of (i) low-temperature conditions to achieve high enantioselectivity (up to 93% ee) together with (ii) long reaction time (up to 7 days) to achieve the desired product yield **123** (up to 93% yield).

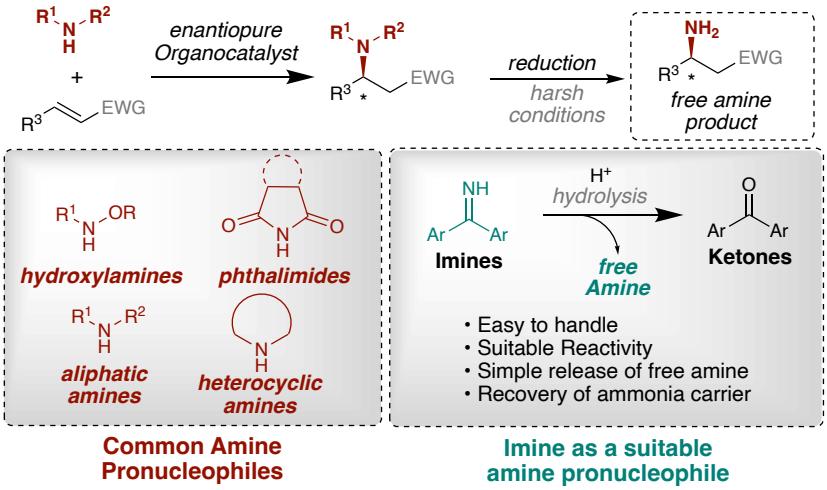
It was postulated that these drawbacks encountered with α,β-unsaturated esters can be addressed by utilising a more efficient covalent mode of catalysis such as the in situ formation of α,β-unsaturated acyl ammonium intermediates using isothiourea catalysts. The Smith group previously showcased this mode of catalysis using isothiourea organocatalysts for various Michael addition and Michael addition-lactonisation reactions showing excellent yield and enantioselectivity.[43,78–80] Hence, isothiourea organocatalysts can be used to access the elusive reactivity of α,β-unsaturated ester substrates *via* the formation of the reactive α,β-unsaturated acyl ammonium intermediate (Scheme 28).



Scheme 28. Formation of the reactive α,β-unsaturated acyl ammonium intermediate using isothiourea organocatalyst.

2.1.3. Intramolecular H-Bonding Activation of Imine Nucleophiles

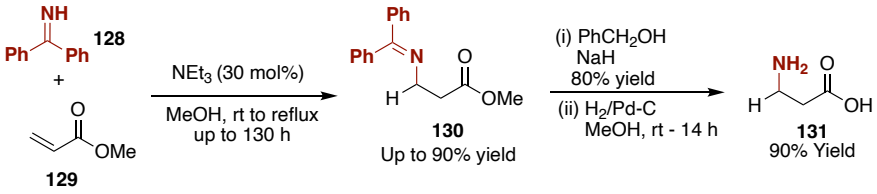
Most of the aforementioned studies for aza-Michael addition reactions utilise various amine nucleophiles such as hydroxylamines[55,58,63,64,69,75] phthalimides[59,62,67], aliphatic[68]/cyclic[77] amines, and heterocyclic amines[60,71]. However, most of these highly used amine nucleophiles require harsh conditions[52,58] to access the free amine product (Scheme 29). Hence, a suitable amine nucleophile was sought to achieve an efficient aza-Michael addition reaction with the following criteria; it should be (i) easy to handle, (ii) demonstrate suitable reactivity, (iii) allow a simple release of the free amine, and (iv) easy recovery of the ammonia carrier. It was considered that these conditions could be fulfilled by imines; they are desirable nucleophiles for aza-Michael addition reactions because of their moderate to good reactivity as nucleophiles. Furthermore, they are easily hydrolysed in acidic conditions to obtain the free amine moiety.



Scheme 29. Common amine nucleophiles are used for aza-Michael addition reactions.

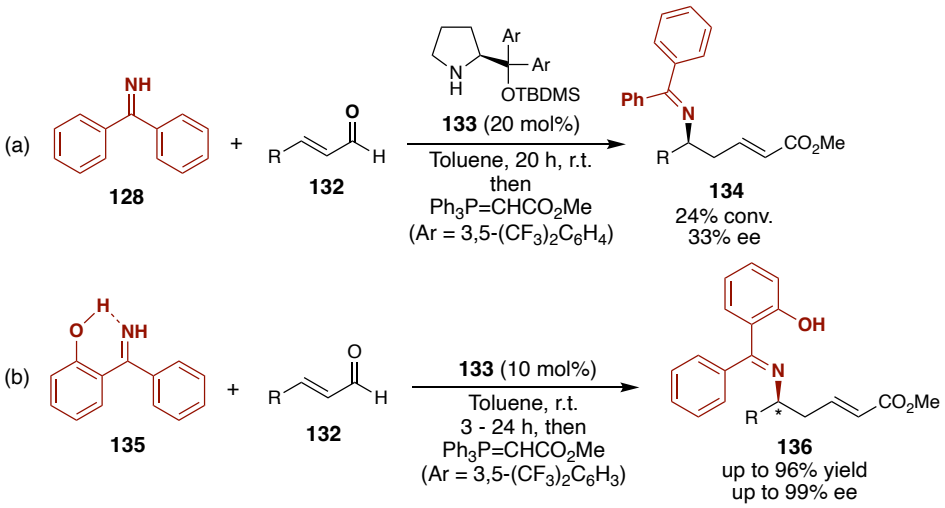
In the literature, Meijere and co-workers have previously showcased benzophenone imine **128** as a suitable amine nucleophile to perform an aza-Michael addition reaction to α,β-

unsaturated esters with excellent yield (90% yield) of the racemic β-imino ester product **130** (Scheme 30). They also obtained the free β-amino acid **131** in excellent yield (90%).[81]



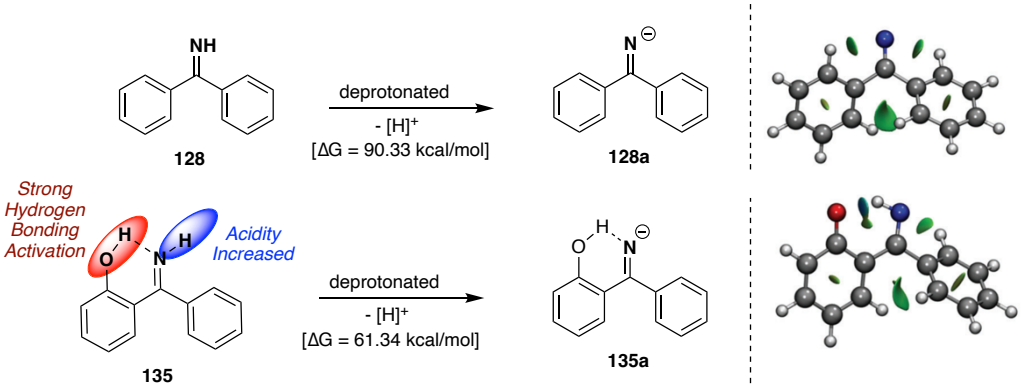
Scheme 30. Use of imine **128** as a nucleophile for aza-Michael addition reactions followed by esterification and hydrogenolysis to obtain the free β-amino acid **131**.

Despite the immense potential of imines as nucleophiles and their ease of hydrolysis to obtain the free amino product, poor reactivity, as reflected by long reaction times, was still observed for the aza-Michael addition reaction to achieve good to excellent yield of the aza-Michael addition product. In 2018 Alemán's group revisited this aza-Michael addition concept by introducing a hydroxyl group *ortho* to the benzophenone imine nucleophile. They proposed an increase in nucleophilicity of the imine *via* an intramolecular H-bonding activation by the hydroxyl group and compared the reactivity of the parent benzophenone imine **128** and the 2-hydroxybenzophenone imine **135** for the aza-Michael addition reaction to α,β-unsaturated aldehydes **132** *via* iminium catalysis (Scheme 31). 2-hydroxybenzophenone imine **135** elicited excellent yield, enhanced enantioselectivity and shortened reaction time for the reaction.[82]



Scheme 31. Alemán's group utilised 2-hydroxybenzophenone imine **135** (b) as a nucleophile for an aza-Michael addition reaction to α,β-unsaturated aldehydes *via* iminium catalysis.

Alemáns group highlighted that the nucleophilicity of imines was associated with the acidity of the hydrogen of the imine group and showed that the introduction of the hydroxyl group *ortho* to the imine (**135**) allows an intramolecular H-bonding interaction that increases the acidity of the imine proton *via* the stabilisation of the imide **135a** (Scheme 32).

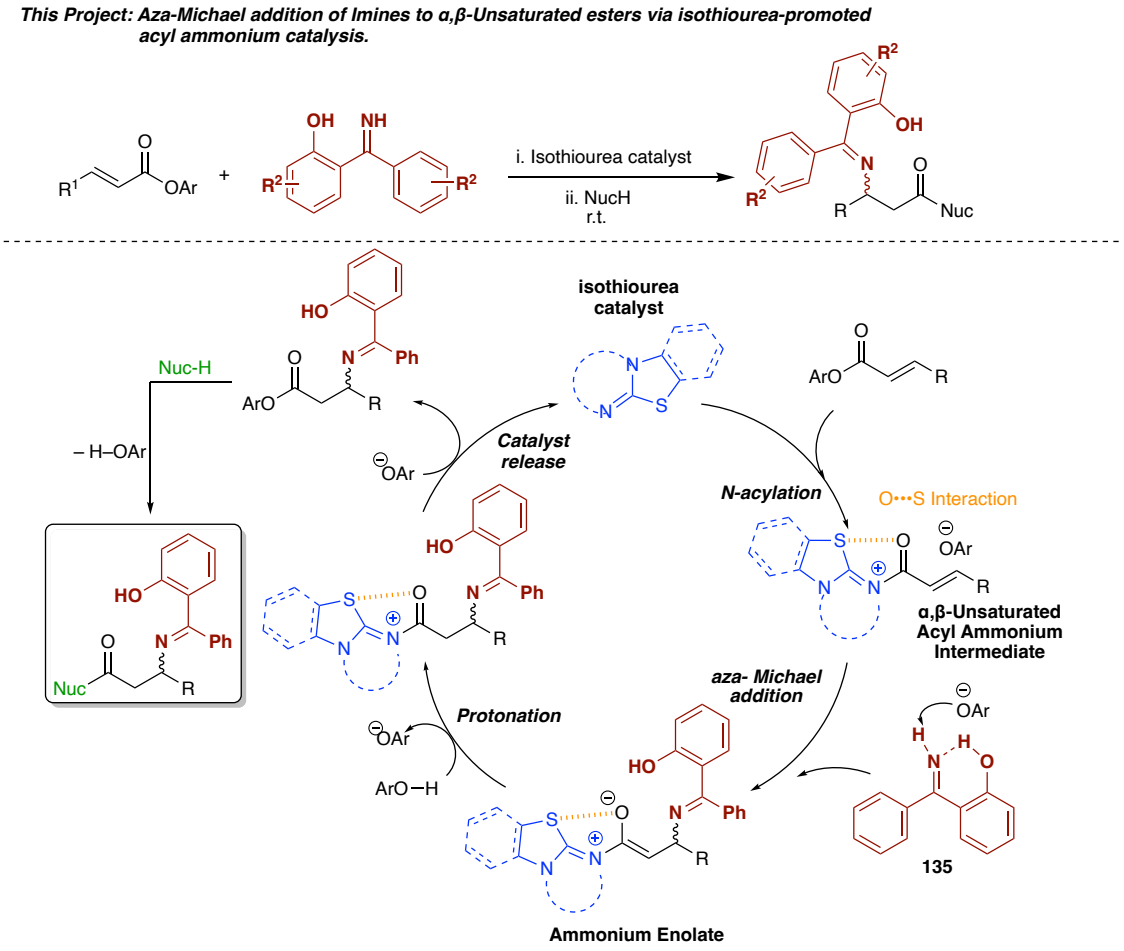


Scheme 32. Gibbs free energy of deprotonation of imine **128** and **135**.

It is evident in the cited studies that (i) enhanced nucleophilic character of the nitrogen atom in amines; (ii) the ease of access to the free amino groups; and (iii) the activation of α,β-unsaturated carbonyl compounds are the critical features to achieve an efficient aza-Michael addition reaction. Thus, the use of isothiourea as an effective Lewis base organocatalyst for the activation of α,β-unsaturated esters *via* the formation of the reactive α,β-unsaturated acyl ammonium intermediates, as previously demonstrated by the Romo and Smith groups, together with the use of 2-hydroxybenzophenone imine substrates provides an exciting route for an aza-Michael addition reaction, which is highly relevant in the synthesis of β-amino acids.

2.2 AIMS AND OBJECTIVES

Building upon these precedents, we considered that the application of isothiourea organocatalysts for the selective aza-Michael addition reaction *via* α,β-unsaturated acyl ammonium catalysis might provide an alternative route for the synthesis of chiral β-amino acids and their derivatives. This project aims to use hydroxy-substituted imine **135** and its derivatives as nucleophilic substrates for the selective aza-Michael addition onto α,β-unsaturated esters to provide β-imino esters in high yield and enantiomeric ratio.

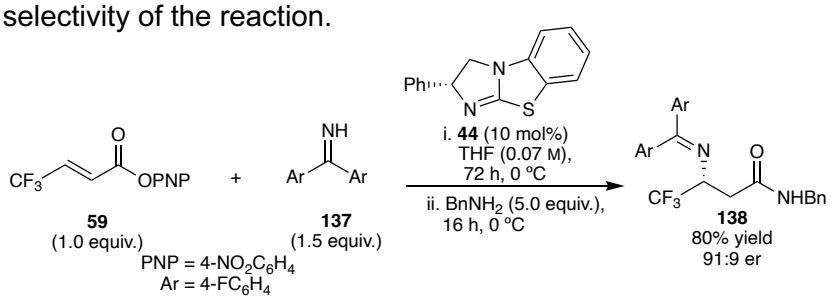


Scheme 33. Design of the isothiourea-catalysed aza-Michael addition of **135** to α,β-unsaturated acyl ammonium catalysis.

2.3 RESULTS AND DISCUSSION

2.3.1 Preliminary Investigations

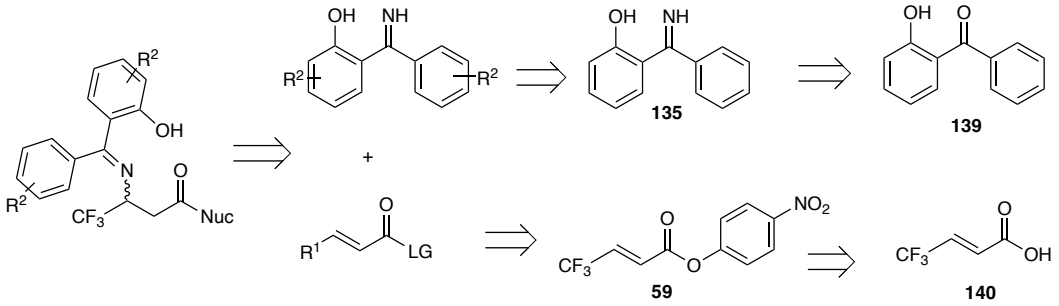
The Smith group performed an initial reaction using unsaturated ester **59** and benzophenone imine **137** using isothiourea **44** organocatalyst to establish the feasibility of the aza-Michael addition reaction (Scheme 34). The reaction had a good yield (80%) and promising enantioselectivity (91:9 er) of the product **138** but at long reaction times of up to 72 h. These results imply that an improvement is needed, such as shortening the reaction time and increasing the selectivity of the reaction.



Scheme 34. Isothiourea-catalysed aza-Michael addition of imine **133** onto α,β-unsaturated ester **58**.

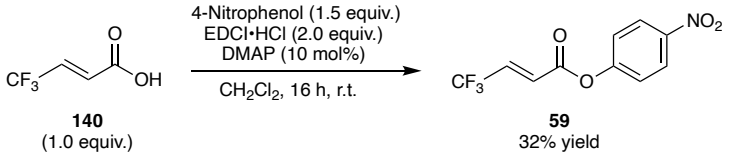
2.3.2 Synthesis of Starting Materials

Building upon the previously established reaction conditions for isothiourea-promoted aza-Michael addition of benzophenone imine **137** to α,β-unsaturated esters **59** (Scheme 35), initial studies prepared the proposed 2-hydroxybenzophenone imine **135** and ester **59** to determine if this combination would lead to increased reactivity and enantioselectivity, with a retrosynthetic analysis depicted in Scheme 35.



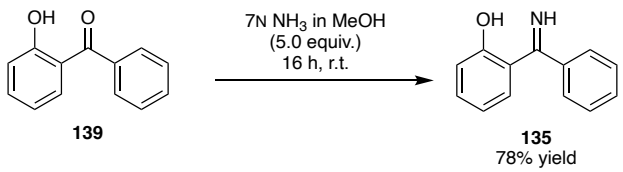
Scheme 35. Retrosynthetic analysis of the target substrates **59** and **135**.

A commercially available precursor **140** was used to synthesise substrate **59** in a DMAP-catalysed esterification reaction with 4-nitrophenol at room temperature to yield the desired product in 32% yield (Scheme 36).[43]



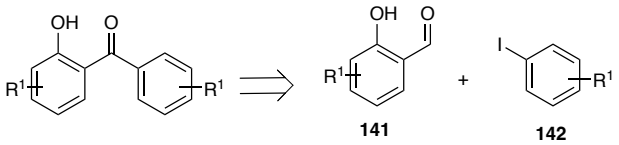
Scheme 36. Synthesis of substrate **59**.

A straightforward synthesis of substrate **135** was performed following a procedure reported by Alemán.[82] Commercially available 2-hydroxybenzophenone **139** was stirred in ammonia in MeOH at room temperature, and the following workup and purification by flash chromatography, **135** was isolated in 78% yield (Scheme 37).



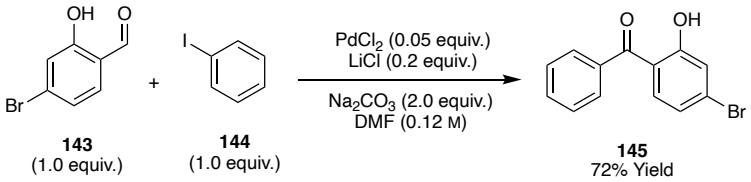
Scheme 37. Synthesis of 2-hydroxybenzophenone imine **135**.

On the other hand, most of the 2-hydroxybenzophenone precursors were not commercially available. Hence, a retrosynthetic analysis for synthesising these precursors was considered utilising 2-hydroxysalycilaldehyde derivative **141** and Iodobenzene derivative **142** as primary starting materials (Scheme 38).



Scheme 38. Retrosynthetic analysis for the target precursor 2-hydroxybenzophenone.

Following the method established by Tarokh[83] in 2014, the desired benzophenone precursors from **141** and **142** were successfully synthesised. An example is the synthesis of precursor **145** using 4-bromosalycilaldehyde **143,** and iodobenzene **144** was achieved at 72% yield as shown in Scheme 39.



Scheme 39. Synthesis of 2-hydroxybenzophenone precursor **145**.

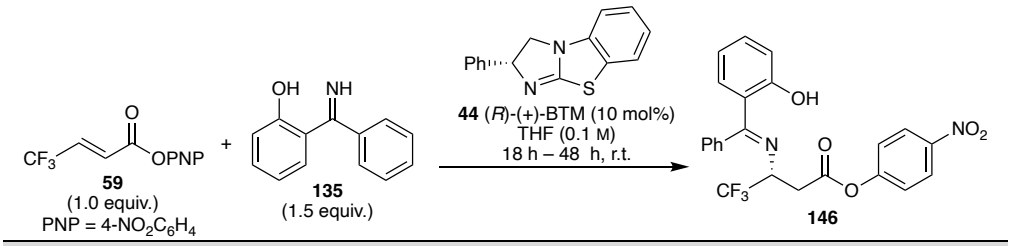
2.3.3 Optimisation of Reaction Conditions

2.3.3.1 Summary of Preliminary Optimisation of Reaction Conditions

After synthesising substrates **59** and **135**, optimisation of the proposed reaction was then investigated by the moderation of the reaction variables, including (i) reaction time, (ii) isothiourea catalyst, (iii) solvent, (iv) reaction temperature, and (v) catalyst loading (Table 2).

Preliminary optimisation was carried out by monitoring the reaction time for the formation of intermediate **146** (Table 1). Results showed that a 48 hour reaction time made no significant difference in yield compared to a 30 hour reaction time (45% Yield, 96:4 er). Hence a 30 hour reaction time was chosen as the optimum condition for the Michael-addition reaction. However, product **146** showed instability during purification and even under room-temperature conditions after purification due to the observed hydrolysis of the ester functional group. Thus, the reaction was quenched with pyrrolidine to form a more stable compound for purification and to provide reliable enantiomeric ratio (er) results.

Table 1. Observed Yield (%) and Enantioselectivity (er) of the Aza-Michael Addition Product **146** at Different Reaction Times (18 – 48 h).

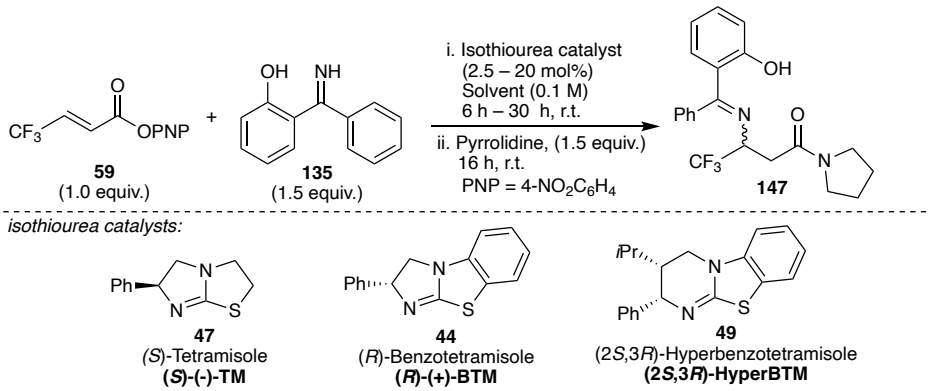


Entry	59 (equiv.)	135 (equiv.)	Reaction time (hrs)	Yield (%)	er[c]
1	1.0	1.5	18	24[a]	95:5
2	1.0	1.5	24	35[a]	96:4
3	1.0	1.5	30	45[a](38[b])	96:4
4	1.0	1.5	48	47[a]	96:4

a- Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*- isolated yield; c- enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate = 1mL•min^{-1}, 5% IPA in Hexane.

Further optimisation (Table 2) under different isothiourea catalyst, catalyst loading, reaction temperatures, reaction times, and. solvent showed that conditions in entry 11 exhibited the highest yield (64% yield) of the product with a consistent enantiomeric ratio (~96:4 er) with (*R*)-BTM **44** as the catalyst, toluene as solvent, at room temperature reaction condition, at 10 mol% catalyst loading, and 1:1.5 ratio of **59** and **135**.

Table 2. Observed Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Product **147** at Different Optimisation Conditions such as (i) Isothiourea Catalyst, (ii) Solvent, (iii) Reaction Temperature, (iv) Catalyst Loading, and (v) Substrate Ratio.

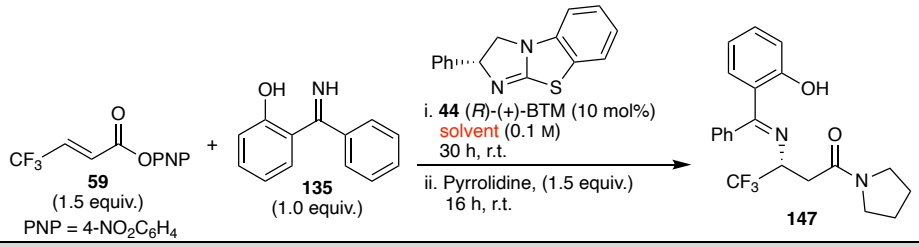


Entry	59 (equiv.)	135 (equiv.)	Solvent (0.1 M)	Catalyst (mol%)	Temp. (ºC)	Yield (%)	er[f]
1	1.0	1.5	THF	**44** (10)	r.t.	38[b,e]	95:5
2	1.0	1.5	THF	**47** (10)	r.t.	33[b,e]	12:88
3	1.0	1.5	THF	**49** (10)	r.t.	14[b,e]	68:32
4	1.0	1.5	CH_2Cl_2	**44** (10)	r.t.	33[b,e]	92:8
5	1.0	1.5	Toluene	**44** (10)	r.t.	58[b,e]	95:5
6	1.0	1.5	Toluene	**44** (10)	40	44[b,e]	93:7
7	1.0	1.5	Toluene	**44** (10)	60	46[b,e]	90:10
8	1.0	1.5	Toluene	**44** (20)	r.t.	54[a,e]	93:7
9	1.0	1.5	Toluene	**44** (5)	r.t.	45[a,e]	83:17
10	1.0	1.5	Toluene	**44** (2)	r.t.	12[a,e]	70:30
11	1.5	1.0	Toluene	**44** (10)	r.t.	64[b,e]	96:4
12	1.5	1.0	Toluene	**44** (10)	r.t.	45[a,d]	95:5
13	1.5	1.0	Toluene	**44** (10)	r.t.	33[a,c]	94:6

a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-6 hours reaction time; *d*-24 hours reaction time; *e*-30 hours reaction time; *f*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate = 1mL•min^{-1}, 5% IPA in Hexane.

A range of 14 solvents was also screened to check if an increase in the product yield may result from using different solvent polarities. Results in Table 3 revealed that toluene still showed the highest yield of the product **147**. Moreover, a general trend can be observed for solvents with dielectric constants (ε) lower than 10.0 exhibiting moderate to excellent enantioselectivity for the observed product (up to 97:3 e.r.). While poor enantioselectivity were observed for solvents with dielectric constants (ε) greater than 10.0, with the exception of acetone (ε = 20.7, 95:5 er).

Table 3. Yield (%) and Enantiomeric Ratio (er) with Different Solvent.



Entry	Solvent (0.1 M)	Yield (%)	er[c]	Dielectric constant (ε)
1	Toluene	64[b]	96:4	2.38
2	CH_2Cl_2	45[a]	95:5	8.93
3	THF	33[a]	95:5	7.58
4	Xylene	42[a]	97:3	2.57
5	MeCN	45[a]	70:30	37.5
6	Acetone	36[a]	95:5	20.7
7	DMF	87[a]	56:44	36.7
8	Cyclohexanone	75[a]	88:12	18.20
9	*i*PrOAc	33[a]	94:6	-
10	Dioxane	36[a]	93:7	2.25
11	1,2-dimethoxyethane	33[a]	82:18	7.20
12	dimethylacetamide	36[a]	66:34	37
13	Dimethyl carbonate	36[a]	95:5	3.09
14	Diethyl ether	39[a]	96:4	4.3

a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate = 1mL•min^{-1}, 5% IPA in Hexane.

2.3.3.2 Preliminary Substrate Scope Using Different Michael Acceptors

After establishing the optimum conditions of the reaction, different α,β-unsaturated esters (Michael acceptors) **148**, **149**, and **150** (Figure 12) were primarily used to assess the scope of the reaction (Scheme 40).

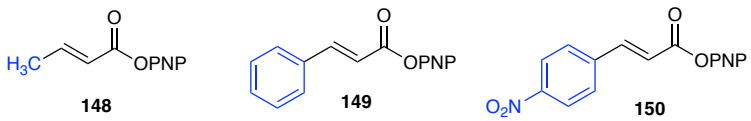
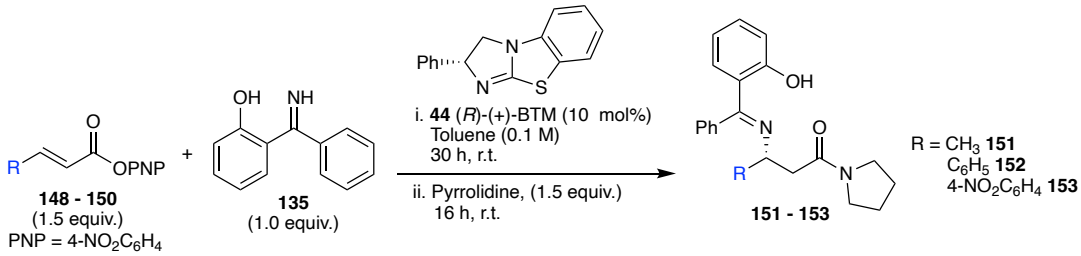


Figure 12. α,β-Unsaturated esters **148**, **149**, and **150** are primarily used for the Michael acceptor scope.



Scheme 40. Isothiourea-catalysed aza-Michael addition of imine **135** onto α,β-unsaturated esters **148**, **149**, and **150.**

All substrates (**148 – 150**) were unreactive based on ^{1}H NMR spectroscopic analysis of the crude reaction mixture showing only the peaks of the unconsumed imine substrate **135** (81% - 99%) and the hydrolysed side product **135** of the imine (1% - 18%), but without the formation of the desired product. The lack of reactivity can be a result of either (i) the observed low solubility of the new substrates in toluene or (ii) the inherent low reactivity of substrates attributed to the poorly electron-withdrawing substituents at C(3) position.

Thus, the reactions for unsaturated esters **148 – 150** (Scheme 39) were repeated using solvents with different polarity (THF and CH_2Cl_2) to verify any solubility issues primarily proposed. However, the formation of the desired products (**146 – 148**) was still not observed in ^{1}H NMR spectroscopic analysis of the crude reaction mixtures despite the substrates being soluble in THF and CH_2Cl_2. Hence, the exploration of more nucleophilic imines was considered in order to expand the scope of this process to less electrophilic esters.

2.3.3.3 Preliminary Imine Substrate Screening.

Further investigation of new parameters for the reaction was examined to overcome the low reactivity of unsaturated esters **148, 149,** and **150**. It was proposed that modulation of the nucleophilicity of the imine substrate may be achieved through the introduction of electron-donating and electron-withdrawing groups (Figure 13). Benzophenone imine substrates **154 - 157** were prepared as shown in Scheme 37 and 38 and were used to assess the reactivity of the substrates (Table 4).

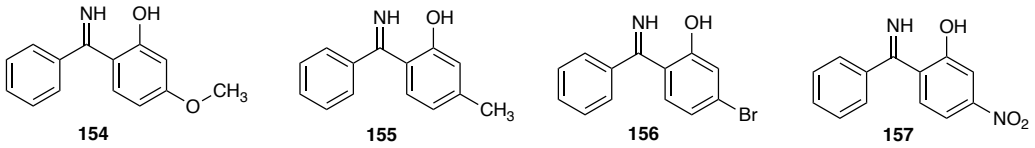
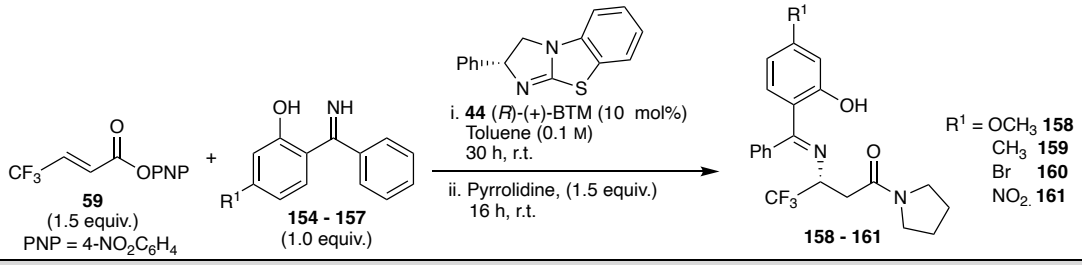


Figure 13. Benzophenone imine substrate **154**, **155**, **156,** and **157**.

Results in Table 4 showed that introducing either electron-donating or electron-withdrawing groups *para* to the imine group showed no increase in the reaction yield but excellent and

consistent enantioselectivity was still maintained. Despite these results, it was thought that benzophenone imine **154** may still show a likely increase in reactivity if further optimisation of the reaction conditions is carried out such as (i) substrate ratio, (ii) reaction concentration, (iii) reaction temperature, (iv) catalyst loading, (v) solvent screening, (vi) addition of Brønsted base, and (vii) reaction time.

Table 4. Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Products using different Imines Nucleophiles (**154** – **157**).



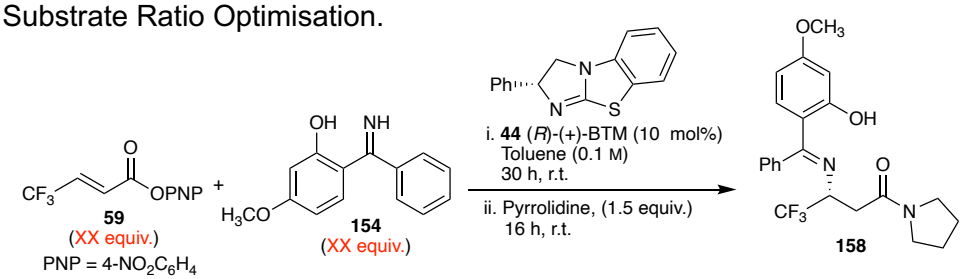
Entry	R^1	Yield (%)	er[d]
1	OCH_3	38[b]	95:5
2	CH_3	27[b]	96:4
3	Br	12[b,c]	96:4
4	NO_2	<10[a]	ND

a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*- racemic mixture; *d*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase, flow rate = 1mL•min^{-1}, 5% IPA in Hexane; ND-not determined.

2.3.3.4 Substrate Ratio Optimisation

The substrate ratio was optimised using **59** and **154** as substrates to assess any possible increase in the yield of product **158** (Table 6). It was observed that the highest yield of the reaction was obtained using the ratio 1:2 of **59** and **158** (Table 5, Entry 3). Moreover, consistent enantioselectivity (≤97:3 er) was observed in all ratios tested indicating the reaction's high selectivity. Thus, a 1:2 ratio of **59** and **158** were used as an optimum substrate ratio for the aza-Michael addition reaction.

Table 5. Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Product **158** under Substrate Ratio Optimisation.



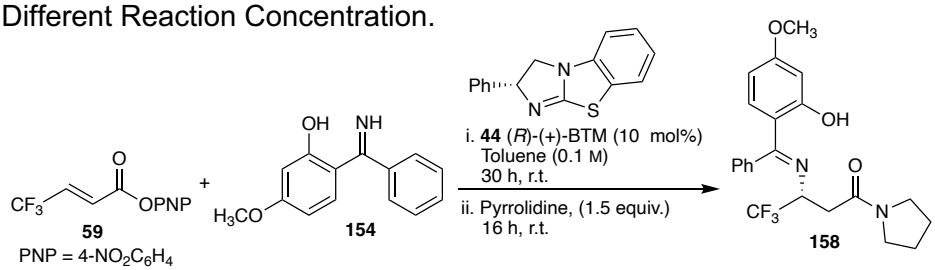
Entry	59 (equiv.)	154 (equiv.)	59 (mmol)	154 (mmol)	Yield (%)	er[c]
1	1.5	1.0	0.15	0.1	38[a]	97:3
2	1.0	1.5	0.1	0.15	42[a]	95:5
3	1.0	2.0	0.1	0.2	54[a]	96:4
4	1.0	5.0	0.1	0.5	49[a]	95:5

a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA in Hexane.

2.3.3.5 Reaction Concentration Optimisation

After establishing the substrate ratio (1:2) for substrates **59** and **154**, the reaction concentration was optimised for the aza-Michael addition protocol (Table 6). Results showed no significant difference in the yield of the product **158** upon varying the concentration of the reaction mixture (~54% NMR yield). At the same time, high and consistent enantioselectivity (≤97:3 er) was observed throughout the reaction conditions. A 0.1 M concentration was chosen as optimum for the aza-Michael addition reaction.

Table 6. Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Product **158** under Different Reaction Concentration.



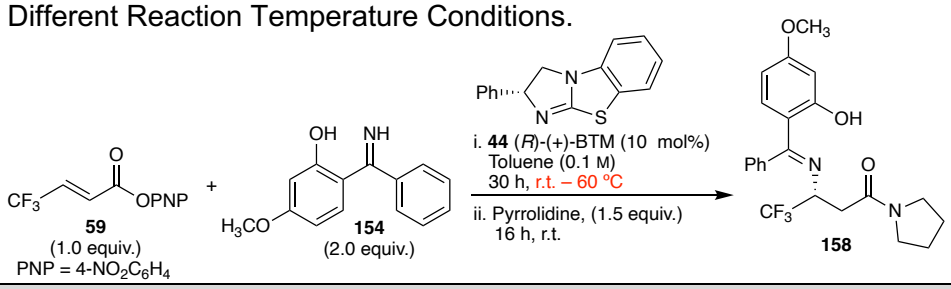
Entry	59 (equiv.)	154 (equiv.)	59 (mmol•L^{-1})	154 (mmol•L^{-1})	Yield (%)	er[c]
1	1.0	2.0	0.1	0.2	54[a]	96:4
2	1.0	2.0	0.2	0.4	56[a]	96:4
3	1.0	2.0	0.05	0.1	53[a]	97:3

a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL·min^{-1}, 5% IPA in Hexane.

2.3.3.6 Reaction Temperature Optimisation

The reaction temperature was then optimised for the aza-Michael addition reaction of **154** to the unsaturated ester **59** after establishing the substrate ratio (1:2) and reaction concentration (0.1 M). Reaction temperatures from room temperature (~20 ° C) to 60 ° C were carried out (Table 7), and results showed that an increase in the reaction temperature diminishes the yield of the product **158** up to 47% yield at 60 ºC; this was accompanied with a significant drop in enantioselectivity to 91:9 er (Table 7, Entry 3). Room temperature conditions for the aza-Michael addition of **154** to the unsaturated ester **59** (Table 7, Entry 1) still exhibited the optimum condition for the reaction as reflected in the yield and high enantioselectivity of the aza-Michael addition product **158** (54% yield, 96:4 er).

Table 7. Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Product **158** under Different Reaction Temperature Conditions.



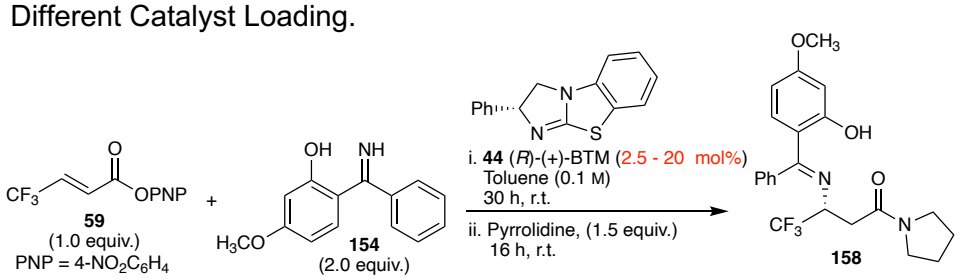
Entry	59 (equiv.)	154 (equiv.)	Temp. (º C)	Yield (%)	er[c]
1	1.0	2.0	r.t. (~20)	54[a]	96:4
2	1.0	2.0	40	52[a]	95:5
3	1.0	2.0	60	47[a]	91:9

a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA in Hexane.

2.3.3.7 Catalyst Loading Optimisation

After establishing the optimum substrate ratio, reaction concentration, and reaction temperature for the reaction, catalyst loading (2.5 mol% – 20 mol%) of (*R*)-BTM **44** was then optimised for the aza-Michael addition reaction of **154** to the unsaturated ester **59** (Table 8).

Table 8. Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Product **158** under Different Catalyst Loading.



Entry	59 (equiv.)	154 (equiv.)	Catalyst Loading (mol%)	Yield (%)	er[c]
1	1.0	2.0	2.5	<10[a]	91:9
2	1.0	2.0	5.0	18[a]	96:4
3	1.0	2.0	10	54[a]	96:4
4	1.0	2.0	20	71[b]	96:4
5	1.0	2.0	0	-	-

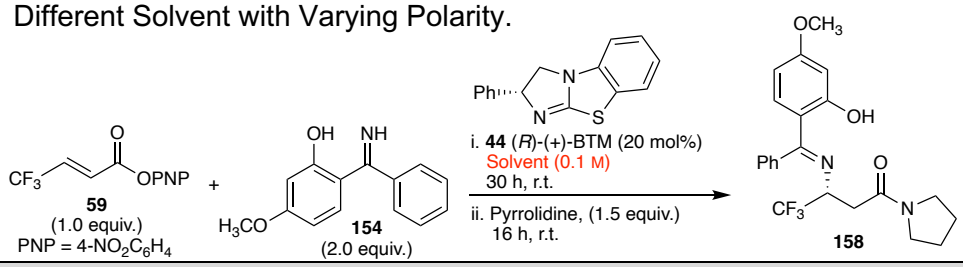
a-Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA in Hexane.

Results showed that a significant increase in yield (71% yield) with consistent enantioselectivity (96:4 er) of the aza-Michael addition product **158** was achieved when using a 20 mol% of (*R*)-BTM **44** catalyst. A lower catalyst loading of (*R*)-BTM **44** showed diminished yield but consistent enantioselectivity for the reaction even at 5 mol% catalyst loading (Table 8, entry 2). Decreasing the catalyst loading to 2.5 mol% of (*R*)-BTM **44** resulted in a trace amount (<10% yield) of the product **158** (Table 8, entry 1). A control experiment was carried out (Table 8, entry 5), and no formation of product **158** was observed, indicating that there was no observed background reaction. Hence, the optimum catalyst loading of the (*R*)-BTM **42** catalyst was at 20 mol% for the aza-Michael addition reaction.

2.3.3.8 Solvent Screening

A solvent screen was again carried out for the reaction using CH_2Cl_2, tetrahydrofuran (THF), and Diethyl ether (Table 9). Results showed that toluene, a non-polar solvent, still elicited a high yield of the Michael addition product **158** at 71% yield compared to the other polar solvents (Table 9, Entry 4). Variation of the solvent polarity did not affect the enantioselectivity of product **158,** as observed in the results in Table 9, showing high selectivity of up to 96:4 er. Thus, toluene was used as the optimum solvent for the aza-Michael addition reaction.

Table 9. Yield (%) and Enantiomeric Ratio (er) of the aza-Michael Addition Product **158** under Different Solvent with Varying Polarity.



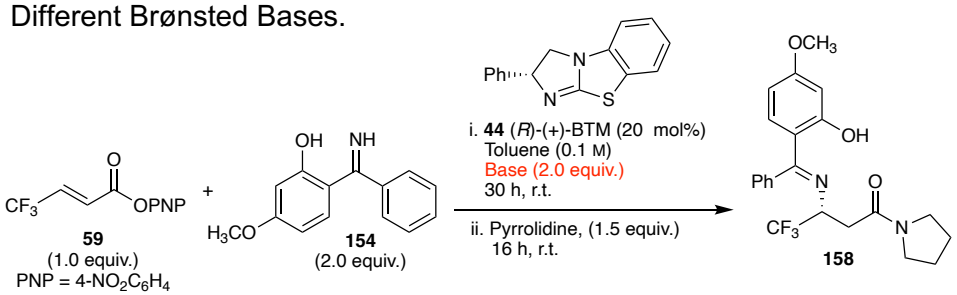
Entry	59 (equiv.)	154 (equiv.)	Solvent (0.1 M)	Yield (%)	er[c]
1	1.0	2.0	CH_2Cl_2	37[a]	96:4
2	1.0	2.0	THF	31[a]	96:4
3	1.0	2.0	Diethyl ether	30[a]	95:5
4	1.0	2.0	Toluene	71[b]	95:5

a-Determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA in Hexane.

2.3.3.9 Addition of Brønsted Base

It was hypothesised that an increase in the yield for the aza-Michael addition product **158** might be observed upon adding a Brønsted base to the reaction mixture. The addition of a base promotes the deprotonation of the imine **154**, which may increase the rate of imine addition to the unsaturated acyl ammonium intermediate. Thus, different organic and inorganic bases were used for these optimisation conditions, as highlighted in table 10. However, results show that presence of a Brønsted base is highly detrimental to the yield and enantioselectivity of the reaction (<10% yield and ~49.7:50.3 er).

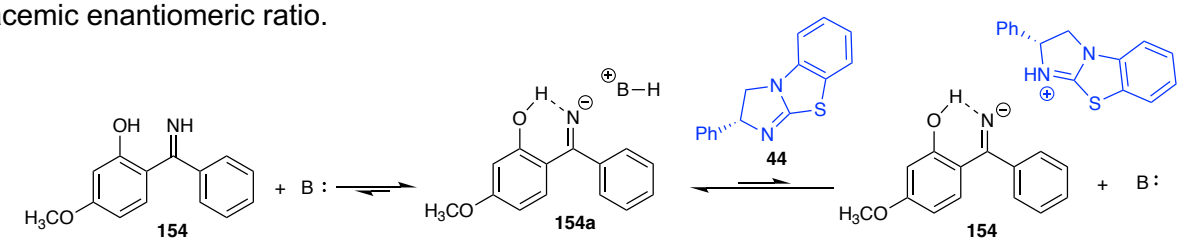
Table 10. Yield (%) and Enantiomeric Ratio (er) of the Aza-Michael Addition Product **158** using Different Brønsted Bases.



Entry	58(equiv.)	149 (equiv.)	Brønsted Base (2.0 equiv.)	Yield (%)	er[c]
1	1.0	2.0	NEt_3	<10[a]	-
2	1.0	2.0	*i*Pr_2NEt	<10[a]	-
3	1.0	2.0	$NaHCO_3$	15[a]	50:50
4	1.0	2.0	Na_2CO_3	<10[a]	-
5	1.0	2.0	Ammonium 4-nitrophenoxide	<10[a]	49:51

a-yield obtained through NMR using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA in Hexane.

The addition of a Brønsted base may enhance the deprotonation of the imine proton producing the ion pair **154a.** However, the ion pair **154a** may also undergo a slow but feasible proton exchange with the Lewis base catalyst **44**, yielding a protonated catalyst and **154a** ion pair resulting in the catalyst's deactivation (Scheme 41). The remaining unreacted base may then promote a slow background aza-Michael reaction resulting in the observed low yield and racemic enantiomeric ratio.

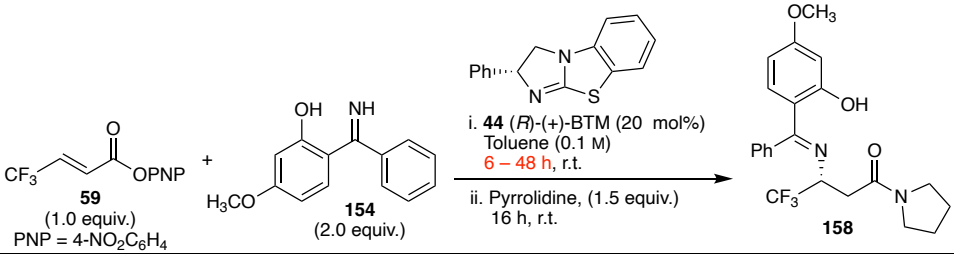


Scheme 41. Formation of ion-pair **154a** showing the deactivation of catalyst **44**.

2.3.3.10 Reaction Time Optimisation

Further optimisation on the reaction time for the aza-Michael addition of **154** to unsaturated ester **59** was then carried out by monitoring the yield of the product **158** at 6 hours, 24 hours, 30 hours, and 48 hours. Table 11 shows that an increase in yield of product **158** was observed with increasing reaction time. A 30-hour reaction time showed the optimum condition for the aza-Michael addition reaction with a product yield of up to 71% of **158** (Table 11, Entry 3). No significant increase in the product yield was then observed at a 48 hour reaction time (Table 11, Entry 4). Moreover, the enantioselectivity of all the reaction conditions was excellent and consistent at 96:4 er.

Table 11. Yield (%) and Enantiomeric Ratio (er) of the aza-Michael Addition Product **158** under Different Reaction Times (6 hrs, 24 hrs, 30 hrs, 48 hrs).



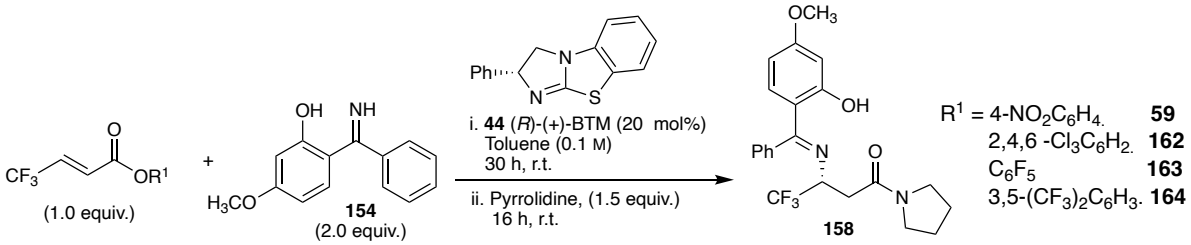
Entry	59 (equiv.)	154 (equiv.)	Reaction Time (hrs)	Yield (%)	er[c]
1	1.0	2.0	6	40[a]	96:4
2	1.0	2.0	24	59[a]	96:4
3	1.0	2.0	30	71[b]	96:4
4	1.0	2.0	48	70[a]	96:4

a-yield obtained through NMR using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA.

2.3.3.11 Aryl Oxide Leaving Group Screening

After establishing the optimum conditions for the aza-Michael addition reaction of imine **154** to the unsaturated ester **59**, the effect of variation of the aryl ester derived leaving group of the Michael acceptor was then carried out (Table 12). Results indicate that 4-nitrophenoxide is the excellent aryloxide leaving group for the reaction, as shown in the aza-Michael addition product **158** at 70% yield (Table 12, Entry 1), as compared to the other aryloxide leaving groups. Moreover, enantioselectivity for the reaction was very consistent (~96:4 er), indicating no significant effect in the selectivity of the aza-Michael addition reaction.

Table 12. Yield (%) and Enantiomeric Ratio (er) with Different Aryloxide Leaving Groups.



Entry	Ester (equiv.)	149 (equiv.)	R	Yield (%)	er[c]
1	1.0	2.0	4-NO_2-C_6H_4	70[b]	95:5
2	1.0	2.0	2,4,6-$Cl_3C_6H_2$	31[b]	97:3
3	1.0	2.0	C_6F_5	42[b]	96:4
4	1.0	2.0	3,5-$(CF_3)_2C_6H_3$	36[a]	96:4

a-yield obtained through NMR using 1,3,5-trimethoxybenzene as an internal standard; *b*-isolated yield; *c*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase with AD-H Column, flow rate =1mL•min^{-1}, 5% IPA in Hexane.

In summary, an optimised set of conditions for the aza-Michael addition reaction of imine **149** to the unsaturated ester **58** was established to furnish product **153** in good yield (71%) and excellent enantioselectivity (96:4 er). Scope of the aza-Michael addition reaction was then carried by (i) using different imine nucleophiles, (ii) using various Michael acceptors, (iii) utilising varied nucleophiles in the second step of the reaction such as cyclic amines and alcohols, (iv) obtaining the free β-amino product and derivatisation, and (v) preparing a gram scale synthesis of the optimised reaction condition to highlight the applicability of the isothiourea-catalysed aza-Michael addition reaction.

2.4 REACTION SCOPE

2.4.1 Nucleophilic Imine Scope

With the established optimised reaction conditions for the aza-Michael addition reaction of imine **154** to the unsaturated ester **59**, the reactivity of the different nucleophilic imines with various electron-donating and electron-withdrawing substituents *para* to the imine group was then evaluated as shown in Figure 14 below.

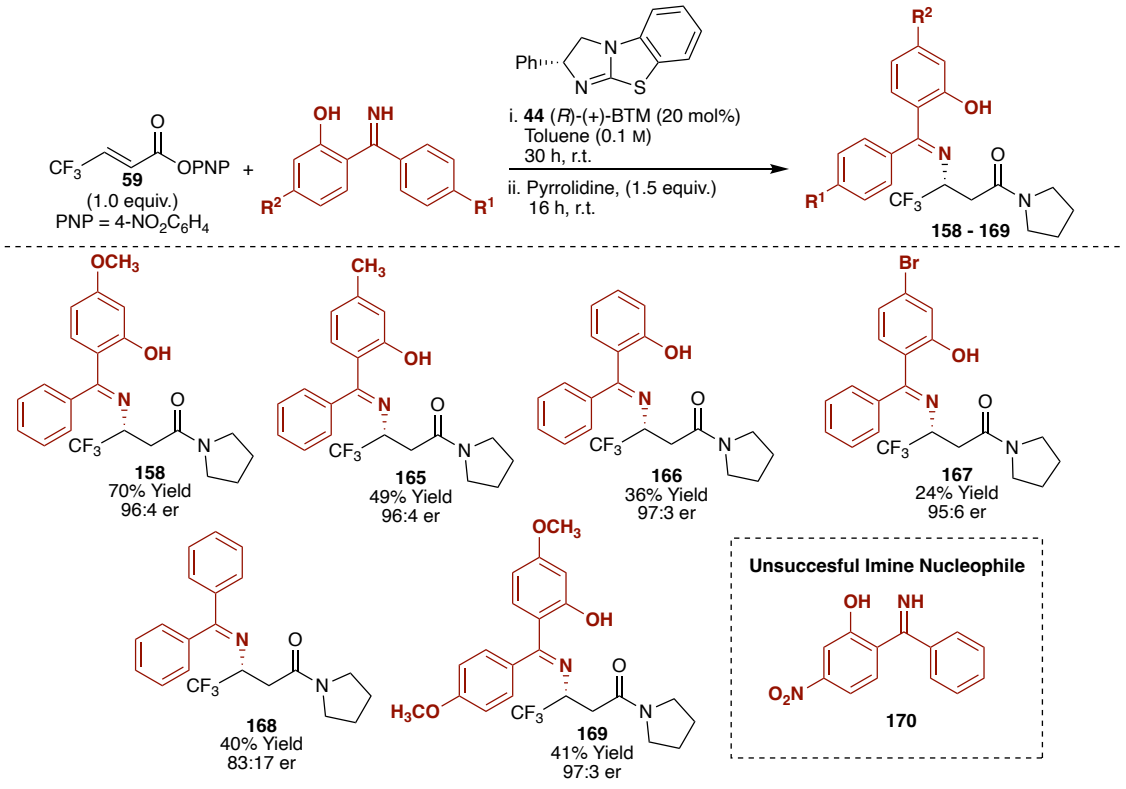


Figure 14. Evaluation of different imine nucleophiles for the aza-Michael addition reaction.

Figure 16 shows a decreasing trend in the reactivity for the aza-Michael addition reaction, as highlighted by the decreasing yield of the aza-Michael addition products **158, 165, 166,** and **167**. Introduction of a methoxy group *para* to the imine showed provided the highest yield for the reaction, as shown by product **158,** which was thought to be attributed to the increased nucleophilicity of the imine group due to the electron-donating mesomeric effect of the methoxy group. Decreasing the electron-donating effect of the group in this position showed a steady drop in the product yield, as shown by β-imino amide product **165** at 49% yield upon introducing a methyl group *para* to the imine. A diminished yield was observed when an electron-withdrawing group (-Br) was introduced at the *para* position of the imine, as shown by the β-imino amide product yield of **167** (24% yield). In contrast, no aza-Michael addition product was observed with a strong electron-withdrawing nitro group (**170**) at the *para* position

of the imine. The introduction of methoxy groups *para* to the imine on both the aryl groups, however, did not significantly increase the yield of the aza-Michael addition product **169** (41% yield). Additionally, utilisation of the parent benzophenone imine (without the *ortho* hydroxyl group) showed no significant difference, as shown in the aza-Michael addition product **168** (40% yield) as compared to the product **166** (36% yield) from the hydroxy-substituted imine., except for the enantiomeric ratio (er) which was further explained in section 2.5.

Excellent enantioselectivity (up to 97:3 er) for most of the aza-Michael addition products was observed for the reaction highlighting the importance of the hydroxyl functionality of the imine. Hence, the parent benzophenone imine **128** (without the *ortho* hydroxyl group) was used for the aza-Michael addition reaction to observe any difference in the enantioselectivity of the products. Results showed that imine **128** showed diminished enantioselectivity for the aza-Michael addition product **168** (83:17 er) compared to using imine **135** for the aza-Michael addition protocol, as reflected in the product **166** (97:3 er). These results demonstrate the importance of the hydroxyl group (further discussed in section 2.5).

2.4.2 Variation of the Michael Acceptor

Variation of the Michael acceptor for the aza-Michael addition reaction was then carried out to assess the applicability of the reaction by utilising a range of electron-withdrawing groups at the C(3) position of the Michael acceptor (Figure 15).

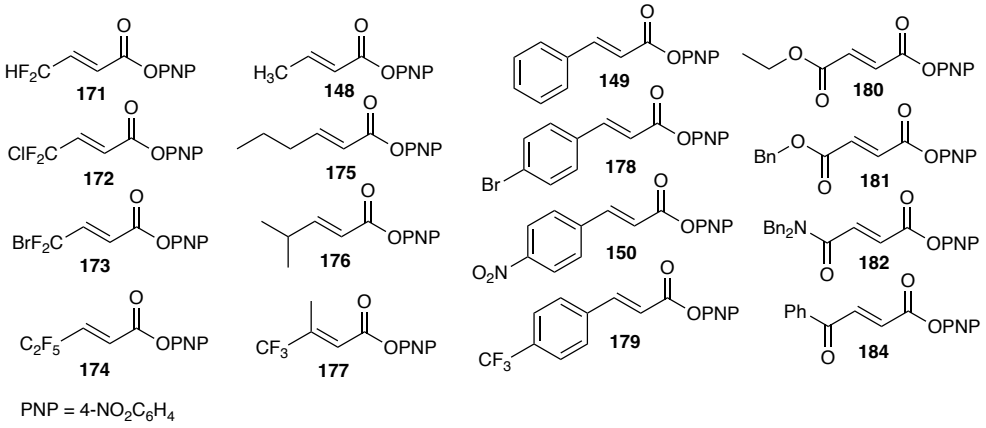
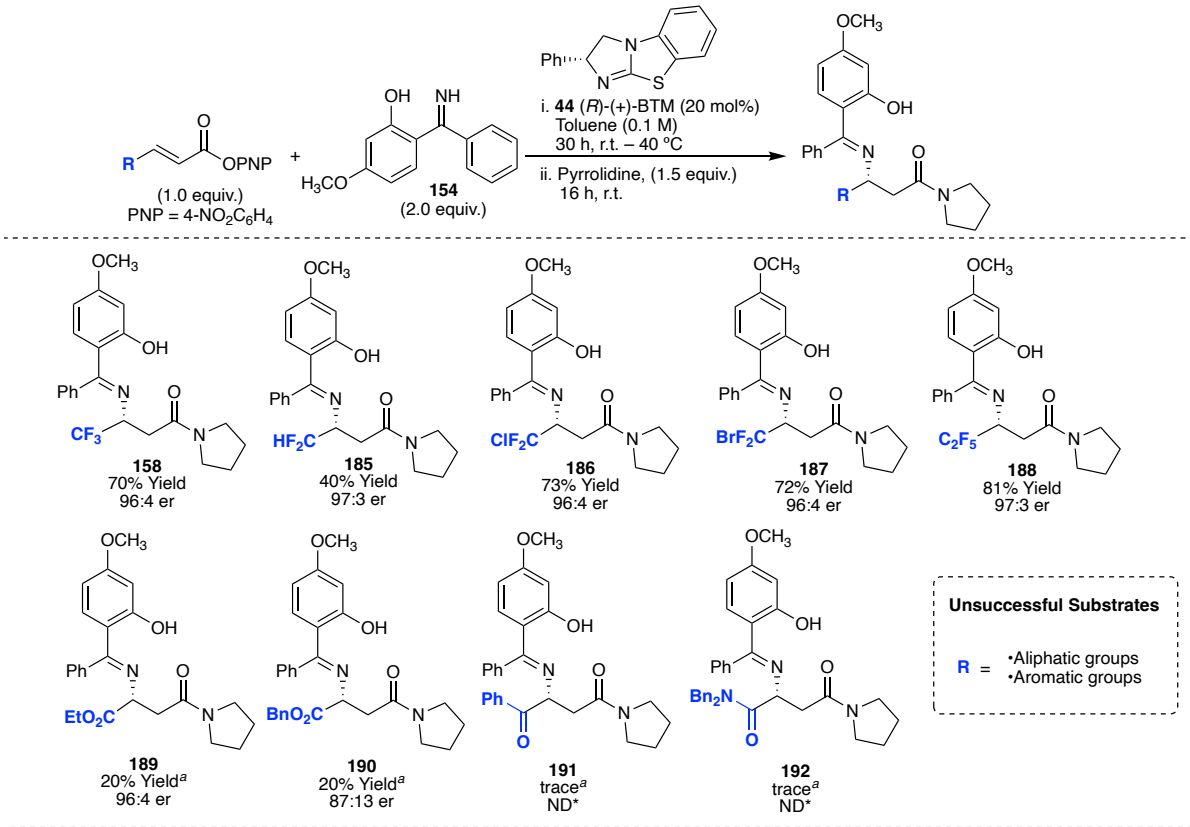


Figure 15. Scope for the Michael acceptor variation.

Upon utilisation of the following Michael acceptors shown in Figure 15, the aza-Michael addition reaction only showed good to excellent yield using highly electron-withdrawing substituents at the C(3) position of the Michael acceptor as highlighted in the yield of the aza-Michael addition products shown in Figure 16. Moreover, imine **154** was used for the Michael acceptor scope owing to its high nucleophilicity compared to the other imine nucleophiles, as shown by the yield of product **158** during the optimisation of the reaction conditions.



a = 40 °C reaction temp; ND = Not determined; * = obtained via crude ^{1}H NMR analysis; enantiomeric ratio (er) obtained using HPLC analysis on a chiral stationary phase specific for each compound.

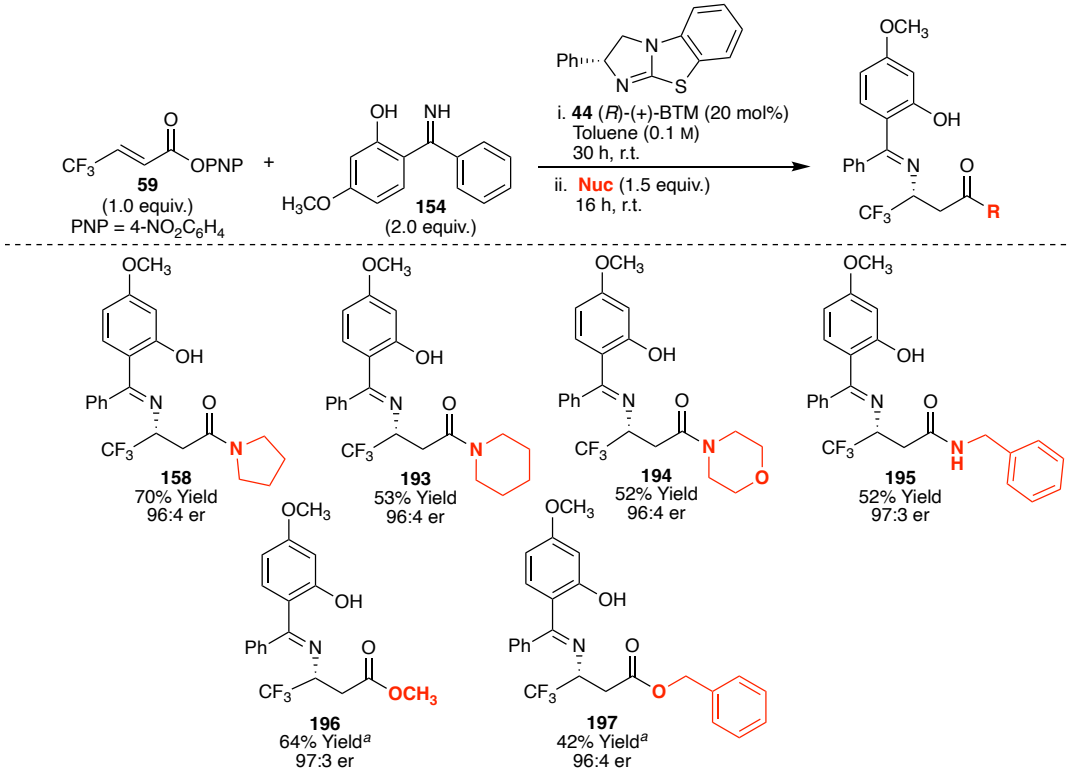
Figure 16. Yield (%) and enantioselectivity (er) of the aza-Michael addition products using different Michael acceptors.

Halogenated and polyhalogenated groups at the C(3) position of the Michael acceptor show moderate to an excellent yield of the aza-Michael addition products (40% - 81% yield) (**158, 185 – 188**). This high reactivity was attributed to their strong electron-withdrawing capability *via* inductive effect, enhancing the electrophilicity of the C(3) position of the Michael acceptor upon formation of the unsaturated acyl ammonium intermediate. Ester groups at the C(3) position of the Michael acceptor did not show any significant reactivity for the aza-Michael addition reaction, as shown by the product yield of **189** and **190** (~20% yield). In contrast, in this position, ketone and amide groups do not show any reactivity for the reaction, as shown by products **191** and **192**, respectively. On the other hand, most of the products showed good to excellent enantioselectivity for the aza-Michael addition reaction (up to 97:3 er), implying the high selectivity of the reaction imposed by the isothiourea organocatalyst.

2.4.3 β-Imino Ester and β-Imino Amide Scope

Variation of the different nucleophiles for the second step was then carried out to further establish the scope of the aza-Michael addition reaction *via* the synthesis of various β-imino

esters and β-imino amide products (Figure 19). Good to excellent yields for the various β-imino ester and β-imino amide derivatives were observed, as highlighted in Figure 17, with **158** showing the highest yield for the product at 70% compared to the various amine and alcohol nucleophiles. Moreover, excellent enantioselectivity for the aza-Michael addition reaction was still observed for all the products in Figure 17, indicating that *in situ* nucleophilic quench of the product after the aza-Michael addition reaction does not provide a significant impact on the enantiointegrity of the reaction.



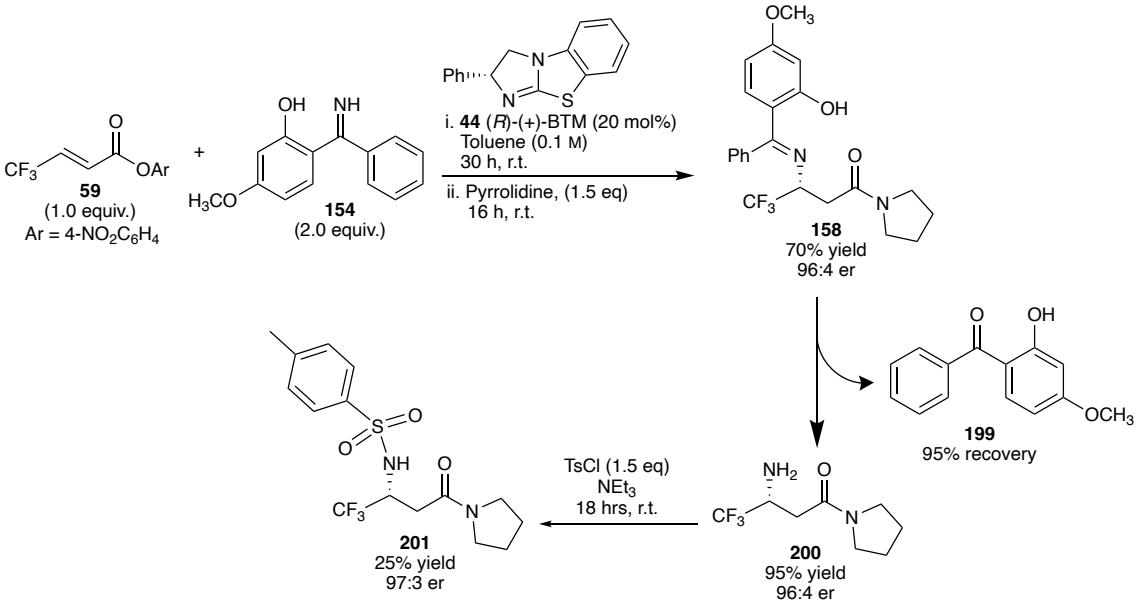
a – addition of DMAP (20 mol%); enantiomeric ratio (er) obtained using HPLC analysis on a chiral stationary phase specific for each compound.

Figure 17. Yield (%) and enantioselectivity (er) of the aza-Michael addition products using different nucleophilic quench in the second step.

2.4.4 Synthesis of Free β-Amino Amides, Derivatisation, and Gram Scale Synthesis

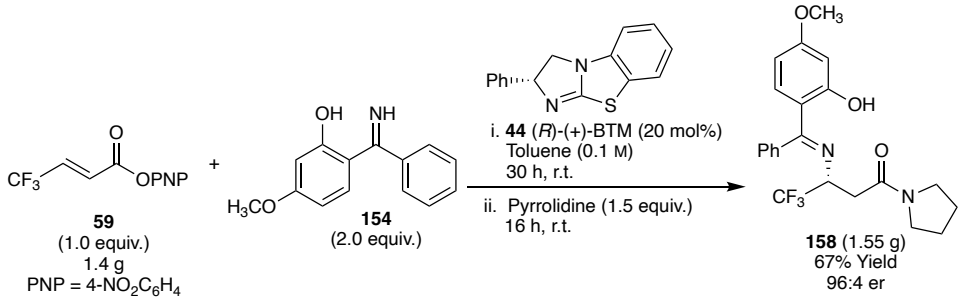
As previously highlighted, the importance for most aza-Michael addition reactions using imines as nucleophiles is easy access to the corresponding free β-amino functionality. With **158** available in high yield and enantioselectivity (70% yield, 96:4 er), simple hydrolysis of the imine functionality was shown in the successful isolation of the free β-amino product **200** with 95% yield with no significant change in the enantioselectivity at 96:4 er (Scheme 42). Moreover, successful recovery of the 2-hydroxybenzophenone **199** at 95% yield was attained, which can be used to form the imine **154** and in principle perform another aza-Michael addition reaction. Therefore, these results emphasise compound **199** as an efficient ammonia carrier for the

isothiourea-catalysed aza-Michael addition protocol. Further derivatisation of compound **200** was then carried out to achieve the chiral sulfonamide **201** in a modest yield but with excellent enantioselectivity (25% yield, 97:3 er) in a straightforward substitution reaction.



Scheme 42. Hydrolysis of the aza-Michael addition product **158** to obtain the free β-amino product **200**, followed by derivatisation to form the chiral sulfonamide compound **201**.

Applicability of the aza-Michael addition protocol was also carried out in a gram-scale synthesis of compound **158,** showing reproducible yield (67%) and enantioselectivity (96:4 er) of the reaction (Scheme 43).

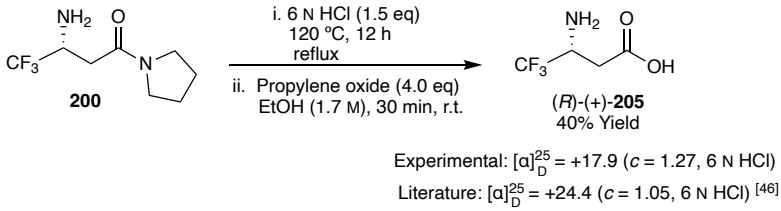


Scheme 43. Gram-scale Synthesis of **158**.

2.5 ABSOLUTE CONFIGURATION, PROPOSED REACTION MECHANISM, AND ENANTIOSELECTIVITY

The absolute configuration within the aza-Michael addition product was assigned by comparison of the specific rotation of the free β-amino acid of compound **205**, *via* the hydrolysis of the readily available free β-amino amide **200** (Scheme 44) to the reported literature($[\alpha]_D^{25}$ = +17.9 (*c* = 1.27, 6 N HCl)) with close similarity to the reported values by

Soloshonok and co-workers ($[\alpha]_D^{25}$ = +24.4 (*c* = 1.05, 6 N HCl)).[84,85] This is consistent with the predicted configuration of the products based on proposed transition state model for (*R*)-(+)-BTM **44**.



Scheme 44. Confirmed absolute configuration by comparing the optical rotation of the synthesized free β-amino acid **205** to the reported free β-amino acid **205.** [84]

For the proposed mechanism, most isothiourea-catalysed conjugate additions follow a similar reaction pathway that starts with the activation of the α,β-unsaturated ester to form the reactive α,β-unsaturated acyl ammonium intermediate. The reactive intermediate then allows the activation of the C(3) position of the intermediate and is then intercepted by a nucleophile and undergoes a conjugate addition reaction. This pathway has been showcased through a plethora of conjugate addition studies by Smith's group for various Michael addition and Michael addition-lactonisation reactions as previously discussed in Chapter 1, Section 1.6.[43,78–80]

For the optimised aza-Michael addition reaction protocol, a similar reaction pathway was proposed for the reaction, as shown in Figure 18. The reaction is initiated by nucleophilic attack of the isothiourea organocatalyst **44** to the α,β-unsaturated ester **59** forming the reactive α,β-unsaturated acyl ammonium intermediate **202**. Formation of the intermediate **202** activates the electrophilicity of the C(3) position of the intermediate enabling the imine **154** nucleophile to engage in an aza-Michael addition, followed by a 4-nitrophenoxide-assisted deprotonation, to form the reactive ammonium enolate **203**. The reactive enolate intermediate **203** was then protonated by *in situ* generated 4-nitrophenol, to obtain the acyl ammonium intermediate **204**. Intermediate **204** then undergoes an aryloxide-facilitated (4-nitrophenoxide) catalyst turnover to obtain the free organocatalyst **44** and release the aza-Michael addition product **146**. Product **146** was then derivatised by adding various nucleophiles (i.e. alcohols, amines) to obtain a variety of β-imino ester and β-imino amide derivatives, as shown in Section 2.4.3.

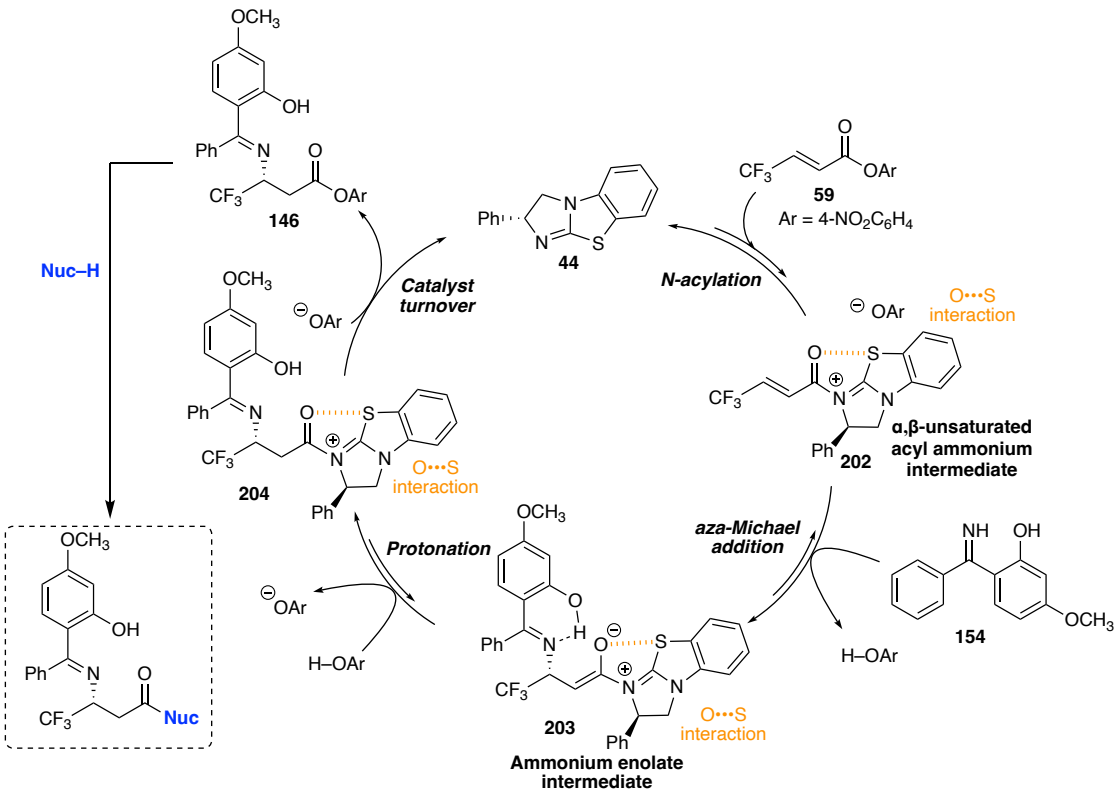


Figure 18. Proposed reaction mechanism for the isothiourea-catalysed aza-Michael Addition of imine **154** to the α,β-unsaturated ester **59.**

Excellent enantioselectivity was observed for most of the products of the optimised isothiourea-catalysed aza-Michael addition reaction protocol. Two important factors were considered for the observed excellent enantioselectivity such as (i) the use of a chiral isothiourea organocatalyst and (ii) the introduction of the hydroxyl group *ortho* to the imine functionality of the imine nucleophile.

Using a chiral isothiourea organocatalyst imposes selectivity on the desired product, most notably during the aza-Michael addition of the imine **154** nucleophile to the reactive α,β-unsaturated acyl ammonium intermediate **202**. Formation of the reactive intermediate **202** *via* the *N*-acylation of the catalyst **44** to the α,β-unsaturated ester **59** provides a plausible stabilising effect and conformational lock on the formed intermediate brought about by the intramolecular 1,5 C=O•••S interaction *via* an effective overlap of the nonbonding orbital of the oxygen in the carbonyl group and the antibonding orbital of the sulfur atom of the catalyst ($n_O \rightarrow \sigma^*_{S\text{-}C}$).[36],[41],[86] Moreover, the phenyl substituent from the enantiopure isothiourea catalyst **44** acts as a stereodirecting group and imposes facial selectivity upon the addition of the imine **154** nucleophile (Figure 19).

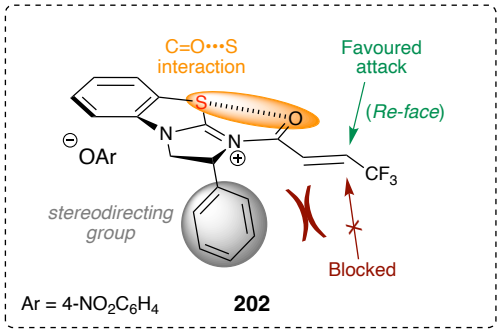
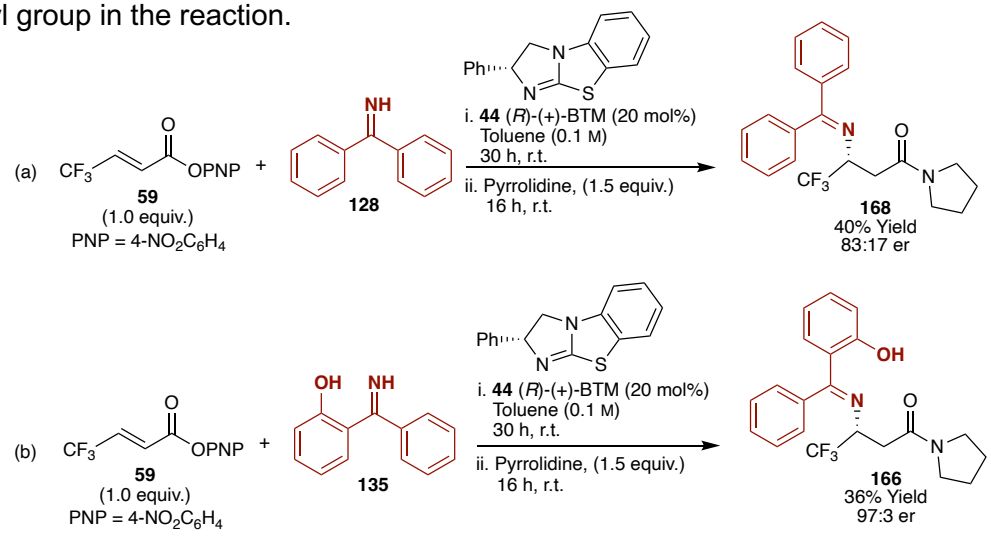


Figure 19. The stabilising effect, conformational lock, and facial selectivity of the α,β-unsaturated acyl ammonium intermediate **202** imposed by the chiral isothiourea organocatalyst **44**.

Additionally, enhanced enantioselectivity was also observed upon introduction of the hydroxyl group *ortho* to the imine as observed in the enantiomeric ratio of product **166** (97:3 er) in comparison to product **168** (83:17 er) (Scheme 45) while showing no significant effect in the yield of the aza-Michael addition products. These results highlight the importance of the hydroxyl group during the enantioselective aza-Michael addition step. Hence, further analysis (e.g. computational analysis) on the aza-Michael addition step of the imine onto the α,β-unsaturated acyl ammonium intermediate is highly recommended to determine the role of the hydroxyl group in the reaction.



Scheme 45. Yield (%) and enantioselectivity (er) comparison of the aza-Michael addition product **168** and **166**.

2.6 CONCLUSION

In summary, a successful protocol for the enantioselective aza-Michael addition reaction of 2-hydroxybenzophenone imine nucleophiles to α,β-unsaturated ester substrates was established *via* the generation of the reactive α,β-unsaturated acyl ammonium intermediate using an enantiopure isothiourea organocatalyst. The optimized aza-Michael addition protocol

provided various β-imino ester and β-imino amides in moderate to excellent yield (20% - 81%) and with high enantioselectivity (up to 97:3 er). The nucleophilicity of the 2-hydroxybenzophenone imines is dependent on the electronic substituent effects within the imine, as observed in the decreasing trend in yield upon the introduction of less electron-donating and electron-withdrawing groups (Figure 16). Moreover, the reactivity of the Michael acceptors in the established aza-Michael addition reaction protocol primarily depends on the electron-withdrawing groups at the C(3) position. The introduction of halogenated and polyhalogenated groups at the C(3) position provides good to excellent reactivity upon formation of the α,β-unsaturated acyl ammonium intermediate for the aza-Michael addition protocol. In contrast, ester, ketone, and amide groups at the C(3) position of the Michael acceptor elicited poor reactivity (Figure 18). Good to excellent results were also observed upon derivatisation of the aza-Michael addition products to obtain β-imino esters, β-imino amides, free β-amino amides, and the synthesis of chiral sulfonamides. On the other hand, the introduction of a hydroxyl group *ortho* to the imine group plays a key role in providing a significant increase in the enantioselectivity of the reaction, however, further analysis (e.g. computational analysis) is highly recommended to determine the role of the hydroxyl group during the aza-Michael addition step. Nevertheless, the introduction of the hydroxyl group provides excellent enantioselectivity of the aza-Michael addition products ($\geq$ 95:5 er).

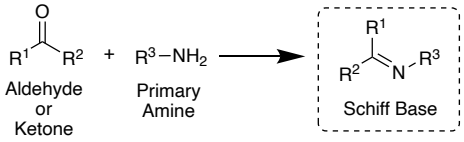
Despite the limitation of the aza-Michael addition protocol only working on ester Michael-acceptors containing strong electron-withdrawing groups at the C(3) position, the optimised protocol still showcased its important applicability, most notably in the synthesis of β-halogenated-β-imino ester and amide derivatives in high yields and enantioselectivity (up to 80% yield, up to 97:3 er) highlighting the potential of chiral isothiourea as efficient organocatalysts for aza-Michael addition reactions. Moreover, this protocol can be applied in the synthesis of unnatural and fluorinated β-amino acid scaffolds which can be incorporated in various protein residues and potential drug lead structures to increases their lipophilicity and introduce potential biological activities. Additionally, this protocol can provide a simple route for the synthesis of enantioenriched β-fluorinated β-lactams which are also considered as potential drug lead structures.

CHAPTER 3: ISOTHIOUREA-CATALYSED SELECTIVE MICHAEL ADDITION OF SCHIFF BASES TO α,β-UNSATURATED ESTER DERIVATIVES

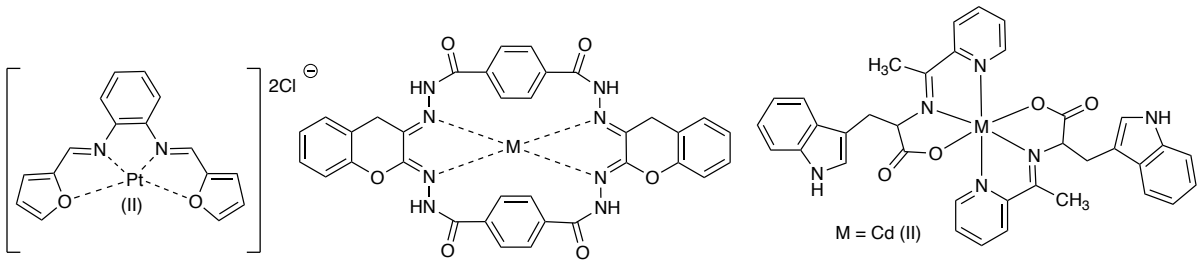
3.1 PROJECT OVERVIEW

3.1.1 Schiff Bases

Schiff bases, discovered by the German Chemist Hugo Schiff in 1864, are a sub-class of imines, also known as ketimines or aldimines, formed from the reaction of primary amines with carbonyl compounds[87] as shown in Scheme 46. Most Schiff bases are known for their reactivity with transition metals to form complexes, and some exhibit biological activities such as antibacterial (**206**),[88] antifungal (**207**),[89] and anti-cancer (**208**)[90] (Figure 20).



Scheme 46. Formation of Schiff bases from the condensation of primary amines and aldehydes or ketones.



206
Antibacterial activity against *B. subtilis* NRRL B-94

207
Antifungla activity against *Aspergillus sp.* and *Penicillium sp.*

208
Anticancer potential against human breast cancer (MDA-MB-231 cells)
IC_{50} = 27 μmol/L
dr not defined

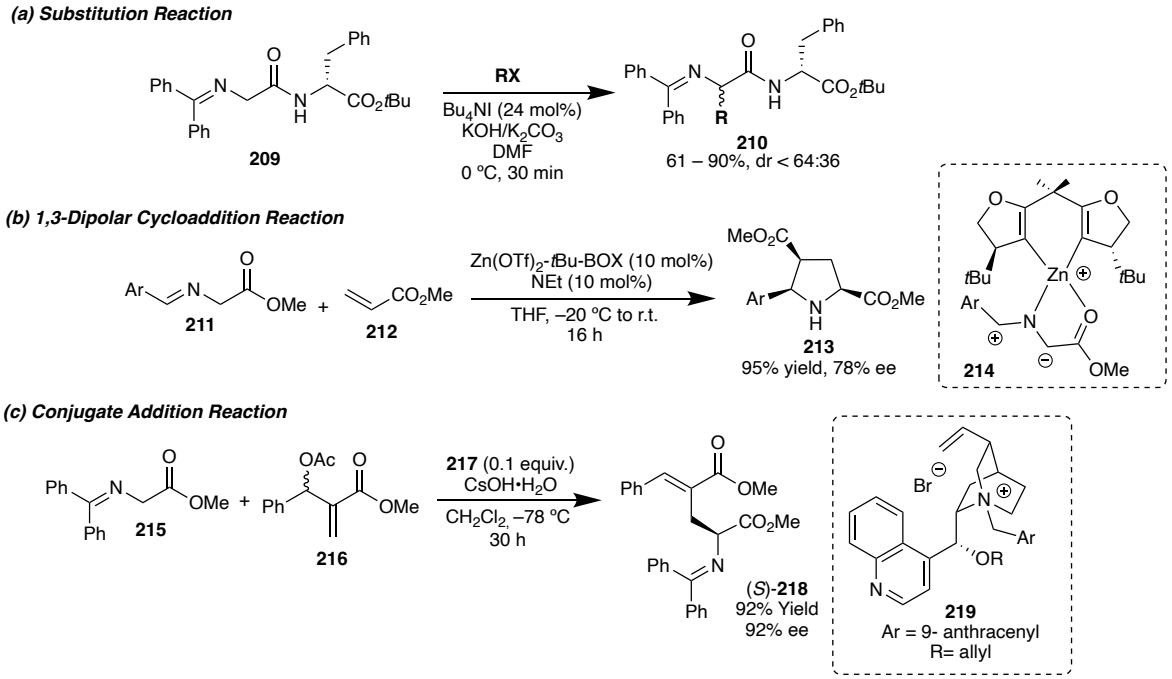
Figure 20. Potential biological activity of Schiff base metal complexes.

Aside from the potential bioactivity of Schiff base complexes, glycine-derived Schiff bases have been extensively explored and utilised for the synthesis of various biologically significant compounds and will be highlighted in the next sections.

3.1.2 Enantioselective Organocatalytic Reactions of Schiff Bases

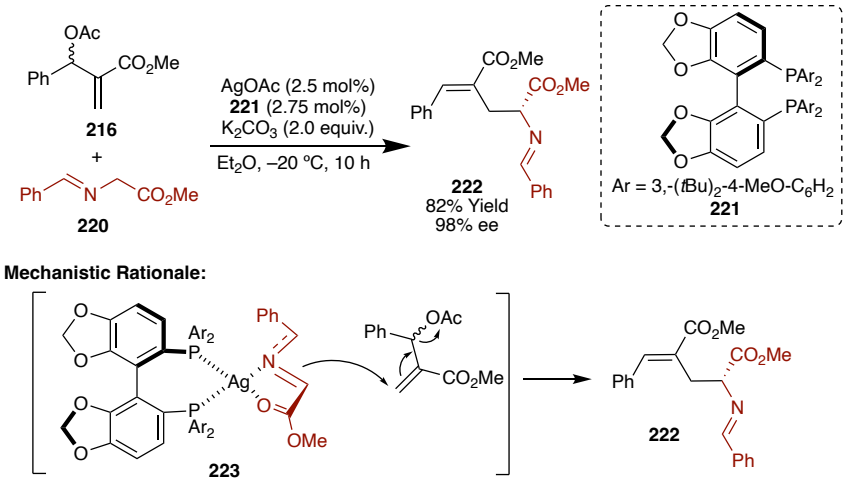
A plethora of research has been conducted for the enantioselective reactions of Schiff base substrates. Most of these reactions include simple substitution,[91–93] cycloaddition,[94,95] and Michael addition reactions.[96,97] An example of a typical substitution reaction is exemplified through the addition of glycine-derived Schiff base **209** to alkyl halides *via* a catalytic phase-transfer alkylation (Scheme 47a).[98] Glycine-derived Schiff bases can also undergo 1,3-dipolar

cycloaddition reactions to form pyrrolidine compounds **213** *via in-situ* formation of azomethine ylide **214** (Scheme 47).[95] Schiff bases can also undergo a Michael addition to α,β-unsaturated ester compounds, which are excellent precursors for γ-amino acids through simple acid hydrolysis (Scheme 47).[96] With the idea of utilising Schiff bases as nucleophiles, this project will focus on the Michael addition of Schiff bases to α,β-unsaturated esters.



Scheme 47. (a) Substitution, (b) cycloaddition, and (c) Michael addition reactions using Schiff bases as nucleophiles.

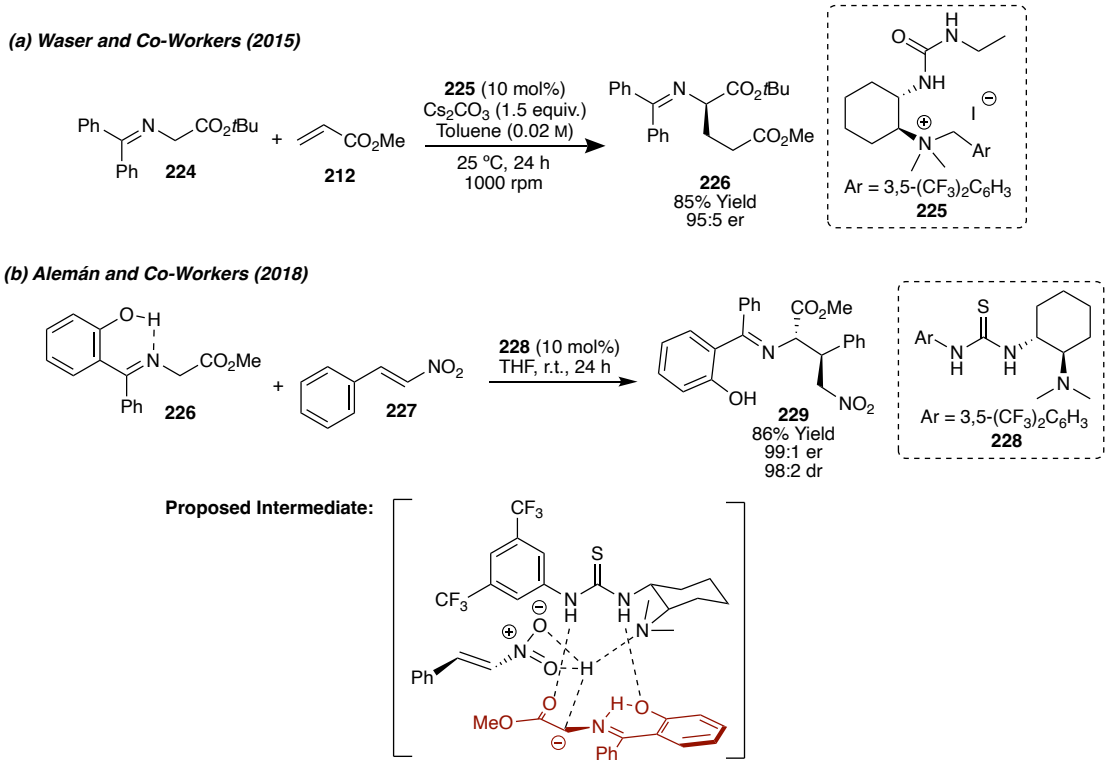
Despite the observed efficiency of Schiff bases on enantioselective organocatalytic Michael additions, most of these reactions rely on activating the Schiff base by, for instance, forming a reactive complex using transition metal.[99–101] One example that utilises transition metals for the activation of Schiff bases was reported by Xu and co-workers in 2017, where they performed an Ag-catalysed selective Michael addition of glycine-derived Schiff base **220** to α,β-unsaturated ester **216** *via* a proposed interaction of the glycine Schiff base to the chiral Ag complex to form the reactive silver-bound azomethine ylide complex **223** (Scheme 48).[102]



Scheme 48. Ag-catalysed Michael addition of **220** to α,β-unsaturated ester **216** *via* the formation of reactive silver-bound azomethine ylide complexes **223**.

On the other hand, various researchers have also demonstrated enantioselective Michael additions of Schiff bases utilising phase-transfer organocatalysts.[96,97,103–108] A typical example is from Waser and co-workers in 2015[104] employed chiral urea-quaternary ammonium salt hybrid **225** acting as a phase-transfer catalyst and an H-bonding organocatalyst for the Michael addition of glycine-derived Schiff base **224** to α,β-unsaturated ester **212** (Scheme 49a).

However, very little work has been developed for the organocatalysed Michael addition of Schiff bases to α,β-unsaturated ester compounds that do not utilise phase-transfer organocatalysts. Recently, Alemán and co-workers in 2018[109] demonstrated a different strategy for the enantioselective-organocatalytic Michael addition of Schiff bases **226** to activated alkenes such as nitroolefins **227** using chiral thiourea **228** as an H-bonding organocatalyst (Scheme 49b). They proposed an enhanced reactivity of the Schiff base **226** from the inherent intramolecular H-bonding activation of the hydroxyl group, increasing the acidity of the methylene proton of the Schiff base, together with the excellent selectivity imposed by the chiral thiourea organocatalyst *via* an intermolecular H-bonding interaction of the catalyst with the formed azomethine ylide after deprotonation as showcased by the proposed intermediate for the proton transfer.

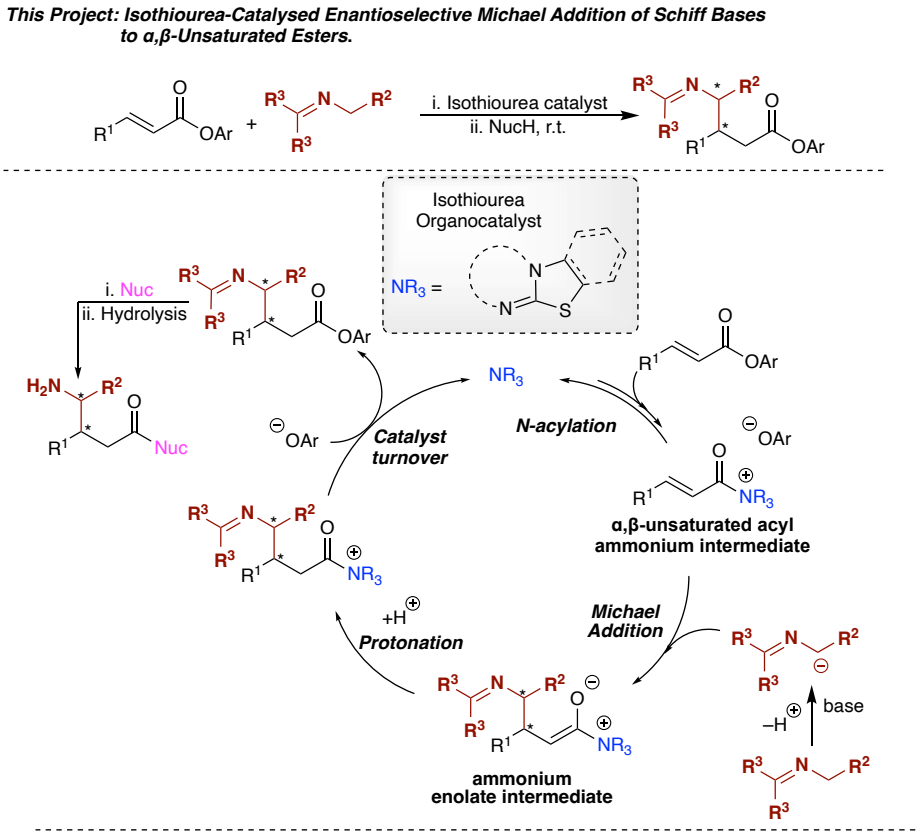


Scheme 49. Examples of the enantioselective-organocatalytic Michael addition of Schiff bases utilising H-bonding catalysis other than phase-transfer catalysis.

To date, only limited organocatalysts outside of these strategies have been used for the enantioselective Michael addition reaction of Schiff bases, and will be developed in this chapter.

3.2 AIMS AND OBJECTIVES

Following the work in chapter 2, this work focuses upon the use of Schiff bases as nucleophiles in conjunction with the generation of an α,β-unsaturated acyl ammonium intermediates derived from α,β-unsaturated ester substrates using isothiourea organocatalysts (Scheme 50).



Scheme 50. Design of the isothiourea-catalysed Michael addition of Schiff bases to α,β-unsaturated ester substrates.

3.3 RESULTS AND DISCUSSION

3.3.1 Synthesis of Starting Materials

Initial studies for the isothiourea-catalysed Michael addition of Schiff bases to α,β-unsaturated esters include the reaction of Schiff base **215** and unsaturated ester **59** to form the Michael-addition adduct. A retrosynthetic analysis for the substrates is depicted in Figure 21.

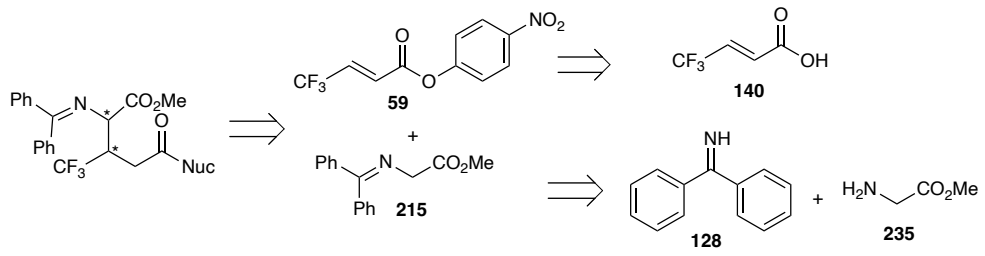


Figure 21. Retrosynthetic analysis of the substrates **215** and **59**.

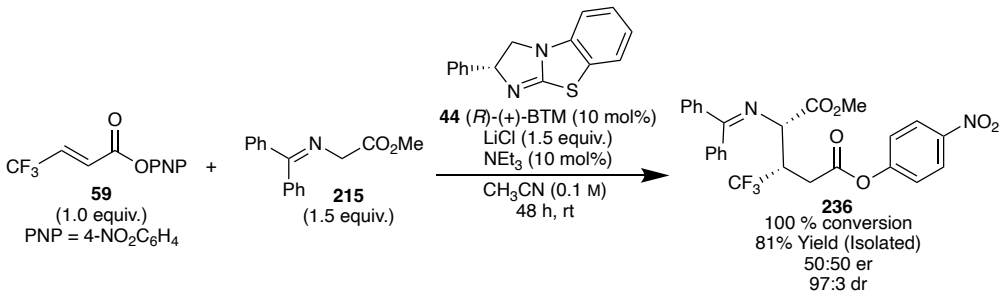
Synthesis of substrate **59** was achieved following the method highlighted in chapter 2, Scheme 35. Synthesis of substrate **215** was then realised by the condensation of precursors **128** and **235** following the procedure reported by the Alemán group. Substrates **128** and the HCl salt of **235** were stirred with anhydrous magnesium sulfate in dichloromethane at 40 ºC for 22 h to obtain the product **215** as a yellow crystalline solid in 34% yield (Scheme 51).[110]

Scheme 51. Synthesis of substrate **215**.

3.3.2. Optimisation of Reaction Conditions

3.3.2.1. Test Reaction

After synthesising substrates **59** and **215**, a test reaction was conducted to observe any formation of the Michael addition product **236** using a preliminary set of conditions for the reaction, as shown in Scheme 52. The presence of triethylamine promotes the formation of the enolate from substrate **215** *via* deprotonation of the α-proton, while the presence of lithium chloride may stabilise the enolate *via* coordination to the oxygen and nitrogen lone pair.

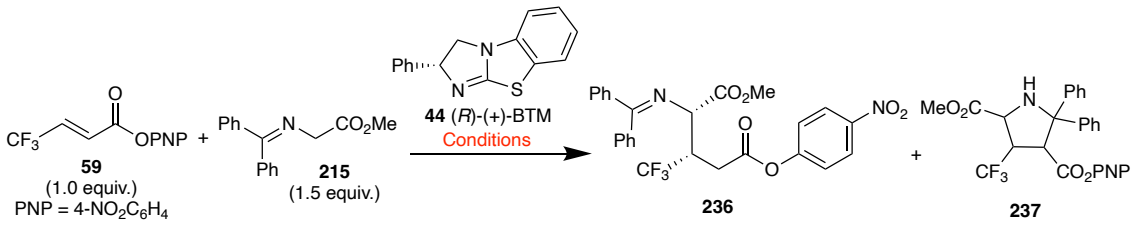


Scheme 52. Preliminary test reaction of **215** and **59**.

Scheme 52 showed the excellent formation of Michael addition product **236** in 81% yield with 100% conversion of substrate **59** and excellent 97:3 dr as observed from the analysis of the ^{1}H NMR of the crude reaction mixture. However, poor enantioselectivity was observed for product **236** (50:50 er) employing 10 mol% of (*R*)-(+)-BTM **44**, consistent with a base-promoted background reaction. Thus, control experiments were conducted to determine if any background reaction was present (Table 13). For most of the reaction conditions shown in Table 13, formation of two prominent products were observed namely the Michael addition product **236** and the formal cycloaddition product **237** while relative configuration for both observed products were still unknown.

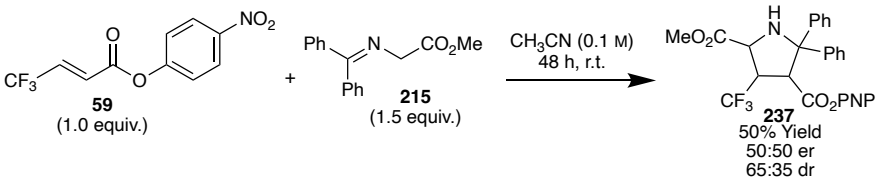
Conditions shown in Table 13, entry 1 showed poor conversion to the desired product **236** (27% yield, 53:47 er, 86:14 dr) while showing prominent formation of product **237** (22% yield). Removal of the catalyst (Table 13, Entries 2 and 3) showed no conversion to the desired product **236** while only showing preference to the formal cycloaddition product **237** (50% yield). The absence of lithium chloride and base (Table 1, Entry 4) showed the formation of product **236** but no improvement for the reaction (19% yield, 50:50 er, 79:21 dr) and mostly prefers product **237** (72% yield) . Both control experiments in Table 1, entries 1 and 4, showed near racemic mixtures (<53:47 er) for product **236** with lowered diastereoselectivity of the reaction (<86:14 dr). Using conditions in Table 13, entry 3, product **237** was isolated (50% yield) but still showed poor enantioselectivity and diastereoselectivity for the reaction (50:50 er, 65:35 dr) as shown in Scheme 53.

Table 13. Control experiments for the Michael addition of imine **215** to ester **59**.



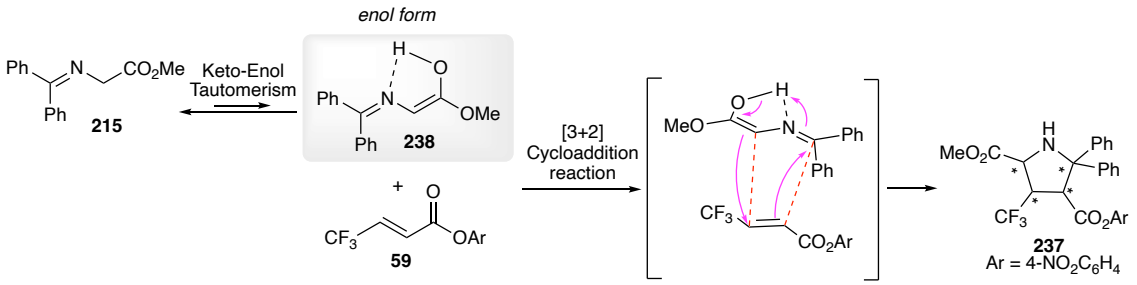
Entry	Conditions	Remaining Substrate 59 (%)[a]	236 Yield (%)[a]	237 Side-Product (%)[a]	236 er[b]	236 dr[a]
1	LiCl (1.5 equiv.) (*R*)-(+)-BTM (10 mol%) CH_3CN (0.1 M) 48 h, rt	25	27	22	53:47	86:14
2	LiCl (1.5 equiv.) CH_3CN (0.1 M) 48 h, rt	45	-	50	-	-
3	CH_3CN (0.1 M) 48 h, rt	45	-	50	-	-
4	(*R*)-(+)-BTM (10 mol%) CH_3CN (0.1 M) 48 h, rt	9	19	72	50:50	79:21

a – Determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.



Scheme 53. Cycloaddition side-product **237** formed in all control experiments (Table 1, Entry 3) at 50% yield with poor selectivity (50:50 er, 65:35 dr).

Moderate to high yields of the side product **237** were predominantly observed in all the control experiments, even with or without the presence of the catalyst (Table 13). It is hypothesised that imine **215** may undergo keto-enol tautomerisation to enol **238,** driven by a stabilising intramolecular H-bonding of the enol to the imine group. Upon formation, enol **238** may readily react with the unsaturated ester **59** *via* a formal [3+2] cycloaddition reaction route (that could be either stepwise *via* ammonium enolate of the **236** or concerted as depicted in Scheme 54) to give the highly substituted pyrrolidine product **237** in moderate yield (50%) at 48 h while relative stereochemistry of product **237** was not determined after isolation.

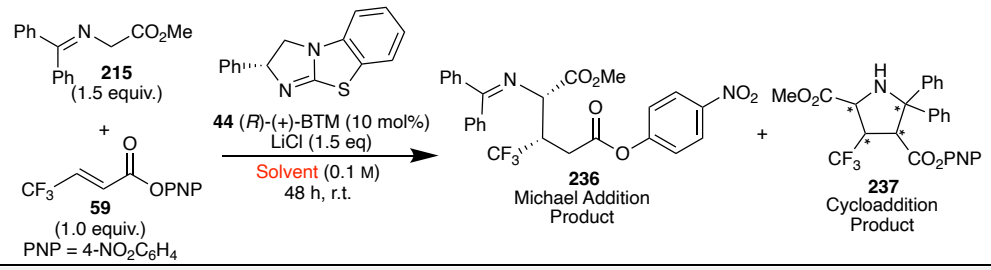


Scheme 54. Proposed reaction mechanism for the formation of **237** *via* a [3+2] cycloaddition reaction route.

3.3.2.2 Solvent Optimisation

Despite the formation of the formal cycloaddition product **237**, additional optimisation through variation of solvent polarity using a variety of solvents such as acetonitrile, dichloromethane, toluene, diethyl ether, methanol, and tetrahydrofuran was investigated (Table 14). Changing the solvent polarity did not improve the yield for formation of the Michael addition product, with the maximum yield of **236** observed at 25% with dichloromethane as the solvent. Poor selectivity was also observed throughout the reaction conditions (< 68:32 er, < 87:13 dr). Moreover, the formation of cycloaddition product **237** was still prominent for all the attempted reaction conditions based on ^{1}H NMR analysis of the crude reaction mixture. Diethyl ether (Table 14, entry 4) as solvent showed the highest preference towards the cycloaddition reaction route with a 96% yield of **237** after 48 hours.

Table 14. Solvent Optimisation for the Michael addition of imine **215** to ester **59**.



Entry	Solvent	Yield[a] of 236 (%)	(236) er[b]	(236) dr[a]	Yield[a] of 237 (%)[a]	Remaining Substrate[a] 59 (%)
1	CH_3CN	19	55:45	79:21	72	9
2	CH_2Cl_2	25	55:45	87:13	45	28
3	$PhCH_3$	7	68:32	75:25	68	25
4	Et_2O	-	-	-	96	3
5	MeOH	-	-	-	50	28
6	THF	<5%	58:42	67:33	47	48

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined using HPLC Analysis on chiral stationary phase.

Hence, it is highly evident that the presence of an ester or a carbonyl group adjacent to the imine may not benefit the reaction presumably due to the formation of the enol tautomer. An attempt to detect the presence of any enol tautomer by ^{1}H NMR of the Schiff base **215** using deuterated chloroform ($CDCl_3$) and deuterated acetonitrile (CD_3CN) was unsuccessful (Figure 22). This is consistent with the Schiff base preferentially existing in the keto form on the NMR timescale. Despite the elusive detection of the enol form of Schiff base **215**, there is a high probability of its formation *in situ* due to the relatively high acidity of the α-proton, that leads eventually to formal cycloaddition product **237**. To circumvent the uncatalysed formation of the enol form and concomitant formal cycloaddition, changing the ester group of the Schiff base into more suitable electron-withdrawing groups for the desired formation of Michael addition products is proposed.

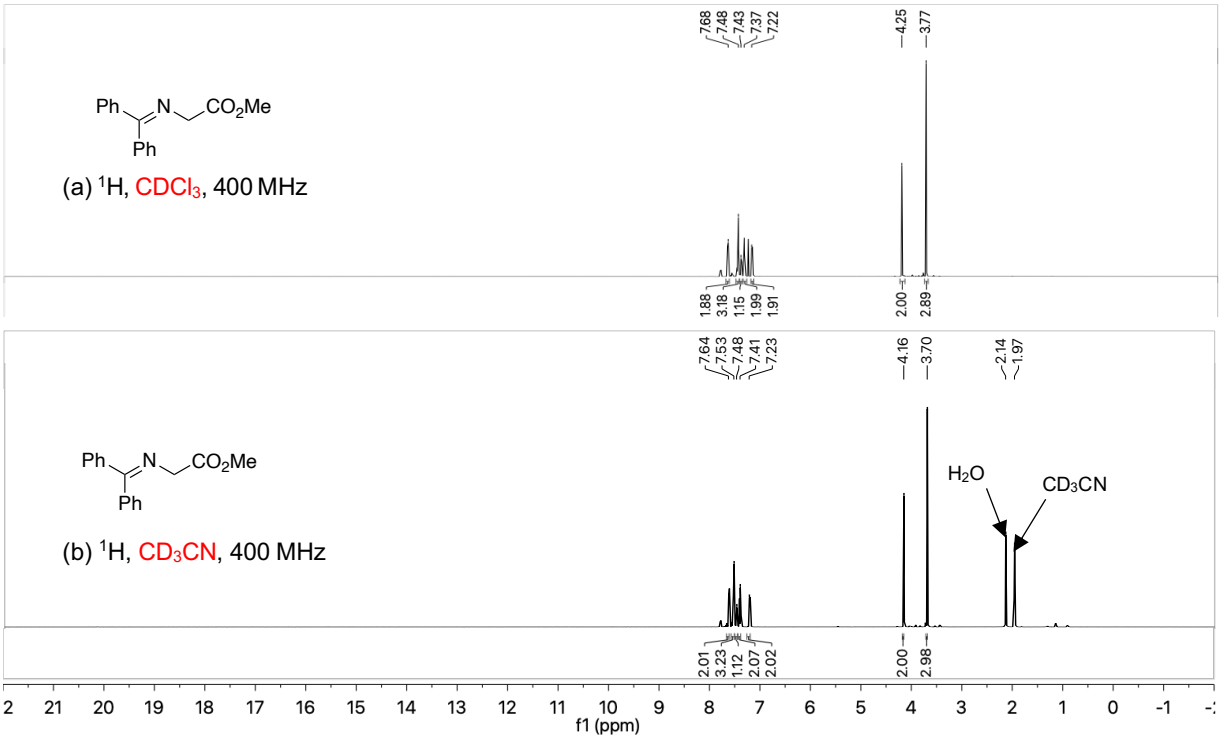


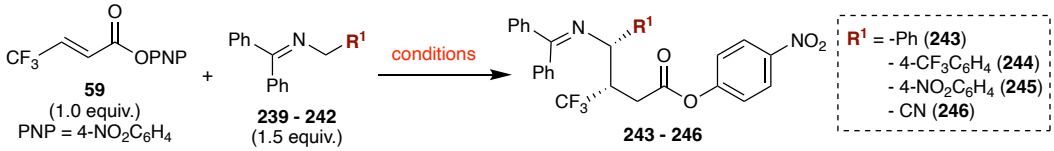
Figure 22. Wide ^{1}H NMR spectra of imine **215** in (a) deuterated chloroform and (b) deuterated acetonitrile showed no presence of the enol tautomer.

3.3.2.3 Preliminary Schiff Base Screening

Based on results above, the ester functionality was changed to either a benzylic substituent or nitrile and tested for reactivity in the Michael addition reaction protocol under various conditions such as [**A**] with base and catalyst, [**B**] only with catalyst, [**C**] only with base, and [**D**] no base and no catalyst (Table 15). Table 15 shows that Schiff base **239** (phenyl substituent) and **240** (4-$CF_3C_6H_4$ substituent) showed essentially no reaction (Entries 1 – 8). Although the incorporation of a nitrile electron withdrawing substituent (**242**) gave promising

yield (88% yield), poor selectivity was still observed for the reaction (<52:48 er, <58:42 dr) (Entries 13 and 16) while a 4-nitrophenyl electron withdrawing substituent (**241**) gave promising yield and selectivity for the Michael addition reaction protocol (43% yield, 88:12 er, 79:21 dr) as shown in Entry 9. Therefore, **241** was used as the Schiff base nucleophile.

Table 15. Schiff Base Screening (**241** – **244**) for the Michael Addition Reaction Protocol in Various Control Experiment Conditions.



Entry	Conditions	R^1	Product Yield (%)[a]	er[b]	dr[a]
1	**A**	Ph (**239**)	-	-	-
2	**B**	Ph (**239**)	-	-	-
3	**C**	Ph (**239**)	-	-	-
4	**D**	Ph (**239**)	-	-	-
5	**A**	4-$CF_3C_6H_4$ (**240**)	trace	-	-
6	**B**	4-$CF_3C_6H_4$ (**240**)	trace	-	-
7	**C**	4-$CF_3C_6H_4$ (**240**)	trace	-	-
8	**D**	4-$CF_3C_6H_4$ (**240**)	trace	-	-
9	**A**	4-$NO_2C_6H_4$ (**241**)	43	88:12	79:21
10	**B**	4-$NO_2C_6H_4$ (**241**)	trace	-	-
11	**C**	4-$NO_2C_6H_4$ (**241**)	40	50:50	78:22
12	**D**	4-$NO_2C_6H_4$ (**241**)	-	-	-
13	**A**	CN (**242**)	84	52:48	58:42
14	**B**	CN (**242**)	trace	-	-
15	**C**	CN (**242**)	88	50:50	56:44
16	**D**	CN (**242**)	-	-	-

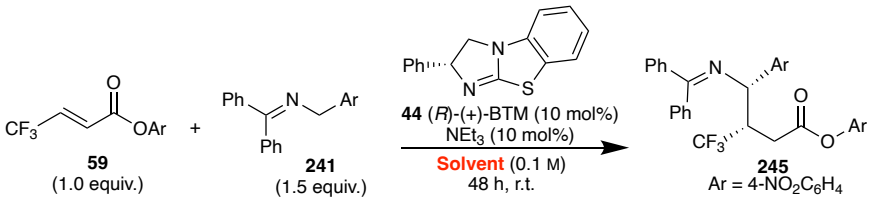
a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase. **Conditions: [A]** = NEt_3, **42** (10 mol%), (*R*)-(+)-BTM (10 mol%), CH_3CN (0.1 M), 48 h, r.t.; **[B]** = **42** (*R*)-(+)-BTM (10 mol%), CH_3CN (0.1 M), 48 h, r.t.; **[C]** = NEt_3 (10 mol%), CH_3CN (0.1 M), 48 h, r.t.; **[D]** = CH_3CN (0.1 M), 48 h, r.t.

3.3.2.4 Preliminary Solvent Screening

Solvents with various polarity were tested for the Michael addition reaction of Schiff base **241** as the pronucleophile to α,β-unsaturated ester **59** (Table 16). Results showed that enhanced yield and selectivity of the Michael addition product **245** for the most common polar and nonpolar aprotic solvents were not observed, as shown in Table 16 (Entries 2 – 7). However

the use of both *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) showed enhanced yield and diastereoselectivity for the Michael addition reaction (<88% yield, ~96:4 dr) as highlighted in Entries 8 and 9. Using DMA led to lower product enantioselectivity for the reaction (67:33 er) as compared to DMF solvent (86:14 er). Hence, DMF was deemed a more suitable solvent for the Michael addition reaction.

Table 16. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** with varying Solvent.



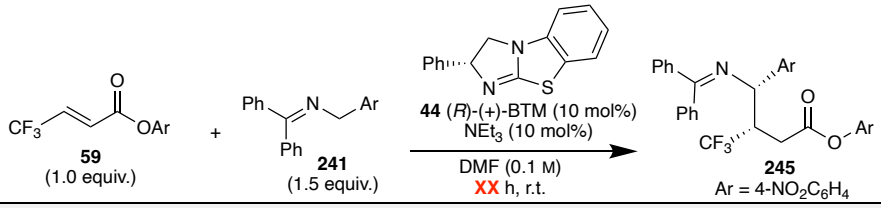
Entry	Solvent	245 Yield (%)[a]	er[b]	dr[a]
1	CH_3CN	43	88:12	77:23
2	CH_2Cl_2	15	80:20	94:6
3	Tetrahydrofuran	12	80:20	86:14
4	Et_2O	trace	-	-
5	Toluene	Trace	-	-
6	Xylene	-	-	-
7	Ethyl Acetate	trace	-	-
8	*N,N*-dimethylformamide (DMF)	82	86:14	96:4
9	*N,N*-dimethylacetamide (DMA)	86	67:33	96:4
10	Dimethylsulfoxide (DMSO)	56	61:39	95:5

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.

3.3.2.5 Reaction Time Optimisation

Using DMF as Solvent, the reaction time for the Michael addition of Schiff base **241** to α,β-unsaturated ester **59** was monitored as shown in Table 17. Full conversion of the ester **59** substrate was reached within 2 hours, giving 81% yield of **245** and good enantioselectivity (86:14 er) as well as excellent diastereoselectivity (95:5 dr) (Entry 2). If the reaction time was extended for up to 48 hours, no significant change in the product yield and selectivity of product **245** (81% yield, 86:14 er, 96:4 dr) was observed.

Table 17. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** with varying Reaction Time.

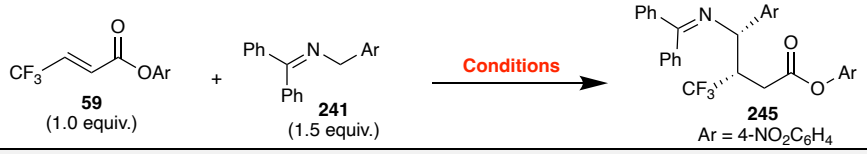


Entry	Reaction Time (h)	245 Yield (%)[a]	er[b]	dr[a]
1	1	71	85:15	95:5
2	2	81	86:14	95:5
3	3	81	86:14	95:5
4	24	81	86:14	96:4
5	48	81	86:14	96:4

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.

With the idea of improving the enantioselectivity of the reaction, additional control experiments were conducted using the newly optimised conditions shown in Table 18. Results of the control experiments indicate that removal of the triethylamine base (Table 18, Entry 2) showed a significant increase in product enantioselectivity (95:5 er) while maintaining excellent diastereoselectivity (96:4 dr) despite exhibiting moderate product yield of **245** (42% yield). Background reaction was mostly observed in the presence of a catalytic amount of base (10 mol% NEt_3) in the mixture, which was supported in the results in Table 18, Entry 3, while no product formation was observed in the absence of base and catalyst (Table 18, entry 4).

Table 18. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** under Various Control Experiment Conditions.

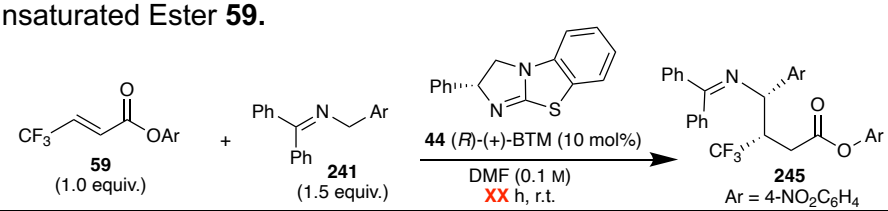


Entry	Conditions	245 Yield (%)[a]	er[b]	dr[a]
1	**44** (*R*)-(+)-BTM (10 mol%) NEt_3 (10 mol%) DMF (0.1 M) 2 h, r.t.	82	86:14	95:5
2	**44** (*R*)-(+)-BTM (10 mol%) DMF (0.1 M) 2 h, r.t.	42	95:5	96:4
3	NEt_3 (10 mol%) DMF (0.1 M) 2 h, r.t.	92	50:50	96:4
4	DMF (0.1 M) 2 h, r.t.	-	-	-

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.

Based on the obtained results in Table 17 and Table 18, additional optimisation on the reaction time was then conducted and monitored for 2 – 24 hours (Table 19). Complete conversion of **59** to **245** was reached at 8 hours reaction time with excellent yield and selectivity for product **245** (~81% yield, 95:5 er, and 96:4 dr). Further optimisation for the Michael addition of **241** to α,β-unsaturated ester **59** was then conducted identifying the optimal (i) type of isothiourea catalyst, (ii) reaction temperature, (iii) substrate ratio, (iv) reaction concentration, and (v) catalyst loading.

Table 19. Additional Reaction Time Optimisation for the Michael Addition of **241** to α,β-Unsaturated Ester **59.**



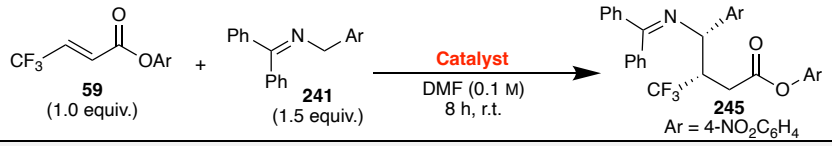
Entry	Reaction Time (h)	245 Yield (%)[a]	er[b]	dr[a]
1	2	42	95:5	96:4
2	3	51	95:5	96:4
3	4	63	95:5	96:4
4	6	71	95:5	96:4
5	8	81	95:5	96:4
6	18	80	95:5	96:4
7	24	80	95:5	96:4

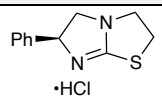
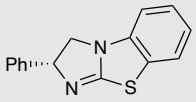
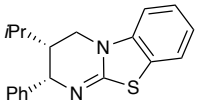
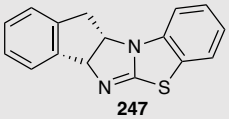
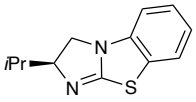
a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.

3.3.2.6 Isothiourea Organocatalyst Screening

Various isothiourea organocatalysts were evaluated for the Michael addition of **241** to α,β-unsaturated ester **59** using the newly optimised conditions for the reaction (Table 20). Catalyst optimisation showed that isothiourea catalyst **44** gave the highest product yield (80%) with excellent selectivity (95:5 er, 96:4 dr) (Table 20, Entry 2). Other isothiourea catalysts only showed moderate to good yield but with slightly lowered selectivity (<92:8 er, 96:4 dr). Thus, isothiourea catalyst **44** was considered optimal.

Table 20. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** using various Isothiourea Organocatalysts.



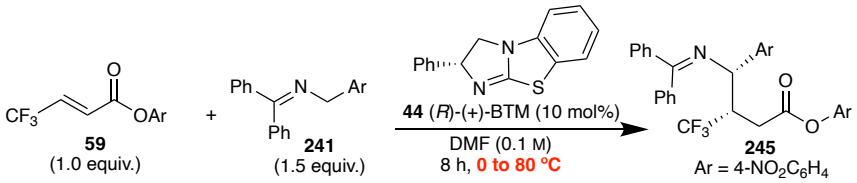
Entry	Catalyst (10 mol%)	245 Yield (%)[a]	er[b]	dr[a]
1	 **52** (*S*)-(-)-Tetramisole	71	21:79	96:4
2	 **44** (*R*)-(+)-BTM	81	95:5	96:4
3	 **53** (2*S*,3*R*)-(+)-HyperBTM	67	92:8	96:4
4	 **247** (2*R*,3*S*)-(+)-Fused BTM	25	91:9	90:10
5	 **248** (*S*)-*i*PrBTM	57	91:9	92:8

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.

3.3.2.7 Reaction Temperature Screening

After establishing the desirable isothiourea catalyst for the Michael addition reaction, reaction temperature screening was performed from 0 ºC to 80 ºC (Table 21). As shown in Table 21, an increase in the temperature beyond room-temperature conditions for the reaction negatively affects the yield (<66%) and selectivity (<88:12 er, down to 89:11 dr) of product **245** (Table 21, Entries 3 – 5). On the other hand, no significant increase in the yield and selectivity was observed when the reaction temperature was dropped to 0 ºC (<86% yield, 95:5 er, 96:4 dr) in comparison to room-temperature conditions (Table 21, Entry 1 and 2). Hence, the room-temperature condition was chosen as the optimal temperature for the reaction for ease of reaction set-up and economic reasons.

Table 21. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** under Different Reaction Temperature Conditions.



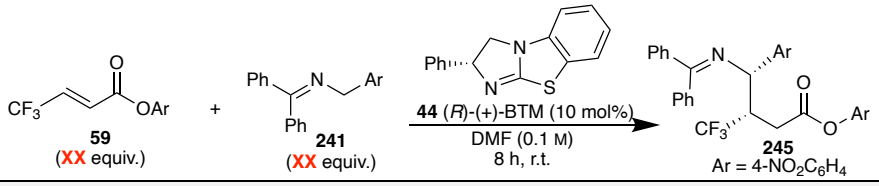
Entry	Reaction Temp. (ºC)	245 Yield (%)[a]	er[b]	dr[a]
1	0	86	95:5	96:4
2	r.t. (~20)	81	95:5	96:4
3	40	62	88:12	94:6
4	60	66	88:12	92:8
5	80	64	81:19	89:11

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase.

3.3.2.8 Substrate Ratio Screening

Further work screened the substrate ratio of Schiff base **241** and α,β- unsaturated ester **59** for this Michael addition (Table 22). Varying the substrate ratio of the Schiff base **241** and ester **59** showed a slight decrease in the yield of the reaction with the lowest yield of **245** at 73% (Table 22, Entry 2) while imposing no effect on the selectivity of the product in either condition (~95:5 er, 96:4 dr). Moreover, Entries 1 and 4 showed the highest yield of product **245** (~83% yield) for the reaction. Of all conditions, conditions in Entry 1 were deemed the optimal substrate ratio condition (1:1.5 equiv) for **59** and **241** as they used the cheaper substrate in excess.

Table 22. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** under Different Substrate Ratio.



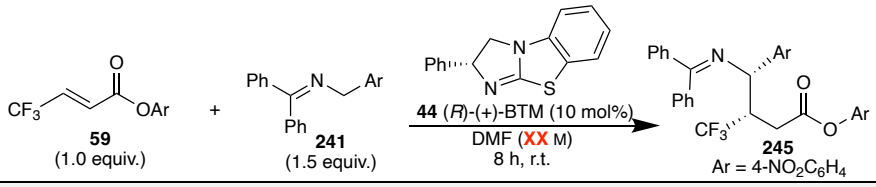
Entry	59 (equiv.)	241 (equiv.)	245 Yield (%)[a]	er[b]	dr[a]
1	1.0	1.5	82	95:5	96:4
2	1.0	2.0	73	95:5	96:4
3	1.5	1.0	74	95:5	96:4
4	2.0	1.0	82	95:5	96:4

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase; Reaction was done at 0.1 mmol scale of limiting reactant.

3.3.2.9 Reaction Concentration Screening

Screening for the optimum concentration (0.05 M, 0.1 M, and 0.2 M) was then carried out for this Michael addition reaction protocol (Table 23). Results show that a 0.1 M concentration is the optimal concentration for the reaction (Table 23, Entry 2). Increasing the reaction concentration (0.2 M) shows a drop in the yield (62%) of product **245** (Table 23, Entry 3), while a diluted reaction mixture (0.05 M) showed a significant drop in yield (47%) of the product **245** (Table 23, Entry 1). Despite the observed decrease in the product yield, the reaction still showed excellent selectivity for most conditions (<96:4 er, 95:5 dr).

Table 23. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** under Various Reaction Concentration.



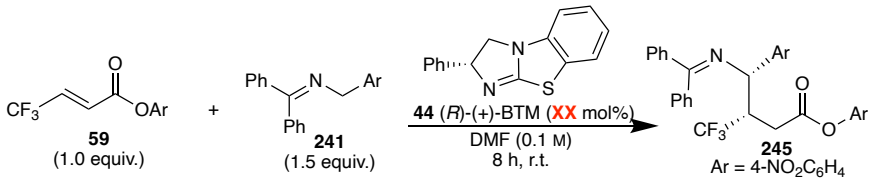
Entry	DMF (XX M)	245 Yield (%)[a]	er[b]	dr[a]
1	0.05	47	94:6	96:4
2	0.1	81	95:5	95:5
3	0.2	62	94:6	95:5

a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase; Reaction was done at 0.1 mmol scale of limiting reactant.

3.3.2.10 Catalyst Loading Optimisation

After establishing the following conditions for the Michael addition reaction of Schiff base **241** and ester **59**, screening for the optimal (*R*)-(+)-BTM **44** catalyst loading was then carried out (Table 24). Table 24 shows that a 10 mol% of (*R*)-(+)-BTM **44** was established as the optimal catalyst loading with the full conversion of substrate **59** and 81% yield of product **245** (Table 24, Entry 1). A decrease in the catalyst loading to 5 mol % showed a significant reduction of the product yield to 35% (Table 24, Entry 2). A further decrease in the catalyst loading to 1 mol% resulted in a further decrease in the product yield to 15% of **245** (Table 24, Entry 4). In both cases, excellent selectivity for the reaction was maintained (95:5 er, >99:1 dr). The reaction with 1 mol% catalyst was also performed with higher concentration (0.2 M DMF) and showed a significant increase by doubling the yield of **245** to 33% not affecting selectivity (Table 24, Entry 5). Hence, a 10 mol % catalyst loading was used as the optimum catalyst loading for the reaction.

Table 24. Yield (%) and Selectivity (er and dr) for the Michael Addition of Schiff base **241** to α,β-Unsaturated Ester **59** under Varied (*R*)-(+)-BTM **44** Catalyst Loading.



Entry	Catalyst Loading (mol%)	245 Yield (%)[a]	er[b]	dr[a]	Remaining Substrate 59 (%)
1	10.0	81	95:5	96:4	-
2	5.0	35	95:5	96:4	51
3	2.5	24	95:5	>99:1	61
4	1.0	15	95:5	>99:1	70
5	1.0[c]	33	95:5	>99:1	60

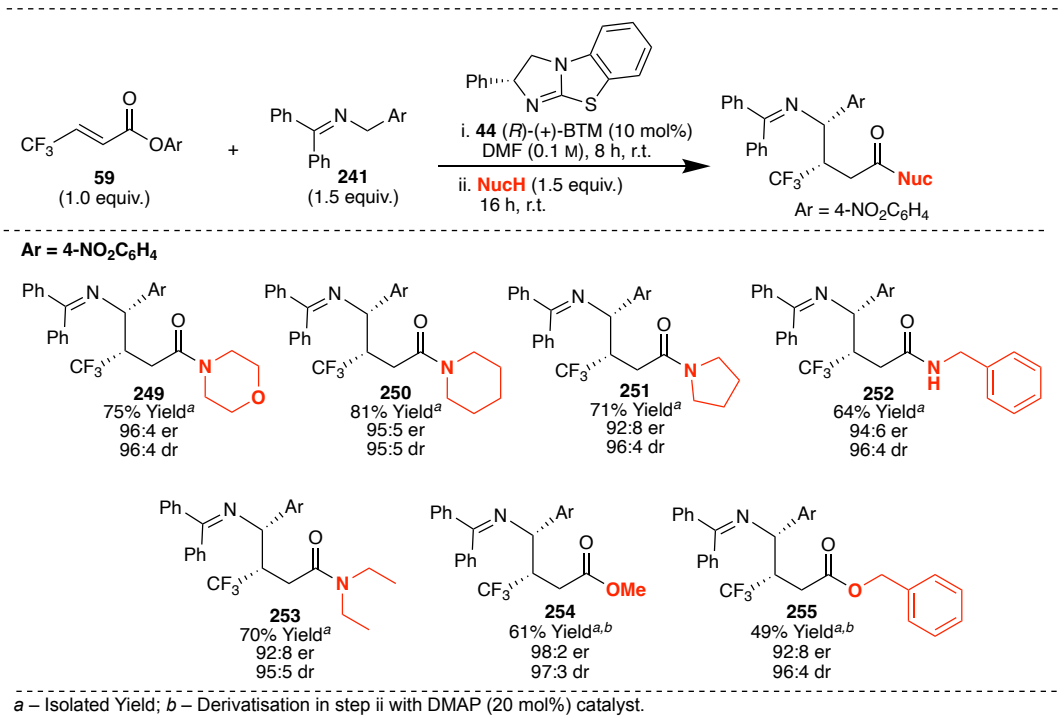
a – Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as Internal standard; *b* – Determined by HPLC analysis on a chiral stationary phase; *c* – Reaction done at 0.2 M concentration.

With reaction conditions optimised, a substrate scope and further derivatisation was then carried out to show the scope of the optimised Michael addition reaction protocol.

3.4 REACTION SCOPE

3.4.1 Derivatisation: Amide and Ester Products

With the established optimum conditions for the Michael addition reaction of Schiff base **241** to α,β-unsaturated ester **59**, different nucleophiles (i.e. amines, alcohols) for the second step of the reaction were then carried out to establish the scope of the reaction in the formation of various ester and amide Michael addition products as shown in Figure 23. The reaction tolerates various amines and alcohols to form a variety of amide (**249** – **253**) and ester (**254** and **255**) products in good to excellent yield (49% – 81% yield). Moreover, excellent selectivity for all amide and ester products was observed (<98:2 er, <97:3 dr), indicating that derivatisation of the product **245** by the addition of various amides and alcohols does not affect the stereochemical integrity of the products.



a – Isolated Yield; *b* – Derivatisation in step ii with DMAP (20 mol%) catalyst.

Figure 23. Ester and amide product (**249 – 255**) derivatisation using amines and alcohols as nucleophiles.

The relative and absolute configuration within (3*S*,4*S*)**-250** (Figure 24) were established unambiguously by single crystal X-ray diffraction crystallography with all other derivatives assigned by analogy.

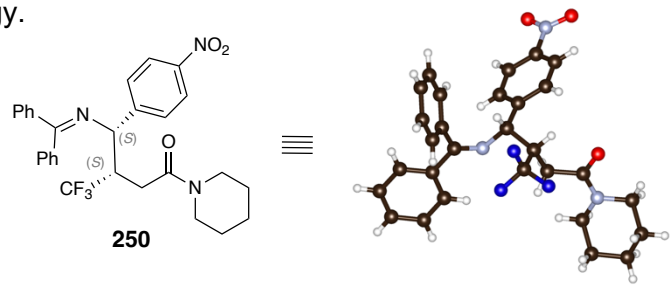


Figure 24. The absolute configuration of compound **250** is the (3*S*,4*S*) diastereomer.

3.4.2 α,β- Unsaturated Ester Scope

Scope for the α,β-unsaturated ester was then carried out using piperidine as the optimal nucleophilic quench after the Michael addition step. A series of α,β-unsaturated ester substrates were tested with groups at the C(3) in varying electron-withdrawing capacity (Figure 25). Results showed that most halogenated and polyhalogenated groups at the C(3) position of the Michael acceptor showed moderate to an excellent yield of the products, as highlighted in products **250, 256 – 259** (21% - 81% yield). An ester group at the C(3)-position elicited excellent yield for product **260** (75% yield) but showed reduced product enantioselectivity (83:17 er) using the optimised conditions, while using a lower reaction

temperature (0 ºC) significantly increased the er of the product (to 92:8 er) without any loss in the yield of product **260**. Amide and ketone groups at the C(3)-position of the Michael acceptor showed diminished yield (<35% yield) for products **261 – 263,** with excellent er for **261** and reduced stereoselectivity for **262** and **263.** The incorporation of C(3)-alkyl or C(3)-aryl groups within the ester did not show any reactivity for the Michael addition, presenting a clear limitation of this protocol.

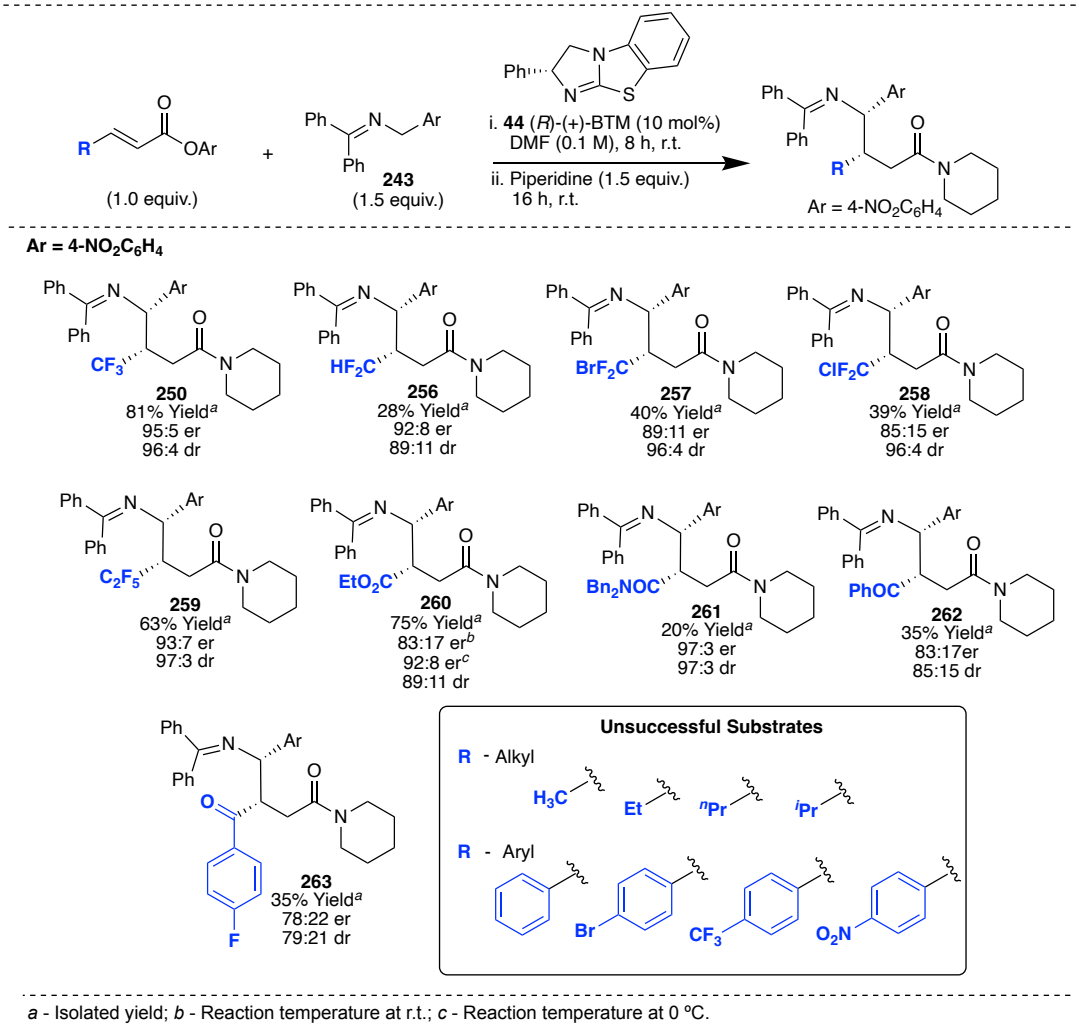


Figure 25. α,β-Unsaturated ester substrate scope for the Michael addition reaction protocol using Schiff base **241** as the nucleophile.

3.4.3 Schiff Base Scope

Scope for the Schiff base was then carried out by varying the aryl groups through the addition of various electron-withdrawing and electron-donating functional groups (Figures 26 and 27). Unfortunately, variation at the methylene group with different aryl groups within the Schiff base did not lead to productive reactivity, with only the *p*-nitrophenyl group at the methylene position giving excellent yield and selectivity for **250** (81% yield, 95:5 er, 96:4 dr). Variation of the aryl group at the methylene position (3-nitrophenyl, 2-nitrophenyl, 4-trifluoromethylphenyl, and

nitrile) of the Schiff base either gives a trace amount of product (**264** – **266**) or no reactivity. A nitrile group at the methylene position of the Schiff base provided the unseparable products **267** and **268** but with poor yield and selectivity. These results indicate the limitation of the reaction with Schiff base **243** to be the only effective nucleophile for this Michael addition reaction protocol.

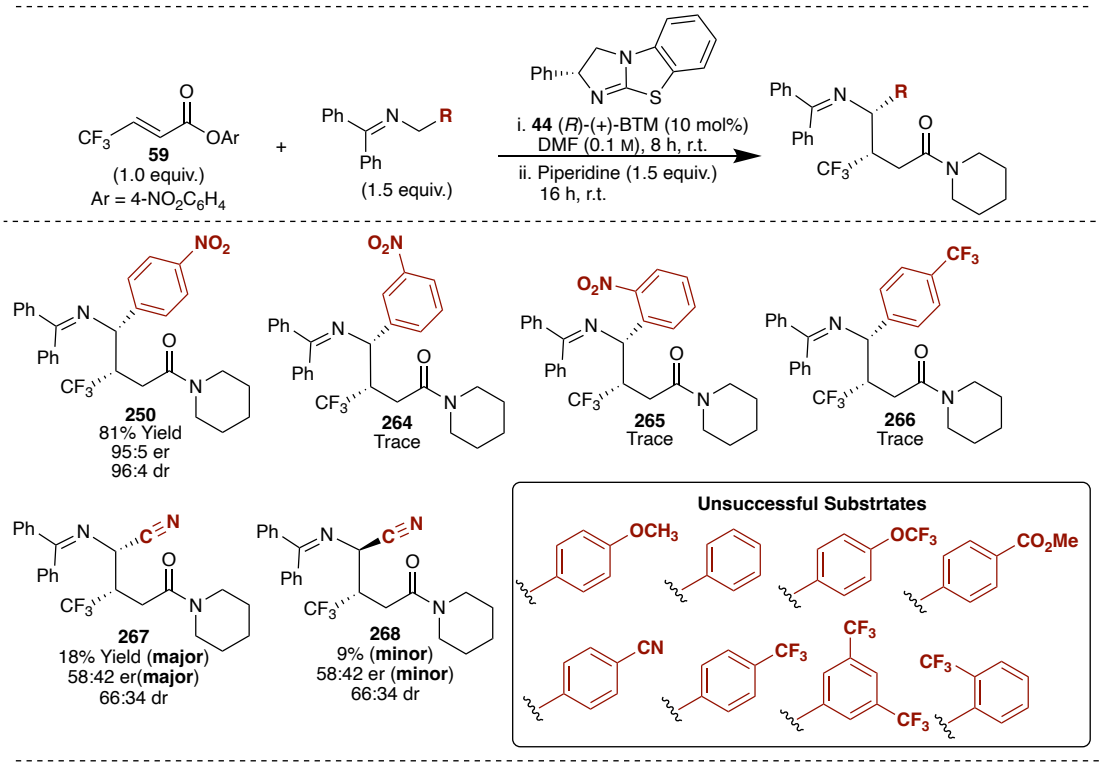


Figure 26. Variation of the group on the methylene position of the Schiff base.

Variation of the diphenyl group of the imine moiety of the Schiff base was also investigated (Figure 29). Variation of the diphenyl groups of the imine moiety showed moderate to excellent yield (24% - 81% yield) with good to excellent selectivity (up to 97:3 er, up to 96:4 dr). The addition of electron-donating groups on both phenyl groups at the *para*-position was detrimental to the reactivity of the Schiff base, as shown in product **269** (24% yield), which can be attributed to the diminished acidity of the methylene proton brought by the mesomeric effect of the para-methoxy groups. This effect can also be the reason for the low yields observed in products **271** and **272** outweighing the electron-withdrawing capability of the halogen groups at the *para* position.

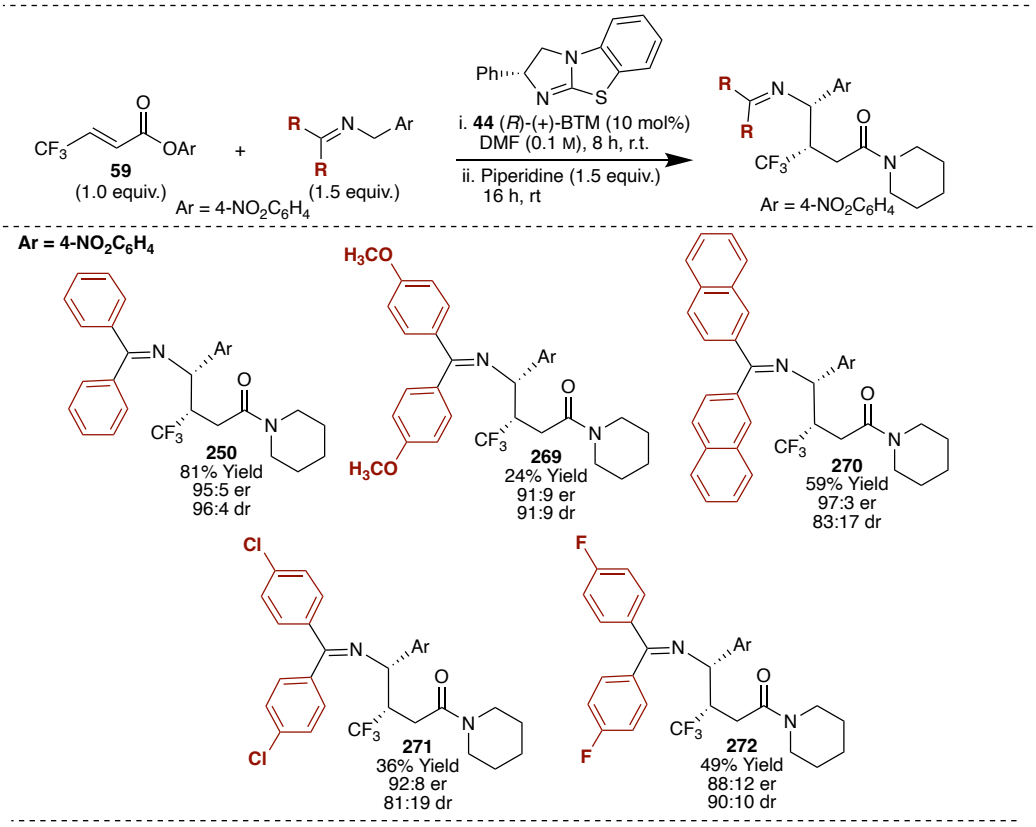
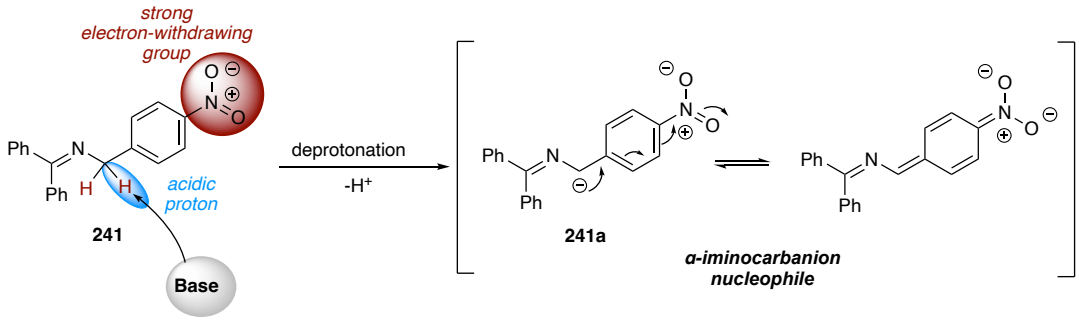


Figure 27. Variation of the diphenyl groups on the imine moiety of the Schiff base.

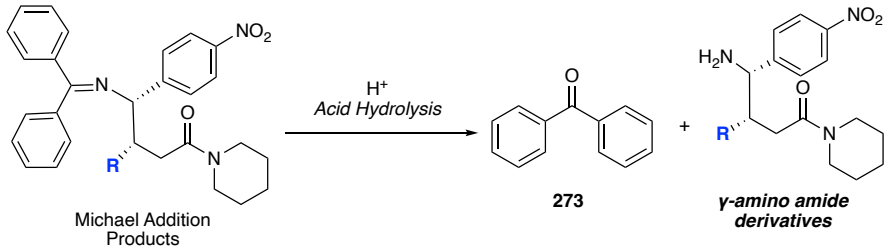
With the results shown in Figures 28 and 29, it can be concluded that the Michael addition of Schiff base to various α,β-unsaturated ester substrates is mainly dependent on the acidity of the methylene protons (Scheme 55). The introduction of a strong electron-withdrawing aryl group, such as a *p*-nitrophenyl group at the methylene part of the Schiff base, increases the acidity of the methylene protons and deprotonation of **241** forms the α-imino carbanion **241a** nucleophile prior to the Michael addition step.



Scheme 55. Deprotonation of **241** to form the α-imino carbanion **241a**.

3.4.4 Derivatisation and Gram Scale Synthesis: 2-Pyrrolidinone Derivatives

After establishing the scope of the Michael addition reaction, derivatisation and scale up was investigated. It was envisioned that hydrolysis of the imine moiety would leads to the free γ-amino amide product that could cyclise to generate the corresponding pyrrolidinone, with recovery of benzophenone **273** (Scheme 56).



Scheme 56. Planned hydrolysis of Michael addition products to obtain the free γ-amino products.

However, hydrolysis of a range of Michael addition products resulted in the formation of the corresponding 2-pyrrolidinone compounds in excellent yield and with no erosion of stereointegrity (Figure 28). High recovery of the benzophenone **273** and piperidine **274** are supporting this hypothesis.

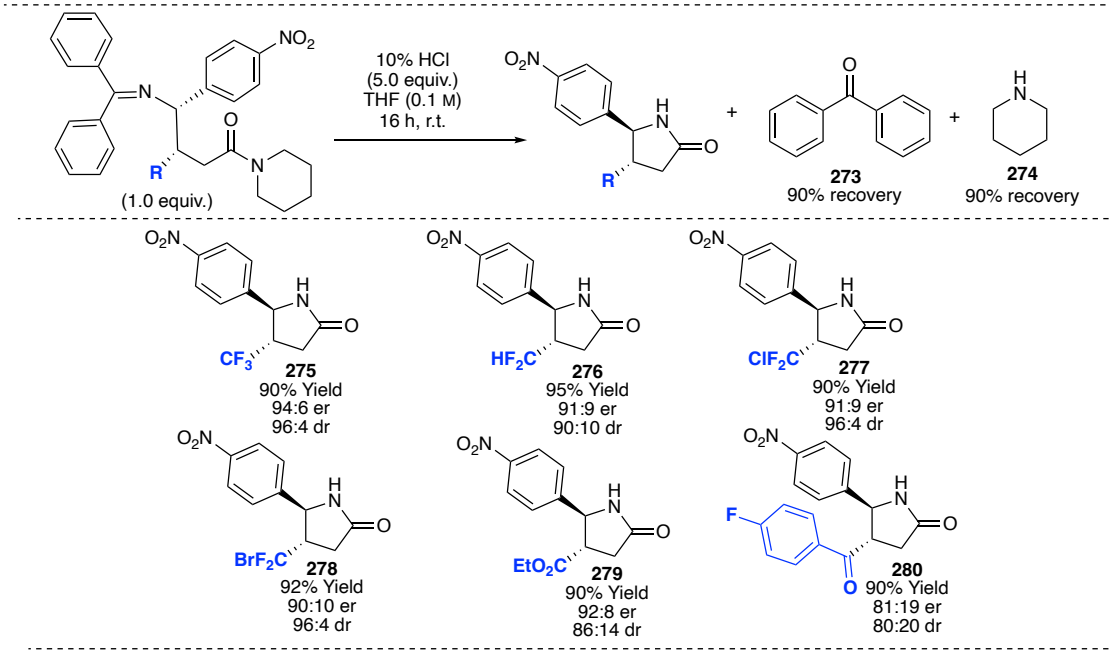
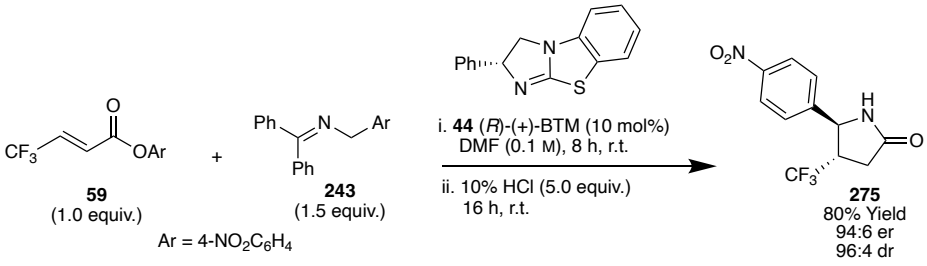


Figure 28. 2-Pyrrolidinone Scope.

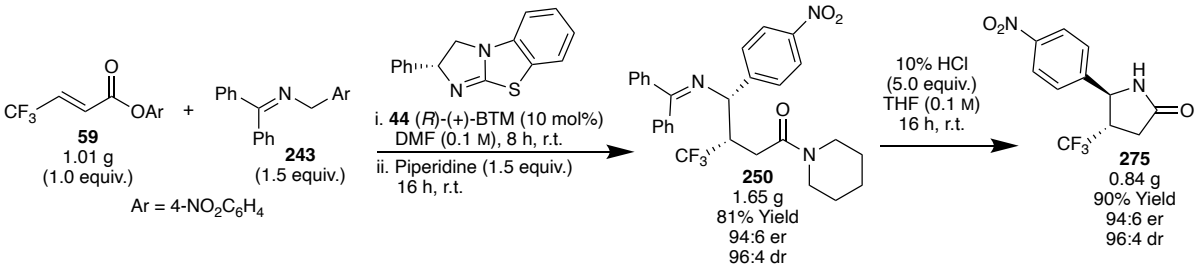
With these results, it was thought that direct synthesis of the 2-pyrrolidinone product could be achieved after the Michael addition step *via in situ* acid-catalysed hydrolysis, without the addition of an amine, to form the amide product in the same reaction vessel. To prove this hypothesis, the reaction was carried out and was observed to obtain the 2-pyrrolidinone product **275** in excellent yield and selectivity (80% yield, 94:6 er, 96:4 dr), which was expected

to be similar to the observed results of product **256** (80% yield, 95:5 er, 96:4 dr). This result highlight the efficiency of the developed method in directly synthesising 2-pyrrolidinone compounds, which are very prevalent in pharmaceutically important compounds.[111] (Scheme 57).



Scheme 57. Direct synthesis of the 2-pyrrolidinone product **275**.

Moreover, a gram-scale synthesis of product **250** was also carried out to assess the applicability of the developed Michael addition reaction on larger scale. Using 1g of acceptor **59** gave **250** in excellent yield and selectivity (1.65 g, 81% yield, 94:6 er, 96:4 dr). Subsequent hydrolysis of the gram-scale product **250** resulted in 2-pyrrolidinone **276** with excellent yield and stereoselectivity (90% yield, ~840 mg, 94:6 er, 96:4 dr) (Scheme 58).



Scheme 58. Gram-scale synthesis of product **250** and subsequent acid-catalysed hydrolysis to form 2-pyrrolidinone **275** in excellent yields and stereoselectivity.

3.5 PROPOSED REACTION MECHANISM

As highlighted in the previous chapter (Chapter 2, section 2.5), most isothiourea-catalysed conjugate addition reactions follow a similar reaction pathway. In the optimized Michael addition of Schiff bases to α,β-unsaturated ester substrates, the reaction is initiated by the formation of the α,β-unsaturated acyl ammonium intermediate **202** *via* *N*-acylation of isothiourea (*R*)-(+)-BTM **44** at the C(1) position of the α,β-unsaturated ester **59**. Intermediate **202** is then intercepted by the α-imino carbanion **241a**, generated by deprotonation of **241**, *via* nucleophilic addition at the C(3)-position of intermediate **202** to form ammonium enolate intermediate **281.** Protonation of the ammonium enolate intermediate **281** liberates 4-nitrophenoxide which then promotes catalyst turnover and release the Michael addition product **245** (Figure 29).

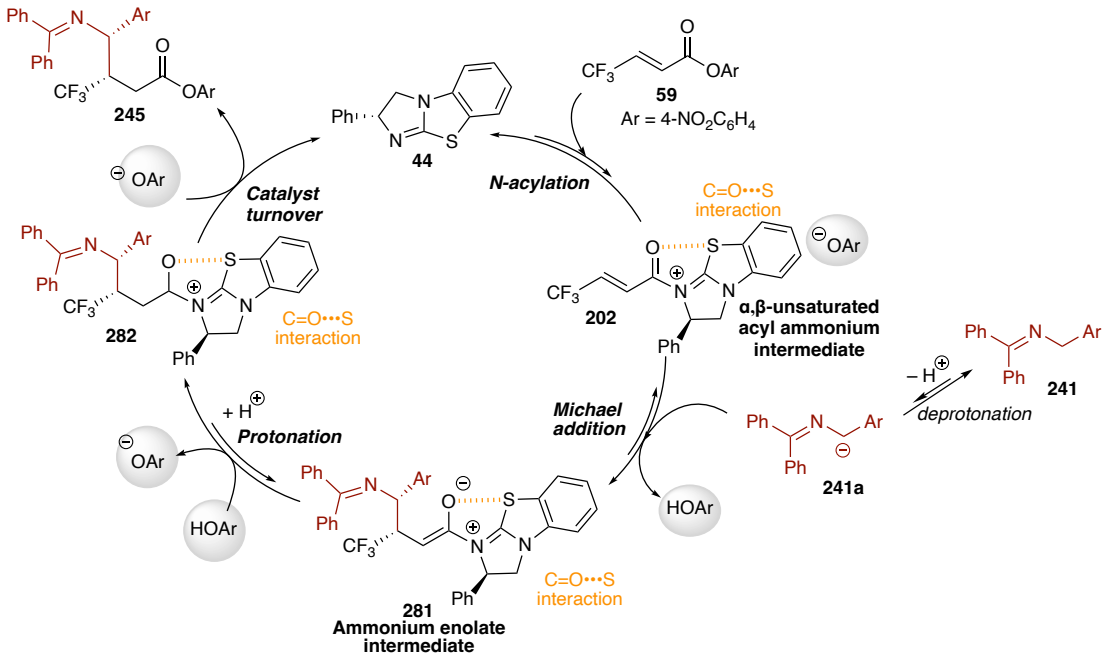


Figure 29. Proposed reaction mechanism for the isothiourea-catalysed Michael addition of Schiff base pronucleophiles **241** to α,β-unsaturated ester **59.**

3.6 STEREOSELECTIVITY AND ABSOLUTE CONFIGURATION

Good to excellent selectivity of the products was observed for the Michael addition reaction of Schiff bases to α,β-unsaturated ester substrates using chiral isothiourea as an organocatalyst. Upon the formation of the α,β-unsaturated acyl ammonium intermediate **202**, (*R*)-(+)-BTM **44** catalyst first imposes a stabilising effect and a conformational lock on the intermediate in the form of an intramolecular 1,5 C=O•••S interaction and the stereodirecting phenyl group as previously highlighted in chapter 2, section 2.5. Moreover, the configuration of the product can be predicted since a known isomer of the catalyst was used ((*R*)-(+)-BTM **44**) for the Michael addition reaction. The configuration at the C(3) position of the Michael addition product can be predicted as (*S*)-configuration after Michael addition since the favoured approach of the nucleophile to intermediate **202** is from the *re*-face (Figure 30a).

On the other hand, the diastereoselectivity for the observed products is highly dependent on the orientation of the nucleophile **241a** during the addition step. Possible orientations (Models I – VI) of the nucleophile **241a** was proposed during the C–C bond with the assumption that during the C-C bond forming step a staggered conformation is adopted within intermediate **202** (Figures 30b). Based on proposed orientations, it is speculated that Model I shows the most favourable orientation of **241a** upon Michael addition to the intermediate **202.** This is suggested to be favoured as it features a (i) potential stabilising interaction between the cationic isothiouronium moiety of **202** and the π-system of either the imine moiety or the 4-nitrophenyl moiety of **241a** (π•••cation interaction) as shown in the Newman projections of

Model I and the (ii) correct (3*S*,4*S*)-configuration of the Michael addition product supported by the single X-ray diffraction crystallography of compound **250** shown in Figure 24. The alternative models either give the incorrect configuration (Model IV to VI) or nonfavourable interaction (Models II) between electron deficient 4-nitrophenyl group. Figure 30c shows a clear interaction of **241a** and intermediate **202** highlighting the proposed π•••cation interaction of the speculated model Model I. Further computational analysis is highly recommended to validate the proposed model and interactions of the transition state.

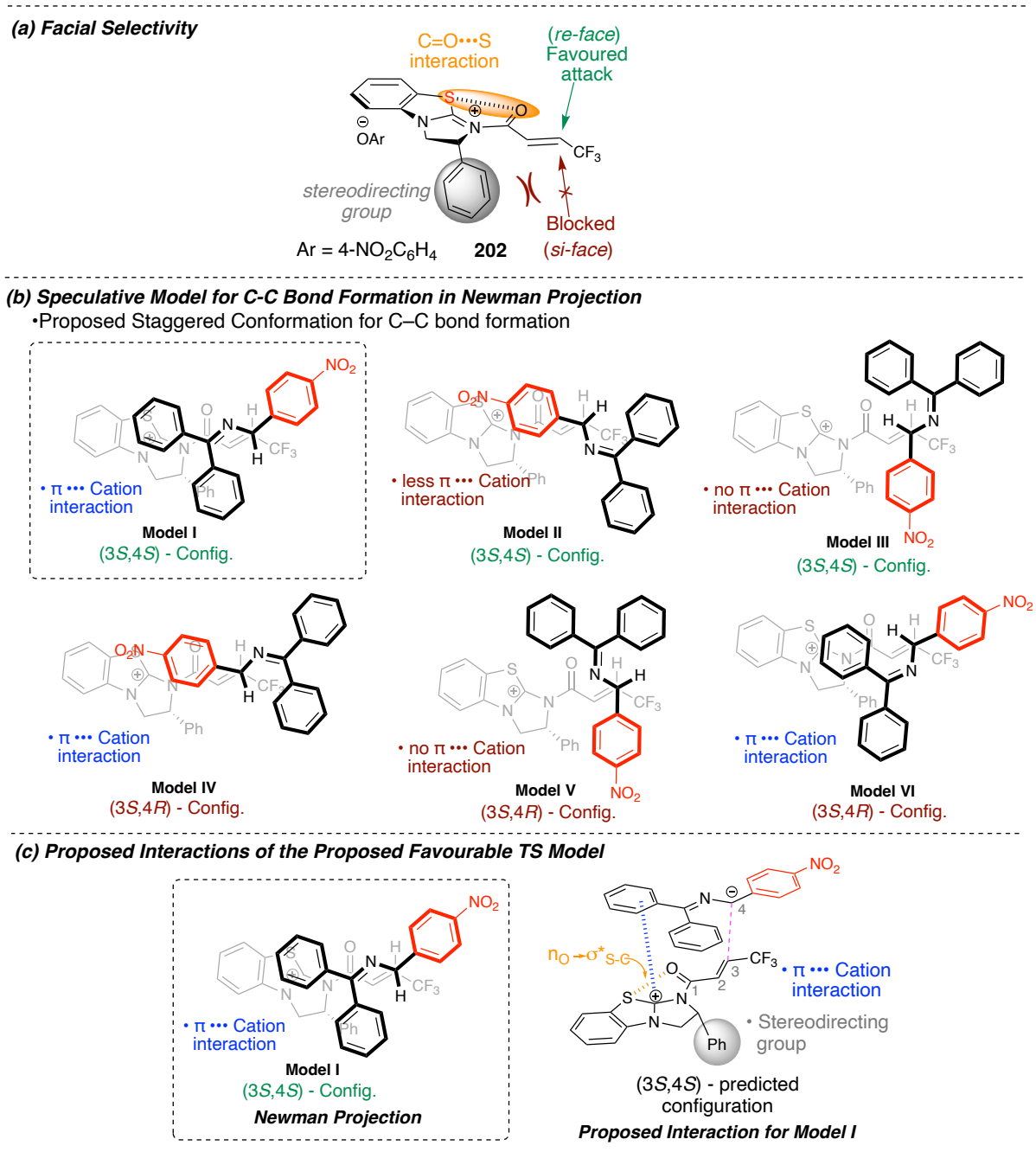
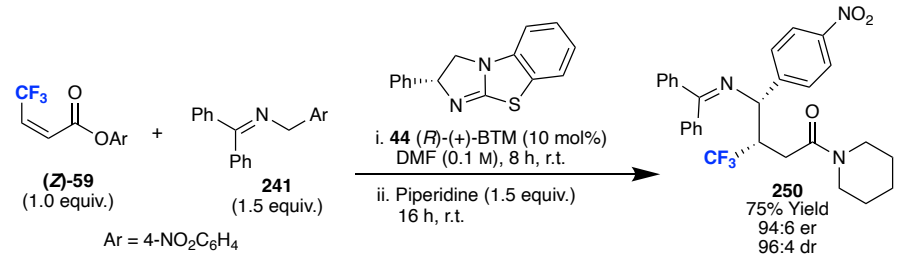


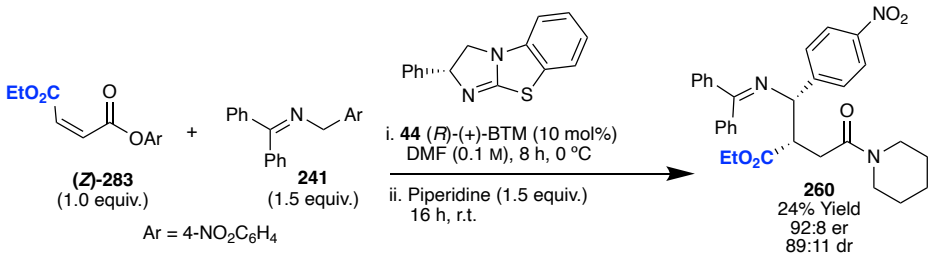
Figure 30. (a) Facial selectivity imposed by the chiral isothiourea-bound organocatalyst and (b) Speculative model for C–C bond formation and (c) proposed interactions of nucleophile **241a** with intermediate **202**.

3.7 EFFECT OF OLEFIN CONFIGURATION

The effect of the α,β-unsaturated ester configuration during the Michael addition was also monitored. Substrate **(*Z*)-59** showed the formation of the corresponding Michael addition products **250** in excellent yield and high selectivity (75% yield, 94:6 er, 96:4 dr) as shown in Scheme 59 with similar results when using substrate **(*E*)-59** (Figure 28). On the other hand, **(*Z*)-283** only elicited 24% yield of the Michael addition product **260**, a much lower yield compared to the yield of product **260** when using substrate **(*E*)-283** shown in Figure 27 at 75% yield while most of the unreacted ester is the **(*E*)-283** after the reaction. Despite the low yield, excellent selectivity (92:8 er, 89:11) for the product **260** were still observed (Scheme 60) which is similar to the selectivity of product **260** in Figure 28.



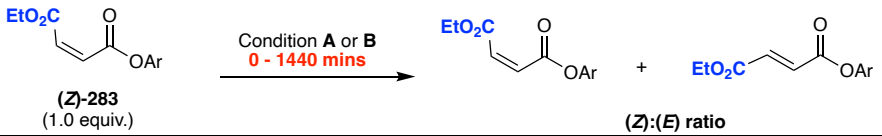
Scheme 59. Michael addition of **241** to **(*Z*)-59** to form **250**.



Scheme 60. Michael addition of **241** to **(*Z*)-283** to form **260**.

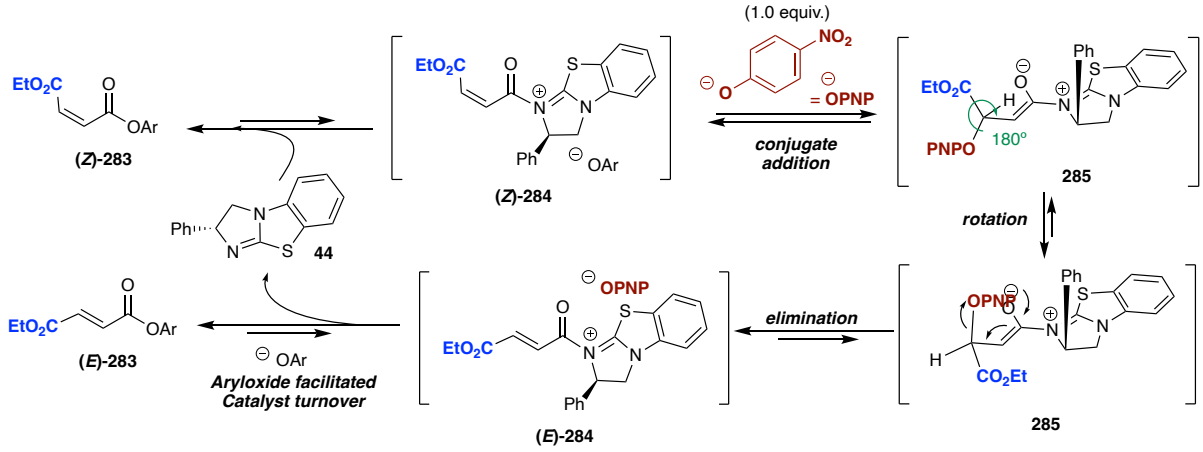
With the observed lower yield of **260** when using **(*Z*)-283** (Scheme 58), control experiments were then performed to observe the isomerisation of **(*Z*)-283** to **(*E*)-283** under various conditions (Table 24). Results in Table 24 shows that isomerisation of **(*Z*)-283** to the thermodynamically more stable **(*E*)-283** isomer was observed in the presence of the **44** (*R*)-(+)-BTM catalyst in both conditions (condition **A** and **B**). Rapid isomerisation was observed in the presence of tetrabutylammonium 4-nitrophenolate (NBu_4OPNP), where conversion to the (*E*) isomer was completed within 90 mins which was previously probed by the Smith group[112] highlighting that the isomerisation proceeds through a reversible conjugate addition of a nucleophile (4-nitrophenolate), rotation, and elimination to obtain the more stable (*E*)-configuration of **283** (Scheme 61).

Table 24. Control Experiments for the Isomerisation of **(*Z*)-283** to **(*E*)-283**.



Time (mins)	(*Z*):(*E*) ratio under Condition A	(*Z*):(*E*) ratio under Condition B
0	100:0	100:0
30	85:15	25:75
90	49:51	0:100
180	42:58	0:100
240	35:65	0:100
300	27:73	0:100
360	23:77	0:100
480	15:85	0:100
1440	0:100	0:100

Condition **A**: **44** (*R*)-(+)BTM (10 mol%), DMF (0.1 M), 0 ºC; Condition **B**: **44** (*R*)-(+)-BTM (10 mol%) NBu_4OPNP (1.0 equiv.) DMF (0.1 M), 0 ºC; Monitored *via* ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.



Scheme 61. Proposed Mechanism for the isomerisation of **(*Z*)-283** to **(*E*)-283** by the Smith group.[112]

Considering the results in Table 24, the potential for isomerisation of the (*Z*)-olefin to the thermodynamically more stable (*E*)-olefin was recognised; indeed for maleates has been well established and highlighted by various studies such as reactions with bromine radicals,[113,114] the use of zwitterionic catalyst,[115] amine catalysts,[116,117] ionic liquids,[118] and cinchona alkaloid-derived organocatalysts,[119] with most mechanisms involving a reversible nucleophilic addition, followed by bond rotation and elimination.

However, despite the significant isomerisation of **(*Z*)-283** to **(*E*)-283**, lower yields (24%) for the Michael addition product **260** were still observed whilst maintaining excellent enantioselectivity (92:8 er) and diastereoselectivity (89:11 dr). Thus, monitoring of the reaction of **243** with **(*Z*)-283** before and after the addition of piperidine was carried out *via* ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

It was observed that after 8 hours, prior to the addition of piperidine, the formation of the Michael addition product was only at 24% and most of the unreacted **283** Michael acceptor (75%) was the (*Z*)-isomer. Addition of piperidine in the second step after 8 hours showed the formation of the final product **260** at 24% yield, which is consistent with the yield observed before the addition of piperidine, while most of the **(*Z*)-283** isomer was fully converted to the **(*E*)-283** isomer (75%) based on the crude ^{1}H NMR analysis of the mixture. The isolated product **260** showed excellent enantioselectivity (92:8 er) and diastereoselectivity (89:11 dr) under the conditions shown in Scheme 57 which is similar to the observed selectivity of product **260** highlighted in Figure 28 that mainly used the **(*E*)-283** isomer. Therefore, the observed results may highly indicate the following: (i) the isomerisation of **(*Z*)-283** is much slower than expected in the presence of imine **243** and (*R*)-(+)-BTM catalyst **44** with DMF as solvent, (ii) the Michael addition of imine **243** only proceeds with the **(*E*)-283** isomer, and (iii) the addition of a secondary amine (e.g. piperidine) promotes rapid isomerisation of the **(*Z*)-283** to the **(*E*)-283** isomer.

3.7 CONCLUSION

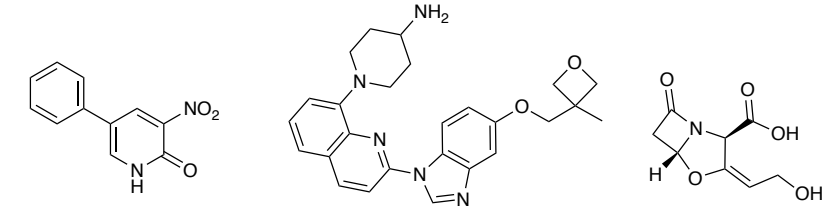
In summary, a successful protocol for the enantioselective Michael addition of Schiff bases to α,β-unsaturated ester substrate was realised using chiral isothiourea as organocatalysts. The optimised conditions for the Michael addition reaction protocol showed moderate to excellent yield (24% - 81% yield) and good to excellent selectivity (<97:3 er, <96:4 dr) for various γ-imino amide and ester products. The nucleophilicity of the Schiff base is highly dependent on the acidity of the methylene proton, which limits the scope of the Schiff base nucleophiles, while strong electron-withdrawing groups at the C(3) position of the α,β-unsaturated ester substrate is necessary for the Michael addition to proceed. The developed method also provided an excellent route for the synthesis of 4,5-disubstituted-2-pyrrolidinone compounds in excellent yield and selectivity (up to 90% yield, <96:4 er, <96:4 dr) by acid-catalysed hydrolysis of the γ-imino amide products or via a one-pot synthesis of the 2-pyrrolidinone compound applying hydrolysis conditions after the Michael addition reaction. Moreover, the reaction showed good utility, most notably in the gram-scale synthesis of the γ-imino amide product or the 2-pyrrolidinone products which were obtained in high yield and selectivity (81% yield, 94:6 er, 96:4 dr).

CHAPTER 4: ISOTHIOUREA-CATALYZED ENANTIO- AND DIASTEREOSELECTIVE SYNTHESIS OF CHROMENO-PYRROLIDINE COMPOUNDS

4.1 PROJECT OVERVIEW

4.1.1 Heterocyclic Compounds: Pyrrolidine Heterocycles

The importance of heterocyclic compounds in the pharmaceutical industry and their synthesis has become one of the main goals of synthetic chemists and has been considered since the 1800s.[120–124] Molecular frameworks, especially heterocyclic compounds, are prevalent constituents of many biologically active compounds and are thus classified as pharmacophores.[125] Examples of these heterocyclic pharmacophores (Figure 31) are Amrinone **286**, a pyridine phosphodiesterase 3 inhibitor and a cardiotonic drug used to decrease the chances of patients with congestive heart failure,[126] Crenolanib **286** with a benzimidazole pharmacophore that is under clinical trials for different cancer treatments including acute myeloid leukemia (AML),[127,128] and the enantiopure heterocyclic compound **287** (Clavulanic acid) as a ß-lactamase inhibitor.[129] Thus, the facile synthesis of these highly soughtafter heterocyclic pharmacophores is of high importance.



286
Amrinone
(Phosphodiesterase 3 Inhibitor)

287
Crenolanib
(Potential Anticancer)

288
Clavulanic Acid
(ß-Lactamase Inhibitor)

Figure 31. Examples of Heterocyclic Pharmacophores.

One particularly important heterocyclic pharmacophore is the pyrrolidine-skeleton. Pyrrolidine is a nitrogen-containing non-aromatic five-membered cyclic compound (**289**) and has been ranked as top 5 of the most frequent nitrogen heterocycles in U.S. FDA approved drugs.[46] Moreover, pyrrolidine-based compounds and its derivatives have shown to be widely present in natural products (mostly in alkaloid natural products) and exhibits various biological activities such as Scalusamide A (**290**) showing antifungal and antibacterial activities,[130] Ficushispimines B (**291**) for anti-hyperglycemic effect,[131] and the cytotoxicity of Bgugaine (**292**) for possible anticancer activity (Figure 32).[132] Additionally, chiral pyrrolidine derivatives have also been extensively studied as an effective organocatalyst in various catalytic and enantioselective reactions.[133] Thus, the development of different synthetic routes for building

these pyrrolidine scaffolds has become an important goal for synthetic chemists around the world.

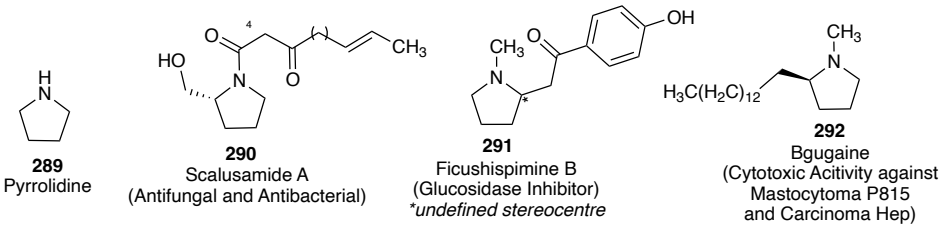


Figure 32. Pyrrolidine **289** and its naturally occurring bioactive derivatives **290**, **291**, and **292**.

4.1.2 1,3-Dipolar Cycloaddition Reactions: Huisgen Reaction

One classical method for the synthesis of five membered heterocycles is through a 1,3-dipolar cycloaddition reaction, coined by Rolf Huisgen in the 1960s,[134] of a zwitterionic "1,3-dipole" structure with a 4π-electron system with three conjugated p-orbitals on three atoms[135,136] and a multiple bond system (double bond or a triple bond) acting as a 2π-electron system, analogous to a dienophile, known as "dipolarophile" in a symmetry-allowed [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] concerted cyclisation reaction as shown in Figure 33.[135–137] The first 1,3-dipolar cycloaddition reaction was reported by Buchner in 1888[138] involving the combination of methyl diazoacetate **293** with dimethyl fumarate **294** to form five-membered heterocyclic-diazo compound **295** (Scheme 62). From there on, different cycloaddition reactions were studied and explored from 1890 - 1960 by different researchers such as E. Beckmann in 1890 for the cycloaddition of nitrones to phenyl isocyanate,[139] A. Michael in 1893 for the cycloaddition of phenyl azide to acetylene dicarboxylic acid esters,[140] H. von Pechmann in 1894 for reporting the preparation of diazomethane,[141] and A. Werner in 1894 for the synthesis of benzonitrile oxide.[142]

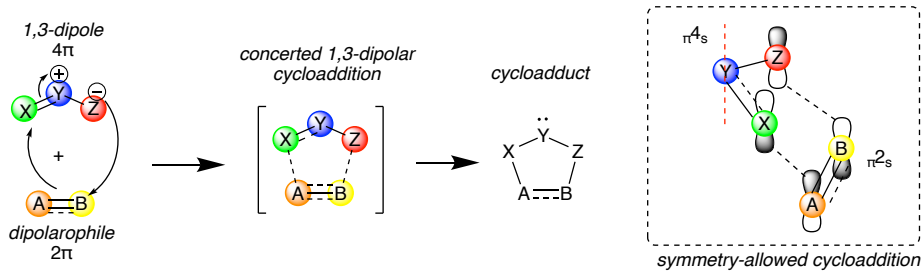
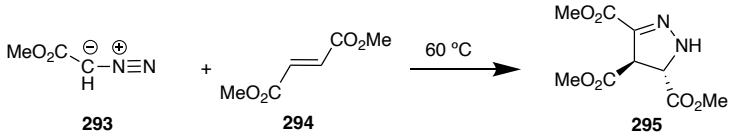


Figure 33. 1,3-dipolar cycloaddition reaction for building five-membered ring system.



Scheme 62. First reported 1,3-dipolar cycloaddition reaction of methyl diazoacetate **293** and dimethyl fumarate **294** by Buchner in 1888.[138]

Rolf Huisgen and his co-workers presented two classification of 1,3-dipoles consisting of carbon, nitrogen, and oxygen centres: (i) the allyl-type 1,3-dipoles and the (ii) propargyl-allenyl-type 1,3-dipoles (Figure 34) which are useful reactive intermediates for the construction various of five-membered heterocycles. One of the highly sought-after routes for the synthesis of five membered heterocycles such as pyrrolidines involves the access to azomethine ylide intermediates that can effectively undergo a 1,3-dipolar cyclisation with an electrophilic alkene. This route of forming pyrrolidine-based heterocycle is the focus of this project.

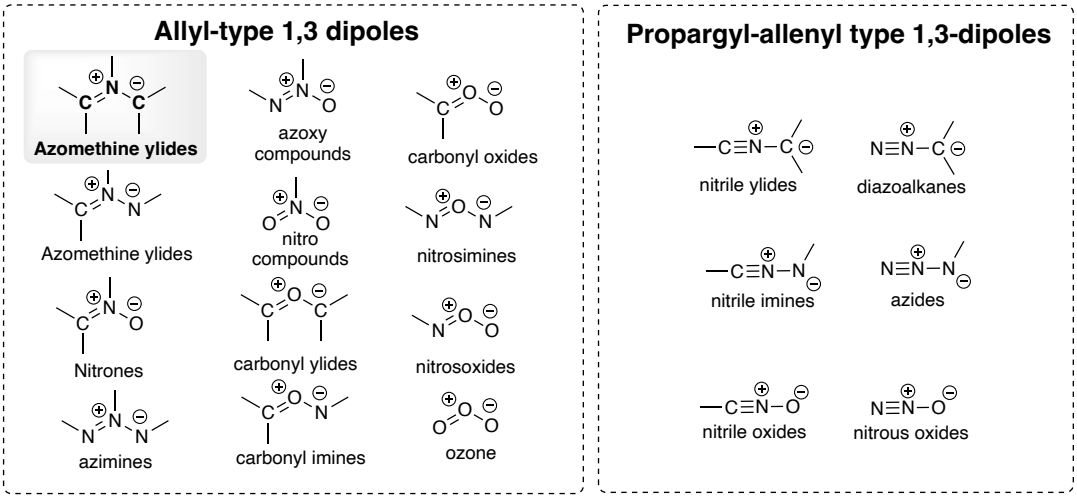


Figure 34. Typical classification of 1,3-dipoles.

4.1.3 Azomethine Ylides: Synthesis of Pyrrolidine Heterocycles

Azomethine ylide, a highly reactive 1,3-dipole ylide intermediate, is a four π-electron system in a three-atom "C-N-C" unit represented by four resonance structures of the zwitterionic form (Figure 35a). Azomethine ylides readily react with electron-poor alkenes (dipolarophiles) *via* a HOMO-LUMO interaction of the electron-rich ylide and the π system of the alkene that undergoes a concerted[143,144] 1,3-dipolar cycloaddition reaction through a thermally allowed suprafacial process ($_{\pi}4_s$ + $_{\pi}2_s$) to form five-membered highly-substituted pyrrolidine ring (Figure 35b).

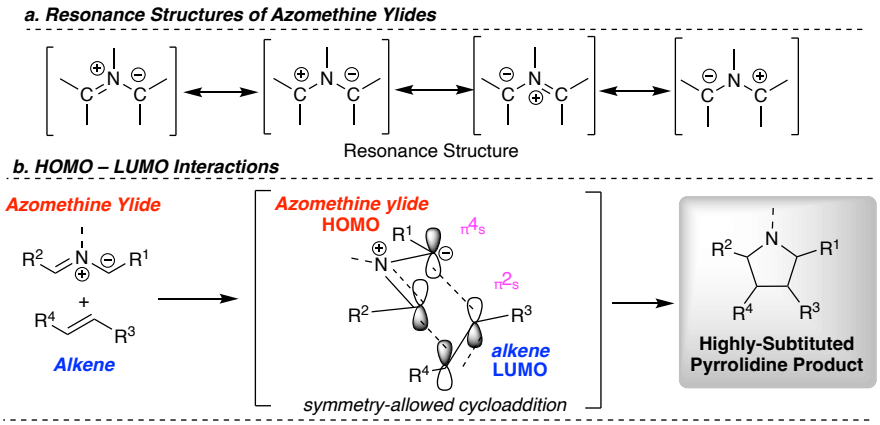
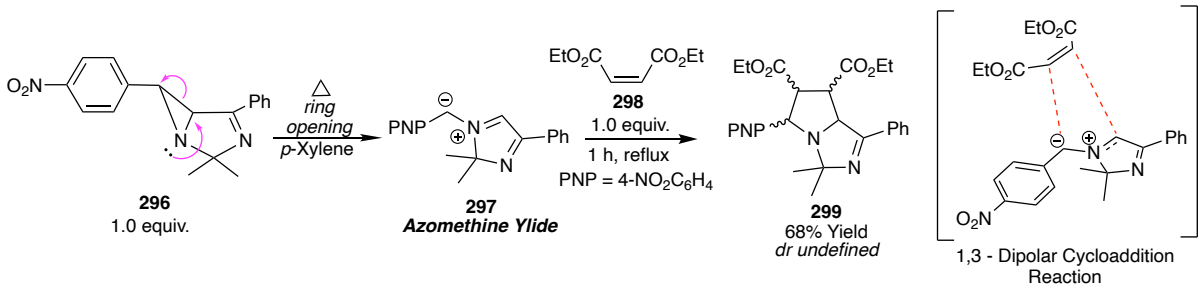


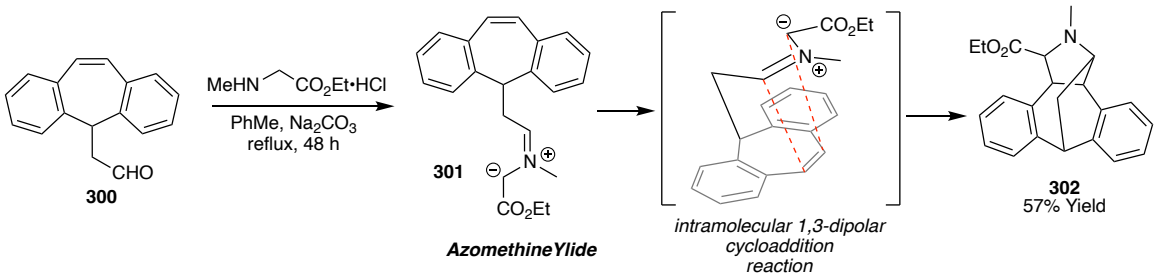
Figure 35. (a) Azomethine ylide intermediate resonance structure and (b) Interaction of the azomethine ylide HOMO and the alkene LUMO forming the highly substituted pyrrolidine product *via* a concerted [3+2] cycloaddition reaction.

One of the most commonly used sources of azomethine ylide intermediates are aziridines. In 1967 Bower and co-workers showed the first [3+2] cycloaddition of an azomethine ylide intermediate from an aziridine compound through the reaction of azomethine ylide **297**, from the thermal heterolytic bond cleavage of 1,3-diazabicyclo[3.1.0]hex-3-ene **296**, with diethyl fumarate **298** to give a 5-membered N-heteroxyclic compound **299** at 68% yield (Scheme 63).[145] This was then followed by various studies utilizing aziridine compounds as azomethine ylide sources as highlighted in a review by Khlebnikov and Novikov in 2012.[146]

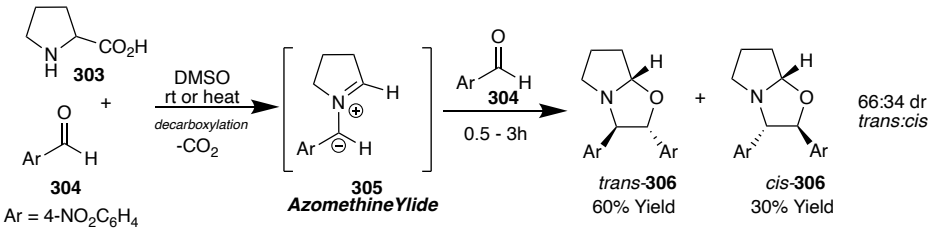


Scheme 63. First 1,3-dipolar cycloaddition reaction of azomethine ylide intermediate **297,** generated from aziridine **296**, with a highly electrophilic alkene **298**.

Imines, on the other hand, are also a widely known source of azomethine ylides as demonstrated by Confalone and co-workers in 1983 through the reaction of *N*-methylglycine ester with various substituted aldehydes **300** to form an *in situ* imine, and in the presence of a base formed the highly reactive azomethine ylide **301** which then undergoes an intramolecular [3+2] cycloaddition reaction to form the carbon-bridged dibenzocycloheptene **302** in moderate yield of 57% (Scheme 64).[147–149] This work was followed by Orsini and co-workers in 1988, showing the reaction of pyrrolidine **303** and various aromatic aldehydes **304** to form the imine, followed by decarboxylation to form the reactive azomethine ylide intermediate **305** and undergoes a cycloaddition reaction with another molecule of aryl aldehyde to form a mixture of **306** (66:34 ratio *trans:cis*) (Scheme 65).[150] However, most of these early reactions are known to be non-stereoselective and always gave mixtures of pyrrolidine products. Thus, a stereoselective route is of high importance for 1,3-dipolar cycloaddition reactions.



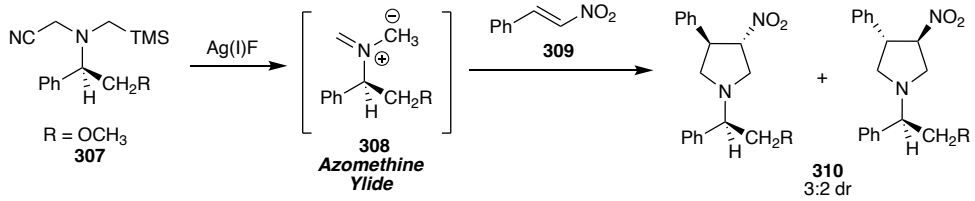
Scheme 64. Synthesis of stable azomethine ylide **301** from aldehyde and *N*-methylglycine ester precursors.



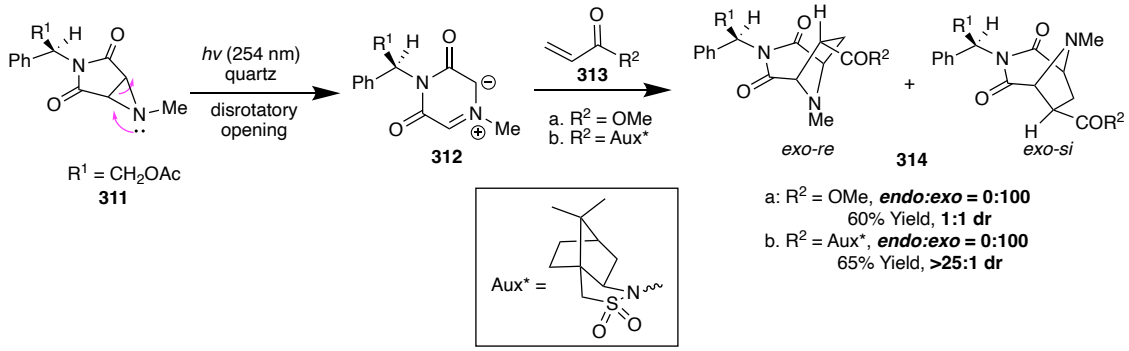
Scheme 65. Cycloaddition reaction of azomethine ylide **305** from pyrrolidine and aryl aldehyde precursors.

4.1.4 Stereoselective 1,3-Dipolar Cycloadditions Using Azomethine Ylides: Synthesis of Pyrrolidines

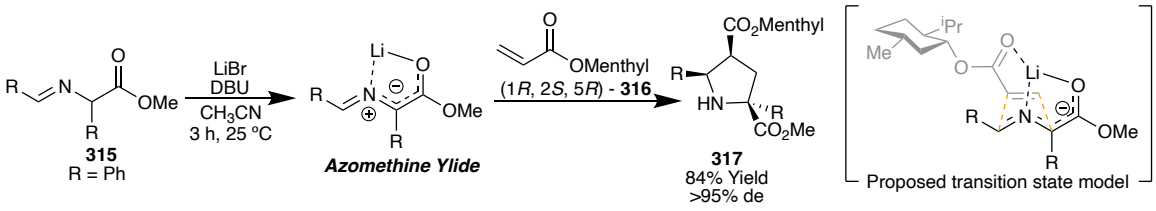
With the idea of developing a stereoselective 1,3-dipolar cycloaddition reaction using azomethine ylides, Padwa and co-workers in 1985 reported the first diastereoselective 1,3-dipolar cycloaddition reaction using a chiral azomethine ylide **308,** generated by the reaction of precursor **307** and Ag(I)F, and an achiral alkene dipolarophile (nitrostyrene) **309** to form the pyrrolidine product **310** (Scheme 66).[151] The concept of chiral azomethine ylides was also explored by Garner and co-workers in 1991 using chiral aziridines **311** as chiral azomethine ylide source to achieve an asymmetric cycloaddition reaction to form the product **314** (Scheme 67).[152] Barr and co-workers, on the other hand, explored α,β-unsaturated esters containing chiral motifs (i.e. menthyl acrylate **316**) to control the stereoselectivity of the reaction *via* a metal-catalysed 1,3-dipolar cycloadditions of imine **315** as the azomethine ylide source (Scheme 68).[153]



Scheme 66. First diastereoselective synthesis of pyrrolidine compound **310**.

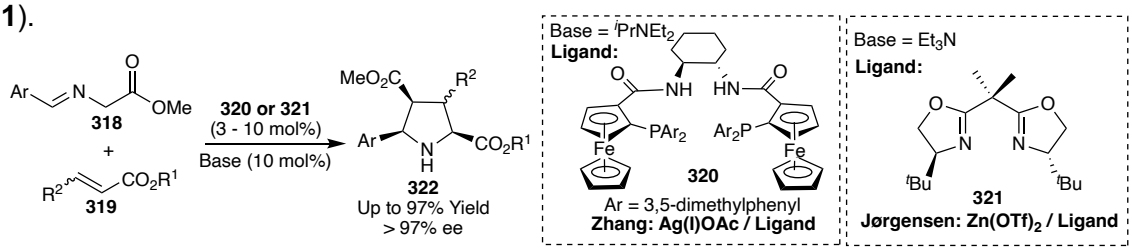


Scheme 67. Chiral aziridines **311** as chiral azomethine ylide source for the asymmetric synthesis of product **314**.



Scheme 68. Stereoselective 1,3-dipolar cycloaddition reaction of chiral dipolarophile **316** to imine **315** for the synthesis of product **317.**

Zhang[154] (chiral Ag-**325** complex) and Jørgensen[95] (chiral Zn-**326** complex) in 2002 independently showed the first catalytic-enantioselective 1,3-dipolar cycloaddition of azomethine ylides from glycine derived Schiff base **318** to different α,β-unsaturated esters **319** giving excellent yields of highly enantioenriched pyrrolidine products **322** in up to 97% yield and with >97% ee (Scheme 69). Their reactions focused on the (i) activation of the imine pronucleophile *via* coordination to the metal complex and (ii) the high enantio- and diastereoselectivity of the pyrrolidine products **322** imposed by the chiral ligands (**320** and **321**).



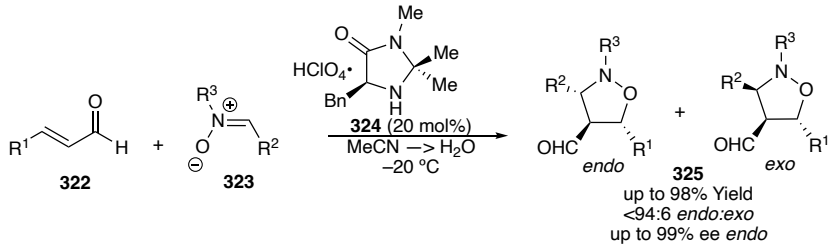
Scheme 69. First reported catalytic-enantioselective 1,3-dipolar cycloaddition independently showcased by Zhang[154] and Jørgensen[95] in 2002.

Following these breakthroughs, a plethora of research has been conducted on the stereoselective 1,3-dipolar cycloaddition of azomethine ylides most notably on imine pronucleophile substrates as highlighted in a review by Najera and Sansano in 2008.[155] However, most of these reaction are metal-catalysed 1,3-dipolar cycloadditions and mostly rely on the (i) activation of the imine pronucleophile *via* metal coordination, (ii) the addition of an external base to effectively form the azomethine ylide intermediate in most of the 1,3-dipolar cycloaddition reactions, and (iii) introduction of chiral ligands to impose enantioselectivity. These factors imply that an improvement in the methodology for 1,3-dipolar cycloadditions is in high demand also including the use of minimal reagents to achieve the same reactivity. One way to alleviate the drawbacks previously mentioned is through asymmetric organocatalysis.

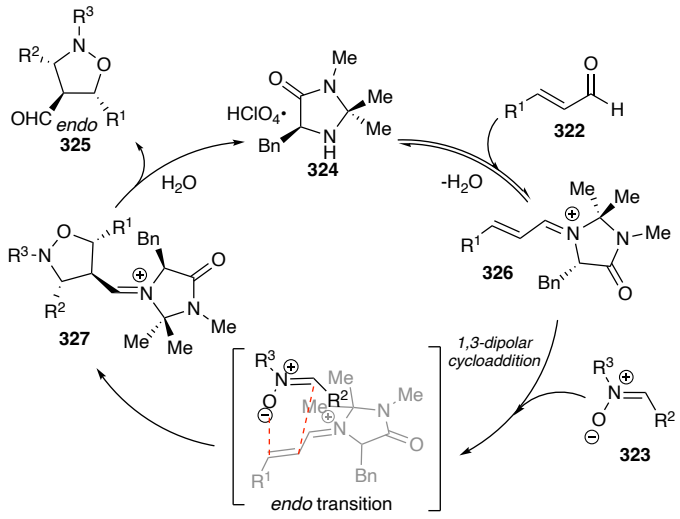
4.1.5 Organocatalysed 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides: Synthesis of Pyrrolidines

One of the most employed modes of catalysis for organocatalytic 1,3-dipolar cycloaddition reactions is through iminium catalysis. This was first showcased by MacMillan's group in

2000[156] through the 1,3-dipolar cycloaddition of crotonaldehyde **322** and nitrones **323** using of imidazolidinone·HCl salt **324** as chiral organocatalyst to give isoxazolidine product **325** in excellent yield, regio- and stereoselectivity (up to 98% yield, up to 94:6 *endo:exo* ratio, and up to 99% ee of *endo* product) shown in Scheme 70. They have showcased that a highly selective reaction can be achieved firstly through the activation of the α,β-unsaturated aldehyde dipolarophile **322** to form the reactive chiral iminium intermediate **326**. This intermediate is then intercepted by the nitrone **323** as a 1,3-dipolar nucleophile to participate in an *endo* 1,3-dipolar cycloaddition to form the heterocyclic core. Hydrolysis of the iminium **327** enables catalyst turnover and the release of isoxazolidine aldehyde **325** in an enantioselective fashion that prefers the *endo* product (Scheme 71).



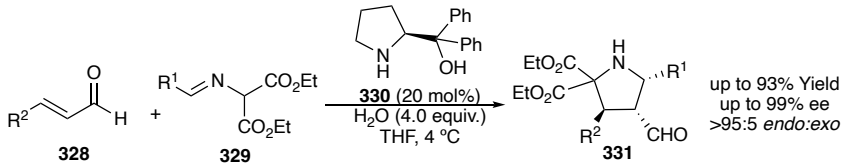
Scheme 70. First enantioselective organocatalytic 1,3-diplar cycloaddition reaction by MacMillan's group.[156]



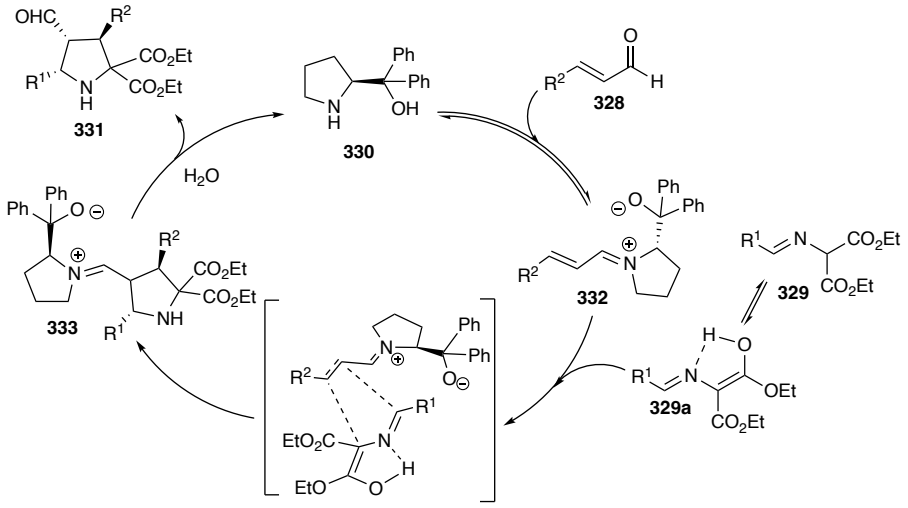
Scheme 71. Proposed reaction mechanism for the organocatalytic 1,3-dipolar cycloaddition of crotonaldehyde **322** and nitrone **323** *via* iminium catalysis.

Inspired by the work of MacMillan, together with the idea of incorporating of azomethine ylides, Vicario and co-workers in 2007 first reported the organocatalysed enantioselective 1,3-dipolar cycloaddition of azomethine ylides[157] using crotonaldehyde **328** as the dipolarophile and imine **329** as pronucleophile with proline **330** as the catalyst to form pyrrolidine product **331** in good to excellent yield and excellent selectivity (up to 93% yield, up to >99 %ee, and >95:5 *endo/exo* selectivity) (Scheme 72). They have exploited a similar activation of crotonaldehyde **333** shown in scheme 70 *via* formation of the α,β-unsaturated iminium intermediate **332** which

is intercepted by azomethine ylide **329a**, masked as the corresponding enol and stabilised by a N-H hydrogen bonding interaction, then undergoes a 1,3-dipolar cycloaddition reaction followed by hydrolysis to give pyrrolidine product **331** with excellent enantio- and diastereoselectivity (Scheme 73).

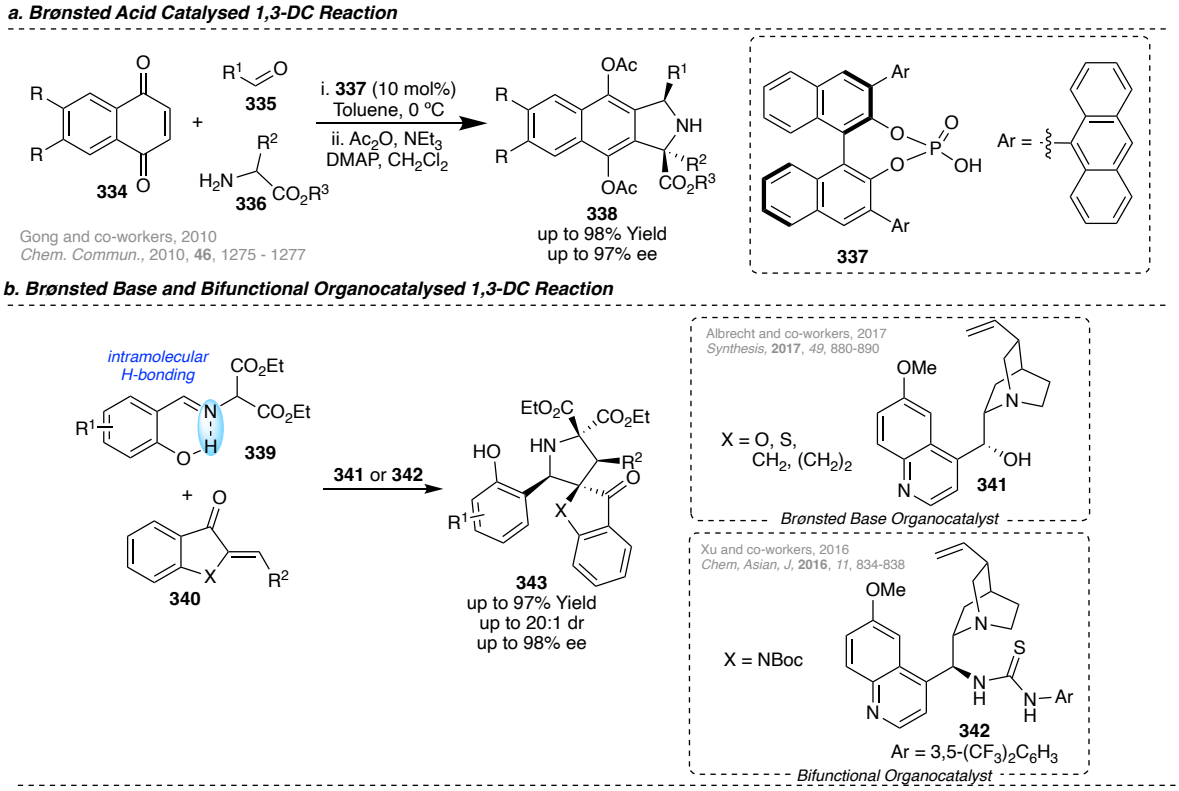


Scheme 72. First enantioselective organocatalytic 1,3-diplar cycloaddition of azomethine ylides by Vicario.[157]



Scheme 73. Proposed reaction mechanism and selectivity for the first enantioselective organocatalytic 1,3-diplar cycloaddition of azomethine ylides *via* iminium catalysis.

After Vicario's work, a plethora of organocatalytic routes for 1,3-dipolar cycloaddition reactions of azomethine ylides were then carried out using different modes of organocatalysis such as (i) the **Brønsted acid catalysis** route as demonstrated by Gong and co-workers[158] utilising chiral phosphoric acid **337** that afforded chiral isoindolines **338** in high yield and enantioselectivity (up to 98% yield, >97% ee) (Scheme 74a) which was then expanded by their group for the synthesis of various biologically important pyrrolidine and spirocyclic oxindole compounds.[76,159–161] The (ii) **Brønsted base catalysis** route was also explored as an organocatalytic route for 1,3-dipolar cycloaddition reactions as demonstrated by Albrecht and co-workers in 2017 utilising quinine **341** as organocatalyst to form the spirocyclic pyrrolidine compounds **343**.[162] Xu and co-workers[163] expanded on this in 2016 utilising a chiral bifunctional Brønsted-base organocatalyst **342** to form a similar spirocyclic pyrrolidine core **343**. Both reactions were assisted by an intramolecular H-bonding exhibited by the imine **339** which favours the formation of the azomethine ylide intermediate (Scheme 74b). This concept was then further employed by Alemán and co-workers in 2018 that uses a similar chiral-bifunctional Brønsted base organocatalyst to access the 1,3-dipolar cycloaddition reaction of imines and nitroolefins.[110]

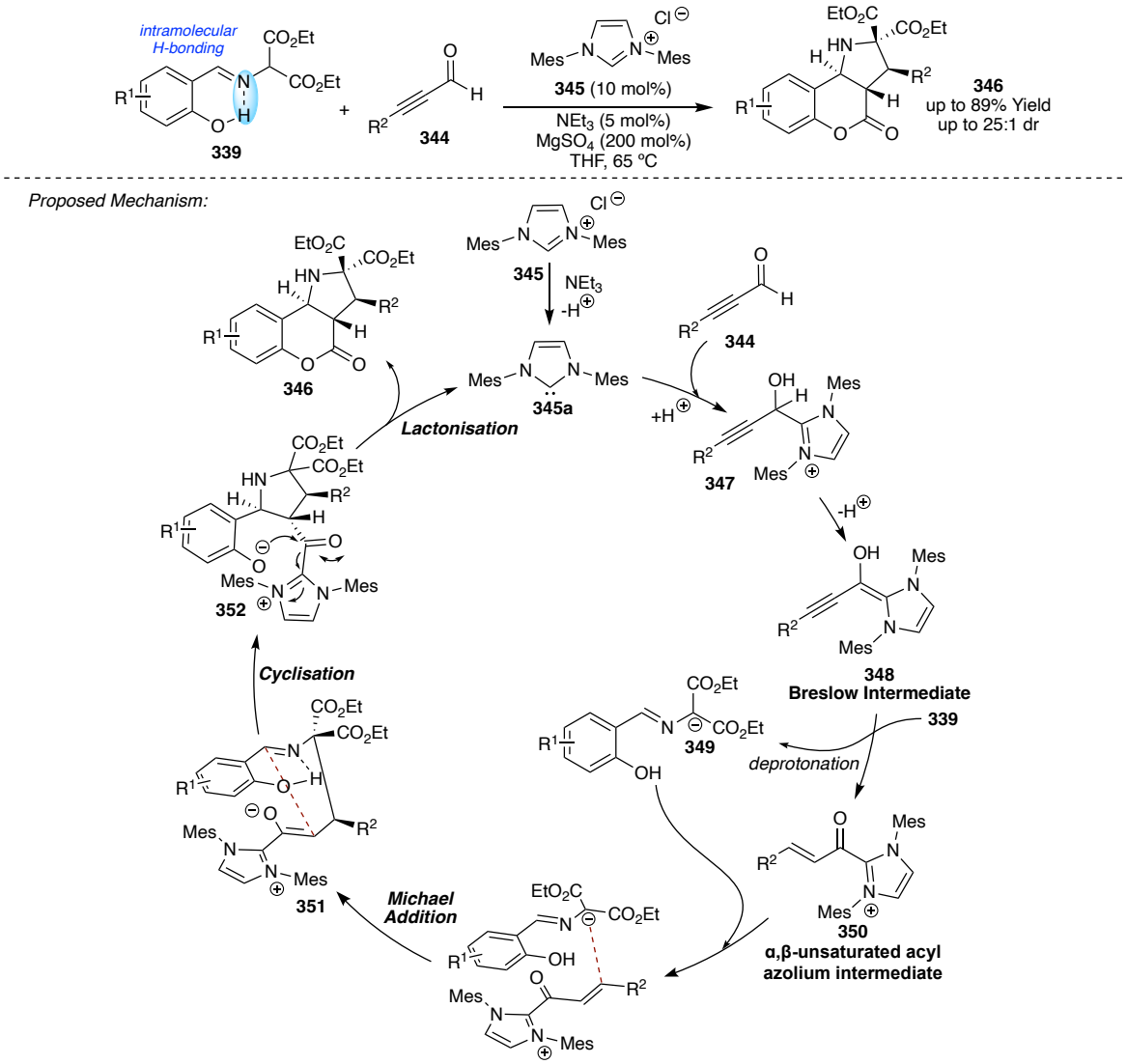


Scheme 74. Brønsted acid and Brønsted base catalysed 1,3-dipolar cycloaddition reactions of azomethine ylides inspired by Vicario and co-workers.

4.1.6 Domino Reactions of Azomethine Ylides: Synthesis of Pyrrolidines

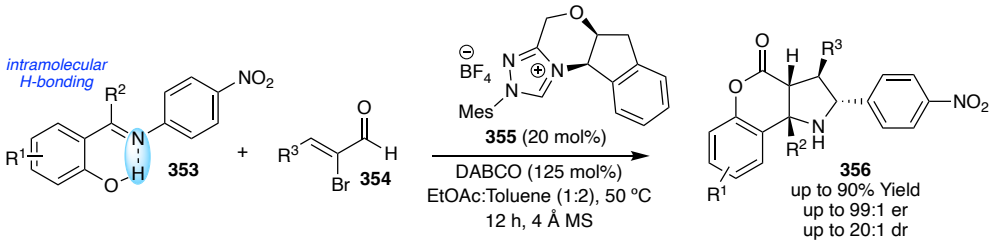
Aside from a concerted 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient olefins to access various pyrrolidine compounds in high enantioselectivity and diastereoselectivity, a domino reaction route can also be envisaged to prepare these important structural motifs. Domino reactions, also known as cascade reactions, is defined as a chemical process that is comprised of two or more consecutive reactions where each reaction only occurs due to the functional group formed in the previous step[164] and this concept can be utilized to access these pyrrolidine compounds. This route was showcased by Wang and co-workers in 2015 to access a range of chromeno-pyrrolidine compounds. The reaction proceeds through activation of alkynyl aldehydes **344** which subsequently form a reactive α,β-unsaturated acyl azolium intermediate using nucleophilic heterocyclic carbenes (NHC) **345** as catalyst, and the intramolecular H-bonding activated Schiff bases **339** as substrates (Scheme 74).[165] Their group proposed a stepwise mechanism for the formation of the pyrrolidine ring which primarily involves the formation of the Breslow intermediate **347** using the *in-situ*-generated NHC catalyst **345a** in the presence of a base (e.g. NEt_3), deprotonation of imine **339** to form **349** and generation of the reactive α,β-unsaturated acyl azolium intermediate **350.** This was then followed by a Michael addition and a diastereoselective cyclisation reaction to form the pyrrolidine core **352**, and subsequent lactonisation to release the active NHC catalyst

and subsequent formation of the chromeno-pyrrolidine product **346** in a highly diastereoselective fashion (up to 25:1 dr) (Scheme 74).



Scheme 75. Synthesis of pyrrolidine core via Michael addition, cyclisation, and lactonisation domino reaction.

This concept was then further explored by Jin and co-workers in 2020 for the formation of chromeno-pyrrolidine compounds **361** in an enantioselective and diastereoselective fashion using imine **358**, α,β-unsaturated-α-bromoaldehyde **359** and chiral NHC catalyst **360** showing excellent yield and selectivity for the pyrrolidine products (up to 90% yield, <99:1 er, <20:1 dr) (Scheme 76).[166] The reaction follows similar reaction mechanism depicted in Scheme 76 where the α,β-unsaturated acyl azolium intermediate is formed by elimination of bromide and then undergoes a stereoselective Michael addition with **353**, followed by a stereospecific cyclisation to form the pyrrolidine core, and lactonisation to generate the desired product and the active NHC catalyst.



Scheme 76. A stereoselective Michael addition, stereospecific cyclisation, and lactonisation domino reaction to form the chromeno-pyrrolidine product **356** in excellent yield and selectivity.

Despite the development of an asymmetric organocatalytic reactions (e.g. 1,3-DC reaction, domino reactions) involving azomethine ylides and electron-deficient alkenes to form various pyrrolidine-derived compounds, these organocatalytic routes either rely on non-covalent mode of catalysis (e.g. H-bonding catalysis, Brønsted acid/base catalysis), while most reactions with a covalent mode of catalysis involves iminium ion catalysis mostly requiring α,β-unsaturated aldehydes as substrate and a pyrrolidine catalyst to form the reactive α,β-unsaturated iminium intermediates. The recently utilised covalent mode of catalysis (e.g. *N*-heterocyclic carbenes (NHCs)), still relies on the reaction of an α,β-unsaturated/alkynyl aldehyde substrate (Scheme 76 and 77) to achieve a similar but highly reactive α,β-unsaturated acyl azolium intermediate **350**. So far, there has been no reports that utilizes and covalently activates α,β-unsaturated esters to react with azomethine ylides for the synthesis of pyrrolidine cores either *via* 1,3-dipolar cycloaddition or domino reactions. Hence, we turned the focus on this premise for this project.

4.2 Aims and Objectives

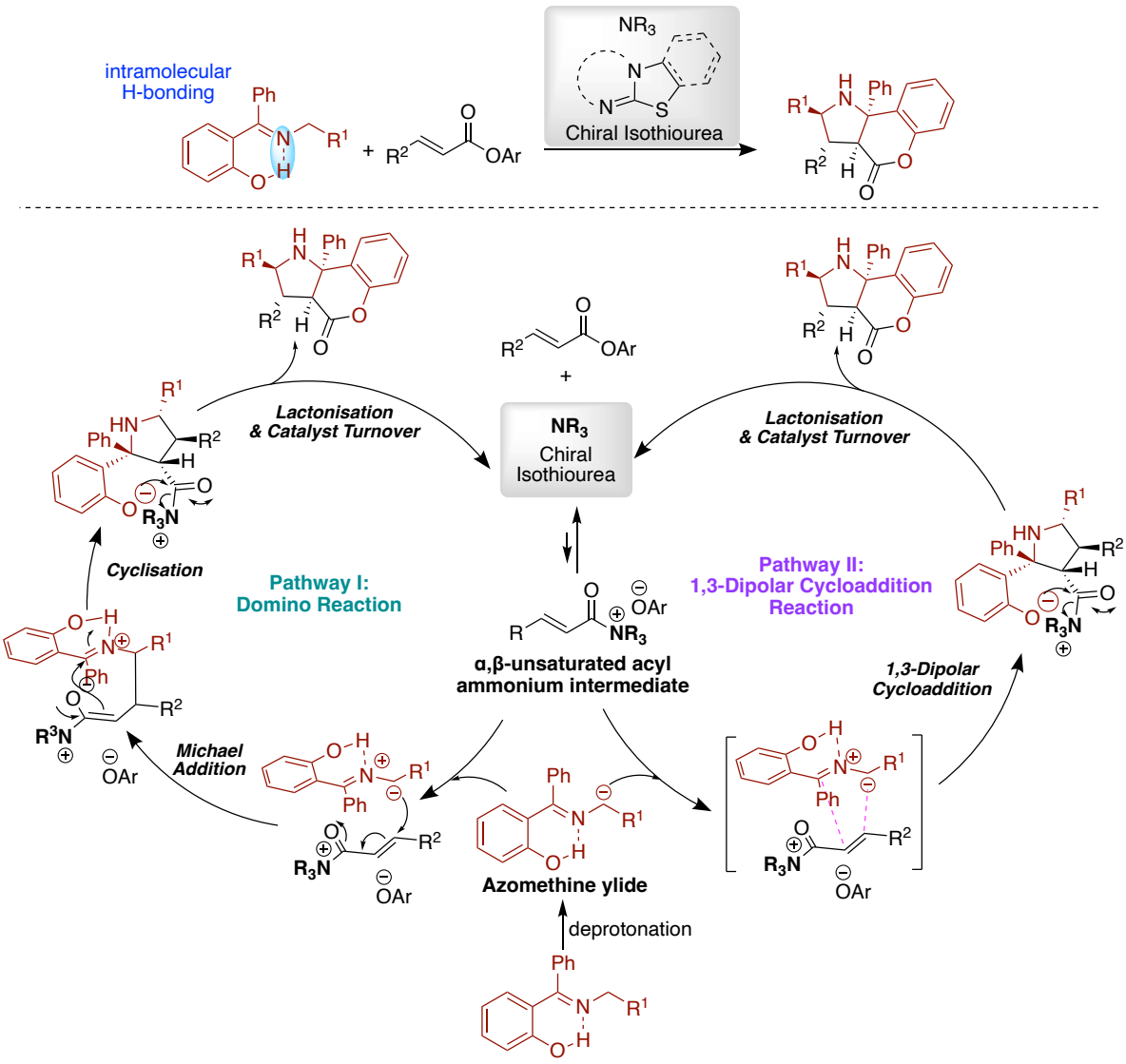
With the idea of utilising the intramolecular H-bonding activation of Schiff bases to favour azomethine ylide formation, together with the activation of α,β-unsaturated esters *via* formation of the reactive α,β-unsaturated acyl ammonium intermediate using a chiral isothiourea organocatalyst, this work will focus on the access of these reactive intermediates to generate pyrrolidine compounds in an enantioselective and diastereoselective fashion.

Project Overview: Isothiourea-Catalysed Enantio- and Diastereoselective Synthesis of Chromeno-Pyrrolidine Compounds.

Two possible reaction mechanisms were proposed for this protocol starting with the activation of the α,β-unsaturated ester forming the α,β-unsaturated acyl ammonium intermediate with the subsequent deprotonation of the Schiff base to form the azomethine ylide. These reactive intermediates can then either undergo (i) **pathway I**: a Michael-addition-cyclisation-lactonisation domino reaction or (ii) **pathway II**: a concerted 1,3-dipolar cycloaddition reaction

favouring the formation of *endo*-pyrrolidine core, followed by a lactonisation reaction to form the desired chromeno-pyrrolidine product. These pathways are hypothesized to be effectively the same in producing the desired chromeno-pyrrolidine product but only differ in concertedness.

This Project: Isothiourea-Catalysed Enantio- and Diasteroselective Synthesis of Chromeno-Pyrrolidine Compounds



4.3 RESULTS AND DISCUSSION

4.3.1 Synthesis of Starting Materials

Initial studies for the isothiourea-catalysed synthesis of the chromeno-pyrrolidine product were conducted by investigating the reaction of Schiff base **357** and the α,β-unsaturated ester **59.** A retrosynthetic analysis for the substrates is depicted in Figure 36.

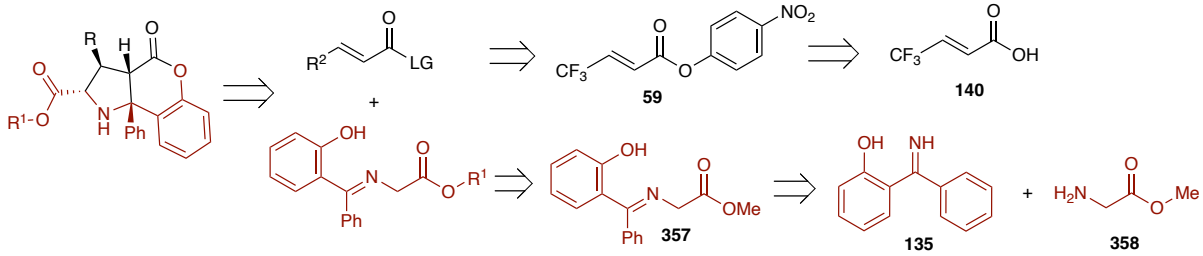
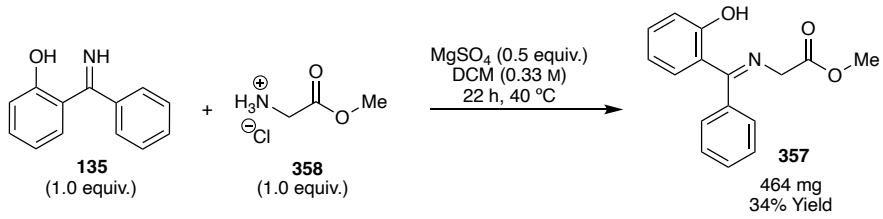


Figure 36. Retrosynthetic analysis of the substrates **59** and **357**.

Synthesis of substrate **59** from the commercially available precursor **140** was previously demonstrated in Scheme 35. Hence, the same protocol was followed. Synthesis of substrate **357** was carried out through the condensation of imine **135** and the HCl salt of **358** precursors with anhydrous magnesium sulfate in dicloromethane at 40 ºC for 22 h. The desired product was obtained as a yellow crystalline solid in 34% yield (Scheme 77).[110]



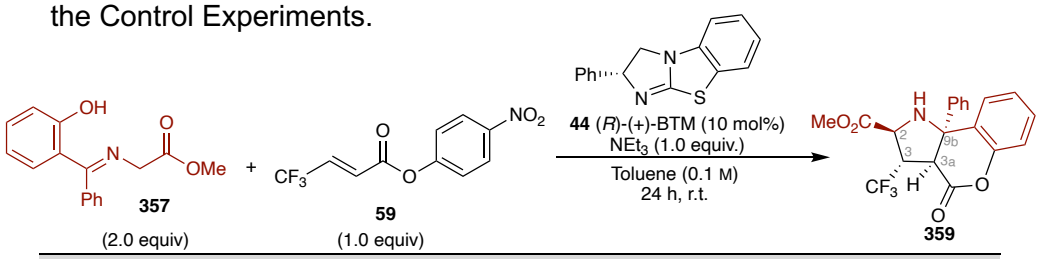
Scheme 77. Synthesis of substrate **357.**

4.3.2 Optimisation of Reaction Conditions

After Synthesizing substrates **59** and **357**, optimisation of the proposed reaction was carried out by variation of reaction variables such as (i) the use of different isothiourea catalysts, (ii) base, (iii) solvent, (iv) reaction temperature, and (v) catalyst loading. To determine the feasibility of the reaction using substrates **59** and **357**, isothiourea catalyst **44**, triethylamine (NEt_3) as base, toluene as solvent, together with control experiments as shown in Table 25. Results in Entry 1, Table 25 showed that, by ^{1}H NMR analysis of the crude reaction mixture, 44% of **59** had converted to chromeno-pyrrolidine product **364** and 55% remained unreacted after 24 h. An excellent diastereomeric ratio (97:3 dr) of **364** was observed but unfortunately, the product **364** was racemic based on HPLC analysis of the isolated product (50:50 er). Thus, control experiments for the reaction protocol were conducted as shown in Entries 2 – 4. Reaction conditions from in entry 2, where the base was omitted, gave product **364** despite

the presence of catalyst **44**. While removal of both the catalyst and the triethylamine base (Entry 4) also showed no formation of product **364**, reaction conditions showed in Entry 3 showed moderate yield (40% yield) of product **364** when the base was present but the catalyst was omitted. Results in the conducted control experiments revealed that the reaction only proceeds in the presence of a base (triethylamine) but also in the absence of the catalyst, leading to a base-promoted background reaction that outcompetes the desired catalytic process. These results indicate the formation of the azomethine ylide from **362** in the presence of base which then readily reacts with the α,β-unsaturated ester **59** to form the chromeno-pyrrolidine product **359** without the participation of the isothiourea catalyst **44**, hence, a racemic mixture of **359** was obtained. To further probe the reaction with the goal of finding a suitable condition (with no base) and improve the enantioselectivity of the chromeno-pyrrolidine product, various leaving groups of the α,β-unsaturated ester substrate were tested. Note: Relative and absolute configuration of product **359** is based on results from Chapter 3, section 3.6 and further discussed in section 4.4 of this chapter.

Table 25. Yield (%) and Selectivity (er and dr) of Product **359** for the Initial Test Reaction and the Control Experiments.



Entry	359 Yield (%)[a]	er[b]	dr[a,f]
1	44	50:50	97:3
2[c]	-	-	-
3[d]	40	50:50	97:3
4[e]	-	-	-

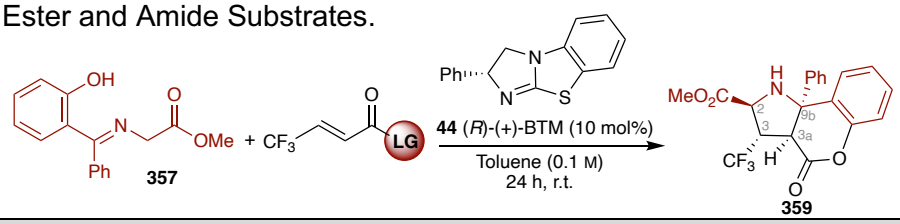
a-obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-Determined by HPLC analysis on a chiral stationary phase; *c*-with catalyst, without triethylamine; *d*-without catalyst, with NEt_3; *e*-without catalyst, without NEt; *f*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

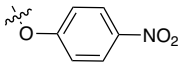
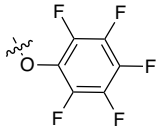
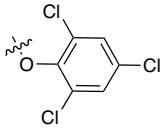
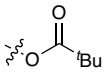
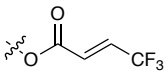
4.3.3 α,β-Unsaturated Ester Screening

Various α,β-unsaturated ester and amide substrates were examined to test the initial conditions in the absence of a base as shown in Table 26. Various leaving groups for the Michael acceptor were tested as shown in Table 26. However, most show no formation of the chromeno-pyrrolidine product **359**, except for mixed pivaloyl anhydride (Table 26, Entry 4) gave trace amounts of the product with excellent diastereoselectivity (97:3 dr) and promising enantioselectivity (70:30 er). Hence, further screening of reaction conditions was carried out,

involving (i) solvent screening, (ii) catalyst screening, (iii) reaction time, and (iv) temperature screening to improve the yield and enantioselectivity of the reaction.

Table 26. Yield (%) and Selectivity (er and dr) of Product **359** using Various α,β-Unsaturated Ester and Amide Substrates.



Entry	Leaving Group (LG)	359 Yield (%)[a]	er[b]	dr[a,c]
1		-	-	-
2		-	-	-
3		-	-	-
4		<10	70:30	97:3
5		-	-	-
6		-	-	-

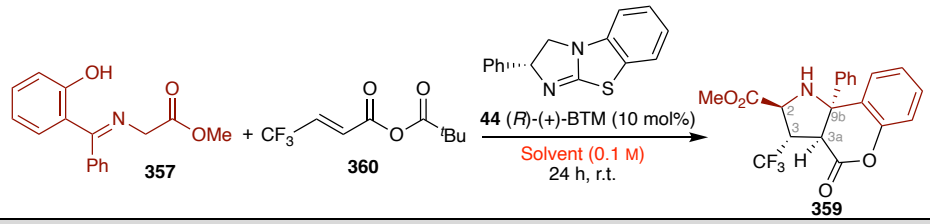
a-obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

4.3.4 Solvent Screening

Solvent screening for the synthesis of the chromeno-pyrrolidine product **359** was approached first using Schiff base **357** and the α,β-unsaturated mixed anhydride **360** under room temperature conditions with 10 mol% (R)-(+)-BTM **44** catalyst. Solvent with varying polarity were tested and results are shown in Table 27. Results in Table 27 showed poor formation of the chromeno-pyrrolidine product **359** from 5% – 11% yield for most of the tested solvents. Most polar aprotic solvents showed little to no formation of the desired product (trace - <6% yield) that was insufficient to determine product stereoselectivity (er and dr). Toluene still showed poor yield (10%) of the product with excellent diastereoselectivity (97:3 dr) but poor enantioselectivity (70:30 er) as shown in Table 27, entry 1. Acetonitrile, on the other hand, showed excellent enantioselectivity and diastereoselectivity (97:3 er, >99:1 dr) for the desired product **359**, albeit in poor yield (~10%) after 24-hour reaction time. With the enhanced

selectivity observed for the chromeno-pyrrolidine product, different isothiourea catalysts were screened.

Table 27. Yield (%) and Selectivity (er and dr) of Product **359** under Various Solvent Polarity.



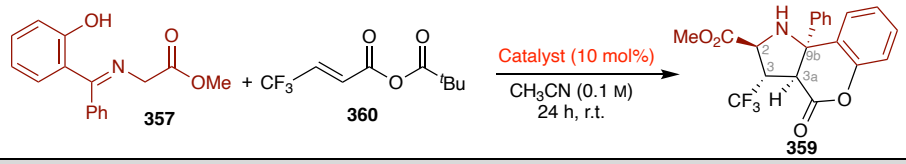
Entry	Solvent	359 Yield (%)[a]	er[b]	dr[a,c]
1	Toluene	<10	70:30	97:3
2	Et_2O	~5	-	-
3	CH_2Cl_2	-	-	-
4	THF	-	-	-
5	CH_3CN	11	97:3	>99:1
6	Ethyl acetate	-	-	-
7	DMF	<6	-	-
8	DMSO	<5	-	-
9	1,2-dimethyl acetamide	<5	-	-

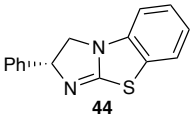
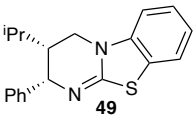
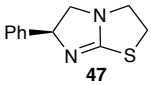
a-obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

4.3.5 Catalyst Screening

Various isothiourea catalysts were tested for the formation of the chromeno-pyrrolidine product **359** and results are shown in Table 28. Isothiourea catalyst **44** still showed the best yield (10%) with excellent stereoselectivity (97:3 er, 99:1 dr) while the rest of the isothiourea catalyst only produced trace amounts of **359**. Following these results, temperature screening was carried out for the reaction to improve the yield of the chromeno-pyrrolidine product.

Table 28. Yield (%) and Selectivity (er and dr) of Product **359** with Various Isothiourea Catalysts.



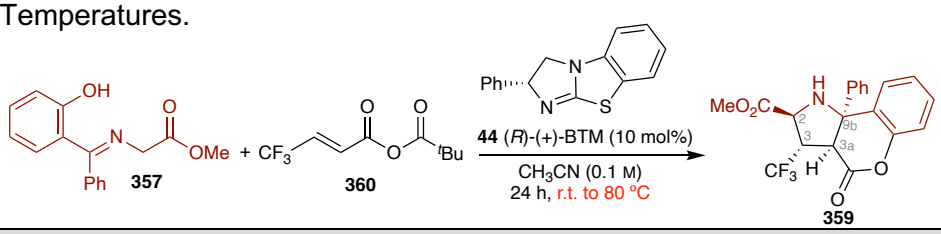
Entry	Catalyst	359 Yield (%)[a]	er[b]	dr[a.c]
1	 **44** (*R*)-(+)-BTM	11	97:3	99:1
2	 **49** (2*S*, 3*R*)-(+)-HyperBTM	~5	-	-
3	 **47** (*S*)-(-)-TM	<5	-	-

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*- determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

4.3.6 Reaction Temperature Screening

Various reaction temperatures, ranging from room temperature to 80 °C, were screened to improve the yield of the chromeno-pyrrolidine product **359** (Table 29). These results showed no significant improvement in the yield and selectivity of product **359** when increasing the reaction temperature from room temperature to 60 ºC. Increasing the temperature to 80 ºC resulted in a decrease in the yield (~5%) and a significant drop in the enantioselectivity (93:7 er). For simplicity, room temperature conditions were subsequently used.

Table 29. Yield (%) and Selectivity (er and dr) of Product **359** using Various Reaction Temperatures.



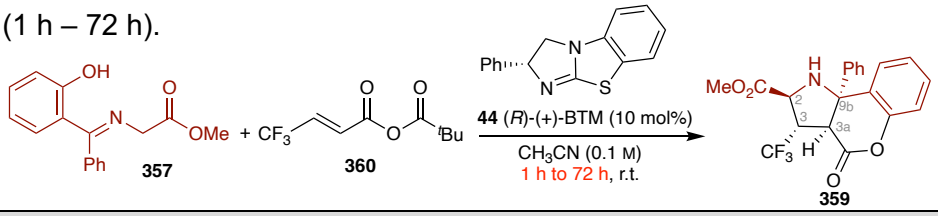
Entry	Temp. (ºC)	359 Yield (%)[a]	er[b]	dr[a,c]
1	rt	11	97:3	99:1
2	40	10	97:3	99:1
3	60	8	97:3	99:1
4	80	~5	93:7	99:1

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

4.3.7 Reaction Time Screening

Screening for the reaction time was then carried out to observe any possible increase in the yield of the chromeno-pyrrolidine product **359**. Reaction was monitored from 1 hour to 72 hours as shown in Table 30. Results indicated that increasing the reaction time does not provide any improvement in the yield of product **359**. Screening showed that for the first 6 hours of the reaction no product was formed, hence, the reaction time was extended to 72 hours to observe any possible increase in conversion. However, extending the reaction time to 72 hours showed no significant difference in the yield of product **359** (12% yield). Hence, all the subsequent screening conditions were run for 24 hours. On the other hand, the observed selectivity of the chromeno-pyrrolidine product **359** still showed excellent results even after 72 hours (97:3 er, 99:1 dr).

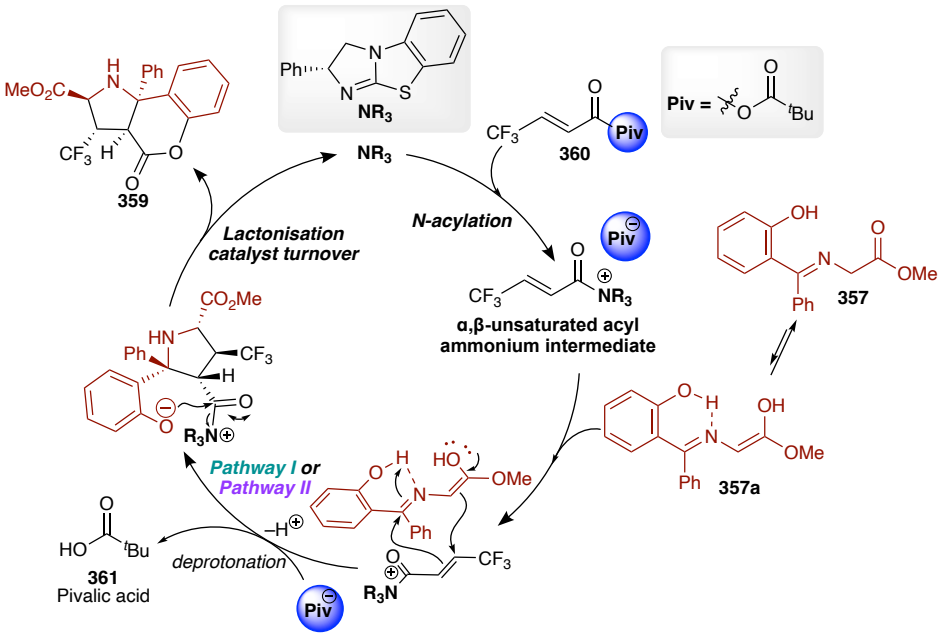
Table 30. Yield (%) and Selectivity (er and dr) of Product **359** under Various Reaction Time (1 h – 72 h).



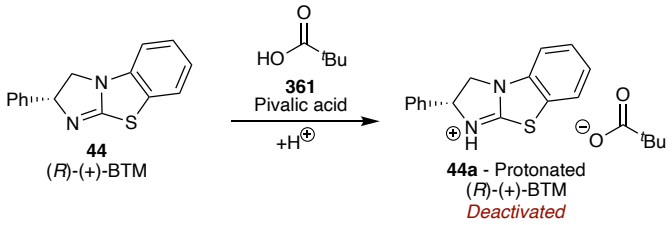
Entry	Reaction Time (h)	359 Yield (%)[a]	er[b]	dr[a,c]
1	1	-	-	-
2	6	-	-	-
3	24	11	97:3	99:1
4	48	11	97:3	99:1
5	72	12	97:3	99:1

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

Based on the results gathered from the optimisation conditions, low yield of the chromeno-pyrrolidine product **359** was still observed all throughout the tested conditions despite varying the solvent, catalyst, reaction temperature, and reaction time. This is presumably reflective of the catalyst being protonated and this deactivated in the reaction in the absence of a suitable base. Analysis on the proposed reaction mechanism was carried out as shown in the below in Scheme 78. Despite having two proposed mechanism for the formation of the pyrrolidine-core, both proposed mechanisms still require the deprotonation of intermediate **357a** by the pivalate anion to form pivalic acid **361**. This is followed by a lactonisation to achieve catalyst turnover and release the chromeno-pyrrolidine product **359.** However, accumulation of pivalic acid **361** (pK_a = 4.93) in the mixture during the reaction results in protonation of isothiourea Lewis-base catalyst **44**, hence, rendering the catalyst deactivated (Scheme 79). Moreover, Catalyst deactivation *via* protonation explains the observed low yield of the chromeno-pyrrolidine product **359** (~10% yield) even after 72 hours reaction time. The yield of the product also corresponds to the catalyst loading of the isothiourea catalyst **44** used in the reaction (10 mol%) suggesting full deactivation after one turnover. Screening of various inorganic base was hoped to improve the yield of product **359** with the possibility of retaining excellent enantio- and diastereoselectivity.



Scheme 78. Proposed Mechanism for the formation of the chromeno-pyrrolidine product **359**.



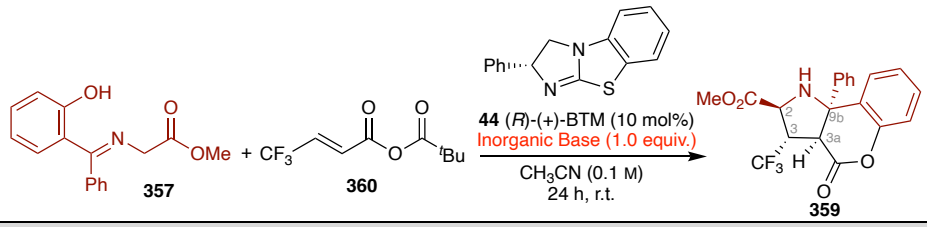
Scheme 79. Possible deactivation of the isothiourea catalyst **44** via protonation in the presence of pivalic acid **361**.

4.3.8 Inorganic Base Screening

Various inorganic bases were screened and added into the preliminary optimised reaction condition to check if enhanced yield of the chromeno-pyrrolidine product **359** was achieved whilst maintaining high enantioselectivity and diastereoselectivity of the product, as shown in Table 31. Results in Table 31 indicate that addition of inorganic bases does not provide any significant increase in the yield of the chromeno-pyrrolidine product **359**, as shown in entries 1 – 4. Most of the utilised inorganic bases were observed to have either poor solubility or deemed insoluble in acetonitrile, hence, there was no possibility of quenching the accumulated pivalic acid **361** during the reaction without triggering the background reaction. Addition of either organic sodium salts or diisopropylethylamine ($^{i}Pr_2NEt$) wer also tested for the reaction (Table 31, Entry 5 - 7), however, most of the additives elicited poor yield (<8%) and significantly reduced enantioselectivity (70:30 er) for the chromeno-pyrrolidine product **359** which might be attributed to any background reaction. With the idea of increasing the yield of the product, it was thought that an *in-situ* preparation of substrate **360** would help increase the

yield of the reaction. For optimal conditions the reaction was monitored to avoid unnecessarily extended reaction times.

Table 31. Yield (%) and Selectivity (er and dr) of Product **359** using Different Inorganic Bases.

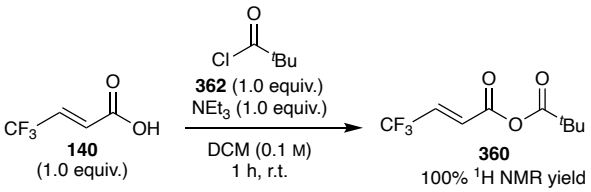


Entry	Inorganic Base	359 Yield (%)[a]	er[b]	dr[a,c]
1	$NaHCO_3$	<10	98:2	>99:1
2	Na_2CO_3	<10	97:3	>99:1
3	$CsCO_3$	-	-	-
4	$CaCO_3$	-	-	-
5[d]	*NaOAc*	<5	-	-
6[d]	*Sodium Pivalate*	<5	-	-
7[e]	*$^iPr_2NEt$*	8	70:30	>99:1

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry; *d*-organic sodium salts; *e*-organic base.

4.3.9 *In situ* Preparation of Anhydride (360) and Reaction Time Screening

In situ preparation of substrate **360** was achieved by the reaction of the acid precursor **140** and pivaloyl chloride **362** at 0 °C showing full conversion to the anhydride substrate after 1 hour, based on the ^{1}H NMR analysis of the crude reaction mixture, as shown in Scheme 80.

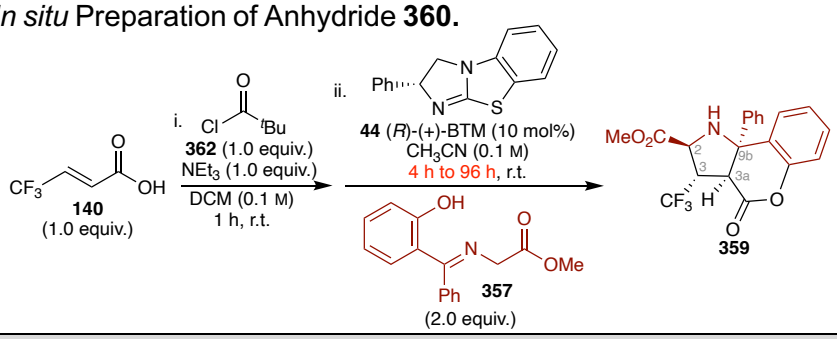


Scheme 80. *In situ* preparation of substrate **360**.

The reaction was then carried out by *in situ* preparation of substrate **360** and monitored from 4 hours to 96 hours as shown in Table 32. The results in Table 32 show an increase in the yield of the chromeno-pyrrolidine product **359** (up to 19%) upon monitoring the time of the reaction from 4 hours to 96 hours together with the *in situ* preparation of the anhydride **360**. There was no significant difference in the yield of product **359** after 48 hours (17% yield) or 96 hours (19% yield) reaction time. Thus, a 48-hour reaction time was considered as the optimal

reaction time. Despite having shown poor reactivity, excellent enantioselectivity and diastereoselectivity were still observed under all reaction conditions (~97:3 er, >99:1 dr). An additional temperature screening was carried out to further improve the yield of product **359**.

Table 32. Yield (%) and Selectivity (er and dr) of Product **359** under Reaction Time Monitoring and *In situ* Preparation of Anhydride **360.**



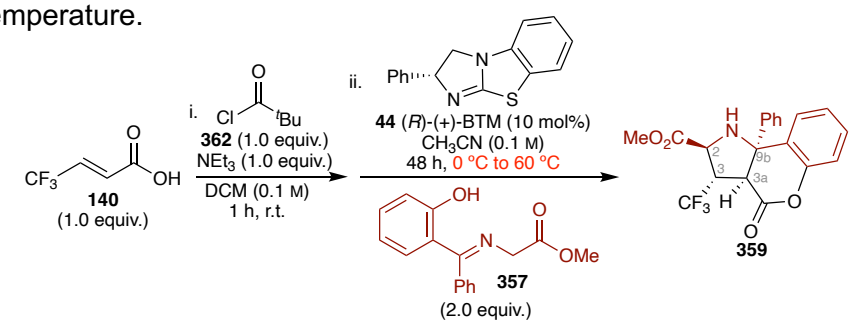
Entry	Reaction Time (h)	359 Yield (%)[a]	er[b]	dr[a,c]
1	4	5	98:2	>99:1
2	24	12	97:3	>99:1
3	48	17	97:3	>99:1
4	72	18	98:2	>99:1
5	96	19	97:3	>99:1

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

4.3.10 Reaction Temperature Screening for New Conditions

Reaction temperature optimisation (Table 33) showed a much lower yields for the chromeno-pyrrolidine product **359** in either 0 ºC (10% yield) or higher temperatures (40 ºC – 60 ºC) (9% yield) while room-temperature conditions exhibited the best yield (17% yield). On the other hand, excellent selectivity (>95:5 er, >99:1 dr) were still observed despite lowered yields at varying reaction temperatures. Further optimisation of the reaction conditions was carried out including (i) substrate ratio optimisation, (ii) reaction concentration, and (iii) catalyst loading optimisation.

Table 33. Yield (%) and Selectivity (er and dr) of Product **359** under Varying Reaction Temperature.



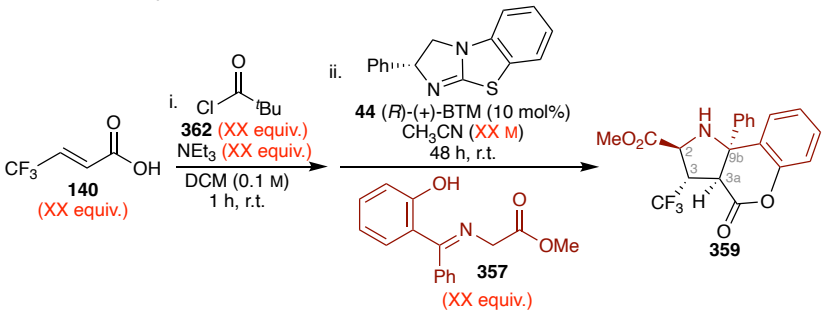
Entry	Reaction Temp. (ºC)	359 Yield (%)[a]	er[b]	dr[a,c]
1	0	10	95:5	>99:1
2	rt	17	97:3	>99:1
3	40	9	97:3	>99:1
4	60	9	97:3	>99:1

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*- determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

4.3.11 Substrate Ratio Optimisation, Reaction Concentration Optimisation, Catalyst Loading Tests.

Optimisation of the substrate ratio of the imine **357** and the *in situ* prepared substrate **360** for formation of the chromeno-pyrrolidine product **359** were carried out and showed in Table 34. However, no significant effect on the yield of product **359** was observed with various ratios of substrates **360** and **357**, with excess anhydride **360** giving off lower product yield. While a 1:1.5 ratio of **360** and **357** was used for economical purposes. In most reaction conditions shown in Table 34, an excellent enantioselectivity and diastereoselectivity was still observed for product **359** (97:3 er, >99:1 dr). Additional optimisation of the reaction concentration was carried in Table 34, entries 4-5. However, no increase in the yield of the chromeno-pyrrolidine product **364** was observed in all the tested reaction concentration conditions (0.05 M, 0.1 M, 0.2 M) as shown in entry 2, entry 5, entry 6. On the other hand, excellent selectivity was still observed in the synthesised product (97:3 er, >99:1 dr) in all the tested reaction conditions.

Table 34. Yield (%) and Selectivity (er and dr) of Product **359** under Different Substrate Ratio of the *in situ* Anhydride **360** and Imine **357**.

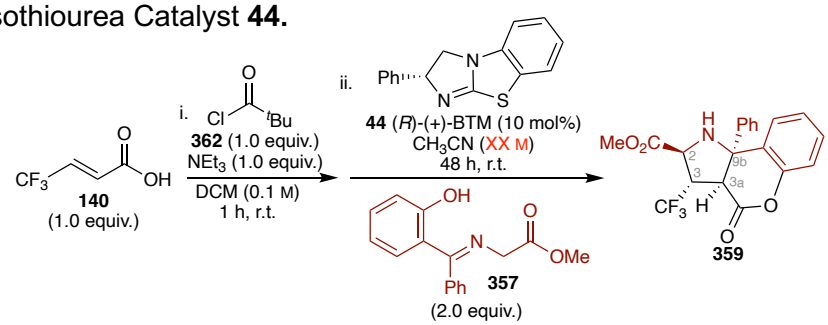


Entry	*In situ* 365 (equiv.)	362 (equiv.)	CH_3CN (XX M)	359 Yield (%)[a]	er[b]	dr[a,c]
1	1.0	2.0	0.1	17	97:3	>99:1
2	1.0	1.5	0.1	20	97:3	>99:1
3	1.5	1.0	0.1	10	97:3	>99:1
4	2.0	1.0	0.1	9	97:3	>99:1
5	1.0	1.5	0.05	19	97:3	>99:1
6	1.0	1.5	0.2	20	97:3	>99:1

a- obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

Despite altering the variables to impose an increase in the yield of the chromeno-pyrrolidine product **359,** the reaction only elicited 20% of the desired product but still with excellent enantioselectivity and diastereoselectivity as shown in most of the optimisation results. It was hypothesised that the observed poor yield of product **359** may be due to the deactivation of the isothiourea catalyst *via* protonation because of the accumulation of pivalic acid **361**. Hence, it was deduced that increasing the catalyst loading by double the amount (20 mol%) should theoretically double the yield of the observed chromeno-pyrrolidine product **359** as shown in Table 35. Increasing the catalyst **44** loading to 20 mol% showed a two-fold increase in the yield of chromeno-pyrrolidine product **359** (37% yield) with maintained enantioselectivity and diastereoselectivity (97:3 er, >99:1 dr).

Table 35. Yield (%) and Selectivity (er and dr) of Product **359** with Various Catalyst Loading of Isothiourea Catalyst **44.**

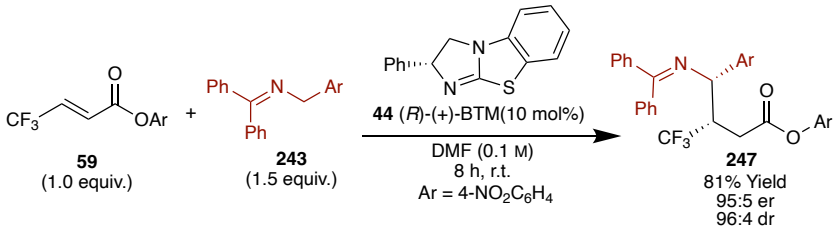


Entry	44 (mol%)	359 Yield (%)[a]	er[b]	dr[a,c]
1	10	21	97:3	>99:1
2	20	37	97:3	>99:1

a-obtained by ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

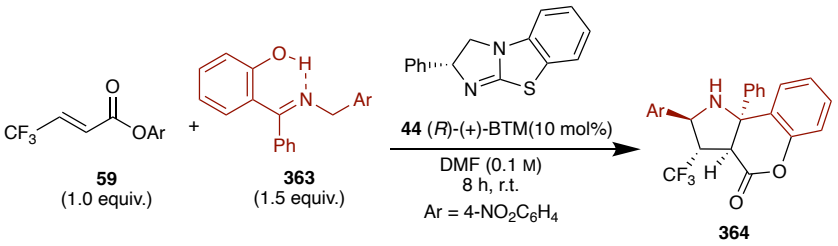
Based on the results obtained in Table 36, increasing the catalyst **44** loading to 20 mol% showed a two-fold increase in the yield of chromeno-pyrrolidine product **359** (37% yield) with enantioselectivity and diastereoselectivity maintained (97:3 er, >99:1 dr). This result supports the hypothesis that a two-fold increase in catalyst loading should result in the two-fold increase in the product **359**. Furthermore, examination of the ^{1}H NMR spectra of the crude reaction mixture in deuterated chloroform ($CDCl_3$) at 10 mol% catalyst loading of (*R*)-(+)-BTM **44** catalyst (Table 36, Entry 1) showed the presence of an apparent triplet at δ = 5.94 ppm indicative of a protonated catalyst as shown in Figure 42, which corroborates with the reported protonated **44a** catalyst (δ = 5.91 ppm).[167]

Despite the observed low product yield, a proof of concept for the formation of the chromeno-pyrrolidine product **359** was shown. The reaction showed formation of the product in excellent enantioselectivity and diastereoselectivity (up to 97:3 er, >99:1 dr). However, a stoichiometric ratio of chiral isothiourea catalyst **44** was needed to provide moderate yield of the chromeno-pyrrolidine product **359**. One of the highlighted limitations in the reaction is the accumulation of pivalic acid **361** during the reaction that results to the deactivation of the catalyst **44** *via* protonation. To improve the yield of the chromeno-pyrrolidine product using substoichiometric amount of catalyst, it was hypothesised that the reaction will be feasible using the Schiff base **363** and reacted with α,β-unsaturated ester **59** at 10 mol% (*R*)-(+)-BTM **44** catalyst with DMF as solvent. The use of Schiff base **363** was based on the results obtained from the successful Michael-addition reaction of Schiff base **243** to form the Michael addition product **247** in excellent yield and selectivity (Scheme 81, 81% yield, 95:5 er, 96:4 er) as shown in chapter 3.



Scheme 81. Formation of product **247** from the successful Michael addition reaction of Schiff base **243** to α,β-unsaturated ester **59.**

Using these results, addition of a hydroxyl group as shown in Schiff base **363** may promote formation of the azomethine ylide *via* deprotonation in DMF solvent, which reacts with the α,β-unsaturated ester **59** to form the chromeno-pyrrolidine product **364** following a similar mechanism shown in Scheme 78. Under these conditions, the overall reaction produces product **364**, the free catalyst **44**, and 4-nitrophenol as the side product.



Scheme 82. Proposed new conditions and substrates for the formation of the chromeno-pyrrolidine product **364**.

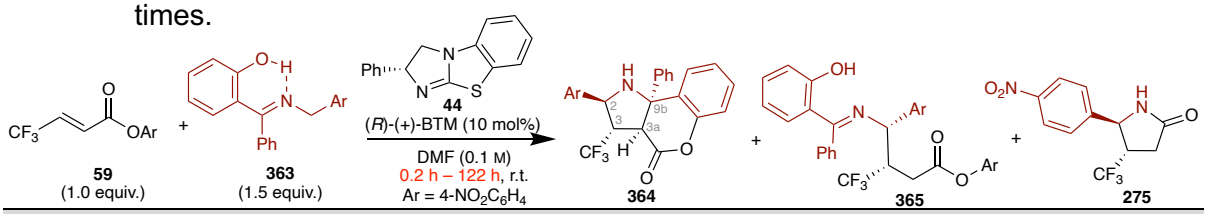
4.3.12 Additional Optimisation Conditions using a Hydroxy-Substituted Schiff Base

A test reaction was performed on the reaction of Schiff base **363** with α,β-unsaturated ester **59** using DMF as solvent and monitored the formation of possible products as shown in Table 37 and Figure 37. Monitoring of the new reaction conditions revealed that the reaction reached near full consumption of the **59** starting material after 2 hours (Table 36, Entry 2) at 94% conversion. However, based on the analysis of the ^{1}H NMR and the ^{19}F NMR spectra of the crude reaction mixture, a mixture of products identified as **364:245:275** were observed after 2 hours with **365** as the major product at 71% yield. This is in accordance with a stepwise mechanism rather than a concerted pericyclic process, where the γ-imino ester **365** is observed as an intermediate and then steadily consumed to form **364**.

Despite showing poor yield at 33%, the isolated chromeno-pyrrolidine product **364** still showed excellent enantioselectivity and diastereoselectivity at 99:1 er and >99:1dr. Purification of the Michael addition product **365** proved to be difficult *via* flash column chromatography as product **365** co-elutes with the excess Schiff base **363** in a range of solvent systems. Hence, enantiomeric ratios for the product **365** were not reported. It could still be demonstrated that the diastereoselectivity (>99:1 dr) based on the ^{1}H NMR analysis is still excellent. Formation

of γ-lactam **275** can be explained by the hydrolysis of product **365** to form the free γ-amine, which is followed by a spontaneous cyclisation.

Table 36. Observed Yield and Selectivity (er and dr) of Product **368** after different reaction times.



Entry	Reaction Time (h)	% Conv.	364 Yield (%)[a]	365 Yield (%)[a]	275 Yield (%)[a]	364 er[b]	364 dr[c]
1	0.2	60	13	47	-	-	>99:1
2	1	94	21	71	1	99:1	>99:1
3	2	100	25	68	2	99:1	>99:1
4	5	100	29	63	3	99:1	>99:1
5	24	100	32	51	9	99:1	>99:1
6	48	100	33	41	17	99:1	>99:1
7	120	100	33	19	29	99:1	>99:1

a- obtained by ^{19}F NMR analysis of the crude reaction mixture; *b*-enantiomeric ratio obtained using HPLC analysis on a chiral stationary phase; *c*-obtained by ^{1}H NMR analysis of the crude reaction mixture and *c*-dr for (2*S*,3*S*,3a*S*,9b*S*) and (2*R*,3*S*,3a*S*,9b*S*) as preliminary assignment of stereochemistry.

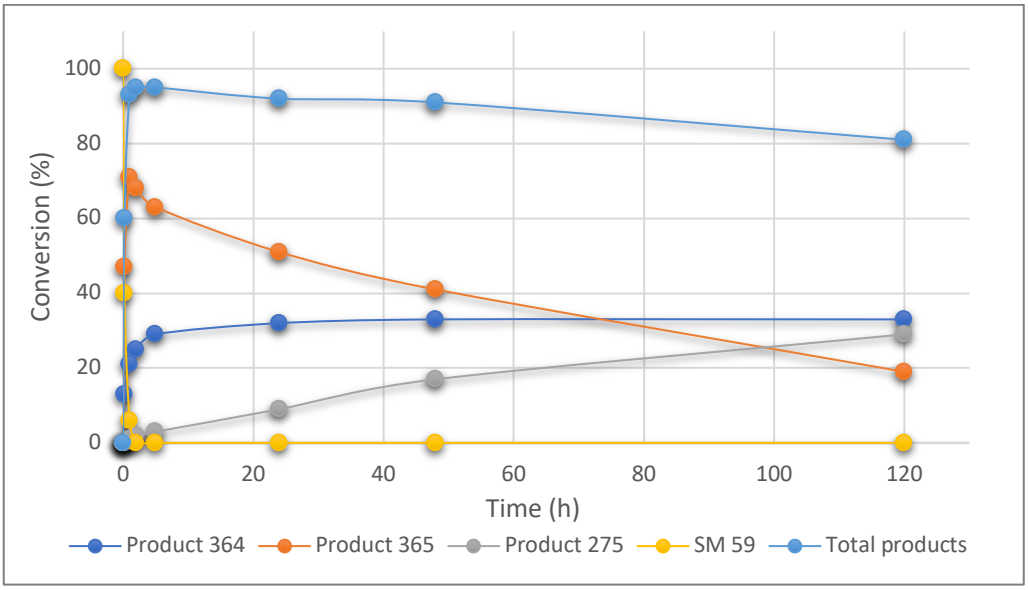
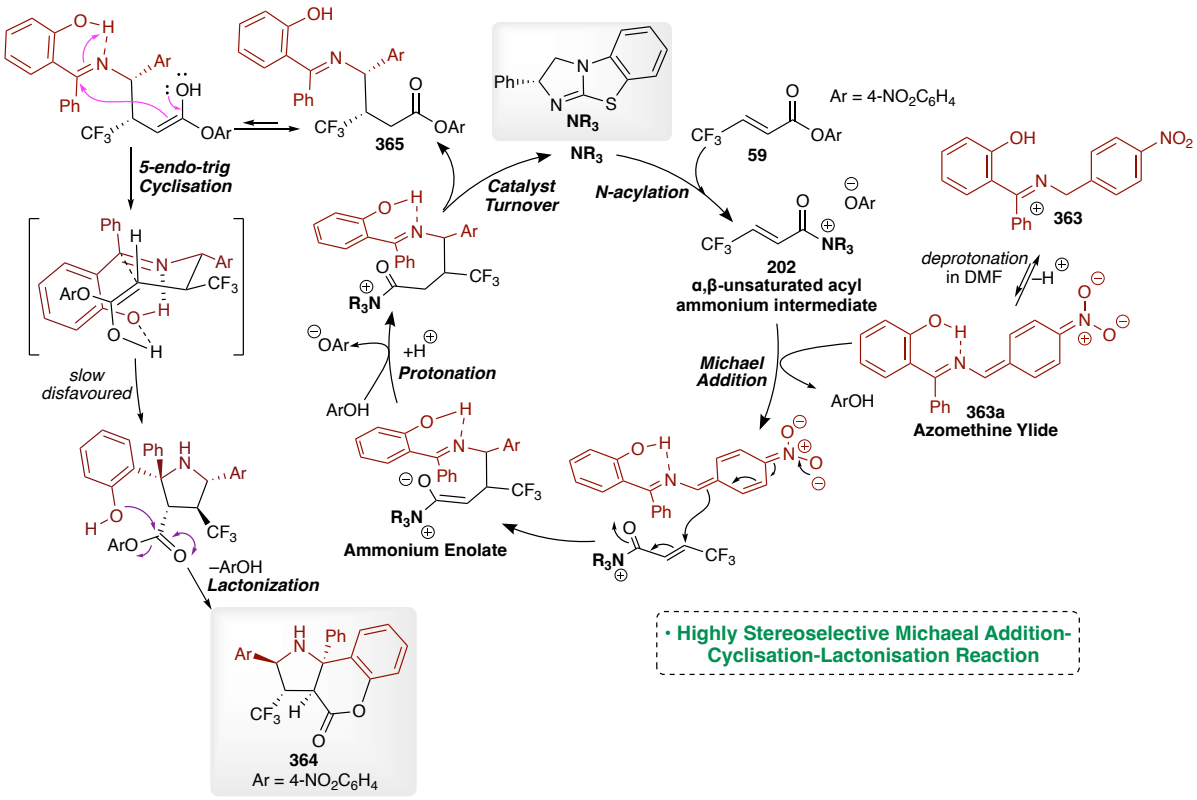


Figure 37. Plot for % conversion of products **364**, **365**, **275**, the total products formed, and the remaining starting material **59** over time.

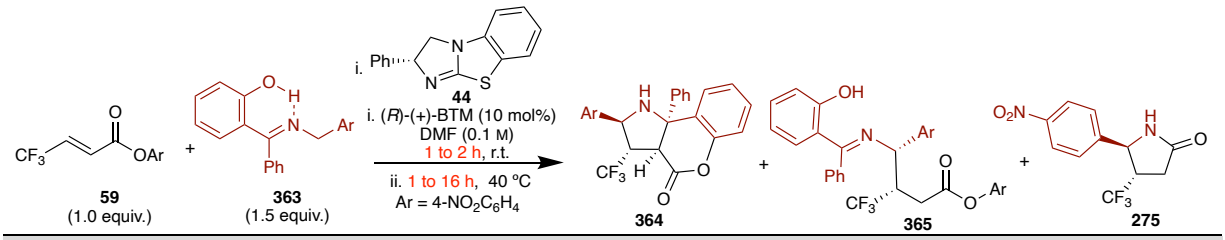
The proposed mechanism for this reaction proceeds *via* an isothiourea-catalysed Michael addition, protonation, and phenoxide rebound catalyst turnover to form product **365** as an intermediate. Tautomerization of **365**, followed by 5-*endo-trig* cyclisation, and lactonisation leads to the desired chromeno-pyrrolidine product **364** (Scheme 83). The main difference in the proposed reaction mechanism previously highlighted in section 4.2 to the proposed reaction mechanism in Scheme 82 is that the catalyst only facilitates the Michael addition reaction of Schiff base **363** to the α,β-unsaturated ester **59**, supported by the rapid formation of product **365**. The formation of product **364** from **365** (Table 36) requires a disfavoured 5-*endo-trig* cyclisation according to Baldwin's rules. This explains the observation of **369** as an intermediate, as catalyst turnover is more facile than cyclisation. The slow cyclisation process also leaves **369** prone to hydrolysis and formation of γ-amine which in turn cyclises to form **275**.



Scheme 83. Proposed Reaction Mechanism for the stereoselective formation of **365** and **364**.

With the observed slow formation of **364** from the disfavoured 5-*endo-trig* cyclisation together with the formation of the γ-lactam **275** over time, additional screening was performed.

Table 37. Yield (%) and Selectivity (er and dr) of Product **364** at Different Reaction Times and Addition of Molecular Sieves.



Entry	Reaction Time (h)	364 Yield (%)[a]	365 Yield (%)[a]	275 Yield (%)[a]	364 er[b]	364 dr[c]
1[d]	1	21	73	1	99:1	>99:1
2[d]	2	25	68	2	99:1	>99:1
3[e]	1	33	58	5	99:1	>99:1
4[e]	2	35	54	7	99:1	>99:1
5[e]	16	40	23	28	99:1	>99:1
6[d,f]	2	25	66	3	99:1	>99:1
7[e,f]	16	48	8	44	99:1	>99:1

a- obtained by ^{19}F NMR analysis of the crude reaction mixture; *b*-determined by HPLC analysis on a chiral stationary phase; *c*-determined by ^{1}H NMR analysis of the crude reaction mixture; *d*-reaction monitoring in step (i) before heating, *e*-reaction monitoring in step (ii) upon heating to 40 ºC; *f*- with activated 4 Å molecular sieves.

Table 37 shows monitoring of the reaction at room temperature in step (i) (Entries 1 and 2), then heated to 40 ºC in step (ii) (Entries 3 to 5), and the reaction with 4 Å molecular sieves (Entries 6 and 7). Results shows that after a 2-hour reaction time at room temperature, near full conversion of substrate **59** was achieved and formation of the chromeno-pyrrolidine product **364** was observed at 25% yield together with the observed **365** intermediate at 68% yield (Table 37, Entry 2). The reaction was then heated to accelerate the cyclisation step. The progress of the reaction was monitored by ^{19}F NMR analysis of the crude mixture. A slow increase in the yield of product **364** (35% yield) was observed after heating the reaction for 2 hours at 40 ºC while no significant change in the yield of intermediate **365** (54% yield) and less than 10% of the γ-lactam **275** was observed under these conditions (Table 37, Entry 4). Hence, the reaction was then heated for a total of 16 hours to increase the yield of **364.** However, results showed that only 40% yield of **364** was observed in the reaction while a significant increase in the γ-lactam **275** was observed at 28% yield accompanied by a significant drop in yield for intermediate **365** intermediate to 23% (Table 37, Entry 5). These results suggest that at higher temperature (40 ºC) hydrolysis of the intermediate **369** was also accelerated.

To prevent hydrolysis of intermediate **365**, 4 Å molecular sieves were added into the reaction mixture as shown in Table 37, Entries 6 to 7. Still near full conversion of substrate **59** was observed (Table 37, Entry 6). After this 2 h period, the reaction was heated to 40 ºC and stirred for 16 hours in the presence of molecular sieves as shown in Table 37, Entry 7. A moderate yield of product **364** (48% yield) was observed after 16 hours while most of the intermediate **365** (8% yield) had been consumed. However, a significant increase in the γ-lactam **275** was observed (44% yield). These results imply that hydrolysis of intermediate **365** was still observed despite the addition of molecular sieves in the reaction mixture. Despite the observed poor to moderate yield of the desired chromeno-pyrrolidine product **364**, excellent enantioselectivity and diastereoselectivity was still observed (99:1 er, >99;1 dr) which infers that the reaction undergoes a highly stereoselective Michael addition, followed by a cyclisation-lactonisation reaction as shown in Scheme 83. Additional optimsation for the reaction conditions is still needed to generate a reaction protocol that is specific to the formation of the chromeno-pyrrolidine product **364**.

4.4 ABSOLUTE CONFIGURATION AND SELECTIVITY

Attempted recrystallisation of product **364** did not lead to suitable crystals for X-ray diffraction. Subsequent studies used a nuclear Overhauser effect (NOE) analysis of product **364** to identify the relative configuration within the product, with the absolute configuration determined using the known selectivity using catalyst (*R*)-BTM in conjugate addition type processes (Figure 38).

Selective irradiation of proton $\mathbf{H_c}$ (3.86 ppm) gives a strong correlation to the phenyl ortho-protons $\mathbf{H_d}$ (7.38 ppm, C(2',6')Ar*H*), while weak correlations were observed with protons $\mathbf{H}_a$ (4.80 ppm, CH_aC$_6$H$_4$NO$_2$) and $\mathbf{H_b}$ (3.55 ppm, CH_bCF$_3$) (Figure 38b). This implies that proton $\mathbf{H_d}$ is of close spatial proximity with $\mathbf{H_c}$ and is on the same face of the pyrrolidine ring. Selective irradiation of proton $\mathbf{H_b}$ (3.55 ppm) results in visible correlation of with proton $\mathbf{H_e}$ (7.45 ppm, C(2,6)Ar*H*-4-NO$_2$) of the 4-nitropheyl group with weak correlations to protons $\mathbf{H}_a$ (4.80 ppm, CH_aC$_6$H$_4$NO$_2$) and $\mathbf{H_c}$ (3.86 ppm, CH_cCO$_2$) (Figure 38c). This result suggests close spatial proximity of proton $\mathbf{H_b}$ with proton $\mathbf{H}_e$ indicating that proton $\mathbf{H_b}$ and the 4-nitrophenyl group are attached to the same face of the pyrrolidine ring. Selective irradiation of proton $\mathbf{H_a}$ (4.80 ppm, CH_aC$_6$H$_4$NO$_2$) also showed clear correlation to protons $\mathbf{H_d}$ (7.38 ppm, C(2',6')Ar*H*) of the phenyl group suggesting close spatial proximity of these protons and indicates that proton $\mathbf{H_a}$ and the phenyl group are on the same face of the pyrrolidine ring (Figure 38d). Strong correlation to proton $\mathbf{H_e}$ of the 4-nitrophenyl group were also observed while weak correlations to protons $\mathbf{H}_a$ (4.80 ppm) and $\mathbf{H_b}$ (3.55 ppm) were visible. Coupled with the known

confiuguration of the isothiourea used in the catalysis, these results support the predicted configuration of the chromeno-pyrrolidine product as (2*S*,3*S*,3a*S*,9b*S*)-**364** (Figure 39).

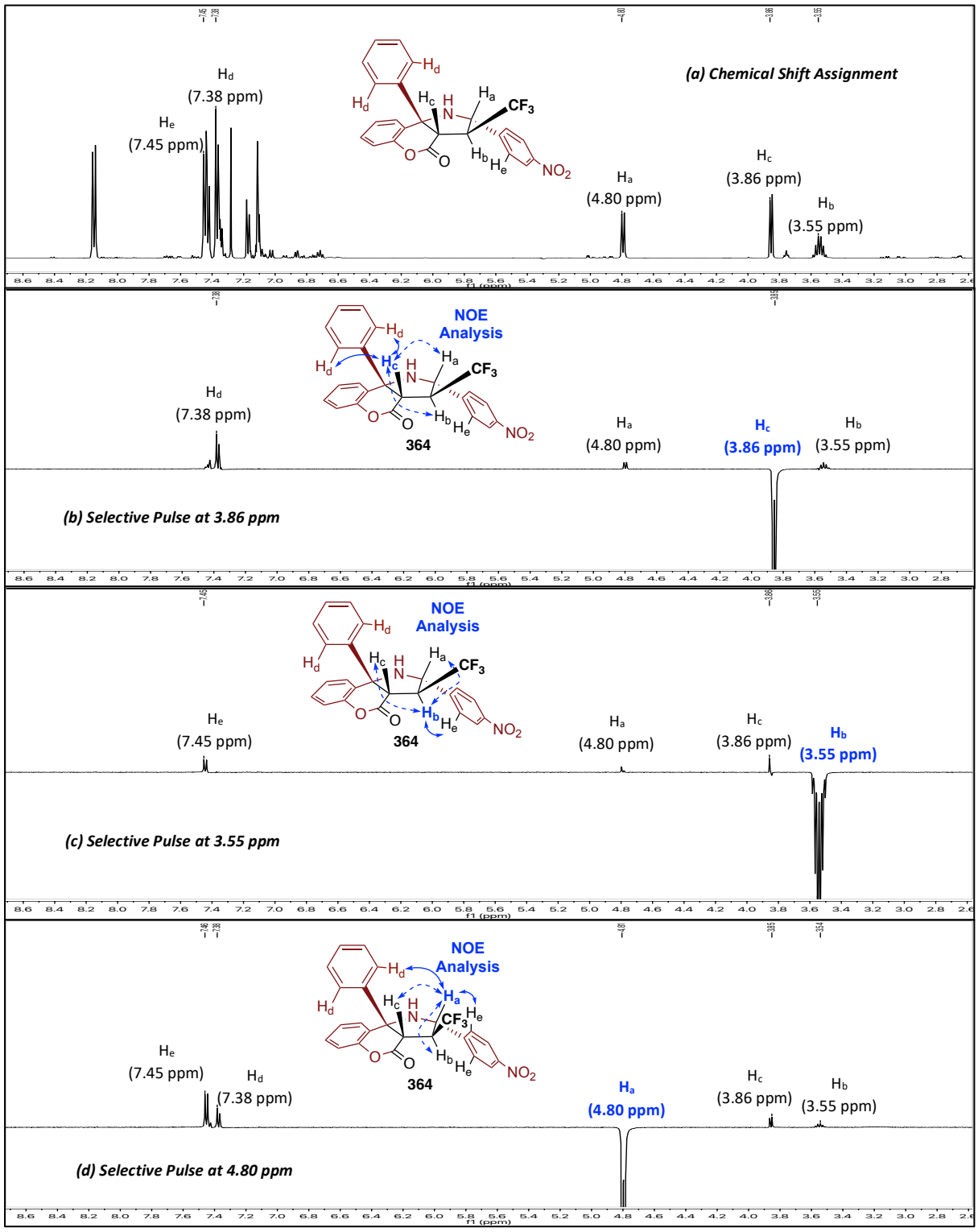
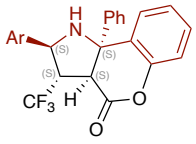


Figure 38. 1D ^{1}H NMR NOE experiments of the chromeno-pyrrolidine product **364** selectively irradiated at chemical shifts (b) 3.86 ppm, (c) 3.55 ppm, and (d) 4.80 ppm.



(2*S*,3*S*,3a*S*,9b*S*)-**364**

Figure 39. Absolute configuration of product **364** based on the NOE analysis.

With the confirmed relative configuration of product **364**, a transition state for the highly stereoselective Michael addition-cyclisation-lactonisation reaction was then proposed based on the proposed mechanism in Scheme 83.

The observed excellent enantioselectivity during the Michael addition of **363a** to the α,β-unsaturated acyl ammonium intermediate **202**, previously highlighted in Chapter 3 section 3.6, was imposed by the following factors: (i) the facial selectivity of the intermediate **202**'s phenyl stereodirecting group (Figure 40a); (ii) the stabilising effect and the conformational lock on the intermediate **202** from the intramolecular 1,5 C=O•••S interaction (Figure 40a); and (iii) the diastereoselectivity proposed to be imposed in part by additional stabilising π•••cation interactions of the deprotonated Schiff base **363a** to the intermediate **202** during the addition reaction depicted in Model **I** providing selectivity to the (3*S*,4*S*)-configuration of intermediate **365,** similar to the Michael addition reaction observed in Chapter 3, section 3.6 together with the confirmed absolute stereochemistry from the single crystal X-ray diffraction analysis of compound **250** (Figure 40b).

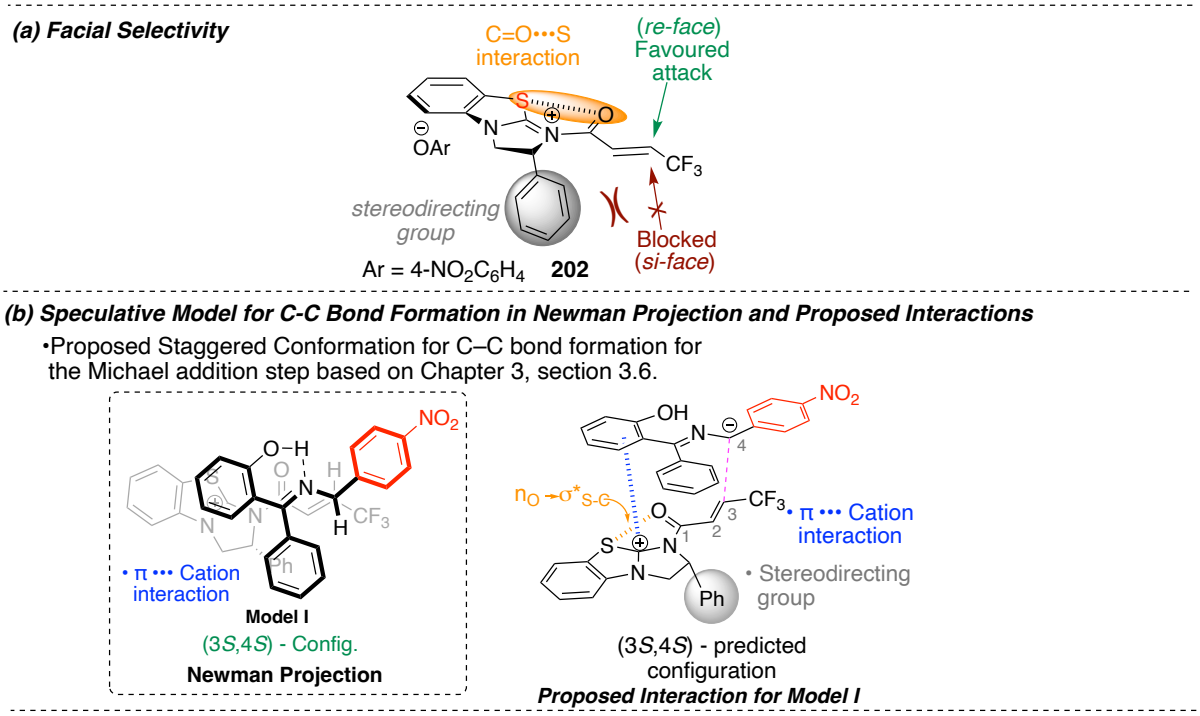


Figure 40. (a) Facial selectivity imposed by the chiral isothiourea-bound organocatalyst; (b) proposed stereoselective Michael addition of the **367a** nucleophile with intermediate **202**.

In addition to the established excellent selectivity in the Michael addition step, a highly selective cyclisation step to form the pyrrolidine core of product **364** *via* the formation of a 5-membered transition state **366** from the enol form of intermediate **365** stabilised by intramolecular H-bonding (Figure 41).

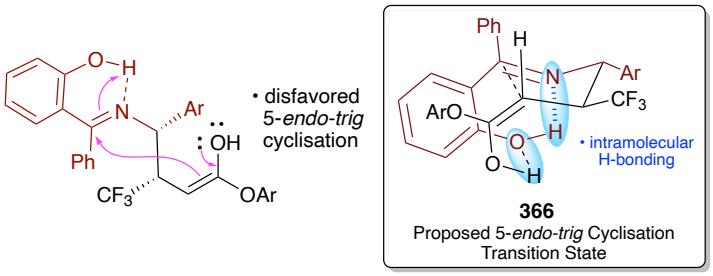


Figure 41. Proposed transition state **366** for the disfavoured 5-*endo-trig* cyclisation step to form the pyrrolidine core.

These following factors were considered for the proposed 5-*endo-trig* cyclisation transition state **366**: (i) the proposed 5-member transition state **366** to form the pyrrolidine core shows the minimum steric hindrance with most of the groups oriented at the equatorial position, (ii) the intramolecular H-bonding of the enol and the hydroxyl group promotes the nucleophilic addition to the C=N, and (ii) the protonation of the C=N bond from the proposed intramolecular H-bonding interaction of the hydroxyl group results in the enhance electrophilicity of the carbon of the C=N and can then undergo a nucleophilic addition from the enol. These proposed factors effectively promotes a 5-*endo-trig* cyclisation, a disfavoured cyclisation step based on Baldwin's rule, and slowly generates the pyrrolidine core, followed by a lactonisation reaction to obtain the desired chromeno-pyrrolidine product **364** as highlighted in Scheme 82.

4.5 CONCLUSIONS AND RECOMMENDATIONS

In summary, results showed that a highly enantio- and diastereoselective formation of the chromeno-pyrrolidine compound can be achieved from the reaction of Schiff base **363** with α,β-unsaturated ester **59** using isothiourea organocatalyst (*R*)-(+)-BTM **44** in moderate yield (48% yield, 99:1 er, >99:1 dr). The reaction initially undergoes a highly stereoselective Michael addition of the Schiff base **363** to the α,β-unsaturated acyl ammonium intermediate **202** to form the ammonium enolate intermediate, followed by protonation and an aryloxide catalyst turnover to form the stable intermediate **365**. The stable intermediate then undergoes a slow but highly stereoselective 5-*endo-trig* cyclisation to form the pyrrolidine core and a lactonisation reaction to form the chromeno-pyrrolidine product **364** in high enantioselectivity and diastereoselectivity.

However, drawbacks in the reaction protocol were observed upon the formation of product **364** such as the (i) hydrolysis of the intermediate **365** followed by a cyclisation to form the γ-

lactam **275** despite the use of anhydrous DMF and the addition of 100 mol% 4 Å molecular sieves, and (ii) the slow formation of the pyrrolidine ring. Hence, additional optimisation is needed to selectively form the chromeno-pyrrolidine product **364** without the formation of the γ-lactam **275** while still maintaining the observed excellent enantioselectivity and diastereoselectivity, exploring (i) different substrate ratios, (ii) reaction concentrations, and (iii) catalyst loadings as well as (iv) alternative catalysts and (v) additives. Unfortunately, due to time constraints this project was halted at this stage and will be subsequently studied further within the ADS group.

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CHAPTER 5: EXPERIMENTAL

5.1 GENERAL EXPERIMENTAL

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N_2) using standard vacuum line techniques. Anhydrous solvents (CH_2Cl_2) were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 C. All other solvents and commercial reagents were used as received without further purification unless otherwise stated.

Room temperature (rt) refers to 20–25 ºC.

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and ILMVAC vacuum controller, or IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL Recirculating Coolers filled with ethylene glycol and set to –6 C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm). Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Keiselgel 60 silica using the solvent system stated. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV/Vis detector using the method stated and cartridges filled with Keiselgel 60 silica.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on either a Shimadzu HPLC consisting of a DGU-$20A_5$ degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven or a Shimadzu HPLC consisting of a DGU-$20A_{5R}$ degassing unit, LC-20AD liquid chromatography pymp, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using DAICEL CHIRALPAK AD-H column using the

method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.

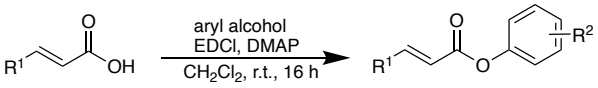
Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumber (ν_{max}) reported in cm^{-1}.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were acquired on either a Bruker AV300 with a BBFO probe (^{1}H 300 MHz; $^{13}C\{^{1}H\}$ 75 MHz), a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz), a Bruker AVII 400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz), a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz), or a Bruker AVIII-HD 700 with a CryoProbe Prodigy TCI probe (^{1}H 700 MHz, $^{13}C\{^{1}H\}$ 176 MHz) in the deuterated solvent stated. All chemicals shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples of thereof. The abbreviation Ar denotes aromatic and app denotes apparent. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), 2D ^{1}H nuclear Overhauser effect spectroscopy (NOESY), 2D ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

Mass spectrometry (*m/z*) data were acquired by nanospray ionisation (NSI) at the University of St Andrews Mass Spectrometry Facility ([A] quoted).

5.2. GENERAL PROCEDURES

General Procedure A1: *Synthesis of α,β-Unsaturated Aryl Esters*



The appropriate amount of α,β-unsaturated acid (1.0 equiv.) was charged in to a flame-dried flask with the appropriate amount of alcohol (1.5 equiv.), EDCI (2.0 equiv.), and DMAP (0.1 equiv.), in CH_2Cl_2 (0.15 M) at room temperature. The resulting solution was stirred for 16 h at room temperature and then concentrated *in vacuo*. The resulting oil was dissolved in EtOAc (100 mL) and washed with aqueous citric acid (10% *w/v*, 3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

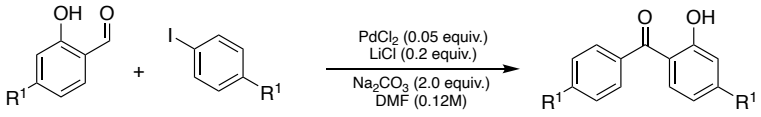
General Procedure A2:

The appropriate amount of carboxylic acid (1.0 equiv.) was dissoleved in CH_2Cl_2 (0.33 M) and added with oxalyl chloride (1.0 equiv) and a few drops of DMF were added. The mixture was then stirred for 1 hour at room temperature. Diisopropylethylamine (2.0 equiv.) and the requisite aryl alcohol (1.0 equiv.) were then added and stirred overnight at room temperature. The mixture was then concentrated *in vacuo* and the residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure A3:

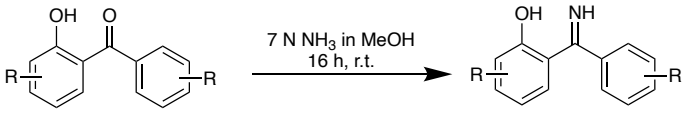
The appropriate amount of the corresponding carboxylic acid (1.0 equiv.) in CH_2Cl_2 (0.1 M) was added with the appropriate aryl alcohol (1.1 equiv.), DCC (1.1 equiv.), and DMAP (0.2 equiv.) at 0 ºC. The mixture was then stirred for 12 hours at room temperature. The mixture was then filtered and concentrated under vacuo. The residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure B: *Synthesis of 2-Hydroxybenzophenone compounds*



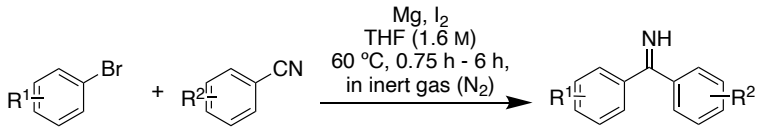
The appropriate amount of 2-hydroxybenzaldehyde derivative (1.0 equiv.), $PdCl_2$ (0.05 equiv.), LiCl (0.2 equiv.), Na_2CO_3 (2.0 equiv.) and DMF (0.12 M) were charged into a round-bottom flask under N_2 atmosphere. The reaction mixture was then heated to 120 ºC, the requisite iodobenzene derivative (2.0 equiv.) was added and the reaction was stirred for 16 h – 20 h. The reaction mixture was added to EtOAc (20 mL), extracted with brine (3 × 20 mL). dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

General Procedure C: *Synthesis of 2-Hydroxybenzophenone Imines*



The appropriate amount of 2-hydroxybenzophenone derivative (1.0 equiv.) was charged with NH_3 (7 N in MeOH) (5.0 equiv.) and the reaction mixture stirred for 6 h – 20 h at room temperature then concentrated *in vacuo*. The residue was purified by flash silica column chromatography under the conditions specified to afford the final product.

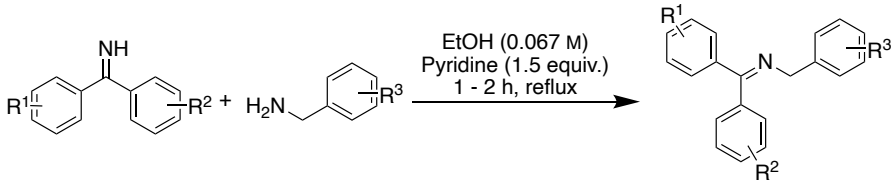
General Procedure D: *Synthesis of benzophenone imine compounds*



The appropriate amount of Mg (1.1 equiv.) was suspended in dry THF and small amount of 4-bromoaryl compound was charged into a flame-dried round-bottom flask under N_2 gas and stirred under reflux conditions. a crystal of I_2 was then added to initiate the reaction, stirred under reflux conditions until color disappears. Then, the remaining 4-bromoaryl (1.1 equiv.) compound was then added via syringe and stirred under gentle reflux for 45 mins. Reaction mixture was cooled to room-temperature and the appropriate amount of benzonitrile compound (1.0 equiv.) was added over 20 minutes and then stirred for additional 6 hours

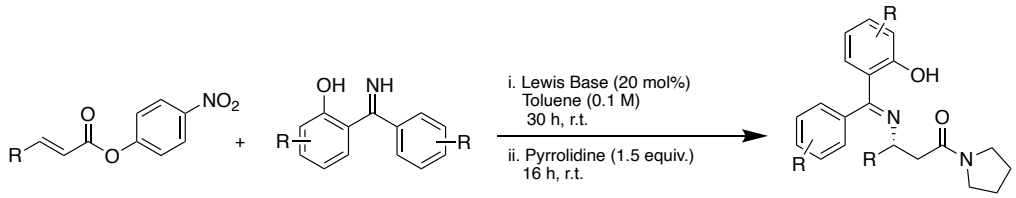
under gentle reflux. Reaction mixture was then cooled to room-temperature and quenched with MeOH and stirred for 20 mins. Reaction mixture was then concentrated under vacuo, dissolved in CH_2Cl_2, washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated to afford the crude product. Mixture was then purified by column chromatography under conditions specified to afford the final product.

General Procedure E: *Synthesis of Diarylmethanimine Schiff Bases*



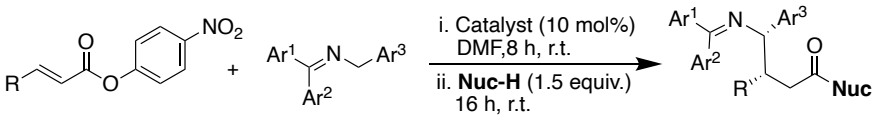
The appropriate amount of benzophenone imine derivative (1.0 equiv.) and benzylamine derivative (1.2 equiv.) was charged into a round-bottom flask with ethanol and pyridine (1.5 equiv.). The reaction mixture was stirred for 1 – 2 hours under reflux conditions until imine is totally consumed. Mixture was concentrated and purified by flash chromatography under conditions specified to afford the final product.

General Procedure F: *Synthesis of β-Amino Substituted Amides*



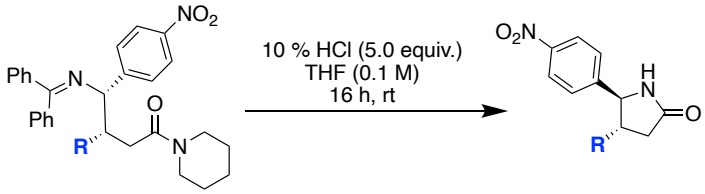
The requisite α,β-Unsaturated aryl ester (1.0 equiv.), 2-hydroxybenzophenone imine (2.0 equiv.), and isothiourea catalyst (20 mol%) were reacted in toluene (0.1 M) were stirred for 30 h at room temperature. The appropriate nucleophile (1.5 equiv.) was added, and the reaction stirred for 16 h at room temperature. The mixture was then concentrated *in vacuo* to give the crude material, which was purified by flash column chromatography under the conditions specified to afford the final product.

General Procedure G: *Synthesis of γ-Imino Substituted Amides and Esters*



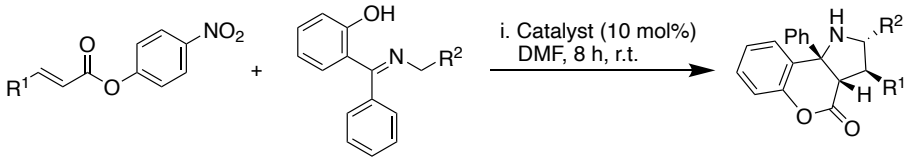
The requisite α,β-Unsaturated aryl ester (1.0 equiv.), diarylmethanimine (1.5 equiv.), and isothiourea catalyst (10 mol%) were reacted in dry dimethylformamide (0.1 M) and stirred for 8 h at room temperature. The appropriate nucleophile (1.5 equiv.) was added and the reaction was stirred for 16 h at room temperature. The mixture was then concentrated *in vacuo* and purified by flash column chromatography under the conditions specified to afford the final product.

General Procedure H: *Synthesis of 2-Pyrrolidinone Derivatives*



The requisite amount of the of γ-imino substituted amide product (1.0 equiv) and 10 % HCl (5.0 equiv.) were reacted in THF (0.1 M) and stirred for 16 h at room temperature. The reaction mixture was then concentrated and purified by flash chromatography under the conditions specified to afford the final product.

General Procedure I: *Synthesis of Chromeno-Pyrrolidine Derivatives*

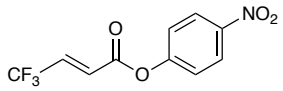


The requisite α,β-Unsaturated aryl ester (1.0 equiv.), diarylmethanimine (1.5 equiv.), and isothiourea catalyst (10 mol%) were reacted in dry dimethylformamide (0.1 M) and stirred for 8 h at room temperature. The mixture was then concentrated *in vacuo* and purified by flash column chromatography under the conditions specified to afford the final product.

5.3 PREPARATION OF STARTING MATERIALS

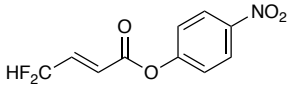
5.3.1 Data for α,β-Unsaturated Aryl Esters

4-Nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (59)



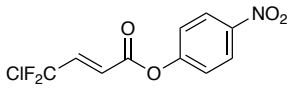
Following **General Procedure A1,** (*E*)-4,4,4-trifluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH_2Cl_2 (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the titled compound (477 mg, 32%) as a colourless crystaline solid. **mp** 86 – 88 ºC (Lit. **mp** 93 – 95ºC)[1]; **IR** ν_{max} (ATR) 3091 (Ar-H), 1739 (C=O), 1132 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.75 (1H, dq, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 1.9, CH=C*H*COOPNP), 7.05 (1H, dq, $^3J_{HH}$ = 15.8, $^3J_{HF}$ = 6.4, CF_3C*H*=CH), 7.37 – 7.41 (2H, m, C(2, 6)Ar*H*), 8.33 – 8.35 (2H, m, C(3, 5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -65.7. Spectroscopic data in agreement with the literature.[1]

4-Nitrophenyl (*E*)-4,4-difluorobut-2-enoate (171)



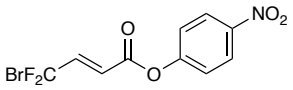
Following **General Procedure A1,** (*E*)-4,4difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH_2Cl_2 (40 mL) was stirred at rt for 16 h, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colourless crystaline solid. **mp** 74 – 76 ºC (Lit. **mp** 74 – 76 ºC)[1]; **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.36 (1H, tdd, $^2J_{HF}$ = 54.5, $^3J_{HH}$ = 3.8, $^4J_{HH}$ =1.1, -CF_2H), 6.55 (1H, dtd, $^3J_{HH}$ = 15.9, $^4J_{HF}$ = 5.9, $^4J_{HH}$ = 1.1, CF_2HCH=C*H*), 7.08 (1H, dtd, $^3J_{HH}$ = 15.9, $^3J_{HF}$ = 10.3, $^3J_{HH}$ = 3.8, CF_2HC*H*=CH), 7.35 – 7.39 (2H, m, C(2,6)Ar*H*), 8.31 – 8.35 (2H, m, C(3,5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -116.9. Spectroscopic data in agreement with the literature.[1]

4-Nitrophenyl (*E*)-3-chloro-4,4-difluorobut-2-enoate (172)



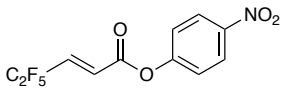
Following **General Procedure A1,** (*E*)-4-chloro-4,4difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.540 mmol), and CH_2Cl_2 (40 mL) was stirred at rt for 16 h, purified by flash chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colorless crystal solid. **mp** 74 – 76 ºC (Lit. **mp** 74 – 76ºC)[1]; **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.63 (1H, dt, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 1.8, C*H*=CHCF$_2$Cl), 7.19 (1H, dt, $^3J_{HH}$ = 15.6, $^3J_{HF}$ = 9.0, CF$_2$ClC*H*=CH), 7.35 – 7.41 (2H, m, C(2,6)Ar*H*), 8.33 – 8.37 (2H, m, C(3,5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -54.5. Spectroscopic data in agreement with the literature.[1]

4-Nitrophenyl (*E*)-3-chloro-4,4-difluorobut-2-enoate (173)



Following **General Procedure A2,** (*E*)-4-bromo-4,4difluorobut-2-enoic acid (523 mg, 2.6 mmol), oxalyl chloride (223 µL, 2.6 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-Nitrophenol (362 mg, 2.6 mmol), ^{i}Pr$_2$NEt (905 µL, 5.2 mmol) was added and the reaction was stirred at rt for 16 h, then purified by flash column chromatography (5:1 Petrol:EtOAc) to give the title compound (432 mg, 52%) as a white crystalline solid. **mp** 78 – 80ºC (Lit. **mp** 79 – 80ºC)[1]. **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.54 (1H, dt, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 1.8, C*H*=CHCF$_2$Cl), 7.23 (1H, m, CF$_2$BrC*H*=CH), 7.37 – 7.41 (2H, m, C(2,6)Ar*H*), 8.33 – 8.37 (2H, m, C(3,5)Ar*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -50.6. Spectroscopic data in agreement with the literature.[1]

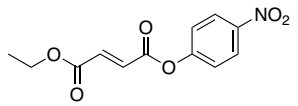
4-Nitrophenyl (*E*)-4,4,5,5,5-pentafluoropent-2-enoate (174)



Following **General Procedure A2,** (*E*)-4,4,5,5,5-pentafluoropent-2-enoic acid (610 mg, 3.2 mmol), oxalyl chloride (275 µL, 3.2 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-Nitrophenol (446 mg, 3.2 mmol), ^{i}Pr$_2$NEt (1.12 mL, 6.4 mmol) was added and the reaction was stirred at rt for 16 h, then purified by flash column chromatography

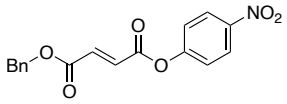
(2:1 Petrol:EtOAc) to give the title compound (800 mg, 80%) as a yellow oil. . **IR** ν_{max} (ATR) 3118 (Ar-H), 1735 (C=O), 1487 – 1531 (C=C), 1342 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 6.81 (1H, d, $^3J_{HH}$ = 15.8 C*H*=CHC$_2$F$_5$), 7.05 (1H, m, C$_2$F$_5$C*H*=CH), 7.37 – 7.41 (2H, m, C(2,6)Ar*H*), 8.33 – 8.37 (2H, m, C(3,5)Ar*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -84.4, -117.4. Spectroscopic data in agreement with the literature.[1]

Ethyl (4-nitrophenyl) fumarate (180)



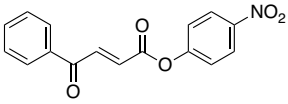
Following **General Procedure A1,** (*E*)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10 mmol), 4-nitrophenol (2.08 g, 15 mmol), EDCI (3.83 g, 20 mmol), DMAP (122 mg, 1 mmol), and 80 mL CH_2Cl_2 was stirred at rt for 16 h and gave the titled compound (889 mg, 34%) as a white solid. **mp** 68 – 69 ºC (Lit. **mp** 67 – 68 ºC)[1]; **IR** ν_{max} (ATR) 3072 (Ar-H), 1716 (C=O), 1514 (N-O), 1489 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.35 (3H, t, $^3J_{HH}$ = 7.1, OCH$_2$C*H*$_3$), 4.32 (2H, q, $^3J_{HH}$ = 7.1, OC*H*$_2$CH$_3$), 7.03 – 7.07 (2H, m, C*H*=C*H*), 7.34 – 7.38 (2H, m, C(2,6)Ar*H*), 8.31 (2H, m, C(3,5)Ar*H*). Spectroscopic data in agreement with the literature.[2]

Benzyl (4-nitrophenyl)fumarate (181)



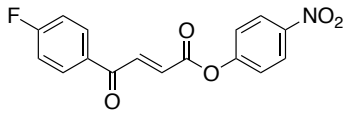
Following **General Procedure A3,** (*E*)-4-(benzyloxy)-4-oxobut-2-enoic acid (645 mg, 3.13 mmol), 4-nitrophenol (440 mg, 3.16 mmol), DCC (710 mg, 3.44 mmol), DMAP (76 mg, 0.63 mmol), and 3 mL CH_2Cl_2 was stirred at rt for 12 h and gave the titled compound (0.607 g, 59%) as a white solid. **mp** 74 – 75 ºC (Lit. **mp** 74 – 76 ºC)[2] ; **IR** ν_{max} (ATR) 3078 (Ar-H), 1716 – 1737 (C=O), 1517 (N-O), 1490 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 5.29 (2H, s, CO$_2$-C*H*$_2$-C$_6$H$_5$), 7.20 – 7.24 (2H, m, C*H*=C*H*), 7.33 – 7.37 (2H, m, C(2,6)Ar*H*-NO$_2$), 7.39 – 7.43 (5H, m, CO$_2$-CH$_2$-Ar*H*), 8.28 – 8.32 (2H, m, C(3,5)Ar*H*-NO$_2$). Spectroscopic data in agreement with the literature.[2]

4-Nitrophenyl (*E*)-4-oxo-4-phenylbut-2-enoate (184)



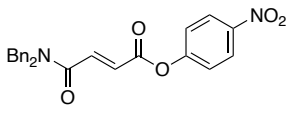
Following **General Procedure A2,** (*E*)-4-oxo-4-phenylbut-2-enoic acid (0.44 g, 2.5 mmol), oxalyl chloride (0.21 mL, 2.5 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-nitrophenol (0.34 g, 2.5 mmol), $^{i}Pr_2NEt$ (0.87 mL, 5.0 mmol) was added and stirred at rt for 16 h and gave the titled product as a yellow solid (0.15 g, 20%). **mp** 127 - 129 ºC (Lit. **mp** 128 – 129 ºC)[3]; **IR** ν_{max} (ATR) 3080 (Ar-H), 1747 (C=O), 1521 (N-O), 1489 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 7.10 (1H, d, $^3J_{HH}$ = 16.6, C*H*=CH-CO-Ph), 7.39 – 7.42 (2H, m, C(2,6)Ar*H*-NO_2), 7.55 – 7.57 (2H, m, C(3,5)Ar*H*), 7.65 – 7.68 (1H, m, C(4)Ar*H*), 8.05 (2H, m, C(2,6)Ar*H*), 8.10 – 8.14 (1H, d, $^3J_{HH}$ = 16.6 CH=C*H*-CO-Ph), 8.31 – 8.35 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data in agreement with the literature.[3]

4-Nitrophenyl (*E*)-4-(4-fluorophenyl)-4-oxobut-2-enoate



Following **General Procedure A2,** (*E*)-4-(4-fluorophenyl)-4-oxobut-2-enoic acid (485 mg, 2.5 mmol), oxalyl chloride (0.21 mL, 2.5 mmol), and few drops of DMF in CH_2Cl_2 (0.33 M) was stirred for 1 hour. Then, 4-nitrophenol (0.34 g, 2.5 mmol), $^{i}Pr_2NEt$ (0.87 mL, 5.0 mmol) was added and stirred at rt for 16 h and gave the titled product as a beige solid (426 mg, 54%). **mp** 130 – 132 ºC; **IR** ν_{max} (ATR): 3115 (Ar-H), 1747 – 1768 (C=O, Ester and Ketone), 1517 (N-O), 1489 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 7.10 (1H, d, $^3J_{HH}$ = 16.6, C*H*=CH-CO-Ph), 7.39 – 7.41 (2H, m, C(2,6)Ar*H*-NO_2), 7.54 – 7.56 (2H, m, C(3,5)Ar*H*), 7.65 – 7.68 (1H, m, C(4)Ar*H*), 8.03 – 8.07 (2H, m, C(2,6)Ar*H*), 8.11 – 8.15 (1H, d, $^3J_{HH}$ = 16.6 CH=C*H*-CO-Ph), 8.31 – 8.35 (2H, m, C(3,5)Ar*H*-NO_2);

4-Nitrophenyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (182)

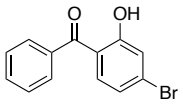


Following **General Procedure A3,** (*E*)-4-(dibenzylamino)-4-oxobut-2-enoic acid (2.08 g, 7.04 mmol), 4-nitrophenol (1.0 g, 7.18 mmol), DCC (1.74 g, 8.44 mmol), DMAP (172 mg, 01.41 mmol), and 7 mL CH_2Cl_2 was stirred at rt for 12 h and gave the titled compound (2.20 g, 75%) as an orange solid. **mp** 62 – 65 ºC (Lit. **mp** 62 – 64ºC)[1]; **IR** ν_{max} (ATR) 3030 (Ar-H), 1741

(C=O), 1587 (N-O), 1440 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 5.29 (2H, s, CO_2-C*H*$_2$-C_6H_5), 7.20 – 7.24 (2H, m, C*H*=C*H*), 7.33 – 7.36 (2H, m, C(2,6)Ar*H*-NO_2), 7.40 – 7.43 (5H, m, CO_2-CH_2-Ar*H*), 8.28 – 8.32 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data in agreement with the literature.[1]

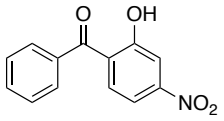
5.3.2 Data for Benzophenone Derivatives

(4-Bromo-2-hydroxyphenyl)(phenl)methanone



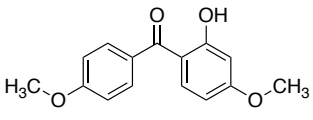
Following **General Procedure B,** 4-bromo-2-hydroxybenzaldehye (289 mg, 1.2 mmol), Iodobenzene (266 µL, 2.4 mmol), $PdCl_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na_2CO_3 (254 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 ºC for 16 hours, then purified by flash column chromatography (2:1 Petrol:EtOAc) to give the title compound (269.5 mg, 72%) as a pale yellow liquid. **IR** ν_{max} (ATR): 3005 (OH), 2843 (Ar-H), 1629 (C=O), 1440 (C=C), ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.02 (1H, dd, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 1.9, C(5)Ar*H*OH-Br), 7.28 (1H, d, $^4J_{HH}$ = 1.9, C(3)Ar*H*OH-Br), 7.46 (1H, d, $^3J_{HH}$ = 8.6, C(6)Ar*H*OH-Br), 7.52 (2H, t, $^3J_{HH}$ = 7.5, C(3,5)Ar*H*), 7.59 – 7.61 (1H, m, C(4)Ar*H*), 7.65 – 7.67 (2H, m, C(2,6)Ar*H*), 12.1 (1H, s, O*H*). Spectroscopic data in agreement with literature.[4]

(2-Hydroxy-4-nitrophenyl)(phenyl)methanone



Following **General Procedure B,** 2-hydroxy-4-nitrobenzaldehye (201 mg, 1.2 mmol), Iodobenzene (266 µL, 2.4 mmol), $PdCl_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na_2CO_3 (254 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 ºC for 6 hours, then purified by flash column chromatography (20:1 Petrol:EtOAc then flush with EtOAc) to give the title compound (66.3 mg, 23%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.59 (2H, dd, $^3J_{HH}$ = 8.3, $^3J_{HH}$ = 6.9 Hz, C(3,5)Ar*H*), 7.68 (1H, m, C(4)Ar*H*), 7.71 – 7.75 (3H, m, C(1,2)Ar*H* and C(5)Ar*H*OH-NO_2), 7.83 (1H, d, C(6)Ar*H*OH-NO_2), 7.94 (1H, d, $^4J_{HH}$ = 2.2, C(3)Ar*H*OH-NO_2), 12.01 (1H, s, O*H*). Spectroscopic data in agreement with the literature.[4]

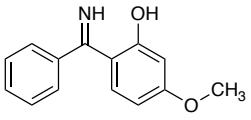
(2-Hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methanone



Following **General Procedure B,** 2-hydroxy-4-methoxybenzaldehye (183 mg, 1.2 mmol), 1-iodo-4-methoxybenzene (562 µL, 2.4 mmol), $PdCl_2$ (10.6 mg, 0.06 mmol), LiCl (10.2 mg, 0.24 mmol), Na_2CO_3 (254 mg, 2.4 mmol), DMF (10 mL) were stirred at 120 º C for 6 hours, then purified by flash column chromatography (2:1 Petrol:EtOAc then flush with EtOAc) to give the title compound (223.8 mg, 72%) as a pale yellow solid. **mp** 108 – 110 ºC (Lit. **mp** 110–112 ºC)[5] ; **IR** ν_{max} (ATR): 3005 (OH), 2843 (Ar-H), 1629 (C=O), 1440 (C=C), 1270 (C-O-CH_3) ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.87 (3H, s, ArH-OC*H*$_3$), 3.89 (3H, s, ArHOH-OC*H*$_3$), 6.42 (1H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.6 Hz, C(5)Ar*H*OH-OCH_3), 6.52 (1H, d, $^4J_{HH}$ = 2.6 Hz, C(3)Ar*H*OH-OCH_3), 6.97 – 7.0 (2H, m, C(3,5)Ar*H*-OCH_3), 7.56 (1H, d, $^3J_{HH}$ = 8.9 Hz, C(6)Ar*H*OH-OCH_3), 7.65 – 7.67 (2H, m, C(2,6)Ar*H*-OCH_3), 12.69 (1H, s, O*H*). Spectroscopic data in agreement with the literature. [5],[6]

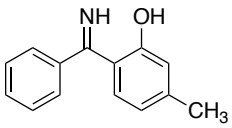
5.3.3 Data for Benzophenone Imine Derivatives

2-(Imino(phenyl)methyl)-5-methoxyphenol (154)



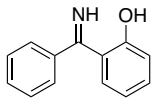
Following **General Procedure C,** (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (685 mg, 3 mmol), and 7N NH_3 in MeOH (2.14 mL, 15 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (0.31 g, 45%) as a yellow solid. **mp** 123 – 126 ºC; **IR** ν_{max} (ATR): 2932 (N-H), 1608 (C=N), 1423 – 1447 (C=C), 1277 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.84 (3H, s, OC*H*$_3$), 6.23 (1H, m, C(4)Ar*H*OH-OCH_3), 6.45 (1H, s, C(6)Ar*H*OH-OCH_3), 7.06 (1H, d, $^3J_{HH}$ = 9.1 Hz, C(3)Ar*H*OH-OCH_3), 7.47 – 7.50 (5H, m, Ar*H*), 8.18 (1H, s, N*H*), 15.07 (1H, s, O*H*). Spectroscopic data in agreement with the literature.[7]

2-(Imino(phenyl)methyl)-5-methylphenol (155)



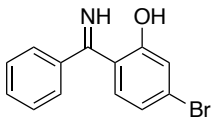
Following **General Procedure C,** (2-hydroxy-4-methylphenyl)(phenyl)methanone (318 mg, 1.5 mmol), and 7N NH_3 in MeOH (1.07 mL, 7.5 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (237.1 mg, 75%) as a yellow solid. **mp** 66 – 70 ºC (Lit. **mp** 69 ºC)[8]; **IR** ν_{max} (ATR): 2845 (N-H), 1616 (C=N), 1429 – 1493 (C=C), 1083 (Ar-CH_3) ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.36 (3H, s, C*H*$_3$), 6.57 (1H, d, $^3J_{HH}$ = 8.0 Hz, C(5)Ar*H*OH-CH_3), 6.88 (1H, s, C(3)Ar*H*OH-CH_3), 7.09 (1H, d, $^3J_{HH}$ = 8.0 Hz, C(6)Ar*H*OH-CH_3), 7.42 (2H, d, $^3J_{HH}$ = 5.5 Hz, C(2,6)Ar*H*), 7.50 – 7.53 (3H, m, C(3,4,5)Ar*H*), 9.14 (1H, s, N*H*), 14.74 (1H, s, O*H*). Spectroscopic data in agreement with the literature.[8]

2-(Imino(phenyl)methyl)phenol (135)



Following **General Procedure C,** (2-hydroxyphenyl)(phenyl)methanone (198 mg, 1 mmol), and 7N NH_3 in MeOH (717.7 µL, 5 mmol) stirred at rt for 16 hours gave the titled compound (153.4 mg, 78%) as a yellow solid. **mp** 82 – 84 ºC (Lit. **mp** 94 – 97 ºC)[9] ; **IR** ν_{max} (ATR): 2826 (N-H), 1589 (C=N), 1462-1508 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.79 (1H, dd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 1.2, HN=C(3)Ar*H*OH), 7.14 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.21, C(5)Ar*H*OH), 7.24 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7, C(4)Ar*H*OH), 7.41 (1H, dd, $^3J_{HH}$ = 8.6, $^4J_{HH}$ = 1.7, C(6)Ar*H*OH), 7.45 – 7.47 (2H, m, HN=CAr*H*), 7.51 – 7.55 (3H, m, HN=CAr*H*), 9.67 (1H, s, N-*H*), 14.26 (1H, bs, O*H*). Spectroscopic data in agreement with the literature. [7],[8],[9]

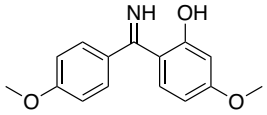
5-Bromo-2-(imino(phenyl)methyl)phenol (156)



Following **General Procedure C,** 2-(imino(phenyl)methyl)-5-methylphenol (260 mg, 0.8 mmol), and 7N NH_3 in MeOH (600 µL, 4.2 mmol) stirred at rt for 16 hours, purified by flash chromatography (2:1 Petrol:EtOAc) to give gave the titled compound (169.7 mg, 65%) as a yellow solid. **mp** 115 – 117 º C; **IR** ν_{max} (ATR): 3038 – 3057 (OH), 1587 (C=N), 1487 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.20 (3H, s, ArOH-Br), 6.97 – 7.0 (2H, m, C(3,6)Ar*H*OH-CH_3), 7.20 (1H, d, $^3J_{HH}$ = 8.5 Hz, C(4)Ar*H*OH-CH_3), 7.40 – 7.44 (2H, m, C(2,6)Ar*H*), 7.50 – 7.53 (3H, m, C(3,4,5)Ar*H*), 9.32 (1H, s, N*H*), 14.45 (1H, bs, O*H*). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_H:

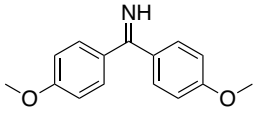
116.7 (*C*(1)ArOH-Br), 120.7 (*C*(5)ArOH-Br), 122.2 (*C*(3)ArOH-Br), 127.3 (*C*(2,6)Ar), 128.4 (*C*(4)ArOH-Br), 128.9 (*C*(3,5)ArOH-Br), 130.4 (*C*(4)ArOH-Br), 128. (*C*(4)Ar), 133.1 (*C*(6)ArOH-Br), 138.1 (*C*(1)Ar), 165.9 (*C*(2)ArOH-Br), 180.3 (*C*=N); **HRMS** (NSI^+) $C_{13}H_{10}BrNO$ ([$M+H^+$]) requires 276.0019, found 276.0012 (-2.5 ppm).

2-(Imino(4-methoxyphenyl)methyl)-5-methoxyphenol



Following **General Procedure C**, (2-hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methanone (136 mg, 0.53 mmol), and 7N NH_3 in MeOH (0.38 mL, 2.65 mmol) stirred at rt for 16 hours, and purified by flash column chromatography (2:1 Petrol:EtOAc then flushed with EtOAc) to give gave the titled compound (95.7 mg, 14%) as a yellow oil. **IR** ν_{max} (ATR): 2963 (Ar-H), 1608 (C=N), 1456 (C=C), 1219 – 1254 (C-O-CH_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.84 (3H, s, ArHOH-OC*H*$_3$), 3.90 (3H, s, ArH-OC*H*$_3$), 6.21 (1H, dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 2.5 Hz, C(5)Ar*H*OH-OCH_3), 6.43 (1H, d, $^4J_{HH}$ = 2.5 Hz, C(3)Ar*H*OH-OCH_3), 7.02 (2H, d, $^3J_{HH}$ = 8.7 Hz, C(3,5)Ar*H*-OCH_3), 7.11 (1H, d, $^3J_{HH}$ = 9.1, C(6)Ar*H*OH-OCH_3), 7.42 (2H, d, $^3J_{HH}$ = 8.7 Hz, C(2,6)Ar*H*-OCH_3), 7.96 (1H, s, N*H*), 15.07 (1H, s, O*H*). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_{Cl}: 55.4 (ArHOH-O*C*H_3), 55.5 (ArH-O*C*H_3), 102.4 (*C*(3)ArHOH-OCH_3), 106.7 (*C*(5)ArHOH-OCH_3), 110.6 (*C*(1)ArHOH-OCH_3), 114.2 (*C*(3,5)ArH-OCH_3), 129.5 (*C*(1,2,6)ArH-OCH_3), 133.6 (*C*(6)ArHOH-OCH_3), 161.3 (*C*(4)ArH-OCH_3), 165.5 (*C*(4)ArHOH-OCH_3), 173.3 (*C*(2)ArHOH-OCH_3), 176.6 (*C*=N); **HRMS** (NSI^+) $C_{15}H_{15}NO_3$ ([$M+H^+$]) requires 258.1125, found 258.1117 (-3.1 ppm).

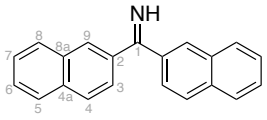
Bis(4-methoxyphenyl)methanimine



Following **General Procedure D**, 4-bromoanisole (690 µL, 5.5 mmol), 4-methoxybenzonitrile (666 mg, 5.0 mmol), Mg (134 mg, 5.5 mmol), THF (8.3 mL), I_2 small crystal, was stirred for 0.45 h – 6 h, quenched with MeOH (0.8 mL) and product was recrystalised using diethyl ether to obtain the product in beige crystal solid (965 mg, 79% yield). **mp** 128 – 129 ºC (Lit: **mp** 128

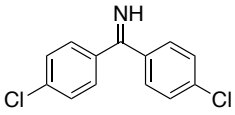
– 129 ºC); **IR** ν_{max} (ATR): 3257 (N-H), 3013 (Ar-H), 1602 (C=N), 1415 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H**:** 3.88 (6H, s, -OCH_3), 6.97 (4H, d, $^3J_{HH}$ = 8.7, HN=C*C*(2,6)Ar$_1$*H*, HN=C*C*(2,6)Ar$_2$*H*), 7.61 (4H, $^3J_{HH}$ = 8.7, HN=C*C*(3,5)Ar$_1$*H*, HN=C*C*(3,5)Ar$_2$*H*); Spectroscopic data in agreement with the literature.[10]

Di(naphthalen-2-yl)methanimine



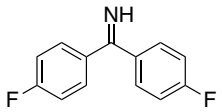
Following **General Procedure D**, 2-bromonaphthalene (1.1 grams, 5.5 mmol), 4-methoxybenzonitrile (766 mg, 5.0 mmol), Mg (134 mg, 5.5 mmol), THF (8.3 mL), I_2 small crystal, was stirred for 0.45 h – 6 h, quenched with MeOH (0.8 mL) and product was recrystalised using diethyl ether to obtain the product in beige crystal solid (630 mg, 50% yield). **mp** 120 - 121 ºC (Lit: **mp** 121.5 – 122 ºC); **IR** ν_{max} (ATR): 3257 (N-H), 3013 (Ar-H), 1602 (C=N), 1415 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H**:** 7.54 – 7.68 (4H, m, C(6,7)*H*Naph), 7.85 – 7.90 (2H, m, C(8)*H*Naph), 7.93 – 7.98 (4H, m, C(4,5)*H*Naph), 8.02 – 8.03 (2H, m, C(3)*H*Naph), 8.11 (2H, m, C(9)*H*Naph), 8.35 (1H, s, N–*H*); Spectroscopic data in agreement with the literature.[11]

Bis(4-chlorophenyl)methanimine



Following **General Procedure D**, 1-bromo-4-chlorobenzene (5.9 grams, 31.1 mmol), 4-chlorobenzonitrile (4.1 grams, 30 mmol), Mg (755 mg, 5.5 mmol), THF (46 mL), I_2 small crystal, was stirred for 0.45 h – 6 h, quenched with MeOH (04.5 mL) and product was recrystalised using diethyl ether to obtain the product in yellow crystal solid (1.73 grams, 23% yield). **mp** 59 – 60 ºC (Lit: **mp** 59 – 60 ºC); **IR** ν_{max} (ATR): 3257 (N-H), 3013 (Ar-H), 1602 (C=N), 1415 (C=C);**^{1}H NMR** (400 MHz, $CDCl_3$), δ_H**:** 7.44 – 7.46 (4H, m, HN=C*C*(2,6)Ar$_1$*H*, HN=C*C*(2,6)Ar$_2$*H*), 7.57 – 7.59 (4H, m, HN=C*C*(3,5)Ar$_1$*H*, HN=C*C*(3,5)Ar$_2$*H*); Spectroscopic data in agreement with the literature.[12]

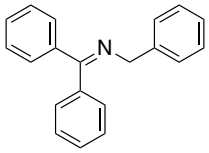
Bis(4-fluorophenyl)methanimine



Following **General Procedure D**, 1-bromo-4-fluorobenzene (3.4 mL, 31.1 mmol), 4-chlorobenzonitrile (3.6 grams, 30 mmol), Mg (755 mg, 5.5 mmol), THF (46 mL), I_2 small crystal, was stirred for 0.45 h – 6 h, quenched with MeOH (4.5 mL), and product was recrystalised using diethyl ether to obtain the product in yellow oil (1.39 grams, 21% yield); **IR** ν_{max} (ATR): 3257 (N-H), 3013 (Ar-H), 1602 (C=N), 1415 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H**:** 7.13 – 7.15 (4H, m, HN=C*C*(2,6)Ar$_1$*H*, HN=C*C*(2,6)Ar$_2$*H*), 7.60 – 7.63 (4H, m, HN=C*C*(3,5)Ar$_1$*H*, HN=C*C*(3,5)Ar$_2$*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) , δ_F: -102.4. Spectroscopic data in agreement with the literature.[13]

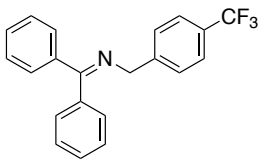
5.3.4 Data for Diarylmethanimine Schiff Bases

***N*-benzyl-1,1-diphenylmethanimine (241)**



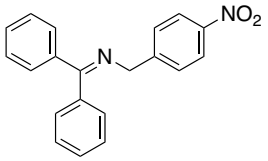
Following **General Procedure E,** diphenylmethanimine (840 µL, 5 mmol), benzylamine (956 µL, 8.75 mmol), pyridine (604 µL, 12 mmol), in ethanol (75 mL) was refluxed for 1 hour, to give the titled compound (1.48 g, 99%) as a colourless solid; **mp** 58 – 59 ºC (Lit: **mp** 58 – 59 ºC);**IR** ν_{max} (ATR): 3059 (Ar-H), 1618 (C=N), 1440 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.64 (2H, s, NC*H*$_2$Ph), 7.22 – 7.25 (3H, m, NCH$_2$C(3,4,5)Ar*H*), 7.37 – 7.49 (10H, m, N=CAr$_1$*H*, N=CAr$_2$*H*), 7.70 – 7.73 (2H, m, NCH$_2$C(2,6)Ar*H*). Spectroscopic data in agreement with the literature.[14]

1,1-Diphenyl-*N*-(4-(trifluoromethyl)benzyl)methanimine (242)



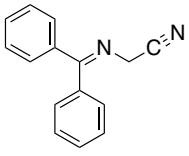
Following **General Procedure E,** diphenylmethanimine (840 µL, 5 mmol), (4-(trifluoromethyl)Phenyl)methanamine (1.25 mL, 8.75 mmol), pyridine (604 µL, 7.5 mmol), in ethanol (75 mL) was refluxed for 1 hour and purified via flash chromatography 4:1 Petrol:EtOAc (R_f = 0.4) to give the titled compound (2.11 g, 99%) as light yellow oil; **IR** ν_{max} (ATR): 3059 (Ar-H), 1618 (C=N), 1446 (C=C), 1119 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.66 (2H, s, NC*H*$_2$Ar-CF_3), 7.20 – 7.23 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.36 – 7.40 (2H, m, NCH$_2$C(2,6)Ar*H*-NO_2), 7.43 – 7.40 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.60 – 7.62 (2H, m, N=CC(2,6)Ar$_1$*H*), 7.71 – 7.73 (2H, m, NCH$_2$C(3,5)Ar*H*-CF_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -62.3. Spectroscopic data in agreement with the literature.[15]

***N*-(4-nitrophenyl)-1,1-diphenylmethanimine (243)**



Following **General Procedure E,** diphenylmethanimine (840 µL, 5 mmol), 4-nitrobenzylamine hydrochloride (1.13 grams, 6mmol), pyridine (604 µL, 7.5 mmol), in ethanol (75 mL) was refluxed for 1 hour and and purified via flash chromatography 4:1 Petrol:EtOAc (R_f = 0.4) to give the titled compound (1.5 g, 95%) as a yellow crystal. **mp** 60 – 62 ºC ;**IR** ν_{max} (ATR): 3061 (Ar-H), 1625 (C=N), 1512 (N-O), 1446 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.69 (2H, s, NC*H*$_2$Ar-NO_2), 7.21 – 7.23 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.40 – 7.53 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.56 – 7.58 (2H, m, NCH$_2$C(2,6)Ar*H*-NO_2), 7.71 – 7.73 (2H, m, N=CC(2,6)Ar$_1$*H*), 8.21 – 8.23 (2H, m, NCH$_2$C(3,5)Ar*H*-NO_2).

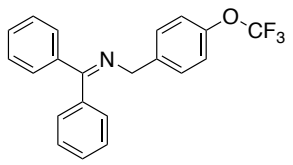
2-((diphenylmethylene)amino)acetonitrile (244)



Following **General Procedure E,** diphenylmethanimine (419 µL, 2.5 mmol), 2-aminoacetonitrile sulfate (675 mg, 3 mmol), pyridine (302 µL, 3.75 mmol), in ethanol (37 mL) was refluxed for 1 hour and and purified via flash chromatography 10:1 Petrol:EtOAc (R_f = 0.31) to give the titled compound (373 mg, 68%) as a yellow oil. **IR** ν_{max} (ATR): 3057 (Ar-H), 2250 (CN), 1616(C=N), 1595 (N-O), 1444 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.22 (2H, s, NC*H*$_2$CN), 7.17 – 7.19 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.36 – 7.52 (6H, m, N=CC(3,4,5)Ar$_1$*H*,

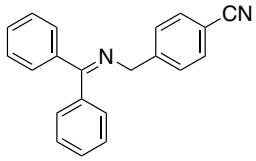
N=CC(3,4,5)Ar$_2$*H*), 7.56 – 7.58 (2H, m, NCH$_2$C(2,6)Ar*H*-NO$_2$), 7.63 – 7.65 (2H, m, N=CC(2,6)Ar$_1$*H*), 8.21 – 8.23 (2H, m, NCH$_2$C(3,5)Ar*H*-NO$_2$).Spectroscopic data in agreement with the literature.[16,17]

1,1-diphenyl-*N*-(4-(trifluoromethoxy)benzyl)methanimine



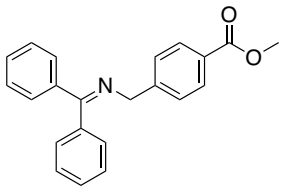
Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), 2-aminoacetonitrile sulfate (688 mg, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour and and purified via flash chromatography 4:1 Petrol:EtOAc (R_f = 0.31) to give the titled compound (1.0 g, 94%) as a yellow oil; **IR** ν_{max} (ATR): 3059 (Ar-H), 1624 (C=N), 1446 (C=C), 1155 (C-F), 1045 (C-O-C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.62 (2H, s, NC*H*$_2$Ar-OCF$_3$), 7.20 – 7.23 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.22 – 7.24 (2H, m, NCH$_2$C(2,6)Ar*H*-CF$_3$),7.40 – 7.51 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.50 – 7.52 (2H, m, NCH$_2$C(3,5)Ar*H*-CF$_3$), 7.71 – 7.73 (2H, m, N=CC(2,6)Ar$_1$*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -57.9 (-OC*F*$_3$). Spectroscopic data in agreement with the literature.[18]

4-(((diphenylmethylene)amino)methyl)benzonitrile



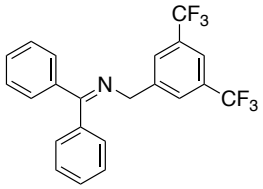
Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), 4-(aminomethyl)benzonitrile hydrochloride (607 mg, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour and and purified via flash chromatography 4:1 Petrol:EtOAc (R_f = 0.31) to give the titled compound (804 mg, 90%) as a yellow solid. **mp** 66 - 68 ºC; **IR** ν_{max} (ATR): 3059 (Ar-H), 2250 (CN, nitrile), 1624 (C=N, imine), 1446 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.65 (2H, s, NC*H*$_2$Ar-CN), 7.21 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.39 – 7.46 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.51 – 7.53 (2H, m, NCH$_2$C(2,6)Ar*H*-CN), 7.62 – 7.64 (2H, m, NCH$_2$C(3,5)Ar*H*-CN), 7.71 – 7.73 (2H, m, N=CC(2,6)Ar$_1$*H*). Spectroscopic data in agreement with the literature.[18]

Methyl 4-(((diphenylmethylene)amino)methyl)benzoate



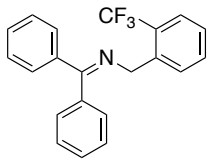
Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), methyl 4-(aminomethyl)benzoate hydrochloride (726 mg, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour and and purified via flash chromatography 4:1 Petrol:EtOAc (R_f = 0.34) to give the titled compound (696 mg, 70%) as a yellow oil; **IR** ν_{max} (ATR): 2953 (Ar-H), 1716 (C=O, ester), 1610 (C=N, imine), 1435(C=C), 1273 (C-C-O stretch, ester), 1105 (O-C-C stretch, ester); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 3.91 (3H, s, -OC*H*$_3$), 4.68 (2H, s, NC*H*$_2$Ar-CO_2Me), 7.20 – 7.23 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.34 – 7.36 (2H, m, NCH_2C(2,6)Ar-CO_2Me), 7.40 – 7.47 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.74 – 7.76 (2H, m, N=CC(2,6)Ar$_1$*H*), 7.63 – 7.65 (2H, m, NCH_2C(3,5)Ar*H*-CO_2Me).

***N*-(3,5-bis(trifluoromethyl)benzyl)-1,1-diphenylmethanimine**



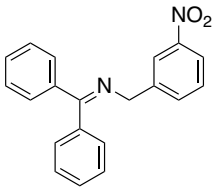
Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), (3,5-bistrifluoromethyl)phenyl)methanimine hydroochloride (808 mg, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour and and purified via flash chromatography 4:1 Petrol:EtOAc (R_f = 0.34) to give the titled compound (1.1 g, 90%) as a yellow solid. **mp** 56 – 58 ºC; **IR** ν_{max} (ATR): 3059 (Ar-H), 1614 (C=N, imine), 1446(C=C), 1118 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.70 (2H, s, NC*H*$_2$Ar(CF_3)$_2$), 7.21 – 7.24 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.41 – 7.54 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.71 – 7.73 (2H, m, N=CC(2,6)Ar$_1$*H*), 7.79 (1H, s, NCH_2C(4)Ar*H*-(CF_3)$_2$), 7.88 (2H, s, NCH_2C(2,6)Ar*H*-(CF_3)$_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -62.8.

1,1-diphenyl-*N*-(2-(trifluoromethyl)benzyl)methanimine



Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), (2-(trifluoromethyl)phenyl)methanamine (504.8 µL, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour, to give the titled compound (969 mg, 95%) as a yellow oil. **IR** ν_{max} (ATR): 3080 (Ar-H), 1624 (C=N), 1445 (C=C), 1111 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.79 (2H, s, NC*H*$_2$Ar-2-CF_3), 7.22 – 7.24 (2H, m, $NCH_2C(2,6)Ar_1$*H*), 7.35 – 7.38 (1H, m, $NCH_2C(4)Ar$*H*-2-CF_3), 7.39 – 7.53 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.56 – 7.60 (1H, m, $NCH_2C(4)Ar$*H*-2-CF_3), 7.64 – 7.66 (1H, m, $NCH_2C(3)Ar$*H*-2-CF_3), 7.73 – 7.75 (2H, m, $NCH_2C(2,6)Ar_2$*H*), 7.77 – 7.79 (1H, m, $NCH_2C(6)Ar$*H*-2-CF_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.3; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 53.6 (N*C*H$_2$Ar-2-CF_3), 125.6 -125.8 (q, $^{3}J_{CF}$ = 5.8, NCH_2*C*(3)Ar-2-CF_3), 126.5 (NCH_2*C*(4)Ar-2-CF_3), 127.6 (N=C*C*(2,6)Ar$_1$), 128.1 - 128.6 (N=C*C*(3,5)Ar$_1$, N=C*C*(3,5)Ar$_2$), 128.7 (N=C*C*(2,6)Ar$_2$), 128.7 (NCH_2*C*(1)Ar-2-CF_3), 129.5 (NCH_2*C*(2)Ar-2-CF_3), 130.2 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 131.9 (NCH_2*C*(5)Ar-2-CF_3), 136.4 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 139.5 (*C*F_3), 139.7 (NCH_2*C*(2)Ar-2-CF_3), 169.8 (*C*=N); **HRMS** (NSI^+) $C_{21}H_{17}F_3N^+$ ([M+H]$^+$) requires 340.1308, found 340.1304 (-0.9 ppm).

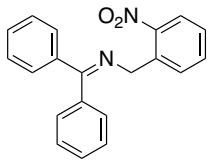
***N*-(3-nitrobenzyl)-1,1-diphenylmethanimine**



Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), (3-nitrophenyl)methanamine (679 mg, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour, to give the titled compound (950 mg, 100%) as a yellow solid. **mp** 54 – 56 ºC; **IR** ν_{max} (ATR): 3062 (Ar-H), 1616 (C=N), 1519 (N-O), 1443 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.91 (2H, s, NC*H*$_2$Ar-3-NO_2), 7.23 – 7.25 (2H, m, $NCH_2C(2,6)Ar_1$*H*),

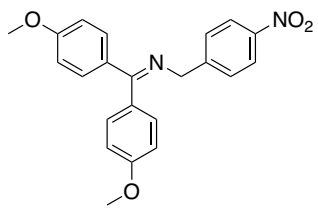
7.36 – 7.44 (3H, m, N=CC(3,4,5)Ar$_1$*H*), 7.45 – 7.47 (1H, m, NCH$_2$C(5)Ar*H*-3-NO$_2$), 7.48 – 7.54 (3H, m, N=CC(3,4,5)Ar$_2$*H*)), 7.62 – 7.66 (1H, m, NCH$_2$C(4)Ar*H*-3-NO$_2$), 7.68 – 7.71 (2H, m, NCH$_2$C(2,6)Ar$_2$*H*), 7.78 – 7.80 (1H, m, NCH$_2$C(2)Ar*H*-3-NO$_2$), 8.00 – 8.02 (1H, m, NCH$_2$C(6)Ar*H*-3-NO$_2$); **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ_C: 54.4 (N*C*H$_2$Ar-3-NO$_2$), 124.6 (NCH$_2$*C*(6)Ar-3-NO$_2$), 127.5 (N=C*C*(2,6)Ar$_1$), 128.2 (N=C*C*(3,5)Ar$_1$), 128.6 (N=C*C*(2,6)Ar$_2$), 128.8 (N=C*C*(3,5)Ar$_2$), 130.3 (NCH$_2$*C*(5)Ar-3-NO$_2$), 130.4 (NCH$_2$*C*(2)Ar-2-NO$_2$), 133.2 (NCH$_2$*C*(4)Ar-2-NO$_3$), 136.3 (NCH$_2$*C*(3)Ar-3-NO$_2$), 136.4 (NCH$_2$*C*(1)Ar-3-NO$_2$), 139.4 (N=C*C*(1)Ar$_1$, N=C*C*(2)Ar$_2$), 170.2 (*C*=N); **HRMS** (NSI$^+$) $C_{20}H_{17}N_2O_2^+$ ([M+H]$^+$) requires 317.1283, found 317.1285 (-0.5 ppm).

***N*-(2-nitrobenzyl)-1,1-diphenylmethanimine**



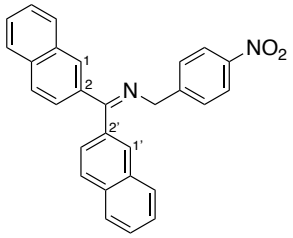
Following **General Procedure E,** diphenylmethanimine (503 µL, 3.0 mmol), (2-nitrophenyl)methanamine (679 mg, 3.6 mmol), pyridine (362 µL, 4.5 mmol), in ethanol (45 mL) was refluxed for 1 hour, to give the titled compound (927 mg, 98%) as a yellow solid. **mp** 66 - 68 ºC; **IR** ν_{max} (ATR): 3062 (Ar-H), 1618 (C=N), 1519 (N-O), 1443 (C=C); **^{1}H-NMR** (400 MHz, CDCl$_3$), δ_H: 4.69 (2H, s, NC*H*$_2$Ar-2-NO$_2$), 7.23 – 7.24 (2H, m, NCH$_2$C(2,6)Ar$_1$*H*), 7.38 – 7.54 (6H, m, N=CC(3,4,5)Ar$_1$*H,* N=CC(3,4,5)Ar$_2$*H*), 7.54 – 7.55 (NCH$_2$C(5)Ar*H*-2-NO$_2$), 7.71 – 7.73 (2H, m, NCH$_2$C(2,6)Ar$_2$*H*), 7.73 – 7.75 (1H, m, NCH$_2$C(6)Ar*H*-2-NO$_2$), 8.12 – 8.14 (NCH$_2$C(4)Ar*H*-2-NO$_2$), 8.26 (NCH$_2$C(3)Ar*H*-2-NO$_2$); **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ_C: 56.5 (N*C*H$_2$Ar-2-NO$_2$), 121.7 (NCH$_2$*C*(4)Ar-2-NO$_2$), 122.6 (NCH$_2$*C*(3)Ar-2-NO$_2$), 127.6 (N=C*C*(2,6)Ar$_1$), 128.2 (N=C*C*(3,5)Ar$_1$), 128.6 (N=C*C*(2,6)Ar$_2$), 128.8 (N=C*C*(3,5)Ar$_2$), 129.2 (NCH$_2$*C*(5)Ar-2-NO$_2$), 130.5 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 133.8 (NCH$_2$*C*(6)Ar-2-NO$_2$), 136.4 (NCH$_2$*C*(1)Ar-2-NO$_2$), 139.3 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$),), 142.9 (NCH$_2$*C*(2)Ar-2-NO$_2$), 170.1 (*C*=N); **HRMS** (NSI$^+$) $C_{20}H_{17}N_2O_2^+$ ([M+H]$^+$) requires 317.1283, found 317.1285 (-0.5 ppm).

1,1-bis(4-methoxyphenyl)-*N*-(4-nitrobenzyl)methanimine



Following **General Procedure E,** bis(4-methoxyphenyl)methanimine (483 mg, 2.0 mmol), (4-nitrophenyl)methanamine (356.2 mg, 2.4 mmol), pyridine (242 µL, 3.0 mmol), in ethanol (30 mL) was refluxed for 1 hour, to give the titled compound (559 mg, 74%) as a yellow oil; **IR** ν_{max} (ATR): 3062 (Ar-H), 1618 (C=N), 1519 (N-O), 1443 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 3.87 (3H, s, Ar_1-4-OCH_3), 3.91 (3H, s, Ar_2-4-OCH_3), 4.75 (2H, s, NCH_2Ar-4-NO_2), 6.91 – 6.93 (2H, m, N=CC(2,6)Ar_1H-4-OCH_3), 7.02 – 7.04 (2H, m, N=CC(3,5)Ar_1H-4-OCH_3), 7.13 – 7.16 (2H, m, N=CC(3,5)Ar_2H-4-OCH_3), 7.55 – 7.57 (2H, m, NCH_2(2,6)Ar*H*-4-NO_2), 7.72 (2H, m, N=CC(2,6)Ar_1H-4-OCH_3), 8.20 – 8.22 (2H, m, NCH_2(3,5)Ar*H*-4-NO_2); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 55.4 (-O*C*H_3), 55.5 (N*C*H_2Ar-4-NO_2), 113.7 (N=C*C*(2,6)Ar_1-4-OCH_3, N=C*C*(2,6)Ar_2-4-OCH_3), 114.1 (N=C*C*(3,5)Ar_1-4-OCH_3, N=C*C*(3,5)Ar_2-4-OCH_3, 123.7 (NCH_2*C*(3,5)Ar-4-NO_2), 128.4 (NCH_2*C*(2,6)Ar-4-NO_2), 129.3 (NCH_2*C*(1)Ar-4-NO_2), 146.6 (NCH_2*C*(4)Ar-4-NO_2), 162.2 – 162.3 (N=C*C*(1)Ar_1-4-OCH_3, N=C*C*(1)Ar_2-4-OCH_3), 163.2 (N=C*C*(4)Ar_1-4-OCH_3, N=C*C*(4)Ar_2-4-OCH_3), 177.1 (*C*=N); **HRMS** (NSI^+) $C_{22}H_{21}N_2O_4^+$ ($[M+H]^+$) requires 377.1486, found 377.1491 (-1.3 ppm).

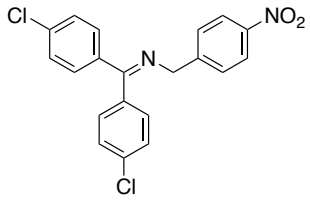
1,1-di(naphthalen-2-yl)-*N*-(4-nitrobenzyl)methanimine



Following **General Procedure E,** di(naphthene-2-yl)methanimine (562 mg, 2.0 mmol), (4-nitrophenyl)methanamine (356.2 mg, 2.4 mmol), pyridine (242 µL, 3.0 mmol), in ethanol (30 mL) was refluxed for 1 hour, to give the titled compound (559 mg, 74%) as a yellow oil; **IR** ν_{max} (ATR): 3053 (Ar-H), 1614 (C=N), 1514 (N-O), 1468 (C=C); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H:

4.80 (2H, s, NC*H*$_2$Ar-4-NO$_2$), 7.37 – 7.49 (2H, m, N=CC(3)*H*-naphthalen-2-yl, N=CC(3')*H*-naphthalen-2-yl), 7.59 – 7.61 (2H, m, NCH$_2$C(2,6)Ar*H*-4-NO$_2$), 7.64 – 7.66 (2H, m, N=CC(6)*H*-naphthalen-2-yl, N=CC(6')*H*-naphthalen-2-yl), 7.78 (1H, m, N=CC(1)*H*-naphthalen-2-yl), 7.85 (1H, m, N=CC(1')*H*-naphthalen-2-yl), 7.90 – 7.91 (2H, m, N=CC(5)*H*-naphthalen-2-yl, N=CC(5')*H*-naphthalen-2-yl), 7.94 – 7.95 (2H, m, N=CC(7)*H*-naphthalen-2-yl, N=CC(7')*H*-naphthalen-2-yl), 8.02 – 8.06 (2H, m, N=CC(4)*H*-naphthalen-2-yl, N=CC(4')*H*-naphthalen-2-yl), 8.23 – 8.25 (2H, m, NCH$_2$C(3,5)Ar*H*-4-NO$_2$), 8.28 – 8.31 (2H, m, N=CC(8)*H*-naphthalen-2-yl, N=CC(8')*H*-naphthalen-2-yl); **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ_C: 56.8 (N*C*H$_2$Ar-4-NO$_2$), 123.7 (NCH$_2$*C*(3,5)Ar-4-NO$_2$), 124.7 (N=C*C*(8)naphthalen-2-yl, N=C*C*(8')naphthalen-2-yl), 125.2 (N=C*C*(3)naphthalen-2-yl, N=C*C*(3')naphthalen-2-yl), 126.9 (N=C*C*(6)naphthalen-2-yl, N=C*C*(6')naphthalen-2-yl), 127.0 – 127.1 (N=C*C*(1)naphthalen-2-yl, N=C*C*(1')naphthalen-2-yl), 127.9 (N=C*C*(7)naphthalen-2-yl, N=C*C*(7')naphthalen-2-yl), 128.1 (N=C*C*(5)naphthalen-2-yl, N=C*C*(5')naphthalen-2-yl), 128.2 – 128.3 (NCH$_2$*C*(2,6)Ar-4-NO$_2$), 132.3 (N=C*C*(2)naphthalen-2-yl, N=C*C*(2')naphthalen-2-yl), 132.8 (N=C*C*(8a)naphthalen-2-yl, N=C*C*(8a')naphthalen-2-yl), 132.9 (N=C*C*(4a)naphthalen-2-yl, N=C*C*(4a')naphthalen-2-yl), 133.3 (NCH$_2$*C*(1)Ar-4-NO$_2$), 146.9 (NCH$_2$*C*(4)Ar-4-NO$_2$), 170.5 (*C*=N); **HRMS** (NSI$^+$) $C_{28}H_{21}N_2O_2^+$ ([M+H]$^+$) requires 417.1591, found 417.1594 (-0.76 ppm).

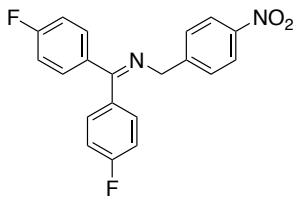
1,1-bis(4-chlorophenyl)-*N*-(4-nitrobenzyl)methanimine



Following **General Procedure E,** bis(4-chlorophenyl)methanimine (250 mg, 1.0 mmol), (4-nitrophenyl)methanamine (226 mg, 1.2 mmol), pyridine (117 µL, 1.5 mmol), in ethanol (15 mL) was refluxed for 1 hour, to give the titled compound (262 mg, 68%) as a yellow solid. **mp** 51 – 52 ºC; **IR** ν_{max} (ATR): 3061 (Ar-H), 1620 (C=N), 1514 (N-O), 1485 (C=C); **^{1}H-NMR** (400 MHz, CDCl$_3$), δ_H: 4.66 (2H, s, NC*H*$_2$Ar-4-NO$_2$), 7.14 – 7.16 (2H, , N=CC(3,5)Ar$_1$*H*-4-Cl), 7.36 – 7.38 (2H, m, N=CC(2.6)Ar$_1$*H*-4-Cl), 7.51 – 7.55 (4H, m, N=CC(3,5)Ar$_2$*H*-4-Cl, NCH$_2$C(2,6)Ar*H*-4-NO$_2$), 7.62 – 7.65 (2H, m, N=CC(2,6)Ar$_2$*H*-4-Cl), 8.21 – 8.24 (NCH$_2$C(3,5)Ar*H*-4-NO$_2$); **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ_C: 56.7 (N*C*H$_2$Ar-4-NO$_2$), 123.7 (NCH$_2$*C*(3,5)Ar-4-NO$_2$), 128.2 (NCH$_2$*C*(2,6)Ar-4-NO$_2$), 128.6 (N=C*C*(2,6)Ar$_1$-4-Cl), 128.9 – 129.3 (N=C*C*(3,5)Ar$_1$-4-Cl, N=C*C*(3,5)Ar$_2$-4-Cl), 129.8 (N=C*C*(2,6)Ar$_2$-4-Cl), 134.1 – 135.3 (N=C*C*(1)Ar$_1$-4-Cl,

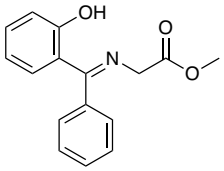
N=C*C*(1)Ar$_2$-4-Cl), 137.0 – 137.3 (N=C*C*(4)Ar$_1$-4-Cl, N=C*C*(4)Ar$_2$-4-Cl), 147.8 (NCH$_2$*C*(1,4)Ar-4-NO$_2$), 167.9 (*C*=N); **HRMS** (NSI$^+$) $C_{20}H_{15}Cl_2N_2O_2^+$ ([M+H]$^+$) requires 385.0505, found 385.0496 (-2.36 ppm).

1,1-bis(4-fluorophenyl)-*N*-(4-nitrobenzyl)methanimine



Following **General Procedure E,** bis(4-fluorophenyl)methanimine (483 mg, 2.0 mmol), (4-nitrophenyl)methanamine (356.2 mg, 2.4 mmol), pyridine (242 µL, 3.0 mmol), in ethanol (30 mL) was refluxed for 1 hour, to give the titled compound (559 mg, 74%) as a yellow solid. **mp** 92 – 94 ºC; **IR** ν_{max} (ATR): 2914 (Ar-H), 1624 (C=N), 1597 (N-O), 1406 (C=C), 1148 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 4.67 (2H, s, NC*H*$_2$Ar-4-NO$_2$), 7.06 – 7.10 (2H, m, N=CC(3,5)Ar$_1$*H*-4-F), 7.17 – 7.26 (4H, m, N=CC(2,3,5,6)Ar$_2$*H*-4-F), 7.53 – 7.55 (2H, m, NCH$_2$C(2,6)Ar*H*-4-NO$_2$), 7.68 – 7.71 (2H, m, N=CC(2,6)Ar$_1$*H*-4-F), 8.21 – 8.24 (2H, m, NCH$_2$C(3,5)Ar*H*-4-NO$_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -111.3 – -109.9 (C-*F*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 56.6 (N*C*H$_2$Ar-4-NO$_2$), 115.2 – 115.4 (N=C*C*(3,5)Ar$_1$-4-F), 116.0 – 116.2 (N=C*C*(2,6)Ar$_2$-4-F), 123.7 (NCH$_2$*C*(3,5)Ar-4-NO$_2$), 128.2 (NCH$_2$*C*(2,6)Ar-4-NO$_2$), 129.5 – 129.6 (N=C*C*(2,6)Ar$_2$-4-F), 130.5 – 130.6 (N=C*C*(2,6)Ar$_1$-4-F), 135.4 (N=C*C*(1)Ar$_1$-4-F, N=C*C*(1)Ar$_2$-4-F), 146.9 (NCH$_2$*C*(1)Ar-4-NO$_2$), 148.1 (NCH$_2$*C*(4)Ar-4-NO$_2$), 165.7 (N=C*C*(4)Ar$_1$-4-F, N=C*C*(4)Ar$_2$-4-F), 171.6 (*C*=N); **HRMS** (NSI$^+$) $C_{20}H_{15}F_2N_2O_2^+$ ([M+H]$^+$) requires 353.1078, found 353.1087 (-2.7 ppm).

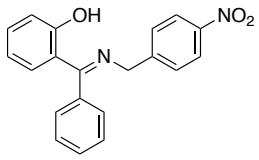
Methyl (*E*)-2-(((2-hydroxyphenyl)(phenyl)methylene)amino)acetate (357)



Following **General Procedure E,** 2-(Imino(phenyl)methyl)phenol (5.1 mmol, 1.0 g), methyl glycinate hydrogen chloride (5.1 mmol, 630 mg), and magnesium sulfate (2.5 mmol, 301 mg),

and CH_2Cl_2 (15 mL) stirred for 22 hrs at 40 ºC, then purified via flash column chromatography with 4:1 petrol:ethyl acetate (R_f = 0.35) to give a yellow solid crystal (34%, 464 mg). **mp** 128 ºC (Lit. **mp** 127–129 ºC) ; **IR** ν_{max} (ATR):): 2920 (Ar-H), 1720 (C=O, esters), 1625 (C=N), 1400 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.79 (1H, s, -OC*H*$_3$), 4.18 (2H, s, -C*H*$_2$CO$_2$CH$_3$), 6.70 (1H, ddd, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2, N=CC(4)Ar*H*-OH), 6.85 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.7, N=CC(4)Ar*H*-OH), 7.05 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.2, N=CC(6)Ar*H*-OH), 7.22 (2H, m, N=CC(2,6)Ar*H*), 7.33 (1H, ddd, $^3J_{HH}$ = 8.7, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.7, N=CC(5)Ar*H*-OH), 7.53 (3H, m, N=CC(3,4,5)Ar*H*), 14.9 (1H, s, -O*H*). Spectroscopic data in agreement with the literature. [19]

(*E*)-2-(((4-nitrobenzyl)imino)(phenyl)methyl)phenol (363)

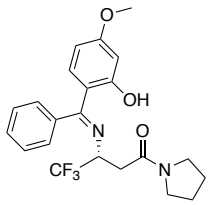


Following **General Procedure E,** 2-(Imino(phenyl)methyl)phenol (5.1 mmol, 1.0 g), (4-nitrophenyl)methanamine hydrogen chloride (6.1 mmol, 1.2 g), and pyridine (7.7 mmol, 0.62 mL), and EtOH (75 mL) stirred for 2 hrs under reflux conditions, then purified via flash column chromatography with 4:1 petrol:ethyl acetate (R_f = 0.35) to give a yellow solid crystal (99%, 1.7 g). **mp** 124 –126 ºC; **IR** ν_{max}: 2914 (Ar-H), 1624 (C=N), 1597 (N-O), 1406 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.67 (2H, s, C=NC*H*$_2$Ar-NO$_2$), 7.19 – 7.21 (2H, m, N=CC(5,6)Ar$_1$*H*-OH), 7.37 – 7.40 (3H, m, N=CC(3,4,5)Ar$_2$*H*), 7.49 – 7.51 (2H, m, N=CC(3,4)Ar$_1$*H*-OH), 7.52 – 7.54 (2H, m, C=NCH$_2$C(2,6)Ar*H*-NO$_2$), 7.69 – 7.71 (2H, m, N=CC(2,6)Ar$_2$*H*), 8.18 – 8.20 (2H, m, C=NCH$_2$C(2,6)Ar*H*-NO$_2$), 15.1 (-O*H*). Spectroscopic data in agreement with the literature.[20]

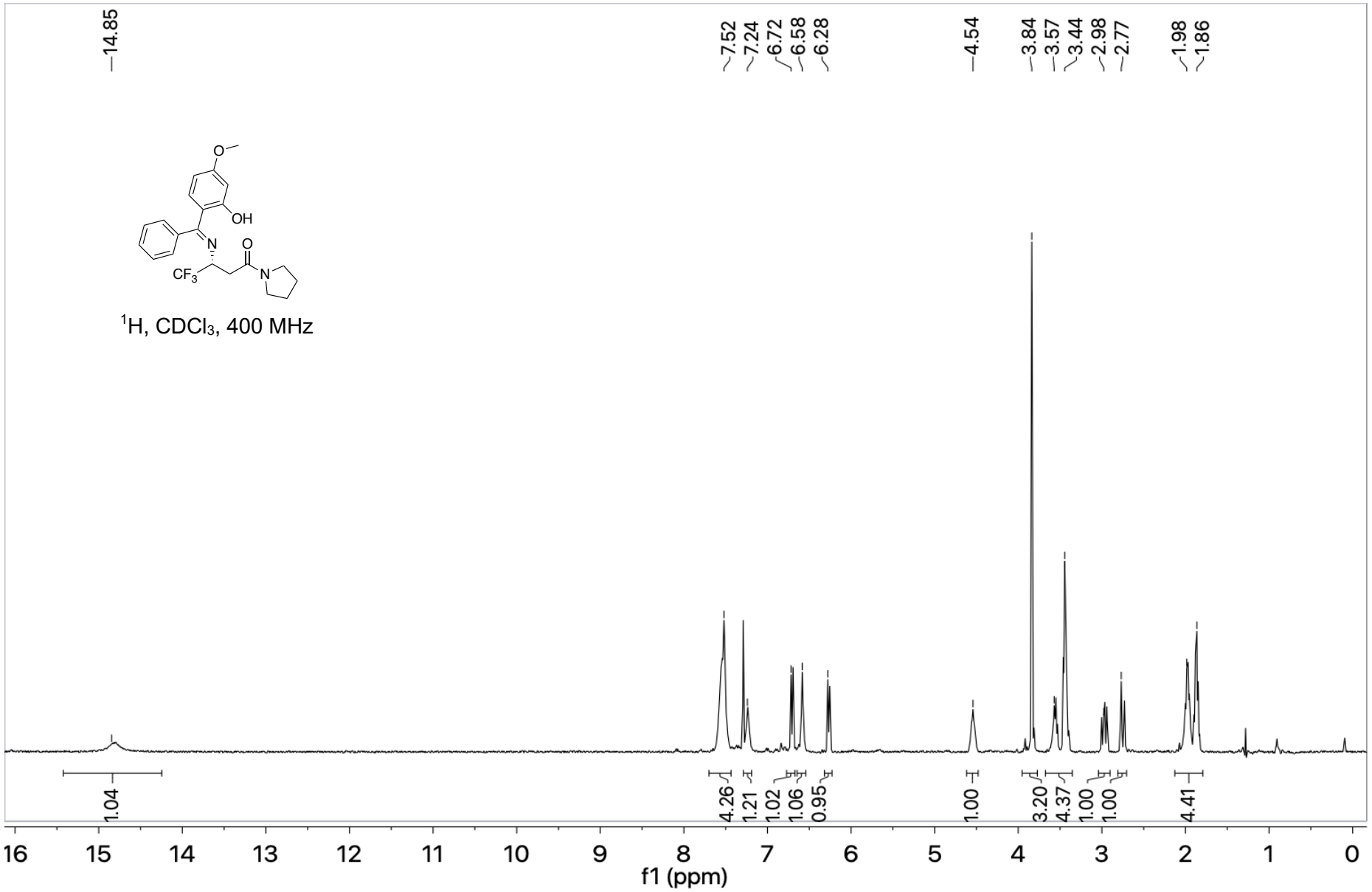
5.4 CHAPTER 2 PRODUCTS

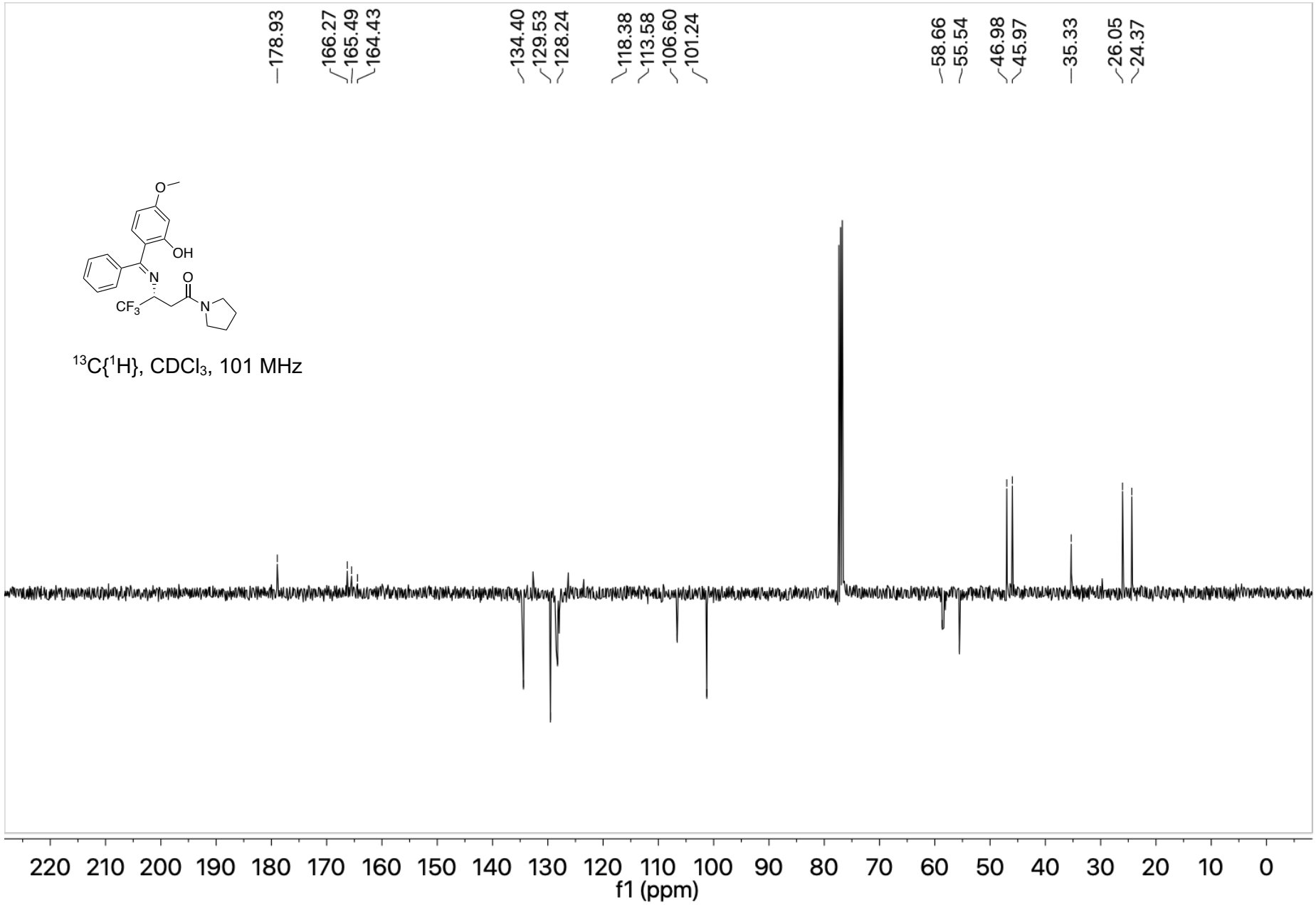
5.4.1 Chapter 2: Isothiourea-Catalysed Aza-Michael Addition Products

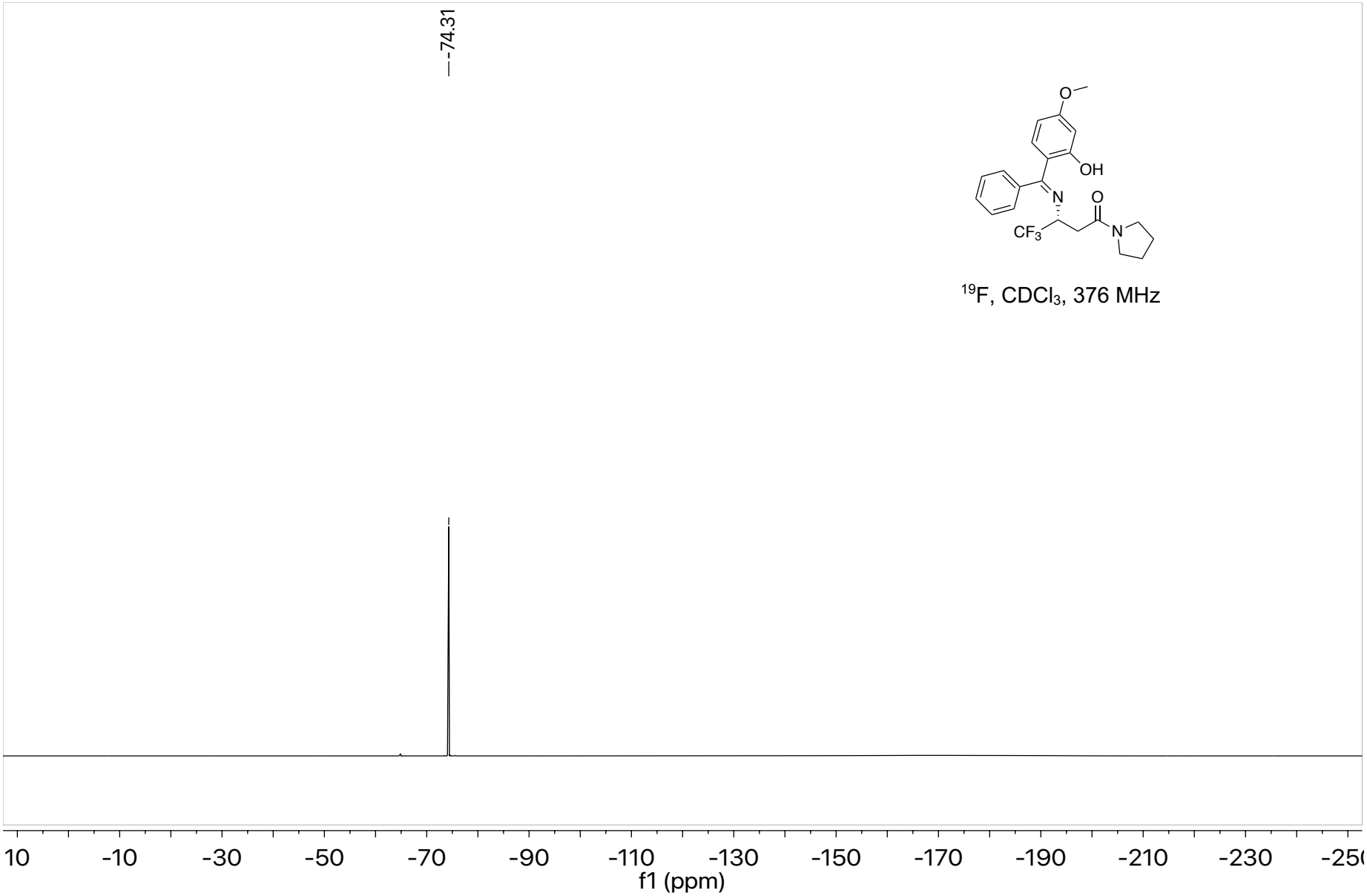
(*R*)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (158)



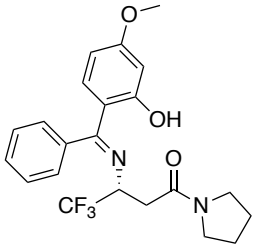
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 μL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.20) to give the titled compound (29.8 mg, 70%) as a yellow oil. $[\alpha]_D^{20}$ +95.5 (*c* = 0.87, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 19.1 min, t_R(*S*): 25.3 min, 95:5 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1624 (C=O), 1605 (C=N), 1444 – 1454 (C=C), 1276 (C-O-CH_3), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.98 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.75 (1H, dd, $^3J_{HH}$ = 15.2, $^4J_{HF}$ = 3.0, COC(2)*H*$_A$H$_B$), 2.98 (1H, dd, $^3J_{HH}$ = 15.2, $^4J_{HF}$ = 10.0, COC(2)H$_A$*H*$_B$), 3.44 – 3.57 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 4.54 (1H, m, COCH$_A$H$_B$C*H*), 6.28 (1H, dd, $^3J_{HH}$ = 9.0, N=CC(5)Ar*H*OH-OCH$_3$), 6.58 (1H, s, N=CC(3)Ar*H*OH-OCH$_3$), 6.72 (1H, dd, $^3J_{HH}$ = 8.9, N=CC(6)Ar*H*OH-OCH$_3$), 7.23 – 7.25 (1H, m, N=CC(4)Ar*H*), 7.51 – 7.53 (4H, m, N=CC(2,3,5,6)Ar*H*), 14.8 (1H, s, N=CC(2)ArO*H*-OCH$_3$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.31 (-C*F*$_3$) ; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H$_2$*C*(3)H$_2$C(4)H$_2$C(5)H$_2$), 26.1 (NC(2)H$_2$C(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 35.3 (C=O*C*H$_A$H$_B$CF$_3$), 45.9 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 47.0 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.54 (O*C*H$_3$), 58.7 (q, $^2J_{CF}$ = 28.3, C=OCH$_A$H$_B$*C*(3)HCF$_3$), 101.2 (N=C*C*(3)ArOH-OCH$_3$), 106.6 (N=C*C*(5)ArOH-OCH$_3$), 114.3 (N=C*C*(1)ArOH-OCH$_3$), 118.4 (*C*F$_3$), 128.2 (N=C*C*(2,3,5,6)ArH), 129.5 (N=C*C*(4)Ar), 134.4 (N=C*C*(1)Ar), 164.4 (N=C*C*(2)ArOH-OCH$_3$), 165.5 (*C*=N), 166.3 (N=C*C*(4)ArOH-OCH$_3$), 178.9 (*C*=O). **HRMS** (NSI$^+$) $C_{21}H_{23}F_3N_2O_3^+$ ([M+H]$^+$) requires 421.1734, found 421.1729 (-1.2 ppm).


14.85
7.52
7.24
6.72
6.58
6.28
4.54
3.84
3.57
3.44
2.98
2.77
1.98
1.86
O
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
1.04
4.26
1.21
1.02
1.06
0.95
1.00
3.20
4.37
1.00
1.00
4.41
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


178.93
166.27
165.49
164.43
134.40
129.53
128.24
118.38
113.58
106.60
101.24
58.66
55.54
46.98
45.97
35.33
26.05
24.37
O
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

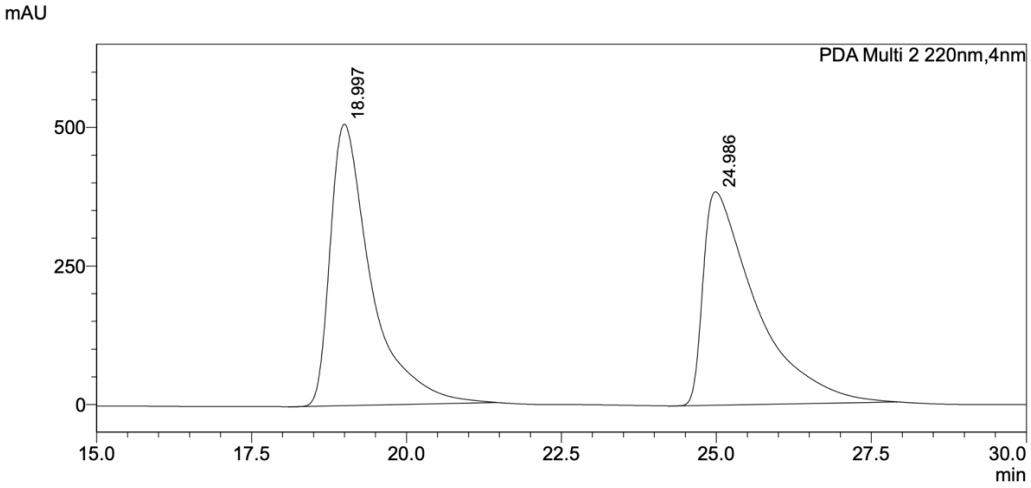

-74.31
O
OH
N
O
CF3
N
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **((*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 19.1 min, t_R(*S*): 25.3 min, 95:5 er.

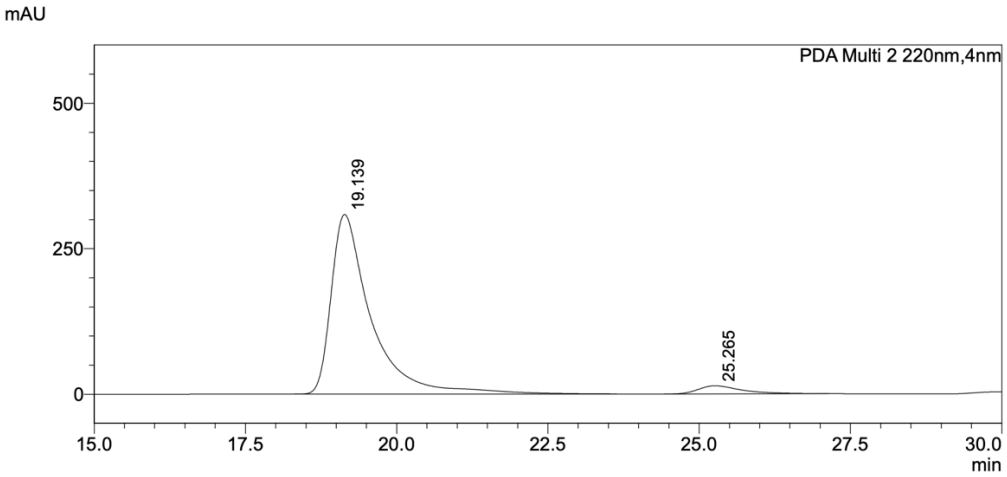


PDA Ch2 220nm

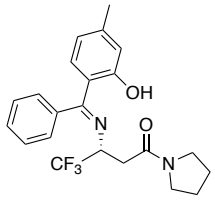
Peak#	Ret. Time	Area%
1	18.997	50.330
2	24.986	49.670
Total		100.000



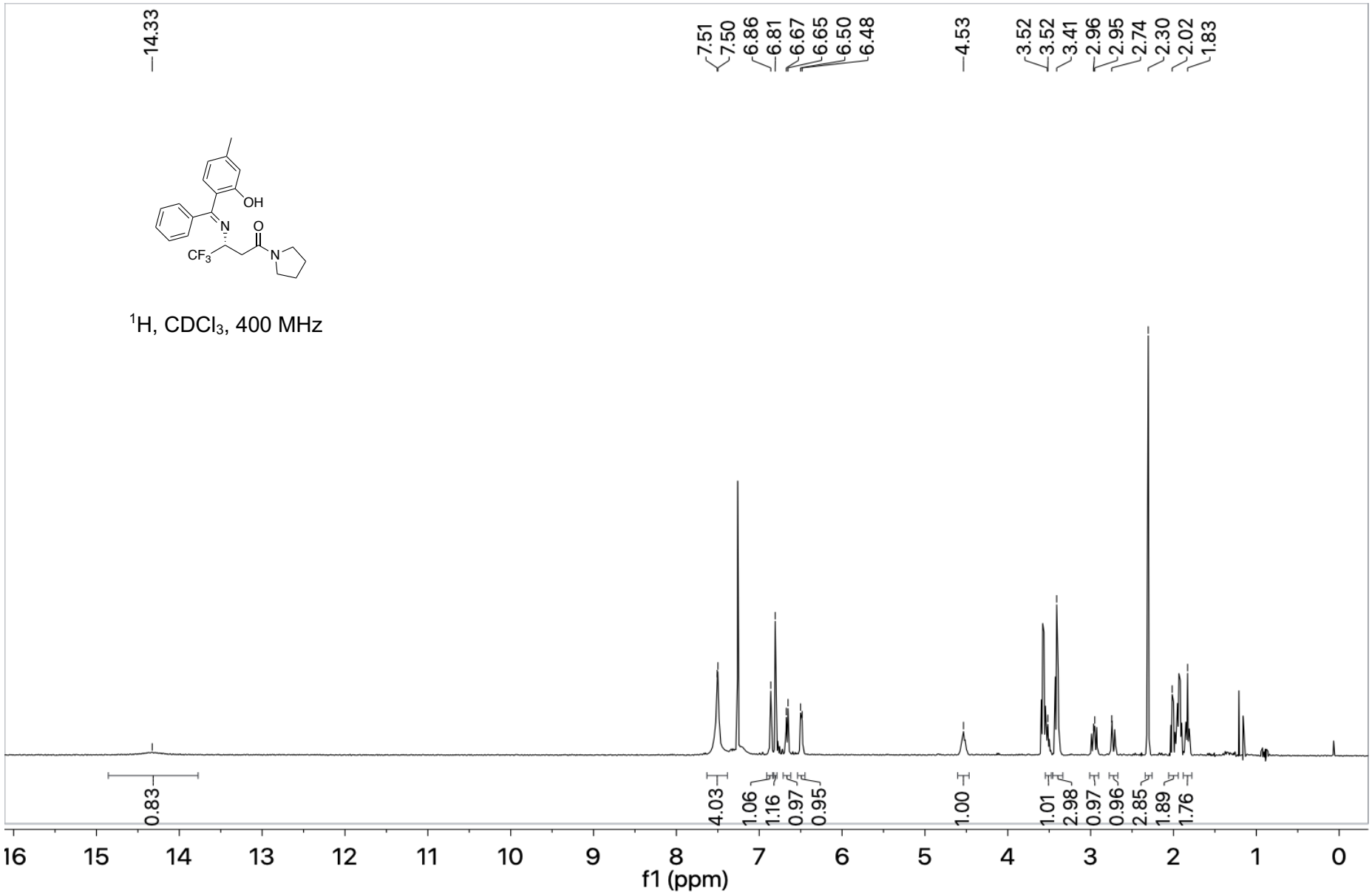
Peak#	Ret. Time	Area%
1	19.139	95.369
2	25.265	4.631
Total		100.000

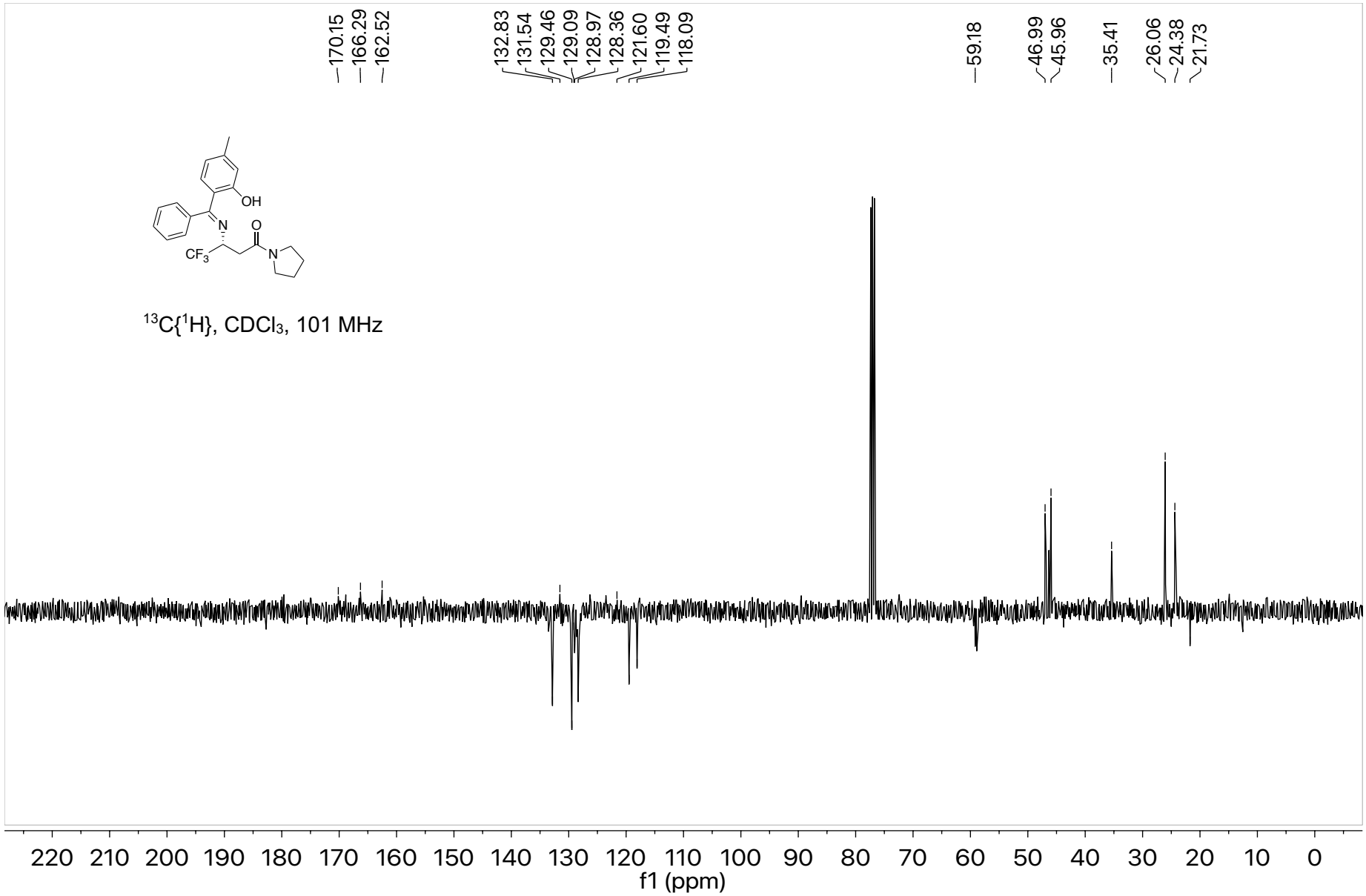


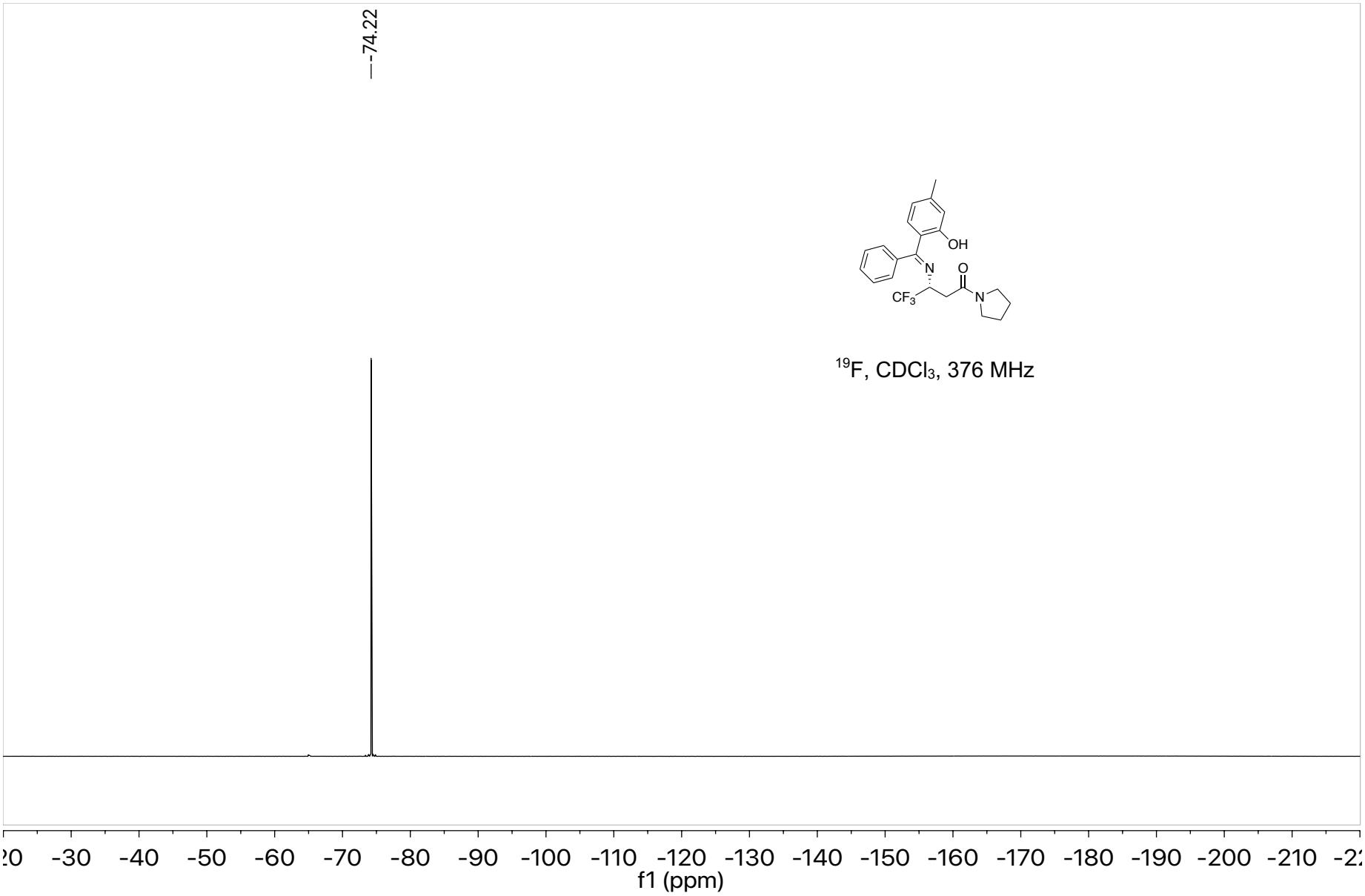
(*R*)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methylphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (165)



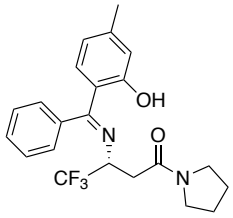
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methylphenol (42.2 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was then added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f =0.53) to give the titled compound (49%, 19.8 mg) as a yellow oil. $[\alpha]_D^{20}$+48.8 (*c* = 0.40, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 12.7 min, t_R(*S*): 15.2 min, 96:4 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1624 (C=O), 1595 (C=N), 1446 (C=C), 1261 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.83 – 2.02 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.30 (3H, s, C*H_3*), 2.74 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 2.9, COC(2)*H_A*H_B), 2.95 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 9.6, COC(2)H$_A$*H_B*), 3.41 – 3.52 (4H, m, N=C(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 4.52 – 4.55 (1H, m, COCH$_A$H$_B$C*H*), 6.49 (1H, dd, $^3J_{HH}$ = 8.2, N=CC(5)Ar*H*OH-CH_3), 6.66 (1H, s, N=CC(6)Ar*H*OH-CH_3), 6.80 – 6.82 (1H, m, N=CC(4)Ar*H*), 6.85 – 8.87 (1H, m, N=CC(3)Ar*H*OH-CH_3), 7.49 – 7.51 (4H, m, N=CC(2,3,5,6)Ar*H*), 14.33 (1H, s, N=CC(2)ArO*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.22 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 21.7 (ArOH-*C*H_3), 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.4 (C=O*C*H$_A$H$_B$CF_3), 46.0 (N*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2), 47.0 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 59.2 (q, $^2J_{CF}$ = 27.3, C=OCH$_A$H$_B$*C*(3)HCF_3), 118.1 (N=C*C*(3)ArOH-CH_3), 119.5 (N=C*C*(5)ArOH-CH_3), 121.60 (N=C*C*(1)ArOH-CH_3), 128.4 (N=C*C*(3,5)Ar), 129.0 (N=C*C*(4)Ar), 129.1 (*C*F_3), 129.5 (N=C*C*(2,6)Ar), 129.5 (N=C*C*(4)Ar), 131.5 (N=C*C*(1)Ar), 132.8 (N=C*C*(6)ArOH-CH_3), 162.5 (N=C*C*(2)ArOH-CH_3), 166.3 (*C*=O), 170.2 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{23}F_3N_2O_2^+$ ([M+H]$^+$) requires 405.1785, found 405.1774 (-2.7 ppm).


14.33
7.51
7.50
6.86
6.81
6.67
6.65
6.50
6.48
4.53
3.52
3.52
3.41
2.96
2.95
2.74
2.30
2.02
1.83
OH
N
O
CF3
N
1H, CDCl3, 400 MHz
0.83
4.03
1.06
1.16
0.97
0.95
1.00
1.01
2.98
0.97
0.96
2.85
1.89
1.76
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


170.15
166.29
162.52
132.83
131.54
129.46
129.09
128.97
128.36
121.60
119.49
118.09
59.18
46.99
45.96
35.41
26.06
24.38
21.73
OH
N
O
CF3
N
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

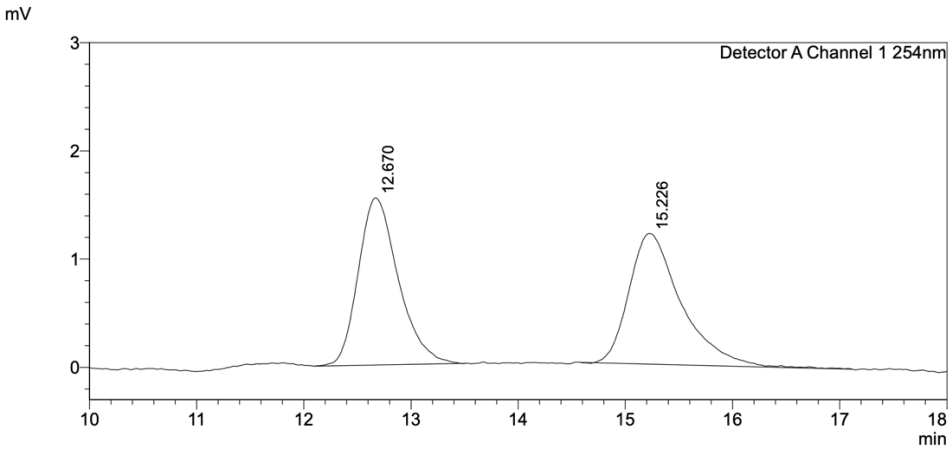

-74.22
OH
N
O
CF3
N
19F, CDCl3, 376 MHz
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

HPLC Data for **(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methylphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*R*): 12.7 min, t_R(*S*): 15.2 min, 96:4 er.

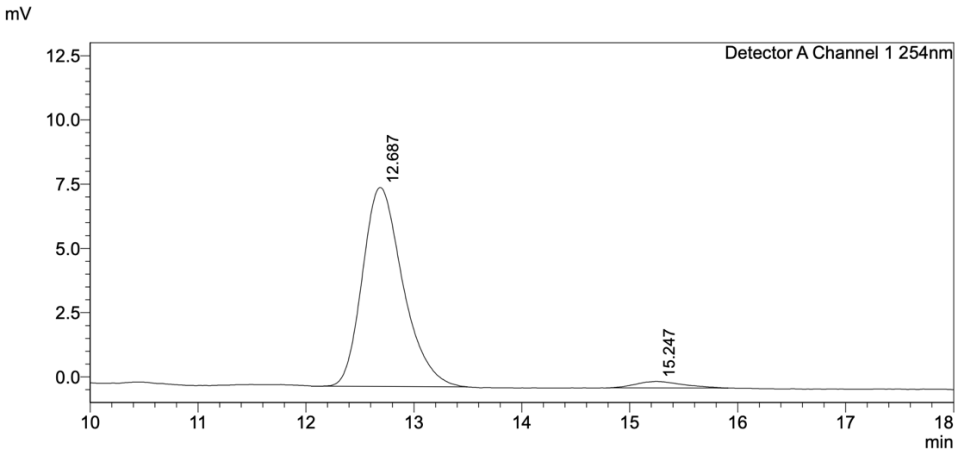


Detector A Channel 1 254nm

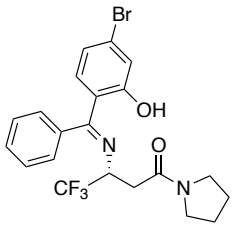
Peak#	Ret. Time	Area%
1	12.670	49.583
2	15.226	50.417
Total		100.000



Peak#	Ret. Time	Area%
1	12.687	96.390
2	15.247	3.610
Total		100.000

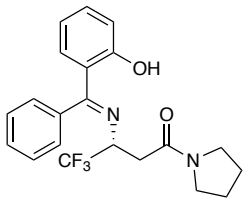


(*R*)-3-(((4-Bromo-2-hydroxyphenyl)(phenyl)methylene)amino)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (167)



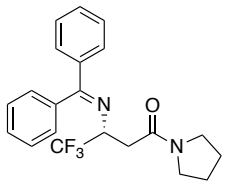
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was then added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (11.3 mg, 24%) as a yellow oil. $[\alpha]_D^{20}$ +33.2 (*c* = 0.37, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ID (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 15.0 min, t_R(*S*): 20.7 min, 96:4 er; **IR** ν_{max} (ATR), 2974 (Ar-H), 1625 (C=O), 1595 (C=N), 1448 (C=C), 1288 (C-O-CH_3), 1259 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.97 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.77 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 2.9, COC(2)*H_A*H_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 9.7, COC(2)H_A*H_B*), 3.44 – 3.52 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 4.56 (1H, m, COC$H_A$$H_B$C*H*), 6.65 (1H, d, $^3J_{HH}$ = 8.6, N=CC(6)Ar*H*OH-Br), 6.82 (1H, dd, $^3J_{HH}$ = 8.6, $^4J_{HH}$ = 1.9, N=CC(5)Ar*H*OH-Br), 7.21 (1H, d, $^4J_{HH}$ = 1.9, N=CC(3)Ar*H*OH-Br), 7.51 – 7.53 (5H, m, N=CC(2,3,4,5,6)Ar*H*), 14.7 (1H, s, N=CC(2)ArO*H*-Br); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.06 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.3 (C=O*C*$H_A$$H_B$$CF_3$), 46.0 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 59.0 (q, $^2J_{CF}$ = 29.3, C=O$CH_A$$H_B$*C*(3)$HCF_3$), 119.0 (*C*(4)ArOH-Br), 120.9 (*C*(3)ArOH-Br), 121.5 (*C*(5)ArOH-Br), 123.4 (*C*F_3), 127.8 (*C*(1)ArOH-Br), 128.5 (*C*(2,3,5,6)Ar), 129.7 (*C*(1)Ar), 132.4 (*C*(1)Ar), 133.8 (*C*(4)Ar), 163.1 (*C*(2)ArOH-Br), 166.19 (*C*=O), 179.4 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{20}{}^{79}BrF_3N_2O_2^+$ ([M+H]$^+$) requires 469.0733, found 469.0727 (-1.3 ppm).

(*R*)-4,4,4-Trifluoro-3-(((2-hydroxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidine-1-yl)butan-1-one (166)



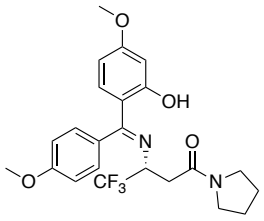
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)phenol (39.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by Biotage® Isolera^{TM} 4[SNAP Ultra 10g, 75 mLmin^{-1}, Petrol:EtOAc (100:0 2CV, 100:0 to 80:20 1 CV, 80:20 25 CV) to give the titled compound (14.0 mg, 36%) as a yellow oil. $[\alpha]_D^{20}$ +35.02 (*c* 1.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 11.9 min, t_R(*R*): 17.2 min, 96:4 er; **IR** ν_{max} (ATR), 2926 (Ar-H), 1647 (C=O), 1609 (C=N), 1447 (C=C), 1261 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.87 – 1.95 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.79 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 3.0, COC(2)*H_A*H_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 9.6, COC(2)H$_A$*H_B*), 3.44 – 3.53 (4H, m, NC(2)*H_2*C(3)H_2C(4)H-$_2$C(5)*H_2*), 4.57 (1H, m, COCH$_A$H$_B$C*H*), 6.70 (1H, ddd, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 1.2, N=CC(5)Ar*H*OH), 6.82 (1H, dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.7, N=CC(6)Ar*H*OH), 7.02 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.2, N=CC(3)Ar*H*OH), 7.33 (1H, ddd, $^3J_{HH}$ = 8.8, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.7, N=CC(4)Ar*H*OH), 7.51 – 7.53 (5H, m, N=CC(2,3,4,5,6)Ar*H*), 14.47 (1H, s, N=CC(2)ArO*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -73.84; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.0 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.5 (C=O*C*H$_A$H$_B$CF_3), 45.9 (N*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2), 47.0 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 59.4 (q, $^2J_{CF}$ = 28.5, C=OCH$_A$H$_B$*C*(3)HCF_3), 117.7 (N=C*C*(3)ArOH), 118.1 (N=C*C*(5)ArOH), 120.2 (*C*F_3), 123.6 (N=C*C*(1)Ar), 128.4 (N=C*C*(3,5)Ar), 129.4 (N=C*C*(2,4,6)Ar), 132.8 (N=C*C*(6)ArOH), 132.9 (N=C*C*(1)ArOH), 133.4 (N=C*C*(4)ArOH), 162.4 (N=C*C*(2)ArOH), 166.4 (*C*=O), 179.8 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{21}F_3N_2O_2^+$ ([M+H]$^+$) requires 391.1628, found 391.1622 (-1.6 ppm).

(*R*)-3-((Diphenylmethylene)amino)-4,4,4-trifluoro-1-(pyrrolidine-1-yl)butan-1-one (168)



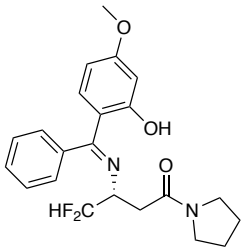
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), diphenylmethanimine (36.2 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (15 mg, 40%) as a yellow oil. $[\alpha]_D^{20}$ +35.0 (*c* = 1.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 250 nm, 30 °C) t_R(*S*): 6.9 min, t_R(*R*): 13.6 min, 83:17 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1633 (C=O), 1598 (C=N), 1448 (C=C), 1276 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.83 – 1.90 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.69 (1H, dd, $^3J_{HH}$ = 15.7, $^4J_{HF}$ = 2.5, COC(2)*H_A*H_B), 2.93 (1H, dd, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 9.6, COC(2)H_A*H_B*), 3.41 – 3.52 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.80 (3H, s, C*H_3*O-ArOH), 3.86 (3H, s, C*H_3*O-Ar), 4.58 – 4.60 (1H, m, COCH$_A$H$_B$C*H*), 7.33 – 7.35 (3H, m, N=CC(3,4,5)Ar$_1$*H*), 7.49 – 7.51 (3H, m, N=CC(3,4,5)Ar$_2$*H*), 7.64 – 7.66 (2H, m, N=CC(2,6)Ar$_1$*H*), 7.82 – 7.84 (2H, m, N=CC(2,6)Ar$_2$*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.1 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 – 26.1 (NC(2)H_2*C*(3)H_2*C*(4)H_2C(5)H_2), 35.5 (C=O*C*H$_A$H$_B$CF$_3$), 45.9 – 47.0 (N*C*(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 60.7 – 61.21 (q, $^2J_{CF}$ = 28.0, C=OCH$_A$H$_B$*C*(3)HCF$_3$), 128.4 (N=C*C*(3,5)Ar$_1$, N=C*C*(3,5)Ar$_2$), 128.95 (*C*F$_3$), 129.1 - 130.1 (N=C*C*(2,4)Ar$_1$, N=C*C*(2,4)Ar$_2$), 139.3 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 167.2 (*C*=O), 174.3 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{21}F_3N_2O^+$ ([M+H]$^+$) requires 375.1679, found 375.1670 (-2.4 ppm).

(*R*)-4,4,4-Trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(4-methoxyphenyl)methylene) amino)-1-(pyrrolidin-1-yl)butan-1-one (169)



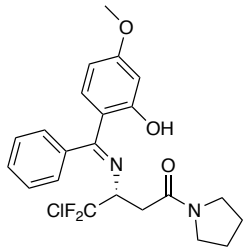
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(4-methoxyphenyl)methyl)-5-methoxyphenol (51.5 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine (12.5 µL, 0.15 mmol) and stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.21) to give the titled compound (18 mg, 41%) as a yellow oil. $[\alpha]_D^{20}$ +57.1 (*c* = 0.92, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 31.5 min, t_R(*R*): 39.9 min, 95:5 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1621 (C=O), 1593 (C=N), 1442 (C=C), 1342 (C-O-CH_3), 1247 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.83 – 1.94 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.69 (1H, dd, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 2.9, COC(2)H_AH_B), 2.93 (1H, dd, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 9.7, COC(2)H_AH_B), 3.41 – 3.52 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 3.80 (3H, s, CH_3O-ArOH), 3.86 (3H, s, CH_3O-Ar), 4.55 – 4.57 (1H, m, COCH_AH_BC*H*), 6.22 (1H, dd, $^3J_{HH}$ = 8.95, $^4J_{HH}$ = 2.43 N=CC(5)Ar*H*OH-OCH_3), 6.44 (1H, d, $^3J_{HH}$ = 2.58, N=CC(3)Ar*H*OH-OCH_3), 6.73 (1H, d, $^3J_{HH}$ = 9.00, N=CC(6)Ar*H*OH-OCH_3), 7.04 – 7.06 (2H, m, N=CC(2,6)Ar*H*-OCH_3), 7.39 – 7.41 (2H, m, N=CC(3,4)Ar*H*-OCH_3), 15.2 (1H, s, N=CC(2)ArO*H*-OCH_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -66.22, -74.11, -74.33 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.5 – 26.2 (NC(2)H_2*C*(3)H_2*C*(4)H_2C(5)H_2), 35.6 (C=O*C*H_AH_BCF_3), 46.1 – 47.1 (N*C*(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 47.0 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 55.4 (*C*H_3O-ArOH), 55.5 (*C*H_3O-Ar), 58.3 – 59.1 (q, $^2J_{CF}$ = 28.6, C=OCH_AH_B*C*(3)HCF_3), 101.36 (*C*(3)ArOH-OCH_3), 106.17 (*C*(5)ArOH-OCH_3), 113.9 (*C*(1)ArOH-OCH_3, *C*(2,6)Ar-OCH_3), 125.29 (*C*(1)Ar-OCH_3), 126.22 (*C*F_3), 129.6 – 129.9 (*C*(3,5)Ar-OCH_3), 134.3 (*C*(6)ArOH-OCH_3), 160.3 (*C*(4)Ar-OCH_3), 164.0 (*C*(4)ArOH-OCH_3), 165.6 (*C*(2)ArOH-OCH_3), 166.7 (*C*=O), 179.0 (*C*=N). **HRMS** (NSI$^+$) $C_{23}H_{25}F_3N_2O_4^+$ ([M+H]$^+$) requires 451.1839, found 451.1827 (-2.7ppm).

(*R*)-4,4-Difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (185)



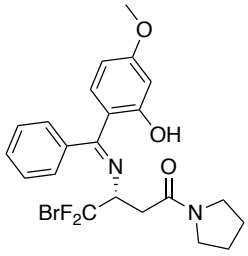
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4-difluorobut-2-enoate (24.3 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was purified by flash column chromatography Hexane:EtOAc (1:1) (R_f = 0.24) to give the titled compound (16.0 mg, 40%) as a yellow oil. $[\alpha]_D^{20}$+23.8 (*c* = 0.72, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 48.5 min, t_R(*R*): 52.1 min, 97:3 er.; **IR** ν_{max} (ATR), 2976 (Ar-H), 1622 (C=O), 1595 (C=N), 1444 (C=C), 1259 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.96 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.72 – 2.74 (2H, qd, $^3J_{HH}$ = 15.7, $^4J_{HH}$ = 3.0, COC(2)*H*$_A$*H*$_B$), 3.45 (4H, m, NC(2)*H*$_2$C(3)H_2C(4)H-$_2$C(5)*H*$_2$), 3.82 (3H, s, ArOH-OC*H*$_3$), 4.24 (1H, m, COCH$_A$H$_B$C*H*), 5.94 (1H, td, $^2J_{HF}$ = 55.8, $^4J_{HH}$ = 3.0, CF_2*H*), 6.23 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.5, N=CC(5)Ar*H*OH-OCH$_3$), 6.52 (1H, s, N=CC(3)Ar*H*OH-OCH$_3$), 6.68 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.44 – 7.46 (5H, m, N=CC(2,3,4,5,6)Ar*H*), 15.3 (1H, s, N=CC(2)ArHO*H*-OCH$_3$). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -125.3 (d, $^2J_{FF}$ = 282.1, -C*F*$_A$F$_B$H), -126.8 (d, $^2J_{FF}$ = 282.0, -CF$_A$*F*$_B$H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H$_2$*C*(3)H$_2$C(4)H$_2$C(5)H$_2$), 26.1 (NC(2)H$_2$C(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 35.1 (C=O*C*H$_A$H$_B$CF$_3$), 45.9 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 46.9 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.0 (-O*C*H$_3$), 58.7 – 59.9 (q, $^2J_{CF}$ = 29.3, C=OCH$_A$H$_B$*C*(3)HCF$_3$), 101.4 (*C*(3)ArOH-OCH$_3$), 106.5 (*C*(5)ArOH-OCH$_3$), 113.3 (*C*(1)ArOH-OCH$_3$), 115.20 (-*C*F$_2$H), 127.8 (*C*(1,2,6)Ar), 128.6 (*C*(3,4,5)Ar), 133.99 (*C*(6)ArOH-OCH$_3$), 165.4 (*C*(2)ArOH-OCH$_3$), 166.1 (*C*(4)ArOH-OCH$_3$), 167.1 (*C*=O), 177.3 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{25}F_2N_2O_3^+$ ([M+H]$^+$) requires 403.1828, found 403.1822 (-1.5ppm).

(*R*)-4-Chloro-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (186)



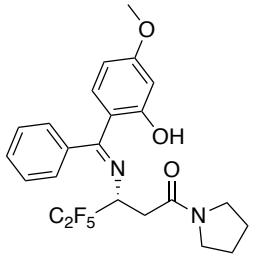
Following **General Procedure F,** 4-nitrophenyl (*E*)-4-chloro-4,4-difluorobut-2-enoate (27.8 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (1:1) (R_f = 0.16) to give the titled compound (31.9 mg, 73%) as a yellow oil. $[\alpha]_D^{20}$ +9.60 (*c* = 1.60, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 22.0 min, t_R(*R*): 29.0 min, 96:4 er; **IR** ν_{max} (ATR), 2974 (Ar-H), 1635 (C=O), 1593 (C=N), 1444 (C=C), 1263 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.96 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.82 (1H, dd, $^3J_{HH}$ = 15.1, $^4J_{HH}$ = 3.2, COC(2)*H_A*H_B), 2.97 (1H, dd, $^3J_{HH}$ = 15.1, $^4J_{HH}$ = 9.2, COC(2)H_A*H_B*) 3.50 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.83 (3H, s, ArOH-OC*H_3*), 4.59 – 4.61 (1H, m, COC$H_A$$H_B$C*H*), 6.26 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.5, N=CC(5)Ar*H*OH-OCH_3), 6.51 (1H, d, $^4J_{HH}$ = 2.3, N=CC(3)Ar*H*OH-OCH_3), 6.71 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.24 (1H, N=CC(4)Ar*H*), 7.51 – 7.53 (4H, m, N=CC(2,3,5,6)Ar*H*), 15.1 (1H, s, N=CC(2)ArHO*H*-OCH_3). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -58.6 (d, $^2J_{FF}$ = 164.8, -C*F_A*F_BCl), -59.8 (dd, $^2J_{FF}$ = 164.8, $^3J_{HF}$ = 2.8, CF_A*F_B*Cl); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 36.8 (C=O*C*$H_A$$H_B$$CF_3$), 46.0 (N*C*(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$), 47.0 (NC(2)$H_2$C(3)$H_2$C(4)$H_2$*C*(5)$H_2$), 55.45 (-O*C*$H_3$), 63.5 – 63.9 (q, $^2J_{CF}$ = 20.2, C=O$CH_A$$H_B$*C*(3)$HCF_2$Cl), 101.3 (N=C*C*(3)ArOH-OCH_3), 106.2 (N=C*C*(5)ArOH-OCH_3), 128.1 (N=C*C*(4)Ar), 128.4 (N=C*C*(2,6)Ar), 129.3 (*C*F_2Cl), 129.4 (N=C*C*(3,5)Ar), 132.9 (N=C*C*(1)Ar), 134.2 (N=C*C*(6)ArOH-OCH_3), 161.2 (N=C*C*(2)ArOH-OCH_3), 164.0 (N=C*C*(1)ArOH-OCH_3), 165.4 (N=C*C*(4)ArOH-OCH_3), 166.4 (*C*=O), 178.4 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{23}ClF_2N_2O_3^+$ ([M+H]$^+$) requires 437.1438, found 437.1429 (-2.1 ppm).

(*R*)-4-Bromo-4,4-difluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (187)



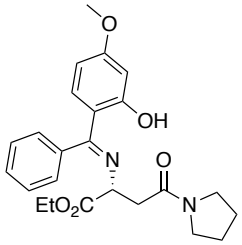
Following **General Procedure F,** 4-nitrophenyl (*E*)-4-Bromo-4,4-difluorobut-2-enoate (32.2 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.24) to give the titled compound (34.6 mg, 72%) as a yellow oil. $[\alpha]_D^{20}$ +70.8 (*c* = 0.67, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C), t_R(*R*): 13.5 min, t_R(*S*): 18.7 min, 96:4 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1637 (C=O), 1591 (C=N), 1442 (C=C), 1261 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.84 – 1.95 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.82 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 3.2, COC(2)*H*$_A$H$_B$), 2.95 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 9.0, COC(2)H$_A$*H*$_B$) 3.44 – 3.56 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.82 (3H, s, ArOH-OC*H*$_3$), 4.46 (1H, $^3J_{HH}$ = 9.0, $^3J_{HH}$ = 3.3, , COCH$_A$H$_B$C*H*), 6.25 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH$_3$), 6.48 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH$_3$), 6.70 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.22 – 7.24 (1H, m, N=CC(4)Ar*H*), 7.50 (4H, m, N=CC(2,3,5,6)Ar*H*), 15.1 (1H, s, N=CC(2)ArHO*H*-OCH$_3$). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -51.2 (d, $^2J_{FF}$ = 160.2, -C*F*$_A$F$_B$Br), -53.9 (d, $^2J_{FF}$ = 160.1, -CF$_A$*F*$_B$Br); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H$_2$*C*(3)H$_2$C(4)H$_2$C(5)H$_2$), 26.1 (NC(2)H$_2$C(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 37.6 (C=O*C*H$_A$H$_B$CF$_3$), 46.0 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$), 47.0 (NC(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.4 (-O*C*H$_3$), 64.7 – 65.1 (q, $^2J_{CF}$ = 22.5, C=OCH$_A$H$_B$*C*(3)HCF$_2$Cl), 101.3 (N=C*C*(3)ArOH-OCH$_3$), 106.2 (N=C*C*(5)ArOH-OCH$_3$), 113.9 (N=C*C*(1)ArOH-OCH$_3$), 124.0 (CF_2Br), 127.9 (N=C*C*(4)Ar), 128.4 (N=C*C*(3,5)Ar), 129.4 (N=C*C*(2,6)Ar), 133.1 (N=C*C*(1)Ar), 134.1 (N=C*C*(6)ArOH-OCH$_3$), 164.0 (N=C*C*(4)ArOH-OCH$_3$), 165.3 (N=C*C*(2)ArOH-OCH$_3$), 166.4 (*C*=O), 178.4 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{24}{}^{79}BrF_2N_2O_3^+$ ([M+H]$^+$) requires 481.3378, found 481.0933 (-0.60 ppm).

(*R*)-4,4,5,5,5-Pentafluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(pyrrolidine-1-yl)pentan-1-one (188)



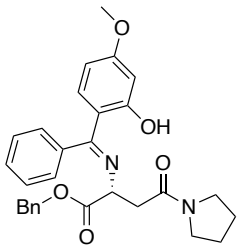
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,5,5,5-pentafluoroppentan-2-enoate (31.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.3 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.20) to give the titled compound (38.1 mg, 81%) as a yellow oil. $[\alpha]_D^{20}$ +95.2 (*c* = 0.31, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 13.9 min, t_R(*S*): 20.6 min, 97:3 er; **IR** ν_{max} (ATR), 2974 (Ar-H), 1622 (C=O), 1593 (C=N), 1445 – 1456 (C=C), 1207 (C_2F_5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.84 – 1.95 (4H, m, N NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.82 (1H, dd, $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 3.9, O=CC(2)*H*$_A$H$_B$), 2.90 (1H, dd, , $^2J_{HH}$ = 15.1, $^3J_{HH}$ = 8.8, O=CC(2)H$_A$*H*$_B$), 3.43 – 3.54 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.83 (3H, s, -OC*H*$_3$), 4.65 – 4.67 (1H, m, O=CCH$_A$H$_B$C(3)*H*), 6.27 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.2, N=CC(5)Ar*H*OH-OCH$_3$), 6.50 (1H, d, $^4J_{HH}$ = 2.4, N=CC(3)Ar*H*OH-OCH$_3$), 6.69 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.17 – 7.19 (1H, m, N=CC(2)Ar*H*), 7.51 – 7.53 (4H, m, N=CC(3,4,5,6)Ar*H*), 14.9 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F -80.9 (-CF$_A$F$_B$C*F*$_3$), -120.6 (d, $^2J_{FF}$ = 272.9, -C*F*$_A$F$_B$CF$_3$), -121.2 (d, $^2J_{FF}$ = 272.9, -CF$_A$*F*$_B$CF$_3$); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 – 26.1 (NC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 35.2 (O=C*C*(2)H$_A$H$_B$), 46.0 – 47.0 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.4 (-O*C*H$_3$), 57.9 (t, $^2J_{CF}$ = 22.2, O=CCH$_A$H$_B$*C*(3)H), 101.2 (N=C*C*(3)ArOH-OCH$_3$), 106.22 (N=C*C*(5)ArOH-OCH$_3$), 113.7 (N=C*C*(1)ArOH-OCH$_3$), 126.2 (N=C*C*(1)Ar), 127.9 (N=C*C*(2,6)Ar), 129.5 (N=C*C*(3,4,5)Ar), 132.7 (-*C*F$_2$CF$_3$), 134.2 (N=C*C*(6)ArOH-OCH$_3$), 139.4 (-CF$_2$*C*F$_3$), 163.7 (N=C*C*(2)ArOH-OCH$_3$), 165.1 (N=C*C*(4)ArOH-OCH$_3$), 166.3 (*C*=O), 178.5 (*C*=N). **HRMS** (NSI$^+$) $C_{23}H_{23}F_5N_2O_3^+$ ([M+H]$^+$) requires 471.1702, found 471.1690 (-2.5 ppm).

Ethyl (*R*)-2-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate (189)



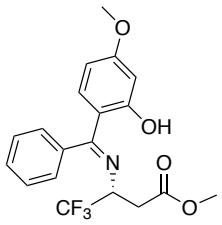
Following **General Procedure F,** ethyl (4-nitrophenyl)fumarate (26.3 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at 40 º C for 30 hrs. Pyrrolidine was added (12.5 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography with 5% MeOH in CH_2Cl_2 (R_f = 0.20) to give the titled compound (8.5 mg, 20%) as a yellow oil. $[\alpha]_D^{20}$ +2.94 (*c* = 1.10, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S*): 34.5 min, t_R(*R*): 44.7 min, 96:4 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1637 (C=O), 1591 (C=N), 1442 (C=C), 1261 (CF_2Br); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, $^3J_{HH}$ = 7.1, $CO_2CH_2CH_3$), 1.93 – 2.04 (4H, m, NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 2.82 (1H, dd, $^2J_{HH}$ = 15.7, $^3J_{HH}$ = 7.7, COC(2)H_AH_B), 2.98 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 5.6, COC(2)H_AH_B) 3.57 – 3.64 (4H, m, NC(2)H_2C(3)H_2C(4)H-$_2$C(5)H_2), 3.81 (3H, s, ArOH-OCH_3), 4.28 (2H, q, $^3J_{HH}$ = 7.1, $CO_2CH_2CH_3$), 4.62 (1H, dd, $^3J_{HH}$ = 7.6, $^3J_{HH}$ = 5.6, , $COCH_AH_BCH$), 6.20 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.46 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.67 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.36 – 7.38 (1H, m, N=CC(4)Ar*H*), 7.47 – 7.49 (4H, m, N=CC(2,3,5,6)Ar*H*), 15.5 (1H, s, N=CC(2)ArHO*H*-OCH_3). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 24.4 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 38.3 (C=OCH_AH_BCHCO-$_2$Et), 45.7 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 46.8 (NC(2)H_2C(3)H_2C(4)H_2C(5)H_2), 55.4 (-OCH_3), 59.8 ($CHCO_2CH_2CH_3$), 61.1 ($CO_2CH_2CH_3$), 101.4 (N=C*C*(3)ArOH-OCH_3), 105.8 (N=C*C*(5)ArOH-OCH_3), 113.7 (N=C*C*(1)ArOH-OCH_3), 128.4 (N=C*C*(2,6)Ar), 129.22 (N=C*C*(3,4,5)Ar), 133.5 (N=C*C*(6)ArOH-OCH_3), 134.5 (N=C*C*(1)Ar), 162.1 (N=C*C*(2)ArOH-OCH_3), 163.7 (N=C*C*(4)ArOH-OCH_3), 166.4 (*C*=OCH_AH_BCHCO$_2$Et), 167.1 (C=OCH_AH_BCH*C*O$_2$Et), 167.8 (*C*=N). **HRMS** (NSI$^+$) $C_{24}H_{28}N_2O_5^+$ ([M+H]$^+$) requires 425.2071, found 425.2063 (-1.9 ppm).

Benzyl (*R*)-2-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-4-oxo-4-(pyrrolidin-1-yl)butanoate (190)



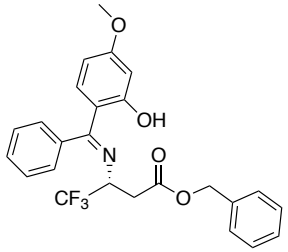
Following **General Procedure F,** Benzyl (4-nitrophenyl)fumarate (32.7 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (12.3 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography with 5% MeOH in CH_2Cl_2 (R_f = 0.42) to give the titled compound (9.7 mg, 20%) as a yellow oil. $[\alpha]_D^{20}$ +2.71 (*c* = 2.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 35.0 min, t_R(*S*): 44.7 min, 87:13 er; **IR** ν_{max} (ATR), 2970 (Ar-H), 1736 (CO_2Bn), 1639 (C=O), 1593 (C=N), 1443 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.80 – 1.98 (4H, m, NC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)H_2), 2.84 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 7.7, O=CC(2)*H*$_A$H$_B$), 3.01 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 5.6, O=CC(2)H$_A$*H*$_B$), 3.40 – 3.64 (4H, m, NC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)*H*$_2$), 3.82 (3H, s, -OC*H*$_3$), 4.67 (1H, dd, $^3J_{HH}$ = 7.5, $^3J_{HH}$ = 5.5, O=CCH$_A$H$_B$C(3)*H*), 5.16 – 5.18 (2H, m, CO_2C*H*$_2$Ph), 6.21 (1H, dd, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH$_3$), 6.47 (1H, dd, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH$_3$), 6.66 (1H, d, $^3J_{HH}$ = 8.9, N=CC(6)Ar*H*OH-OCH$_3$), 7.30 – 7.46 (10H, m, N=CC(2,3,4,5,6)Ar*H* & CO_2CH_2C(2,3,4,5,6)Ar*H*), 15.5 (1H, bs, -O*H*). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 – 26.0 (NC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$C(5)H$_2$), 38.3 (O=C*C*(2)H$_A$H$_B$), 45.7 – 46.7 (N*C*(2)H$_2$C(3)H$_2$C(4)H$_2$*C*(5)H$_2$), 55.4 (-O*C*H$_3$), 59.9 (O=CCH$_A$H$_B$*C*(3)H), 67.1 (CO_2*C*H$_2$Ph), 101.4 (N=C*C*(3)ArOH-OCH$_3$), 105.8 (N=C*C*(5)ArOH-OCH$_3$), 113.7 (N=C*C*(1)ArOH-OCH$_3$), 128.2 (N=C*C*(2,6)Ar), 128.3 (N=C*C*(1,3,5)Ar & CO_2CH_2*C*(1)Ar), 128.4 (N=C*C*(4)Ar), 128.5 (CO_2CH_2*C*(3,5)Ar), 128.8 (CO_2CH_2*C*(4)Ar), 133.6 (N=C*C*(6)ArOH-OCH$_3$), 163.7 (N=C*C*(4)ArOH-OCH$_3$), 166.2 (N=C*C*(2)ArOH-OCH$_3$), 167.7 (*C*=O-pyrrolidinyl), 170.8 (*C*O_2CH_2Ph), 176.2 (*C*=N). **HRMS** (NSI$^+$) $C_{29}H_{30}N_2O_5^+$ ([M+H]$^+$) requires 487.2228, found 487.2222 (-1.2 ppm).

Methyl (*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene) amino)butanoate (196)



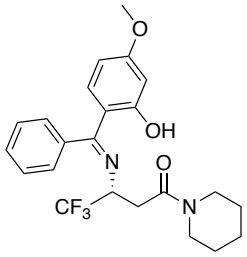
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Methanol (12.5 µL, 0.15 mmol) and DMAP (2.5 mg, 20 mol%) was added and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography (10:1 Petrol:Ethyl acetate) (R_f = 0.13) to give the titled compound (24.4 mg, 64 %) as a yellow oil. $[\alpha]_D^{20}$ +91.9 (*c* = 0.36, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 5.92 min, t_R(*S*): 9.13 min, 97: 3 er; **IR** ν_{max} (ATR), 2957 (Ar-H), 1743 (C=O), 1593 – 1605 (C=N), 1442 (C=C), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.84 – 2.86 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.7, COC(2)H_AH_B), 2.90 – 2.95 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 9.2, COC(2)H_AH_B), 3.68 (3H, s, CO_2CH_3), 3.84 (3H, s, ArOH-OCH_3), 4.36 (1H, m, $COCH_AH_BC(3)H$), 6.26 – 6.28 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.55 – 6.56 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.69 – 6.73 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.25 – 7.27 (1H, m, N=CC(2)Ar*H*), 7.36 – 7.38 (1H, m, N=CC(6)Ar*H*), 7.54 – 7.56 (3H, m, N=CC(3,4,5)Ar*H*), 14.6 (1H, s, -O*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$): -74.58 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 40.3 (CO*C*(2)$H_AH_BCHCF_3$), 55.9 (CO_2CH_3), 57.7 (ArOH-O*C*H_3), 58.0 (q, $^3J_{CF}$ = 28.9, $COCH_AH_BCHCF_3$), 101.2 (N=C*C*(3)ArOH-OCH_3), 106.2 (N=C*C*(5)ArOH-OCH_3), 113.9 (N=C*C*(1)ArOH-OCH_3), 123.6 (N=C*C*(1)Ar), 125.8 (-*C*F_3), 127.6 (N=C*C*(2,6)Ar), 132.9 (N=C*C*(3,4,5)Ar), 134.9 (N=C*C*(6)ArOH-OCH_3), 163.9 (N=C*C*(2)ArOH-OCH_3), 165.1 (N=C*C*(4)ArOH-OCH_3), 172.1 (*C*O_2CH_3), 178.8 (*C*=N); **HRMS** (NSI$^+$) $C_{19}H_{18}F_3NO_4^+$ ([M+H]$^+$) requires 382.1261, found 382.1255 (-1.6 ppm).

Benzyl (*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino) butanoate (197)



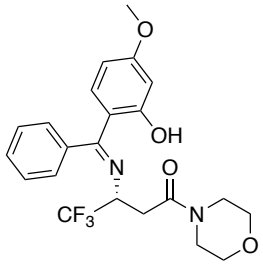
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Benzylalcohol (12.5 µL, 0.15 mmol) and DMAP (2.5 mg, 20 mol%) was added and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography (10:1 Petrol:Ethyl acetate) (R_f = 0.33) to give the titled compound (19.3 mg, 42%) as a yellow oil. $[\alpha]_D^{20}$ +78.4 (*c* = 0.45, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 8.13 min, t_R(*S*): 10.8 min, 96:4 er; **IR** ν_{max} (ATR), 2933 (Ar-H), 1741 (C=O), 1593 – 1616 (C=N), 1444 (C=C), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.86 – 2.91 (1H, dd, $^2J_{HH}$ = 15.9, $^3J_{HH}$ = 3.6, COC(2)H_AH_B), 2.96 – 3.03 (1H, dd, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 9.5, COC(2)H_AH_B), 3.86 (3H, s, ArOH-OCH_3), 4.35 – 4.37 (1H, m, COCH_AH_BC(3)*H*), 5.11 – 5.13 (2H, m, CO_2CH_2Ph), 6.28 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.5, N=CC(5)Ar*H*OH-OCH_3), 6.60 (1H, d, $^4J_{HH}$ = 2.5, N=CC(3)Ar*H*OH-OCH_3), 6.65 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.13 – 7.23 (2H, m, N=CC(2,6)Ar*H*), 7.27 – 7.29 (5H, m, CO_2CH_2C(2,3,4,5,6)Ar*H*), 7.48 – 7.50 (3H, m, N=CC(3,4,5)Ar*H*), 14.5 (1H, bs, -O*H*); **^{19}F NMR (376 MHz)**: -74.5 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 33.5 (CO*C*(2)H_AH_BCHCF_3), 55.6 (-OCH_3), 58.5 (COCH_AH_BC*H*CF_3), 67.0 (CO_2CH_2Ph), 101.2 (N=C*C*(3)ArOH-OCH_3), 106.7 (N=C*C*(5)ArOH-OCH_3), 113.5 (N=C*C*(1)ArOH-OCH_3), 123.1 (-*C*F_3),127.9 (N=C*C*(1)Ar), 128.2 (N=C*C*(2,6)Ar), 128.3 (CO_2CH_2*C*(2,6)Ar), 128.4 – 128.5 (CO_2CH_2*C*(3,4,5)Ar), 128.6 (N=C*C*(3,4,5)Ar), 134.3 (N=C*C*(6)ArOH-OCH_3), 135.3 (CO_2CH_2*C*(1)Ar), 164.4 (N=C*C*(2)ArOH-OCH_3), 165.2 (N=C*C*(3)ArOH-OCH_3), 169.0 (*C*=O), 179.0 (*C*=N). **HRMS** (NSI$^+$) $C_{25}H_{23}F_3NO_4^+$ ([M+H]$^+$) requires 458.1574, found 458.1563 (-2.4 ppm).

(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-(piperidin-1-yl)butan-1-one (193)



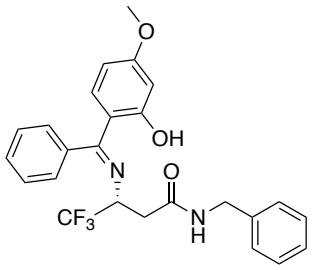
Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Piperidine was added (14.8 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.21) to give the titled compound (23.0 mg, 53%) as a yellow oil. $[\alpha]_D^{20}$ +89.0 (*c* = 0.50, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 12.2 min, t_R(*R*): 16.3 min, 96:4 er; **IR** ν_{max} (ATR), 2941 (Ar-H), 1620 (C=O), 1593 (C=N), 1445 (C=C), 1259 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.58 – 1.60 (6H, m, NC(2)H_2C(3)*H_2*C(4)*H*-$_2$C(5)*H_2*C(6)H_2), 2.79 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 3.0, O=CC(2)*H_A*H_B), 3.06 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 9.5, O=CC(2)H_A*H_B*), 3.43 – 3.57 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)H_2C(6)*H_2*), 3.83 (3H, s, -OC*H_3*), 4.49 – 4.51 (1H, m, O=CC$H_A$$H_B$C(3)*H*), 6.27 (1H, dd, $^3J_{HH}$ =9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.51 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.68 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.23 (1H, s, N=CC(2)Ar*H*), 7.49 – 7.51 (4H, m, N=CC(3,4,5,6)Ar*H*), 14.9 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.15 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 37.9 (O=C*C*(2)$H_A$$H_B$), 43.9 (NH*C*$H_2$Ph), 55.5 (-O*C*$H_3$), 58.8 – 59.4 (q, $^2J_{CF}$ = 23.3 O=CC$H_A$$H_B$*C*(3)H), 101.3 (N=C*C*(3)ArOH-OCH_3), 106.4 (N=C*C*(5)ArOH-OCH_3), 113.8 (N=C*C*(1)ArOH-OCH_3), 125.8 (-*C*F_3), 127.4 (NHCH_2*C*(3,4,5)Ph), 127.6 (N=C*C*(2,6)ArH), 128.3 (NHCH_2*C*(2,6)Ph), 128.5 (N=C*C*(1)Ar), 129.4 (NHCH_2*C*(1)Ph), 164.2 (N=C*C*(2)ArOH-OCH_3), 165.3 (N=C*C*(4)ArOH-OCH_3), 167.8 (*C*=O), 179.2 (*C*=N). **HRMS** (NSI$^+$) $C_{23}H_{25}F_3N_2O_4^+$ ([M+H]$^+$) requires 435.1890, found 435.1878 (-2.8 ppm).

(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino)-1-morpholinobutan-1-one (194)



Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Morpholine was added (12.9 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (2:1) (R_f = 0.19) to give the titled compound (22.6 mg, 52%) as a yellow oil. $[\alpha]_D^{20}$ +86.0 (*c* = 0.45, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 $mLmin^{-1}$, 220 nm, 30 °C) t_R(*R*): 14.7 min, t_R(*S*): 20.1 min, 96:4 er; **IR** ν_{max} (ATR), 2990 (Ar-H), 1645 (C=O), 1593 (C=N), 1444 (C=C), 1259 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.74 (1H, dd, $^2J_{HH}$ = 15.4, $^3J_{HH}$ = 2.9, O=CC(2)H_AH_B), 3.04 (1H, dd, $^2J_{HH}$ = 15.3, $^3J_{HH}$ = 9.67, O=CC(2)H_AH_B), 3.48 – 3.66 (8H, m, NC(2)H_2C(3)H_2C(5)H_2C(6)H_2O), 3.84 (3H, s, -OCH_3), 4.48 – 4.50 (1H, m, $COCH_AH_BCH$), 6.47 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH_3), 6.55 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH_3), 6.70 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH_3), 7.22 – 7.24 (1H, m, N=CC(2)Ar*H*), 7.46 – 7.52 (4H, m, N=CC(3,4,5,6)Ar*H*), 14.75 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.21 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 33.5 (O=C*C*(2)H_AH_B), 42.2 – 46.3 (N*C*(2)H_2C(3)H_2C(5)H_2*C*(6)H_2O), 55.5 (-O*C*H_3), 58.8 (q, $^2J_{CF}$ = 22.9, C=OCH_AH_B*C*(3)HCF_3), 66.6 – 66.8 (NC(2)H_2*C*(3)H_2*C*(5)H_2C(6)H_2O), 101.3 (N=C*C*(3)ArOH-OCH_3), 106.6 (N=C*C*(5)ArOH-OCH_3), 113.6 (N=C*C*(1)ArOH-OCH_3), 126.0 (-*C*F_3), 128.2 (N=C*C*(1)Ar), 128.4 (N=C*C*(2,6)Ar), 129.5 (N=C*C*(3,4,5)Ar), 134.3 (N=C*C*(6)ArOH-OCH_3), 164.3 (N=C*C*(4)ArOH-OCH_3), 165.2 (N=C*C*(2)ArOH-OCH_3), 166.7 (*C*=O), 179.0 (*C*=N). **HRMS** (NSI$^+$) $C_{22}H_{23}F_3N_2O_4^+$ ([M+H]$^+$) requires 437.1683, found 437.1673 (-2.3 ppm).

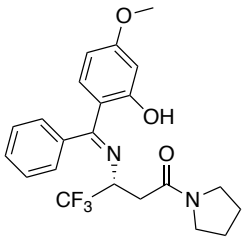
(*R*)-*N*-Benzyl-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)methylene)amino) Butanamide (195)



Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4-difluorobut-2-enoate (26.1 mg, 0.1 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (45.4 mg, 0.2 mmol), (*R*)-(+)-BTM (5.1 mg, 0.02mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Benzylamine was added (16.4 µL, 0.15 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.18) to give the titled compound (23.8 mg, 52%) as a yellow oil. $[\alpha]_D^{20}$ +108.8 (*c* = 0.51, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak OD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S*): 13.0 min, t_R(*R*): 14.9 min, 97:3 er; **IR** ν_{max} (ATR), 2956 (Ar-H), 1743 (O=CNHBn) 1604 (C=O), 1595 (C=N), 1442 (C=C), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.72 – 2.76 (2H, m, O=CC(2)H_AH_B), 3.85 (3H, s, -OCH_3), 4.26 – 4.30 (1H, dd, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 5.3, O=CCH_AH$_B$Ph), 4.42 – 4.44 (1H, m, O=CCH$_A$H$_B$C(3)*H*), 4.52 – 4.56 (1H, dd, $^2J_{HH}$ = 15.-, $^3J_{HH}$ = 6.4, O=CCH$_A$$H_B$Ph), 6.11 (1H, d, $^3J_{HH}$ = 6.4, O=CN*H*), 6.31 (1H, dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.6, N=CC(5)Ar*H*OH-OCH$_3$), 6.49 (1H, d, $^4J_{HH}$ = 2.6, N=CC(3)Ar*H*OH-OCH$_3$), 6.67 (1H, d, $^3J_{HH}$ = 9.0, N=CC(6)Ar*H*OH-OCH$_3$), 7.07 – 7.10 (2H, m, NHCH$_2$C(2,6)Ar*H*), 7.13 – 7.15 (3H, m, NHCH$_2$C(3,4,5)Ar*H*), 7.20 – 7.22 (2H, m, N=CC(2,6)Ar*H*), 7.48 – 7.50 (3H, m, N=CC(3,4,5)Ar*H*), 14.9 (1H, s, -O*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.49 (-CF_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 37.9 (O=C*C*(2)H_AH_B), 43.9 (NH*C*H$_2$Ph), 55.5 (-O*C*H$_3$), 58.8 – 59.4 (q, $^2J_{CF}$ = 23.3 O=CCH$_A$H$_B$*C*(3)H), 101.3 (N=C*C*(3)ArOH-OCH$_3$), 106.4 (N=C*C*(5)ArOH-OCH$_3$), 113.8 (N=C*C*(1)ArOH-OCH$_3$), 125.8 (-*C*F$_3$), 127.4 (NHCH$_2$*C*(3,4,5)Ph), 127.7 (N=C*C*(2,6)ArH), 128.3 (NHCH$_2$*C*(2,6)Ph), 128.6 (N=C*C*(1)Ar), 129.4 (N=C*C*(3,4,5)Ar), 134.2 (N=C*C*(6)ArOH-OCH$_3$), 137.6 (NHCH$_2$*C*(1)Ph), 164.2 (N=C*C*(2)ArOH-OCH$_3$), 165.3 (N=C*C*(4)ArOH-OCH$_3$), 167.8 (*C*=O), 179.2 (*C*=N). **HRMS** (NSI$^+$) $C_{25}H_{23}F_3N_2O_4^+$ ([M+H]$^+$) requires 457.1734, found 457.1724 (-2.2 ppm).

5.4.2 Gram Scale Synthesis

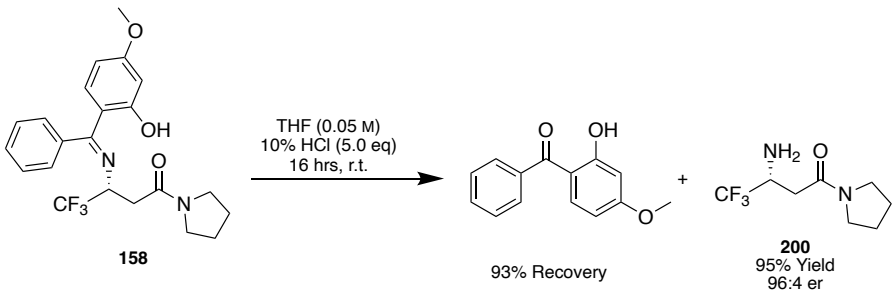
(*R*)-4,4,4-trifluoro-3-(((2-hydroxy-4-methoxyphenyl)(phenyl)methylene)amino)-1-(pyrrolidin-1-yl)butan-1-one (158)



Following **General Procedure F,** 4-nitrophenyl (*E*)-4,4,4,-trifluorobut-2-enoate (1.436 g, 5.5 mmol), 2-(imino(phenyl)methyl)-5-methoxyphenol (2.50 g, 11.0 mmol), (*R*)-(+)-BTM (277.6 mg, 1.1 mmol), and toluene (0.1 M) was stirred at room temperature for 30 hrs. Pyrrolidine was added (678 µL, 8.25 mmol) and the reaction was stirred at rt for 16 hrs. The crude mixture was then purified by flash column chromatography Hexane:EtOAc (4:1) (R_f = 0.20) to give the titled compound (1.55 g, 67%) as a yellow oil. $[\alpha]_D^{20}$ +95.5 (*c* = 0.87, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 19.1 min, t_R(*S*): 25.3 min, 95:5 er; **IR** ν_{max} (ATR), 2976 (Ar-H), 1624 (C=O), 1605 (C=N), 1444 – 1454 (C=C), 1276 (C-O-CH_3), 1261 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.86 – 1.98 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.75 (1H, dd, $^3J_{HH}$ = 15.4, $^4J_{HF}$ = 3.0, COC(2)*H_A*H_B), 2.98 (1H, dd, $^3J_{HH}$ = 15.2, $^4J_{HF}$ = 10.0, COC(2)H$_A$*H_B*), 3.44 – 3.57 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.84 (3H, s, OC*H_3*), 4.53 – 4.55 (1H, m, COCH$_A$H$_B$C*H*), 6.28 (1H, dd, $^3J_{HH}$ = 9.0, N=CC(5)Ar*H*OH-OCH_3), 6.58 (1H, s, N=CC(3)Ar*H*OH-OCH_3), 6.72 (1H, dd, $^3J_{HH}$ = 8.9, N=CC(6)Ar*H*OH-OCH_3), 7.23 – 7.25 (1H, m, N=CC(4)Ar*H*), 7.51 – 7.53 (4H, m, N=CC(2,3,5,6)Ar*H*), 14.8 (1H, s, N=CC(2)ArO*H*-OCH_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -74.31 (-C*F_3*) ; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 24.4 (NC(2)H_2*C*(3)H_2C(4)H_2C(5)H_2), 26.1 (NC(2)H_2C(3)H_2*C*(4)H_2C(5)H_2), 35.3 (C=O*C*H$_A$H$_B$CF_3), 45.9 (N*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2), 47.0 (NC(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 55.54 (O*C*H_3), 58.7 (q, $^2J_{CF}$ = 28.3, C=OCH$_A$H$_B$*C*(3)HCF_3), 101.2 (N=C*C*(3)ArOH-OCH_3), 106.6 (N=C*C*(5)ArOH-OCH_3), 114.28 (N=C*C*(1)ArOH-OCH_3), 118.4 (*C*F_3), 128.2 (N=C*C*(2,3,5,6)ArH), 129.5 (N=C*C*(4)Ar), 134.4 (N=C*C*(1)Ar), 164.4 (N=C*C*(2)ArOH-OCH_3), 165.5 (*C*=N), 166.3 (N=C*C*(4)ArOH-OCH_3), 178.9 (*C*=O). **HRMS** (NSI$^+$) $C_{21}H_{23}F_3N_2O_3^+$ ([M+H]$^+$) requires 421.1734, found 421.1729 (-1.2 ppm).

5.4.3 Hydrolysis of Product 158

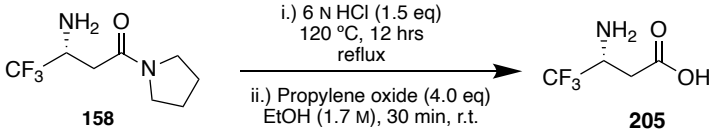
(*R*)-3-amino-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (200)



Compound **5** (292 mg, 0.7 mmol), THF (0.05 M), and 10% HCl (1.1 mL, 3.45 mmol) was stirred at room temperature for 16 hrs. The crude mixture was purified by flash column chromatography MeOH to give the titled compound **25** (138 mg, 95% yield) as an off-white solid. $[\alpha]_D^{20}$ +96.1 (*c* = 0.84, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 12.9 min, t_R(*R*): 18.3 min, 96:4 er; **IR** ν_{max} (ATR), 3116 (NH_2), 2981 (Ar-H), 1715 (C=O), 1618 (Amide stretch), 1390 (C=C), 1296 (CF_3); **^{1}H NMR** (400 MHz, D_2O) δ_H: 1.90 – 1.98 (4H, m, NC(2)H_2C(3)*H_2*C(4)*H_2*C(5)H_2), 2.64 – 2.69 (1H, dd, $^2J_{HH}$ = 16.8, $^3J_{HH}$ = 9.4, COC(2)*H_A*H_BCHCF_3), 2.82 – 2.86 (1H, dd, $^2J_{HH}$ = 15.9, $^3J_{HH}$ = 3.4, COC(2)H_A*H_B*CHCF_3), 3.43 – 3.55 (4H, m, NC(2)*H_2*C(3)H_2C(4)H_2C(5)*H_2*), 3.90 (1H, s, COCH_AH_BC*H*CF_3). **^{19}F{^{1}H} NMR** (376 MHz, D_2O), δ_F: -77.47 (-C*F_3*); **^{13}C{^{1}H} NMR** (101 MHz, D_2O) δ_C: 23.9 – 25.2 (N*C*(2)H_2C(3)H_2C(4)H_2*C*(5)H_2), 33.2 (CO*C*H_AH_BCHCF_3), 46.3 – 47.4 (NC(2)H_2*C*(3)H_2*C*(4)H_2C(5)H_2), 50.0 (q, $^2J_{CF}$ = 33.0, COCH_AH_B*C*HCF_3), 128.5 (-*C*F_3), 170.3 (*C*=O). **HRMS** (NSI$^+$) $C_8H_{14}F_3N_2O^+$ ([M+H]$^+$) requires 211.1053, found 211.1047 (-2.8 ppm).

5.4.4 Absolute Configuration of Compound 205

(*R*)-3-amino-4,4,4-trifluorobutanoic acid (205)

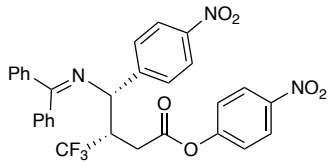


Compound **158** (41.3 mg, 0.2 mmol) was added with 6 N HCl (0.4 mL) stirred at 120 °C for 12 hrs. The crude mixture was then dried to obtain a crude beige solid. The crude solid was then added with dried EtOH (1.7 M) and propylene oxide (56 µL, 0.8 mmol) and the reaction mixture was stirred for 30 minutes. The mixture was then concentrated under vacuo and the crude solid was then washed with propanol to obtain the solid product (12.7 mg, 40% yield) as an off-white solid **mp** 173–175 ºC; $[\alpha]_D^{20}$ +17.9 (*c* = 1.27, 6N HCl) (literature $[\alpha]_D^{25}$ +24.4 (*c* = 1.05, 6N HCl))[21]; **IR** ν_{max} (ATR), 3387 (NH_2), 3045 (OH) 1615 (C=O), 1430 (CH_2 bend), 1296 (CF_3); **^{1}H NMR** (400 MHz, CD_3OD) δ_H: 2.49 – 2.51 (1H, m, COC(2)$H_AH_BCHCF_3$), 2.73 – 2.75 (1H, m, COC(2)$H_AH_BCHCF_3$), 3.93 – 3.95 (1H, m, $COCH_AH_BCHCF_3$). **^{19}F{^{1}H} NMR** (400 MHz, CD_3OD), δ_F: -77.9 (-CF_3). Data in agreement with literature.[21]

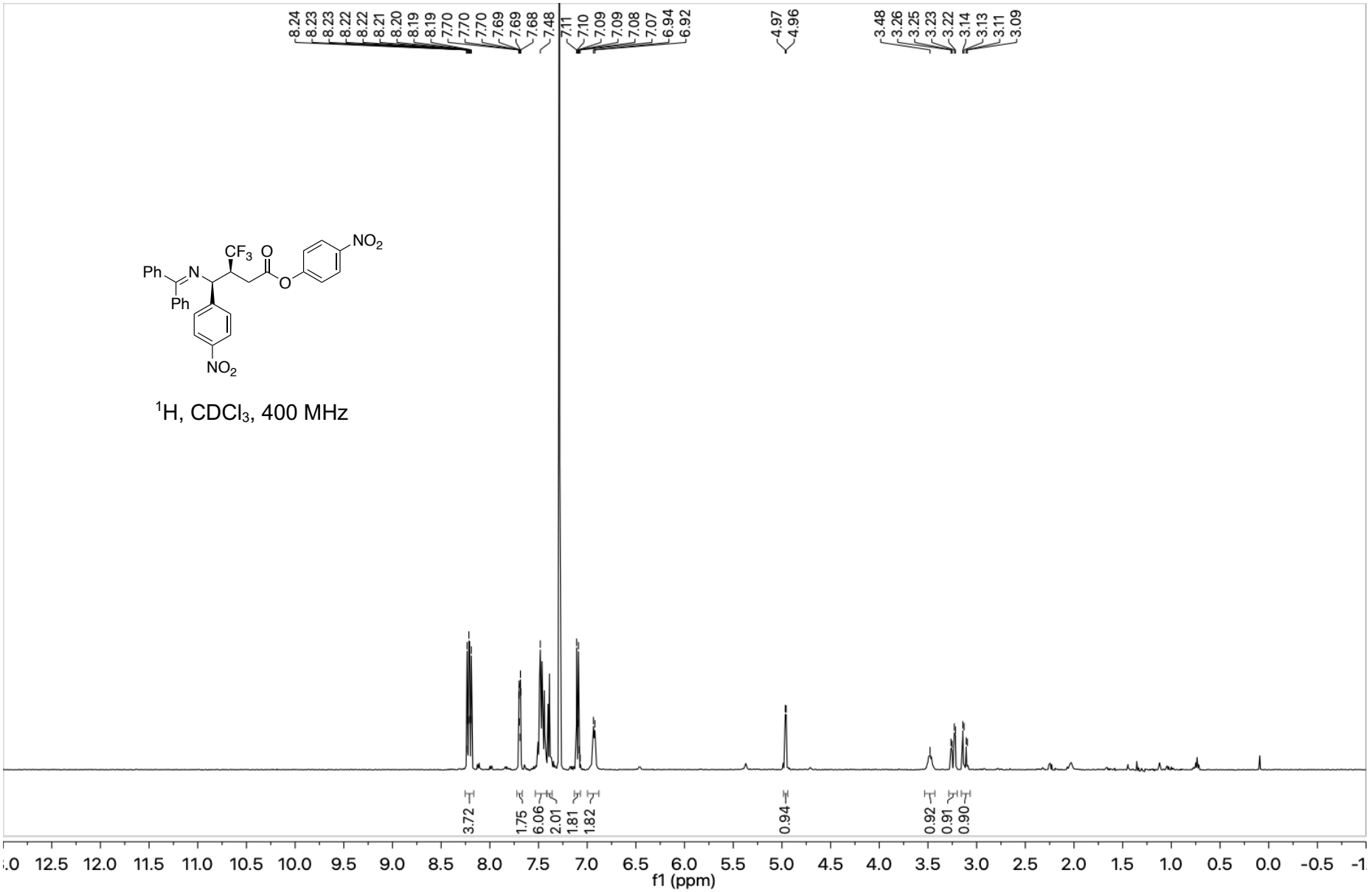
5.5 CHAPTER 3 PRODUCTS

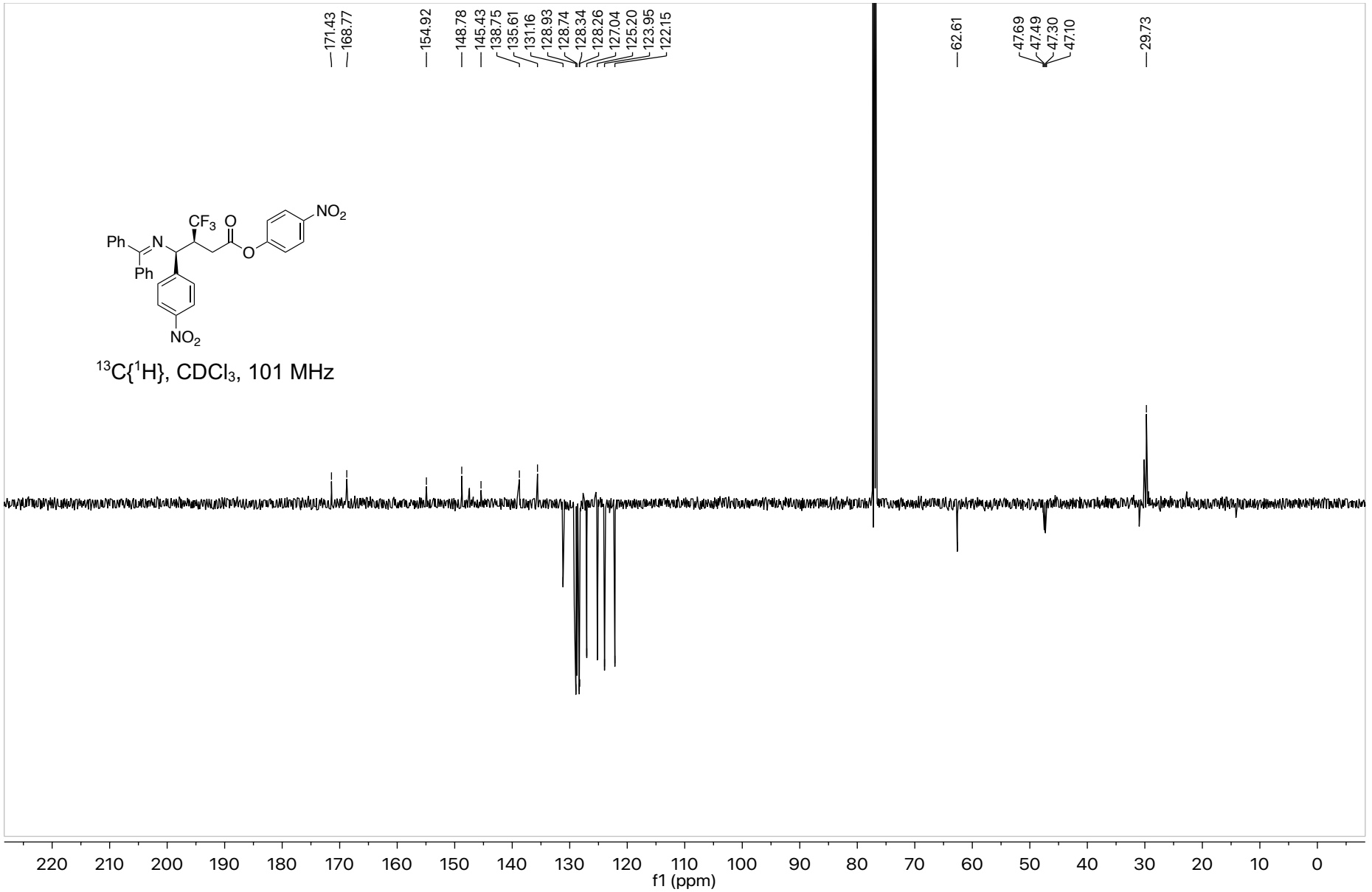
5.5.1 Chapter 3: Isothiourea-Catalysed Michael Addition Products

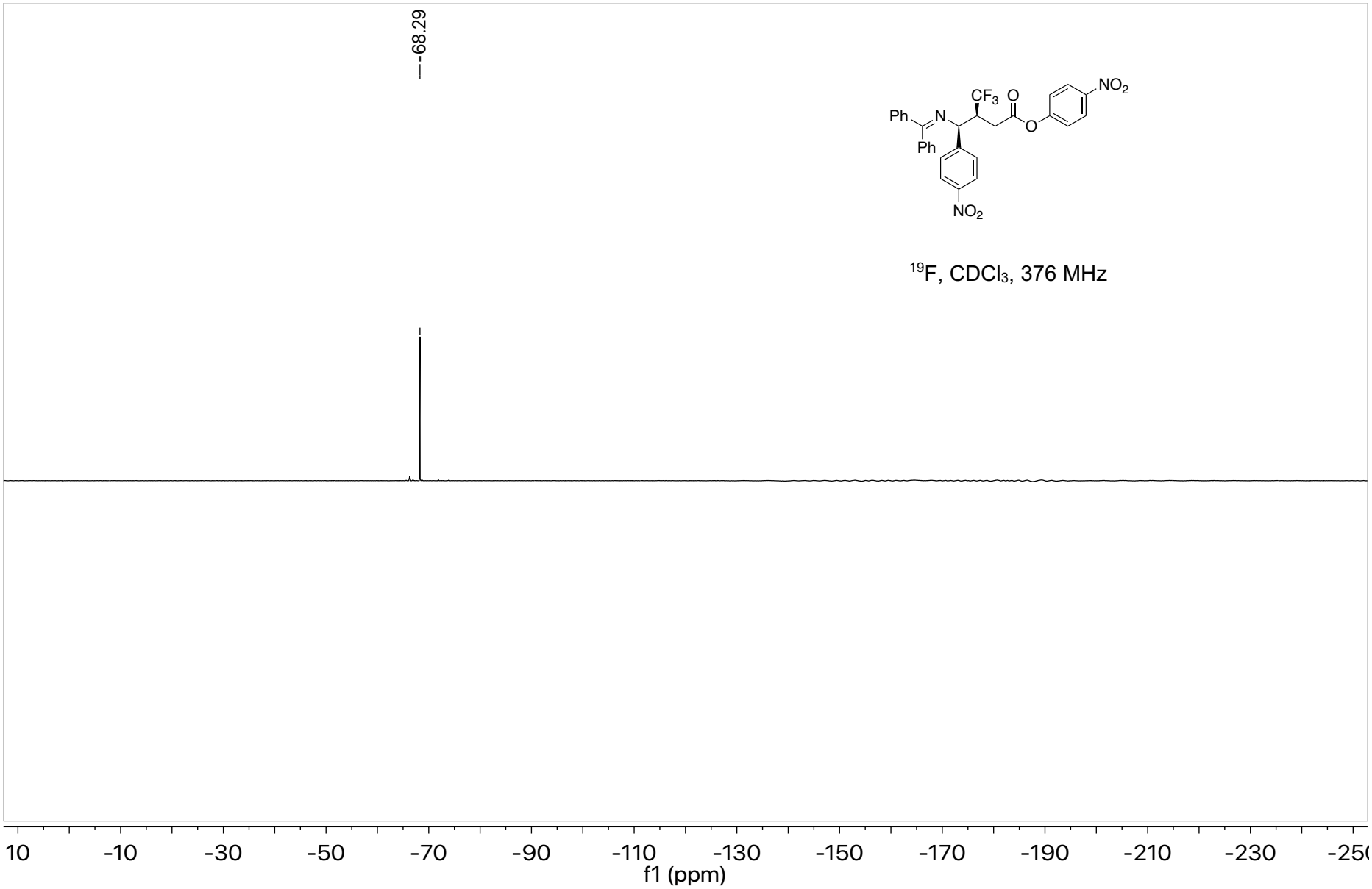
4-nitrophenyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-Trifluorobutanoate (245)



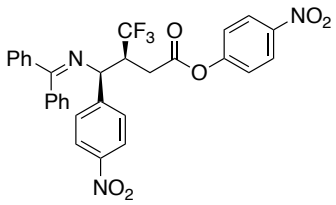
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.6 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs, purified by flash chromatography 10:1 Petrol:EtOAc (R_f = 0.21) to give the titled compound as an inseparable mixture of diastereomers (95:5 dr) as an colorless oil (47 mg, 81%). $[\alpha]_D^{20}$ –20.4 (*c* 1.0, $CHCl_3$)); **Chiral HPLC analysis.** Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S,R*): 30.4 min, t_R(*S,S*): 55.1 min, 5:95 er; **IR** ν_{max} (ATR)2922 (Ar-H), 1766 (C=O ester), 1523 (N-O stretch), 1346 (NO_2 sym), 1113 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 3.12 (1H, dd, $^3J_{HH}$ = 17.3, $^4J_{HF}$ = 6.4, CH_AH$_B$CO$_2$Ar), 3.24 (1H, dd, $^3J_{HH}$ = 17.3, $^4J_{HF}$ = 5.8, CH$_A$$H_BCO_2$Ar), 3.47 – 3.49 (1H, m, CHCH$_A$H$_B$CO$_2$Ar), 4.96 (1H, d, $^3J_{HH}$ =4.48, CHCHCH$_A$H$_B$CO$_2$Ar), 6.93 (2H, d, $^3J_{HH}$ = 6.87, N=CC(2,6)Ar$_1$$H$), 7.09 – 7.11 (2H, m, CO$_2$C(2,6)ArH-NO$_2$), 7.38 – 7.40 (2H, m, N=CC(4)Ar$_1$$H$ and N=CC(4)Ar$_2$$H$), 7.46 – 7.48 (6H, m, N=CC(3,5)Ar$_1$$H$, N=CC(3,5)Ar$_2$$H$, C=NCHC(2,6)Ar$_3$$H$-NO$_2$), 7.68 – 7.70 (2H, m, N=CC(2,6)Ar$_2$$H$), 8.21 – 8.23 (4H, m, CO$_2$C(3,5)Ar$_4$$H$-NO$_2$, C=NCHC(3,5)Ar$_3$$H$-NO$_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.29; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.7 (*C*H$_A$H$_B$CO$_2$Ar), 47.1 – 47.7 (q, $^2J_{CF}$ = 24.9, *C*HCH$_A$H$_B$CO$_2$Ar), 62.6 (C=N*C*HPh-NO$_2$), 122.1 (CO$_2$*C*(2,6)Ar-NO$_2$), 123.9 (C=NCH*C*(3,5)Ar$_3$-NO$_2$), 125.2 (CO$_2$*C*(3,5)Ar-NO$_2$), 127.0 (N=C*C*(2,6)Ar$_1$), 128.3 (-*C*F$_3$), 128.4 (N=C*C*(3,5)Ar$_1$, N=C*C*(3,5)Ar$_2$,), 128.7 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.9 (N=C*C*(2,6)Ar$_2$), 131.2 (C=NCH*C*(2,6)Ar$_3$-NO$_2$), 135.6 (N=C*C*(1)Ar$_1$), 138.8 (N=C*C*(1)Ar$_2$), 145.4 (CO$_2$*C*(4)Ar-NO$_2$), 147.8 (C=NCH*C*(4)Ar$_3$-NO$_2$), 148.8 (C=NCH*C*(1)Ar$_3$-NO$_2$), 154.9 (CO$_2$*C*(1)Ar-NO$_2$),168.8 (*C*O$_2$Ar-NO$_2$), 171.4 (*C*=N). **HRMS** (NSI$^+$) $C_{21}H_{21}F_3N_2O_2^+$ ([M+Na]$^+$) requires 600.1353, found 600.1343 (-1.7 ppm).


8.24
8.23
8.23
8.22
8.22
8.21
8.20
8.19
8.19
7.70
7.70
7.70
7.69
7.69
7.68
7.48
7.11
7.10
7.09
7.09
7.08
7.07
6.94
6.92
4.97
4.96
3.48
3.26
3.25
3.23
3.22
3.14
3.13
3.11
3.09
Ph
N
Ph
CF3
O
O
NO2
NO2
1H, CDCl3, 400 MHz
3.72
1.75
6.06
2.01
1.81
1.82
0.94
0.92
0.91
0.90
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


171.43
168.77
154.92
148.78
145.43
138.75
135.61
131.16
128.93
128.74
128.34
128.26
127.04
125.20
123.95
122.15
62.61
47.69
47.49
47.30
47.10
29.73
Ph
N
Ph
CF3
O
O
NO2
NO2
13C{1H}, CDCl3, 101 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

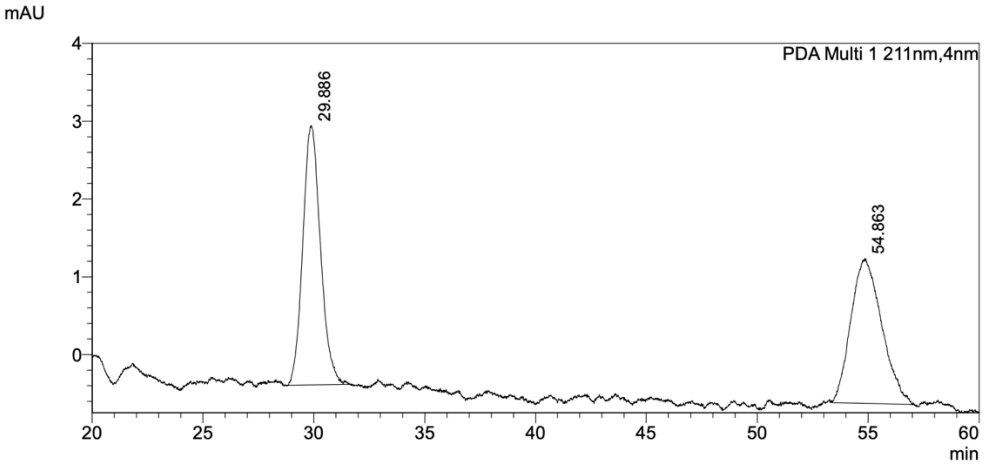

-68.29
Ph
N
Ph
CF3
O
O
NO2
NO2
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **4-nitrophenyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate**: Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S,R*): 30.4 min, t_R(*S,S*): 55.1 min, 5:95 er.



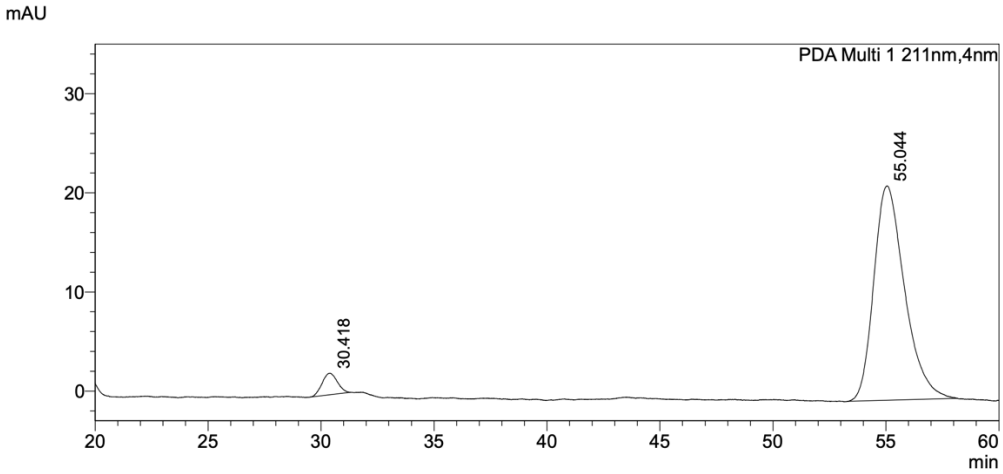
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	29.886	50.747
2	54.863	49.253
Total		100.000

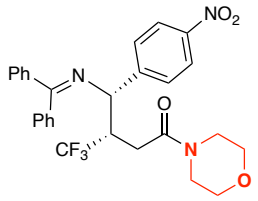


PDA Ch1 211nm

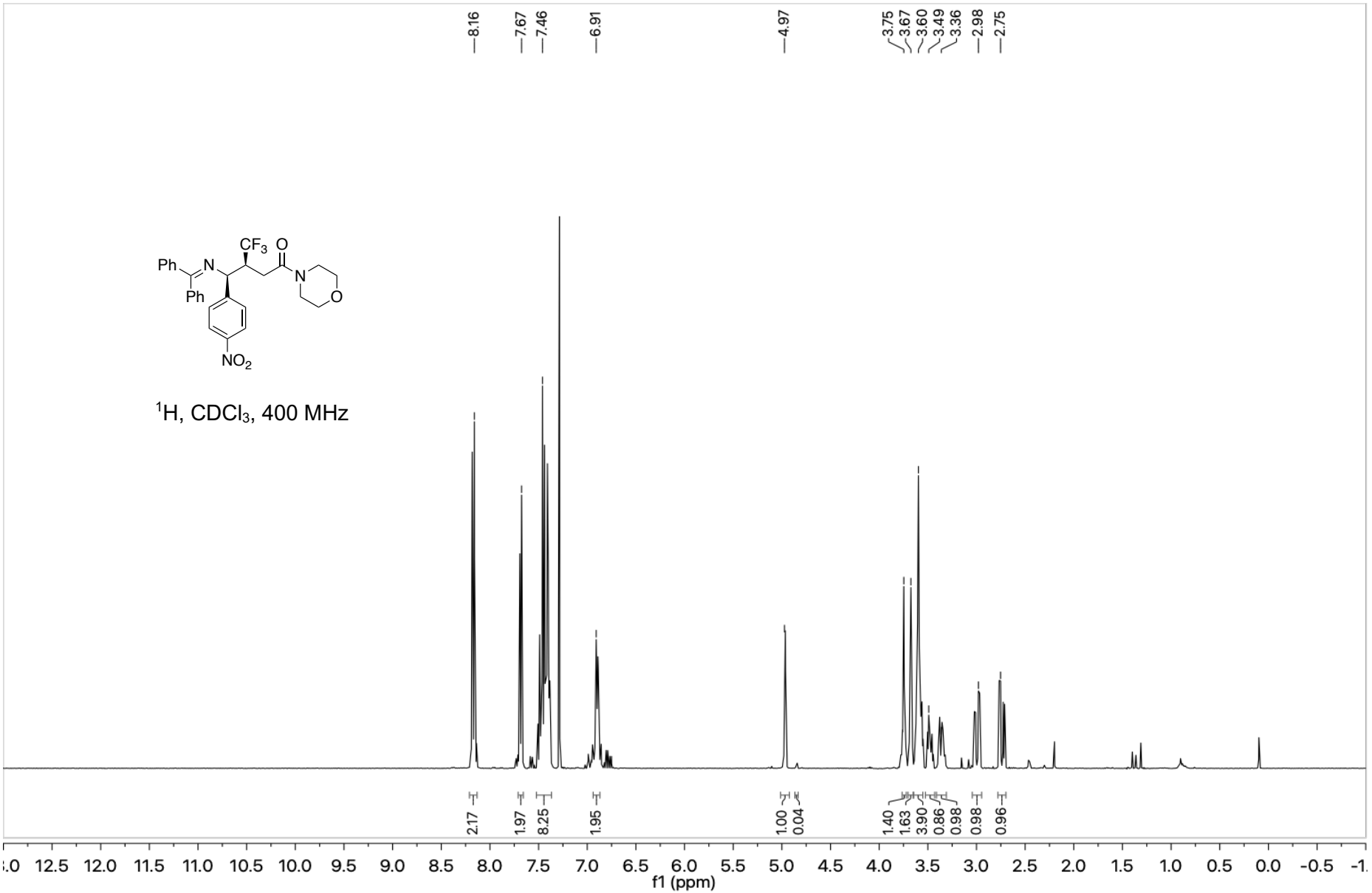
Peak#	Ret. Time	Area%
1	30.418	4.760
2	55.044	95.240
Total		100.000

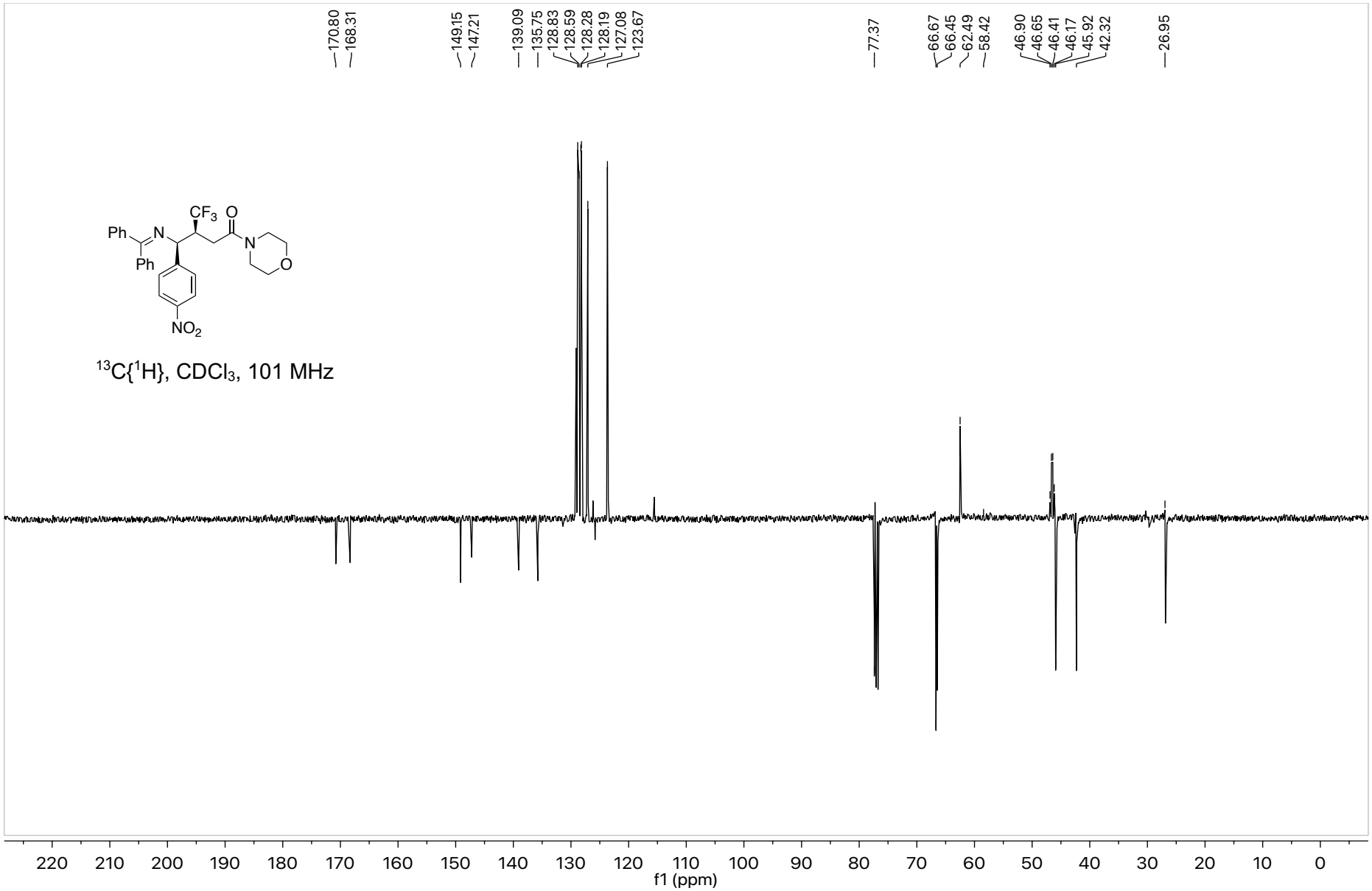


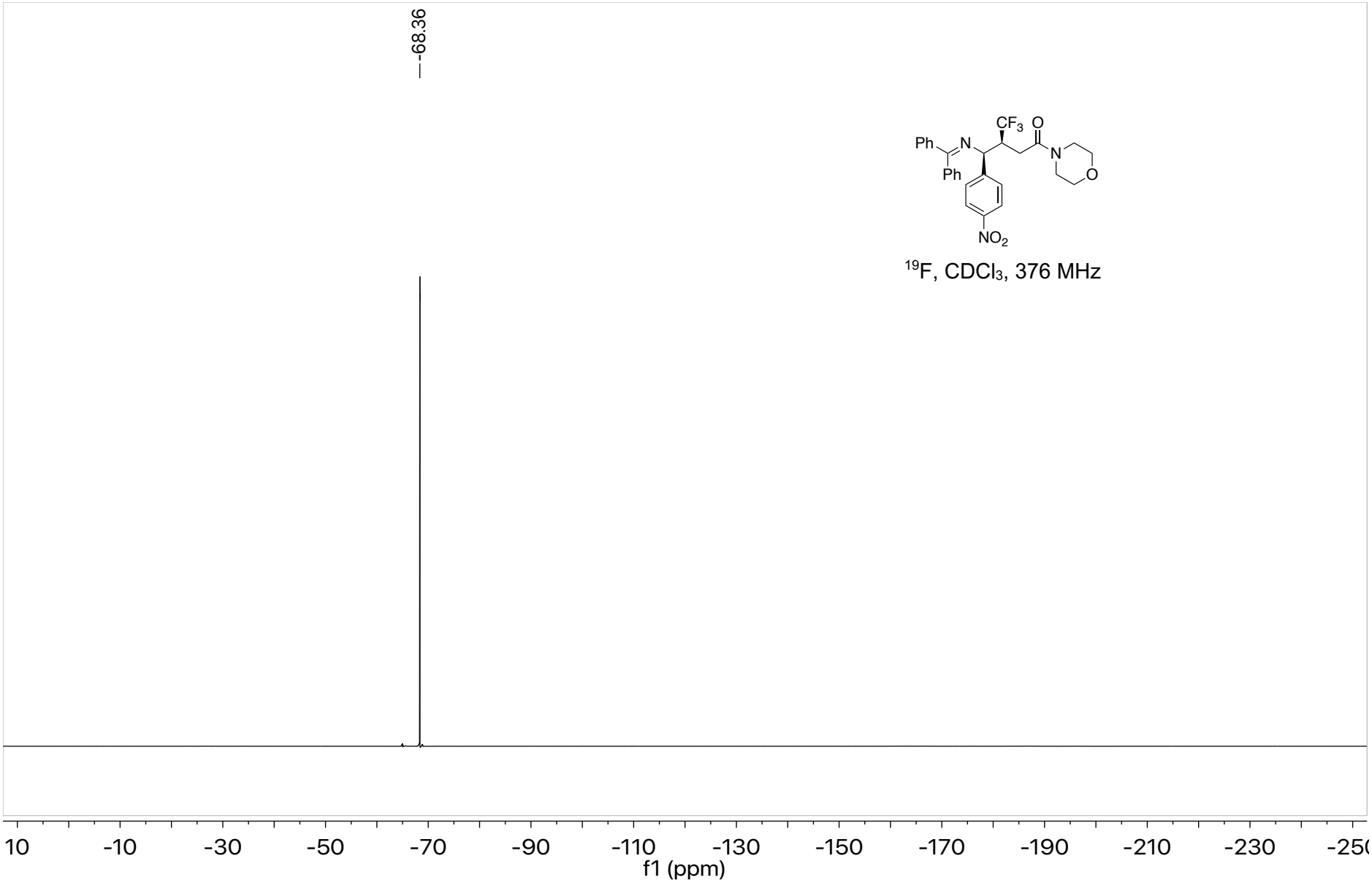
(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-morpholinobutan-1-one (249)



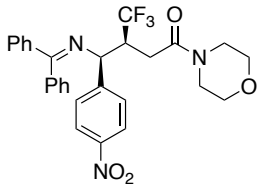
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with morpholine (12.9 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Petrol:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a colorless oil (39 mg, 75%). $[\alpha]_D^{20}$ – 1.13 (*c* 3.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,R*): 19.1 min, t_R(*S,S*): 23.6 min, 6:94 er; **IR** ν_{max} (ATR)2922 (Ar-H), 1643 (C=O amide), 1519 (N-O stretch), 1444 (C=C), 1344 (NO_2 sym), 1111 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.75 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HH}$ = 5.74, $CF_3CHCH_AH_B$), 2.98 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.2, $F_3CCHCHAHBCO$), 3.36 – 3.49 (2H, m, $CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 3.58 – 3.60 (4H, m, $CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 3.66 – 3.68 (2H, m, $CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$) 3.74 – 3.76 (1H, m, $F_3CCHCH_AH_B$), 4.97 (1H, d, $^3J_{HH}$ = 3.5, $C{=}NCHAr_3\text{-}NO_2$), 6.90 – 6.92 (2H, m, $N{=}CC(4)Ar_1H$, $N{=}CC(4)Ar_2H$), 7.45 – 7.46 (8H, m, $N{=}CC(2,3,5,6)Ar_1H$, $N{=}CC(2,3,5,6)Ar_1H$), 7.66 – 7.68 (2H, m, $C{=}NCHC(2,6)Ar_3H\text{-}NO_2$), 8.15 – 8.17 (2H, m, $C{=}NCHC(3,5)Ar_3H\text{-}NO_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.4; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 26.9 ($F_3CCHCH_AH_B$), 42.3 – 45.9 ($CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 46.65 (q, $^2J_{CF}$ = 24.4), 66.5 – 66.7 ($CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 123.7 ($C{=}NCHC(3,5)Ar_3\text{-}NO_2$), 127.1 ($N{=}CC(4)Ar_1$, $N{=}CC(4)Ar_2$), 128.2 ($N{=}CC(3,5)Ar_1$, $N{=}CC(3,5)Ar_2$), 128.3 (CF_3), 128.6 ($N{=}CC(2,5)Ar_1$, $N{=}CC(2,6)Ar_2$), 128.8 ($C{=}NCHC(2,6)Ar_3\text{-}NO_2$), 135.6 – 139.1 ($N{=}CC(1)Ar_1$, $N{=}CC(1)Ar_2$), 147.2 ($C{=}NCHC(4)Ar_3\text{-}NO_2$), 149.2 ($C{=}NCHC(1)Ar_3\text{-}NO_2$), 168.3 ($F_3CHCH_AH_BCON$), 170.8 (*C*=N). **HRMS** (NSI$^+$) $C_{28}H_{27}F_3N_3O_4^+$ ($[M+H]^+$) requires 526.1955, found 526.1944 (-0.85 ppm).


8.16
7.67
7.46
6.91
4.97
3.75
3.67
3.60
3.49
3.36
2.98
2.75
CF3
O
Ph
N
Ph
N
O
NO2
1H, CDCl3, 400 MHz
2.17
1.97
8.25
1.95
1.00
0.04
1.40
1.63
3.90
0.86
0.98
0.98
0.96
f1 (ppm)


170.80
168.31
149.15
147.21
139.09
135.75
128.83
128.59
128.28
128.19
127.08
123.67
77.37
66.67
66.45
62.49
58.42
46.90
46.65
46.41
46.17
45.92
42.32
26.95
Ph
N
Ph
CF3
O
N
O
NO2
13C{1H}, CDCl3, 101 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

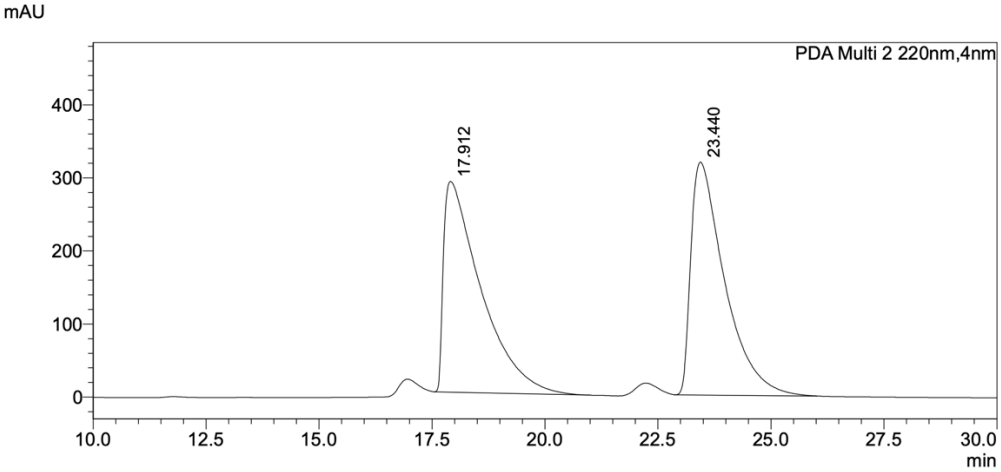

-68.36
Ph
N
Ph
CF3
O
N
O
NO2
19F, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for (***S***)-3-((***S***)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-morpholinobutan-1-one: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,R*): 19.1 min, t_R(*S,S*): 23.6 min, 6:94 er.



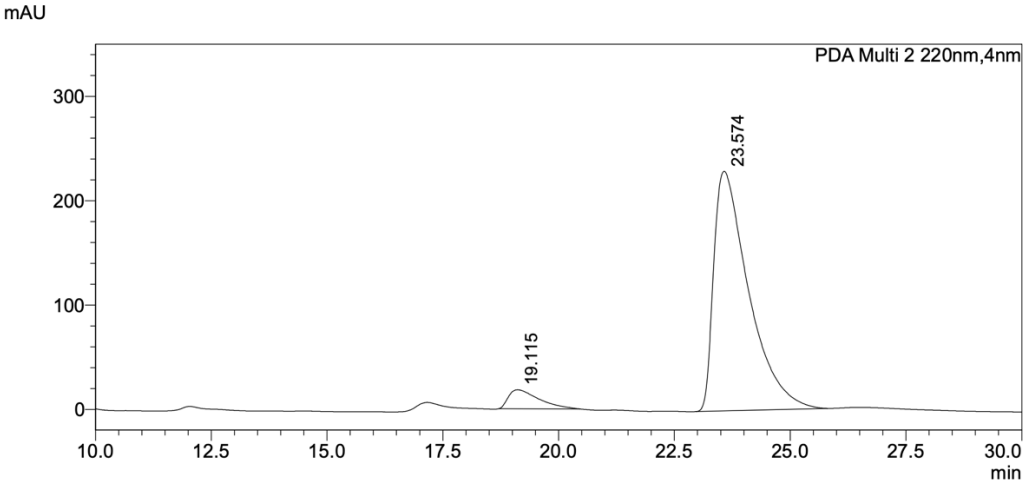
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	17.912	50.087
2	23.440	49.913
Total		100.000

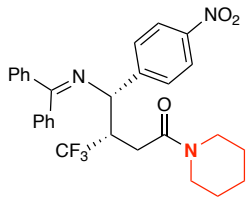


PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	19.115	6.454
2	23.574	93.546
Total		100.000

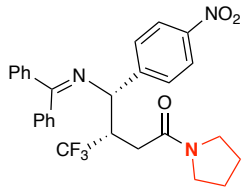


(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one (250)



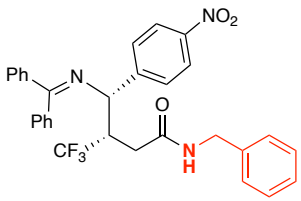
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.23) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a garnet red solid (42.4 mg, 81%). **mp** 136 – 138 ºC, $[\alpha]_D^{20}$ -6.1 (*c* 4.3, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*S,S*): 17.9 min, t_R(*S,R*): 27.4 min, 95:5 er; **IR** ν_{max} (ATR) 2939 (Ar-H), 1629 (C=O amide), 1519 (N-O stretch), 1445 (C=C), 1342 (NO_2 sym), 1107 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 1.45 – 1.59 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.71 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HF}$ = 5.8, F_3CCHC$H_A$$H_B$), 3.04 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HF}$ = 5.2, F_3CCHC$H_A$$H_B$), 3.32 – 3.51 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.74 – 3.76 (1H, m, F_3CCHC$H_A$$H_B$), 4.96 (1H, d, $^3J_{HH}$ = 3.5, C=NCHAr$_3$-NO_2), 6.90 – 6.92 (2H, m, N=CC(4)Ar$_1$$H$, N=CC(4)Ar$_2$$H$), 7.45 – 7.47 (8H, m, N=CC(2,3,5,6)Ar$_1$$H$, N=CC(2,3,5,6)Ar$_2$$H$), 7.70 – 7.73 (2H, m, C=NCHC(2,6)Ar$_3$$H$-$NO_2$), 8.16 – 8.18 (2H, m, C=NCHC(3,5)Ar$_3$$H$-$NO_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.3; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.4 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 26.9 (F_3CCHCH$_A$$H_B$), 43.2 and 46.6 (CON$C(2)H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$$C(6)H_2$), 46.4 ($F_3CCHCH_A$$H_B$), 62.6 (C=N$CHAr_3$-$NO_2$), 123.6 (C=NCH$C$(3,5)Ar$_3$-$NO_2$), 127.1 (N=C$C$(4)Ar$_1$, N=C$C$(4)Ar$_2$), 128.2 (N=C$C$(2,3,5,6)Ar$_1$, N=C$C$(2,3,5,6)Ar$_2$), 128.6 ($CF_3$), 128.9 (C=NCH$C$(2,6)Ar$_3$-$NO_2$), 135.8 and 139.2 (N=C$C$(1)Ar$_1$, N=C$C$(1)Ar$_2$), 147.1 (C=NCH$C$(4)Ar$_3$-$NO_2$), 149.3 (C=NCH$C$(1)Ar$_3$-$NO_2$), 167.7 ($F_3$CCHCH$_A$$H_B$$C$O), 170.6 ($C$=N); **HRMS** (NSI$^+$) $C_{29}H_{29}F_3N_3O_3^+$ ([M+H]$^+$) requires 524.2163, found 524.2143 (-2.5 ppm).

(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (251)



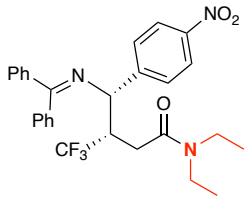
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with pyrrolidine (12.3 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 3:1 Hexane:EtOAc (R_f = 0.20) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a garnet red oil (36 mg, 71%). $[\alpha]_D^{20}$ -8.7 (*c* 3.6, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 13.6 min , t_R(*S,S*): 17.7 min, 7:93 er; **IR** ν_{max} (ATR) 2951 (Ar-H), 1639 (C=O amide), 1519 (N-O stretch), 1444 (C=C), 1344 (NO_2 sym), 1109 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 1.72 – 1.95 (4H, m, CONC(1)H_2C(2)H_2C(3)H_2C(4)H_2), 2.62 (1H, dd, $^3J_{HH}$ = 16.4, $^4J_{HF}$ = 6.0, F_3CCHC$H_A$$H_B$), 2.95 (1H, dd, $^3J_{HH}$ = 16.4, $^4J_{HF}$ = 6.25, F_3CCHC$H_A$$H_B$), 3.22 – 3.46 (CONC(1)$H_2$C(2)$H_2$C(3)$H_2$C(4)$H_2$), 3.77 ($F_3CCHCH_A$$H_B$), 4.93 (1H, d, $^3J_{HH}$ = 3.97, C=NCHAr$_3$-NO_2), 6.90 – 6.92 (2H, m, N=CC(4)Ar$_1$$H$, N=CC(4)Ar$_2$$H$), 7.43 – 7.45 (8H, m, N=CC(2,3,5,6)Ar$_1$$H$, N=CC(2,3,5,6)Ar$_2$$H$), 7.66 – 7.68 (2H, m, C=NCHC(2,6)Ar$_3$$H$-$NO_2$), 8.13 – 8.15 (2H, m, C=NCHC(3,5)Ar$_3$$H$-$NO_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.5; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.3 – 25.9 (CONC(1)$H_2$$C(2)H_2$$C(3)H_2$C(4)$H_2$), 29.1 ($F_3CCHCH_A$$H_B$), 45.9 – 46.6 (CON$C(1)H_2$C(2)$H_2$C(3)$H_2$$C(4)H_2$), 46.4 (q, $^2J_{CF}$ = 24.7), 62.6 (C=NCHAr$_3$-NO_2), 123.6 (C=NCHC(3,5)Ar$_3$-NO_2), 127.1 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 – 128.3 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.6 (CF_3), 128.9 (C=NCHC(2,6)Ar$_3$-NO_2), 135.8 and 139.1 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.2 (C=NCHC(4)Ar$_3$-NO_2), 149.3 (C=NCHC(1)Ar$_3$-NO_2), 167.9 (F_3CCHCH$_A$$H_B$$C$O), 170.5 ($C$=N); **HRMS** (NSI$^+$) $C_{28}H_{27}F_3N_3O_3^+$ ([M+H]$^+$) requires 510.1999, found 510.1988 (-2.2 ppm).

(*S*)-*N*-benzyl-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanamide (252)



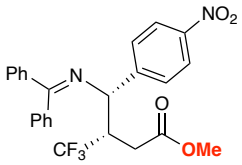
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with benzylamine (16.4 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 3:1 Hexane:EtOAc (R_f = 0.50) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a garnet red oil (35 mg, 64%). $[\alpha]_D^{20}$ -5.1 (*c* 3.5, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 25.9 min, t_R(*S,R*): 49.6 min, 94:6 er; **IR** ν_{max} (ATR) 2929 (Ar-H), 1658 (C=O amide), 1519 (N-O stretch), 1447 (C=C), 1344 (NO_2 sym), 1111 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.68 (1H, dd, $^3J_{HH}$ = 16.0, $^4J_{HF}$ = 6.6, $F_3CHCH_AH_BCO$), 2.93 (1H, dd, $^3J_{HH}$ = 16.0, $^4J_{HF}$ = 5.0, $F_3CCHCH_AH_BCO$), 3.57 – 3.59 (1H, m, $F_3CCHCH_AH_BCO$), 4.25 (1H, dd, $^2J_{HH}$ = 14.6, $^3J_{HH}$ = 5.8, $CONHCH_AH_BPh$), 4.37 (1H, dd, $^2J_{HH}$ = 14.6, $^3J_{HH}$ = 5.4, $CONHCH_AH_BPh$), 4.96 (1H, d, $^3J_{HH}$ = 3.3, C=NC*H*Ar$_3$-NO_2), 5.79 (1H, t, $^3J_{HH}$ = 5.7, $CONHCH_AH_BPh$), 6.90 (2H, d, $^3J_{HH}$ = 7.21, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.18 – 7.20 (2H, m, $CONHCH_AH_BC(2,6)Ar$*H*), 7.31 – 7.33 (3H, m, $CONHCH_AH_BC(3,4,5)Ar$*H*), 7.39 – 7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.66 – 7.68 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.16 – 8.18 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.4; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 31.0 ($F_3CCHCH_AH_BCO$), 43.9 ($CONHCH_AH_BPh$), 46.8 (q, $^2J_{CF}$ = 24.4, $F_3CCHCH_AH_BCO$), 62.4 (C=N*C*HAr$_3$-NO_2), 123.8 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.1 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 127.7 (*C*F3), 127.9 ($CONHCH_AH_BC$(2,6)Ph), 128.2 – 128.3 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.6 ($CONHCH_AH_BC$(3,4,5)Ph), 128.9 (C=NCH*C*(2,6)Ar$_3$-NO_2), 130.9 (C=NCH*C*(4)Ar$_3$-NO_2), 135.7 and 139.1 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$) 137.7 ($CONHCH_AH_BC$(1)Ph), 149.1 (C=NCH*C*(1)Ar$_3$-NO_2), 169.4 (*C*=O), 170.8 (*C*=N); **HRMS** (NSI$^+$) $C_{31}H_{27}F_3N_3O_3^+$ ([M+H]$^+$) requires 546.2004, found 546.1987 (-2.3 ppm).

(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-*N*,*N*-diethyl-4,4,4-trifluorobutanamide (253)



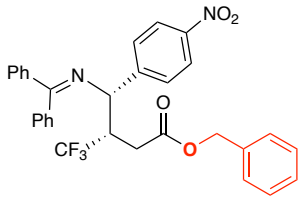
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with diethylamine (15.5 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.49) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a garnet red oil (36 mg, 70%). $[\alpha]_D^{20}$ -0.7 (*c* 3.6, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S,S*): 8.1 min, t_R(*S,R*): 13.1 min, 92:8 er; **IR** ν_{max} (ATR) 2979 (Ar-H), 1639 (C=O amide), 1519 (N-O stretch), 1447 (C=C), 1342 (NO_2 sym), 1105 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 0.97 (3H, t, $^3J_{HH}$ = 7.1, CON(CH_2CH_3)), 1.21 (3H, t, $^3J_{HH}$ = 7.1, CON(CH_2CH_3)), 2.68 (1H, dd, $^3J_{HH}$ = 16.5, $^4J_{HF}$ = 5.4, $F_3CCHCH_AH_BCO$), 3.09 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 5.6, $F_3CCHCH_AH_BCO$), 3.24 – 3.34 (4H, m, CON(CH_2CH_3)$_2$), 3.76 – 3.78 (1H, m, $F_3CCHCH_AH_BCO$), 4.98 (1H, d, $^3J_{HH}$ = 4.2, C=NCHAr$_3$-NO_2), 6.88 – 6.90 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.39 – 7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.69 – 7.71 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.15 – 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.3; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 12.9 – 14.3 (CON(CH_2CH_3)$_2$), 27.1 ($F_3CCHCH_AH_BCO$), 40.9 – 42.2 (CON(CH_2CH_3)$_2$), 46.7 (q, $^2J_{CF}$ = 24.3, $F_3CCHCH_AH_BCO$), 62.4 (C=NCHAr$_3$-NO_2), 123.6 (C=NCHC(3,5)Ar$_3$-NO_2), 127.1 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.5 (CF_3), 128.9 (C=NCHC(2,6)Ar$_3$-NO_2), 130.8 (C=NCHC(4)Ar$_3$-NO_2), 135.8 and 139.2 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 149.3 (C=NCHC(1)Ar$_3$-NO_2), 168.6 (*C*=O), 170.6 (*C*=N); **HRMS** (NSI$^+$) $C_{28}H_{29}F_3N_3O_3^+$ ([M+H]$^+$) requires 512.2155, found 512.2150 (-1.1 ppm).

Methyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate (254)



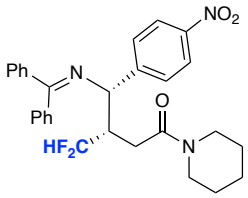
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with methanol (20.2 µL, 0.5 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:CH_2Cl_2 (R_f = 0.21) to give the titled compound as an inseparable mixture of diastereomers (97:3 dr) as a colorless oil (29 mg, 61%). $[\alpha]_D^{20}$ +5.1 (*c* 0.85, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,S*): 32.1 min, t_R(*S,R*): 55.3 min, 98:2 er; **IR** ν_{max} (ATR) 2953 (Ar-H), 1739 (C=O, ester), 1521 (N-O stretch), 1447 (C=C), 1346 (NO_2 sym), 1113 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.82 (1H, dd, $^3J_{HH}$ = 17.0, $^4J_{HF}$ = 5.9, $F_3CCHC\mathit{H}_A\mathit{H}_BCO$), 2.99 (1H, dd, $^3J_{HH}$ = 17.0, $^4J_{HF}$ = 5.9, $F_3CCHCH_A\mathit{H}_BCO$), 3.40 – 3.42 (1H, m, $F_3CC\mathit{H}CH_AH_BCO$), 3.55 (3H, s, $CO_2C\mathit{H}_3$), 4.90 (1H, d, $^3J_{HH}$ = 4.2, C=NC*H*Ar_3-NO_2), 6.91 – 6.93 (2H, m, N=CC(4)$Ar_1\mathit{H}$, N=CC(4)$Ar_2\mathit{H}$), 7.40 – 7.48 (8H, m, N=CC(2,3,5,6)$Ar_1\mathit{H}$, N=CC(2,3,5,6)$Ar_2\mathit{H}$), 7.67 – 7.69 (2H, m, C=NCHC(2,6)$Ar_3\mathit{H}$-NO_2), 8.16 – 8.18 (2H, m, C=NCHC(3,5)$Ar_3\mathit{H}$-NO_2);**^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.5; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.5 ($F_3CCH\mathit{C}H_AH_BCO$), 47.4 (q, $^2J_{CF}$ = 24.9, $F_3C\mathit{C}HCH_AH_BCO$), 52.1 ($CO_2\mathit{C}H_3$), 62.6 (C=N*C*HAr_3-NO_2), 123.8 (C=NCH*C*(3,5)Ar_3-NO_2), 127.1 (N=C*C*(4)Ar_1, N=C*C*(4)Ar_2), 128.2 – 128.3 (N=C*C*(2,3,5,6)Ar_1, N=C*C*(2,3,5,6)Ar_2), 128.6 (*C*F_3), 128.9 (C=NCH*C*(2,6)Ar_3-NO_2), 135.7 – 138.8 (N=C*C*(1)Ar_1, N=C*C*(1)Ar_2), 147.3 (C=NCH*C*(1)Ar_3-NO_2), 149.0 (C=NCH*C*(4)Ar_3-NO_2), 170.9 (*C*=N), 171.4 (*C*=O); **HRMS** (NSI$^+$) $C_{25}H_{22}F_3N_2O_4^+$ ([M+H]$^+$) requires 471.1519, found 471.1523 (-0.8 ppm).

Benzyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate (255)



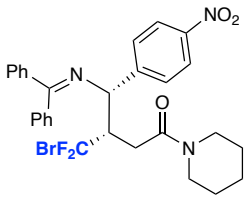
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with benzyl alcohol (54 µL, 0.5 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:CH_2Cl_2 (R_f = 0.21) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a colorless oil (27 mg, 49%). $[\alpha]_D^{20}$ – 27.4 (*c* 0.7, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IC (99:1 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.4 min, t_R(*S,S*): 17.2 min, 8:92 er; **IR** ν_{max} (ATR) 3062 (Ar-H), 1737 (C=O, ester), 1521 (N-O stretch), 1447 (C=C), 1346 (NO_2 sym), 1113 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.85 (1H, dd, $^3J_{HH}$ = 17.2, $^4J_{HF}$ = 5.7, $F_3CCHCH_AH_BCO$), 3.07 (1H, dd, $^3J_{HH}$ = 17.2, $^4J_{HF}$ = 5.9, $F_3CCHCH_AH_BCO$), 3.43 (1H, m, $F_3CCHCH_AH_BCO$), 4.90 (1H,m ,C=NC*H*Ar_3-NO_2), 4.93 – 5.00 (2H, m, CO_2CH_2Ph), 6.90 (2H, m, N=CC(4)Ar_1H, N=CC(4)Ar_2H), 7.23 (2H, m, CO_2CH_2C(2,6)Ar*H*), 7.35 – 7.52 (11H, m, N=CC(2,3,5,6)Ar_1H, N=CC(2,3,5,6)Ar_2H, CO_2CH_2C(3,4,5)Ar*H*), 7.68 – 7.70 (2H, m, C=NCHC(2,6)Ar_3H-NO_2), 8.11 – 8.13 (2H, m, C=NCHC(3,5)Ar_3H-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -68.5; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.6 ($F_3CCHCH_AH_BCO$), 47.1 (, $^2J_{CF}$ = 24.9, $F_3CCHCH_AH_BCO$), 62.6 (C=N*C*HAr_3-NO_2), 66.9 (CO_2CH_2Ph), 123.8 (C=NCH*C*(3,5)Ar_3-NO_2), 127.1 (N=C*C*(4)Ar_1, N=C*C*(4)Ar_2), 128.2 (N=C*C*(2,3,5,6)Ar_1, N=C*C*(2,3,5,6)Ar_2), 128.3 (*C*F_3), 128.4 (CO_2CH_2C(4)Ar), 128.5 (CO_2CH_2C(1)Ar), 128.6 (CO_2CH_2C(3,5)Ar), 128.6 (CO_2CH_2C(1,2)Ar), 128.9 (C=NCH*C*(2,6)Ar_3-NO_2), 135.7 – 138.8 (N=C*C*(1)Ar_1, N=C*C*(1)Ar_2), 147.3 (C=NCH*C*(4)Ar_3-NO_2), 148.9 (C=NCH*C*(1)Ar_3-NO_2), 170.8 (*C*=O), 170.9 (*C*=N); **HRMS** (NSI$^+$) $C_{31}H_{25}F_3N_2O_4Na^+$ ([M+Na]$^+$) requires 569.1659, found 569.1656 (-0.54 ppm).

(3*S*,4*S*)-3-(difluoromethyl)-4-((diphenylmethylene)amino)-4-(4-nitrophenyl)-1-(piperidin-1-yl)butan-1-one (256)



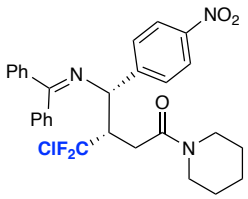
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4-difluorobut-2-enoate (24.3 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:EtOAc (R_f = 0.47) to give the titled compound as an inseparable mixture of diastereomers (89:11 dr) as a colorless oil (14.2 mg, 28%). $[\alpha]_D^{20}$ -19.3 (*c* 1.4, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 12.5 min, t_R(*S,S*): 15.2 min, 8:92 er; **IR** ν_{max} (ATR) 2937 (Ar-H), 1622 (C=O, amide), 1520 (N-O Stretch), 1445 (C=C), 1344 (NO_2 sym); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 1.49 – 1.63 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.66 (1H, dd, $^3J_{HH}$ = 16.5, $^4J_{HF}$ = 4.9, $HF_2CCHCH_AH_B$), 2.73 (1H, dd, $^3J_{HH}$ = 16.5, $^4J_{HF}$ = 7.3, $HF_2CCHCH_AH_B$), 3.24 (1H, m, $HF_2CCHCH_AH_B$), 3.38 – 3.53 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 4.89 (1H, d, $^3J_{HH}$ = 4.9, C=NCHAr$_3$-NO_2), 5.77 – 6.05 (1H, td, $^2J_{HF}$ = 66.3, $^3J_{HH}$ = 3.4, CF_2H), 6.92 (2H, m, N=CC(4)Ar$_1$$H$, N=CC(4)Ar$_2$$H$), 7.39 – 7.47 (8H, m, N=CC(2,3,5,6)Ar$_1$$H$, N=CC(2,3,5,6)Ar$_2$$H$), 7.69 – 7.71 (2H, m, C=NCHC(2,6)Ar$_3$$H$-$NO_2$), 8.16 – 8.18 (2H, m, C=NCHC(3,5)Ar$_3$$H$-$NO_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -125.7 – -119.8 (2F, d, $^2J_{FH}$ = 282.3, CF_2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.4 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 27.4 ($HF_2CCHCH_AH_B$), 43.0 – 46.6 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 46.6 (t, $^2J_{CF}$ = 18.7, $HF_2CCHCH_AH_B$), 63.1 (C=NCHAr$_3$-NO_2), 114.9 – 119.8 ($^1J_{CF}$ = 242.3, CF_2H), 123.6 (C=NCHC(3,5)Ar$_3$-NO_2), 127.2 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 – 128.4 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.8 (C=NCHC(2,6)Ar$_3$-NO_2), 136.0 and 139.2 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.1 (C=NCHC(4)Ar$_3$-NO_2), 149.9 (C=NCHC(1)Ar$_3$-NO_2), 168.6 (C=O), 170.3 (C=N); **HRMS** (NSI$^+$) $C_{29}H_{30}F_2N_3O_3^+$ ([M+H]$^+$) requires 506.2242, found 506.2246 (-0.75 ppm).

(*S*)-4-bromo-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one (257)



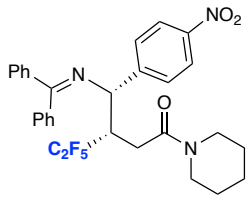
Following **General Procedure G,** 4-nitrophenyl (*E*)-4-bromo-4,4-difluorobut-2-enoate (32.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:EtOAc (R_f = 0.41) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a colorless oil (28.4 mg, 40 %). $[\alpha]_D^{20}$ +6.0 (*c* 1.6, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S,R*): 9.7 min, t_R(*S,S*): 12.2 min, 11:89 er; **IR** ν_{max} (ATR) 2938 (Ar-H), 1633 (C=O, amide), 1519 (N-O stretch), 1445 (C=C), 1344 (NO_2 sym); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 1.41 – 1.61 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.76 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 4.9, $BrF_2CCHCH_AH_B$), 3.17 (1H, dd, $^3J_{HH}$ = 16.9, $^4J_{HF}$ = 6.3, $BrF_2CCHCH_AH_B$), 3.29 – 3.43 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.95 – 3.97 (1H, m, $BrF_2CCHCH_AH_B$), 5.11 (1H, d, $^3J_{HH}$ = 3.0, C=NCHAr$_3$-NO_2), 6.90 – 6.92 (2H, m, N=CC(4)Ar$_1$$H$, N=CC(4)Ar$_2$$H$), 7.40 – 7.48 (8H, m, N=CC(2,3,5,6)Ar$_1$$H$, N=CC(2,3,5,6)Ar$_2$$H$), 7.68 – 7.70 (2H, m, C=NCHC(2,6)Ar$_3$$H$-$NO_2$), 8.16 – 8.18 (2H, m, C=NCHC(3,5)Ar$_3$$H$-$NO_2$); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: - 46.2 – - 44.9 (2F, d, $^3J_{FH}$ = 158.5, CF_2Br); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.5 – 26.4 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 28.9 ($BrF_2CCHCH_AH_B$), 43.2 – 46.6 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 54.3 (t, $^2J_{CF}$ = 17.9, $BrF_2CCHCH_AH_B$), 63.9 (C=NCHAr$_3$-NO_2), 123.6 (C=NCHC(3,5)Ar$_3$-NO_2), 127.4 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 – 128.3 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.5 (-CF_2Br), 129.1 (C=NCHC(2,6)Ar$_3$-NO_2), 135.8 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.1 (C=NCHC(4)Ar$_3$-NO_2), 149.5 (C=NCHC(1)Ar$_3$-NO_2), 167.5 (C=O), 170.9 (C=N); **HRMS** (NSI$^+$) $C_{29}H_{29}{}^{79}BrF_2N_3O_3^+$ ([M+H]$^+$) requires 584.1355, found 584.1357 (0.36 ppm).

(*S*)-4-chloro-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one (258)



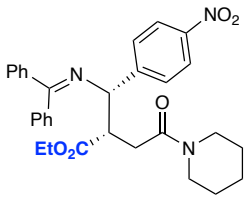
Following **General Procedure G,** 4-nitrophenyl (*E*)-4-chloro-4,4-difluorobut-2-enoate (27.8 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:EtOAc (R_f = 0.53) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a colorless oil (21.1 mg, 39 %). $[\alpha]_D^{20}$ – 4.3 (*c* 2.1, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S,R*): 9.6 min, t_R(*S,S*): 12.2 min, 15:85 er; **IR** ν_{max} (ATR) 2938 (Ar-H), 1639 (C=O, amide), 1520 (N-O stretch), 1445 (C=C), 1342 (NO_2 sym); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.40 – 1.61 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.72 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 4.6, $ClF_2CCHCH_AH_B$), 3.18 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 5.2, $ClF_2CCHCH_AH_B$), 3.29 – 3.52 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.93 – 3.95 (1H, m, $ClF_2CCHCH_AH_B$), 5.12 (1H, d, $^3J_{HH}$ = 3.0, C=NC*H*Ar_3-NO_2), 6.92 – 6.93 (2H, m, N=CC(4)Ar_1H, N=CC(4)Ar_2H), 7.43 – 7.48 (8H, m, N=CC(2,3,5,6)Ar_1H, N=CC(2,3,5,6)Ar_2H), 7.70 – 7.72 (2H, m, C=NCHC(2,6)Ar_3H-NO_2), 8.16 – 8.17 (2H, m, C=NCHC(3,5)Ar_3H-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: - 46.2 – - 44.9 (2F, d, $^3J_{FH}$ = 158.4, CF_2Cl); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.5 – 26.4 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 28.9 ($ClF_2CCHCH_AH_B$), 43.2 – 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 54.3 (t, $^2J_{CF}$ = 18.1, $ClF_2CCHCH_AH_B$), 63.9 (C=N*C*HAr_3-NO_2), 123.6 (C=NCH*C*(3,5)Ar_3-NO_2), 127.4 (N=C*C*(4)Ar_1, N=C*C*(4)Ar_2), 128.2 – 128.3 (N=C*C*(2,3,5,6)Ar_1, N=C*C*(2,3,5,6)Ar_2), 128.5 (-*C*F_2Cl), 129.1 (C=NCH*C*(2,6)Ar_3-NO_2), 135.7 (N=C*C*(1)Ar_1, N=C*C*(1)Ar_2), 145.4 (C=NCH*C*(1)Ar_3-NO_2), 147.1 (C=NCH*C*(4)Ar_3-NO_2), 167.5 (*C*=O), 171.7 (*C*=N); **HRMS** (NSI$^+$) $C_{29}H_{29}ClF_2N_3O_3^+$ ([M+H]$^+$) requires 540.1860, found 540.1858 (-0.37 ppm).

(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,5,5,5-pentafluoro-1-(piperidin-1-yl)pentan-1-one (259)



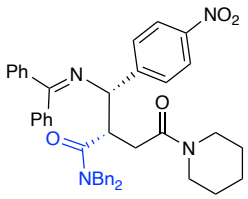
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,5,5,5-pentafluoropent-2-enoate (31.1 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.34) to give the titled compound as an inseparable mixture of diastereomers (97:3 dr) as a colorless oil (36.5 mg, 63 %). $[\alpha]_D^{20}$ +3.7 (*c* 3.1, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 5.9 min, t_R(*S,S*): 11.4 min, 7:93 er; **IR** ν_{max} (ATR) 2941 (Ar-H), 1645 (C=O, amide), 1522 (N-O Stretch), 1445 (C=C), 1344 (NO_2 sym); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.35 – 1.60 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.78 (1H, dd, $^3J_{HH}$ = 17.5, $^4J_{HF}$ = 4.7, $F_5C_2CHCH_AH_B$), 3.20 – 3.22 (1H, m, $F_5C_2CHCH_AH_B$), 3.37 – 3.48 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.90 – 3.92 (1H, m, $F_5C_2CHCH_AH_B$), 5.12 (1H, d, $^3J_{HH}$ = 2.6, C=NC*H*Ar$_3$-NO_2), 6.88 – 6.90 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.38 – 7.47 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.68 – 7.70 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.14 – 8.16 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -82.63 (-CF_2CF_3), - 116.7 – - 118.4 (2F, d, $^3J_{FH}$ = 272.0, CF_2CF_3); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.3 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 26.6 ($F_5C_2CHCH_AH_B$), 42.9 (t, $^2J_{CF}$ = 18.1, $F_5C_2CHCH_AH_B$), 43.2 – 46.4 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 62.2 (C=NCHAr$_3$-NO_2), 116.2 (-CF_2CF_3), 123.6 (C=NCHC(3,5)Ar$_3$-NO_2), 127.2 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 – 128.3 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.4 (-CF_2CF_3), 129.0 (C=NCHC(2,6)Ar$_3$-NO_2), 135.8 – 139.4 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.1 (C=NCHC(1)Ar$_3$-NO_2), 149.3 (C=NCHC(4)Ar$_3$-NO_2), 167.2 (*C*=O), 169.5 (*C*=N); **HRMS** (NSI$^+$) $C_{30}H_{29}F_5N_3O_3^+$ ([M+H]$^+$) requires 574.2124, found 574.2128 (-0.69 ppm).

Ethyl (*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanoate (260)



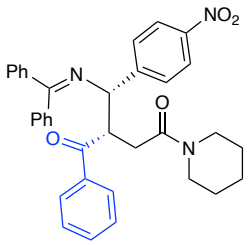
Following **General Procedure G,** Ethyl (4-nitrophenyl) fumarate (26.5 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at 0 ºC for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (89:11 dr) as a colorless oil (39.6 mg, 75 %). $[\alpha]_D^{20}$ – 5.0 (*c* 4.0, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 16.8 min, t_R(*S,R*): 25.6 min, 91:9 er; **IR** ν_{max} (ATR) 2938 (Ar-H), 1730 (C=O, ester),1638 (C=O, amide), 1519 (N-O stretch), 1344 (NO_2 sym); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 0.96 (3H, t, $^3J_{HH}$ = 7.1, $CO_2CH_2CH_3$), 1.50 – 1.65 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.49 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.1, $EtO_2CCHCH_AH_B$), 3.05 (1H, dd, $^2J_{HH}$ = 16.2, $^3J_{HH}$ = 10.7, $EtO_2CCHCH_AH_B$), 3.42 – 3.47 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.57 – 3.59 (1H, m, $EtO_2CCHCH_AH_B$), 3.84 (1H, dq, $^2J_{HH}$ = 10.7, $^3J_{HH}$ = 7.1, $CO_2CH_AH_BCH_3$), 3.97 (1H, dq, $^2J_{HH}$ = 10.8, $^3J_{HH}$ = 7.2, $CO_2CH_AH_BCH_3$), 4.84 (1H, d, $^3J_{HH}$ = 6.4, C=NC*H*Ar$_3$-NO_2), 6.90 – 6.92 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.38 – 7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.66 – 7.68 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.16 – 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 13.9 ($CO_2CH_2CH_3$), 24.5 – 26.3 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 31.3 ($EtO_2CCHCH_AH_B$), 42.8 – 46.5 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 49.9 ($EtO_2CCHCH_AH_B$), 60.6 ($CO_2CH_2CH_3$), 66.5 (C=NCHAr$_3$-NO_2), 123.5 (C=NCHC(3,5)Ar$_3$-NO_2), 127.4 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.3 – 128.4 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.6 (C=NCHC(2,6)Ar$_3$-NO_2), 135.9 – 139.2 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.1 (C=NCHC(4)Ar$_3$-NO_2), 149.9 (C=NCHC(1)Ar$_3$-NO_2), 169.2 ($EtO_2CCHCH_AH_BC$=O), 170.4 (*C*=N), 173.0 ($EtO_2CCHCH_AH_BC$=O); **HRMS** (NSI$^+$) $C_{31}H_{34}N_3O_5^+$ ([M+H]$^+$) requires 528.2493, found 528.2475 (+3.4 ppm).

(*S*)-*N*,*N*-dibenzyl-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanamide (261)



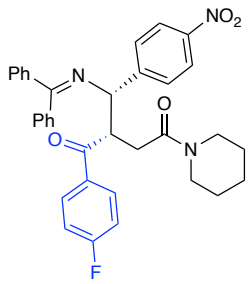
Following **General Procedure G,** (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (41.6 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (97:3 dr) as a colorless oil (26.4 mg, 20 %). $[\alpha]_D^{20}$ +6.3 (*c* 1.2, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.5 min ,t_R(*S,S*): 32.3 min, 3:97 er; **IR** ν_{max} (ATR): 2936 (Ar-H), 1638 (C=O, amide), 1519 (N-O stretch), 1344 (NO_2 sym); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.52 – 1.62 (6H, m, CONC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)*H*$_2$C(6)H_2), 2.60 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 3.6, Bn_2NOCCHC*H*$_A$H$_B$), 3.17 – 3.19 (1H, m, , Bn_2NOCCHCH$_A$*H*$_B$), 3.43 – 3.53 (4H, m, CONC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)*H*$_2$), 3.93 – 3.95 (1H, m, Bn_2NOCC*H*CH$_A$H$_B$), 4.04 – 4.40 (2H, d, $^2J_{HH}$ = 15.8, CON(C*H*$_A$H$_B$Ph)$_2$), 4.75 (1H, s, C=NC*H*Ar$_3$-NO_2), 4.82 – 4.91 (CON(CH$_A$*H*$_B$Ph)$_2$), 6.76 (2H, d, $^3J_{HH}$ = 7.4, CON(CH$_2$C(4)Ar*H*)$_2$), 6.90 – 6.91 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.07 – 7.08 (4H, m, CON(CH$_2$C(3,5)Ar*H*)$_2$), 7.22 – 7.23 (4H, m, CON(CH$_2$C(2,6)Ar*H*)$_2$), 7.37 – 7.53 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.69 – 7.71 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 7.93 – 7.95 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.5 – 26.4 (CONC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$*C*(5)H$_2$C(6)H$_2$), 33.4 (Bn_2NOCCH*C*H$_A$H$_B$), 42.9 – 46.8 (CON*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$*C*(6)H$_2$), 46.0 (Bn_2NOC*C*HCH$_A$H$_B$), 49.0 - 50.6 (CON(*C*H$_2$Ph)$_2$), 66.8 (C=N*C*HAr$_3$-NO_2), 123.5 (C=NCH*C*(3,5)Ar$_3$-NO_2), 126.6 (CON(CH$_2$*C*(4)Ar)$_2$), 127.6 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 (CON(CH$_2$*C*(2,3,5,6)Ar)$_2$), 128.3 – 128.5 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.7 (C=NCH*C*(2,6)Ar$_3$-NO_2), 137.0 (CON(CH$_2$*C*(1)Ar)$_2$), 137.2 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 146.9 (C=NCH*C*(1)Ar$_3$-NO_2), 150.4 (C=NCH*C*(4)Ar$_3$-NO_2), 169.6 (*C*ONC$_6$H$_{10}$), 173.8 (*C*=N, *C*ON(CH$_2$Ph)$_2$); **HRMS** (NSI$^+$) $C_{43}H_{43}N_4O_4^+$ ([M+H]$^+$) requires 679.3278, found 679.3279 (-0.03 ppm).

(*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-1-phenyl-4-(piperidin-1-yl)butane-1,4-dione (262)



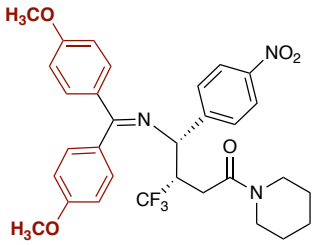
Following **General Procedure G,** (*E*)-4-oxo-4-phenylbut-2-enoate (29.7 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (85:15 dr) as a colorless oil (19.6 mg, 35 %). $[\alpha]_D^{20}$ +47.9 (*c* 2.0, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) **major diastereomer** t_R(*S,R*): 25.8 min ,t_R(*S,S*): 48.7 min, 15:85 er; **IR** ν_{max} (ATR): 2932 (Ar-H), 1633 (C=O, amide), 1519 (N-O stretch), 1344 (NO_2 sym); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.55 – 1.70 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.60 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 2.9, PhOCCHCH_AH$_B$), 3.21 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 9.8, PhOCCHCH$_A$$H_B$), 3.42 – 3.44 (4H, m, CONC(2)H_2C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)H_2), 4.73 – 4.75 (2H, m, C=NC*H*Ar$_3$-NO_2, PhOCC*H*CH$_A$H$_B$), 6.77 – 6.79 (2H, d, $^3J_{HH}$ = 7.2, CON(CH$_2$C(4)Ar*H*)$_2$), 7.27 – 7.40 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.46 – 7.48 (3H, m, COC(3,4,5)Ar*H*), 7.64 – 7.65 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 7.79 (COC(2,6)Ar*H*), 7.97 – 7.99 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.3 (CONC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$*C*(5)H$_2$C(6)H$_2$), 33.2 (PhOCCH*C*H$_A$H$_B$), 42.8 – 46.6 (CON*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$*C*(6)H$_2$), 50.5 (PhOC*C*HCH$_A$H$_B$), 67.2 (C=N*C*HAr$_3$-NO_2), 123.4 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.2 ((N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 – 128.5 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$, CO*C*(3,4,5)Ar), 128.6 (CO*C*(2,6)Ar), 128.9 (C=NCH*C*(2,6)Ar$_3$-NO_2), 132.5 (CO*C*(1)Ar), 137.5 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 146.9 (C=NCH*C*(1)Ar$_3$-NO_2), 147.3 (C=NCH*C*(4)Ar$_3$-NO_2), 169.3 (*C*ONC$_6$H$_{10}$), 169.9 (*C*=N), 201.7(*C*OPh); **HRMS** (NSI$^+$) $C_{35}H_{33}N_3O_4^+$ ([M+H]$^+$) requires 560.2549, found 560.2528 (-2.8 ppm).

(*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-1-(4-fluorophenyl)-4-(piperidin-1-yl)butane-1,4-dione (263)



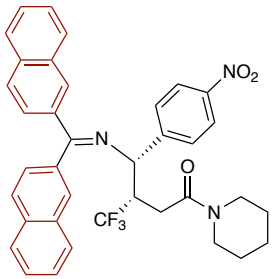
Following **General Procedure G,** (*E*)-4-(4-fluorophenyl)-4-oxobut-2-enoate (31.5 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 6:1 Hexane:EtOAc (R_f = 0.06) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a yellow oil (21.7 mg, 38 %). $[\alpha]_D^{20}$ +13.9 (*c* 2.2, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (90:10 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.3 min, t_R(*S,S*): 30.7 min 78:22 er; **IR** ν_{max} (ATR): 2933 (Ar-H), 1633 (C=O, amide), 1521 (N-O stretch), 1344 (NO_2 sym); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.61 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.65 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.1, 4-F-PhOCCHC$H_A$$H_B$), 3.21 (1H, dd, $^2J_{HH}$ = 16.2, $^3J_{HH}$ = 10.5, 4-F-PhOCCHCH$_A$$H_B$), 3.40 – 3.44 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 4.63 – 4.65 (1H, m, 4-F-PhOCC*H*CH$_A$H$_B$), 4.73 (1H, d, $^3J_{HH}$ = 7.2, C=NC*H*Ar$_3$-NO_2), 6.78 – 6.80 (2H, m, CON(CH_2C(4)Ar*H*)$_2$), 6.94 – 6.95 (2H, m, 4-F-Ar*H*C(2,6)CO), 7.32 – 7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.63 – 7.65 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2)), 7.83 – 7.85 (2H, m, 4-F-Ar*H*C(3,5)CO), 8.01 – 8.03 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$), δ_F: -106.0 (4-*F*-ArCO); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.3 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 33.5 (4-F- PhOCCH*C*H$_A$H$_B$), 42.8 – 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 50.5 (4-F-PhOC*C*HCH$_A$H$_B$), 67.2 (C=N*C*HAr$_3$-NO_2), 115.2 – 115.4 (4-F-Ar*C*(2,6)CO), 123.4 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.2 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 – 128.5 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.8 (C=NCH*C*(2,6)Ar$_3$-NO_2), 130.8 (4-F-Ar*C*(1)CO), 131.1 (4-F-ArC(3,5)CO), 134.0 – 135.8 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 146.9 (C=NCH*C*(4)Ar$_3$-NO_2), 149.4 (C=NCH*C*(1)Ar$_3$-NO_2), 166.6 (4-F-Ar*C*(4)CO), 169.2 (*C*ONC$_6$H$_{10}$), 170.1 (*C*=N), 200.2 (*C*OAr). **HRMS** (NSI$^+$) $C_{35}H_{33}FN_3O_4^+$ ([M+H]$^+$) requires 578.2449, found 578.2467 (-3.1 ppm).

(*S*)-3-((*S*)-((bis(4-methoxyphenyl)methylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one (269)



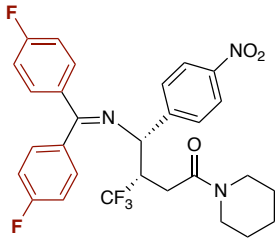
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.5 mg, 0.1 mmol), 1,1-bis(4-fluorophenyl)-*N*-(4-nitrobenzyl)methanimine (26.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.1 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 1:1 Hexane:EtOAc (R_f = 0.34) to give the titled compound as an inseparable diastereomer (81:19 dr) as a yellow oil (13.5 mg,23 %). $[\alpha]_D^{20}$ – 121.7 (*c* 1.4, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S,R*): 23.5 min, t_R(*S,S*): 27.5 min, 81:19 er; **IR** ν_{max} (ATR): 2937 (Ar-H), 1639 (C=O, amide), 1597 (N-O stretch), 1344 (C=C), 1247 (C-O stretch, alkyl aryl ether, 1107 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.38 – 1.66 (6H, m, CONC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)*H*$_2$C(6)H_2), 2.67 – 2.71 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HH}$ = 5.6, F-$_3$CCHC*H*$_A$H$_B$), 2.98 – 3.03 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HH}$ = 5.1, F_3CCHCH$_A$*H*$_B$), 3.28 – 3.52 (4H, m, CONC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)*H*$_2$), 3.74 – 3.76 (1H, m, F_3CC*H*CH$_A$H$_B$), 3.86 (6H, s, -OC*H*$_3$), 4.97 – 4.98 (1H, d, $^3J_{HH}$ = 3.4, C=NC*H*Ar-NO_2), 6.81 – 6.83 (2H, m, N=CC(2,6)Ar$_1$*H*-OCH_3), 6.89 – 6.92 (4H, m, N=CC(3,5)Ar$_1$*H*-OCH_3, N=CC(3,5)Ar$_2$*H*-OCH_3), 7.46 – 7.48 (2H, m, C=NCHC(2,6)Ar*H*-NO_2), 7.64 – 7.64 (2H, m, N=CC(2,6)Ar$_2$*H*-OCH_3), 8.15 – 8.16 (2H, m, C=NCHC(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$), δ_F: -68.2 (C*F*$_3$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.4 (CONC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$*C*(5)H$_2$C(6)H$_2$), 26.9 (F_3CCH*C*H$_A$H$_B$), 43.2 – 46.6 (CON*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$*C*(6)H$_2$), 46.9 – 46.7 (F_3C*C*HCH$_A$H$_B$), 55.3 – 55.4 (-Ar$_1$-O*C*H$_3$, -Ar$_2$-O*C*H$_3$), 62.5 (C=N*C*HAr-NO_2), 113.5 – 113.8 (N=C*C*(3,5)Ar$_1$-OCH_3, N=C*C*(3,5)Ar$_2$-OCH_3), 123.5 (C=NCH*C*(3,5)Ar-NO_2), 128.2 (-*C*F$_3$), 128.3 (C=NCH*C*(2,6)Ar-NO_2), 128.7 – 130.6 (N=C*C*(2,6)Ar$_1$-OCH_3, N=C*C*(2,6)Ar$_2$-OCH_3), 132.5 (N=C*C*(1)Ar$_1$-OCH_3, N=C*C*(1)Ar$_2$-OCH_3), 147.1 (C=NCH*C*(4)Ar-NO_2), 149.7 (C=NCH*C*(1)Ar-NO_2), 159.8 – 161.7 (N=C*C*(4)Ar$_1$-CH_3, N=C*C*(4)Ar$_2$-CH_3), 167.7 (*C*=O), 169.7 (*C*=N). **HRMS** (NSI$^+$) $C_{31}H_{33}F_3N_3O_5^+$ ([M+H]$^+$) requires 584.2367, found 584.2366 (-0.14 ppm).

(*S*)-3-((*S*)-((di(naphthalen-2-yl)methylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one (270)



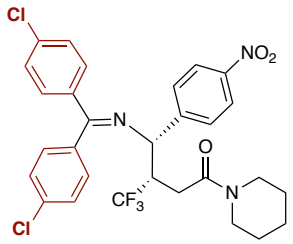
Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.5 mg, 0.1 mmol), 1,1-di(naphthalene-2-yl)-*N*-(4-nitrobenzyl)methanimine (62.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.1 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.36) o give the titled compound as an inseparable diastereomer (83:17 dr) as a yellow oil (32.9 mg, 59 %). $[\alpha]_D^{20}$ – 50.2 (*c* 3.3, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 19.5 min, t_R(*S,R*): 26.5 min, 97:3 er; **IR** ν_{max} (ATR): 2939 (Ar-H), 1635 (C=O, amide), 1519 (N-O Stretch), 1344 (C=C), 1107 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.43 – 1.66 (6H, m, CONC(2)H_2C(3)*H*$_2$C(4)*H*$_2$C(5)*H*$_2$C(6)H_2), 2.76 – 2.82 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HH}$ = 5.5, F_3CCHC*H*$_A$H$_B$), 3.09 – 3.15 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.2, F_3CCHCH$_A$*H*$_B$), 3.30 – 3.57 (4H, m, CONC(2)*H*$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$C(6)*H*$_2$), 3.81 – 3.83 (1H, m, F$_3$CC*H*CH$_A$H$_B$), 5.07 (1H, d, $^3J_{HH}$ = 3.57, C=NC*H*Ar-NO_2), 7.08 – 7.48 (3H, m, Naph*H*), 7.49 – 7.51 (2H, m, C=NCHC(2,6)Ar*H*-NO_2), 7.54 – 7.65 (3H, m, Naph*H*), 7.70 – 7.78 (4H, m, N=CC(1,10)Ar$_1$*H*, N=CC(1,10)Ar$_2$*H*), 7.88 – 7.98 (4H, m, Naph*H*), 8.17 – 8.20 (2H, m, N=CCHC(3,5)Ar*H*-NO_2), 8.28 – 8.31 (1H, dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 1.7, Naph*H*); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$), δ_F: -68.1 (C*F*$_3$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.5 – 26.4 (CONC(2)H$_2$*C*(3)H$_2$*C*(4)H$_2$*C*(5)H$_2$C(6)H$_2$), 27.1 (F_3CCH*C*H$_A$H$_B$), 43.3 – 46.6 (CON*C*(2)H$_2$C(3)H$_2$C(4)H$_2$C(5)H$_2$*C*(6)H$_2$), 46.2 – 46.9 (q, $^2J_{CF}$ = 24.4, F_3C*C*HCH$_A$H$_B$), 62.9 (C=N*C*HAr=NO_2), 123.6 – 128.4 (*C*-Naph), 128.6 (*C*F$_3$), 129.0 – 134.6 (*C*-Naph), 147.2 (C=NCH*C*(4)Ar-NO_2), 149.3 (C=NCH*C*(1)Ar-NO_2), 167.6 (*C*=O), 170.6 (*C*=N); **HRMS** (NSI$^+$) $C_{37}H_{33}F_3N_3O_3^+$ ([M+H]$^+$) requires 624.2469, found 624.2463 (-0.96 ppm).

(*S*)-3-((*S*)-((bis(4-fluorophenyl)methylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one (271)



Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.5 mg, 0.1 mmol), 1,1-bis(4-fluorophenyl)-*N*-(4-nitrobenzyl)methanimine (52.9 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.1 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 3:1 Hexane:EtOAc (R_f = 0.46) =to give the titled compound as an inseparable diastereomer (90:10 dr) as a yellow oil (27.4 mg, 49 %). $[\alpha]_D^{20}$ – 14.7 (*c* 2.7, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,S*): 13.6 min, t_R(*S,R*): 17.6 min, 88:12 er; **IR** ν_{max} (ATR): 2939 (Ar-H), 1633 (C=O, amide), 1521 (N-O stretch), 1346 (C=C), 1153 - 1109 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.35 – 1.65 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.67 – 2.72 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.4, F_3CCHC$H_A$$H_B$), 2.96 – 3.02 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.2, F_3CCHC$H_A$$H_B$), 3.26 – 3.51 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.75 – 3.77 (1H, m, F_3CC*H*C$H_A$$H_B$) 4.92 – 4.93 (1H, d, $^3J_{HH}$ = 3.2, C=NC*H*Ar-NO_2), 6.87 – 6.90 (2H, m, N=CC(3,5)Ar$_1$*H*-F), 7.06 – 7.13 (4H, m, N=CC(2,6)Ar$_1$*H*-F, N=CC(2,6)Ar$_2$*H*-F), 7.44 – 7.46 (2H, m, C=NCHC(2,6)Ar*H*-NO_2), 7.65 – 7.69 (2H, m, N=CC(3,5)Ar$_2$*H*-F), 8.16 – 8.18 (2H, m, C=NCHC(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$), δ_F:-110.9, -109.2 (Ar$_1$-*F*, Ar$_2$-*F*), -68.3 (C*F*$_3$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.5 – 26.4 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 26.8 (F_3CCH*C*$H_A$$H_B$), 43.2 – 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 46.9 – 46.7 (q, $^2J_{CF}$ = 24.3, F_3C*C*HC$H_A$$H_B$), 62.7 (C=N*C*HAr=$NO_2$), 115.2 – 115.5 (d, $^1J_{CF}$ = 21.8, N=C*C*(4)Ar1-F). 115.8 – 116.0 (d, $^1J_{CF}$ = 21.7, N=C*C*(4)Ar$_2$-F), 123.7 (C=NCH*C*(3,5)Ar-NO_2), 128.1 (C=NCH*C*(2,6)Ar-NO_2), 129.1 (*C*F_3), 130.8 – 130.9 (N=C*C*(1)Ar$_1$-F, N=C*C*(1)Ar$_2$-F), 147.3 (C=NCH*C*(1)Ar-NO_2), 148.8 (C=NCH*C*(4)Ar-NO_2), 167.4 (*C*=O), 168.5 (*C*=N). **HRMS** (NSI$^+$) $C_{29}H_{27}F_5N_3O_3^+$ ([M+H]$^+$) requires 560.1967, found 560.1953 (-2.52 ppm).

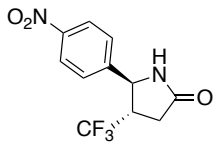
(*S*)-3-((*S*)-((bis(4-chlorophenyl)methylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one (272)



Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.5 mg, 0.1 mmol), 1,1-bis(4-fluorophenyl)-*N*-(4-nitrobenzyl)methanimine (57.8 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.1 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 3:1 Hexane:EtOAc (R_f = 0.44) to give the titled compound as an inseparable diastereomer (81:19 dr) as a yellow oil (21.3 mg,36 %). $[\alpha]_D^{20}$ – 44.8 (*c* 2.1, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,S*): 14.6 min, t_R(*S,R*): 17.2 min, 92:8 er; **IR** ν_{max} (ATR): 2939 (Ar-H), 1637 (C=O, amide), 1521 (N-O stretch), 1346 (C=C), 1109 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.35 – 1.65 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.66 – 2.73 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.4, F_3CCHC$H_A$$H_B$), 2.95 – 3.00 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.2, F_3CCHC$H_A$$H_B$), 3.25 – 3.51 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.76 – 3.78 (1H, m, F_3CCHC$H_A$$H_B$), 4.92 – 4.93 (1H, d, $^3J_{HH}$ = 3.2, C=NCHAr-NO_2), 6.82 – 6.84 (2H, m, N=CC(2,6)$Ar_1$$H$-Cl), 7.36 – 7.40 (4H, m, N=CC(3,5)$Ar_1$$H$-Cl, N=CC(3,5)$Ar_2$$H$-Cl), 7.43 – 7.45 (2H, m, C=NCHC(2,6)ArH-NO_2), 7.59 – 7.62 (2H, m, N=CC(2,6)$Ar_2$$H$-Cl), 8.16 – 8.18 (2H, m, C=NCHC(3,5)ArH-NO_2); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$), δ_F: -68.3 (CF_3); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4 – 26.4 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 26.8 (F_3CCH$C$$H_A$$H_B$), 43.2 – 46.7 (CONC(2)$H_2$C(3)$H_2$C(4)$H_2$C(5)$H_2$C(6)$H_2$), 46.9 – 46.7 (q, $^2J_{CF}$ = 24.3, F_3CCHC$H_A$$H_B$), 62.8 (C=N$C$HAr=$NO_2$), 123.7 (C=NCH$C$(3,5)Ar-$NO_2$), 128.1 (C=NCH$C$(2,6)Ar-$NO_2$), 128.6 (N=C$C$(2,6)$Ar_1$-Cl). 128.6 – 129.1 (N=C$C$(3,5)$Ar_1$-Cl, N=C$C$(3,5)$Ar_2$-Cl), 130.1 (N=C$C$(2,6)$Ar_2$-Cl), 133.6 – 135.5 (N=C$C(4)Ar_1$-Cl, N=C$C(1)Ar_2$-Cl), 137.2 – 137.4 (N=C$C(1)Ar_1$-Cl, N=C$C(2)Ar_2$-Cl), 147.3 (C=NCH$C$(4)Ar-$NO_2$), 148.6 (C=NCH$C$(1)Ar-$NO_2$), 167.3 ($C$=O), 168.4 ($C$=N). **HRMS** (NSI$^+$) $C_{29}H_{27}Cl_2F_3N_3O_3^+$ ([M+H]$^+$) requires 592.1376, found 592.1363 (-2.21 ppm).

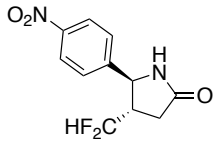
5.5.2. Synthesis of 4,5-disubstitutedpyrrolidin-2-one Compounds

(4*S*,5*S*)-5-(4-nitrophenyl)-4-(trifluoromethyl)pyrrolidin-2-one (275)



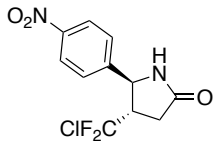
Following **General Procedure H,** (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one **250** (78.7 mg, 0.15 mmol) was stirred with 10% HCl (230 µL, 0.75 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.53) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a beige solid (73.9 mg, 90 %). **mp** 98 – 100 ºC, $[\alpha]_D^{20}$ +11.2 (*c* 1.2, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 11.5 min, t_R(*S,S*): 13.6 min, 94:6 er; **IR** ν_{max} (ATR): 3219 (N-H), 1639 (C=O amide), 1519 (N-O Stretch), 1384 (NO_2 sym), 1111 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.61 – 2.67 (1H, dd, $^3J_{HH}$ = 17.8, $^4J_{HH}$ = 6.7, NHCH(Ar)CH(CF_3)C*H*$_A$H$_B$C=O), 2.76 – 2.83 (1H, dd, $^3J_{HH}$ = 17.8, $^4J_{HH}$ = 10.2, NHCH(Ar)CH(CF_3)CH$_A$*H*$_B$C=O), 3.00 – 3.03 (1H, m, NHCH(Ar)C*H*(CF_3)CH$_A$H$_B$C=O), 4.99 (1H, d, $^3J_{HH}$ = 5.2, NHC*H*(Ar)CH(CF_3)CH$_A$H$_B$C=O), 7.19 (1H, bs, N-*H*), 7.55 – 7.57 (2H, m, C(2,6)Ar*H*-NO_2), 8.29 – 8.31 (2H, m, C(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -71.9; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.9 (NHCH(Ar)CH(CF_3)*C*H$_A$H$_B$C=O), 46.9 – 47.6 (NHCH(Ar)*C*H(CF_3)CH$_A$H$_B$C=O), 56.9 (NH*C*H(Ar)CH(CF_3)CH$_A$H$_B$C=O), 124.6 (*C*(3,5)Ar-NO_2), 126.9 (*C*(2,6)Ar-NO_2), 127.48 (-*C*F_3), 147.2 (*C*(1)Ar-NO_2), 148.2 (*C*(6)Ar-NO_2), 174.7 (*C*=O); **HRMS** (NSI$^+$) $C_{11}H_{10}F_3N_2O_3^+$ ([M+H]$^+$) requires 275.0633, found 275.0638 (-1.8 ppm).

(4*S*,5*S*)-4-(difluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one (276)



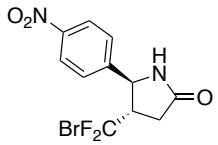
Following **General Procedure H,** ((3*S*,4*S*)-3-(difluoromethyl)-4-((diphenylmethylene)amino)-4-(4-nitrophenyl)-1-(pipe-ridin-1-yl)butan-1-one (57.2 mg ,0.1 mmol) was stirred with 10% HCl (100 µL, 0.5 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.50) to give the titled compound as an inseparable mixture of diastereomers (90:10 dr) as a colorless oil (24.3, 95%). $[\alpha]_D^{20}$ +10.1 (*c* 1.0, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 35.4 min, t_R(*S,S*): 37.9 min, 8:92 er; **IR** ν_{max} (ATR): 2926 (Ar-H), 1701 (C=O, amide), 1519 (N-O stretch), 1348 (NO_2 sym), 1039 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.48 – 2.54 (1H, m, NHCH(Ar)CH(CF_2H)C*H*$_A$H$_B$C=O), 2.66 – 2.72 (1H, m, NHCH(Ar)CH(CF_2H)CH$_A$*H*$_B$C=O), 2.73 – 2.84 (1H, m, NHCH(Ar)C*H*(CF_2H)CH$_A$H$_B$C=O), 4.96 – 4.97 (1H, d, $^3J_{HH}$ = 4.7, NHCH(Ar)C*H*(CF_2H)CH$_A$H$_B$C=O), 5.82 – 6.11 (1H, td, $^2J_{HF}$ = 55.7, $^3J_{HH}$ = 3.7, NHCH(Ar)CH(CF_2*H*)CH$_A$H$_B$C=O), 6.66 (N-*H*), 7.54 – 7.56 (2H, m, C(2,6)Ar*H*-NO_2), 8.28 – 8.30 (2H, m, C(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -125.0 – 120.9 (d, $^2J_{FF}$ = 284.8, C*F*$_2$H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.6 (NHCH(Ar)CH(CF_2H)*C*H$_A$H$_B$C=O), 46.9 – 47.6 (t, $^2J_{CF}$ = 21.2, NHCH(Ar)*C*H(CF_2H)CH$_A$H$_B$C=O), 56.3 (NH*C*H(Ar)CH(CF_2H)CH$_A$H$_B$C=O), 113.1 – 117.9 (t, $^1J_{CF}$ = 243.0, *C*F_2H), 124.5 (*C*(3,5)Ar-NO_2), 126.9 (*C*(2,6)Ar-NO_2), 148.0 (*C*(1)Ar-NO_2), 148.1(*C*(4)Ar-NO_2), 175.3 (*C*=O). **HRMS** (NSI$^+$) $C_{11}H_9F_2N_2O_3^-$ ([M-H]$^-$) requires 255.0587, found 255.0586 (-0.39 ppm).

(4*S*,5*S*)-4-(chlorodifluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one (277)



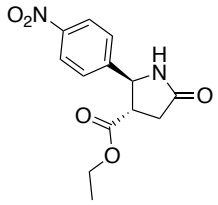
Following **General Procedure H,** (*S*)-4-chloro-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one (108 mg, 0.20 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.55) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a colorless oil (52 mg, 90%). $[\alpha]_D^{20}$ +18.1 (*c* 1.8, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 31.8 min, t_R(*S,S*): 33.5 min, 9:91 er; **IR** ν_{max} (ATR): 3113 (Ar-H), 1705 (C=O, amide), 1521 (N-O stretch), 1350 (NO_2 sym); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.65 – 2.71 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 6.0, NHCH(Ar)CH(CF_2Cl)C$H_A$$H_B$C=O), 2.80 – 2.87 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 9.9, NHCH(Ar)CH(CF_2Cl)C$H_A$$H_B$C=O), 3.12 – 3.22 (1H, m, NHCH(Ar)C*H*(CF_2Cl)C$H_A$$H_B$C=O), 5.03 – 5.04 (1H, dd, $^3J_{HH}$ = 4.5, NHC*H*(Ar)CH(CF_2Cl)C$H_A$$H_B$C=O), 6.91 (N-*H*), 7.56 – 7.58 (2H, m, 2H, m, C(2,6)Ar*H*-NO_2), 8.29 – 8.31 (2H, m, 2H, m, C(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -58.3 – 56.4 (d, $^2J_{FF}$ = 166.9, C*F*$_2$Cl); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 31.1 (NHCH(Ar)CH(CF_2Cl)*C*$H_A$$H_B$C=O), 53.3 – 53.7 (t, $^2J_{HH}$ = 24.6, NHCH(Ar)*C*H(CF_2Cl)C$H_A$$H_B$C=O), 57.7 (NH*C*H(Ar)CH(CF_2Br)C$H_A$$H_B$C=O), 124.6 (*C*(3,5)Ar-$NO_2$), 127.1 (*C*(2,6)Ar-$NO_2$), 129.5 (*C*$F_2$Cl), 147.4 (*C*(4)Ar-$NO_2$), 148.2 (*C*(1)Ar-$NO_2$), 174.4 (*C*=O); **HRMS** (NSI$^+$) $C_{11}H_{10}ClF_2N_2O_3^+$ ([M+H]$^+$) requires 291.0343, found 291.0338(-1.56 ppm).

(4*S*,5*S*)-4-(bromodifluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one (278)



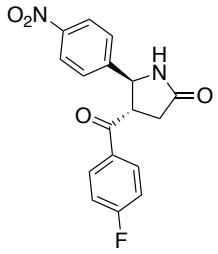
Following **General Procedure H,** (*S*)-4-bromo-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one (mg ,0.2 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.52) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a colorless oil (61.6 mg, 92%). $[\alpha]_D^{20}$ +15.3 (*c* 1.5, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*S,R*): 35.7 min, t_R(*S,S*): 38.1 min, 91:9 er; **IR** ν_{max} (ATR): 3111 (Ar-H), 1705 (C=O, amide), 1519 (N-O stretch), 1350 (NO_2 sym), 1101 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.65 – 2.71 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 5.9, NHCH(Ar)CH(CF_2Br)CH_AH$_B$C=O), 2.79 – 2.86 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 9.9, NHCH(Ar)CH(CF_2Br)CH$_A$$H_B$C=O), 3.11 – 3.21 (1H, m, NHCH(Ar)C*H*(CF_2Br)CH$_A$H$_B$C=O), 5.02 – 5.03 (1H, dd, $^3J_{HH}$ = 4.4, NHC*H*(Ar)CH(CF_2Br)CH$_A$H$_B$C=O), 6.61 (N-*H*), 7.56 – 7.58 (2H, m, 2H, m, C(2,6)Ar*H*-NO_2), 8.29 – 8.32 (2H, m, 2H, m, C(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -52.4 – 49.9 (d, $^2J_{FF}$ = 164.5, C*F*$_2$Br); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 31.7 (NHCH(Ar)CH(CF_2Br)*C*H$_A$H$_B$C=O), 54.9 – 55.4 (t, $^2J_{HH}$ = 22.2, NHCH(Ar)*C*H(CF_2Br)CH$_A$H$_B$C=O), 57.9 (NH*C*H(Ar)CH(CF_2Br)CH$_A$H$_B$C=O), 122.9 (*C*F_2Br), 124.6 (*C*(3,5)Ar-NO_2), 127.1 (*C*(2,6)Ar-NO_2), 147.4 (*C*(4)Ar-NO_2), 148.2 (*C*(1)Ar-NO_2), 174.0 (*C*=O); **HRMS** (NSI$^+$) $C_{11}H_9{}^{81}BrF_2N_2O_3^+$ ([M+Na]$^+$) requires 356.9663, found 356.9653 (-2.80 ppm).

Ethyl (2*S*,3*S*)-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (279)



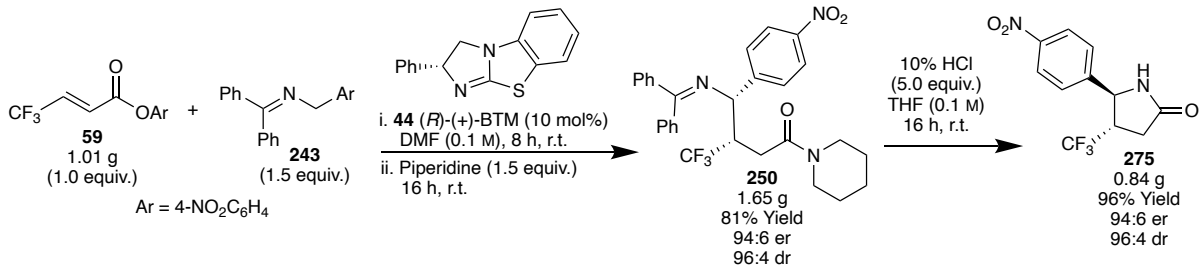
Following **General Procedure H,** Ethyl (*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanoate (106 mg, 0.2 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.40) to give the titled compound as an inseparable mixture of diastereomers (86:14 dr) as a colorless oil (50 mg, 90%). $[\alpha]_D^{20}$ +148.8 (*c* 0.4, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 33.8 min, t_R(*R,S*): 37.5 min, 92:8 er; **IR** ν_{max} (ATR): 2983 (Ar-H), 1730 (C=O, ketone), 1701 (C=O, amide), 1519 (N-O stretch), 1348 (NO_2 sym); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 1.28 – 1.32 (3H, t, $^3J_{HH}$ = 7.2, OCH_2CH_3), 2.78 – 2.81 (2H, d, $^3J_{HH}$ = 9.2, NHCH(Ar)CH(CO_2Et)CH_2C=O), 3.08 – 3.16 (1H, td, $^3J_{HH}$ = 9.2, $^3J_{HH}$ = 6.8, NHCH(Ar)C*H*(CO_2Et)CH_2C=O), 4.21 – 4.28 (2H, m, OC$H_2$$CH_3$), 5.15 – 5.17 (1H, d, $^3J_{HH}$ = 6.8, NHC*H*(Ar)CH(CO_2Et)CH_2C=O), 6.84 (1H, s, N-*H*), 7.57 – 7.60 (2H, m, C(2,6)Ar*H*-NO_2), 8.27 – 8.30 (2H, m, C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.2 (OCH_2CH_3), 33.4 (NHCH(Ar)CH(CO_2Et)CH_AH_BC=O), 48.7 (NHCH(Ar)CH(CO_2Et)CH_AH_BC=O), 59.4 (NHCH(Ar)CH(CO_2Et)CH_AH_BC=O), 61.9 (OCH_2CH_3), 124.4 (*C*(3,5)Ar-NO_2), 127.0 (*C*(2,6)Ar-NO_2), 127.7 (*C*(1)Ar-NO_2), 148.0 (*C*(4)Ar-NO_2), 171.4 (CO_2Et), 175.3 (*C*=O);**HRMS** (NSI$^+$) $C_{13}H_{14}N_2O_5Na^+$ ([M+Na]$^+$) requires 301.0795, found 301.0788 (-2.3 ppm).

(4*S*,5*S*)-4-(4-fluorobenzoyl)-5-(4-nitrophenyl)pyrrolidin-2-one (280)



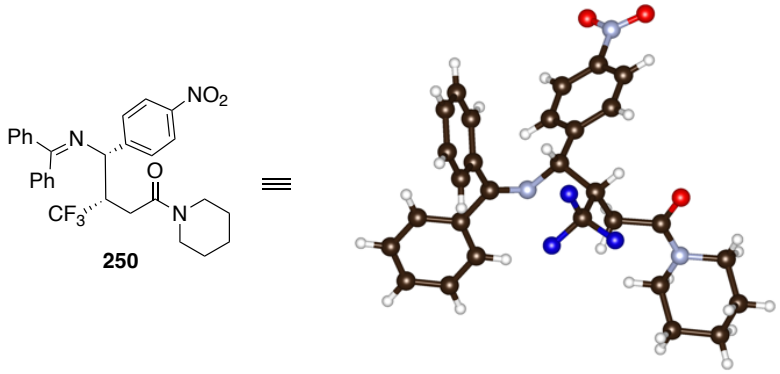
Following **General Procedure H,** (*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-1-(4-fluorophenyl)-4-(piperidin-1-yl)butane-1,4-dione (116 mg, 0.2 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.40) to give the titled compound as an inseparable mixture of diastereomers (80:20 dr) as a colorless oil (59 mg, 90%). $[\alpha]_D^{20}$ +50.6 (*c* 0.8, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,S*): 72.1 min, t_R(*S,R*): 80.9 min, 81:19 er; **IR** ν_{max} (ATR): 2924 (Ar-H), 1701 (C=O, ketone), 1685 (C=O, amide), 1597 (N-O stretch), 1348 (NO_2 sym); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 2.66 – 2.72 (1H, dd, $^3J_{HH}$ = 17.1, $^4J_{HF}$ = 8.9, NHCH(Ar)CH(COPh)C*H*$_A$H$_B$C=O), 2.92 – 2.99 (1H, dd, $^3J_{HH}$ = 17.1, $^4J_{HF}$ = 9.9, NHCH(Ar)CH(COPh)CH$_A$*H*$_B$C=O), 3.97 – 4.03 (1H, ddd, $^3J_{HH}$ = 9.9, $^3J_{HH}$ = 8.9, $^3J_{HH}$ = 6.6, NHCH(Ar)C*H*(COPh)CH$_A$H$_B$C=O), 5.48 – 5.50 (1H, d, $^3J_{HH}$ = 6.6, NHC*H*(Ar)CH(COPh)CH$_A$H$_B$C=O), 6.40 (1H, bs, N-*H*), 7.14 – 7.18 (2H, m, O=CC(3,5)Ar*H*-F), 7.55 – 7.57 (2H, m, C(2,6)Ar*H*-NO_2), 7.86 – 7.89 (2H, m, O=CC(2,6)Ar*H*-F), 8.24 – 8.26 (2H, m, C(3,5)Ar*H*-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: -102.5 (4-*F*-C_6H_4C=O); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 35.0 (NHCH(Ar)CH(COPh)*C*H$_A$H$_B$C=O), 51.4 (NHCH(Ar)*C*H(COPh)CH$_A$H$_B$C=O), 58.2 (NHCH(Ar)*C*H(COPh)CH$_A$H$_B$C=O), 116.2 – 116.5 (O=C*C*(3,5)Ar-F), 124.5 (*C*(3,5)Ar-NO_2), 126.9 (*C*(2,6)Ar-NO_2), 131.3 – 131.4 (O=C*C*(2,6)Ar-F), 147.9 (*C*(4)Ar-NO_2), 148.3 (*C*(1)Ar-NO_2), 165.1 (O=C*C*(1)Ar-F), 168.1 (O=C*C*(4)Ar-F), 174.6 (NHCH(Ar)CH(COPh)CH$_A$H$_B$*C*=O), 195.2 (4-F-C_6H_4*C*=O); **HRMS** (NSI$^+$) $C_{18}H_{13}FN_2O_4Na^+$ ([M+Na]$^+$) requires 351.0752, found 351.0751 (-0.27 ppm).

5.5.3 Grams Scale Synthesis



Following **General Procedure G,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (1.01 g, 3.9 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (1.84 g, 5.8 mmol), (*R*)-(+)-BTM (97.4 mg, 0.38 mmol), and anhydrouds DMF (39 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (573 µL, 5.8 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.23) to give the titled compound **250** as an inseparable mixture of diastereomers (96:4 dr) as a garnet red solid (1.65 g, 81%). **Chiral HPLC analysis.** Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 17.9 min, t_R(*S,R*): 27.4 min, 94:6 er. Following **General Procedure H,** (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one **250** (1.65 g, 3.2 mmol) was stirred with 10% HCl (5.8 mL, 16.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.53) to give the titled compound **275** as an inseparable mixture of diastereomers (96:4 dr) as a beige solid (0.84 g, 96 %); **Chiral HPLC analysis.** Chiralpak IA (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 11.5 min, t_R(*S,S*): 13.6 min, 94:6 er.

5.5.4 Absolute Configuration of Product 250



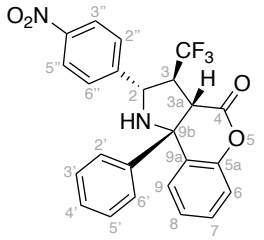
250

Crystal data for **250**: $C_{29}H_{28}F_3N_3O_3$, MW = 523.56, garnet-coloured prism, hexagonal space group *P* 6_1; *a* = 9.4175(0) Å, *b* = 9.4175(0) Å, *c* = 51.0090(0) Å, *α* = 90º, *β* = 90º *γ* = 120º, *V* = 3917.9 $Å^3$. X-ray diffraction data was collected at 173 K using a Rigaku XtaLAB P100 diffractometer using multilayer mirror monochromated Cu-Kα radiation and the structures were solved by direct methods and refined using full-matrix least square analysis.

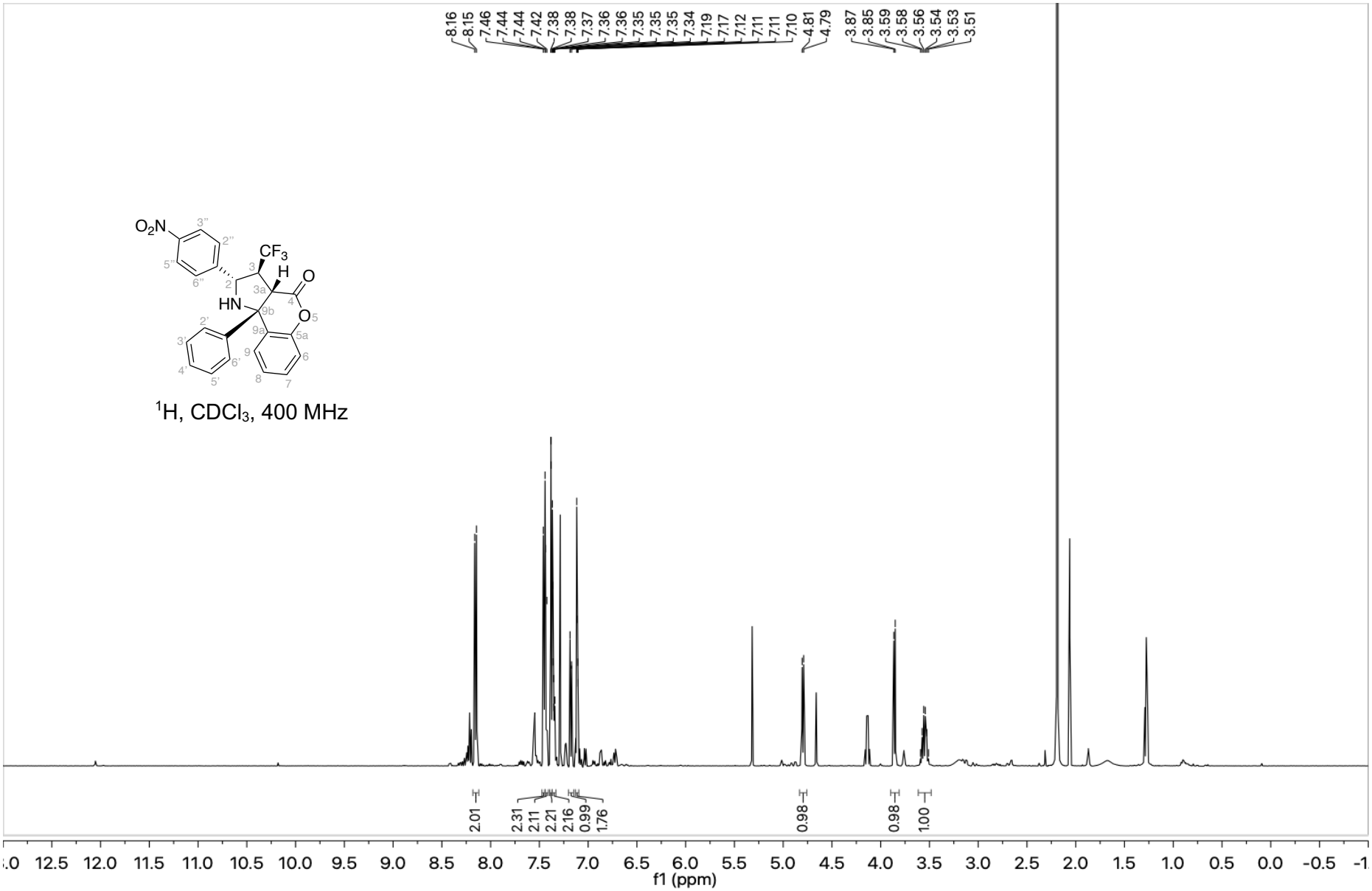
5.6 CHAPTER 4 PRODUCTS

5.6.1 Chapter 4: Isothiourea-Catalysed Michael-Addition-Cyclisation-Lactonisation Reaction

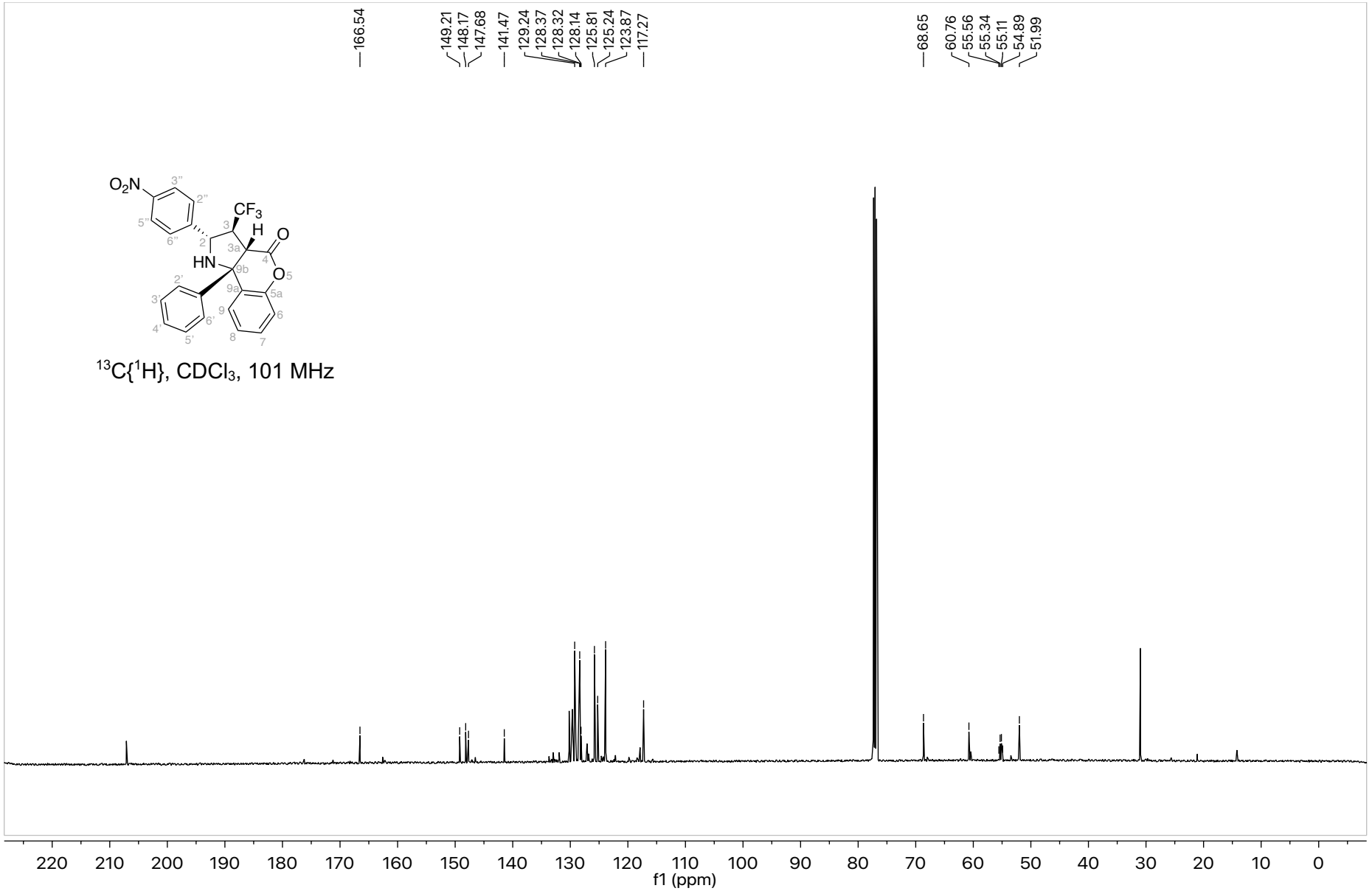
(2*S*,3*S*,3a*S*,9b*S*)-2-(4-nitrophenyl)-9b-phenyl-3-(trifluoromethyl)-2,3,3a,9b-tetrahydro-chromeno[4,3-*b*]pyrrol-4(1*H*)-one (364)

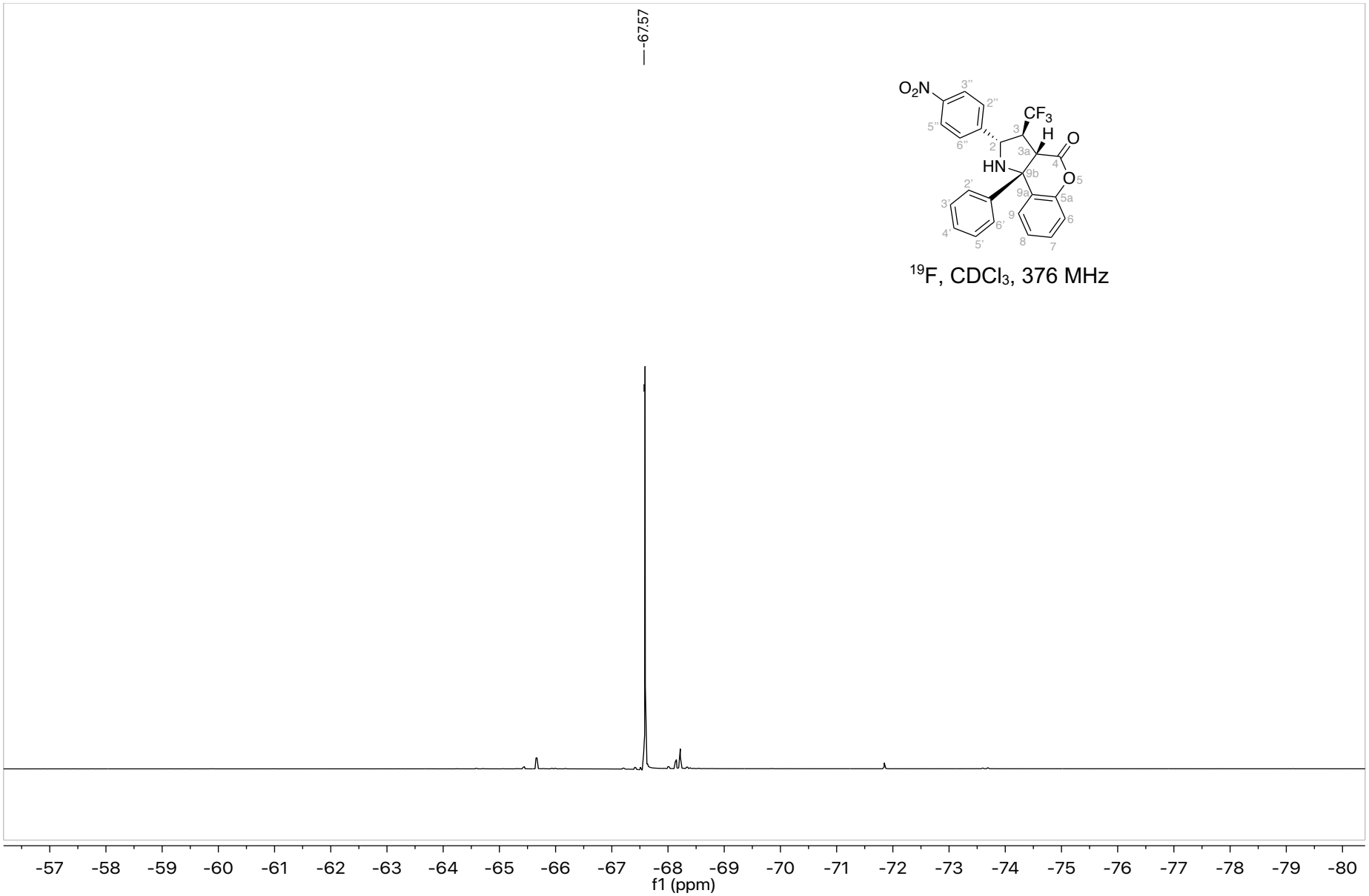


Following **General Procedure I,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), (*E*)-2-(((4-nitrobenzyl)imino)(phenyl)methyl)phenol (49.8 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrouds DMF (1 mL) was stirred at rt for 8 hrs, purified by flash chromatography 4:1 Petrol:EtOAc (R_f = 0.21) to give the titled compound as an inseparable mixture of diastereomers (>99:1 dr) as a yellow oil (21.7 mg, 48%). **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*,3a*R*,9b*R*): 33.6 min, t_R(2*S*,3*S*,3a*S*,9b*S*): 44.3 min, >1:99 er; **IR** ν_{max} (ATR): 3062 (Ar-H), 1770 (C=O), 1519 (N-O stretch), 1346 (NO_2 sym), 1113 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 3.55 (1H, m, C(3)*H*-CF_3), 3.86 (1H, d, $^3J_{HH}$ = 7.2, C(3a)*H*CHCF_3), 4.80 (1H, d, $^3J_{HH}$ = C(2)*H*CHCF_3), 7.10 – 7.12 (2H, m, C(3',5')Ar*H*), 7.17 – 7.18 (1H, m, C(6)Ar*H*), 7.35 – 7.37 (2H, m, C(7)Ar*H*, C(4')Ar*H*), 7.37 – 7.38 (2H, m, C(2',6')Ar*H*), 7.43 – 7.45 (2H, m, C(8,9)Ar*H*), 7.46-7.47 (2H, m, C(2",6")Ar*H*-4-NO_2), 8.14 – 8.15 (2H, m, C(3",5")Ar*H*-4-NO_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: –67.6 (-C*F*$_3$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 51.9 (*C*(3a)CHCF_3), 55.1 (q, $^2J_{CF}$ = 28.2, *C*(3)HCF_3), 60.8 (*C*(2)CHCF_3), 68.7 (*C*(9b)ArH), 117.3 (*C*(6)Ar), 123.9 (*C*(3",5")Ar-NO_2), 125.2 (*C*(9a)Ar), 125.8 (*C*(2',6')Ar), 128.1 (*C*(8)Ar), 128.3 (*C*(9)Ar), 128.4 (*C*(3",5")Ar-NO_2), 129.2 (*C*(7)Ar, *C*(4')Ar), 141.5 (*C*(1')Ar), 147.7 (*C*(4")Ar-NO_2), 148.2 (*C*(1")Ar-NO_2), 149.2 (*C*(5a)Ar), 166.5 (*C*=O); **HRMS** (NSI$^+$) $C_{24}H_{18}F_3N_2O_4^+$ ([M+H]$^+$) requires 455.1218, found 455.1208 (-2.2 ppm).

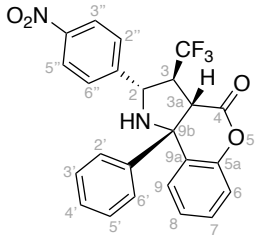


^{1}H, $CDCl_3$, 400 MHz


166.54
149.21
148.17
147.68
141.47
129.24
128.37
128.32
128.14
125.81
125.24
123.87
117.27
68.65
60.76
55.56
55.34
55.11
54.89
51.99
O2N
CF3
H
O
HN
O
13C{1H}, CDCl3, 101 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

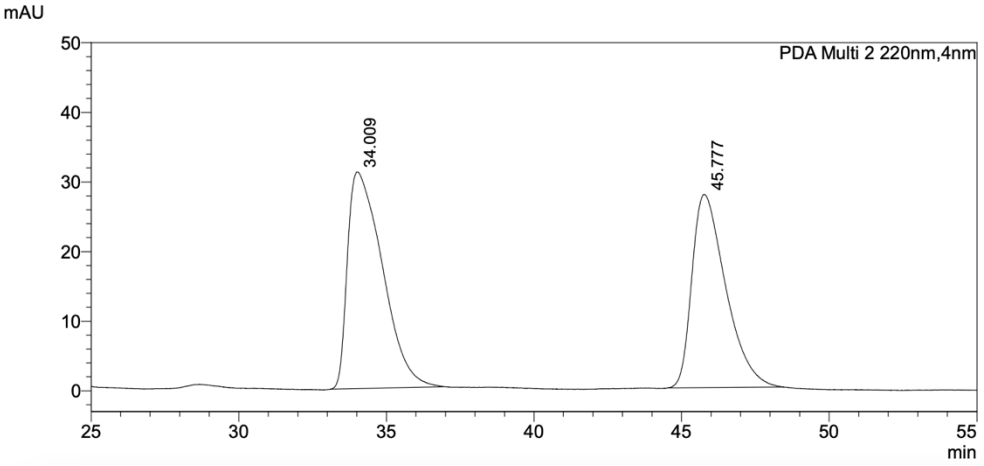

-67.57
O_2N
3''
2''
5''
6''
CF_3
3
H
2
3a
O
4
HN
9b
O
5
2'
9a
5a
3'
6'
9
6
4'
5'
8
7
^{19}F, $CDCl_3$, 376 MHz
-57 -58 -59 -60 -61 -62 -63 -64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80
f1 (ppm)

HPLC Data for **(2*S*,3*S*,3a*S*,9b*S*)-2-(4-nitrophenyl)-9b-phenyl-3-(trifluoromethyl)-2,3,3a,9b-tetrahydro-chromeno[4,3-*b*]pyrrol-4(1*H*)-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*R*,3*S*,3a*S*,9b*S*): 33.6 min, t_R(2*S*,3*S*,3a*S*,9b*S*): 44.3 min, >1:99 er.



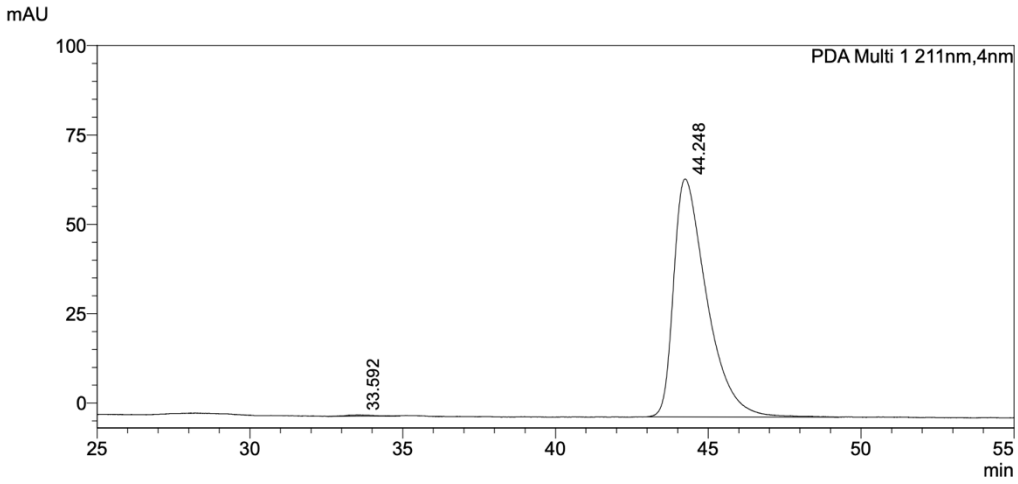
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	34.022	52.554
2	45.778	47.446
Total		100.000

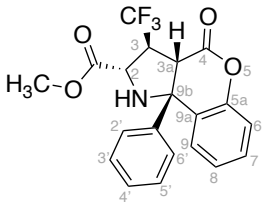


PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	33.592	0.318
2	44.248	99.682
Total		100.000



Methyl (2*S*,3*S*,3a*S*,9b*S*)-4-oxo-9b-phenyl-3-(trifluoromethyl)-1,2,3,3a,4,9b-hexahydro-chromeno[4,3-*b*]pyrrole-2-carboxylate (359)



Following **General Procedure I,** (*E*)-4,4,4-trifluorobut-2-enoic pivalic anhydride **45** (22.4 mg, 0.1 mmol), methyl (*E*)-2-(((2-hydroxyphenyl)(phenyl)methylene)amino)acetate **35** (40.5 mg, 0.15 mmol), and CH_3CN (1 mL) was stirred at rt for 48 hrs, then purified by flash column chromatography with 1:1 Petrol:EtOAc (R_f = 0.39) to give the titled compound as a yellow oil (7.82 mg, 20%). **Chiral HPLC analysis.** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*,3a*S*,9b*S*): 10.9 min, t_R(2*R*,3*R*,3a*R*,9b*R*): 44.3 min, 99:1 er; **IR** ν_{max} (ATR): 3062 (Ar-H), 1770 (C=O), 1519 (N-O stretch), 1346 (NO_2 sym), 1113 (C-F); **^{1}H-NMR** (400 MHz, $CDCl_3$), δ_H: 3.36 – 3.38 (1H, d, $^3J_{HH}$ = 4.9, N-*H*), 3.52 – 3.54 (1H, d, $^3J_{HH}$ = 9.6, C(3a)*H*CHCF$_3$), 3.55 (3H, s, -OC*H*$_3$), 3.73 – 3.84 (1H, m, C(3)*H*CF$_3$), 4.18 – 4.21 (1H, t, $^3J_{HH}$ = 4.9, C(2)*H*CHCF$_3$), 7.13 – 7.15 (1H, m, C(7)Ar*H*), 7.17 – 7.19 (1H, m, C(8)Ar*H*), 7.28 – 7.32 (1H, m, C(6)Ar*H*), 7.34 (4H, m, C(2',3',5',6')Ar*H*), 7.35 – 7.36 (1H, m, C(4')Ar*H*), 7.37 – 7.39 (1H, m, C(9)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: –69.7 (-C*F*$_3$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 49.2 (q, $^2J_{CF}$ = 29.5, *C*(3)CF$_3$), 52.4 (*C*(3a)CHCF$_3$), 52.8 (-O*C*H$_3$), 59.2 (*C*(2)HCHCF$_3$), 69.8 (*C*(9b)CHCF$_3$), 117.4 (*C*(7)Ar), 124.1 (*C*(1')Ar), 125.0 (*C*(8)Ar), 125.7 (*C*(3',5')Ar), 127.4 (*C*F$_3$), 128.2 (*C*(9)Ar), 128.6 (*C*(6)Ar), 129.1 (*C*(2',6')Ar), 130.6 (*C*(4')Ar), 141.3 (*C*(9a)Ar), 150.2 (*C*(5a)Ar), 165.8 (*C*(4)=O), 171.3 (*C*O$_2$CH$_3$); **HRMS** (NSI$^+$) $C_{20}H_{16}F_3NO_4Na^+$ ([M+Na]$^+$) requires 414.0929, found 414.0918 (-2.7 ppm).

5.7 REFERENCES

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